PLOS | MEDICINE

RESEARCH ARTICLE

Diet during pregnancy and infancy and risk of allergic or autoimmune disease: A systematic review and meta-analysis

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Citation: Garcia-Larsen V, Ierodiakonou D, Jarrold K, Cunha S, Chivinge J, Robinson Z, et al. (2018) Diet during pregnancy and infancy and risk of allergic or autoimmune disease: A systematic review and meta-analysis. PLoS Med 15(2): e1002507. https://doi.org/10.1371/journal.pmed.1002507

Academic Editor: Sanjay Basu, Stanford University, UNITED STATES

Received: July 24, 2017

Accepted: January 15, 2018

Published: February 28, 2018

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Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: This work was funded by the Food Standards Agency grant FS305005 to RJB, VGL and JLB https://www.food.gov.uk/science/research/allergy-research/fs305005. The Food Standards Agency commissioned this work, commissioned external peer review of the study protocol, statistical methods and study report, and

Abstract

Background

There is uncertainty about the influence of diet during pregnancy and infancy on a child's immune development. We assessed whether variations in maternal or infant diet can influence risk of allergic or autoimmune disease.

Methods and findings

Two authors selected studies, extracted data, and assessed risk of bias. Grading of Recommendations Assessment, Development and Evaluation (GRADE) was used to assess certainty of findings. We searched Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica dataBASE (EMBASE), Web of Science, Central Register of Controlled Trials (CENTRAL), and Literatura Latino Americana em Ciências da Saúde (LILACS) between January 1946 and July 2013 for observational studies and until December 2017 for intervention studies that evaluated the relationship between diet during pregnancy, lactation, or the first year of life and future risk of allergic or autoimmune disease. We identified 260 original studies (964,143 participants) of milk feeding, including 1 intervention trial of breastfeeding promotion, and 173 original studies (542,672 participants) of other maternal or infant dietary exposures, including 80 trials of maternal ($n = 26$), infant ($n = 32$), or combined ($n = 22$) interventions. Risk of bias was high in 125 (48%) milk feeding studies and 44 (25%) studies of other dietary exposures. Evidence from 19 intervention trials suggests that oral supplementation with nonpathogenic micro-organisms (probiotics) during late pregnancy and lactation may reduce risk of eczema (Risk Ratio [RR] 0.78; 95% CI 0.68–0.90; $I^2 = 61\%$; Absolute Risk Reduction 44 cases per 1,000; 95% CI 20–64), and 6

approved the decision to submit this manuscript for publication.

Competing interests: I have read the journal's policy and the authors of this manuscript have the following competing interests: RJB, VGL, JLB, SC, and DI received support from the UK Food Standards Agency for the submitted work. MT received a consultation fee from the UK Food Standards Agency for methodological work on this systematic review. No other support was received from any organisation for the submitted work. The authors have no financial relationships with any organisations that might have an interest in the submitted work in the previous three years. RJB was a co-investigator and author of two of the trials included in this systematic review. The authors report no other relationships or activities that could appear to have influenced the submitted work.

Abbreviations: CCT, controlled clinical trial; CENTRAL, Central Register of Controlled Trials; COT, Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment; EMBASE, Excerpta Medica dataBASE; GRADE, Grading of Recommendations Assessment, Development and Evaluation; LILACS, Literatura Latino Americana em Ciências da Saúde; MEDLINE, Medical Literature Analysis and Retrieval System Online; OR, odds ratio; RCT, randomised controlled trial; RR, Risk Ratio; SACN, Scientific Advisory Committee on Nutrition; sIgE, specific immunoglobulin E; TIDM, type 1 diabetes mellitus; TSA, trial sequential analysis; WAO, World Allergy Organization.

trials suggest that fish oil supplementation during pregnancy and lactation may reduce risk of allergic sensitisation to egg (RR 0.69, 95% CI 0.53–0.90; I^2 = 15%; Absolute Risk Reduction 31 cases per 1,000; 95% CI 10–47). GRADE certainty of these findings was moderate. We found weaker support for the hypotheses that breastfeeding promotion reduces risk of eczema during infancy (1 intervention trial), that longer exclusive breastfeeding is associated with reduced type 1 diabetes mellitus (28 observational studies), and that probiotics reduce risk of allergic sensitisation to cow's milk (9 intervention trials), where GRADE certainty of findings was low. We did not find that other dietary exposures—including prebiotic supplements, maternal allergenic food avoidance, and vitamin, mineral, fruit, and vegetable intake—influence risk of allergic or autoimmune disease. For many dietary exposures, data were inconclusive or inconsistent, such that we were unable to exclude the possibility of important beneficial or harmful effects. In this comprehensive systematic review, we were not able to include more recent observational studies or verify data via direct contact with authors, and we did not evaluate measures of food diversity during infancy.

Conclusions

Our findings support a relationship between maternal diet and risk of immune-mediated diseases in the child. Maternal probiotic and fish oil supplementation may reduce risk of eczema and allergic sensitisation to food, respectively.

Author summary

Why was this study done?

- There is uncertainty about the effects of specific dietary variations in early life on risk of immune-mediated disease.

What did the researchers do and find?

- We undertook a systematic review of observational and intervention studies of maternal diet during pregnancy and lactation and infant diet during the first year of life to evaluate whether dietary exposures in early life influence risk of allergic or autoimmune disease.
- We found that supplementation with micro-organisms (probiotics) during late pregnancy and breastfeeding may reduce risk of eczema, and fish oil supplementation during pregnancy and breastfeeding may reduce risk of sensitisation to food allergens.
- We found more limited data that longer duration of breastfeeding may reduce risk of eczema and type 1 diabetes mellitus.

What do these findings mean?

- A mother's diet during pregnancy and lactation may influence her child's risk of developing allergic disease.

Introduction

Immune-mediated health conditions such as allergic and autoimmune diseases appear to have increased in prevalence in many countries and are leading causes of chronic illness in young people [1]. There is evidence that early dietary exposures may influence the development of these diseases, but a comprehensive analysis of the relationship between all dietary exposures during pregnancy, lactation, or the first year of life and risk of allergic or autoimmune disease has not been undertaken [1]. Relevant dietary exposures may include intake of individual foods or food groups, nutrients or nutrient groups, dietary supplements, avoidance of specific allergenic foods, timing of introduction of specific foods or food groups to the infant diet, overall dietary pattern, and duration of breastfeeding. A recent World Allergy Organization guideline recommended probiotic and prebiotic supplements for eczema prevention [2,3], but European, North American, and Australasian guidelines do not support this [4–6]. Several guidelines recommend exclusive breastfeeding for at least 4 to 6 months to reduce risk of eczema, food allergy, and wheezing [4,5,7], and a recent Australasian guideline recommends oily fish or omega-3 fatty acid supplements during pregnancy to reduce eczema [6]. Recent focused systematic reviews support a relationship between breastfeeding and reduced asthma risk [8,9] and between probiotics and prebiotics and reduced eczema risk [2,10,11]. In order to inform United Kingdom dietary recommendations for infants and their pregnant or lactating mothers, we undertook an updated and comprehensive systematic review of diet during pregnancy and infancy and risk of allergic sensitisation, allergic disease, or autoimmune disease.

Methods

This review is reported in accordance with PRISMA guidance. The review is part of a series of systematic reviews commissioned by the UK Food Standards Agency in order to inform UK dietary recommendations for infants and their pregnant or lactating mothers, under the title 'Review of scientific published literature on infant feeding and development of atopic and autoimmune disease'. The protocols for the systematic reviews were registered with the International Prospective Register of Systematic Reviews (PROSPERO CRD42013003802 'Review A:milk feeding'; CRD42013004239 'Review B:timing of allergenic food introduction'; CRD42013004252 'Review C:maternal and infant diet') on 5 August 2013, prior to title screening or selecting any studies from the search results. This manuscript reports findings from the majority of the project, comprising Reviews A and C, 'milk feeding' and 'maternal and infant diet'. Review B, regarding timing of introduction of allergenic foods, and one part of Review C, regarding use of hydrolysed infant formula, have been published separately [12,13]. Thus, this manuscript describes outcomes for maternal or infant intake of individual foods or food groups, nutrients or nutrient groups, dietary supplements, maternal allergenic food avoidance, timing of introduction of solid foods or nonallergenic foods to the infant diet, overall dietary pattern and duration of breastfeeding. This manuscript does not include timing of introduction of allergenic foods (milk, soya, egg, peanuts, tree nuts, fish, seafood, wheat) to the infant diet or use of hydrolysed formula in infants. Measures of dietary diversity and objective measures of nutritional status (with the exception of blood vitamin D level) were not included in these systematic reviews. These measures were considered to be too indirect as indicators of dietary intake to be used to inform public health guidance in the UK. As part of this project, we also searched for other systematic reviews covering the same topic published since 1 January 2011.

Study interventions and comparators

Studies of total breastfeeding duration, exclusive breastfeeding duration [14], and timing of solid food introduction were included in Review A 'milk feeding'. Studies of any other nutritional exposure, ranging from dietary pattern to specific micronutrient supplementation and from single to multifaceted interventions, were included in Review C 'maternal and infant diet'. For observational studies, data on dietary exposures were acquired from interviews, health records, diaries, and questionnaires. With the exception of blood vitamin D level, we did not include assessments of nutrient status as an exposure, and we did not include measures of dietary diversity as an exposure.

Study designs and populations

We included all intervention trials, and observational studies described as cohort, case control or cross-sectional analytic studies. Intervention trials were classified as randomised controlled trials (RCTs), where the method of treatment allocation was random, and as controlled clinical trials (CCTs), where treatment allocation was nonrandom and likely to lead to significant imbalance between treatment groups. CCTs were analysed separately from RCTs. Prospective and retrospective observational studies were analysed separately. We included studies of diet during pregnancy or lactation and of infant feeding between birth and 12 months of age. We excluded studies in which participants or their mothers were defined by the presence of a pre-existing disease state, including very low birth weight or very premature infants.

Study outcomes

Allergic and autoimmune outcomes were selected on the basis of their population prevalence in children and young adults [15]. We included diseases with a prevalence of at least 1 in 1,000 in children/adolescents or young adults (aged $<$40 years) but did not include rarer diseases. We did not include pernicious anaemia or adult-onset rheumatoid arthritis despite a high prevalence in middle-aged and elderly people because their prevalence in young people is lower than 1 in 1,000, and prospective studies of infant feeding in relation to diseases of older adults were thought unlikely to have been reported. Allergic outcomes that met our inclusion criteria were asthma or wheeze, eczema, allergic rhinitis and/or conjunctivitis, food allergy (defined by food challenge, medical diagnosis, or self/parent report), allergic sensitisation, i.e., skin prick or specific immunoglobulin E (sIgE) assessment, and total immunoglobin E (IgE) level. We categorised asthma as wheeze, recurrent wheeze, or atopic wheeze depending on the definition used in the original publication, and we included measures of lung function, specifically bronchial hyper-reactivity, forced vital capacity, peak expiratory flow rate, and forced expiratory volume in 1 second. Physician-diagnosed asthma was included within the category 'recurrent wheeze', unless defined as a single episode of wheeze. Autoimmune diseases that met our inclusion criteria were type 1 diabetes mellitus (TIDM) (doctor diagnosed or serological diagnosis), coeliac disease defined serologically or clinically (positive Immunoglobulin A tissue Transglutaminase antibodies on one or more visits or a positive small bowel biopsy), inflammatory bowel disease, autoimmune thyroid disease, juvenile rheumatoid arthritis, vitiligo, and psoriasis, all as doctor diagnosis. For clinical allergic outcomes, we grouped age at assessment as 0–4 years, 5–14 years, and $\geq$15 years. Allergic sensitisation and autoimmune diseases were not stratified by age at outcome assessment.

Data sources

We searched The Cochrane Library (2013, Issue 7), Excerpta Medica dataBASE (EMBASE) (1947 to July 2013), Literatura Latino Americana em Ciências da Saúde (LILACS) (1982 to

July 2013), Medical Literature Analysis and Retrieval System Online (MEDLINE) (1946 to July 2013), and Web of Science (1970 to July 2013) on 25 July 2013. We reran the searches for intervention trials and systematic reviews on 26 February 2017 and for intervention trials again on 15 December 2017. We included all studies published up to that date and studies in progress or completed but unpublished studies identified through http://apps.who.int/trialsearch/. Both peer-reviewed publications and abstract publications were included. We reviewed the bibliography of eligible studies for possible additional publications and included all eligible publications, regardless of the language. Study authors were not contacted for original data. The search strategies were extensively piloted and refined to optimise sensitivity, comparing search results with those of other systematic reviews. The search strategies are shown in S1 Text.

Study selection

Title and abstract screening was undertaken by a team of 9 trained researchers (RJB, VGL, DI, NG, KJ, JC, ZR, AR, PD). Two researchers undertook title screening independently and met to agree upon included and excluded titles. Their screening was checked by a third person, and uncertainties were resolved at a weekly team meeting between February and April 2014, 2015, and 2017 (RB, SC, VGL). The full texts of all potentially eligible studies were reviewed.

Risk of bias assessment

Risk of bias assessment was undertaken in duplicate, using modified versions of the Cochrane Collaboration Risk of Bias tool for intervention trials and the National Institute for Clinical Excellence methodological checklist for cohort and case–control studies [16]. Risk of bias domains for intervention trials were Selection bias (sequence generation and allocation concealment), Assessment bias (blinding of outcome assessors and validity of the outcome assessment tool), and Attrition bias (considered high when $<$70% of randomised participants had outcome data). Risk of bias domains for observational studies were Selection bias (low if cases and controls came from similar populations and participation rate $\geq$80%), Assessment bias (the validity of exposure and outcome assessment tools), and Confounding bias (whether study design and analysis accounted for most potential confounders). We separately included an assessment of Conflict of Interest for each study, judged as low where there was no evidence of industry involvement in study design, analysis, interpretation, or publication and no evidence that study authors received remuneration from relevant industry partners for other activities.

Data extraction

Data extraction was undertaken in duplicate. Disagreements and uncertainties about data coding and risk of bias were discussed within the team. For foreign language studies, data were extracted by VGL together with a native speaker of the relevant language (see Acknowledgemnts section). We extracted all relevant data from included studies, including data not able to be meta-analysed. Data were extracted using either raw frequencies or crude or adjusted effect estimates. Random effects meta-analysis was undertaken, and where this was not possible, study results were summarised in a narrative table.

Data selection for analysis

For intervention trials, we extracted outcome data that adhered to the intention-to-treat principle in preference to data based on per protocol analyses. Where studies included multiple intervention groups, we performed pairwise comparisons where we split the number of events

and no events in the unexposed/control group to prevent double counting. Where studies reported data at multiple timepoints, we extracted the most complete dataset available beyond the intervention period (i.e., from 1 year of age onwards); this is the dataset with the largest denominator or, where the denominator is identical for multiple time points, the largest numerator (number of events). Where studies reported multiple assessments of the same outcome at the same timepoint, clinical assessments were selected in preference to serological assessments, and skin prick in preference to sIgE assessment of allergic sensitisation. For observational studies of breastfeeding or timing of solid or other food introduction to the infant diet, data were only included in meta-analysis where the reference group was complete, i.e., 'less than' a certain duration or, in some cases, 'never'. Where more than one exposure group was compared with the reference group, we analysed data for the latest exposure group. For all observational studies, adjusted effect estimates were used in preference to unadjusted estimates for meta-analysis if both were reported.

Data synthesis

Pooled results for binary outcomes were presented as Risk Ratio (RR) calculated using the Mantel–Haenszel method, with continuity correction of 0.5 for zero cell frequencies, and odds ratios (ORs) were pooled using the generic inverse variance method using R (version 3.1.0 2014-04-10, www.r-project.org). For continuous outcomes measured using similar scales, data were summarised as mean differences with 95% CI. Key findings are presented in a Summary of Findings table with Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment of certainty of findings [17]. Heterogeneity was quantified using I^2 and classified as low ($I^2 < 25\%$), moderate (I^2 25%–50%), high (I^2 50%–75%) or extreme ($I^2 > 75\%$). Data were not pooled where $I^2 \geq 80\%$. We assessed for publication bias using Funnel plots and Egger asymmetry tests where there were ≥ 10 studies in a meta-analysis. We undertook a priori defined subgroup analyses for meta-analyses with > 5 studies according to overall risk of bias; disease risk; study design; conflict of interest; for some analyses, by features of the intervention or exposure assessment; and method of outcome assessment. Data that could not be included in meta-analysis were reported narratively, and the outcomes of both meta-analyses and narrative reports were considered when interpreting data and making conclusions. Trial sequential analysis (TSA) was used to quantify the statistical reliability of moderate or high certainty findings using 2-sided 5% significance and 80% power to estimate optimum heterogeneity-adjusted information sizes needed to identify relative risk reductions of 20% and 30%. Control event rates were estimated using random effects meta-analyses of the pooled proportions from the largest studies included in the meta-analysis and compared with event rates from large population-based studies. TSA quantifies the statistical reliability of data in a cumulative meta-analysis in a similar way to an interim analysis in a single randomised clinical trial.

Results

Our original search identified 16,289 original titles. Title, abstract, and full text screening yielded a total of 343 titles (260 original studies; 964,143 participants) of milk feeding and 281 titles (173 original studies; 542,672 participants) of maternal and infant diet, including 80 trials of maternal ($n = 26$), infant ($n = 32$), or combined ($n = 22$) interventions. Full details of the search results are shown in Fig 1 (PRISMA flow chart), and characteristics of included studies and risk of bias are summarised in S1 Appendix. Risk of bias was high in 125 (48%) studies of milk feeding and 44 (25%) studies of maternal and infant diet (most commonly due to attrition bias in intervention studies and confounding bias in observational studies). Key findings are shown in Table 1, which includes a GRADE assessment of certainty for each finding [18], and

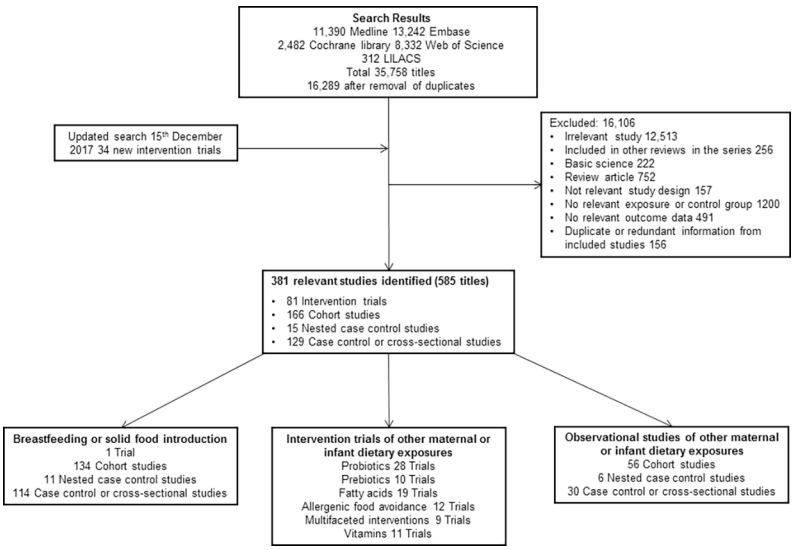


Fig 1. PRISMA flow chart. CENTRAL, Central Register of Controlled Trials; EMBASE, Excerpta Medica dataBASE; LILACS, Literatura Latino Americana em Ciências da Saúde; MEDLINE, Medical Literature Analysis and Retrieval System Online.

https://doi.org/10.1371/journal.pmed.1002507.g001

in Figs 2–9. The full report, with a detailed description of the methodology used and all review findings, is available on the Food Standards Agency website (https://www.food.gov.uk/science/research/allergy-research/fs305005ac). Summary reports to the Food Standards Agency for studies of milk feeding and studies of maternal and infant diet are in S2 Text and S3 Text, respectively. Detailed appraisal of findings underlying the 2 reports are in S1 Data and S2 Data, respectively, and all data used for meta-analyses are in S3 Data. An associated statement by the Committee on Toxicity is available on the Food Standards Agency website (https://cot.food.gov.uk/cotstatements/cotstatementsyrs/cot-statements-2017/statementonrevsaandc).

Breastfeeding duration and timing of solid food introduction

One intervention trial (17,046 participants) and 259 observational studies (947,097 participants) reported the association between total breastfeeding, exclusive breastfeeding or timing of solid food introduction, and allergic or autoimmune diseases. The intervention trial found reduced eczema in the first year of life in centres allocated to deliver a breastfeeding promotion intervention. Meta-analyses of 24 observational studies showed an association between total breastfeeding duration and reduced recurrent wheeze at 5 to 14 years (e.g., Fig 2), but we also found evidence of publication bias. Meta-analyses of 31 observational studies showed an association between total and exclusive breastfeeding duration and reduced TIDM (e.g. Fig 3). Associations were statistically significant for retrospective studies but not for prospective studies. The GRADE certainty of these breastfeeding findings was low to very low. There was no association found for other allergic outcomes or for the other autoimmune diseases studied (coeliac disease, 12 studies; inflammatory bowel disease, 13 studies; juvenile rheumatoid arthritis, 3 studies; autoimmune thyroid disease, 1 study).

Intervention trials of other maternal or infant dietary exposures

Probiotic and prebiotic supplementation. Twenty-eight intervention trials (6,705 participants) evaluated probiotic supplements. These were either single or multiple organisms, given as capsules, powder, or part of a drink or infant formula milk, at a dose of 1 to 10 billion

Table 1. GRADE assessment and summary of key findings.

GRADE of evidence assessment							Summary of findings		Absolute Risk Reduction*	
No of studies and design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Other considerations	Relative risk	GRADE of evidence	Control Risk	Risk Difference
									Cases per 1,000 population	Cases per 1,000 population
Intervention: Breastfeeding promotion intervention vs no intervention **Outcome: Eczema at age 0–4** **Study design: RCT**										
1 RCT Eczema	Not Serious Unblinded outcome assessment	Serious No effect seen at age 6–7 years, and no clear evidence for an effect seen at age 16 years. No association seen in observational studies.	No	Serious Wide CIs	No	No association found between exclusive breastfeeding duration and eczema in an observational analysis of this trial	**OR 0.54 95% CI 0.31–0.95**	⊗⊗○○ **Low**	**200 (low risk)** **300 (high risk)** **400 (very high risk)**	**81 cases 95% CI 8–128** **112 cases 95% CI 11–183** **135 cases 95% CI 12–229**
Exposure: Total breastfeeding duration—Breastfed ever versus never **Outcome: Recurrent wheeze at age 5–14 and Type 1 Diabetes Mellitus** **Study design: Prospective or retrospective studies**										
14 prospective (13 PC, 1 NCC all in meta-analysis) 13 retrospective (2 RC, 4 CC, 7 CS, 1 RC, and 1 CS not in meta-analysis) Recurrent wheeze	Not serious 4 prospective studies, and 7 retrospective studies, at high risk of bias, but no subgroup difference according to risk of bias	Not serious I^2 = 29% prospective, 47% retrospective. Study estimates vary from 0.38 to 1.15 prospective; 0.51 to 1.28 retrospective. Similar findings not consistently seen for wheeze at age 5–14 years, nor for wheeze or recurrent wheeze at ages 0–4 or 15+ years.	Not serious Mixed study populations, but several studies included large numbers of participants from representative populations	No Large numbers of participants and events, with relatively narrow CIs	Serious Asymmetrical Funnel plot for all studies combined Egger P = 0.012	Analysis of other cut-offs for duration of total breastfeeding showed a similar association between longer BF duration and reduced risk of recurrent wheeze at age 5–14, but with evidence of publication bias; no evidence of subgroup differences by adjustment of analysis; by disease risk; by risk of bias; or by prospective versus retrospective study design	**ProspectiveOR = 0.85 (0.76, 0.95)** **Retrospective OR = 0.90 (0.81, 1.00)** **Pooled effect OR = 0.88 (0.82, 0.94)**	⊗○○○ **Very Low**	**50 (low risk)** **100 (high risk)** **150 (very high risk)**	**6 cases 95% CI 3–9** **11 cases 95% CI 5–16** **16 cases 95% CI 8–24**
7 prospective (4 PC, 3 in meta-analysis; 3 NCC, all in meta-analysis) 28 retrospective (27 CC, 24 in meta-analysis; 1 CS in meta-analysis) TIDM	Not serious 4 prospective studies, and 11 retrospective studies, at high risk of bias	Serious I^2 = 0% prospective, 55% retrospective. Study estimates vary from 0.76 to 1.67 prospective; 0.14 to 2.44 retrospective. Significant difference between prospective studies, with no association seen, and retrospective studies, where breastfeeding was associated with reduced TIDM.	Not serious 3 studies used serological diagnosis in populations at high inherited risk of TIDM, others used clinical diagnosis in more representative populations	No Large numbers of studies and events	No Symmetrical funnel plot for all studies combined Egger P = 0.81	Analysis of other cut-offs for duration of total breastfeeding showed a similar pattern of a significant association between longer BF duration and reduced odds of TIDM in retrospective studies, where clinical TIDM was used for outcome assessment; but no consistent evidence of a relationship seen in prospective studies, where serological TIDM was usually used for outcome assessment	**ProspectiveOR = 1.12 (0.77, 1.61)** **Retrospective OR = 0.75 (0.65, 0.87)** **Pooled effect OR = 0.78 (0.68, 0.89)**	⊗○○○ **Very Low**	**1 (low risk)** **10 (high risk)** **100 (very high risk)**	**Prospective0.2 cases 95% CI 0.1–0.3** **2 cases 95% CI 1–3** **20 cases 95% CI 10–30**
Exposure: Exclusive breastfeeding duration greater than 3–4 months versus less than 3–4 months **Outcome: Type 1 Diabetes Mellitus** **Study design: Prospective or retrospective studies**										

(*Continued*)

Table 1. (Continued)

GRADE of evidence assessment							Summary of findings		Absolute Risk Reduction*	
No of studies and design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Other considerations	Relative risk	GRADE of evidence	Control Risk Cases per 1,000 population	Risk Difference Cases per 1,000 population
5 prospective (5 PC, 4 in meta-analysis) 5 retrospective (5 CC, all in meta-analysis) TIDM	Not serious 2 prospective studies, and 3 retrospective studies, at high risk of bias; no subgroup difference according to risk of bias	Not serious I^2 = 21% prospective, 31% retrospective. Study estimates vary from 0.35 to 1.00 prospective; 0.18 to 1.08 retrospective. Nonsignificant difference between prospective studies, with no association seen, and retrospective studies, where longer exclusive breastfeeding was associated with reduced TIDM.	Not serious Prospective studies used serological diagnosis in populations at high inherited odds of TIDM, retrospective studies used clinical diagnosis in more representative populations	Not serious Reasonable numbers of studies and events.	Not tested ($n < 10$)	Analysis of other cut-offs for duration of exclusive breastfeeding showed a similar pattern of a significant association between longer duration and reduced odds of TIDM in retrospective studies, where clinical TIDM was used for outcome assessment; but no consistent evidence of a relationship seen in prospective studies, where serological TIDM was used for outcome assessment	**ProspectiveOR = 0.77 (0.56, 1.05)** **Retrospective OR = 0.62 (0.48, 0.81)** **Pooled effect OR = 0.68 (0.55, 0.83)**	⊗⊗○○ **Low**	**1 (low risk)** **10 (high risk)** **100 (very high risk)**	**0.3 cases 95% CI 0.2 to 0.4** **3 cases 95% CI 2 to 4** **30 cases 95% CI 16 to 42**
Intervention: Maternal or infant probiotic supplement vs no probiotic supplement **Outcome: Eczema, atopic eczema or cow's milk sensitisation at age 0–4** **Study design: RCT**										
23 RCT (19 in meta-analysis) 1 CCT Eczema	Not Serious <20% of studies had a high risk of bias	Serious I^2 = 61% Eczema Study estimates vary from 0.14 to 1.34; subgroup analysis suggests greatest effect if postnatal component includes maternal supplementation	No	No	No	Most RCTs were undertaken in populations at high risk of eczema due to family history of allergic disease. No evidence of an effect on eczema beyond age 0–4.	**RR = 0.78 (0.68, 0.90)**	⊗⊗⊗○ **Moderate**	**200 (low risk)** **300 (high risk)** **400 (very high risk)**	**44 cases 95% CI 20–64** **66 cases 95% CI 30–96** **88 cases 95% CI 40–128**
11 RCT Atopic Eczema	Not Serious <20% of studies had a high risk of bias	Serious I^2 = 0% Study estimates vary from 0.47 to 1.36. But no beneficial effect seen at age 5–14 years RR 0.99 (0.80, 1.22; I^2 = 0%).	No	No	No Egger P = 0.70	Most RCTs were undertaken in populations at high risk of eczema due to family history of allergic disease.	**RR = 0.78 (0.65, 0.92)**	⊗⊗⊗○ **Moderate**	**100 (low risk)** **150 (high risk)** **200 (very high risk)**	**22 cases 95% CI 8–35** **33 cases 95% CI 12–53** **44 cases 95% CI 16–70**
97 RCT (8 in meta-analysis) Cow's milk sensitisation	Not Serious <20% of studies had a high risk of bias	Not Serious I^2 = 0% Study estimates vary from 0.14 to 0.98. No beneficial effect seen for allergic sensitisation to other allergens.	Serious Milk sensitisation is a surrogate measure of clinical food allergy. No effect of the intervention was seen on clinical food allergy.	Serious Low event numbers and borderline statistical significance	Not tested ($n < 10$) No evidence of publication bias in Funnel plots for other forms of allergic sensitisation	Most RCTs were undertaken in populations at high risk of eczema due to family history of allergic disease	**RR = 0.60 (0.37, 0.96)**	⊗⊗○○ **Low**	**30 (low risk)** **100 (high risk)** **300 (very high risk)**	**12 cases 95% CI 1–19** **40 cases 95% CI 4–63** **120 cases 95% CI 12–189**

(*Continued*)

Table 1. (Continued)

GRADE of evidence assessment							Summary of findings		Absolute Risk Reduction*	
No of studies and design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Other considerations	Relative risk	GRADE of evidence	Control Risk Cases per 1,000 population	Risk Difference Cases per 1,000 population
Intervention: Infant prebiotic supplement versus no prebiotic supplement **Outcome: Eczema at age 0–4** **Study design: RCT**										
9 RCT (7 in meta-analysis) Eczema	Serious 4 studies with high risk of attrition bias, 5 with high risk of conflict of interest	Serious I^2 = 57% Study estimates vary from 0.14 to 1.64	Serious 6 studies restricted inclusion to infants fully formula fed from birth, 3 days, < 2 weeks, <6 weeks (n = 2) and <8 weeks; 3 other studies used co-interventions–hydrolysed formula and probiotics	Serious Wide CIs, borderline statistical significance	Not tested (n<10)	3 RCTs were undertaken in populations at high risk due to family history of allergic disease, 4 at normal risk, and 1 at low risk due to absence of family history of allergic disease. All studies used galactooligosaccharides, usually combined with other oligosaccharides; 2 studies combined the intervention with probiotic(s).	**RR = 0.75 (0.56, 1.01)**	○○○○ **No evidence**	-	-
Intervention: Maternal fish oil (n-3 PUFA) vs no fish oil **Outcome: Allergic sensitisation to egg** **Study design: RCT**										
6 RCT Allergic sensitisation to egg	Not Serious 2 studies with unclear overall risk of bias and 2 studies with unclear risk of conflict of interest	Not Serious I^2 = 15% Study estimates vary from 0.45 to 1.02. No significant effect seen for allergic sensitisation to other allergens, but direction of effect is inconsistent with that seen for egg.	Serious Egg sensitisation is a surrogate measure of clinical food allergy. No effect of the intervention was seen on clinical food allergy.	Not serious Limits of 95% CI are all important effects at a population level.	Not tested ($n < 10$)	All RCTs were undertaken in populations at high risk of allergy due to family history of allergic disease. Subgroup analysis suggests effect is greatest if treatment is given during pregnancy.	**RR = 0.69 (0.53, 0.90)**	⊗⊗⊗○ **Moderate**	**100 (low risk)** **150 (high risk)** **200 (very high risk)**	**31 cases 95% CI 10–47** **46 cases 95% CI 15–71** **62 cases 95% CI 20–94**
Intervention: Multifaceted interventions vs control **Outcome: Allergic rhinitis at age 0–4** **Study design: RCT**										
3 RCT (2 in meta-analysis) Allergic rhinitis	Not serious No study with high risk of bias or high risk of conflict of interest	Not serious I^2 = 0% Study estimates vary from 0.58 to 0.61	Serious Both studies in meta-analysis included environmental control measures such as dust mite and tobacco smoke avoidance	Serious Sparse data, inconsistent with data for ages 5–14 years, where no effect was seen. Study not included in meta-analysis found no effect.	Not tested ($n < 10$)	All RCTs were undertaken in populations at high risk due to family history of allergic disease. All studies included delayed introduction of allergenic foods and maternal allergenic food avoidance	**RR = 0.61 (0.44, 0.84)**	⊗⊗○○ **Low**	**50 (low risk)** **100 (high risk)** **150 (very high risk)**	**20 cases 95% CI 8–28** **39 cases 95% CI 16–56** **59 cases 95% CI 24–84**
Intervention: Multifaceted interventions vs control **Outcome: Wheeze or recurrent wheeze at age 5–14** **Study design: RCT**										

(*Continued*)

Table 1. (Continued)

GRADE of evidence assessment							Summary of findings		Absolute Risk Reduction*	
No of studies and design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Other considerations	Relative risk	GRADE of evidence	Control Risk	Risk Difference
									Cases per 1,000 population	Cases per 1,000 population
2 RCT Wheeze	Not serious No study with high risk of attrition bias or high risk of conflict of interest	Not serious $I^2 = 0\%$ Study estimates vary from 0.50 to 0.59	Serious Both studies included environmental control measures such as dust mite and tobacco smoke avoidance, which are known to reduce respiratory symptoms	Serious Sparse data, inconsistent with data for age 0–4 and lung function data, where no effect was seen	Not tested ($n < 10$)	All RCTs were undertaken in populations at high risk due to family history of allergic disease. Both studies included delayed introduction of allergenic foods and maternal allergenic food avoidance	**RR = 0.57 (0.41, 0.81)**	⊗⊗○○ **Low**	**100 (low risk)** **150 (high risk)** **200 (very high risk)**	**43 cases 95% CI 19–59** **65 cases 95% CI 29–89** **86 cases 95% CI 38–118**
4 RCT Recurrent wheeze	Not serious 1 study high risk of attrition bias, and no study with high risk of conflict of interest	Not serious $I^2 = 0\%$ Study estimates vary from 0.64 to 1.41	Serious 3 studies included environmental control measures such as dust mite and tobacco smoke avoidance, which are known to reduce respiratory symptoms	Serious Sparse data, inconsistent with data for age 0–4 and lung function data, where no effect was seen	Not tested ($n < 10$)	All RCTs were undertaken in populations at high risk due to family history of allergic disease. All studies included delayed introduction of allergenic foods; three also included maternal allergenic food avoidance.	**RR = 0.77 (0.61, 0.97)**	⊗⊗○○ **Low**	**50 (low risk)** **100 (high risk)** **150 (very high risk)**	**12 cases 95% CI 2–20** **23 cases 95% CI 3–39** **35 cases 95% CI 5–59**
Intervention: Maternal vitamin A vs no vitamin A **Outcome: Lung function at age 11 years** **Study design: RCT**										
1 RCT Lung function	Not serious Low risk of bias	Very serious Supplementation with the vitamin A precursor beta carotene in the same trial had no effect on lung function. Neither vtamin A nor beta carotene had an effect on risk of wheeze. Separate trial with similar design but lower vitamin A dose as part of a multivitamin intervention found no effect on FEV1 or FVC at age 8.	Serious Study population was a poor rural Nepalese population at risk of vitamin A deficiency	Serious Single study, with wide CIs	Not tested ($n < 10$)	Dose response relationship between maternal postpartum serum retinol levels and lung function outcomes	**Mean Difference** **FEV_1 46mls (6, 86)** **FVC 46mls (8, 84)**	○○○○ **No evidence**	-	-

* Absolute risk reduction is expressed per 1,000 people treated. Control risks were derived from control event rates in included studies or, where data were sparse or unrepresentative from included studies, from large international surveys such as the ISAAC survey [19]. Abbreviations: BF, breastfeeding; CC case control; CS, cross-sectional; NCC, nested case control; OR, odds ratio; PC, prospective cohort; RC, retrospective cohort; RCT, randomised controlled trial; RR, Risk Ratio; TIDM, type 1 diabetes mellitus

https://doi.org/10.1371/journal.pmed.1002507.t001

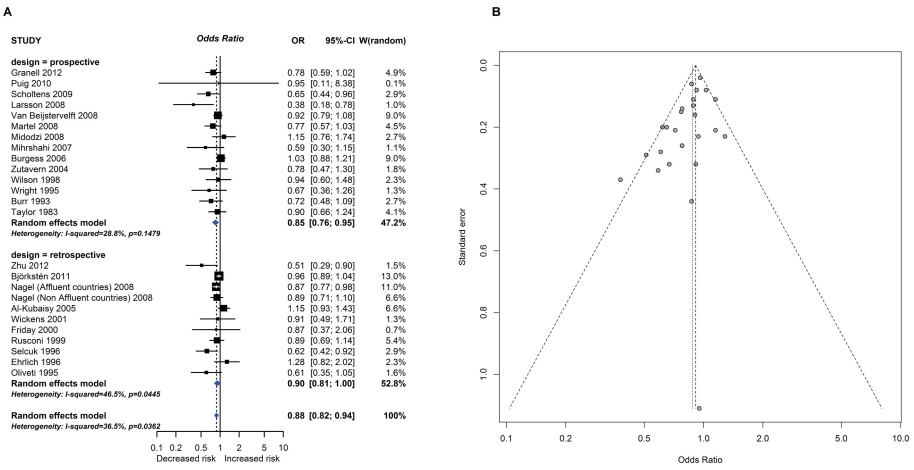


Fig 2. Observational study findings for a relationship between breastfeeding ever and recurrent wheeze at age 5–14 years (A) and a Funnel plot for this analysis showing evidence of publication bias (B). Egger test $P = 0.012$. CI, confidence interval; OR, odds ratio; W, weight.

https://doi.org/10.1371/journal.pmed.1002507.g002

colony-forming units per day. Meta-analysis showed an association between probiotic supplementation and reduced eczema (Fig 4; 19 studies; RR 0.78; 95% CI 0.68–0.90; $I^2 = 61\%$) or 'atopic' eczema (Fig 4; 11 studies; RR 0.78; 95% CI 0.65–0.92; $I^2 = 0\%$) at age $\leq$ 4 years and reduced allergic sensitisation to cow's milk at age 1 to 2 years (Fig 5; 97 studies). No significant association was seen with eczema at age 5 to 14 years, nor with allergic sensitisation to other allergens. The GRADE certainty of these findings was moderate for eczema and low for cow's milk sensitisation. Subgroup analysis for eczema showed a significant difference between supplementing mothers during the postnatal period (9 interventions, RR 0.64; 95% CI 0.51–0.80; $I^2 = 59\%$) and studies that just supplemented infants during the postnatal period (11 interventions, RR 0.93; 95% CI 0.81–1.06; $I^2 = 31\%$; test for subgroup difference $P = 0.016$). Ten intervention trials (4,242 participants) evaluated prebiotic supplements (always a galacto-oligosaccharide) either alone or combined with other prebiotics or with probiotics. Nine studies involved comparison of an infant formula milk with versus without prebiotic. Meta-analysis showed no clear evidence that prebiotic supplementation reduces eczema at age $\leq$ 4 years (Fig 6; 7 studies; RR 0.75; 95% CI 0.56–1.01; $I^2 = 57\%$) and no association at age 5 to 14 years. There was no association between probiotics or prebiotics and other allergic outcomes. In our updated search on 15 December 2017, we identified one publication reporting no effect of a perinatal probiotic supplement on risk of coeliac disease at age 13 years from the trial of Kukkonen [20]. No other studies reported autoimmune outcomes.

Polyunsaturated fatty acid supplementation. Nineteen intervention trials (14,479 participants) evaluated fatty acid supplements. These were given as fish oil supplements in 12 trials, advice to eat oily fish in 1 trial, supplementation of infant formula milk with omega-3 fatty acids in 3 trials, and other oils in 3 trials. Comparators were corn, soya, canola, olive, sunflower, or vegetable oil, or no supplement. Meta-analysis showed an association between omega-3 polyunsaturated fatty acid supplementation using fish oil during pregnancy and lactation and reduced allergic sensitisation to egg at 1 year (Fig 7; 6 studies; RR 0.69 95% CI 0.53–0.90; $I^2 = 15\%$). No significant association was seen with allergic sensitisation to other allergens. The GRADE certainty of this finding was moderate. Subgroup analysis showed a significant difference between studies which supplemented mothers during pregnancy (4 studies; RR 0.55 95% CI 0.40–0.76; $I^2 = 0\%$) and studies which supplemented during lactation only (2

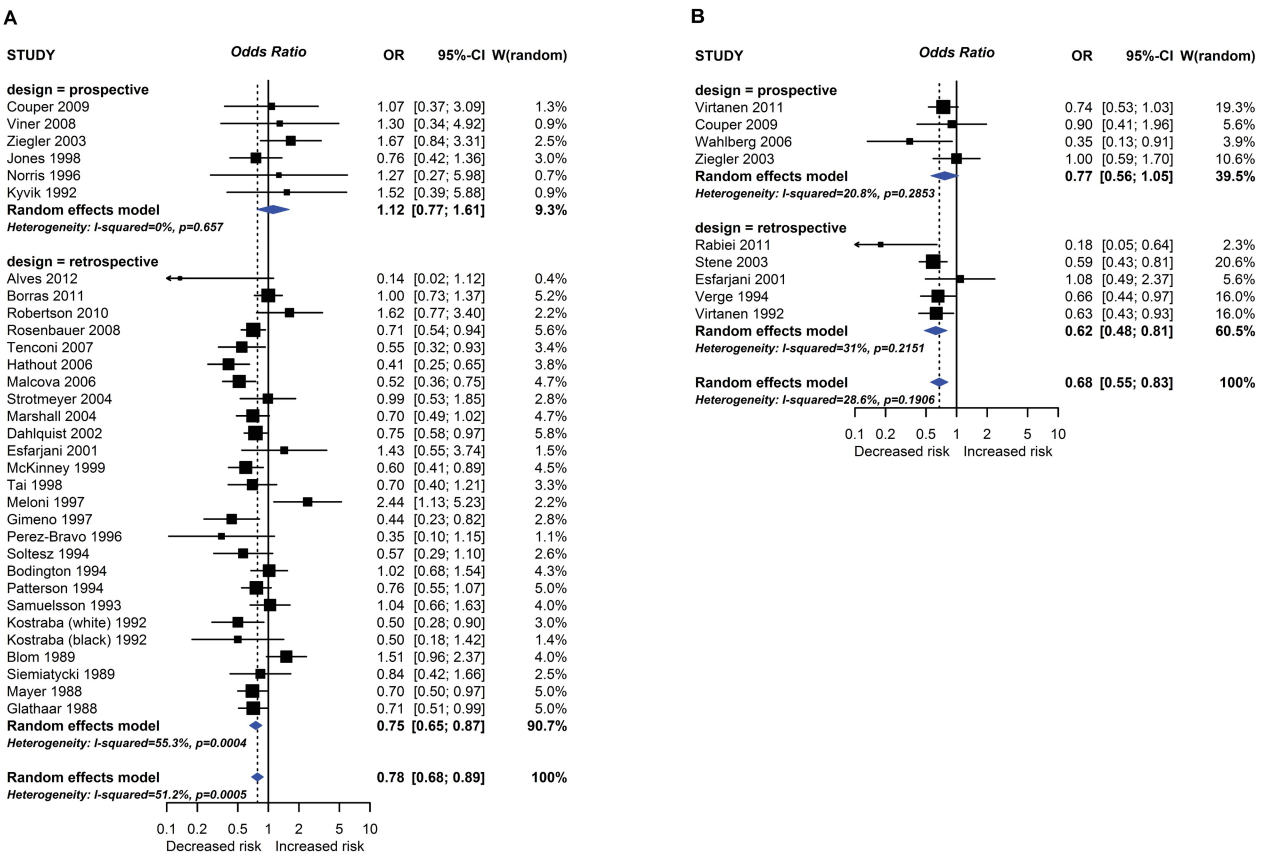


Fig 3. Observational study findings for a relationship between breastfeeding ever (A) or exclusive breastfeeding for ≥3–4 months (B) and type 1 diabetes mellitus. CI, confidence interval; OR, odds ratio; W, weight.

https://doi.org/10.1371/journal.pmed.1002507.g003

studies; RR 0.92 95% CI 0.65–1.28; I^2 = 0%; test for subgroup difference P = 0.032). Similarly, for allergic sensitisation to peanut, there was reduced risk in the subgroup of studies which supplemented mothers during pregnancy (2 studies; RR 0.62 95% CI 0.40–0.96 I^2 = 0%). There was no association between omega-3 polyunsaturated fatty acid supplementation and other allergic outcomes. Data were sparse and inconclusive for food allergy and for omega-6 supplementation and allergic outcomes. No autoimmune outcomes were reported, and no new trials were identified in our update search on 15 December 2017.

Maternal allergenic food avoidance and multifaceted interventions. Twelve intervention trials (1,945 participants) evaluated maternal allergenic food avoidance during pregnancy (2 trials), lactation (6 trials), or both (4 trials). The foods excluded were milk alone (2 trials), egg alone (1 trial), milk and egg (3 trials), or multiple foods (6 trials). We did not find that maternal allergenic food avoidance during pregnancy or lactation reduces risk of allergic disease or TIDM development. Nine trials (2,317 participants) evaluated multifaceted interventions—defined as an intervention with more than one category of dietary intervention. Six trials included promotion of prolonged breastfeeding, avoidance of allergenic foods for mother or infant, and delayed solid food introduction; 6 included environmental control measures to reduce dust mite, pet, or tobacco smoke exposure; 7 used an alternative formula milk as part of the intervention. Meta-analysis shown in Fig 8 found an association between multifaceted interventions and reduced allergic rhinitis at age ≤ 4 years (2 studies; RR 0.61 95% CI 0.44–0.84; I^2 = 0%), but not at age 5 to 14 years (4 studies). We also found an association between

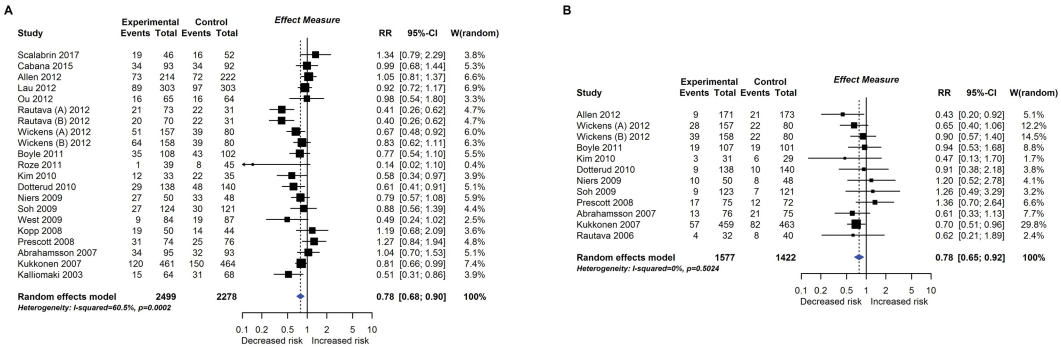


Fig 4. RCT findings for probiotic supplementation compared with no probiotics and risk of eczema (A) or atopic eczema (B) at age ≤4 years. CI, confidence interval; RCT, randomised controlled trial; RR, risk ratio; W, weight.

https://doi.org/10.1371/journal.pmed.1002507.g004

multifaceted interventions and reduced wheeze (2 studies; RR 0.57 95% CI 0.41–0.81; $I^2 = 0\%$) and recurrent wheeze (4 studies; RR 0.77 95% CI 0.61–0.97; $I^2 = 0\%$) at age 5–14 years. There was no association at age ≤ 4 years (4 studies), nor with measures of lung function. The GRADE certainty of findings for multifaceted interventions and wheeze or rhinitis was low, there were no autoimmune outcomes reported, and no new trials were identified in our update search on 15 December 2017.

Vitamin and mineral supplementation. Eleven intervention trials (15,753 participants) evaluated vitamin and mineral supplements. Two trials used vitamin A in infants; 1 used vitamin A or beta carotene in pregnancy; 2 used vitamin C or E during pregnancy; 3 used vitamin D during pregnancy; 1 used vitamin D during pregnancy and infancy; and 2 used multivitamins during pregnancy. Meta-analysis shown in Fig 9 found no association between vitamin supplementation and risk of wheeze (5 studies), recurrent wheeze (6 studies), or eczema (5 studies) at age 0 to 4 years, nor for these outcomes at other ages or other allergic outcomes. One trial reported an association between vitamin A (but not beta carotene) supplementation during pregnancy and increased lung function in childhood [21]. This was not consistent with findings from another similar trial [22]. No autoimmune outcomes were reported, and no new trials were identified in our update search on 15 December 2017.

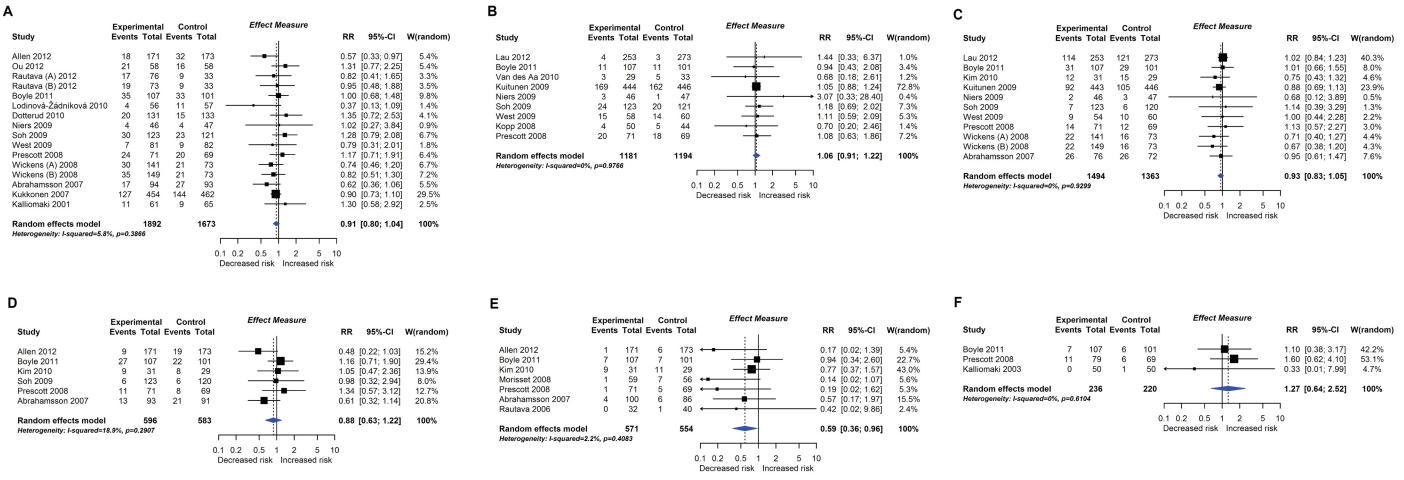


Fig 5. RCT findings for probiotic supplementation compared with no probiotics and risk of allergic sensitisation to any allergen (A), any inhalant allergen (B), any food allergen (C), egg (D), milk (E), or peanut (F). CI, confidence interval; RCT, randomised controlled trial; RR, risk ratio; W, weight.

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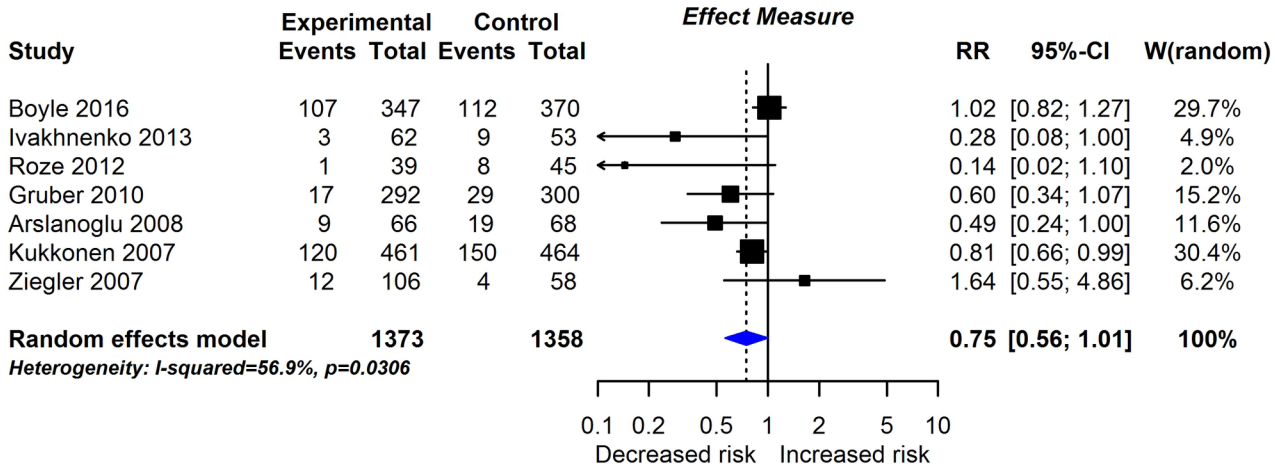


Fig 6. RCT findings for prebiotic supplementation compared with no prebiotics and risk of eczema at age ≤4 years. CI, confidence interval; RCT, randomised controlled trial; RR, risk ratio; W, weight.

https://doi.org/10.1371/journal.pmed.1002507.g006

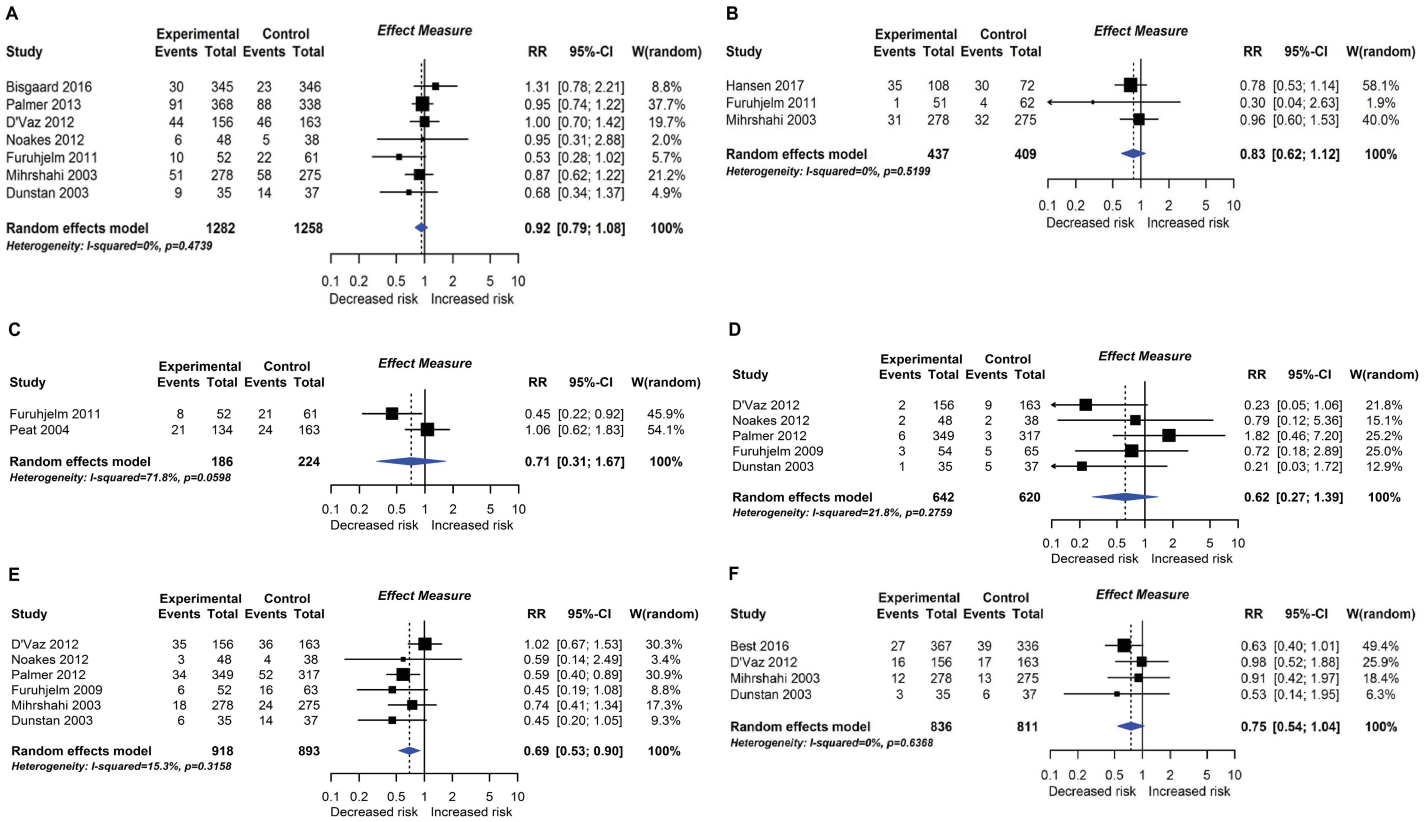


Fig 7. RCT findings for omega-3 polyunsaturated fatty acid supplementation compared with no polyunsaturated fatty acids and risk of allergic sensitisation to any allergen (A), any inhalant allergen (B), any food allergen (C), milk (D), egg (E), or peanut (F). CI, confidence interval; RCT, randomised controlled trial; RR, risk ratio; W, weight.

https://doi.org/10.1371/journal.pmed.1002507.g007

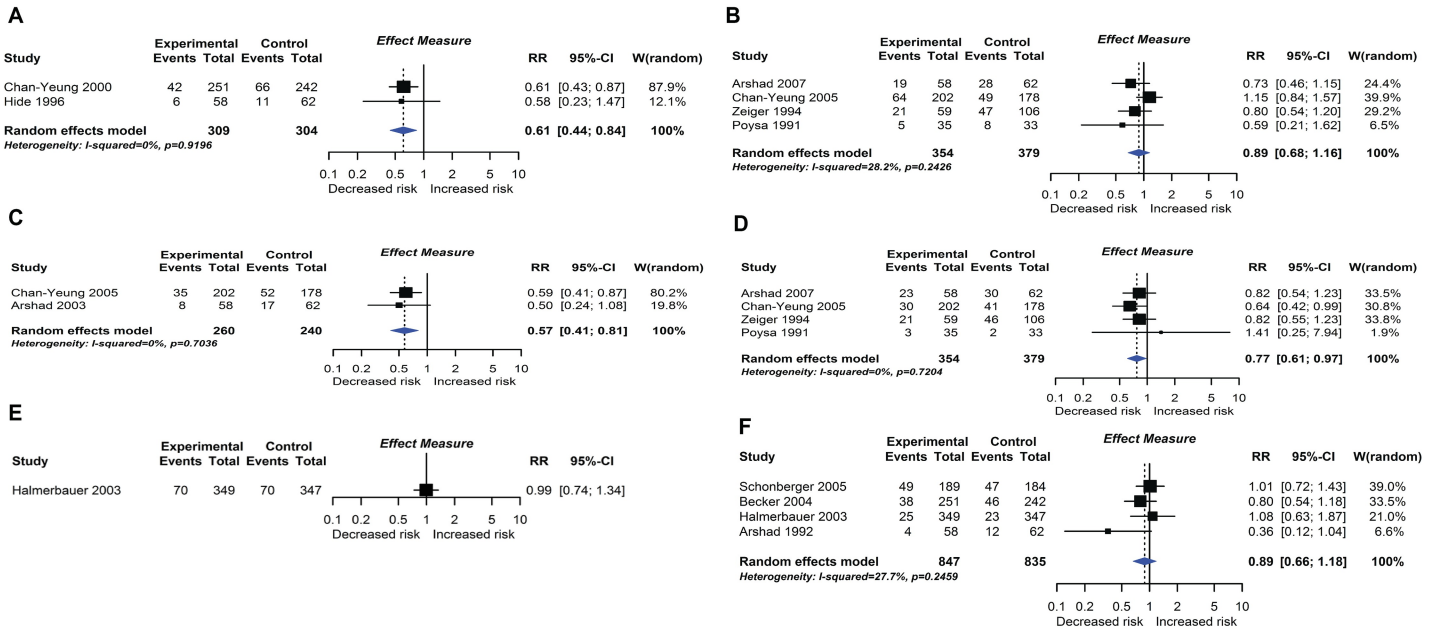


Fig 8. Randomised controlled trial findings for multifaceted dietary interventions compared with no multifaceted intervention and risk of allergic rhinitis at age ≤4 years (A) or 5–14 years (B), wheeze (C) or recurrent wheeze (D) at age 5–14 years, and wheeze (E) or recurrent wheeze (F) at age ≤4 years. CI, confidence interval; RCT, randomised controlled trial; RR, risk ratio; W, weight.

https://doi.org/10.1371/journal.pmed.1002507.g008

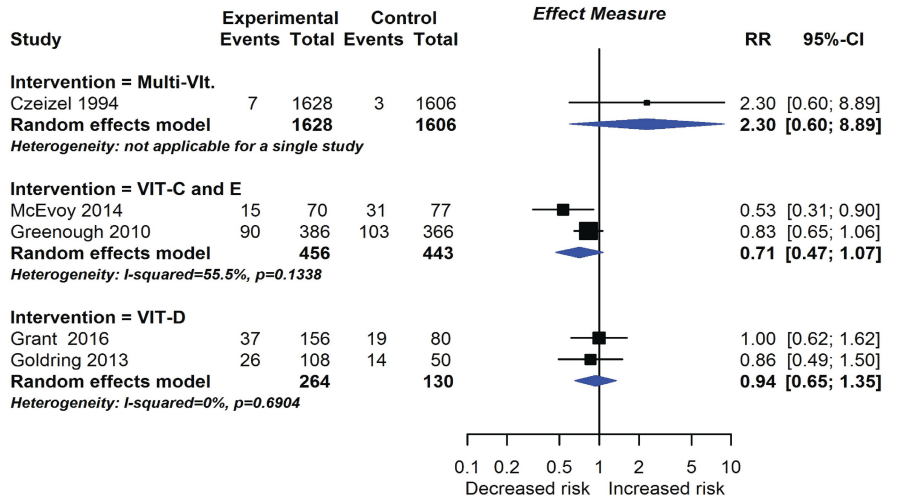
Observational studies of other maternal or infant dietary exposures

Ninety-two observational studies (485,733 participants) evaluated other maternal or infant dietary exposures, including fruit and vegetable intake (35 studies), classified as fruits, vegetables, citrus fruits, nuts, or sometimes as individual foods or food groups; fat and fatty acid intake (26 studies), classified as total fat intake, omega 3 or omega 6 poly-unsaturated fatty acids or other types of fatty acids, and specific fatty acids (we also included fish intake and fish oil supplementation in this group); vitamin and mineral intake (50 studies), including antioxidant vitamins A, C, E, and their precursors, vitamin D and folic acid, mineral intake, and blood vitamin D levels; and a wide range of 'other dietary exposures' (47 studies), including dietary pattern, maternal allergenic food avoidance, alcohol, tea or coffee intake, and maternal or infant meat, cereal, milk, or egg intake. Opportunities for meta-analysis of these observational studies were very limited due to heterogeneity of exposure assessment methods and reporting —all analyses are described in the full Food Standards Agency report (https://www.food.gov.uk/science/research/allergy-research/fs305005ac). Overall, there was no consistent association between these dietary exposures and risk of allergic outcomes or those autoimmune diseases studied (TIDM, 23 studies; coeliac disease, 2 studies; inflammatory bowel disease, 2 studies; juvenile idiopathic arthritis, 1 study). There was insufficient evidence to either support or refute the intervention trial findings for fish oil supplementation and allergic sensitization to foods, in the observational studies of fatty acid intake during pregnancy.

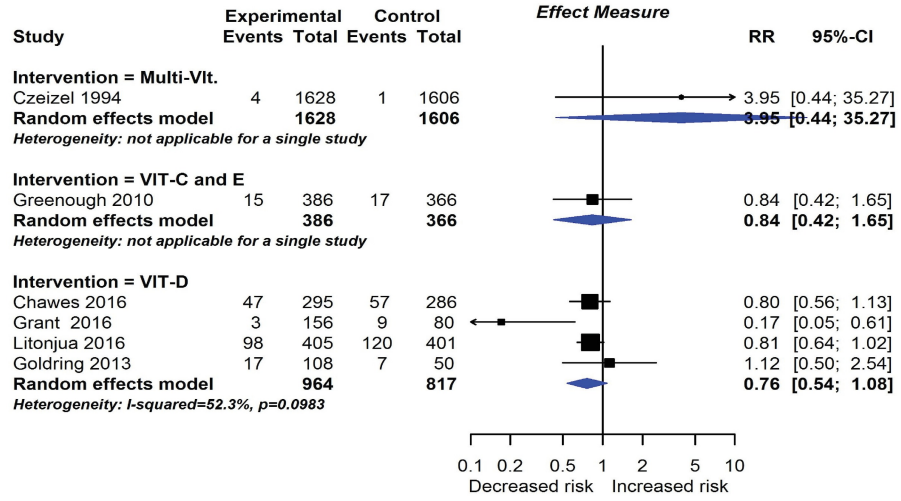
Trial sequential analysis of moderate or high certainty findings

We used TSA to evaluate whether probiotics reduce risk of eczema by ≥20% or ≥30%. The heterogeneity-adjusted optimal information size for detection of a 20% relative risk reduction for eczema was 3,780 study participants, and TSA for this outcome is shown in Fig 10. The optimal information size has not been reached, but the monitoring boundary has been crossed,

A


Study
Experimental Events Total
Control Events Total
Effect Measure
RR 95%-CI
Intervention = Multi-Vit.
Czeizel 1994 7 1628 3 1606 2.30 [0.60; 8.89]
Random effects model 1628 1606 2.30 [0.60; 8.89]
Heterogeneity: not applicable for a single study
Intervention = VIT-C and E
McEvoy 2014 15 70 31 77 0.53 [0.31; 0.90]
Greenough 2010 90 386 103 366 0.83 [0.65; 1.06]
Random effects model 456 443 0.71 [0.47; 1.07]
Heterogeneity: I-squared=55.5%, p=0.1338
Intervention = VIT-D
Grant 2016 37 156 19 80 1.00 [0.62; 1.62]
Goldring 2013 26 108 14 50 0.86 [0.49; 1.50]
Random effects model 264 130 0.94 [0.65; 1.35]
Heterogeneity: I-squared=0%, p=0.6904
0.1 0.2 0.5 1 2 5 10
Decreased risk
Increased risk

B


Study
Experimental Events Total
Control Events Total
Effect Measure
RR 95%-CI
Intervention = Multi-Vit.
Czeizel 1994 4 1628 1 1606 3.95 [0.44; 35.27]
Random effects model 1628 1606 3.95 [0.44; 35.27]
Heterogeneity: not applicable for a single study
Intervention = VIT-C and E
Greenough 2010 15 386 17 366 0.84 [0.42; 1.65]
Random effects model 386 366 0.84 [0.42; 1.65]
Heterogeneity: not applicable for a single study
Intervention = VIT-D
Chawes 2016 47 295 57 286 0.80 [0.56; 1.13]
Grant 2016 3 156 9 80 0.17 [0.05; 0.61]
Litonjua 2016 98 405 120 401 0.81 [0.64; 1.02]
Goldring 2013 17 108 7 50 1.12 [0.50; 2.54]
Random effects model 964 817 0.76 [0.54; 1.08]
Heterogeneity: I-squared=52.3%, p=0.0983
0.1 0.2 0.5 1 2 5 10
Decreased risk
Increased risk

C

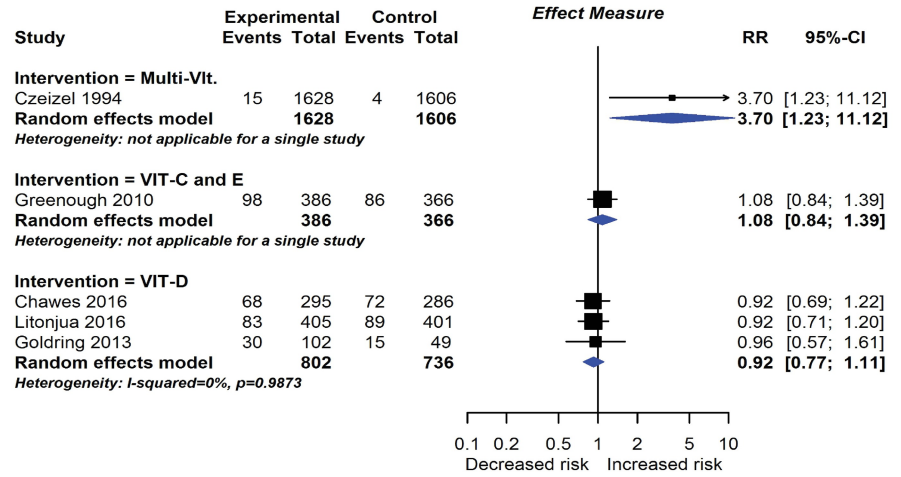

Study
Experimental Events Total
Control Events Total
Effect Measure
RR 95%-CI
Intervention = Multi-Vit.
Czeizel 1994 15 1628 4 1606 3.70 [1.23; 11.12]
Random effects model 1628 1606 3.70 [1.23; 11.12]
Heterogeneity: not applicable for a single study
Intervention = VIT-C and E
Greenough 2010 98 386 86 366 1.08 [0.84; 1.39]
Random effects model 386 366 1.08 [0.84; 1.39]
Heterogeneity: not applicable for a single study
Intervention = VIT-D
Chawes 2016 68 295 72 286 0.92 [0.69; 1.22]
Litonjua 2016 83 405 89 401 0.92 [0.71; 1.20]
Goldring 2013 30 102 15 49 0.96 [0.57; 1.61]
Random effects model 802 736 0.92 [0.77; 1.11]
Heterogeneity: I-squared=0%, p=0.9873
0.1 0.2 0.5 1 2 5 10
Decreased risk
Increased risk

Fig 9. RCT findings for vitamin supplementation compared with no vitamin supplementation and risk of wheeze (A), recurrent wheeze (B), or eczema (C) at age ≤4 years. CI, confidence interval; RCT, randomised controlled trial; RR, risk ratio; W, weight.

https://doi.org/10.1371/journal.pmed.1002507.g009

suggesting that this treatment reduces eczema risk by ≥20%. Findings were similar for ≥30% risk reduction, for atopic eczema, and for the subgroup of studies that supplemented lactating mothers during the postnatal period (Fig 10). TSA for studies that didn't supplement lactating mothers showed evidence of futility (Fig 10). We also used TSA to evaluate whether maternal fish oil supplementation reduces risk of allergic sensitisation to egg by ≥20% or ≥30% (Fig 11). The optimal information size for detection of a 20% relative risk reduction was 6,786 participants, which has not been reached, and the monitoring boundary has not been crossed, suggesting that further studies are required to confirm the effect.

Discussion

Principal findings

In this systematic review of diet during pregnancy and infancy and risk of allergic or autoimmune disease, we found a relationship between maternal diet during pregnancy and lactation and eczema or allergic sensitisation to food during childhood. Positive health effects were found for probiotic and fish oil supplements. We found weaker support for the hypotheses that multifaceted interventions reduce risk of allergic rhinitis and wheeze; that longer duration of breastfeeding is associated with reduced eczema, TIDM, and wheezing; and that longer exclusive breastfeeding is associated with reduced TIDM. There was no association between other dietary exposures and risk of allergic or autoimmune diseases, including timing of solid food introduction, prebiotic supplementation, maternal allergenic food avoidance, and vitamin, mineral, fruit, or vegetable intake. Previously, we reported that hydrolysed formula does not appear to influence risk of allergic or autoimmune diseases and that early peanut or egg introduction to the infant diet reduces risk of peanut or egg allergy [12,13]. Taken together, our findings suggest that while infant diet may influence immune development through allergen-specific mechanisms, maternal diet during prenatal life and lactation may have broader effects on the developing immune system. Future efforts to promote immune health through the life course should consider maternal dietary interventions during pregnancy and lactation as an important area of investigation. Our finding that probiotic supplements such as *Lactobacillus rhamnosus* at a dose of 1 to 10 billion colony-forming units per day may reduce risk of eczema is consistent with a recent World Allergy Organization (WAO) systematic review and guideline, although we rated the certainty of findings as stronger than the WAO group, who downgraded the certainty to very low due to risk of selection and attrition bias in the trials, variation in probiotic(s) used, and variation in the timing of the probiotic supplement intervention [3,10]. Our subgroup analysis and TSA findings provide new evidence that maternal (rather than infant) supplementation may be important for this intervention. In contrast, we did not find support for the WAO group's recommendation to use prebiotic supplements such as galacto-oligosaccharides for preventing eczema due to our serious concerns about risk of bias, inconsistency, imprecision, and indirectness, some of which were shared by the WAO group [2,23]. Although microbial exposures have long been postulated as influencing risk of allergic disease, a clear mechanism through which probiotics might reduce risk of eczema is currently lacking. Our finding that fish oil supplementation during pregnancy may reduce allergic sensitisation to the most common food allergens affecting young children, hen's egg and peanut, is new. In contrast to our findings for probiotics, those for fish oil have a plausible mechanistic basis, since fish oil has known anti-inflammatory effects [24].Further work is

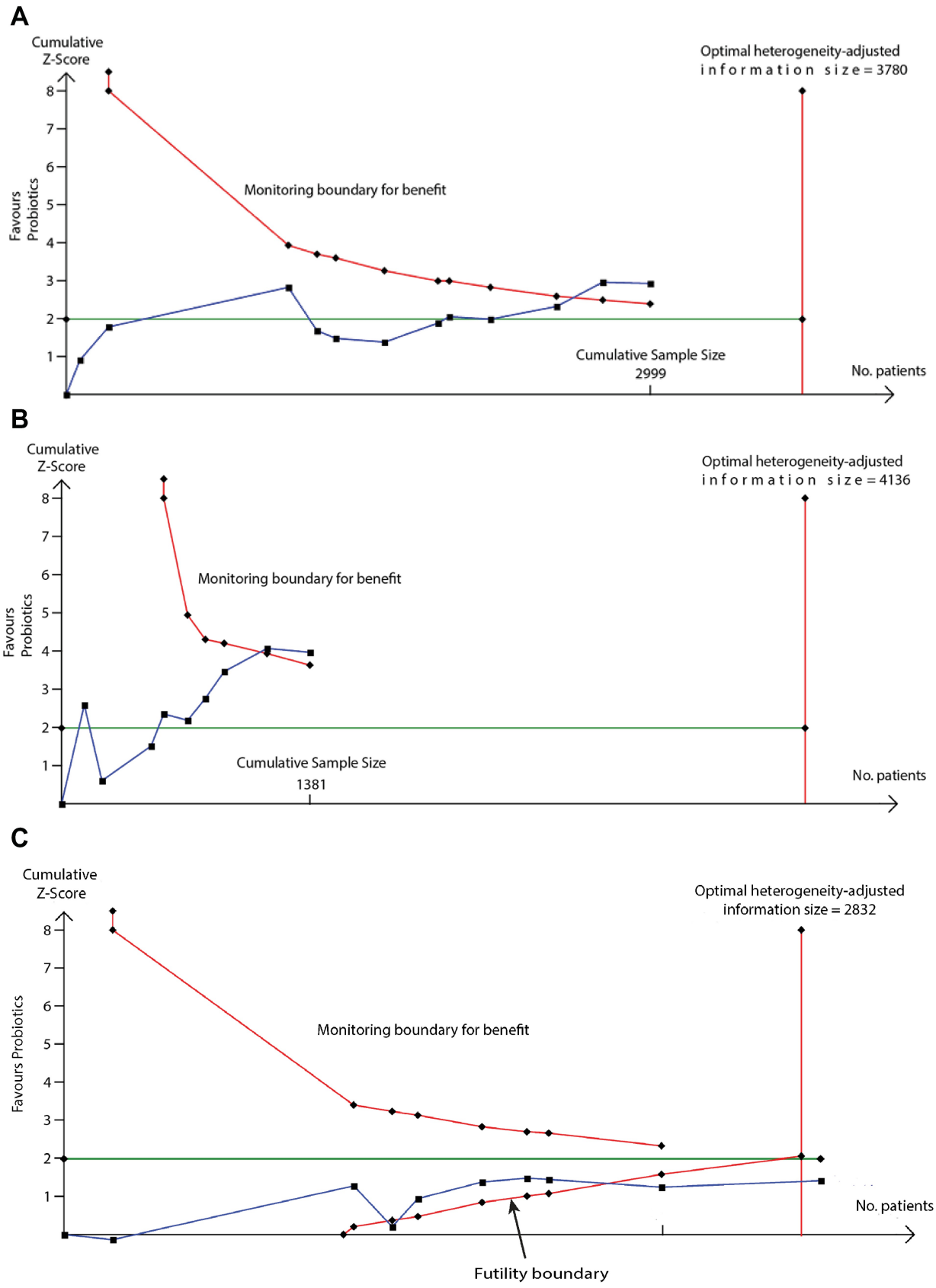

A
Cumulative Z-Score
Optimal heterogeneity-adjusted information size = 3780
Favours Probiotics
Monitoring boundary for benefit
Cumulative Sample Size
2999
No. patients
B
Cumulative Z-Score
Optimal heterogeneity-adjusted information size = 4136
Favours Probiotics
Monitoring boundary for benefit
Cumulative Sample Size
1381
No. patients
C
Cumulative Z-Score
Optimal heterogeneity-adjusted information size = 2832
Favours Probiotics
Monitoring boundary for benefit
No. patients
Futility boundary

Fig 10. TSA of intervention trials evaluating the effect of probiotics on risk of eczema (A) and the subgroups of studies that did (B) or did not (C) supplement lactating mothers during the postnatal period. The vertical red line is the optimal information size, i.e., the cumulative sample size required to establish with 80% power and 5% 2-sided significance whether the intervention reduces risk of the outcome by ≥20%, allowing for repeatedly meta-analysing the accumulating studies. The horizontal green line is a z score of +1.96, equal to two-sided $P = 0.05$. The cumulative Z-statistic (blue line) does not reach the optimal information size in analysis of all studies (A) or maternal supplementation studies (B) but does cross the trial sequential monitoring boundary (curved red line), showing evidence for ≥20% relative risk reduction. The cumulative Z-statistic (blue line) for studies without maternal supplementation (C) crosses the futility boundary and reaches the optimal information size without crossing ±1.96, indicating evidence of futility such that further trials of this intervention are not required. Findings were similar for ≥30% relative risk reduction and for eczema associated with allergic sensitisation. No., number; TSA, trial sequential analysis.

https://doi.org/10.1371/journal.pmed.1002507.g010

required to clarify whether the effect of fish oil on allergic sensitisation leads to reduced risk of clinical food allergy. We did not find support for recent Australasian guidelines or other systematic reviews suggesting that fish or fish oil supplementation may reduce eczema risk [6,25,26]. Other findings were of low or very low GRADE certainty and are not likely to impact infant feeding guidance at present. The findings for multifaceted interventions and reduced risk of rhinitis or wheezing are unlikely to be related to dietary components of the interventions, and the findings that longer breastfeeding or exclusive breastfeeding duration may reduce risk of TIDM, eczema, and wheezing are not likely to change current breastfeeding recommendations [14]. Others have reported stronger support for an association between breastfeeding duration and reduced risk of wheezing or other allergic outcomes, but only by pooling quite heterogeneous data [8,9]. Our meta-analyses of observational studies of breastfeeding duration and wheezing found new evidence of publication bias, which also suggests that previous reports of links between breastfeeding and wheezing may be misleading. We did not find evidence to support a role for vitamin D supplementation in preventing wheezing or other outcomes. This is consistent with a WAO systematic review [27] that was undertaken prior to the publication of two key vitamin D trials. Two other recent analyses concluded that prenatal vitamin D supplementation may reduce risk of recurrent wheeze. A systematic review of prenatal vitamins and allergic outcomes did not identify one of our included trials and made a data entry error in another trial (Goldring et al. control and active data switched) [28]. A meta-analysis of the two largest trials, undertaken by their authors, also had positive findings but did not include the other two published studies which we identified [29]. Overall, we found relatively few opportunities for meaningful meta-analysis in the observational studies, due mainly to variations in exposure definition and assessment. Even when observational

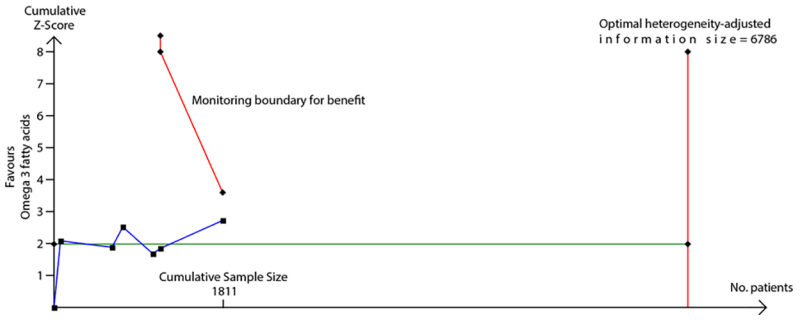


Fig 11. TSA of intervention trials evaluating the effect of fish oil supplementation on risk of allergic sensitisation to egg. The vertical red line is the optimal information size, i.e., the cumulative sample size required to establish with 80% power and 5% 2-sided significance whether the intervention reduces risk of the outcome by ≥20%, allowing for repeatedly meta-analysing the accumulating studies. The horizontal green line is a z score of +1.96, equal to two-sided $P = 0.05$. The cumulative Z-statistic (blue line) does not reach the optimal information size and does not cross the trial sequential monitoring boundary (curved red line), indicating no clear evidence for ≥20% relative risk reduction. Findings were similar for ≥30% relative risk reduction. No., number; TSA, trial sequential analysis.

https://doi.org/10.1371/journal.pmed.1002507.g011

study meta-analysis is possible, differences between populations studied or methods of exposure assessment can lead to increased variability of findings and thereby reduce statistical power compared with a single large, well-conducted study. This may partly explain the stronger findings in relation to intervention trials of dietary supplements than for observational studies of dietary pattern or specific nutritional intake.

Interpretation

Our key findings suggest that a mother's diet during pregnancy and lactation may influence the risk that her child develops allergic disease, and this has implications for future research in this field. There are two specific implications for pregnant women. First, a daily probiotic supplement such as *L. rhamnosus*, taken from around 36 to 38 weeks gestation through the first 3 to 6 months of lactation, may reduce risk of eczema in the child. Although probiotics are generally considered safe, their pro-inflammatory effects may have potential adverse consequences when used earlier in pregnancy, and serious adverse effects in people with intestinal disorders or immune deficiency have been documented [30][31]. Second, a fish oil supplement, taken from around 20 weeks gestation through the first 3 to 4 months of lactation, may reduce risk of allergic sensitisation to egg or peanut in the child. In one included trial, the fish oil intervention was administered via advice to consume at least 2 servings per week of low mercury oily fish (farmed salmon), which is consistent with current United States Food and Drug Administration guidance [32]. It was not possible to reliably assess whether the findings in this small trial differed significantly from the findings in higher dose fish oil supplementation trials.

Strengths and limitations of the study

This comprehensive and wide-ranging systematic review has highlighted key dietary interventions that may reduce risk of allergic outcomes, information which will be useful for pregnant women and their healthcare providers. However, for many dietary exposures, data were inconclusive or inconsistent, such that we are unable to exclude the possibility of beneficial or harmful effects. One limitation of this study is the 2013 search date for observational studies, such that review findings that are derived from these studies may benefit from an update in due course. We included abstract publications, since their exclusion can lead to publication bias; however, their inclusion carries a risk of methodological bias due to the lack of peer review. While the list of dietary exposures included was comprehensive, we did not evaluate food diversity during infancy, which has been suggested as an important factor in relation to allergic outcomes, and we did not evaluate objective markers of nutritional status, with the exception of blood vitamin D level [33]. This means that we may have missed important relationships for food diversity or nutritional markers. Given the volume of titles included in this systematic review, we were unable to contact the corresponding authors of included studies for data verification, as has been recommended by some authors [34]. Finally, some outcome measures were reported using a wide variety of assessment tools—for example, wheeze and recurrent wheeze were defined in several different ways—and this may have contributed to some of the statistical heterogeneity seen in meta-analyses. There is a need for more well-powered intervention trials of dietary interventions, given the positive findings with some specific dietary supplements identified here.

Conclusions and policy implications

These findings, together with our previous findings regarding hydrolysed formula and allergenic food introduction to the infant diet, suggest that current infant feeding guidance needs revision. Guideline committees will need to carefully consider the key findings together with

an evaluation of the safety, acceptability, and cost implications of advising probiotic or fish oil supplementation for pregnant and lactating women.

Supporting information

S1 PRISMA Checklist. PRISMA Checklist.
(DOC)

S1 Text. Systematic review search strategies.
(DOCX)

S2 Text. Review A (milk feeding) over-arching report.
(DOC)

S3 Text. Review C (maternal and infant diet) over-arching report.
(DOC)

S1 Appendix. Characteristics of included studies and risk of bias tables.
(DOCX)

S1 Data. Review A (milk feeding) report files.
(ZIP)

S2 Data. Review C (maternal and infant diet) report files.
(ZIP)

S3 Data. Data used for meta-analyses.
(XLSX)

Acknowledgments

We are grateful to the independent experts, Professor Graham Devereux and Dr Carina Venter, and to members of the UK Food Standards Agency, the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT), and the UK Scientific Advisory Committee on Nutrition (SACN) for their comments on the study protocol and versions of the full report. We are grateful to Dr Yujie Zhao, Mr Szymon Mikolajewski, Dr Andre F Amaral, Dr Mari Kihara, Dr Christian Nielsen, Mr Radoslav Latinovic, Dr Stephanie MacNeill, Dr Andreas Forsters, Dr Daniel Munblit, Dr Sze-Chin Tan, and Dr Claudia Gore for their assistance with translation of foreign language reports. We are grateful to Tim Reeves for writing the search strategy and undertaking the initial literature search and to Jacqueline Cousins of the St. Mary's library at Imperial College London for assistance with literature search training. We are grateful to Ulugbek Nurmatov and Nara Tagiyeva-Milne for assistance with data extraction, to Evangelia Andreou for assistance with creating tables and figures for the full report, and to Thomas Clark for assistance with manuscript submission.

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Diet during pregnancy and infancy, and risk of allergic or autoimmune disease: a systematic review and meta-analysis

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Table S1 Characteristics of included intervention trials of breastfeeding duration or solid food introduction and allergic outcomes

Study	Design	N Intervention / Control	Country	Intervention	Disease risk	Age at outcome (years)	Outcomes reported (method of assessment)
Kramer, 2001 [1]; Kramer, 2007 [2]	cluster RCT	8865/8181	Belarus	TBF. Breastfeeding promotion program based on the WHO/UNICEF baby friendly hospital initiative, versus standard local breastfeeding policies	Normal	1, 6.5	AD (Hanifin and Rajka, ISAAC); Wheeze (ISAAC); AR (ISAAC); AS (SPT)

AD: atopic dermatitis; AR: allergic rhinitis; AS: allergic sensitisation; DD doctor diagnosis; EBF: exclusive breastfeeding; FA: food allergy; ISAAC: International Study of Asthma and Allergies in Children; OFC: oral food challenge; RCT: randomised controlled trial; SPT: skin prick test

Table S2 Characteristics of included observational studies of breastfeeding or solid food introduction, and risk of allergic outcomes

Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Alho, 1990 [3]	PC	2,130	Finland	Birth cohort, population representative sample born 1985-1986 (normal risk of disease)	TBF, Q	2	Wheeze (DD Wheeze)
Allen, 2009 [4]; Koplin, 2010 [5]	PC	310/50	Australia	Part of the **HealthNUTS study**. Representative cohort of infants recruited from routine immunisation clinics 2008-2010	TBF, Q	1	SPT to food; FA (OFC)
Alm, 2008[6]; Goksor, 2009/11 [7,8]	PC	4,987	Sweden	Infants of Western Sweden. Population birth cohort of infants born in 2003	TBF, SFI, Q	1, 1.4, 4.5	Wheeze (ever; ≥3 episodes of wheeze in past year); FA (DD); AD (parent reported)
Bacopoulou, 2009 [9]	PC	6,643	Greece	Population based sample of neonates born in 1983	EBF, Q	7	Wheeze (DD)
Benn, 2004 [10]; Linneberg 2006 [11]	PC	34,793	Denmark	**DNBC study**. Population based birth cohort of children born between 1997-2002	EBF, Q/I	1.5	AD (Physician assessment and parent report)
Bergmann, 2000 [12]; Bergmann, 2002 [13] Kulig, 2000 [14]	PC	1,314	Germany	**MAS study**. Atopic risk enriched cohort of infants born in 1990 in 5 German cities	TBF, Q/I	6, 7	Wheeze (Physician assessment); RC (Physician assessment, Parent reported RC ever)
Berth-Jones, 1997 [15]	PC	413	UK	Infants born in 1992 and registered with the two major Leicester obstetric units	TBF, Q	1	AD (Physician assessment)

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Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Besednjak-Kocijancic, 2010 [16]	PC	408/24	Slovenia	Infants with a positive history of parental allergy	EBF, Unclear	1, 5	FA (Infants with a positive history of parental allergy)
Bisgaard, 2009 [17]; Giwercman, 2010 [18]	PC	354	Denmark	**COPSAC study**. Infants of mothers with a history of doctor-diagnosed asthma, recruited from August 1998 to December 2001	TBF, EBF, Q/I	2, 3	AD (Hanifin and Rajka criteria); Wheeze (Parent report)
Burr, 1989; Burr, 1993; Burr, 1993 (b) [19-21]; Burr, 1997 [22]	PC	483	UK	Infants with family history of allergic diseases in South Wales	TBF, D, Q	1, 6.7, 7	Wheeze (Parent reported wheeze; Wheeze ever, DD); AD (physician assessment); sIgE aero (any); RC (Parent reported)
Burgess, 2006 [23]	PC	4,964	Australia	**Mater-University of Queensland Study of Pregnancy**. Population based birth cohort of infants born 1981-1984	TBF, Q	14	Wheeze (Parent reported asthma)
Businco, 1987 [24]; Bruno, 1995 [25]	PC	244	Italy	Infants of atopic parents recruited from hospital and born in 1985-1988	TBF, I	0-2, 2, 8	Wheeze DD asthma (≥3 episodes of wheeze); AD (physician assessment); RC (Physician assessment); sIgE to any, Total IgE
Cano Garcinuno, 2003 [26]	PC	234	Spain	Children born in 1998-2002 attending primary health centre	EBF, Q	3	Wheeze (DD)

S1_Tables

Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Caudri, 2013; Scholtens, 2009 [27,28]; Kerkhof, 2003 [29]	PC	3,115	Netherlands	**PIAMA**. Population-based study of children born in 1996-1997 (normal risk of disease)	EBF, TBF, Q	1, 8	Wheeze (Current wheeze; Parent reported current or ever wheeze (+/- sIgE); ISAAC; BHR: methacholine PC_{20}); sIgE aero; AD (UK Working Party Criteria)
Cogswell, 1987 [30]	PC	73/32	UK	Birth cohort of infants with family history of hay fever or asthma	EBF, D	5	SPT to any
Chuang, 2011[31]	PC	18,773	Taiwan	**Taiwan Birth Cohort Study**. Population representative sample born in 1995 (normal risk of disease)	TBF, SFI, R/I	1.5	AD (Physician assessment)
da Costa Lima, 2003; Menezes, [32,33]	PC	4,297	Brazil	**Pelotas Birth Cohort**. Population based birth cohort of infants born in 1982 in the city of Pelotas	EBF, TBF, Q/I	18, 22	Wheeze (ISAAC)
Dell, 2001; Midodzi, 2008 [34,35]; Midodzi, 2010 [36]	PC; CS	2,711	Canada	**National Longitudinal Survey of Children and Youth (NLSCY**) and the **Canadian Early Childhood Development Cohort Study** (part of NLSCY). First of longitudinal surveys of 12-24 months old children representative of the Canadian population	TBF, Q	2, 5, 9	Wheeze (≥2 episodes of wheeze; Preschool wheeze: <5 years but not beyond 6 years; Parent reported wheeze; DD)
Devereux, 2006 [37]	PC	1,704	Scotland, UK	Population based birth cohort of infants born in 1998	TBF, Q	5	Wheeze ; AD; RC (ISAAC); SPT aero

S1_Tables

Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Dogaru, 2012 [38]	PC	1,458	UK	Population based sample of children of white and south Asian ethnic origin born between 1993 and 1997, part of the Leicestershire cohorts	TBF, Q	12	Wheeze (Spirometry)
Elliott, 2008; Granell, 2012; Sherriff, 2001 [39-41]; Abd, 2012 [42]; Lack, 2003 [43]	PC	9,100	UK	**ALSPAC study**. Population based cohort of children born 1991-1992	EBF, TBF, Q	3, 3.5, 7, 7.5	Wheeze (DD asthma plus current wheeze; Parent reported wheeze; BHR: (methacholine PC_{20}); SPT to any food; Visible flexural dermatitis; Parent reported AD; Parent report of food reaction (DBPCFC)
Eneli, 2006 [44]	PC	536	Germany	**The Child Health and Environment Cohort Study**. community based in urban area, born 1994 (normal risk of disease)	TBF, Q	10	Wheeze (BHR hypertonic saline PC_{15})
Farooqi, 1998 [45]	PC	1,453	UK	Representative sample of general practice born in 1975-84	TBF, R	16	Wheeze (DD of recurrent episodes of wheeze after the age of two years); AD (DD); RC (DD)
Fergusson, 1983; Horwood, 1995 [46,47]	PC	1,110	New Zealand	Christchurch Child Development Study. Population based cohort of infants born in 1977 in the Christchurch urban region	EBF, R/I		Wheeze (Parental report)
Fredriksson, 2007 [48]	PC	1,933	Finland	Population-based study of children born between 1984 and 1989	TBF, SFI, Q	15	Wheeze (ATS questionnaire: wheezing apart from colds or wheezing most days or nights during the past year; DD)

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Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Forster, 1990[49]	PC	145	Germany	Babies hospitalised in 1985	TBF, Q	1.5	AD (Parental report)
Galbally, 2013 [50]	PC	4,507	Australia	**Longitudinal Study of Australian Children**. Population based study of infants born between March 2003 and February 2004 and were enrolled in the Australian Medicare database	TBF, I	1	Wheeze (Parent reported wheezing ≥4 nights per week)
Gruber 2010 [51]	PC	167/15	Central Europe	**MIPS-1 study**. Infants born in 2006 without family history of allergy, randomised to a prebiotic formula intervention if fully formula fed < 8 weeks	EBF, Q	1	sIgE CM, or egg; Total IgE
Gruskay 1982 [52]	PC	328 FH+/ 580 FH-	USA	Children born in 1961-1966 in a private paediatric practice	TBF, Unclear/Q	3, 5, 15	Wheeze (Physician assessment of recurrent wheezing); AD (Physician assessment); RC (parent reported)
Guida, 2009 [53]	PC	3,041	France	Population based birth cohort of infants born in 2003	TBF, Q	1	Wheeze (Parent reported)
Gustafsson, 2000 [54]	PC	94	Sweden	Children with atopic dermatitis attending allergic clinic or referred by child welfare clinics	TBF, Q	7, 8	Wheeze (≥3 episodes of physician diagnosed wheezing); FA (Parent report of food reaction); SPT any
Halken, 1991[55]	PC	276	Denmark	Population based birth cohort of children born in 1985	TBF, Q	1.5	Wheeze (≥2 episodes of physician diagnosed wheeze)

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Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Harris, 2001[56]; Zutavern, 2004 [57]	PC	622	UK	Population based birth cohort of children born between 1993 and 1995 in three general practices in Ashford	TBF, SFI, I	2	AD (UK Working Party Criteria)
Hagendorens, 2005 [58]; Sariachvili, 2007 [59]; Sariachvili 2010 [60]	PC	693	Belgium	**PIPO study**. Recruited from university service, born 1997-2001 (normal risk of disease)	TBF, Q	1 4	Wheeze (Parent reported current wheeze); AD (Parent reported); sIgE any
Hesselmar, 2010 [61]	PC	184	Sweden	**ALLERGYFLORA study**. Population based study of babies selected from antenatal clinics between 1998 and 2003 - mainly high risk of allergic disease	EBF, TBF, SFI, I	0.5, 1.5	Wheeze (DD asthma; ≥3 episodes of wheeze); FA (Physician assessment: history +/- investigations); AD (UK Working Party Criteria); sIgE to food
Hetzner, 2009 [62]	PC	7,900	USA	**Early Child Longitudinal Study Birth Cohort**. Nationally representative sample of children born during 2001	EBF, I	2	Wheeze (DD)
Hide, 1981[63]; Arshad, 1992 [64]	PC	843	UK	**The Isle of Wight study**. Born in 1977-1978 (normal risk of disease)	EBF, TBF, SFI, D/Q	1	Wheeze (Wheeze ever; Parent reported wheeze); RC (Parent reported rhinitis symptoms); AD (DD); RC (Physician assessment), SPT to any, CM or egg
Hikino, 2001[65]	PC	21,766/2,381	Japan	All children born in 1993-1995 attending well-baby check-ups funded by Fukuoka City	TBF, Q	1.5	FA (DD); AD (Physician assessment)

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Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Hong, 2011 [66]	PC	970/361	USA	**Boston Birth Cohort**. Predominantly African-American mother-infant pairs.	EBF, TBF, Q/I	2.5	sIgE to food
Hoppu, 2002 [67]	PC	114/27	Finland	Birth cohort of infants with a family history of atopy	EBF, TBF, I	1	SPT to any
Host, 1991 [68]	PC	315/16	Denmark	Population birth cohort of infants from the municipality of Odense born in 1985	EBF, R/Q/I	1	FA (OFC)
Howie, 1990 [69]	PC	618	UK	Population based birth cohort of infants born between 1983 and 1986 in Dundee	TBF, R/D	1	AD (Physician assessment)
Huang, 2013 [70]	PC	684	China	Mother-infant pairs registered in Putuo District, Changzheng Town Community Health Service Center Child Health Clinic within the period from January to December, 2008	EBF, Q	2	Wheeze (ISAAC)
Huurre, 2008 [71]	PC	98/29	Finland	Cohort of infants whose mother participated in a nutritional intervention trial during pregnancy	EBF, TBF, I	1	SPT any
Joseph, 2011 [72]	PC	594/178	USA	**WHEALS STUDY.** Recruited from hospital prenatal care and born in 2005	SFI, I	3	sIgE CM, egg, PN
Juto, 1980 [73]	PC	56/NA	Sweden	Population based birth cohort of infants born in 1977	TBF, Q	0.25	Total IgE

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Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Kajosaari, 1991[74]	PC	135	Finland	Exclusively breastfed infants with solid food introduction at 6 months versus 3 months	EBF, SFI, Unclear	1, 5	AD (Hanifin and Rajka) , FA (parental report), asthma (DD)
Karmaus, 2008 [75]; Ogbuanu, 2009 [76]; Soto-Ramırez, 2012 [77]	PC	1,336	UK	**Isle of Wight Prevention Study**. Population based birth cohort of infants born in semi-rural areas between 1989 and 1990	TBF, Q	10, 18	Wheeze (ISAAC and DD asthma, spirometry)
Kaufman, 1976 [78]	PC	94	USA	Birth cohort of infants from allergic mothers	TBF, Unclear	2	Wheeze (DD)
Kellberger, 2012 [79]	PC	3,785/314	Germany	**SOLAR.** Community based random sample of all pupils aged 9-11 years in 1995-1996 as part of ISAAC study, with follow-up survey 2002-2003	EBF, Q	9-18	Ever AR (ISAAC)
Kemeny, 1991[80]	PC	180	UK	Population based birth cohort of infants born at Dulwich and King's College Hospitals in London	EBF, TBF, Unclear	1	Wheeze (≥2 episodes); FA (Parent report of ≥2 food reactions); AD (unclear); SPT and sIgE to CM, egg; Total IgE
Kerr, 1981[81]	PC	269	New Zealand	Birth cohort hospital based, born 1977-1978 (normal risk of disease)	TBF, I	0.5	Wheeze (Parent reported)
Kim, 2011 [82]	PC	1177/61	Korea	Population based birth cohort of infants born in Seoul between July 2006 and August 2007	EBF, SFI, Q/I	1	FA (Parent report of ≥ 2 food reactions)

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Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Kitz, 2006 [83]	PC	131	Germany	Birth cohort of infants at increased risk for atopy participating in RCT on infant feeding intervention	EBF, D	1	AD (Hanifin and Rajka criteria)
Klinnert, 2001 [84]	PC	145	USA	Birth cohort of infants at increased risk for atopy born between 1985 and 1987	TBF, Q	8	Wheeze (DD)
Kramer, 2003; Kramer, 2009; Kramer, 2009 (b) [85-87]	PC	13,889/455	Belarus	**PROBIT**. Observational analysis of data from a cluster RCT of the UNICEF baby friendly initiative intervention. Infants born 1996-1997	EBF, I	6.5	Current AR (ISAAC); SPT aero
Kull, 2002 [88]	PC	3,790	Sweden	**BAMSE study**. Population based cohort of children born between 1994-1996	EBF, TBF, Q	2	Wheeze (Self-reported wheeze; ≥3 episodes of wheeze OR inhaled corticosteroids); FA (DD); Parent reported OR DD AD; RC (Parent reported symptoms)
Kusel, 2005 [89]	PC	263/107	Australia	Birth cohort of children at high risk of developing atopic disease born 1996-8	TBF, Unclear	5	SPT any
Larsson, 2008 [90]	PC	4779	Sweden	**DBH study**. Preschool children aged 1–6 years surveyed in 2000 and 2005	TBF, SFI, Q	9	Wheeze (DD), AD (ISAAC); Current RC (DD, ISAAC)
Marini, 1996 [91]	PC	Unclear	Italy	Infants with family history of allergy whose mothers were invited to participate in an allergy prevention program	EBF, TBF, SFI, Q	3	Wheeze (Physician assessment; ≥3 episodes of wheeze); AD and RC (Physician assessment)

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Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Matheson, 2007 [92]	PC	5,729/2,610	Australia	**Tasmanian Asthma Study.** Population based cohort born in 1961	EBF, Q	44	RC (Physician assessment)
Midwinter, 1987 [93]	PC	453	UK	Children born to parents with a family history of atopy in 1979-1981	EBF, Unclear	5	Wheeze (DD asthma)
Mihrshahi, 2007 [94]	PC	516	Australia	**CAPS study**. Observational analysis of participants from a RCT of omega-3 fatty acid supplementation. Infants born in 1997-1999 with family history of asthma or wheezing	EBF, TBF, SFI, I	5	Wheeze (DD plus current wheeze); AD (Visible flexural dermatitis or DD AD); SPT to any
Milner, 2004 [95]	PC	8,071	USA	National Maternal and Infant Health Survey and Longitudinal Follow Up. Representative US population born in 1988. Black, low socioeconomic status, and premature infants intentionally overrepresented	TBF, Q	3	Wheeze (DD)
Miskelly, 1988 [96]	PC	482	UK	Infants from antenatal clinics with family history of allergy randomised into a dietary intervention program	TBF, D	1	AD (Physician assessment)
Miyake, 2008 [97]; Miyake, 2009 [98]	PC	763	Japan	**OMCHS study**. Population based birth cohort of infants born in 2002-2003	EBF, TBF, Q	2	Wheeze (ISAAC); AD (Physician assessment)

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Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Morgan, 2004; Morgan, 2004 (b) [99,100]	PC	257	UK	Infants from five prospective randomised dietary trials conducted in the UK between 1993 and 1997. One LBW, 2 premature and 2 appropriate weight/gestation cohorts	TBF, I	0.25	Parent reported AD; Physician assessment
Moore, 1985 [101]	PC	475	UK	Infants born in a hospital in 1979-1980 with family history of AD or asthma, participating in a dietary intervention program	EBF, SFI, D/I	0.25	AD (Physician assessment)
Morales, 2012 [102]	PC	467	Spain	**INMA project**. Population based birth cohort of infants born 2004-2006	TBF, Q/I	1	Wheeze; AD (Parent reported)
Muiño, 2008 [103]	PC	897	Brazil	Population based cohort of infants born in 1993	TBF, Q	12	Wheeze (Parent reported current wheeze; Persistent wheeze: parent reported wheeze at 1, 4 and 8-10 year assessments; Early transient wheeze: parent reported)
Nielsen, 2013 [104]	PC	5429	Demark	Population based birth cohort of infants born in 1995	EBF,	0.5	Wheeze (unclear)
Nwaru, 2010 [105]; Erkkola, 2012; Nwaru, 2013 [106,107]; Virtanen, 2010 [108]	PC	3,675	Finland	**DIPP study**. Infants at high risk (HLA) for TIDM born between 1996-2004 invited to the allergy study between 1998 and 2000	EBF, TBF, D	0.5, 5	Wheeze (DD plus ISAAC; DD plus ISAAC (+/- sIgE)); AD (ISAAC); sIgE to aero, CM, egg or food; RC (Modified ISAAC questionnaire)
Oddy, 2003 [109]	PC	243	USA	Birth cohort of infants participating in the Infant Immune Study in Tucson, Arizona.	EBF, TBF, Q	1	Wheeze (Parent reported wheeze ever)

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Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Oddy, 1999; Oddy, 2003; Oddy, 2004 [110-112]	PC, NCC	2,456	Australia	**Western Australia Pregnancy Cohort**. Recruited from antenatal clinics born in 1989-1992 (normal risk of disease)	EBF, TBF, D/I/Q	1, 6, 8	Wheeze (DD; parent reported current wheeze; DD asthma and ≥3 episodes of wheeze); SPT aero
Odelram, 1996 [113]	PC	70/23	Sweden and Finland	Birth cohort of infant with family history and high cord blood IgE born in 1989-1990	EBF, D	1.5	sIgE to CM, SPT to any, total IgE
Perez Tarazona, 2010 [114]	PC	620	Spain	Population based birth cohort of infants born in 2007-2008 in Valencia	TBF, Q	1	Wheeze (Parent reported wheeze)
Pesonen, 2006 [115]	PC	160/19	Finland	Population based birth cohort of infants born in 1981	EBF, I	5	FA (Parent report of ≥ 2 food reactions)
Porch, 1998 [116]	PC	130	USA	Infants recruited from prenatal services with family history of allergy (high risk of disease)	TBF, D	1	ISAAC - current AD
Poysa, 1990; Poysa, 1992 [117,118]	PC	120/41	Finland	High risk of disease, born 1979-1980	EBF, I	5, 10	Total IgE; SPT aero
Pratt, 1984 [119]	PC	198	UK	Recruited in antenatal clinics, normal risk of disease	EBF, TBF, D/I	4.5, 5	AD (DD; Physician assessment)
Puig, 2010 [120]	PC	368	Spain	**Part of AMICS**. Population based cohort of infants born in 1996-1998 in Barcelona	TBF, Q	6	Wheeze (DD)

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Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Purvis, 2005 [121]	PC	550	New Zealand	**Auckland Birth weight Collaborative study.** Birth cohort with representative sample of babies born in 1996-1997	EBF, TBF, Q	3.5	AD (UK Working Party Criteria)
Rhodes, 2001[122]	PC	63	UK	Hospital based, born 1976-1977, family history of allergy (high risk of disease)	TBF, Q	22	Wheeze (Current wheeze and BHR)
Rothenbacher, 2005 [123]	PC	803	Germany	Recruited from university service, born in 2000-2001 (normal risk of disease)	EBF, TBF, Q/I	2	Wheeze (DD)
Rowntree, 1985 [124]	PC	80/20	UK	Recruited from hospital and family history of atopy	TBF, I	5	sIgE to CM, egg
Rullo, 2007; Rullo, 2009; Rullo, 2009 (b); Rullo, 2010 [125-128]	PC	101	Brazil	Recruited from hospital (high risk of asthma)	EBF, Q/I	1.5, 2.5, 4, 5	Wheeze (≥3 episodes of wheeze in past year; Persistent wheeze: ever wheezing treated with inhaled corticosteroids and beta-2 agonists in the past year)
Ruiz 1992 [129]	PC	39	UK	Recruited from hospital and family history of atopy (high risk of disease)	TBF, SFI, Unclear	1	AD (Hanifin and Rajka criteria)
Saarinen, 1995 [130] Saarinen, 1979 [131]	PC	Unclear	Finland	Recruited from hospital and born in 1975 (normal risk of disease)	EBF, TBF, R	0-1, 1, 5, 17	Wheeze (Physician assessment); FA (Parent report of food reaction); AD (Parent reported or DD); sIgE to CM; Total IgE

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Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Sears, 2002 [132]; Mandhane 2007 [133]	PC	1,037	New Zealand	**Dunedin Multidisciplinary Health and Development Research Study**. Population based cohort of infants born between 1972-1973	TBF, EBF, R/I	9, 26	SPT aero; wheeze (Current wheeze plus BHR (methacholine PC_{20})
Shaheen, 1996 [134]	PC	395/44	Guinea-Bissau	Young adults part of a cohort recruited for a survey of aged 0-6 year children in 1978-80 and living in a semi-rural district of Bissau	TBF, I	21	SPT aero
Shohet, 1985 [135]	PC	368	Israel	Cohort born in 1980	EBF, I	0.5	AD (Hanifin and Lobitz criteria)
Schoetzau, 2002 [136]	PC	829/92	Germany	**GINI study**. Term newborn infants born 1995-8 from 2 regions of Germany who participated in an intervention program according to risk of allergy	EBF, D	1	sIgE CM
Schonberger, 2005 [137]	PC	443	Netherlands	**PREVASC study**. Cohort analysis of participants in an intervention trial, born in 1997-2000 with a family history of asthma	TBF, D/Q	2	Wheeze (ISAAC)
Sicherer, 2010 [138]	PC	503/140	USA	**The Consortium of Food Allergy Research.** Atopic children recruited from clinical services	TBF, SFI, I	1	sIgE to PN
Siltanen, 2003 [139]	PC	285/53	Finland	Infants recruited from maternal hospital born in 1994-1995	EBF, Q	4	RC (Physician assessment); sIgE any; SPT any, Total IgE
Silva, 2005 [140]	PC	73	Brazil	Recruited from health services in urban area, born in 1998 (high risk of disease)	EBF, Q	4	Wheeze (Physician assessment of ≥3 episodes of wheeze)

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Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Silvers, 2009; Silvers, 2011 [141,142]	PC	889/249	New Zealand	**New Zealand Asthma and Allergy Cohort Study**. Population based birth cohort of infants born 1997-2001	EBF, TBF, Q	1, 5	Wheeze (DD plus current wheeze; Parent reported wheeze); FA (DD); AD (parent reported); SPT any
Simon, 2008 [143] ; Wang, 2007[144]; Wegienka, 2006 [145]; Salam, 2003 [146]	PC	372	USA	**CAS study**. Middle class mother-infant pairs enrolled in a health maintenance organisation in 1987-89	EBF, TBF, R/I	0.5, 6, 7	Wheeze (current DD; Transient wheezing: wheezing in the last 12 months at ages of 1,2 and/or 4 years but not at age of 6 years); SPT aero
Snijders, 2007; Snijders, 2008 [147,148]	PC	2,505	Netherlands	**KOALA study**. Population based birth cohort of infants born between 2000-2002 (consisting of cohorts with conventional and alternative lifestyle)	TBF, SFI, Q	2	Wheeze (≥4 episodes); sIgE-to any, aero, CM, egg, PN; Total IgE; AD (parent reported)
Soto-Ramirez, 2013 [149]	PC	2,833	USA	Population-based birth cohort selected from nationally distributed consumer opinion panel of 500,000 households (2005-2007)	TBF, Q	1	Wheeze (Parent reported current wheeze)
Strachan, 1997 [150]; Strachan, 1996 [151]; Lewis, 1995; Lewis, 1996 [152,153]; Butland, 1997 [154]	PC	12,835	UK	**British Cohort Studies**. Infants born in England, Wales, and Scotland in 1958 and 1970	EBF, TBF, I	5, 16, 35	Wheeze (Parent reported); SPT aero; RC (DD); current AR (parent reported)
Strassburger, 2010 [155]	PC	325/94	Brazil	Recruited from hospital, born 2001-2002	EBF, I	3.5	SPT aero

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Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Sunyer, 2006 [156]	PC	462	Spain	Population representative sample born in 1997-1998 (normal risk of disease)	TBF, Q	6.5	Wheeze (DD)
Sunyer, 2001 [157]	PC	596	Tanzania	Cohort born in 1995-1996 in urban area (normal risk of disease)	TBF, Q	4	Wheeze (ISAAC)
Taylor, 1983 [158] ; Taylor, 1984 [159]	PC	12,608	UK	**CHES study**. Population based cohort of children born in England, Scotland, and Wales in 1970	TBF, I	5, 6, 7	Wheeze (Parent reported DD); AD and RC (Parent reported)
Tennant, 2008 [160] Tennant, 2010 [161]	PC	392	UK	**Newcastle Thousand Families Study**. Population based sample of subject born in 1947 who were either traced through the National Health Service Central Register or contacted the study team in response to media publicity in the mid 1990	TBF, I/Q	14, 50, 51	Wheeze (Spirometry)
Tian, 2009 [162]	PC	472	China	Infants from urban areas born in 2004-2006 (normal risk of disease)	TBF, I	2	Wheeze (Physician assessment)
Van Asperen, 1983 [163]	PC	79/44	Australia	Cohort recruited from medical service, born in 1980-1981 with family history of atopy	EBF, SFI, I	1, 1.3	RC (Physician assessment); SPT food
Van Beijstervelft, 2008 [164]	PC	24,018	Netherlands	Netherlands Twin Register: born in 1987-2000 (normal risk of disease)	TBF, Q	5	Wheeze (DD)
van der Voort, 2012 [165]	PC	5,368	Netherlands	**Generation R study**. Population-based multicultural birth cohort of infants born between 2002 and 2009	EBF, TBF, Q	1, 4	Wheeze (ISAAC)

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Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Vandenplas, 1988 [166]	PC	75/9	Belgium	Infants with family history of atopy	EBF, Unclear	0.33	sIgE CM; SPT CM; Total IgE
van Merode, 2007 [167]	PC	222	Netherlands	**PREVASC study**: cohort born in 2005 with family history of asthma (high risk of disease)	EBF, Q	1	Wheeze (ISAAC)
Venter, 2009 [168]	PC	891/58	UK	Population based cohort recruited from antenatal clinics and born in 2001-2002	EBF, TBF, SFI, Q	1, 3	FA (OFC); SPT to food
Watson,2013 [169]	PC	369	New Zealand	Recruited from Polynesian women, non-random sample (high risk of disease)	EBF, Q/I	1.5	Wheeze (ISAAC)
Wetzig, 2000 [170]	PC	475	Germany	**LARS study**. High allergy risk or low birth weight children born within one year in the City and District of Leipzig	TBF, Q	1	AD (Physician assessment)
Wilson, 1998 [171]	PC	545	UK	**Dundee infant feeding study.** Population based cohort of infants born between 1983-1986	EBF, TBF, Q	7	Wheeze (Self-reported wheeze; DD)
Wright, 2002 [172]	PC	499	USA	Part of a metropolitan Boston prospective birth cohort study of infants born between 1994-1996 with family history of asthma or recruited from a Boston hospital	TBF, Q/I	0-1	Wheeze (Parent reported)

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Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Wright, 1989; Wright, 1995 [173,174]; Wright, 1999 [175]; Wright, 1994 [176]	PC	988	USA	**Tucson Children's Respiratory Study**. Healthy newborn infants recruited from local health maintenance organisation born in 1980-1984 (normal risk of disease)	TBF, SFI, Q/I	1, 6	Wheeze (DD; ≥4 episodes of wheeze in past year); Total IgE; RC (Parent reported)
Yamamoto, 2011 [177]	PC	1344	Japan	**Tokyo Children's Health Illness and Development study (T-CHILD)**	TBF, Q	3	Wheeze (ISAAC)
Zutavern, 2006; Zutavern, 2008 [178,179]	PC	606	UK	Cohort recruited from general practices and born in 1993-1995 (normal risk of disease)	EBF, TBF, SFI, Q/I	2, 5.5, 6	Wheeze (Parent reported current wheeze); AD (DD); SPT aero; sIgE any, food, aero, CM, egg, PN
Friday, 2000 [180]	RC	94	Unclear	Unclear	TBF, Unclear	10?	Wheeze (Physician assessed asthma); sIgE CM
McConnochie, 1986 [181]	RC	223	USA	Historical cohort with subjects were drawn from the patient population of a five-paediatrician group practice in a suburb of Rochester, New York	TBF, R/I	8	Wheeze (ATS guideline: wheezing with and without colds or most days or nights; DD)
Monego, 1989 [182]	RC	144	Italy	144 Italian infants retrospectively followed to examine association between breastfeeding and allergic diseases	TBF, D	4	AD (DD)
Rona, 2005 [183]	RC	1,213	Chile	Infants born in a hospital in 1974-1978	TBF, R	27	Wheeze (ECRHS questionnaire, BHR (methacholine PC_{20}); SPT aero

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Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Mai, 2007 [184]	NCC	723	Canada	Cases and controls selected from records of the Manitoba Health Services Insurance Plan and all were born 1995	EBF, Q	10	Wheeze (Canadian Asthma Consensus Guidelines: symptoms plus variable airway obstruction)
Martel, 2008 [185]	NCC	1,578	Canada	Data originating from 3 interlinked administrative health databases on children health in the first 10 years of life	TBF, Q	<10	Wheeze (DD plus asthma medication)
Maskell, 2010 [186]; Oliver, 2010 [187]; Munro, 2011 [188]	NCC	117/31	UK	**EuroPrevall UK.** Cases and age-matched controls selected from a population based birth cohort of infants born in 2008	EBF, SFI, D/R	1	Wheeze (Parent reported); FA (DBPCFC)
Ronmark, 1999 [189]	NCC	258	Sweden	**Obstructive Lung Disease in Northern Sweden Study**. 7-8 years old children enrolled in school in 1996 in northern Sweden (born 1988-1989)	TBF, Q	8	Wheeze (DD plus ISAAC; Physician assessment (+/- sensitisation))
Camara, 2003 [190]	CC	91	Brazil	Cases and control were children who sought ED care	TBF, Q	12	Wheeze (wheezing that required therapy with inhaled β2-agonists as judged by the attending physician)
DesRoches, 2010 [191]	CC	403/202	Canada	Hospital based cases and controls recruited 1998-2004	TBF, SFI, Q	<1.5	FA (Physician assessment: history +/- investigations)
Djenouhat, 2011 [192]	CC	450/150	Algeria	Hospital based cases and family controls, born 1999-2005	TBF, Unclear	0.3	FA (Physician assessment: history +/- investigations)
Fox, 2009 [193]	CC	283/133	UK	Cases and controls were children referred for suspected FA to a large paediatric service	TBF, Q	<4	FA (Physician assessment: history +/- investigations)

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Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Ghaderi, 2014 [194]	CC	200	Iran	Unclear source of population. Sex and age matched controls	TBF, I	5	AD (DD)
Haileamlak, 2005 [195]	CC	732	Ethiopia	Children age 1- 5 years. Cases were defined according to the ISAAC criteria for AD and confirmed by clinical examination	TBF, SFI, I	5	AD (ISAAC)
Infante-Rivard, 1993 [196]	CC	914	Canada	Cases were 3- and 4-year-old children with a first-time diagnosis of asthma made by a paediatrician 1988-90. Age and area matched controls chosen from computerized family allowance files for the target region	TBF, I	3.5	Wheeze (DD)
Juca, 2012 [197]	CC	590	Brazil	Adolescents 13 to 14 years of age from Cuiabá, Mato Grosso State taking part in ISAAC	EBF, TBF, Q	14	Wheeze (ISAAC)
Karunasekera, 2001 [198]	CC	582	Sri Lanka	Hospital-based cases aged 1-10 years old with age matched controls from inpatient clinics	TBF, SFI, Q	10	Wheeze (Physician assessment)
Kramer, 1981 [199]	CC	470	Canada	Cases and controls were1 month to 20 years old children attending dermatology clinics visits	EBF, TBF, I	<20	AD (Hanifin and Lobitz criteria)
Mavale-Manuel, 2003 [200]	CC	199	Mozambique	Children aged 18 months to 8 years attending paediatrics clinic with history of asthma with age-match controls attending the clinic immediately after selection of the index case	TBF, Q/I	8	Wheeze (DD plus asthma medication)

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Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Oliveti, 1995 [201]	CC	262	USA	Cases and age matched controls were identified using rosters of patients followed during the previous year. he majority of children from each group were insured by Medicaid (low income)	TBF, Q	9	Wheeze (DD plus asthma medication)
Porro, 1993 [202]	CC	465	Italy	Hospital based study with matched controls (normal risk of disease)	TBF, Q	<1.6	Wheeze (Parent reported)
Ratageri, 2000 [203]	CC	180	India	Hospital-based study (normal risk of disease)	EBF, Unclear	9	Wheeze (DD asthma using International Paediatric Consensus Group Criteria)
Rosas Vargas 2002 [204]	CC	148	Mexico	Hospital-based study, cases born in 2000 (normal risk of disease)	TBF, Q	3	Wheeze (DD)
Rylander 1993 [205]	CC	550	Sweden	Cases from a health service and control from population (normal risk of disease)	EBF, I	4	Wheeze (Physician assessment)
Ventura, 1988 [206]	CC	339/148	Italy	Italian Working Group on CMPA. Cases selected from 15 paediatric centres and age and area matched controls from well-baby clinics	TBF, I	<1	FA (Physician assessment: history +/- investigations)
Whu, 2007 [207]	CC	261	USA	Hospital-based study cases born in 2000	EBF, I	2, 5.5	Wheeze (Parent report, current)
Wickens, 2001 [208]	CC	474	New Zealand	Population-based study	TBF, I	6.5	Wheeze (ISAAC)
Zhu, 2012 [209]	CC	542	China	Population-based study	TBF, Q	14	Wheeze (DD)

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Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Alper, 2006 [210]	CS	858	Turkey	7 years old children randomly selected from seven primary schools in Bursa in 1999	TBF, Q	7	Wheeze (Parent reported wheeze classified using Martinez criteria)
Al-Kubaisy, 2005 [211]	CS	2,262	Iraq	Primary school urban and rural children	TBF, Q	12	Wheeze (DD plus ISAAC)
Awasthi, 2004 [212] Björkstén, 2011 [213] ; Flohr, 2011 [214] Nagel, 2009 [215]; Kuyucu, 2004 [216]	CS	103,716	Worldwide	**ISAAC Phase 2**. Schoolchildren aged 8–12 years from 27 centres in 21 affluent and non-affluent countries **ISAAC Phase 3.** Schoolchildren aged 6-7 years from different countries and geographic regions **ISAAC Phase 3-India.** Schoolchildren aged 6-7 and 13-14 years old from India	TBF, Q	7, 12, 14	Wheeze (Parent reported current wheeze; Parent reported asthma (+/- SPT); Spirometry; BHR hypertonic saline PC15); AD ever; RC (ISAAC)
Berjon, 1987 [217]	CS	2,690/148	Spain	Patients attending a paediatric allergy clinic in Valladolid, Spain between 1970 and 1984, with and without diagnosed food allergy	TBF, Unclear	14	FA (DD)
Castro-Rodriguez, 2010 [218]; Chong Neto, 2007 [219]	CS	3,003	Brazil, Spain	**EISL study**. One-year old infants from urban and rural primary care health clinics born in 2004-2006	EBF, Q	1, 1.4	Wheeze (ISAAC, parent reported wheeze ever)
Civelek, 2001[220]	CS	1,533	Turkey	Representative sample of schoolchildren in 5 cities	EBF, TBF, Q	11	AD (ISAAC)
Ehlayel, 2008 [221]	CS	1,278	Qatar	Children 0-5 years old attending primary healthcare centres for routine immunisation	EBF, Q	5	AR ever (ISAAC); FA (DD)

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Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Ehrlich, 1996 [222]	CS	620	South Africa	Second year black elementary school (7- 8 years) children.	TBF, Q/I	9	Wheeze (ISAAC)
Evenhouse, 2005 [223]	CS	16,903	USA	**National Longitudinal Study of Adolescent Health (Add Health).** Nationally representative samples of adolescents from 80 school districts, 1994	TBF, Q	12-18	Wheeze (Unclear)
Girolomoni, 2003 [224]	CS	1369	Italy	Representative sample of children attending the fourth grade at elementary school	TBF, Q	9	AD (UK Working Party Criteria)
Han, 2009 [225]	CS	21,371	Taiwan	Elementary and middle school children aged 6-15 years old in 2004	TBF, Q	15	Wheeze (ISAAC)
Karino, 2008 [226]	CS	9615	Japan	University students aged 18–19 years enrolled from 2003 through 2005.	TBF, Q	18	Wheeze (Self-reported asthma); AD (Self-reported); RC (DD)
Kucukosmanoglu, 2008 [227]	CS	1015/20	Turkey	Hospital based selection of 8-18 months old Infants born in 2001-2002	TBF, SFI, Q/I	1	SPT to egg
Kuehr, 1992 [228]	CS	1470/201	Germany	Schoolchildren between 6 and 8 years of age	TBF, Q	8	SPT aero
Kurt, 2008 [229] Kurt, 2007 [230]	CS	25,843	Turkey	**PARFAIT**. Prevalence and Risk Factors of Allergies in Turkey. Population representative sample of children aged 9-15 years old	TBF, Q	15	Wheeze; AD (Current; Parent reported); current RC (parent reported)
Liu 2012 [231]	CS	8733/397	China	Sample of children from kindergarten and elementary schools in Shenyang	EBF, Q	8	RC (ATS questionnaire)

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Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Miyake, 2003 [232]	CS	6845	Japan	12-15 years old children from all public junior high schools in Suita, Japan.	(EBF, TBF) Q	15	Wheeze; current RC (ISAAC)
Nakamura, 1999 [233]	CS	3850	Japan	All 3 year old children participating in a health check-up in 1997	TBF, Q	3	AD (DD)
Paton, 2012 [234]	CS	15,142/592	Australia	Representative primary school entrants 2006-2009	EBF, TBF, Q	7	FA (Parent-reported food reaction to any nut)
Prietsch, 2006 [235]	CS	685	Brazil	Population representative sample of infants aged 12-15 months	EBF, Q	13	Wheeze (unclear)
Rusconi, 1999; Rusconi, 2005 [236,237]	CS	16933	Italy	**SIDRIA** survey of a representative sample of children aged 6-7 years old	TBF, Q	7	Wheeze (Parent reported persistent wheezing≥1 in first 2 years, and in past 12 months); Transient early wheeze (wheeze in first 2 years but not past 12 months; ISAAC)
Rust, 2001 [238]	CS	6783	USA	**NHANES III survey**. Children ages 2 months to 5 years from non-institutionalized U.S. population	TBF, I	<6	Wheeze (DD; DD asthma ever)
Salem, 2002 [239]	CS	424	Iraq	Population representative sample of children aged 0.16-2 years old	EBF, Q	5	Wheeze (Wheeze ever)

Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Selcuk, 1997 [240]	CS	5412	Turkey	Children 7-12 years of 18 primary schools	TBF, Q	12	Wheeze (Parent reported wheeze ever; Parent reported current asthma); AD (parent reported current); r RC (Parent reported ever)
Suwanpromma, 2012 [241]	CS	215	Thailand	Schoolchildren aged 6-18 years	TBF, Q	18	Wheeze (Spirometry; BHR hypertonic saline PC_{15})
Takemura, 2002 [242]	CS	23828	Japan	**The Tokorozawa Childhood Asthma and Pollinosis Study.** Representative sample of children in public elementary schools (normal risk of disease)	EBF, TBF, Q	15	Wheeze (ATS questionnaire: DD asthma plus ≥2 episodes of wheeze)
Tanaka, 2009 [243]	CS	1957	Japan	**Fukuoka Child Health Study.** All 3-year old children who had the examination at public health centres in Fukuoka city	EBF, TBF, Q	3	Wheeze (ISAAC); AD (ISAAC; current dermatitis)
Visser, 2010 [244]	CS	1115	Netherlands	**EISL study**. One-year old infants from urban and rural primary care health clinics born in 2004-2006	TBF, Q	1	Wheeze (Parent reported wheeze ever; ≥3 episodes of wheeze)
Wang, 2006 [245]	CS	8733	China	Population representative sample of children in elementary schools and nurseries (normal risk of disease)	EBF, TBF, Q	10	Wheeze (ISAAC)

Any: a panel of aero and food allergens; AD: atopic dermatitis; ATS: American Thoracic Society; BHR: bronchial hyper-responsiveness; CM: cow's milk; CC: Case Control; CS: Cross-sectional; D: diary; DBPCFC: double blind placebo controlled food challenge; DD: doctor diagnosed; EBF: exclusive breastfeeding; ECRHS: European Community Respiratory Health Survey; FA: food allergy; I: interview; ISAAC: International Study of Asthma and Allergies in Children; OFC: open food challenge; PC: prospective cohort; PC_{15}: provocative concentration to reduce by 15% a measure of lung function (usually forced expiratory volume in 1 second [FEV_1]); PN: peanut; aero: aeroallergen; Q: questionnaire; R:

medical records, Re-C: retrospective cohort; RC: rhino-conjunctivitis; SFI: solid food introduction; SPT: allergen skin prick test; sIgE: allergen-specific IgE; TBF: total breastfeeding.

Table S3 Characteristics of included observational studies of breastfeeding or solid food introduction, and risk of autoimmune diseases

Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Couper, 1999 [246]; Couper, 2009 [247]	PC	548/~30	Australia	**BABYDIAB study.** First degree relatives of diabetic children	TBF, EBF, D/Q/I	2	TIDM (serology)
Frederikson, 2012 (abstract) [248]; Fronczak, 2003 [249]; Lamb, 2013 [250]; Norris, 2003 [251]; Lamb 2008 [252]	PC, NCC	1,698	USA	**DAISY study**. High risk children via HLA screening, or Colorado register	TBF, EBF, SFI, Q/I	4, <7, 9, 13	TIDM (serology; DD)
Holmberg, 2007 [253]; Karlen, 2012 [254]; Wahlberg, 2006 [255]	PC	3,788/~51	Sweden	**ABIS study.** General population in Southeast Sweden	TBF, EBF, Q	1, 2, 6	TIDM (serology)
Ludvigsson, 2003 [256]	PC	205	Sweden	Relatives of diabetics	TBF, Q	2	TIDM (serology)
Viner, 2008 [257]	PC	11,211/61	UK	Unclear	TBF, Q	>10	TIDM (DD)
Virtanen, 1992 [258]; Virtanen, 1998 [259]; Hypponen, 1999 [260]; Virtanen, 2000 [261]	PC, NCC	697/43	Finland	**Childhood Diabetes in Finland Study**. Siblings of diabetic children	TBF, Q	7, <25	TIDM (serology; DD)
Virtanen, 2011 [262]	PC	~4,000/ ~160	Finland	Odu and Tampere University Hospitals	TBF, EBF, Q	5	TIDM (serology; DD)
Jones, 1998 [263]	NCC	518/60	UK	Hospital admission	TBF, R	5.0-9	TIDM (DD)

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Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Kimpimaki, 2001 [264]	NCC	455/65	Finland	Turku, Oulu and Tampere Hospital births	TBF, EBF, Q	<4	TIDM (DD)
Kyvik, 1992 [265]	NCC	228/76	Denmark	National Service Conscript records	TBF, R	<20	TIDM (DD)
Norris, 1996 [266];	NCC	171/18	USA	Siblings or offspring of Barbara Davies Centre Diabetics	TBF, Q/R	<7	TIDM (DD)
Robertson, 2010 [267]	NCC	1444/361	UK	AMND and SSG register, hospital births	TBF, R	<15	TIDM (DD)
Savilahti, 2009 [268]	NCC	6209/45	Finland	NHI database	TBF, SFI, R	12	TIDM (DD)
Ahadi, 2011 [269]	CC	202/101	Iran	Hospital admission	TBF, Q/I	7	TIDM (DD)
Alves, 2012 [270]	CC	246/123	Brazil	Siblings	TBF, EBF, SFI, I	7	TIDM (DD)
Ashraf, 2010 [271]	CC	195/128	USA	Children's hospital	TBF, Q	<10	TIDM (DD)
Baruah, 2011 [272]	CC	86/43	India	Endocrinology ward	TBF, EBF, I	<18	TIDM (DD)
Bener, 2009 [273]	CC	340	Qatar	Endocrinology clinic and community	TBF, I	<16	TIDM (DD)
Blom, 1989 [274]	CC	867/339	Sweden	Paediatric referral and population register	TBF, Q	7	TIDM (DD)

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Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Bodington, 1994 [275]	CC	393/209	UK	Independent sources and population register	TBF, Q	<15	TIDM (DD)
Borras, 2011 [276]	CC	1,530/306	Spain	Diabetes register and Catalonia birth register	TBF, R	Not reported	TIDM (DD)
Dahlquist, 2002 [277]	CC	2,226/610	Austria, Latvia, Lithuania, Luxembourg and UK	**EURODIAB**. Diabetes register and population register	TBF, SFI, Q/I	<15	TIDM (DD)
Esfarjani, 2001 [278]	CC	104/52	Iran	Endocrine clinic and paediatric OPD attendance	TBF, EBF, SFI, Q	<14	TIDM (DD)
Gimeno, 1997 [279]	CC	626/313	Brazil	Juvenile Diabetes Association or hospital records	TBF, EBF, Q	<18	TIDM (DD)
Hathout, 2006 [280]	CC	402/102	USA	Diabetes hospital care and Hospital Well Child clinics	TBF, Q/I	7	TIDM (DD)
Kostraba, 1992 [281]; Kostraba, 1993 [282]	CC	264/132-white 108/54-black	USA	Alleghany Hospital diabetes register Colorado IDDM Registry and motor vehicle driver register	TBF, EBF, Q/I	10, <18	TIDM (DD)
Liese, 2012 [283]	CC	709/505	USA	SEARCH surveillance (Colorado and South Carolina research centres)	EBF, SFI, I	<20	TIDM (DD)
Majeed, 2011 [284]	CC	310/96	Iraq	Hospital admission or OPD	TBF, SFI, Q	<17	TIDM (DD)

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Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Malcova, 2006 [285]	CC	2,334/868	Czech Republic	Czech Childhood Diabetes Register and diabetes clinic	TBF, Q	<15	TIDM (DD)
Marshall, 2004 [286]	CC	577/196	UK	Paediatric clinic and Local Health Authority Register	TBF, I	<16	TIDM (DD)
Mayer, 1988 [287]	CC	747/268	USA	Colorado IDDM Registry or Barbara Davies Centre	TBF, Q/I	<18	TIDM (DD)
McKinney, 1999 [288]	CC	521/196	UK	Yorkshire Childhood Diabetes Register and Family Health Service Authority Register	TBF, I	<16	TIDM (DD)
Meloni, 1997 [289]	CC	200/100	Italy	Paediatric clinic or hospital admission	TBF, SFI, Q	<17	TIDM (DD)
Patterson, 1994 [290]	CC	1,548/258	UK	Diabetes register, hospital discharge, Health Service records	TBF, EBF, R	<15	TIDM (DD)
Perez-Bravo, 1996 [291]	CC	165/80	Chile	Santiago de Chile registry	TBF, SFI, Q/I	<15	TIDM (DD)
Perez-Bravo, 2003 [292]	CC	250/143	Chile	School volunteers	TBF, Q	8	TIDM (DD)
Rabiei 2011 [293]	CC	300/100	Iran	Diabetes register	EBF, SFI, Q	11	TIDM (DD)
Rami, 1999 [294]	CC	609/114	Austria	Austrian diabetes register	TBF, EBF, Q	<15	TIDM (DD)
Rosenbauer, 2008 [295]	CC	2631/760	Germany	Hospital based surveillance system ESPD and local registration office records	TBF, SFI, Q/I	<5	TIDM (DD)
Sadauskaite-Kuehne, 2004 [296]; Skrodeniene, 2010 [297]	CC	1,944/803	Sweden/ Lithuania	Population register and outpatients	TBF, EBF, Q	7, 9	TIDM (DD)
Samuelsson, 1993 [298]	CC	1,089/297	Sweden	Paediatric department and population register	TBF, EBF, Q/R	<15	TIDM (DD)

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Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Siemiatycki, 1989 [299]	CC	482/161	Canada	Hospital admission	TBF, I	<17	TIDM (DD)
Sipetic, 2005 [300]	CC	315/105	Serbia	Hospital admission	TBF, I	<16	TIDM (DD)
Soltesz, 1994 [301]	CC	305/130	Hungary	Incidence register	TBF, EBF, Q	<14	TIDM (DD)
Stene, 2000 [302]	CC	1156/85	Norway	National Childhood Diabetes register	EBF, Q	<15	TIDM (DD)
Stene, 2003 [303]	CC	2213/545	Norway	Diabetes register	EBF, SFI, Q	9	TIDM (DD)
Strotmeyer, 2004 [304]	CC	485/247	China	Diabetes register and population register	TBF, SFI, Q	10	TIDM (DD)
Tai, 1998 [305]	CC	310/117	Taiwan	Taipei City	TBF, I	8	TIDM (DD)
Telahun, 1994 [306]	CC	129/55	Ethiopia	Ethio-Swedish Children's Hospital Diabetic Clinic	TBF, Q	<15	TIDM (DD)
Tenconi, 2007 [307]	CC	477/159	Italy	Diabetes register or paediatric admissions	TBF, R/I/Q	16	TIDM (DD)
Thorsdottir, 2000 [308]	CC	220/55	Iceland	Statistical Bureau of Iceland	TBF, EBF, I	12	TIDM (DD)
Verge, 1994 [309]	CC	475/217	Australia	New South Wales diabetes register and school records	TBF, Q	<15	TIDM (DD)
Virtanen, 1993 [310]	CC	1,380/690	Finland	Finnish National Population Registry	TBF, EBF, Q	14	TIDM (DD)
Visalli, 2003 [311]	CC	900/150	Italy	**EURODIAB study** register and school records	TBF, SFI, Q	6-18	TIDM (DD)

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Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Wadsworth, 1997 [312]	CC	639/276	UK	**BPASU** reporting system and District Health Authority Immunisation Register	TBF, Q	<5	TIDM (DD)
Glatthaar, 1988 [313]	CS	946/~200	Australia	School register	TBF, Q	<18	TIDM (DD)
Hummel, 2000 [314]; Hummel, 2007 [315]; Ziegler, 2003 [316]	PC	1460/~68	Germany	**German BABYDIAB study**. Offspring of mothers and/or fathers with TIDM born in Germany between 1989 and 2000	EBF, TBF, SFI, Q	2, 5, 8	TIDM (serology), CD (IgA-tTG)
Norris, 2005 [317]	PC	1560	USA	**DAISY study**. Children at increased risk for TIDM were enrolled at birth from 1993 to 2006 and/or identified by newborn screening for HLA genotype	TBF, Q/I	<5	CD (IgA-tTG)
Welander, 2010 [318]	PC	9,414/ ~29	Sweden	**ABIS study**. Population based study of babies born between Oct 1997 and Oct 1999.	TBF, D/I	8.4	CD (IgA-tTG and biopsy)
Ascher, 1997 [319]	CC	81/8	Sweden	Cases of coeliac disease were compared with siblings at high genetic risk (DQA1*0501-DQB1*02), in whom the diagnosis was excluded	TBF, I	<18	CD (ESPGHAN criteria)
Auricchio, 1983 [320]	CC	437/190	Italy	Source of cases unknown, controls unaffected siblings	TBF, R/I	<18	CD (ESPGHAN criteria)
Baron, 2005 [321]	CC	444/222	France	Cases from EPIMAD registry (1988-97) with community-based sex, age, region matched controls	TBF, EBF, I	<17	IBD (DD)
Bergstrand, 1983 [322]	CC	616/308	Sweden	Cases were residents of Stockholm County diagnosed with Crohn's disease between 1955 and 1974 with sex, age, residence matched controls from population registry in Stockholm County	TBF, Q/I	20	IBD (Unclear)

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Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Castiglione, 2011 [323]	CC	1,030/ 468	Italy	Cases from gastroenterology units; controls comprised from physicians, nurses, and support services professionals from the participating sites	TBF, Q	16-66	IBD (ECCO guideline)
Corrao, 1997 [324]	CC	1,252/ 626	Italy	Cases identified in clinics with controls sex and age matched hospital-based control	TBF, I	18-65	IBD (DD including histology)
Decker 2010 [325]	CC	866/123	Germany	Cases from paediatric gastroenterology clinics; controls from ophthalmology and dental clinics	TBF, Q	<18	CD (DD); IBD (DD)
Ellis, 2012 [326]	CC	655/246	Australia	**CLARITY**. Cases from paediatric rheumatology clinic; controls from paediatric surgery unit born in the same area	TBF; SFI, Q/I	18	JRA (DD)
Falth-Magnusson, 1996 [327]	CC	336/72	Sweden	Cases from paediatric department records, born in 1987-1989. Reference children were age matched from same county.	TBF, EBF, R/Q	<2	CD (ESPGHAN criteria)
Fort, 1990 [328]	CC	189/59	USA	Cases being followed up in clinics with sibling or other controls	TBF, SFI, I	15	Autoimmune thyroid Disease (DD)
Gearry, 2010 [329]	CC	1,253/ 653	New Zealand	Canterbury Inflammatory Bowel Disease Project. Cases selected from patient advertising, letters to patients from their doctor, patient support groups; Community based (Electoral Roll) controls	TBF, R/Q	>20	IBD (DD)

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Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Gilat, 1987 [330]	CC	1,497/ 499	9 countries: USA, Canada, UK, Sweden, Denmark, Holland, France, Italy, Israel	The International IBD Study Group: Cases and matched controls from several health centres (normal risk of disease)	TBF, Q/I	<25	IBD (DD)
Greco, 1988 [331]	CC	2,150/ 201	Italy	Hospital-based cases born in 1976-1983 with age and area matched controls	EBF, R/Q	2	CD (ESPGHAN criteria)
Gruber, 1996 [332]	CC	144/54	USA	Children diagnosed with Crohn's disease with mothers who were volunteers from the Western New York Chapter of the Crohn's and Colitis Foundation of America, Inc. with age matched unrelated controls	EBF, TBF, Q	<22	IBD (Unclear)
Hansen, 2011[333]	CC	534/ 267	Denmark	All patients diagnosed with IBD in Copenhagen City and County (private and public sector) in 2003-4 with age, sex, ethnicity and area matched control with orthopaedic problems	TBF, Q	38	IBD (Copenhagen Diagnostic Criteria)
Ivarsson, 2002 [334]	CC	1,272/ 392	Sweden	Cases selected from CD Register born in 1992-1996 and sex age and area matched controls from the national population register	TBF, SFI, Q	2, 15	CD (ESPGHAN criteria)
Koletzko, 1991 [335]	CC	231/93	Unclear	Source of cases unclear. Sibling controls	EBF, TBF, SFI, Q	15	IBD (DD including histology)

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Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Mason, 1995 [336]	CC	133/54	USA	Children seen at the outpatient paediatric rheumatology clinics with playmates matched for age and race as controls	TBF, SFI, I	6	JRA (DD)
Pacilio, 2010 [337]	CC	278/139	Unclear	Unclear source of cases and controls. Cases aged 0.5-2 years old with age matched healthy controls	TBF, Unclear	2	CD (Unclear)
Peters, 2001 [338]	CC	270/133	Germany	All newly diagnosed patients aged <10 years old were identified from paediatricians and a biannual meeting of the German Coeliac Disease Society in 1985–1995. Sex and aged matched control selected from population registry	TBF, Q	< 10	CD (ESPGHAN criteria)
Roberts 2009 [339]	CC	248,521/ 90	UK	Cases identified from hospital admission codes, controls the rest of the population with linked record data	TBF, R	<24	CD (ICD codes 269.0 (ICD-8) or 579.0 (ICD-9) or K90.0 (ICD-10))
Rosenberg, 1996 [340]	CC	468/ 137	Canada	Cases from a health service and matched control from population	TBF, SFI, Q	<18	JRA (American College of Rheumatology criteria)
Sonntag, 2007 [341]	CC	1,974/ 1,096	Germany	Cases identified from different sources and controls from partners (normal risk of disease)	TBF, Q	40	IBD (DD including histology)
Thompson, 1999 [342]	NCC	243/27	UK	Cases and matched for gender and social class controls were selected from the 1946 National Survey of Health & Development (NSHD) and the 1958 National Child Development Study (NCDS), two on-going, longitudinal birth cohort studies in UK.	TBF, R/I	33-43	IBD (DD)

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Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Wang, 2013 [343]	CC	2,616/ 1,308	China	Cases from several health centres and matched controls from friends or neighbours (normal risk of disease)	TBF, I	<70	IBD (Chinese diagnostic guideline including histology)

CC: case control; CD: coeliac disease; CS: Cross-sectional; DD: doctor diagnosis; EBF: exclusive breastfeeding; IA: Islet autoantibodies; IBD: Inflammatory bowel disease; I: interview ; NCC: nested case control; PC: prospective cohort; Q: questionnaire; R: medical records; SFI: solid food introduction; TBF: total breastfeeding

Table S4 Characteristics of included intervention trials of other maternal or infant dietary exposures and allergic outcomes

Study	Design	N Intervention / Control	Country	Intervention	Study Details	Disease risk	Age at outcome (years)	Outcomes reported (method of assessment)
Falth-Magnusson, 1987 [344] Falth-Magnusson, 1992 [345] Ludvigsson, 2003 [346]	RCT	108/104	Sweden	**Allergenic food avoidance** (maternal)	Pregnant women. Cow's milk and egg exclusion from 28 weeks gestation to delivery.	High	1.5, 5	AR (physician assessment); Asthma (≥3 episodes of wheeze); AD (Hanifin and Lobitz); AS (SPT); FA (history); Total IgE; TIDM (serology)
Jirapinyo, 2013 [347]	RCT	30/32	Thailand	**Allergenic food avoidance** (maternal)	Lactating women. Cow's milk exclusion during lactation up to 4 months postpartum	High	<0.5	AD (unclear)
Lilja, 1989 [348]	RCT	84/87	Sweden	**Allergenic food avoidance** (maternal)	Pregnant women. Milk and egg exclusion during third trimester, versus 1 litre milk and 1 egg per day	High	1.5	Asthma (physician assessment); AS (SPT); Allergic rhinitis (physician assessment); AD (physician assessment); FA (history)
Hattevig, 1990 [349]; Paronen, 2000 [350]; Hattevig, 1999 [351]; Hattevig, 1989 [352]; Sigurs, 1992 [353]	CCT	54/67	Sweden	**Allergenic food avoidance** (maternal)	Lactating women. Cow's milk, egg and fish exclusion during first 3 months post- partum	High	0.25, 1.5, 4, 10	AS (SPT); TIDM (serology), AD, Asthma, Wheeze; AR; FA (history), Total IgE

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Study	Design	N Intervention / Control	Country	Intervention	Study Details	Disease risk	Age at outcome (years)	Outcomes reported (method of assessment)
Herrmann, 1996 [354]	CCT	50/50	Germany	**Allergenic food avoidance** (maternal)	Pregnant/lactating women. Cow's milk and egg exclusion from 28 weeks gestation through lactation, versus 1 litre cow's milk and 1 egg/day	High	1	AD (DD); AS (sIgE)
Kilburn, 1998 [355]	CCT	15/96	UK	**Allergenic food avoidance** (maternal)	Lactating women. Milk, egg, fish and nuts exclusion throughout lactation	High	1.5	AD (Hanifin and Rajka), AS (SPT)
Metcalfe, 2016 [356]	RCT	40, 44, 36	Australia	**Allergenic food avoidance** (maternal)	First 6 weeks of lactation. Randomised to high-egg diet (>4 eggs per week), low-egg diet (1-3 eggs per week) and egg-free diet	High	0.33	AS (sIgE egg)
Becker, 2004 **[357]** Chan-Yeung, 2000 **[358]** & 2005 **[359]**;Wong, 2013 **[360]** Protudjer, 2011 **[361]**; Carlsten, 2013 **[362]**	RCT	281/268	Canada	**Multifaceted including maternal allergenic food avoidance**	**CAPPS Study.** Pregnant/lactating women. BF encouraged for 4 months, allergenic food exclusion during pregnancy/lactation, delayed solid (6 months) and allergenic (12 months) food, whey pHF if necessary, environmental control	High	1, 7, 15	Asthma; Recurrent wheeze (ISAAC and modified ECRHS); AS (SPT); AR (DD); AD (DD); BHR (PC_{20}); Lung function (FEV_1)

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Study	Design	N Intervention / Control	Country	Intervention	Study Details	Disease risk	Age at outcome (years)	Outcomes reported (method of assessment)
Hide, 1994 **[363]** Hide, 1996,**[364]** Arshad, 1992 **[365]** Arshad, 2003 **[366]** Arshad, 2007 **[367]** Scott, 2012 **[368]**	RCT	71/68	UK	**Multifaceted including maternal allergenic food avoidance**	**Isle of Wight Study.** Lactating women. Allergenic food exclusion during lactation, delayed allergenic (9-11 months) food, soya hydrolysate if necessary, environmental control.	High	1, 2, 4, 8, 18	Recurrent wheeze (≥3 episodes); BHR (PC_{20}); AD (Physician assessment); FA (OFC; Physician assessment); AS (SPT, total IgE); AR (physician assessment); Total IgE
Lovegrove, 1994 **[369]**	RCT	12/14	UK	**Multifaceted including maternal allergenic food avoidance**	CM exclusion during pregnancy and lactation with hydrolysed milk if necessary. BF encouraged for 6 months and EHF if needed	High	1	AD (DD)
Shao, 2006 **[370]**	RCT	23/23	China	**Multifaceted including maternal allergenic food avoidance**	Lactating women. EBF encouraged for 4 months, allergenic food exclusion during lactation, delayed solid (4 months) and allergenic (6-12 months) food, pHF if necessary	High	1.5	AD (Wolkerstorfer score); AS (SPT)
Zeiger, 1992 **[371]** Zeiger, 1989, **[372]** Zeiger 1994 **[373]**	RCT	103/185 [seen at 4 months]	USA	**Multifaceted including maternal allergenic food avoidance**	Pregnant/lactating women. Allergenic food exclusion during pregnancy/lactation, delayed allergenic (1-3 years) food, casein eHF if necessary	High	1, 4, 7	AD (Hanifin and Rajka Criteria); AR (DD); FA - Any (DD), Wheeze (≥2 physician diagnosed episodes); AS (SPT)
Halmerbauer, 2002, 2003 **[374,375]**	RCT	349/347	UK, Germany, Austria	**Multifaceted**	**SPACE Study.** EBF encouraged beyond 3 months, delayed solid (6 months) and allergenic (1-3 years) food, environmental control	High	1	AD (DD); AS (SPT, sIgE); Wheeze (Parent reported wheeze ever), Asthma (≥3 episodes of wheeze); FA (DD)

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Study	Design	N Intervention / Control	Country	Intervention	Study Details	Disease risk	Age at outcome (years)	Outcomes reported (method of assessment)
Matthew, 1977 **[376]**	RCT	27/35	UK	**Multifaceted**	BF encouraged for 6 months, delayed solid food (3 months) and allergenic food (6 months), soy milk if necessary, environmental control	High	1	AD (Physician assessment); AS (Total IgE)
Poysa, 1991 **[377]** Poysa 1989 **[378]** Kuikka 1985 **[379]**	RCT	Unclear - outcome reported in 35/33	Finland	**Multifaceted**	EBF encouraged for 3 months, solid food and cow's milk formula after 3 months plus environmental control	High	5, 10	Asthma (≥3 episodes of wheeze); AR (Physician assessment); AS (SPT, total IgE); FA (oral food challenge); AD (Hanifin and Rajka)
Schonberger, 2005 **[137]**	RCT	222/221	The Netherlands	**Multifaceted**	**PREVASC study.** BF encouraged to ≥6 months, delayed solid and allergenic (6 months) food, eHF if formula introduced, environmental control	High	2	AD (ICHPPC); Wheeze (Dutch Guideline ‘‘Asthma in Children’’ and ISAAC); AS (sIgE)
Boyle 2015 **[380] [381]** Boyle 2016 [382]	RCT	432/431	Australia, Singapore, England and Ireland	**Prebiotic** Immunofortis GOS/FOS + AOS	**PATCH Study**. Term infants with ≥one parent with allergic disease, and formula introduction <18 weeks. Intervention until 6 months. Co- intervention with partially hydrolysed formula	High	1	AD (Hanifin and Rajka) AS (total IgE, sIgE milk, sIgE egg)
Gruber 2010 **[383]** Gruber 2015 [384]	RCT	414/ 416	Netherlands, Austria, Switzerland, Italy, Germany	**Prebiotic** Immunofortis GOS/FOS + AOS	**MIPS-1 Study.** Full formula feeds <8 weeks	Low	1, 5	AS (sIgE to CM or egg; total IgE); AD (UKWPC), AD (DD); Wheeze (DD); AR (DD); FA (DD)

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Study	Design	N Intervention / Control	Country	Intervention	Study Details	Disease risk	Age at outcome (years)	Outcomes reported (method of assessment)
Ivakhnenko 2013 **[385]**	RCT	80/ 80	Ukraine	**Prebiotic** GOS/FOS	Fully formula fed – no breastfeeding at all. Intervention until 2 months.	Normal	1.5	AD (Harrigan and Rabinowitz); FA (unclear)
Moro 2006 **[386]**, van Hoffen 2009 **[387]**, Arslanoglu 2008 **[388]** Arslanoglu 2012 **[389]**	RCT	129/ 130	Italy	**Prebiotic** Immunofortis	Formula commenced <2 weeks, and full formula feeds <6 weeks	High	0.5, 2, 5	Allergic sensitisation (sIgE to CM; total IgE), AD (Harrigan and Rabinowitz), Wheeze (≥3 episodes), Allergic rhinoconjunctivitis (physician assessment)
Sierra, 2015 **[390]**	RCT	188/ 177	Spain	**Prebiotic** Nutradefense. GOS	Infants aged <2 months, exclusively formula fed for ≥15 days. Intervention until 1 year.	Normal	1	AD (physician assessment); Wheeze (physician assessment); AS (SPT); FA (unclear)
Ziegler 2007**[391]**	RCT	150/ 76	USA	**Prebiotic** GOS/Polydextrose +/- lactulose	Full formula feeds <2 weeks	Normal	0.3	AD (unclear)
Chien, 2016 [392]	RCT	Unclear – outcome reported in 45 (synbiotic), 39 (prebiotic), 45 (control)	Singapore	**Prebiotic & Synbiotic** B. breve scGOS/lcGOS	Mixed fed infants born by elective Caesarean. Infant formula supplemented with scGOS/lcFOS (0.8g/100ml) and B. breve M-16V (7.5x108CFU/100ml), or formula with scGOS/lcFOS (0.8g/100ml), or control formula from birth until 4 months.	Unclear	0.4	AD (unclear)

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Study	Design	N Intervention / Control	Country	Intervention	Study Details	Disease risk	Age at outcome (years)	Outcomes reported (method of assessment)
Kukkonen 2007 **[393]** Kuitunen 2009 **[394]** Kukkonen 2011**[395]**	RCT	610/ 613	Finland	**Synbiotic** L. rhamnosus, B. breve, P. freudenreichii; GOS	Pregnant women (2-4 weeks before delivery) and infants up to 6 months. Representative population	High	2, 5	AD (UK Working party criteria), Wheeze (≥2 episodes + interval symptoms), ARC (symptoms + sensitisation), Allergic sensitisation (Total IgE and SPT/sIgE to common allergens)
Roze 2012 **[396]**	RCT	48/ 49	France	**Synbiotic** L. rhamnosus; GOS/FOS	Infants (first 6 months). Full formula feeds until randomised (up to day 3)	Normal	0.5	AD (UK Working party criteria)
Van der Aa 2010 **[397]**	RCT	46/ 44	Netherlands	**Synbiotic** B. breve; GOS/FOS	Whey-based formula combined with Synbiotic, for 3 months. Infants who already had AD, with SCORAD >15	High	1	Wheeze (≥3 episodes), Allergic sensitisation (Total IgE)
Abrahamsson 2007 **[398]** Abrahamsson 2013 **[399]**	RCT	117/ 115	Sweden	**Probiotic** L.reuteri	Pregnant women (week 36) and infants (for 12 months)	High	2, 7	AD (Seymour), Wheeze (single, or ≥2 episodes), ARC (watery discharge ≥2 times with same allergen), Allergic sensitisation (SPT common allergens)
Allen 2012 **[400]** Allen 2014 **[401]**	RCT	220/ 234	UK	**Probiotic** L. salivarius, L. paracasei, B. animalis, B. bifidum	Pregnant women (week 36) and infants (for 6 months)	High	2	AD (DD), Allergic sensitisation (SPT common allergens, CM, Egg), Wheeze (unclear), ARC (unclear), Food Allergy (parent report)

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Study	Design	N Intervention / Control	Country	Intervention	Study Details	Disease risk	Age at outcome (years)	Outcomes reported (method of assessment)
Boyle 2011 **[402]**	RCT	125/ 125	Australia	**Probiotic** L. rhamnosus	Pregnant women (week 36)	High	1	AD (UK Working party criteria), Wheeze (wheeze + loose API), Allergic sensitisation (SPT common allergens)
Cabana, 2015 [403]	RCT	93/ 92	USA	**Probiotic** Lactobacillus GG	Birth to 6 months to infants daily	High	2	Wheeze (unclear); AD (unclear)
De Leon 2007 **[404]** Simon 2007 **[405]**	RCT	Total = 33	Philippines	**Probiotic** Lactobacillus Bifidobacterium	Birth to 4 months to infants, or to their breastfeeding mothers	High	0.5	AD (unclear) Allergic sensitisation (Total IgE)
Dotterud 2010 **[406]** Simpson, 2015 [407]	RCT	211/ 204	Norway	**Probiotic** L. rhamnosus, B. animalis, L. acidophilus	Mothers only (36 weeks gestation to 3 months after birth)	Normal	2, 6	AD (UKWPC), Wheeze (≥3 episodes + ICS, parent report), ARC (DD, parent report), Allergic sensitisation (SPT common allergens, sIgE)
Enomoto 2014 **[408]**	CCT	130/36	Japan	**Probiotic** B. longum, B. breve	Pregnant women (week 36) and infants (for 6 months)	Normal	1.5	AD (Hanifin and Rajka), Wheeze (physician assessment), ARC (physician assessment)
Huurre 2008 **[409]**	RCT	72/ 68	Finland	**Probiotic** L. rhamnosus, B. animalis	Infants (for 6 months)	High	1	AD (Hanifin and Rajka), Allergic sensitisation (SPT common allergens)

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Study	Design	N Intervention / Control	Country	Intervention	Study Details	Disease risk	Age at outcome (years)	Outcomes reported (method of assessment)
Kalliomaki 2001 **[410]** Kalliomaki 2003 **[411]** Kalliomaki 2007 **[412]** Rautava 2002 **[413]**	RCT	77/ 82	Finland	**Probiotic** L. rhamnosus	Mothers and infants; from 2–4 weeks before expected delivery and 6 months of age	High	2	AD (relapsing itchy lesions with typical location), Wheeze (symptoms + ICS), ARC (symptoms with allergen exposure), Food Allergy (CMA by DBPCFC), Allergic sensitisation (Total IgE and SPT/sIgE to common allergens)
Kim 2010 **[414]**	RCT	57/ 55	Korea	**Probiotic** B. bifidum, B. animalis, L. acidophilus	Pregnant women and infants from 4 to 6 months	High	1	AD (Hanifin and Rajka), Allergic sensitisation (Total IgE and sIgE to common allergens)
Kopp 2008 **[415]**	RCT	54/ 51	Germany	**Probiotic** L. rhamnosus	Mothers (2-4 weeks before birth until 3 months post birth) and infants (months 4-6)	High	2	AD (UK Working party criteria), Wheeze (≥5 episodes), Allergic sensitisation (Total IgE and sIgE to common allergens)
Lau 2012 **[416]**	RCT	303/ 303	Germany	**Probiotic** E. coli, E. faecalis	Infant from 5 weeks up to 7 months age	High	2	AD (Hanifin and Rajka), Allergic sensitisation (Total IgE and sIgE)

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Study	Design	N Intervention / Control	Country	Intervention	Study Details	Disease risk	Age at outcome (years)	Outcomes reported (method of assessment)
Lodinová-Žádníková 2010 **[417]**	RCT	56/ 57	Czech Republic	**Probiotic** E. coli	Infants - birth to age 4 weeks	High	1	AD (unclear), Food allergy (unclear), Wheeze (unclear) Allergic sensitisation (Total IgE and sIgE to common allergens)
Lundelin, 2016 [418] Luoto, 2014 [419]	RCT	31, 31, 32	Finland	**Probiotic** L. rhamnosus GG, B. lactis, L. paracasei ST11, B.longum BL999	Perinatal administration of probiotic to preterm infants (32-36 weeks gestation)	Normal	1	Wheeze (ISAAC); ARC ISAAC); AD (ISAAC); FA (unclear)
Morisset 2008 **[420]**	RCT	59/ 56	France	**Probiotic** Fermented formula without live bacteria	Infant – from birth or weaning, to age 1 year	High	1	Food allergy (CMA by physician assessment) Allergic sensitisation (sIgE to cow's milk)
Niers 2009 **[421]** Gorissen, 2014 [422]	RCT	78/ 78	Netherlands	**Probiotic** B. bifidum, B. animalis, Lc. lactis	**PANDA study.** Pregnant women during the last 6 weeks of pregnancy and their infants until age 1 year	High	2, 6	AD (modified ECRHS, UKWPC), Wheeze (physician assessment), AS (Total IgE and SPT/sIgE to common allergens), Food allergy (physician assessment); ARC (ISAAC); Lung function (FEV1)
Ou 2012 **[423]**	RCT	95/ 96	Taiwan	**Probiotic** L. rhamnosus	Pregnant women (third trimester) and then breastfeeding mothers, or directly to infants, until age 6 months	High	3	AD (ISAAC), Wheeze (ISAAC), ARC (ISAAC), Allergic sensitisation (sIgE to common allergens)

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Study	Design	N Intervention / Control	Country	Intervention	Study Details	Disease risk	Age at outcome (years)	Outcomes reported (method of assessment)
Taylor 2007 **[424]**, Prescott 2008 **[425]** Jensen 2012 **[426]**	RCT	115/ 111	Australia	**Probiotic** L. acidophilus	Infants until 6 months	High	1, 2.5, 5	AD (DD), Food allergy (any food - physician assessment), Wheeze (DD), ARC (symptoms + sensitisation), Allergic sensitisation (SPT common allergens)
Rautava 2006 **[427]**	RCT	38/ 43	Finland	**Probiotic** B. animalis, L. rhamnosus	Infant formula; infants until age 1 year	Normal	1	AD (Hanifin and Rajka), Food allergy (CMA by DBPCFC) Allergic sensitisation (SPT food allergens)
Rautava 2012 **[428]**	RCT	82/ 78	Finland	**Probiotic** B. longum, L. rhamnosus	Infants fed daily until age 1 year	High	2	AD (Hanifin and Rajka), Allergic sensitisation (SPT common allergens)
Scalabrin 2009 **[429]** Scalabrin 2014 **[430]** Scalabrin 2017 [431]	RCT	95/ 95	USA	**Probiotic** L. rhamnosus	Infants (first 12 months) fed extensively hydrolysed formula from 14 days	Normal	0.4, 3, 5	Allergic sensitisation (sIgE to common allergens), AD (unclear), Wheeze (unclear), ARC (unclear), Food Allergy (unclear)
Soh 2009 **[432]** Loo 2014 **[433]**	RCT	127/ 126	Singapore	**Probiotic** L. rhamnosus, B. longum	Cow's milk-based infant formula supplemented with Probiotic; infants up to 6 months of age	High	1	AD (Seymour), Allergic sensitisation (Total IgE and SPT/sIgE to common allergens) Food allergy (physician assessment), ARC (physician assessment)

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Study	Design	N Intervention / Control	Country	Intervention	Study Details	Disease risk	Age at outcome (years)	Outcomes reported (method of assessment)
West 2009 **[434]** West 2013 **[435]**	RCT	89/ 90	Sweden	**Probiotic** L paracasei	To infant from 4 until 13 months	Normal	1, 8-9	AD (itchy rash with typical distribution, or DD), Wheeze (DD), ARC (DD), Allergic sensitisation (Total IgE and sIgE to common allergens) Food allergy (physician assessment)
Wickens 2008 **[436]** Wickens 2012 **[437]** Wickens 2013 **[438]**	RCT	341/ 171	New Zealand	**Probiotic** L. rhamnosus, B. animalis	To pregnant women (35 weeks gestation to end up of BF or 6 months post-partum) and infants from 2-16 days of birth to 2 years	High	2, 4, 6	AD (UKWPC); Wheeze (ISAAC); ARC (ISAAC); Allergic sensitisation (SPT common allergens)
Berman, 2015 [439]	RCT	Unclear – total 114	USA	**Fatty acids** Ω-3	DHA (Ω -3) or EPA (Ω -3) rich fish oil prenatal supplementation, or soy oil	Unclear	3	Wheeze (parent report); AD (parent report)
Birch, 2010 **[440]** Foiles, 2015 [441]	RCT	88/ 90	USA	**Fatty acids** Ω-3 and Ω-6	**DIAMOND study.** DHA (Ω-3) and arachidonic acid Ω -6) supplemented formula for first year	Normal	3, 4	Wheeze (DD); AD (DD); ARC (DD); FA (DD)
Bisgaard, 2016 [442]	RCT	365/371	Denmark	**Fatty acids** Ω-3	**COPSAC trial.** Fish oil (2.4g/d Ω -3 LCPUFA), or olive oil to pregnant women 24 weeks gestation until 1 week post-partum	Normal	5	Wheeze (physician assessment); AD (Hanifin and Rajka); AS (SPT, sIgE); ARC (DD); Lung function (FEV1)
Harslof, 2014 [443]	RCT	61/ 60	The Netherlands	**Fatty acids** Ω-6	**EFATOP trial.** Borage oil (100 mg GLA) daily from 1-2 weeks to 6 months age, or sunflower oil	High	1	AD (UKWPC); AS (sIgE); Total IgE

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Study	Design	N Intervention / Control	Country	Intervention	Study Details	Disease risk	Age at outcome (years)	Outcomes reported (method of assessment)
Lucas, 1999 **[444]**	RCT	75/ 79	Denmark	**Fatty acids** Ω-3	Fish oil (1.2g/d Ω-3 PUFA), or sunflower oil to infants from 9 to 18 months	Normal	1.5	AS (total IgE)
van Gool, 2003 **[445]**	RCT	55/ 76	Germany	**Fatty acids** Ω-6	100mg/day GLA supplementation of mothers during lactation, or infant formula (160mg/day) in first 5 months	High	1	AD (Hanifin); Total IgE
Kitz, 2006 [83]	RCT	154/155	UK	**Fatty acids** Ω-3 and Ω-6	0.3% arachidonic acid (Ω -6), 0.32% DHA (Ω -3) supplemented formula from birth to 6 months	Normal	0.75	AD (parent report); Wheeze/Asthma (parent report, DD)
Linnamaa, 2010 **[446]**	RCT	151/162	Finland	**Fatty acids** Ω-6	3g/day blackcurrant seed oil (essential fatty acid) during pregnancy and exclusive breastfeeding, 1ml/day to infant to age 2, or olive oil	Normal	1	AD (H&R); AS (SPT); Total IgE
Mihrshahi, 2003 **[447]** Peat, 2004 **[448]** Marks, 2006 **[449]**	RCT	312/304	Australia	**Fatty acids** Ω-3	**CAPS trial.** 500mg fish oil (=184mg n-3 PUFA) daily from 6 months, or in formula if introduced before then, plus canola oil (high in n-3 PUFA) for family, plus environmental control, until 5 y age	High	1.5, 3, 5	Asthma (ISAAC/ parent report), FEV_1; AD (ISAAC, UKWPC); AR (ISAAC); AS (SPT); Total IgE
Damsgaard, 2007 **[450]**	RCT	45/ 49	Denmark	**Fatty acids** Ω-3	Fish oil ~3.4mls/day (571mg EPA, 381mg DHA) from 9 to 12 months	Normal	1	Total IgE

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Study	Design	N Intervention / Control	Country	Intervention	Study Details	Disease risk	Age at outcome (years)	Outcomes reported (method of assessment)
Palmer, 2012 & 2013 **[451,452]** Best, 2015 & 2016 [453,454]	RCT	368/338	Australia	**Fatty acids** Ω-3	**DOMINO trial.** Fish oil capsules with 800mg DHA, 100mg EPA daily from 21 weeks gestation to delivery, or vegetable oil	High	1, 3, 6	AD (physician assessment, ISAAC); Wheeze (physician assessment, ISAAC), FA (physician assessment); AR (physician assessment, ISAAC); AS (SPT)
Dunstan, 2003 **[455]**	RCT	52/ 46	Australia	**Fatty acids** Ω-3	Fish oil 4g daily from 20 weeks gestation to delivery, containing 2.07g DHA, 1.02g EPA, from 20 week of gestation until delivery or olive oil	High	1	FA (history), Asthma (≥2 episodes of wheeze), AD (DD); AS (SPT)
D'Vaz, 2012 **[456]**	RCT	218/202	Australia	**Fatty acids** Ω-3	Daily fish oil with 280mg DHA and 110mg EPA (changed to 250/60 part way through trial) from birth to 6 months, or 650mg olive oil	High	1	AD (´typical skin lesions´); AS (SPT); FA (parent report + SPT); Wheeze (unclear)
Furuhjelm, 2009 **[457]** Furuhjelm, 2011 **[458]**	RCT	70/ 75	Sweden	**Fatty acids** Ω-3	Daily fish oil (1.6 g EPA, 1.1 g DHA) from 25 weeks gestation to end of lactation (or through 3.5 months of breastfeeding), or soy oil	High	1, 2	AS (SPT and sIgE); FA (parent report + SPT/sIgE); AR (seasonal symptoms); Wheeze (DD, ≥ 3 episodes of wheezing), AD (parent report, Seymour criteria)

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Study	Design	N Intervention / Control	Country	Intervention	Study Details	Disease risk	Age at outcome (years)	Outcomes reported (method of assessment)
Lauritzen, 2005 **[459]**	RCT	62/ 60	Denmark	**Fatty acids** Ω-3	**Lactation**. 4.5 g fish oil daily (=~1.5 g/d of n-3 LCPUFA) from 1-2 week to 4 months, or olive oil	Normal	2.5	Wheeze (parent report), FA (parent report); AD (DD); Total IgE
Olsen, 2008 **[460]** Hansen, 2017 [461]	RCT	266/267	Denmark	**Fatty acids** Ω-3	**Pregnant women**. Fish oil 4g/day (1.28g EPA, 920mg DHA) from 30 weeks of gestation to delivery	Normal	16, 24	Asthma (DD, ISAAC, physician assessment); AS (sIgE); AR (DD, ISAAC); Lung function (FEV1);
Dotterud, 2013 **[462]**	CCT	2,860/5,743	Norway	**Fatty acids** Ω-3	**PACT trial.** Oily fish twice/week and 5ml cod liver oil (1.2 g n-3 PUFA) daily through pregnancy and to infant from 4–6 weeks with oily fish twice/ week from 6 months	Normal	2	Wheeze/Asthma (parent report; DD); AD (Parent report)
Imhoff- Kunsch, 2011 **[463]**	RCT	547/547	Mexico	**Fatty acids** Ω-3	400 mg DHA daily from ~20 weeks gestation to delivery, or corn/soy oil	Normal	0.5	Wheeze (parent report)
Noakes, 2012 **[464]**	RCT	62/ 61	USA	**Fatty acids** Ω-3	**SiPS trial**. 2 x 150g portions/week of farmed salmon (~163mg EPA, 331mg DHA per day) from 20 weeks gestation to delivery	High	0.5	Wheeze (study assessment); AD (Physician assessment); AS (SPT)

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Study	Design	N Intervention / Control	Country	Intervention	Study Details	Disease risk	Age at outcome (years)	Outcomes reported (method of assessment)
Aage, 2015 [465]	RCT	2145/ 2200	Guinea-Bissau	**Vitamins**	Neonates supplemented with Vitamin A 50,000 IU plus 10IU vitamin E, or 10IU vitamin E alone, at time of BCG vaccination. Population at high risk of vitamin A deficiency.	Normal	10	AS (SPT); Wheeze (ISAAC); AD (ISAAC)
Chawes, 2016 [442]	RCT	315/308	Denmark	**Vitamins**	**COPSAC** Vitamin D3 (2400 IU/d) to pregnant women 24 weeks gestation to 1 week post-partum, or placebo. All women also took 400 IU/day of vitamin D3.	Normal	3	Wheeze (physician assessment); AD (Hanifin and Rajka); AS (SPT, sIgE)
Checkley, 2010 **[466]** Checkley, 2011 [467]	cluster RCT	803, 885, 771	Nepal	**Vitamins**	**NIPPS 2 study.** Vitamin A (23,300 IU) or Beta Carotene (42mg) versus peanut oil placebo weekly from preconception through lactation, in married women at high risk of vitamin A deficiency	Normal	11	Wheeze (ISAAC, DD); LF (FEV_1; FVC; PEF)
Czeizel, 1994 **[468]**; Dobo, 1998 **[469]**	RCT	2090/2032	Hungary	**Vitamins**	**Hungarian Optimal Family Planning Programme**. Multivitamins from preconception to second missed period, in women who wanted to become pregnant	Normal	1, 6	Wheeze (physician assessment); Recurrent wheeze (physician assessment); AD (physician assessment); FA (unclear)

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Study	Design	N Intervention / Control	Country	Intervention	Study Details	Disease risk	Age at outcome (years)	Outcomes reported (method of assessment)
Devakumar, 2015 [470]	RCT	600/600	Nepal	**Vitamins**	Micronutrient daily supplement (800μg Vit A, 10mg Vit E, 5μg Vit D, 1.4mg Vit B1, 1.4mg Vit B2, 18mg Niacin, 1.9mg Vit B6, 2.6μg Vit B12, 400μg Folic acid, 70mg Vit C, 30mg Iron, 15mg Zinc, 2mg Copper, Selenium 65μg, Iodine 150μg) versus iron 60mg and folic acid 400μg, to pregnant women in the second and third trimester. Population at risk of micronutrient deficiencies.	Normal	8	Lung function (FEV1, FVC); Wheeze (ISAAC); AR (ISAAC)
Grant, 2016 [471]	RCT	87, 86, 87	New Zealand	**Vitamins**	Vitamin D daily from 27 weeks gestation to birth (pregnant women) and birth to 6 months (infants) at 1000 IU/ 400 IU, or 2000 IU/ 800 IU, versus placebo	Normal	1.5	Wheeze (DD); AS (SPT, sIgE)
Greenough, 2010 **[472]**	RCT	1199/1205	UK	**Vitamins**	**Vitamins in Pre-eclampsia trial.** Vitamin C (100mg) and Vitamin E (400IU) from 14-21 weeks to delivery, in women with clinical risk factors for pre-eclampsia.	Normal	1	Wheeze (parent-reported); Recurrent wheeze (parent-reported); AD (parent-reported)
Goldring, 2013 **[473]**	RCT	120/60	UK	**Vitamins**	Vitamin D 200,000 IU bolus at 27 weeks or 800IU daily from 27 weeks to delivery, versus no treatment Ethnically stratified as Asian, Middle Eastern, Black, White.	Normal	3	Wheeze (ISAAC); Recurrent wheeze (≥episodes); AR (ISAAC); AS (SPT); AD (ISAAC); FA (physician assessment); total IgE

Study	Design	N Intervention / Control	Country	Intervention	Study Details	Disease risk	Age at outcome (years)	Outcomes reported (method of assessment)
Kiraly, 2013 **[474]**	RCT	227/235	Guinea-Bissau	**Vitamins**	Vitamin A 100,000-200,000 IU at 6-9 months age, versus no supplement, in infants with no history of measles or vitamin A supplementation. Population at risk of vitamin A deficiency.	Normal	7	AS (SPT)
Litonjua, 2016 [475]	RCT	Unclear – 881 total	USA	**Vitamins**	Vitamin D (4000 IU/d) versus placebo from 10-18 weeks gestation to delivery. All women also received 400 IU/d vitamin D as part of a multivitamin supplement.	High	3	Wheeze (physician assessment); AD (DD); AS (total IgE, sIgE)
McEvoy, 2014**[476]**	RCT	89/90	USA	**Vitamins**	**Vitamin C** 500mg daily from ≤22 weeks gestation to delivery versus corn starch, in women aged ≥15 years old who reported being current smokers (≥1 cigarette per day) randomised at 22 weeks of gestation	Normal	1	Wheeze (unclear); LF (spirometry)

AD: atopic dermatitis; AOS acidic oligosaccharides; API Asthma Predictive Index; AR: Allergic Rhinitis; ARC: Allergic Rhinoconjunctivis; AS: allergic sensitisation; B. Bifidobacterium; BF: breastfeeding; BHR: bronchial hyper-responsiveness; CM: cow's milk; CCT controlled clinical trial; DBPCFC: double blind placebo-controlled food challenge; DD doctor's diagnosis in the community (Physician assessment refers to assessment by a study physician); DHA: docosahexanoic acid; E. Escherichia; ECRHS European Community Respiratory Health Survey; eHF extensively hydrolysed formula; EPA: eicosapentaenoic acid; FA: food allergy; FEV_1 forced expiratory volume in one second; FOS long-chain fructo-oligosaccharides; FVC; forced vital capacity; GLA gamma linolenic acid; GOS galacto-oligosaccharides; ICHPPC: International Classification of Health Problems in Primary Care; ICS inhaled corticosteroids; ISAAC International Study of Asthma and Allergies in Childhood; IU International Units; L. Lactobacillus; Lc. Lactococcus; LCPUFA: long chain polyunsaturated fatty acid; LF: lung function;

OFCs oral food challenges; PEF: peak expiratory flow; pHF: partially hydrolysed formula; RCT randomised controlled trial; SPT skin prick test; sIgE allergen-specific Immunoglobulin E sensitisation; TIDM: type 1 diabetes mellitus UKWPC: the UK Working Party Criteria (to define AD; Seymour criteria and UKWPC are both modifications of the Hanifin and Rajka criteria).

Table S5 Characteristics of included observational studies of other maternal or infant dietary exposures and risk of allergic outcomes

Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Alm, 2009 [6]; Goksor, 2011; [477] Alm, 2012;[478]	PC	4,941	Sweden	**Infants of Western Sweden**: Population based birth cohort of infants born in the region in 2003	Infant vitamin intake [any]; infant fish, fat intake; Dietary Pattern; vegetarianism in the family, gluten, type of fat on bread, lactic acid (yoghurt, fermented vegetables); vegetables; alcohol, Q	1	AD (parent reported); FA (DD)
Andreasyan, 2007; [479]	PC	498	Australia	**CARHS.** Some of the participants at high risk for sudden infant death syndrome born in 1988-1989 were identified in the northern region of Tasmania through school records	Fruit syrup; fruit juice (orange); honey, Q	9	AD, wheeze and RC (ISAAC Q); SPT any
Back, 2009 [480]	PC	123	Sweden	The first 206 babies born in 1998 recruited at University Hospital of Umea. All children were prescribed vitamin A&D supplements from 6 weeks to 24 months of age	Infant vitamin intake [any], Q	6	AD, wheeze and rec wheeze (ISAAC Q)
Baiz, 2013[481]	PC	239	France	**EDEN.** Population based birth cohort with pregnant women recruited from prenatal clinics in Nancy and Poitiers, < 24th weeks of gestation in 2003	Vitamin D cord blood, S	1, 2, 3, 5	AD (DD); RC (ISAAC Q); Rec wheeze (DD asthma plus medication and/or current symptoms)
Bekkers, 2012 [482]; Willers, 2008 [483]	PC	3,786	The Netherlands	**PIAMA.** Population based birth cohort of children born in 1996/97 recruited prenatally, Netherlands. The children were allocated to an intervention study or natural history study depending on their family risk for allergy	Maternal vitamin supplement [any] and Vitamin D cord blood, Q	2, 8	AD (DD); LF (BHR, spirometry); sIgE any; Wheeze (ISAAC); Rec wheeze (DD asthma plus ≥4 episodes of wheeze); Total IgE; sIgE-aero; sIgE to food

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Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
;Bertelsen, 2013 [484]	PC	54,740	Norway	**MoBa study.** Population birth cohort with pregnant women recruited at ~17 weeks of pregnancy with children born between 2000 and 2005 in Denmark	Probiotics (milk based), Q	0.5, 3	AD (parent reported); Rec wheeze (parent reported asthma)
Bisgaard, 2009 [17]	PC	354	Denmark	**COPSAC study.** Healthy newborns of mothers with a history of doctor-diagnosed asthma recruited in Copenhagen, Denmark between 1998 and 2001	Alcohol, Q	3	Rec wheeze (physician assessment)
Carmargo, 2010 [485]	PC	823	New Zealand	**The New Zealand Asthma and Allergy Cohort study.** Population based birth cohort with pregnant women recruited at maternity care centres in Wellington and Christchurch 1997-2001	Vitamin D cord blood, S	1.25, 3, 5	Wheeze (parent reported wheeze); Rec wheeze (DD asthma plus medication and/or current symptoms)
Romieu, 2007; [486] Chatzi, 2008 [487]	PC	468	Spain	**Menorca birth cohort.** Population based birth cohort with women recruited from antenatal care at all general practices in Menorca between 1997-1998	Fruits, legumes, nuts, vegetables; Dietary Pattern-adherence to Mediterranean diet; cereal; dairy; meat; white meat; maternal fish intake, Q	4.6; 6.5	SPT-aero; Atopic wheeze (parent reported wheeze plus positive SPT); Rec wheeze (parent reported ≥1 episodes of wheeze) AD (DD, parent reported); AS (any, food, aeroallergen by sIgE)
de Jong, 2012 [488]; De Jong, 2012 [489]; Leermakers, 2013; [490]	PC	8742	The Netherlands	**GENERATION R.** Population based birth cohort , with pregnant women recruited < 25 weeks gestation in Rotterdam	Maternal vitamin supplement [any]; maternal fish intake, Q	4	AD and wheeze (ISAAC Q)

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Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Dubakiene, 2012 [491]; Butiene, 2011[492]; Oliver, 2010; [187] Grimshaw, 2012 [493]	PC NCC	1158 123/41	Lithuania; UK	**EuroPrevall birth cohort.** Over 12,000 newborns in 9 European countries 2005–2009 using a standardised approach across 9 European countries. Lithuanian birth cohort compared cases with age-matched controls; UK birth cohort compared each case with two controls	Maternal allergenic food avoidance to milk or egg; Infant mineral intake; infant fat intake; maternal fish oil supplement; Dietary carbohydrates; Wheat; dietary energy; dietary protein, Q	1, 2	AD (parent reported) SPT to food; FA any (DD with DBPCFC)
Dunlop, 2006 [494]	PC	1326	Slovakia	**Slovak birth cohort.** The 1st 250 pregnant women delivering at maternity hospitals in the selected study sites were recruited between 1997 and 1999	Citrus fruits, Q	1	AD (physician assessment)
Fergusson, 1990 [495]	PC	1,067	New Zealand	**Christchurch child development study.** A cohort of children born in the Christchurch urban region New Zealand during mid1977	Fruits, vegetables, cereal, meat, R/D	10	AD (Physician assessment; DD , duration of > 3years and use of regular medication)
Fitzsimon, 2007 [496]	PC	631	Ireland	**LIFE-WAYS.** cohort of children born in 2002 whose mother had completed FFQ during pregnancy were followed up from birth through general practice records	Maternal fat, fruit and vegetable intakes, Q	3	Rec wheeze (physician assessment of asthma)
Gale, 2008 [497]	PC	440	UK	Population based birth cohort with pregnant women recruited on their first visit to midwives' antenatal booking clinic in 1991	Maternal plasma Vitamin D, S	0.75, 9	AD (UKWPC, visible AD on examination, parent reported); Rec wheeze (Parent reported asthma)
Harris, 2001; [56] Zutavern, 2004 [57]	PC	604/ 622	UK	Population based birth cohort of newly pregnant women who presented at one of three general practices in Ashford, Kent UK between 1993 and 1995	Rice; cereal; meat	2, 5.5	AD (DD; visible AD on examination); SPT aero; Rec wheeze (Parent reported)

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Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Hesselmar, 2010 [61]	PC	184	Sweden	**ALLERGYFLORA.** Birth cohort in Sweden enriched with children with family history of allergies	Fruits, I/Q	0.5/1.5	AD (physician assessment, and full-filling Williams' criteria); FA CM (physician assessment plus OFC); sIgE any
Hypponen, 2004; [498] Hypponen, 2001 [499]	PC	10,366 /81	Finland	**Northern Finland Birth Cohort.** Population based birth cohort with women recruited between the 24th and 28th week of gestation in Oulu and Lapland in 1995-1966	Infant vitamin intake [any], Q	31, 2	SPT aero; rec wheeze (self-reported asthma plus medication and/or symptoms)
Hoppu, 2000 [67]	PC	115	Finland	Birth cohort of infants of breastfeeding mothers (for at least 3 months) with a positive family history of atopic disease	Maternal intake of vitamins, fats, R	1	AS (SPT to any)
Jedrychowski, 2008 [500]; Jedrychowski 2011 [501]	PC	469	USA and Poland	Prospective birth cohort of infants from non-smoking healthy mothers who gave birth at 29 - 43 weeks of gestation between 2001 and 2004	Maternal fish intake, Q	1, 2	AD (physician assessment); Wheeze (parent reported)
Kemp, 2011 [502]	PC	310	Tasmania	**THIS.** Cohort of infants at high risk for sudden infant death syndrome born in 1988-1989 were identified in the northern region of Tasmania through school records	Maternal allergenic food avoidance (peanut), Q	3.5	sIgE to peanut
Kull, 2006; [503] Magnusson, 2013 [504];	PC	3230	Sweden	**BAMSE.** Prospective birth cohort of newborns in a predefined area of Stockholm, between 1994 and 1997	Infant fish intake, infant vitamin intake, Q	4, 12	Wheeze (Self-reported wheeze; ≥3 episodes of wheeze OR inhaled corticosteroids); FA (DD); Parent reported OR DD AD; RC (Parent reported symptoms); AS (sIgE)

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Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Martindale, 2005; [505] Devereux, 2006; [37] Devereux, 2007 [506]; Willers, 2007[507]	PC	3230	Scotland	**Aberdeen birth cohort**. Population based birth cohort with pregnant women recruited 1997-99 while attending a hospital antenatal clinic at ~12weeks gestation	Infant fish intake; maternal vitamin intake and mineral intake; Fruits; citrus fruits; fruit juice; vegetables; green leafy vegetables; apples; Maternal fat intake from different sources; whole grain products, Q	2, 4, 5, 12	AR (DD); AS-any (sIgE); Rec wheeze (≥ 3 episodes in past year); AD (ISAAC, UKWPC); LF (Spirometry); RC and wheeze (ISAAC Q)
Lack, 2003 [43]; Shaheen, 2009 [508]; Wills, 2013[509]; Granell, 2008 [510]	PC; NCC	11,352	UK	**ALSPAC.** The study enrolled pregnant women living in the Avon Health Authority are, UK, expected to delivery between 1991 and 1992. Cases and controls, who did and did not develop food allergy respectively, were not matched	Allergenic food avoidance (peanuts/nuts); allergenic food avoidance (soybean meat); peanut; Dietary Patterns: 'Traditional'; 'Health Conscious'; 'Processed'; 'Confectionery'; 'Vegetarian'; 'Processed'; 'Vegetarian'; maternal plasma vitamin and vitamin supplement [any], Q	0.5, 2.5, 3.5, 7, 7.5, 8, 8.7	FA peanut (DD); Rec wheeze (parent reported persistent wheeze, DD asthma); AD (parent reported); LF (BHR slope, FEV_1); RC (parent reported); SPT aero; Total IgE
Laitinen, 2005 [511]	PC	95	Finland	Children with a family history of AD (mother, father and/or older sibling with AD, AR or asthma), who participated in a prospective allergy prevention study (probiotic intervention trial)	Infant fat, mineral, and vitamin intake [any]; Dietary carbohydrates; dietary energy; dietary protein, D	0.5, 1	AD (physician assessment); FA cow's milk (physician assessment)

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Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Lange, 2010 [512]; Litonjua, 2006; [513] Camargo, 2007 [514]	PC	1376	USA	**Project Viva study**. Population based birth cohort with pregnant women at <22 weeks of gestation recruited from 8 obstetric offices of a large multispecialty suburban/urban group practice in eastern Massachusetts US between 1999 and 2002	Dietary Pattern derived from Principal Component Analysis - Alternate Healthy Eating Index for pregnancy (AHEI-P); Adherence to intake of Mediterranean foods; maternal vitamin and mineral intake; infant vitamin and vitamin supplement [any]; fruits and vegetables, Q	2, 3	AD (DD); Wheeze (parent reported); Rec wheeze (parent reported in at least one questionnaire at 1,2,3 years old, ≥2 episodes of wheeze plus medication and/or current symptoms)
Liu, 2011 [515]	PC	649	USA	**Boston Birth Cohort.** Mother-infant pairs recruited at birth at Boston Medical Centre	Vitamin D cord blood, S	2	sIgE cow's milk; sIgE egg; sIgE food; sIgE peanut
Marini, 1996 [91]	PC	68	Italy	Infants with family history of allergy born in maternity wards of 3 hospitals from 1989 whose mothers were refused to participate in an allergy prevention intervention program	Citrus fruit; meat, Q	1, 3	AD (DD; parent reported); RC (Physician assessment + parent reported); Rec wheeze (physician assessment > 3 episodes of wheeze); sIgE to food; sIgE aero; sIgE any
Mommers, 2009; [516] Magdelijn, 2011; [517] Cremers, 2011[518]	PC	2465	The Netherlands	**KOALA.** Population based birth cohort with healthy pregnant women recruited in week 10 -14 of their pregnancy from an ongoing PC study on pregnancy-related pelvic girdle pain and through posters in organic food shops, anthroposophical, physician offices, and midwives	Maternal plasma vitamin D and vitamin supplement [any], S, Q	2, 5, 6.5 , 7	AD (UKWPC, (ISAAC); LF (spirometry); sIgE any; Total IgE; Wheeze (ISAAC Q); Rec wheeze (DD asthma plus medication)

Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Maslova, 2012 [519]; Maslova, 2013 [520] [521]; Linneberg, 2004; [522]	PC	28,758	Denmark	**DNBC.** Population based birth cohort with pregnant women recruited between 1996 and 2002 at ~12weeks gestation	Maternal vitamin intake; maternal intake of peanut and pistachio; tree nuts alcohol; artificially-sweetened non-carbonated soft drinks, Q	1.5, 7	AD (parent reported + DD); ARC (DD + Medication registry); RC (DD); Rec wheeze (DD asthma plus ≥1 episode of wheeze in the last year)
Magnus, 2013 [523] Haberg, 2009 [524]	NCC, PC	32,077	Norway	Cases with asthma & non asthmatic controls were recruited from the participants of the Norwegian Mother and Child Cohort Study	Maternal plasma vitamin d and vitamin supplement [any] S, R	1.5, 3	Rec wheeze (DD or asthma medication); Wheeze (parent reported)
Milner, 2004 [95]	PC	8,073	USA	**NMIH.** Survey of mothers who gave birth in 1988 with a follow-up survey conducted in 1991. Blacks, individuals with low socioeconomic status, and premature infants were intentionally overrepresented in the survey sample	Infant vitamin intake [any], Q	3	FA any (DD); Rec wheeze (DD asthma)
Miskelly, 1988 [96]	PC	482	UK	Infant recruited through two antenatal clinics in South Wales born to mothers with positive allergy history in at least one member of family, whose mothers were asked to participate in allergy preventive program	Fruits; meat; meat other than beef, D	1	AD (Physician assessment and parent reported); Wheeze (parent reported)
Miyake, 2009 [525] and 2010 [526-528] and 2011 [529,530]; Satio, 2010 [526]	PC	763	Japan	**OMCHS.** Population birth cohort with pregnant women between the 5-39th week of pregnancy recruited from a university hospital and three obstetric hospitals in municipalities of Osaka between 2001 and 2003	Maternal mineral, fat, fish, and vitamin intake; fruits; apples; citrus fruits; vegetables; green and yellow vegetables; Dietary patterns derived from Factor Analysis; dairy; cheese; milk; egg; meat; yoghurt, Q	0.33, 2	AD and wheeze (parent reported DD, ISAAC)

Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Morales, 2012 [531]	PC	1,724	Spain	**INMA Project**. Population based birth cohort study with pregnant women attending their first routine specialized antenatal care visit in 4 study areas: Menorca (1997-98), Valencia (2003-05), Sabadell (2004-06), Gipuzkoa (2006-08)	Maternal plasma Vitamin D, S	1, 4, 5	Wheeze (parent reported); Rec wheeze (DD asthma plus medication and/or current symptoms)
Morgan, 2004 [100]	PC	257	UK	Healthy preterm births (<37 weeks gestational) from 3 hospitals in southeast England	Fruits, vegetables; Cereal; rice; rusks; desserts; meat; meat with vegetables, I	1	AD (Physician assessment and parent reported)
Narita, 2011; [532] Ohya, 2011 [533]	PC	1,463	Japan	**T-CHILD.** Population based birth cohort of Japanese mother-infant pairs with women recruited ~ second trimester in Tokyo	Maternal vitamin, mineral, fish intake; total energy intake, Q	0.6, 1.5, 3	AD (parent reported ISAAC Q); Wheeze (parent reported ISAAC Q); Rec wheeze (DD asthma)
Nwaru, 2010, 2011, 2012 and 2013 [105,106,534,535] [536,537]; Niinisto, 2012 [538]; Lumia, 2011; [539] Erkkola, 2012; [107]; Maijaliisa, 2011; [540]; Uusitalo 2008 [541] Erkkola, 2009; [542] Marjamaki, 2010; [543]	PC	5,619	Finland	**DIPP**. Prospective birth cohort of children at high risk of TIDM (HLA genotype conferred susceptibility) born between 1997 and 2004 in Oulu and Tampere University Hospital Finland	Maternal vitamin D, maternal fish and margarine intake; infant fish intake; malaceous fruits; green leafy vegetables; berries; citrus fruits; fruit juice; fruits; vegetables and roots; nuts and pulses; potatoes; fruits and berries; root vegetables; fruits and vegetables; vegetables; cabbage; carrots; Various cereals, dairy products, meat, egg, alcohol, rice, tea, coffee, chocolate, sweets, Q	0.5, 5, <10	AD and RC (DD, parent reported ISAAC); sIgE aero; sIgE cm; sIgE egg; sIgE food; Rec atopic wheeze (DD asthma + positive IgE); Rec wheeze (DD asthma); Wheeze (ISAAC); Rec wheeze (DD asthma plus medication and/or current symptoms)

Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Oien, 2010 [544]	PC	3,067	Norway	**PACT**. A controlled primary intervention study on allergic diseases conducted in the central part of Norway in the city of Trondheim. Inclusion in the control cohort began in September 2000, and the interventional programme started in a separate cohort in July 2002	Maternal fish/ fish oil; vegetable intake, Q	2	AD (ISAAC); Rec wheeze (DD asthma)
Pike, 2012 [545]	PC	739	UK	**SWS**. Population birth cohort with 20-34 year old women recruited pre-conception from general practitioners in Southampton between 1998 and 2002 and subsequently become pregnant	Maternal plasma vitamin D and vitamin intake, S, Q	1, 3, 6	LF (EV_1, FVC, BHR slope); SPT any; Wheeze (parent reported ISAAC Q); Rec wheeze (DD asthma)
Roduit, 2012 [546]	PC	1,041	Austria, Finland, France, Germany, and Switzerland	**PASTURE**. Population based birth cohort with women recruited in third trimester of pregnancy from rural areas in 5 European countries (Austria, Finland, France, Germany, and Switzerland) and divided into 2 groups: those who lived or worked on family run farms and those not living on a farm from the same area	Infant fat source introduction; fruits and vegetables; Cereal; bread; chocolate; cake; Farm milk' - either boiled or not boiled; meat, D	1, 4	AD (DD)
Rothers, 2011 [547]	PC	208	US	**IIS.** Prospective birth cohort study of healthy children born to pregnant women who planned to obtain care for their new-borns from collaborating paediatricians	Vitamin D cord blood, S	1, 2, 3, 5	RC (DD); sIgE aero; SPT aero: Total IgE; Rec wheeze (DD asthma)

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Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Sausenthaler, 2007 [548]; Zutavern, 2006; [178] Zutavern, 2008; [179]	PC	2,540	Germany	**LISA.** Population based cohort study of newborns recruited between 1997 and1999 from 4 German cities: Munich, Leipzig, Wesel, and Bad Honnef	Maternal fat intake; maternal fish intake; fruits; vegetables; apples; bananas; strawberries; citrus fruits; fruit juice; cabbage; salad; celery; sweet peppers; spinach; nuts; carrots; seeds; tomatoes; cereal, milk, cheese; yoghurt, Q	1, 2, 6	AD (DD, parent reported), AS (any, food, aeroallergen by sIgE)
Sicherer, 2010 [138]	PC	503	USA	**The Consortium of Food Allergy Research** enrolled infants at 3 to 15 months of age with likely egg or milk allergy but without previously known peanut allergy	Peanut, Q	1	sIgE to peanut
Strassburger, 2010 [155]	PC	338	Brazil	Birth cohort study nested in a dietary intervention randomized field trial in the city of São Leopoldo, southern Brazil in 2002	Salty pureed food; fruit juice, R	3.5	SPT aero; Wheeze (parent reported)
Venter, 2009; [168] Dean, 2007 [549]	PC	937	UK	**The Isle of Wight cohort.** Population based birth cohort recruited through antenatal clinics and included all babies born on the Isle of Wight UK between 2001 and 2002	Maternal allergenic food avoidance, Q	2	AS peanut (SPT)
Wang, 2007 [144]	PC	1,760	Taiwan	**Taiwan National Birth Cohort Study** (Pilot study). Representative samples recruited post-natally using the national birth registration data in 2003	Maternal mineral supplement; maternal seafood intake/ fish oil supplementation ; gingseng, Q	0.5	AD (DD)
Weisse, 2012 [550]	PC	272	Germany	**LINA.** Population based birth cohort with mother–child pairs recruited between 2006 and 2008 in Leipzig	Maternal plasma Vitamin D and Vitamin D cord blood, S	1, 2	AD (DD, parent reported); FA any (DD, Total IgE; sIgE)

Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
West, 2012 [551]	PC	319	Australia	Mother-infant pairs from a pregnancy cohort, recruited in Perth, Western Australia from 2005 to 2008. Pregnant women with a family history of allergic diseases recruited to participate in a postnatal infant dietary intervention study	Maternal mineral and vitamin intake, Q	1	AD (DD); FA any (history of reaction to food plus positive SPT-food; SPT any) Wheeze (DD)
Whitrow, 2009 [552]	PC	490	Australia	**Generation 1.** Population based birth cohort of women and their children recruited in the first 16 weeks of pregnancy between 1998 and 2000 from 4 antenatal clinics in Adelaide	Maternal vitamin intake, Q	3.5, 5.5	Rec wheeze (DD asthma)
Calvani, 2006 [553]	RC	988	Italy	**APAL**. Children attending outpatients allergy clinic in Rome between 2001-2002	Maternal fat intake, Q		AS aero, food, cow's milk, egg (SPT)
Jones, 2012 [554]	RC	231	Western Australia	Children with family history of atopy derived from a larger birth cohort in 2002-2009	Maternal vitamin supplement [any] and Vit D cord blood, S, Q	1	AD (DD or evidence of typical skin lesions) ; FA any (history of reaction to food plus positive SPT-food); Rec wheeze (unclear)
Allen, 2013 [555]	NCC	2,758/ 240	Australia	**HealthNUTS.** Cases & controls recruited from population-based sampling from governmental immunisation clinics in Melbourne	Infant plasma Vitamin D, S, Q	1	AD (DD); FA any, egg, peanut (DD with OFCs)
Sariachvili, 2010 [60]	NCC	557/ 252	Belgium	**PIPO Cohort.** cases and controls with data regarding development of AD and timing of introduction of solid foods were identified from this PC	Fruits, fruit juice, vegetables; cereal meat, Q	4	AD (parent reported, ISAAC Q)
Binkley, 2011 [556]	CC	1,413/ 1,300	Canada	Cases & controls were anaphylaxis registry's previous survey respondents, all having had previous anaphylactic food allergy reactions, although only cases to peanuts	Maternal vitamin supplement [any]; maternal allergenic food avoidance, Q	<18	FA peanut (DD)

S1_Tables

Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Dai, 1993 [557]	CC	70	China	Children from the community and they had to reside there the last year	Maternal allergenic food avoidance [more than one food group]: any, Q	0.5	Rec wheeze (unclear)
DesRoches, 2010 [191]	CC	401/ 202	Canada	Cases and controls were recruited from the Paediatric University Centre between 1998-2004	Allergenic food avoidance (nut); allergenic food avoidance (soya); allergenic food avoidance (peanut), Q	<1.5	FA peanut (history of a clinical reaction within 60 minutes of exposure to peanuts, combined with positive IgE and/or SPT to peanut)
Fox, 2009 [193]	CC	293/ 133	UK	Cases and controls from specialist food allergy clinics, with cases sensitised to peanut and controls sensitised to egg but not peanut	Peanut, Q	<4	FA peanut (DD DBPCFC)
Lopez Campos, 2001 [558]	CC	75/58	Mexico	Asthmatic patients were recruited from Allergy clinics and control patients from familial medicine clinics of Hospital de Especialidades, Mexico	Chocolate; mango, Q	6-10	Rec wheeze (DDA asthma)
Mullins, 2012 [559]	CC	115/ 115	Australia	Cases were peanut allergic patients born in Australian Capital Territory and population matched-controls: Australia	Infant plasma vitamin D, S	6	FA peanut (history of acute systemic allergic reaction within 2 hours of known food exposure, combined with a SPT to the relevant food)
Oliveti, 1995 [201]	CC	263/ 131	USA	Cases & controls were identified from rosters of patients followed up at the Rainbow Babies & Children's Hospital continuity care clinic, Ohio	Alcohol, R	4-9	Rec wheeze (DD asthma)
Salam, 2005 [560]	CC	691/ 279	USA	Children's Health Study: cases and controls selected from school-children who participated in a population-based study: USA	Maternal fat intake, Q	9-16	Re wheeze (DD asthma)
Castro-Rodriguez, 2010 [218]	CS	1,409/ 594	Spain	**EISL**: Spanish population attending primary healthcare clinics, cases with wheeze in first year of life and controls without: Spain	Maternal fat intake; Mediterranean diet; 'industrial food', Q	1.4	Wheeze (SAAC)

Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
de Batlle, 2008 [561]	CS	1,476/ 402	Mexico	Participants were recruited from a random sample of children in primary school in the Mexicali province, Mexico	Dietary pattern intake in pregnant mothers, Q	6-7	Wheeze and rec wheeze (parent reported); RC (parent reported)
Dela Bianca, 2012 [562]	CS	467	Brazil	Participants were infants aged from 12 to 15 months who attended 9 selected health centres for routine immunisations.	Processed food, Q	1	Rec wheeze (parent reported ≥1 episode of wheezing in the past year)
Riedler, 2001 [563]	CS	812/ unclear	Austria, Germany, and Switzerland	**ALEX STUDY TEAM**: cases were children of farming families and controls of non-farming families from the study schools: Austria, Germany, & Switzerland	Farm milk/environment, I	9	AD (DD); RC (parent reported); sIgE aero; Rec wheeze (DD asthma; asthma ≥1 episode of wheezing in the past year)

AD: atopic dermatitis; AS: allergic sensitisation; AR: allergic rhinitis; ARC: allergic rhinoconjunctivitis; BHR bronchial hyper-responsiveness; CC: case-control study; CS: cross-sectional study; DBPCFC: double blind placebo-controlled food challenge; DD: Doctor diagnosis (community); FA: food allergy; FEV_1: forced expiratory volume in 1 second; ISAAC International Study of Allergy and Asthma in Children; LF lung function; OFCs oral food challenges; PC: Prospective cohort study; PEF: peak expiratory flow; Physician assessment is assessment by study physician; Q: questionnaire; SPT: skin prick test, sIgE specific IgE.

Table S6 Characteristics of included observational studies of other maternal or infant dietary exposures and risk of autoimmune disease

Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Brekke, 2007 [564] Brekke, 2010 [565]; Wahlberg, 2006; [566]	PC	8,694	Sweden	**ABIS:** Population based birth cohort of children born in Southeast Sweden between 1997 and 1999	Infant vitamin intake [any] and maternal vitamin supplement [any]; potatoes and root vegetables; other vegetables; coffee, Q	1, 2.5, 8.4, 17	TIDM (serology); CD (DD + IgA-tTG +symptoms)
Fronczak, 2003 [249]; Lamb 2008 [252]; Simpson, 2011[567]; Norris, 1996 [568]; Frederikson, 2012 [248]; Lamb, 2013; [250]	PC; NCC	222,222/ 16 1698/49	USA	**DAISY**: Prospective birth cohort of children at increased risk for TIDM recruited 1993 to 2004 in Denver, Colorado. Cases & their non-diabetic siblings, as controls, taken from diabetes care clinics & Colorado IDDM registry	Maternal vitamin intake; maternal fish intake; infant plasma vitamin D; fruits; vegetables; potatoes; root vegetables, Q	4, 9, 15	CD (positive IgA-tTG on 2 visits or a positive small bowel biopsy and one tTG-positive); TIDM (serology)
Hypponen, 2004 [498] Hypponen, 2001 [499]	PC	10,366/81	Finland	**Northern Finland Birth Cohort:** Population based birth cohort with women recruited between the 24th and 28th week of gestation in Oulu and Lapland in 1995-1966	Infant vitamin intake [any], Q	31, 2	TIDM (DD)

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Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Nwaru, 2010, 2011, 2012 and 2013 [105,535,537] [534] [106]; Niinisto, 2012 [538]; Lumia, 2011 [539] ; Erkkola, 2012 [107]; Virtanen, 2006 and 2011 [569,570]; Uusitalo, 2008; [541]	PC	3,730	Finland	**DIPP**: Prospective birth cohort of children at high risk of TIDM (HLA genotype conferred susceptibility) born between 1997 and 2004 in Oulu and Tampere University Hospital Finland	Maternal fish and margarine intake; infant fish intake; Wheat , Rye, Oats, Barley, Other cereals (maize, rice, millet, and buckwheat); cereal; Other cereals (maize, rice, millet, and buckwheat); milk; milk and dairy; cheese; meat; egg; alcohol; rice; tea; coffee; chocolate; chocolate and sweets; dairy, Q	0.5, 5, <10	TIDM (serology; DD WHO criteria))
Harsunen, 2012 [571]	NCC	33/33	Germany	**BABYDIET study**: cases were study children who developed islet autoantibodies and TIDM during BABYDIET study follow-up and controls were children from the same original study cohort who did not: Germany	Dietary energy intake, D	<18	TIDM (DD)
Miettinen, 2012 [572]	NCC	686/343	Finland	All selected from the Finnish Maternity Cohort, with cases identified from the Finnish Diabetes Register	Maternal plasma Vitamin D, I	3.4	TIDM (DD)
Savilahti, 2009 [268]	NCC	6,209/45	Finland	Cases and controls taken from the NHI database, Finland	Vegetables, R/D	11.5	TIDM (DD)
Sørensen, 2012 [573]	NCC	328/109	Norway	Cases and controls selected from a population birth cohort linked to Norwegian Childhood Diabetes Registry	Maternal plasma Vitamin D, S	<15	TIDM (DD)
Ahadi, 2011 [269]	CC	202/101	Iran	Cases were diagnoses of TIDM referred to Children's Medical Centre Hospital and matched controls	Infant vitamin intake [any], Q	6.7	TIDM (DD)
Ashraf, 2010 [271]	CC	195	USA	Cases and controls selected from electronic medical records	Infant mineral intake, Q	10	TIDM (DD)

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Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Baron, 2005 [321]	CC	444/222	France	Cases with Crohn's disease were identified from the **EPIMAD** registry with matched controls from the same area identified by random digit dialling: France; Cases with ulcerative colitis were identified from the EPIMAD registry with matched controls from the same area	Vegetables ; flour meat, I	<17	IBD-CR (DD); IBD-UC (DD)
Ellis, 2012 [326]	CC	655/246	Australia	**CLARITY:** cases were recruited during a clinic visit to Royal Children's Hospital, with diagnosed JIA using ILAR criteria: controls were patients in for elective surgery, also at the Royal Children's Hospital Day Surgery Unit	Maternal iron, multivitamin, folate, calcium, fish oil, vitamin D supplement; alcohol; coffee, Q	0-18	JIA (DD; ILAR criteria)
Bener, 2009 [273]	CC	340/170	Qatar	Cases were insulin dependent or had a venous blood glucose >6.7mmol/L on 2 occasions with matched healthy controls selected from the community	Infant vitamin intake [any], I/Q	<16	TIDM (DD)
EURODIAB substudy 2 study group, 1999 [574]	CC	2,934/746	Luxembourg, N. Ireland, Romania, Lithuania, Bulgaria and Australia	**EURODIAB**: cases were <15years at TIDM diagnosis and matched with population-based controls.	Infant vitamin intake [any], I/Q	<15	TIDM (DD; WHO criteria)
Gilat, 1987 [330]	CC	504/167	9 countries: USA, Canada, UK, Sweden, Denmark, Holland, France, Italy, Israel	**The International IBD Study Group**: cases were patients with proven Crohn's Disease in 14 centres across 9 countries with 2 controls per case, one with a different minor GI disease and the other with minor non-GI disease taken from hospitals or clinics.	Maternal vitamin supplement [any], Q	<25	IBD-CR (DD); IBD-UC (DD)

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Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Majeed, 2011 [284]	CC	395/96	Iraq	Cases were TIDM patients admitted to hospitals or primary health centres in Basrah and controls were attendees to outpatients of the same institutions for non-diabetic complaints	Coffee; tea, Q	15-17	TIDM (DD)
Malcova, 2005 [285]	CC	2,334/868	Czech Republic	Cases were identified from the Czech Childhood Diabetes Register, with unrelated aged-match controls selected from among the schoolmates of cases	Infant vitamin intake [any], Q	7	TIDM (DD)
Rosenbauer, 2007 and 2008 [295,575]	CC	2,631/760	Germany	German study of newly diagnosed TIDM cases selected from a hospital-based surveillance system ESPED and controls from local registration office records	Coffee, Q	<5	TIDM (DD)
Sipetic, 2003 [576]; Sipetic, 2005 [577]	CC	315/105	Serbia	Cases and controls were children admitted to hospital due to allergic conditions 1994-97	Alcohol; coca cola, nitrosamine-rich foods, coffee, Q	1-16	TIDM (maternal report; DD WHO criteria)
Stene, 2003 [578], Stene, 2008 [579]	CC	2213/545	Norway	**Norwegian Childhood Diabetes Study Group**: cases were all children on the diabetes registry diagnosed 1997-2000 and controls were matched from the national population registry	Infant vitamin intake [any]; infant oil supplement; maternal vitamin/fish supplement [any], Q	8.8	TIDM (DD; WHO criteria)
Stene, 2000 [302]	CC	1131/84	Norway	Cases were TIDM patients in Vest-Agder & on the National Childhood Diabetes Register 1982-98 and controls were selected randomly from the population register for the same age and period	Maternal vitamin supplement [any] ; maternal fish oil supplement, Q	<15	TIDM (DD)
Svensson, 2005 [580]	CC	1152/475	Denmark	Cases identified from the Danish National Register of incident cases diagnosed 1996-99 and matched controls from the Danish Population Register	Infant vitamin intake [any], Q	8.4	TIDM (DD)

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Study	Design	N/n cases	Country	Population	Exposures and method of assessment	Age at outcome (years)	Outcomes reported (method of assessment)
Strotmeyer, 2004; [304]	CC	688/ 247	China	**DiaMond:** WHO Multinational Project; cases selected from TIDM incidence registries 1985-98 and matched controls from local population	Vegetables; fruits; steamed bread; rice; noodles; meat, Q	9.7	TIDM (DD; WHO criteria)
Tenconi, 2007 [307]	CC	429/131	Italy	Cases identified from TIDM population registry 1988-2000 and matched controls selected from hospitalised patients, not affected by metabolic disease or cancer	Maternal vitamin supplement [any], Q	15.5	TIDM (DD)
Virtanen, 1994 [581]	CC	1136/600	Finland	**Childhood Diabetes in Finland**: cases were newly diagnosed TIDM with matched controls selected from the general population	Coffee, Q		TIDM (DD)
Visalli, 2003 [311]	CC	900/150	Italy	**EURODIAB Italy**: Cases with TIDM selected from within the EURODIAB study, born 1977-89, with controls selected from school records for the same period	Infant vitamin intake [any]; fruits, vegetables; meat; tea; coffee, Q	12	TIDM (DD; WHO criteria)

AR: allergic rhinitis; CC: case-control study; CD Coeliac disease; CR Crohn's disease; DD: Doctor diagnosis (community); FA: food allergy; GADA: Glutamic acid decarboxylase antibodies; GI: gastro-intestinal; IA2A: tyrosine phosphatase IA2 antibodies; IAA: insulin autoantibodies; ILAR: International League of Associations for Rheumatology; IBD: inflammatory bowel disease; JIA: juvenile idiopathic arthritis; NCC: nested case-control study; PC: Prospective cohort study; Physician assessment is assessment by study physician; Q: questionnaire; RC: retrospective cohort; SPT: skin prick test; sIgE specific IgE; TIDM: type 1 diabetes mellitus; tTG: Antibodies to tissue transglutaminase; UC: ulcerative colitis ; WHO: World Health Organisation

Table S7 Risk of bias in intervention trials of breastfeeding promotion or solid food introduction and allergic outcomes

Study	Design	N Intervention/ Control	Assessment	Selection	Attrition	Overall Bias	Conflict of Interest
Kramer, 2001 [1]; Kramer, 2007 [2]	cluster RCT	8865/8181	Low	Low	Low	Low	Low

RCT randomised controlled trial

Table S8 Risk of bias in observational studies of breastfeeding or solid food introduction, and risk of allergic outcomes

Study	Design	N/n cases	Assessment	Selection	Confounding	Overall Bias	Conflict of interest
Alho, 1990 [3]	PC	2,130	Unclear	Low	High	High	Low
Allen, 2009 [4]; Koplin, 2010 [5]	PC	310/50	Low	Low	Low	Low	Low
Alm, 2008[6]; Goksor, 2009/11 [7,8]	PC	4,987	Unclear	Unclear	High	High	Low
Bacopoulou, 2009 [9]	PC	6,643	Unclear	Unclear	High	High	Unclear
Benn, 2004 [10]; Linneberg 2006 [11]	PC	34,793	Low	Low	Low	Low	Low
Bergmann, 2000 [12]; Bergmann, 2002 [13] Kulig, 2000 [14]	PC	1,314	Low	High	Low	High	Low
Berth-Jones, 1997 [15]	PC	413	Unclear	Low	High	High	Low
Besednjak-Kocijancic, 2010 [16]	PC	408/24	Unclear	Unclear	High	High	Unclear
Bisgaard, 2009 [17]; Giwercman, 2010 [18]	PC	354	Low	Low	Low	Low	Low
Burr, 1989; Burr, 1993; Burr, 1993 (b) [19-21]; Burr, 1997 [22]	PC	483	Low	Low	Low	Low	Low

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Study	Design	N/n cases	Assessment	Selection	Confounding	Overall Bias	Conflict of interest
Burgess, 2006 [23]	PC	4,964	Low	Low	Low	Low	Low
Businco, 1987 [24]; Bruno, 1995 [25]	PC	244	Low	Low	Low	Low	Low
Cano Garcinuno, 2003 [26]	PC	234	Unclear	Low	Low	Unclear	Low
Caudri, 2013; Scholtens, 2009 [27,28]; Kerkhof, 2003 [29]	PC	3,115	Low	Low	Low	Low	Low
Cogswell, 1987 [30]	PC	73/32	Unclear	Low	High	High	Low
Chuang, 2011[31]	PC	18,773	Low	Low	Low	Low	Low
da Costa Lima, 2003; Menezes, [32,33]	PC	4,297	Low	High	Low	High	Low
Dell, 2001; Midodzi, 2008 [34,35]; Midodzi, 2010 [36]	PC; CS	2,711	Unclear	Low	Low	Unclear	Low
Devereux, 2006 [37]	PC	1,704	Low	Low	Low	Low	Unclear
Dogaru, 2012 [38]	PC	1,458	Low	Low	Low	Low	Low
Elliott, 2008; Granell, 2012; Sherriff, 2001 [39-41]; Abd, 2012 [42]; Lack, 2003	PC	9,100	Low	Low	Low	Low	Low

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Study	Design	N/n cases	Assessment	Selection	Confounding	Overall Bias	Conflict of interest
[43]							
Eneli, 2006 [44]	PC	536	Low	Low	Low	Low	Unclear
Farooqi, 1998 [45]	PC	1,453	Low	High	Low	High	Low
Fergusson, 1983; Horwood, 1995 [46,47]	PC	1,110	Low	Low	Low	Low	Low
Fredriksson, 2007 [48]	PC	1,933	Low	Low	Low	Unclear	Low
Forster, 1990[49]	PC	145	Unclear	Low	Unclear	Unclear	Low
Galbally, 2013 [50]	PC	4,507	Low	Low	Low	Low	Low
Gruber 2010 [51]	PC	167/15	Low	Low	High	High	High
Gruskay 1982 [52]	PC	328 FH+/ 580 FH-	Unclear	High	High	High	Low
Guida, 2009 [53]	PC	3,041	Unclear	Unclear	Low	Unclear	Low
Gustafsson, 2000 [54]	PC	94	Unclear	Low	Low	Unclear	Low
Halken, 1991[55]	PC	276	Low	Low	Low	Low	Low
Harris, 2001[56]; Zutavern, 2004 [57]	PC	622	Low	Low	Low	Low	Low
Hagendorens, 2005 [58]; Sariachvili,	PC	693	Unclear	Low	Low	Unclear	Low

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Study	Design	N/n cases	Assessment	Selection	Confounding	Overall Bias	Conflict of interest
2007 [59]; Sariachvili 2010 [60]							
Hesselmar, 2010 [61]	PC	184	Low	Low	High	High	Low
Hetzner, 2009 [62]	PC	7,900	Unclear	Low	High	High	Low
Hide, 1981[63]; Arshad, 1992 [64]	PC	843	Low	Low	Low	Low	Low
Hikino, 2001[65]	PC	21,766/2,381	Unclear	Low	Low	Unclear	Low
Hong, 2011 [66]	PC	970/361	Low	Unclear	Low	Unclear	Low
Hoppu, 2002 [67]	PC	114/27	Low	Low	High	High	Low
Host, 1991 [68]	PC	315/16	Unclear	Low	High	High	Unclear
Howie, 1990 [69]	PC	618	Low	Low	Low	Low	Low
Huang, 2013 [70]	PC	684	Unclear	Low	High	High	Low
Huurre, 2008 [71]	PC	98/29	Low	Low	Low	Low	Unclear
Joseph, 2011 [72]	PC	594/178	Unclear	Low	Low	Unclear	Low
Juto, 1980 [73]	PC	56/NA	Unclear	Low	High	High	Unclear
Kajosaari, 1991[74]	PC	135	Low	Unclear	High	High	Low

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Study	Design	N/n cases	Assessment	Selection	Confounding	Overall Bias	Conflict of interest
Karmaus, 2008 [75]; Ogbuanu, 2009 [76]; Soto-Ramırez, 2012 [77]	PC	1,336	Low	Low	Low	Low	Low
Kaufman, 1976 [78]	PC	94	Unclear	Low	High	High	Low
Kellberger, 2012 [79]	PC	594/178	Unclear	Low	Low	Unclear	High
Kemeny, 1991[80]	PC	180	Unclear	Low	High	High	Unclear
Kerr, 1981[81]	PC	269	Unclear	Low	High	High	Low
Kim, 2011 [82]	PC	1,177/61	Unclear	Low	Low	Unclear	Low
Kitz, 2006 [83]	PC	131	Unclear	Low	High	High	Unclear
Klinnert, 2001 [84]	PC	145	Low	Low	Low	Low	Low
Kramer, 2003; Kramer, 2009; Kramer, 2009 (b) [85-87]	PC	13,889/455	Unclear	Low	Low	Unclear	Low
Kull, 2002 [88]	PC	3790	Low	Low	Low	Low	Low
Kusel, 2005 [89]	PC	263/107	Unclear	Low	Low	Unclear	Unclear
Larsson, 2008 [90]	PC	4779	Low	Low	Low	Low	Low
Marini, 1996 [91]	PC	Unclear	Unclear	Low	Low	Unclear	Unclear

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Study	Design	N/n cases	Assessment	Selection	Confounding	Overall Bias	Conflict of interest
Matheson, 2007 [92]	PC	5,729/2,610	Unclear	Low	Low	Unclear	High
Midwinter, 1987 [93]	PC	453	Unclear	Low	Low	Unclear	Unclear
Mihrshahi, 2007 [94]	PC	516	Low	Low	Low	Low	Low
Milner, 2004 [95]	PC	8,071	Low	Unclear	Low	Unclear	Low
Miskelly, 1988 [96]	PC	482	Low	Low	High	High	Low
Miyake, 2008 [97]; Miyake, 2009 [98]	PC	763	Low	High	Low	High	Low
Morgan, 2004; Morgan, 2004 (b) [99,100]	PC	257	Low	Low	Low	Low	Low
Moore, 1985 [101]	PC	475	Low	Low	Low	Low	Low
Morales, 2012 [102]	PC	467	Unclear	Low	Low	Unclear	Low
Muiño, 2008 [103]	PC	897	Low	Low	High	High	Low
Nielsen, 2013 [104]	PC	5,429	Low	Low	Low	Low	Low
Nwaru, 2010 [105]; Erkkola, 2012; Nwaru, 2013 [106,107]; Virtanen, 2010 [108]	PC	3,675	Low	Low	Low	Low	Low

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Study	Design	N/n cases	Assessment	Selection	Confounding	Overall Bias	Conflict of interest
Oddy, 2003 [109]	PC	243	Low	Unclear	High	High	Low
Oddy, 1999; Oddy, 2003; Oddy, 2004 [110-112]	PC, NCC	2,456	Low	Low	Low	Low	Low
Odelram, 1996 [113]	PC	70/23	Unclear	Low	High	High	Unclear
Perez Tarazona, 2010 [114]	PC	620	Unclear	Low	High	High	Low
Pesonen, 2006 [115]	PC	160	Low	Low	Low	Low	Low
Porch, 1998 [116]	PC	130	Low	Low	High	High	Low
Poysa, 1990; Poysa, 1992 [117,118]	PC	68	Unclear	Low	High	High	Unclear
Pratt, 1984 [119]	PC	198	Low	Low	High	High	Low
Puig, 2010 [120]	PC	368	Low	Low	Low	Low	Low
Purvis, 2005 [121]	PC	550	Unclear	High	Low	High	Low
Rhodes, 2001[122]	PC	63	Unclear	High	High	High	Low
Rothenbacher, 2005 [123]	PC	803	Low	Low	Low	Low	Low
Rowntree, 1985 [124]	PC	80/20	Unclear	Low	High	High	Unclear
Rullo, 2007; Rullo,	PC	101	Low	Low	Low	Low	Low

Study	Design	N/n cases	Assessment	Selection	Confounding	Overall Bias	Conflict of interest
2009; Rullo, 2009 (b); Rullo, 2010 [125-128]							
Ruiz 1992 [129]	PC	39	Unclear	High	High	High	Low
Saarinen, 1995 [130] Saarinen, 1979 [131]	PC	Unclear	Unclear	Low	High	High	Unclear
Sears, 2002 [132]; Mandhane 2007 [133]	PC	1,037	Low	Low	High	High	Low
Shaheen, 1996 [134]	PC	395/44	Unclear	Unclear	Low	Unclear	Low
Shohet, 1985 [135]	PC	368	Unclear	Low	High	High	Unclear
Schoetzau, 2002 [136]	PC	829	Low	High	Low	High	Low
Schonberger, 2005 [137]	PC	443	Low	Low	Low	Low	Low
Sicherer, 2010 [138]	PC	503/140	Unclear	Low	High	High	Low
Siltanen, 2003 [139]	PC	285/53	Unclear	Low	High	High	High
Silva, 2005 [140]	PC	73	Unclear	Unclear	High	High	Unclear
Silvers, 2009; Silvers, 2011 [141,142]	PC	889/249	Low	Low	Low	Low	Low
Simon, 2008 [143] ; Wang, 2007[144];	PC	372	Low	Low	Low	Low	Low

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Study	Design	N/n cases	Assessment	Selection	Confounding	Overall Bias	Conflict of interest
Wegienka, 2006 [145]; Salam, 2003 [146]							
Snijders, 2007; Snijders, 2008 [147,148]	PC	2,505	Low	Low	Low	Low	Low
Soto-Ramirez, 2013 [149]	PC	2,833	Low	High	Low	High	Low
Strachan, 1997 [150]; Strachan, 1996 [151]; Lewis, 1995; Lewis, 1996 [152,153]; Butland, 1997 [154]	PC	1,369/730	Low	Low	Low	Low	Unclear
Strassburger, 2010 [155]	PC	325/94	Unclear	Low	Low	Unclear	Low
Sunyer, 2006 [156]	PC	462	Low	Low	Low	Low	Low
Sunyer, 2001 [157]	PC	596	Low	Unclear	Low	Unclear	Low
Taylor, 1983 [158] ; Taylor, 1984 [159]	PC	12,608	Low	Low	Low	Low	Low
Tennant, 2008 [160] Tennant, 2010 [161]	PC	392	Low	Low	Low	Low	Low
Tian, 2009 [162]	PC	472	Unclear	Low	Low	Unclear	Low
Van Asperen, 1983 [163]	PC	79/44	Unclear	Low	High	High	Low

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Study	Design	N/n cases	Assessment	Selection	Confounding	Overall Bias	Conflict of interest
Van Beijstervelft, 2008 [164]	PC	24,018	Low	Low	Low	Low	Low
van der Voort, 2012 [165]	PC	5,368	Low	Low	Low	Low	Low
Vandenplas, 1988 [166]	PC	75	Unclear	Low	High	High	Unclear
van Merode, 2007 [167]	PC	222	Low	Low	Low	Low	Low
Venter, 2009 [168]	PC	891/58	Unclear	Low	High	High	Low
Watson,2013 [169]	PC	369	Low	Low	High	High	Low
Wetzig, 2000 [170]	PC	475	Low	Low	High	High	Low
Wilson, 1998 [171]	PC	545	Low	Low	High	High	Low
Wright, 2002 [172]	PC	499	Low	Low	Low	Low	Low
Wright, 1989; Wright, 1995 [173,174]; Wright, 1999 [175]; Wright, 1994 [176]	PC	988	Unclear	Low	Low	Unclear	Low
Yamamoto, 2011 [177]	PC	1,344	Unclear	Low	High	High	Low
Zutavern, 2006; Zutavern, 2008 [178,179]	PC	606	Low	Low	Low	Low	Low
Friday, 2000 [180]	RC	94	Unclear	Low	High	High	Low

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Study	Design	N/n cases	Assessment	Selection	Confounding	Overall Bias	Conflict of interest
McConnochie, 1986 [181]	RC	223	Low	Low	Low	Low	Low
Monego, 1989 [182]	RC	144	Low	Low	High	High	Low
Rona, 2005 [183]	RC	1,213	Unclear	Low	Low	Unclear	Low
Mai, 2007 [184]	NCC	723	Low	Low	Low	Low	Low
Martel, 2008 [185]	NCC	1,578	Unclear	High	Low	High	Low
Maskell, 2010 [186]; Oliver, 2010 [187]; Munro, 2011 [188]	PC; NCC	700	Low	Unclear	Unclear	Unclear	Low
Ronmark, 1999 [189]	NCC	258	Unclear	Low	Low	Unclear	Low
Camara, 2003 [190]	CC	91	Unclear	Low	High	High	Low
DesRoches, 2010 [191]	CC	403/202	Unclear	Low	Unclear	Unclear	Low
Djenouhat, 2011 [192]	CC	450	Unclear	Unclear	Unclear	Unclear	Low
Fox, 2009 [193]	CC	283/133	Low	Unclear	High	High	Low
Ghaderi, 2014 [194]	CC	200	Low	Unclear	High	High	Low
Haileamlak, 2005 [195]	CC	732	Unclear	High	Low	High	Low

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Study	Design	N/n cases	Assessment	Selection	Confounding	Overall Bias	Conflict of interest
Infante-Rivard, 1993 [196]	CC	914	Unclear	Low	Low	Unclear	Low
Juca, 2012 [197]	CC	590	Low	Low	High	High	Low
Karunasekera, 2001 [198]	CC	582	Unclear	Unclear	Low	Unclear	Low
Kramer, 1981 [199]	CC	470	Low	Low	High	High	Low
Mavale-Manuel, 2003 [200]	CC	199	High	Unclear	High	High	Low
Oliveti, 1995 [201]	CC	262	Low	Unclear	High	High	Low
Porro, 1993 [202]	CC	465	Unclear	Low	High	High	Low
Ratageri, 2000 [203]	CC	180	Low	Low	Low	Low	Low
Rosas Vargas 2002 [204]	CC	148	Unclear	Low	High	High	Low
Rylander 1993 [205]	CC	550	Unclear	Low	Low	Unclear	Unclear
Ventura, 1988 [206]	CC	339/148	Unclear	Unclear	High	High	Low
Whu, 2007 [207]	CC	261	Low	Low	Low	Low	Unclear
Wickens, 2001 [208]	CC	474	Low	Low	Low	Low	Low
Zhu, 2012 [209]	CC	542	Unclear	High	High	High	Low

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Study	Design	N/n cases	Assessment	Selection	Confounding	Overall Bias	Conflict of interest
Alper, 2006 [210]	CS	858	Unclear	Low	Low	Unclear	Low
Al-Kubaisy, 2005 [211]	CS	2,262	Unclear	Low	High	High	Unclear
Awasthi, 2004 [212] Björkstén, 2011 [213] ; Flohr, 2011 [214] Nagel, 2009 [215]; Kuyucu, 2004 [216]	CS	2,471	Unclear	Unclear	Low	Unclear	Low
Berjon, 1987 [217]	CS	2,690/148	Unclear	Unclear	High	High	Low
Castro-Rodriguez, 2010 [218]; Chong Neto, 2007 [219]	CS	3,003	Low	Low	Low	Low	Low
Civelek, 2001[220]	CS	1533	Unclear	Low	Low	Unclear	High
Ehlayel, 2008 [221]	CS	1,278	Low	Low	Low	Low	Low
Ehrlich, 1996 [222]	CS	620	Unclear	Low	Low	Unclear	Low
Evenhouse, 2005 [223]	CS	16,903	Unclear	Low	Low	Unclear	Low
Girolomoni, 2003 [224]	CS	1,369	Unclear	High	High	High	Low
Han, 2009 [225]	CS	21,371	Unclear	High	Low	High	Low

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Study	Design	N/n cases	Assessment	Selection	Confounding	Overall Bias	Conflict of interest
Karino, 2008 [226]	CS	9,615	Unclear	Low	Low	Unclear	Low
Kucukosmanoglu, 2008 [227]	CS	1,015/20	Unclear	High	High	High	Low
Kuehr, 1992 [228]	CS	1,470/201	Unclear	High	High	High	Unclear
Kurt, 2008 [229] Kurt, 2007 [230]	CS	25,843	Low	Low	Low	Low	Low
Liu 2012 [231]	CS	8733	Unclear	Unclear	High	High	Unclear
Miyake, 2003 [232]	CS	6,845	Unclear	High	Low	High	Low
Nakamura, 1999 [233]	CS	3,850	Unclear	Low	Low	Unclear	Low
Paton, 2012 [234]	CS	15,142/592	Low	Unclear	High	High	Low
Prietsch, 2006 [235]	CS	685	Unclear	Unclear	High	High	Unclear
Rusconi, 1999; Rusconi, 2005 [236,237]	CS	16,933	Unclear	Low	High	High	Low
Rust, 2001 [238]	CS	6,783	Unclear	Low	Low	Unclear	Low
Salem, 2002 [239]	CS	424	Low	High	High	High	Low
Selcuk, 1997 [240]	CS	5,412	Low	Low	Low	Low	Low

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Study	Design	N/n cases	Assessment	Selection	Confounding	Overall Bias	Conflict of interest
Suwanpromma, 2012 [241]	CS	215	Unclear	Low	High	High	Low
Takemura, 2002 [242]	CS	23828	Unclear	Low	Low	Unclear	Low
Tanaka, 2009 [243]	CS	1957	Unclear	Unclear	Unclear	Unclear	Unclear
Visser, 2010 [244]	CS	1115	Unclear	Low	Low	Unclear	Low
Wang, 2006 [245]	CS	8733	Low	Low	High	High	Low

CC Case Control study; CS Cross-sectional study; NCC Nested Case Control study; PC Prospective Cohort; RC Retrospective Cohort

Table S9 Risk of bias in observational studies of breastfeeding or solid food introduction, and risk of autoimmune diseases

Study	Design	N/n cases	Assessment	Selection	Confounding	Overall Bias	Conflict of interest
Couper, 1999 [246]; Couper, 2009 [247]	PC	317/70	Unclear	Unclear	High	High	Low
Frederikson, 2012 (abstract) [248]; Fronczak, 2003 [249]; Lamb, 2013 [250]; Norris, 2003 [251]; Lamb 2008 [252]	PC	1,698	Low	Low	Low	Low	Low
Holmberg, 2007 [253]; Karlen, 2012 [254]; Wahlberg, 2006 [255]	PC	3788/~51	Low	Low	Low	Low	Low
Ludvigsson, 2003 [256]	PC	205	Unclear	Low	Low	Unclear	Unclear
Viner, 2008 [257]	PC	11211/61	Unclear	High	Low	High	Low
Virtanen, 1992 [258]; Virtanen, 1998 [259]; Hypponen, 1999 [260]; Virtanen, 2000 [261]	PC, NCC	697/43	Low	Low	Low	Low	Low
Virtanen, 2011 [262]	PC	~4000/~160	Unclear	Low	High	High	Low
Jones, 1998 [263]	NCC	518/60	Low	High	High	High	Low
Kimpimaki, 2001 [264]	NCC	455/65	Unclear	High	Low	High	Low

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Study	Design	N/n cases	Assessment	Selection	Confounding	Overall Bias	Conflict of interest
Kyvik, 1992 [265]	NCC	228/76	Low	Unclear	High	High	Low
Norris, 1996 [266];	NCC	171/18	Low	Low	Low	Low	Low
Robertson, 2010 [267]	NCC	1444/361	Low	Unclear	Low	Unclear	Low
Savilahti, 2009 [268]	NCC	6209/45	Low	High	High	High	Low
Ahadi, 2011 [269]	CC	202/101	Unclear	Unclear	Low	Unclear	Low
Alves, 2012 [270]	CC	246/123	Unclear	Unclear	Low	Unclear	Low
Ashraf, 2010 [271]	CC	195/128	Unclear	High	High	High	Low
Baruah, 2011 [272]	CC	86/43	Unclear	Unclear	High	High	Low
Bener, 2009 [273]	CC	340	Unclear	Unclear	High	High	Low
Blom, 1989 [274]	CC	867/339	Unclear	Low	High	High	Low
Bodington, 1994 [275]	CC	393/209	Unclear	High	High	High	Low
Borras, 2011 [276]	CC	1530/306	Unclear	Unclear	High	High	Low
Dahlquist, 2002 [277]	CC	2226/610	Unclear	Low	Low	Unclear	Low
Esfarjani, 2001 [278]	CC	104/52	Low	Unclear	High	High	Low

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Study	Design	N/n cases	Assessment	Selection	Confounding	Overall Bias	Conflict of interest
Gimeno, 1997 [279]	CC	626/313	Low	Low	Low	Low	Low
Hathout, 2006 [280]	CC	402/102	Unclear	Unclear	Unclear	Unclear	Low
Kostraba, 1992 [281]; Kostraba, 1993 [282]	CC	264/132-white; 108/54-black	Unclear	Low	High	High	Low
Liese, 2012 [283]	CC	709/505	Unclear	Low	High	High	Low
Majeed, 2011 [284]	CC	310/96	Low	Unclear	Low	Unclear	Low
Malcova, 2006 [285]	CC	2334/868	Unclear	High	Low	High	Low
Marshall, 2004 [286]	CC	577/196	Unclear	Low	High	High	Low
Mayer, 1988 [287]	CC	747/268	Unclear	High	Low	High	Low
McKinney, 1999 [288]	CC	521/196	Unclear	Low	Low	Unclear	Low
Meloni, 1997 [289]	CC	200/100	Unclear	Unclear	Low	Unclear	Low
Patterson, 1994 [290]	CC	1548/258	Low	Unclear	Low	Unclear	Low
Perez-Bravo, 1996 [291]	CC	165/80	Unclear	Unclear	High	High	Low
Perez-Bravo, 2003 [292]	CC	250/143	Unclear	Unclear	High	High	Low
Rabiei 2011 [293]	CC	300/100	Low	Unclear	Low	Unclear	Low

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Study	Design	N/n cases	Assessment	Selection	Confounding	Overall Bias	Conflict of interest
Rami, 1999 [294]	CC	609/114	Unclear	Unclear	High	High	Low
Rosenbauer, 2008 [295]	CC	2631/760	Unclear	High	Low	High	Low
Sadauskaite-Kuehne, 2004 [296]; Skrodeniene, 2010 [297]	CC	1944/803	Low	Unclear	Low	Unclear	Low
Samuelsson, 1993 [298]	CC	1089/297	Unclear	Low	Low	Unclear	Low
Siemiatycki, 1989 [299]	CC	482/161	Unclear	Low	Low	Unclear	Low
Sipetic, 2005 [300]	CC	315/105	Unclear	Low	Low	Unclear	Low
Soltesz, 1994 [301]	CC	305/130	Unclear	Low	Low	Unclear	Low
Stene, 2000 [302]	CC	1156/85	Low	High	Low	High	Low
Stene, 2003 [303]	CC	2213/545	Unclear	Low	Low	Unclear	Low
Strotmeyer, 2004 [304]	CC	485/247	Unclear	Unclear	Low	Unclear	Low
Tai, 1998 [305]	CC	310/117	Unclear	Low	Low	Unclear	Low
Telahun, 1994 [306]	CC	129/55	Low	Unclear	High	High	Low
Tenconi, 2007 [307]	CC	477/159	Unclear	Unclear	Low	Unclear	Low

Study	Design	N/n cases	Assessment	Selection	Confounding	Overall Bias	Conflict of interest
Thorsdottir, 2000 [308]	CC	220/55	Low	Low	Low	Low	Low
Verge, 1994 [309]	CC	475/217	Unclear	Unclear	High	High	Low
Virtanen, 1993 [310]	CC	1380/690	Low	Low	Low	Low	Low
Visalli, 2003 [311]	CC	900/150	Unclear	Low	Low	Unclear	Low
Wadsworth, 1997 [312]	CC	639/276	Unclear	Low	Low	Unclear	Low
Glatthaar, 1988 [313]	CS	946/~200	Unclear	Unclear	Low	Unclear	Low
Hummel, 2000 [314]; Hummel, 2007 [315]; Ziegler, 2003 [316]	PC	1460/~68	Low	Low	Low	Low	Low
Norris, 2005 [317]	PC	1560	Low	High	High	High	Low
Welander, 2010 [318]	PC	9414/~29	Unclear	High	High	High	Low
Ascher, 1997 [319]	CC	81/8	Unclear	Low	High	High	Low
Auricchio, 1983 [320]	CC	437/190	Low	Unclear	High	High	Low
Baron, 2005 [321]	CC	444/222	Unclear	Low	Low	Unclear	Low
Bergstrand, 1983 [322]	CC	616/308	Unclear	High	High	High	Low
Castiglione, 2011 [323]	CC	1030/468	Unclear	Unclear	High	High	Low

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Study	Design	N/n cases	Assessment	Selection	Confounding	Overall Bias	Conflict of interest
Corrao, 1997 [324]	CC	1252/626	Unclear	Unclear	Low	Unclear	Low
Decker 2010 [325]	CC	866/123	Unclear	Low	Low	Unclear	Low
Ellis, 2012 [326]	CC	655/246	Unclear	High	Low	Unclear	Low
Falth-Magnusson, 1996 [327]	CC	336/72	Low	Low	High	High	Unclear
Fort, 1990 [328]	CC	189/59	Unclear	Unclear	High	High	Low
Gearry, 2010 [329]	CC	1253/653	Low	High	Low	High	Low
Gilat, 1987 [330]	CC	1497/499	Unclear	Unclear	Unclear	Unclear	Low
Greco, 1988 [331]	CC	2150/201	Low	Low	High	High	High
Gruber, 1996 [332]	CC	144/54	Low	Unclear	Low	Unclear	High
Hansen, 2011[333]	CC	534/267	Unclear	High	Low	High	Low
Ivarsson, 2002 [334]	CC	1272/392	Low	High	High	High	Low
Koletzko, 1991 [335]	CC	231/93	Low	Low	Low	Low	Low
Mason, 1995 [336]	CC	133/54	Unclear	Low	High	High	Low

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Study	Design	N/n cases	Assessment	Selection	Confounding	Overall Bias	Conflict of interest
Pacilio, 2010 [337]	CC	278/139	Unclear	Unclear	High	High	Low
Peters, 2001 [338]	CC	270/133	Low	High	Low	High	Low
Roberts 2009 [339]	CC	248521/ 90	High	Unclear	High	High	Low
Rosenberg, 1996 [340]	CC	468/137	Unclear	Unclear	High	High	Low
Sonntag, 2007 [341]	CC	1974/1096	Low	High	High	High	Low
Thompson, 1999 [342]	NCC	243/27	Low	Unclear	High	High	Low
Wang, 2013 [343]	CC	2616/1308	Unclear	Unclear	High	High	Low

CC Case Control study; CS Cross-sectional study; NCC Nested Case Control study; PC Prospective Cohort

Table S10 Risk of bias in intervention trials of other interventions and allergic or autoimmune outcomes

Study	Design	N Intervention / Control	Assessment	Selection	Attrition	Overall	Conflict of interest
Falth-Magnusson, 1987 [344] Falth-Magnusson, 1992 [345] Ludvigsson, 2003 [346]	RCT	108/104	High	Unclear	Low	High	Low
Jirapinyo, 2013 [347]	RCT	30/32	Unclear	Unclear	Low	Unclear	Low
Lilja, 1989 [348]	RCT	84/87	Low	Unclear	Low	Unclear	Low
Hattevig, 1990 [349]; Paronen, 2000 [350]; Hattevig, 1999 [351]; Hattevig, 1989 [352]; Sigurs, 1992 [353]	CCT	54/67	Unclear	Unclear	Low	Unclear	Unclear
Herrmann, 1996 [354]	CCT	50/50	Unclear	High	Unclear	High	Low
Kilburn, 1998 [355]	CCT	15/96	Unclear	High	Low	High	Low
Metcalfe, 2016 [582]	RCT	40, 44, 36	Low	Low	High	High	Low
Becker, 2004 [357] Chan-Yeung, 2000 [358] & 2005 [359];Wong, 2013 [360] Protudjer, 2011 [361]; Carlsten, 2013 [362]	RCT	281/268	Low	Low	Low	Low	Low
Hide, 1994 [363] Hide, 1996,[364] Arshad, 1992 [365] Arshad, 2003 [366] Arshad, 2007 [367]	RCT	71/68	Low	Low	Low	Low	Low

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Study	Design	N Intervention / Control	Assessment	Selection	Attrition	Overall	Conflict of interest
Scott, 2012 [368]							
Lovegrove, 1994 [369]	RCT	12/14	Unclear	Unclear	Low	Unclear	Low
Shao, 2006 [370]	RCT	23/23	Low	Unclear	Low	Unclear	Low
Zeiger, 1992 [371] Zeiger, 1989, [372] Zeiger 1994 [373]	RCT	103/185	Low	Low	High	High	Low
Halmerbauer, 2002, 2003 [374,375]	RCT	349/347	Low	Unclear	Low	Unclear	Low
Matthew, 1977 [376]	RCT	27/35	Low	Unclear	Low	Unclear	High
Poysa, 1991 [377] Poysa 1989 [378] Kuikka 1985 [379]	RCT	35/33	Low	Unclear	Low	Unclear	Low
Schonberger, 2005 [137]	RCT	222/221	Unclear	Unclear	Low	Unclear	Unclear
Boyle 2015 [380] [381] Boyle 2016 [382]	RCT	432/431	Low	Low	Low	Low	High
Gruber 2010 [383] Gruber 2015 [384]	RCT	414/ 416	Low	Low	Unclear	Unclear	High
Ivakhnenko 2013 [385]	RCT	129/ 130	Low	Low	High	High	High
Moro 2006 [386], van Hoffen 2009 [387], Arslanoglu 2008 [388] Arslanoglu 2012 [389]	RCT	80/80	Unclear	Low	High	High	Unclear
Sierra, 2015 [390]	RCT	188/ 177	Low	Unclear	High	High	High

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Study	Design	N Intervention / Control	Assessment	Selection	Attrition	Overall	Conflict of interest
Ziegler 2007[391]	RCT	150/ 76	Unclear	Unclear	Low	Unclear	High
Chien, 2016 [392]	RCT	Unclear – outcome reported in 45 (synbiotic), 39 (prebiotic) / 45 (control)	Unclear	Unclear	Unclear	Unclear	Unclear
Kukkonen 2007 [393] Kuitunen 2009 [394] Kukkonen 2011[395]	RCT	610/ 613	Low	Unclear	Low	Unclear	Unclear
Roze 2012 [396]	RCT	48/ 49	Low	Low	Low	Low	High
Van der Aa 2010 [397]	RCT	46/ 44	Low	Low	Unclear	Unclear	High
Abrahamsson 2007 [398] Abrahamsson 2013 [399]	RCT	117/ 115	Unclear	Low	Low	Unclear	High
Allen 2012 [400] Allen 2014 [401]	RCT	220/ 234	Unclear	Unclear	Low	Unclear	Unclear
Boyle 2011 [402]	RCT	125/ 125	Low	Low	Low	Low	Low
Cabana, 2015 [403]	RCT	93/92	Unclear	Unclear	Low	Unclear	Unclear
De Leon 2007 [404] Simon 2007 [405]	RCT	Total = 33	Low	Unclear	Unclear	Unclear	Unclear
Dotterud 2010 [406] Simpson, 2015 [407]	RCT	211/ 204	Low	Low	High	High	Unclear

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Study	Design	N Intervention / Control	Assessment	Selection	Attrition	Overall	Conflict of interest
Enomoto 2014 [408]	CCT	130/36	Unclear	High	High	High	High
Huurre 2008 [409]	RCT	72/ 68	Low	Unclear	Unclear	Unclear	Low
Kalliomaki 2001 [410] Kalliomaki 2003 [411] Kalliomaki 2007 [412] Rautava 2002 [413]	RCT	77/ 82	Low	Low	Unclear	Unclear	Unclear
Kim 2010 [414]	RCT	57/ 55	Low	Low	Low	Low	Unclear
Kopp 2008 [415]	RCT	54/ 51	Low	Low	Low	Low	Unclear
Lau 2012 [416]	RCT	303/ 303	Low	Low	Low	Low	High
Lodinová-Žádníková 2010 [417]	RCT	56/57	Unclear	Unclear	Low	Unclear	Unclear
Lundelin, 2016 [418] Luoto, 2014 [419]	RCT	31 (prebiotic), 31 (probiotic)/ 32 (placebo)	Low	Low	Unclear	Unclear	High
Morisset 2008 [420]	RCT	59/ 56	Unclear	Low	Low	Unclear	Unclear
Niers 2009 [421] Gorissen, 2014 [422]	RCT	78/ 78	Low	Unclear	High	High	High
Ou 2012 [423]	RCT	95/ 96	Low	Unclear	Low	Unclear	Unclear
Taylor 2007 [424], Prescott 2008 [425] Jensen 2012 [426]	RCT	115/ 111	Low	Low	Unclear	Unclear	Low

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Study	Design	N Intervention / Control	Assessment	Selection	Attrition	Overall	Conflict of interest
Rautava 2006 [427]	RCT	38/ 43	Unclear	Unclear	Low	Unclear	Low
Rautava 2012 [428]	RCT	82/ 78	Low	Low	Low	Low	Low
Scalabrin 2009 [429] Scalabrin 2014 [430] Scalabrin 2017 [431]	RCT	95/ 95	Low	Low	High	High	High
Soh 2009 [432] Loo 2014 [433]	RCT	127/ 126	Low	Unclear	Low	Unclear	Unclear
West 2009 [434] West 2013 [435]	RCT	89/ 90	Low	Unclear	Low	Unclear	Low
Wickens 2008 [436] Wickens 2012 [437] Wickens 2013 [438]	RCT	341/ 171	Low	Low	Low	Low	Low
Berman, 2015 [583]	RCT	Unclear – total 114	Unclear	Unclear	Unclear	Unclear	Unclear
Birch, 2010 [440] Foiles, 2015 [441]	RCT	88/ 90	Low	Unclear	High	High	High
Bisgaard, 2016 [584]	RCT	365/371	Low	Low	Low	Low	Low
Harslof, 2014 [443]	RCT	75/ 79	Low	Low	High	High	Low
Lucas, 1999 [444]	RCT	154/155	Unclear	Low	Low	Unclear	High
van Gool, 2003 [445]	RCT	61/ 60	Low	Unclear	Low	Unclear	High
Kitz, 2006 [83]	RCT	55/ 76	Low	Unclear	Low	Unclear	Unclear

Study	Design	N Intervention / Control	Assessment	Selection	Attrition	Overall	Conflict of interest
Linnamaa, 2010 [446]	RCT	151/162	Unclear	Low	Low	Unclear	Low
Mihrshahi, 2003 [447] Peat, 2004 [448] Marks, 2006 [449]	RCT	312/304	Low	Low	Low	Low	Low
Damsgaard, 2007 [450]	RCT	45/ 49	Low	Low	High	High	Low
Palmer, 2012 & 2013 [451,452] Best, 2015 & 2016 [453,454]	RCT	368/338	Low	Low	Low	Low	Low
Dunstan, 2003 [455]	RCT	52/ 46	Low	Low	Low	Low	Low
D'Vaz, 2012 [456]	RCT	218/202	High	Low	Unclear	High	Low
Furuhjelm, 2009 [457] Furuhjelm, 2011 [458]	RCT	70/ 75	Low	Low	Low	Low	Unclear
Lauritzen, 2005 [459]	RCT	62/ 60	Unclear	Unclear	High	High	Low
Olsen, 2008 [460] Hansen, 2017 [461]	RCT	266/267	Unclear	Unclear	Low	Unclear	Low
Dotterud, 2013 [462]	RCT	2,860/5,743	Low	High	Unclear	High	Low
Imhoff- Kunsch, 2011 [463]	RCT	547/547	Low	Low	Low	Low	Low
Noakes, 2012 [464]	RCT	62/61	Low	Low	Unclear	Unclear	Low
Aage, 2015 [465]	RCT	2145/ 2200	Low	Low	High	High	Low

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Study	Design	N Intervention / Control	Assessment	Selection	Attrition	Overall	Conflict of interest
Chawes, 2016 [442]	RCT	315/308	Low	Low	Low	Low	Low
Checkley, 2010 [466] Checkley, 2011 [467]	cluster RCT	803, 885, 771	Low	Unclear	High	High	Low
Czeizel, 1994 [468]; Dobo, 1998 [469]	RCT	2090/2032	Low	Unclear	Low	Unclear	Low
Devakumar, 2015 [470]	RCT	600/600	Low	Low	High	High	Unclear
Grant, 2016 [471]	RCT	173/ 87	Low	Low	Low	Low	Low
Greenough, 2010 [472]	RCT	1199/1205	Unclear	Unclear	High	High	Low
Goldring, 2013 [473]	RCT	120/60	Low	Low	Low	Low	Low
Kiraly, 2013 [474]	RCT	227/235	Unclear	Low	High	High	Low
Litonjua, 2016 [475]	RCT	Unclear – 881 total	Low	Low	Low	Low	Low
McEvoy, 2014[476]	RCT	89/90	Low	Low	Low	Low	Low

RCT Randomised Controlled Trial; CCT Controlled Clinical Trial

Table S11 Risk of bias in observational studies of other maternal or infant dietary exposures and risk of allergic outcomes

Study	Design	N/n cases	Assessment	Selection	Confounding	Overall Bias	Conflict of interest
Alm, 2009 [6]; Goksor, 2011; [477] Alm, 2012;[478]	PC	4941	Low	High	Low	High	Low
Andreasyan, 2007; [479]	PC	498	Unclear	Low	Unclear	Unclear	Low
Back, 2009 [480]	PC	123	Low	High	Low	High	Unclear
Baiz, 2013[481]	PC	239	Low	Low	Low	Low	Unclear
Bekkers, 2012 [482]; Willers, 2008 [483]	PC	3786	Unclear	Low	Low	Unclear	Low
;Bertelsen, 2013 [484]	PC	54,740	Unclear	Unclear	Low	Unclear	Unclear
Bisgaard, 2009 [17]	PC	354	Low	Low	Low	Low	Low
Carmargo, 2010 [485]	PC	823	Low	Low	Low	Low	Low
Romieu, 2007; [486] Chatzi, 2008 [487]	PC	468	Low	Low	Low	Low	Low
de Jong, 2012 [488]; De Jong, 2012 [489]; Leermakers, 2013; [490]	PC	7,210	Low	Low	Low	Low	Low
Dubakiene, 2012 [491]; Butiene, 2011[492]; Oliver, 2010; [187] Grimshaw, 2012 [493]	PC, NCC	128	Low	Low	Unclear	Unclear	Low
Dunlop, 2006 [494]	PC	1326	Low	High	Low	High	Low

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Study	Design	N/n cases	Assessment	Selection	Confounding	Overall Bias	Conflict of interest
Fergusson, 1990 [495]	PC	1,067	Low	Low	High	High	Low
Fitzsimon, 2007 [496]	PC	631	Low	Low	Low	Low	Low
Gale, 2008 [497]	PC	440	Low	Low	Unclear	Unclear	Low
Harris, 2001; [56] Zutavern, 2004 [57]	PC	604,622	Low	Low	Low	Low	Low
Hesselmar, 2010 [61]	PC	184	Low	Low	High	High	Low
Hypponen, 2004; [498] Hypponen, 2001 [499]	PC	10,366/81	Unclear	Unclear	Low	Unclear	Low
Hoppu, 2000 [67]	PC	115	Low	Low	Unclear	Unclear	Low
Jedrychowski, 2008 [500]; Jedrychowski 2011 [501]	PC	469	Low	Low	Low	Low	Low
Kemp, 2011 [502]	PC	310	Unclear	High	Low	High	Low
Kull, 2006; [503] Magnusson, 2013 [504];	PC	3,230	Low	Low	Low	Low	Low
Martindale, 2005; [505] Devereux, 2006; [37] Devereux, 2007 [506]; Willers, 2007[507]	PC	3,230	Low	Low	Low	Low	Low
Lack, 2003 [43]; Shaheen, 2009 [508]; Wills, 2013[509]; Granell, 2008 [510]	PC; NCC	11,352	Low	Low	Low	Low	Low
Laitinen, 2005 [511]	PC	95	Unclear	Unclear	Low	Unclear	Low

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Study	Design	N/n cases	Assessment	Selection	Confounding	Overall Bias	Conflict of interest
Lange, 2010 [512]; Litonjua, 2006; [513] Camargo, 2007 [514]	PC	1,376	Low	Low	Low	Low	Low
Liu, 2011 [515]	PC	649	Low	Unclear	Low	Unclear	Low
Marini, 1996 [91]	PC	68	Unclear	Low	Low	Unclear	Unclear
Mommers, 2009; [516] Magdelijn, 2011; [517] Cremers, 2011[518]	PC	2,465	Low	Low	Low	Low	Low
Maslova, 2012 [519]; Maslova, 2013 [520] [521]; Linneberg, 2004; [522]	PC	28,758	Low	Low	Low	Low	Low
Magnus, 2013 [523] Haberg, 2009 [524]	NCC, PC	32,077	Low	Unclear	Low	Unclear	Low
Milner, 2004 [95]	PC	8,073	Low	Unclear	Low	Unclear	Low
Miskelly, 1988 [96]	PC	482	Low	Low	High	High	Unclear
Miyake, 2009 [525] and 2010 [526-528] and 2011 [529,530]; Satio, 2010 [526]	PC	763	Low	Low	Low	Low	Low
Morales, 2012 [531]	PC	1,724	Unclear	Low	Low	Unclear	Low
Morgan, 2004 [100]	PC	257	Unclear	Low	Low	Unclear	Unclear
Narita, 2011; [532] Ohya, 2011 [533]	PC	1,463	Unclear	Unclear	Unclear	Unclear	Low

Study	Design	N/n cases	Assessment	Selection	Confounding	Overall Bias	Conflict of interest
Nwaru, 2010, 2011, 2012 and 2013 [105,106,534,535] [536,537]; Niinisto, 2012 [538]; Lumia, 2011; [539] Erkkola, 2012; [107]; Maijaliisa, 2011; [540]; Uusitalo 2008 [541] Erkkola, 2009; [542] Marjamaki, 2010; [543]	PC	5,619	Low	Low	Low	Low	Low
Oien, 2010 [544]	PC	3,067	Low	Low	Low	Low	Low
Pike, 2012 [545]	PC	739	Low	Low	Low	Low	Low
Roduit, 2012 [546]	PC	1,041	Low	Low	Low	Low	Unclear
Rothers, 2011 [547]	PC	208	Low	Low	Low	Low	Low
Sausenthaler, 2007 [548]; Zutavern, 2006; [178] Zutavern, 2008; [179]	PC	2,540	Low	Low	Low	Low	Low
Sicherer, 2010 [138]	PC	503	Low	Low	Low	Low	Unclear
Strassburger, 2010 [155]	PC	338	Low	Low	Low	Low	Low
Venter, 2009; [168] Dean, 2007 [549]	PC	937	Low	Low	High	High	Low
Wang, 2007 [144]	PC	1,760	Low	Low	Low	Low	Low
Weisse, 2012 [550]	PC	272	Low	High	Low	High	Low

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Study	Design	N/n cases	Assessment	Selection	Confounding	Overall Bias	Conflict of interest
West, 2012 [551]	PC	319	Low	High	Low	High	Low
Whitrow, 2009 [552]	PC	490	Low	Low	Low	Low	Low
Calvani, 2006 [553]	RC	988	Unclear	Low	Low	Unclear	Low
Jones, 2012 [554]	RC	231	Unclear	Low	Low	Unclear	Low
Allen, 2013 [555]	NCC	2,758/240	Low	Low	Low	Low	Low
Sariachvili, 2010 [60]	NCC	557/252	Low	Low	Low	Low	Unclear
Binkley, 2011 [556]	CC	1,413/1,300	Unclear	Unclear	High	High	Low
Dai, 1993 [557]	CC	70	Unclear	Unclear	High	High	Unclear
DesRoches, 2010 [191]	CC	401/202	Low	Low	Low	Low	Low
Fox, 2009 [193]	CC	293/133	Low	Unclear	Unclear	Unclear	Unclear
Lopez Campos, 2001 [558]	CC	75/58	Unclear	Unclear	Unclear	Unclear	Unclear
Mullins, 2012 [559]	CC	115/115	Low	Unclear	Low	Unclear	Low
Oliveti, 1995 [201]	CC	263/131	Low	Unclear	Low	Unclear	Low
Salam, 2005 [560]	CC	691/ 279	Unclear	Unclear	Low	Unclear	Low

S1_Tables

Study	Design	N/n cases	Assessment	Selection	Confounding	Overall Bias	Conflict of interest
Castro-Rodriguez, 2010 [218]	CS	1,409/ 594	Unclear	High	Low	High	Low
de Batlle, 2008 [561]	CS	1,476/402	Unclear	High	Low	High	Low
Dela Bianca, 2012 [562]	CS	467	Low	Unclear	Low	Unclear	Low
Riedler, 2001 [563]	CS	812	Unclear	High	Low	High	Low

CC Case Control study; CS Cross-sectional study; NCC Nested Case Control study; PC Prospective Cohort; RC Retrospective Cohort

Table S12 Risk of bias in observational studies of other maternal or infant dietary exposures and risk of autoimmune disease

Study	Design	N/n cases	Assessment	Selection	Confounding	Overall Bias	Conflict of interest
Brekke, 2007 [564] Brekke, 2010 [565]; Wahlberg, 2006; [566]	PC	8694	Low	Low	Low	Low	Low
Fronczak, 2003 [249]; Lamb 2008 [252]; Simpson, 2011[567]; Norris, 1996 [568]; Frederikson, 2012 [248]; Lamb, 2013; [250]	PC; NCC	222,222/ 16 1698/49	Low	Low	Low	Low	Low
Hypponen, 2004 [498] Hypponen, 2001 [499]	PC	10,366/81	Unclear	Low	Low	Unclear	Low
Nwaru, 2010, 2011, 2012 and 2013 [105,535,537] [534] [106]; Niinisto, 2012 [538]; Lumia, 2011 [539] ; Erkkola, 2012 [107]; Virtanen, 2006 and 2011 [569,570]; Uusitalo, 2008; [541]	PC	3730	Low	Low	Low	Low	Low
Harsunen, 2012 [571]	NCC	33/33	Unclear	Unclear	Low	Unclear	Low
Miettinen, 2012 [572]	NCC	686/343	Low	Unclear	Low	Unclear	Low
Savilahti, 2009 [268]	NCC	6209/45	Low	Unclear	High	High	Low
Sørensen, 2012 [573]	NCC	328/109	Low	Low	Low	Low	Low

Study	Design	N/n cases	Assessment	Selection	Confounding	Overall Bias	Conflict of interest
Ahadi, 2011 [269]	CC	202/101	Unclear	Unclear	Low	Unclear	Low
Ashraf, 2010 [271]	CC	195	Unclear	High	Unclear	High	Low
Baron, 2005 [321]	CC	444/222	Unclear	Low	Low	Unclear	Low
Ellis, 2012 [326]	CC	655/246	Unclear	Unclear	Low	Unclear	Low
Bener, 2009 [273]	CC	340/170	Unclear	Low	Low	Unclear	Low
EURODIAB substudy 2 study group, 1999 [574]	CC	2934/746	Low	Low	Low	Low	Low
Gilat, 1987 [330]	CC	504/167	Low	Unclear	Low	Unclear	Low
Majeed, 2011 [284]	CC	395/96	Unclear	Unclear	Unclear	Unclear	Unclear
Malcova, 2005 [285]	CC	2334/868	Unclear	Low	Unclear	Unclear	Low
Rosenbauer, 2007 and 2008 [295,575]	CC	2631/760	Low	Unclear	Low	Unclear	Low
Sipetic, 2003 [576]; Sipetic, 2005 [577]	CC	315/105	Low	Unclear	High	High	Low
Stene, 2003 [578], Stene, 2008 [579]	CC	2213/545	Unclear	High	Low	High	Unclear
Stene, 2000 [302]	CC	1131/84	Unclear	High	Low	High	Low
Svensson, 2005 [580]	CC	1152/475	Low	Low	Low	Low	Low

S1_Tables

Study	Design	N/n cases	Assessment	Selection	Confounding	Overall Bias	Conflict of interest
Strotmeyer, 2004; [304]	CC	688/247	Unclear	Unclear	Low	Unclear	Low
Tenconi, 2007 [307]	CC	429/131	Unclear	Unclear	Low	Unclear	Unclear
Virtanen, 1994 [581]	CC	1136/600	Unclear	Low	High	High	Low
Visalli, 2003 [311]	CC	900/150	Unclear	Low	Low	Unclear	Low

CC Case Control study; NCC Nested Case Control study; PC Prospective Cohort; RC Retrospective Cohort

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract pages
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Introduction, paragraph 1
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Introduction, paragraph 1
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Abstract, and Methods paragraph 1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Methods, paragraphs 2, 3 and 4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Methods, paragraph 5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	S1_Search
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Methods, paragraph 6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Methods, paragraph 8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Methods, paragraph 9

PRISMA 2009 Checklist

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Methods, paragraph 7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Methods, paragraph 10
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Methods, paragraph 10

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Methods, paragraph 10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Methods, paragraph 10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	S1_Tables
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	S1_Tables
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figs 2 to 9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figs 2 to 9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Fig 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Figs 10 to 11
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discussion, paragraph

			1
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Discussion, paragraph 3
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Discussion, paragraphs 2 and 4
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Financial Disclosure

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097 For more information, visit: **www.prisma-statement.org**.

Diet during pregnancy and infancy, and risk of allergic or autoimmune disease: a systematic review and meta-analysis

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Web of Science 99

Appendix 1 Search Strategies for other systematic reviews

Medline

1. breast feeding.ab,ti.
2. breastfeeding.ab,ti.
3. breast fed.ab,ti.
4. breastfed.ab,ti.
5. Breast Feeding/
6. Milk, Human/
7. formula?.ab,ti.
8. hydrolysed.ab,ti.
9. bottlefed.ab,ti.
10. bottle fed.ab,ti.
11. (bottle adj3 feed$).ab,ti.
12. Infant Formula/
13. Bottle Feeding/
14. wean$.ab,ti.
15. Weaning/
16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. complementary food?.ab,ti.
18. (introduc$ adj2 food?).ab,ti.
19. wean$.ab,ti.
20. Weaning/
21. solid?.ab,ti.
22. semi-solid?.ab,ti.
23. baby food?.ab,ti.
24. Infant Food/
25. Infant Nutritional Physiological Phenomena/
26. breast feeding.ab,ti.
27. breastfeeding.ab,ti.
28. breast fed.ab,ti.
29. breastfed.ab,ti.
30. Breast Feeding/
31. Milk, Human/
32. formula?.ab,ti.
33. hydrolysed.ab,ti.

34. bottlefed.ab,ti.
35. bottle fed.ab,ti.
36. (bottle adj3 feed$).ab,ti.
37. Infant Formula/
38. Bottle Feeding/
39. liquid?.ab,ti.
40. milk.ab,ti.
41. Milk/
42. egg?.ab,ti.
43. Egg Proteins/
44. Egg Proteins, Dietary/
45. nut?.ab,ti.
46. peanut?.ab,ti.
47. almond?.ab,ti.
48. (brazil? adj5 nut?).ab,ti.
49. walnut?.ab,ti.
50. pecan?.ab,ti.
51. pistachio?.ab,ti.
52. cashew?.ab,ti.
53. hazelnut?.ab,ti.
54. macadamia?.ab,ti.
55. Nuts/
56. Arachis hypogaea/
57. Prunus/
58. Bertholletia/
59. Juglans/
60. Carya/
61. Pistacia/
62. Anacardium/
63. Corylus/
64. Macadamia/
65. wheat.ab,ti.
66. Triticum/
67. soya.ab,ti.
68. Soybeans/
69. gluten$.ab,ti.
70. Glutens/

71. fish.ab,ti.
72. Fishes/
73. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72
74. Diet/
75. Diet Therapy/
76. Nutritional Sciences/
77. Child Nutrition Sciences/
78. diet.ab,ti.
79. diets.ab,ti.
80. Diet, Mediterranean/
81. mediterranean diet$.ab,ti.
82. dietetic.ab,ti.
83. dietary.ab,ti.
84. eat.ab,ti.
85. eating.ab,ti.
86. intake.ab,ti.
87. nutrient?.ab,ti.
88. nutrition.ab,ti.
89. Diet, Vegetarian/
90. vegetarian?.ab,ti.
91. vegan$.ab,ti.
92. Diet, Macrobiotic/
93. macrobiotic?.ab,ti.
94. Food/
95. food$.ab,ti.
96. feed.ab,ti.
97. feeding.ab,ti.
98. cereal$.ab,ti.
99. grain$.ab,ti.
100. granary.ab,ti.
101. wholegrain.ab,ti.
102. wholewheat.ab,ti.
103. whole wheat.ab,ti.
104. wheat.ab,ti.

105. wheatgerm.ab,ti.
106. rye.ab,ti.
107. barley.ab,ti.
108. oat?.ab,ti.
109. exp Cereals/
110. root?.ab,ti.
111. tuber?.ab,ti.
112. exp Vegetables/
113. vegetable$.ab,ti.
114. onion$.ab,ti.
115. spinach.ab,ti.
116. chard.ab,ti.
117. tomato$.ab,ti.
118. pepper$.ab,ti.
119. carrot$.ab,ti.
120. beetroot.ab,ti.
121. asparagus.ab,ti.
122. garlic.ab,ti.
123. pumpkin.ab,ti.
124. sprouts.ab,ti.
125. broccoli.ab,ti.
126. cabbage$.ab,ti.
127. celery.ab,ti.
128. ginger.ab,ti.
129. potato$.ab,ti.
130. crisps.ab,ti.
131. fries.ab,ti.
132. syrup.ab,ti.
133. honey.ab,ti.
134. Honey/
135. Fruit/
136. fruit$.ab,ti.
137. apple?.ab,ti.
138. pear?.ab,ti.
139. banana?.ab,ti.
140. orange?.ab,ti.
141. grape?.ab,ti.

142. kiwi?.ab,ti.
143. citrus.ab,ti.
144. grapefruit?.ab,ti.
145. pulses.ab,ti.
146. beans.ab,ti.
147. lentil?.ab,ti.
148. chickpea?.ab,ti.
149. legume?.ab,ti.
150. lupin?.ab,ti.
151. soy.ab,ti.
152. soya.ab,ti.
153. nut?.ab,ti.
154. almond?.ab,ti.
155. peanut?.ab,ti.
156. groundnut?.ab,ti.
157. Nuts/
158. seed?.ab,ti.
159. sesame.ab,ti.
160. mustard.ab,ti.
161. Seeds/
162. exp Meat/
163. meat.ab,ti.
164. beef.ab,ti.
165. pork.ab,ti.
166. lamb.ab,ti.
167. poultry.ab,ti.
168. chicken.ab,ti.
169. turkey.ab,ti.
170. duck.ab,ti.
171. fish.ab,ti.
172. Fatty Acids/
173. exp Fatty Acids, Omega-3/
174. exp Fatty Acids, Omega-6/
175. omega-3.ab,ti.
176. omega-6.ab,ti.
177. PUFA.ab,ti.
178. fat.ab,ti.

179. fats.ab,ti.
180. fatty.ab,ti.
181. egg.ab,ti.
182. eggs.ab,ti.
183. exp Eggs/
184. Bread/
185. bread.ab,ti.
186. oil.ab,ti.
187. oils.ab,ti.
188. oily.ab,ti.
189. omega.ab,ti.
190. exp Seafood/
191. seafood.ab,ti.
192. shellfish.ab,ti.
193. crustacean?.ab,ti.
194. mollusc?.ab,ti.
195. Shellfish/
196. Dairy Products/
197. dairy.ab,ti.
198. exp Milk/
199. milk.ab,ti.
200. Infant Formula/
201. formula?.ab,ti.
202. hydrolysed.ab,ti.
203. Infant Food/
204. yoghurt.ab,ti.
205. probiotic.ab,ti.
206. prebiotic?.ab,ti.
207. butter.ab,ti.
208. herb?.ab,ti.
209. spice?.ab,ti.
210. chilli$.ab,ti.
211. condiment?.ab,ti.
212. exp Condiments/
213. Beverages/
214. beverage?.ab,ti.
215. fluid intake.ab,ti.

216. water.ab,ti.
217. drink$.ab,ti.
218. exp Food Preservation/
219. pickled.ab,ti.
220. bottled.ab,ti.
221. canned.ab,ti.
222. canning.ab,ti.
223. smoked.ab,ti.
224. preserved.ab,ti.
225. preservatives.ab,ti.
226. nitrosamine.ab,ti.
227. hydrogenation.ab,ti.
228. fortified.ab,ti.
229. nitrates.ab,ti.
230. nitrites.ab,ti.
231. ferment$.ab,ti.
232. processed.ab,ti.
233. antioxidant$.ab,ti.
234. genetic modif$.ab,ti.
235. genetically modif$.ab,ti.
236. Cooking/
237. cooking.ab,ti.
238. cooked.ab,ti.
239. grill.ab,ti.
240. grilled.ab,ti.
241. fried.ab,ti.
242. fry.ab,ti.
243. roast.ab,ti.
244. bake.ab,ti.
245. baked.ab,ti.
246. stewing.ab,ti.
247. stewed.ab,ti.
248. casserol$.ab,ti.
249. broil.ab,ti.
250. broiled.ab,ti.
251. boiled.ab,ti.
252. poach.ab,ti.

253. poached.ab,ti.
254. steamed.ab,ti.
255. barbecue$.ab,ti.
256. chargrill$.ab,ti.
257. salt.ab,ti.
258. salting.ab,ti.
259. salted.ab,ti.
260. fiber.ab,ti.
261. fibre.ab,ti.
262. polysaccharide$.ab,ti.
263. starch.ab,ti.
264. starchy.ab,ti.
265. carbohydrate$.ab,ti.
266. lipid$.ab,ti.
267. linoleic acid$.ab,ti.
268. sugar$.ab,ti.
269. sweetener$.ab,ti.
270. saccharin$.ab,ti.
271. aspartame.ab,ti.
272. sucrose.ab,ti.
273. xylitol.ab,ti.
274. cholesterol.ab,ti.
275. hydrogenated lard.ab,ti.
276. dietary protein.ab,ti.
277. dietary proteins.ab,ti.
278. protein intake.ab,ti.
279. animal protein$.ab,ti.
280. total protein$.ab,ti.
281. vegetable protein$.ab,ti.
282. plant protein$.ab,ti.
283. exp Dietary Carbohydrates/
284. exp Dietary Fats/
285. exp Dietary Fiber/
286. exp Dietary Proteins/
287. exp Dietary Supplements/
288. exp Food Additives/
289. exp Vitamins/

290. supplements.ab,ti.
291. supplement.ab,ti.
292. vitamin$.ab,ti.
293. retinol.ab,ti.
294. carotenoid$.ab,ti.
295. tocopherol.ab,ti.
296. folate$.ab,ti.
297. folic acid.ab,ti.
298. methionine.ab,ti.
299. riboflavin.ab,ti.
300. thiamine.ab,ti.
301. niacin.ab,ti.
302. pyridoxine.ab,ti.
303. cobalamin.ab,ti.
304. mineral$.ab,ti.
305. sodium.ab,ti.
306. iron.ab,ti.
307. calcium.ab,ti.
308. selenium.ab,ti.
309. iodine.ab,ti.
310. magnesium.ab,ti.
311. potassium.ab,ti.
312. zinc.ab,ti.
313. copper.ab,ti.
314. phosphorus.ab,ti.
315. manganese.ab,ti.
316. chromium.ab,ti.
317. phytochemical.ab,ti.
318. polyphenol$.ab,ti.
319. phytoestrogen$.ab,ti.
320. genistein.ab,ti.
321. saponin$.ab,ti.
322. coumarin$.ab,ti.
323. flavonoid$.ab,ti.
324. polyphenol$.ab,ti.
325. flavonol$.ab,ti.
326. flavone$.ab,ti.

327. isoflavone$.ab,ti.
328. catechin$.ab,ti.
329. ascorbic acid$.ab,ti.
330. hydroxy cholecalciferol$.ab,ti.
331. hydroxycholecalciferol$.ab,ti.
332. tocotrienol$.ab,ti.
333. carotene$.ab,ti.
334. cryptoxanthin$.ab,ti.
335. lycopene$.ab,ti.
336. lutein$.ab,ti.
337. zeaxanthin$.ab,ti.
338. selenium$.ab,ti.
339. organic diet?.ab,ti.
340. Food, Organic/
341. 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169 or 170 or 171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181 or 182 or 183 or 184 or 185 or 186 or 187 or 188 or 189 or 190 or 191 or 192 or 193 or 194 or 195 or 196 or 197 or 198 or 199 or 200 or 201 or 202 or 203 or 204 or 205 or 206 or 207 or 208 or 209 or 210 or 211 or 212 or 213 or 214 or 215 or 216 or 217 or 218 or 219 or 220 or 221 or 222 or 223 or 224 or 225 or 226 or 227 or 228 or 229 or 230 or 231 or 232 or 233 or 234 or 235 or 236 or 237 or 238 or 239 or 240 or 241 or 242 or 243 or 244 or 245 or 246 or 247 or 248 or 249 or 250 or 251 or 252 or 253 or 254 or 255 or 256 or 257 or 258 or 259 or 260 or 261 or 262 or 263 or 264 or 265 or 266 or 267 or 268 or 269 or 270 or 271 or 272 or 273 or 274 or 275 or 276 or 277 or 278 or 279 or 280 or 281 or 282 or 283 or 284 or 285 or 286 or 287 or 288 or 289 or 290 or 291 or 292 or 293 or 294 or 295 or 296 or 297 or 298 or 299 or 300 or 301 or 302 or 303 or 304 or 305 or 306 or 307 or 308 or 309 or 310 or 311 or 312 or 313 or 314 or 315 or 316 or 317 or 318 or 319 or 320 or 321 or 322 or 323 or 324 or 325 or 326 or 327 or 328 or 329 or 330 or 331 or 332 or 333 or 334 or 335 or 336 or 337 or 338 or 339 or 340
342. allerg$.ab,ti.
343. asthma$.ab,ti.
344. wheeze.ab,ti.
345. wheezing.ab,ti.

346. bronchial hyperresponsiveness.ab,ti.
347. bronchial hyperreactivity.ab,ti.
348. Forced expiratory volume.ab,ti.
349. FEV1.ab,ti.
350. "FEV 1".ab,ti.
351. "FEV0.5".ab,ti.
352. "FEV 0.5".ab,ti.
353. Forced vital capacity.ab,ti.
354. FVC.ab,ti.
355. Peak expiratory flow rate.ab,ti.
356. PEFR.ab,ti.
357. AD.ab,ti.
358. neurodermatitis.ab,ti.
359. rhinitis.ab,ti.
360. besniers prurigo.ab,ti.
361. rhinoconjunctivitis.ab,ti.
362. hayfever.ab,ti.
363. (hay adj fever).ab,ti.
364. poll?nosis.ab,ti.
365. SAR.ab,ti.
366. (pollen adj allergy).ab,ti.
367. conjunctivitis.ab,ti.
368. immunoglobulin e.ab,ti.
369. Total IgE.ab,ti.
370. autoimmune disease?.ab,ti.
371. diabetes.ab,ti.
372. diabetic.ab,ti.
373. type 1.ab,ti.
374. c?eliac disease.ab,ti.
375. crohn$ disease.ab,ti.
376. Inflammatory Bowel Disease?.ab,ti.
377. Ulcerative colitis.ab,ti.
378. (Lympho$ adj3 thyroiditi$).ab,ti.
379. (Thyroiditi$ adj3 autoimmune).ab,ti.
380. (Hashimoto$ adj3 (syndrome? or thyroiditi$ or disease?)).ab,ti.
381. (Thyroiditi$ adj3 (post-partum or postpartum)).ab,ti.
382. Graves? disease.ab,ti.

383. Basedow$ disease.ab,ti.
384. exophthalmic goiter?.ab,ti.
385. (Still? Disease adj3 (juvenile or onset)).ab,ti.
386. (Juvenile adj3 arthriti$).ab,ti.
387. vitiligo.ab,ti.
388. Psorias?s.ab,ti.
389. (Arthriti? adj3 Psoria$).ab,ti.
390. atopic disease.ab,ti.
391. atopic dermatitis.ab,ti.
392. (food? adj3 sensiti$).ab,ti.
393. (food? adj3 toleran$).ab,ti.
394. (food? adj3 intoleran$).ab,ti.
395. ((aero or air$) adj3 allergen?).ab,ti.
396. (aeroallergen? adj3 sensiti$).ab,ti.
397. (allergen? adj3 sensiti$).ab,ti.
398. skin prick test$.ab,ti.
399. atopy.ab,ti.
400. hypersensitiv$.ab,ti.
401. Hypersensitivity/
402. exp Food Hypersensitivity/
403. Respiratory Hypersensitivity/
404. Asthma/
405. Bronchial Hyperreactivity/
406. Forced Expiratory Volume/
407. Vital Capacity/
408. Peak Expiratory Flow Rate/
409. AD/
410. Neurodermatitis/
411. Rhinitis/
412. Rhinitis, Allergic, Perennial/
413. Rhinitis, Allergic, Seasonal/
414. Conjunctivitis/
415. Immunoglobulin E/
416. Autoimmune Diseases/
417. Diabetes Mellitus, Type 1/
418. Celiac Disease/
419. Crohn Disease/

420. Inflammatory Bowel Diseases/
421. Colitis, Ulcerative/
422. Thyroiditis, Autoimmune/
423. Hashimoto Disease/
424. Postpartum Thyroiditis/
425. Graves Disease/
426. Arthritis, Juvenile Rheumatoid/
427. Vitiligo/
428. Psoriasis/
429. Arthritis, Psoriatic/
430. Dermatitis, Atopic/
431. Hypersensitivity, Immediate/
432. 342 or 343 or 344 or 345 or 346 or 347 or 348 or 349 or 350 or 351 or 352 or 353 or 354 or 355 or 356 or 357 or 358 or 359 or 360 or 361 or 362 or 363 or 364 or 365 or 366 or 367 or 368 or 369 or 370 or 371 or 372 or 373 or 374 or 375 or 376 or 377 or 378 or 379 or 380 or 381 or 382 or 383 or 384 or 385 or 386 or 387 or 388 or 389 or 390 or 391 or 392 or 393 or 394 or 395 or 396 or 397 or 398 or 399 or 400 or 401 or 402 or 403 or 404 or 405 or 406 or 407 or 408 or 409 or 410 or 411 or 412 or 413 or 414 or 415 or 416 or 417 or 418 or 419 or 420 or 421 or 422 or 423 or 424 or 425 or 426 or 427 or 428 or 429 or 430 or 431
433. infant?.ab,ti.
434. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four" or "twenty five" or "twenty six") adj week?).ab,ti.
435. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four") adj month?).ab,ti.
436. 434 or 435
437. (old or age?).ab,ti.
438. 436 and 437
439. (("one year?" or "two year?") adj3 (old or age?)).ab,ti.
440. ((first or second or two) adj3 "year? of life").ab,ti.
441. Infant/
442. Infant, Newborn/
443. (maternal or pregnan$).ab,ti.
444. (lactat$).ab,ti.
445. (mother?).ab,ti.

446. 433 or 438 or 439 or 440 or 441 or 442 or 443 or 444 or 445
447. MEDLINE.tw.
448. systematic review.tw.
449. meta-analysis.pt.
450. intervention$.ti.
451. 447 or 448 or 449 or 450
452. 16 or 73 or 341
453. 432 and 446 and 451 and 452
454. limit 453 to yr="2011 -Current"

Embase

1. breast feeding.ab,ti.
2. breastfeeding.ab,ti.
3. breast fed.ab,ti.
4. breastfed.ab,ti.
5. breast feeding/
6. breast milk/
7. formula?.ab,ti.
8. hydrolysed.ab,ti.
9. bottlefed.ab,ti.
10. bottle fed.ab,ti.
11. (bottle adj3 feed$).ab,ti.
12. artificial milk/
13. bottle feeding/
14. wean$.ti,ab.
15. weaning/
16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. complementary food?.ab,ti.
18. (introduc$ adj2 food?).ab,ti.
19. wean$.ab,ti.
20. weaning/
21. solid?.ab,ti.
22. semi-solid?.ab,ti.
23. baby food?.ab,ti.
24. baby food/
25. infant nutrition/
26. breast feeding.ab,ti.
27. breastfeeding.ab,ti.
28. breast fed.ab,ti.
29. breastfed.ab,ti.
30. breast feeding/
31. breast milk/
32. formula?.ab,ti.
33. hydrolysed.ab,ti.
34. bottlefed.ab,ti.
35. bottle fed.ab,ti.

36. (bottle adj3 feed$).ab,ti.
37. artificial milk/
38. bottle feeding/
39. liquid?.ti,ab.
40. milk.ti,ab.
41. milk/
42. egg?.ti,ab.
43. egg/
44. egg protein/
45. nut?.ab,ti.
46. peanut?.ab,ti.
47. almond?.ab,ti.
48. (brazil? adj5 nut?).ab,ti.
49. walnut?.ab,ti.
50. pecan?.ab,ti.
51. pistachio?.ab,ti.
52. cashew?.ab,ti.
53. hazelnut?.ab,ti.
54. macadamia?.ab,ti.
55. nut/
56. peanut/
57. almond/
58. Brazil nut/
59. exp walnut/
60. pecan/
61. pistachio/
62. cashew nut/
63. hazelnut/
64. Corylus avellana/
65. Macadamia/
66. wheat.ti,ab.
67. exp wheat/
68. soya.ti,ab.
69. soybean/
70. gluten$.ti,ab.
71. gluten/
72. fish$.ti,ab.

73. fish/
74. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73
75. diet/
76. diet therapy/
77. nutritional science/
78. diet.ti,ab.
79. diets.ti,ab.
80. Mediterranean diet/
81. mediterranean diet$.ab,ti.
82. dietetic.ab,ti.
83. dietary.ab,ti.
84. eat.ab,ti.
85. eating.ab,ti.
86. intake.ab,ti.
87. nutrient?.ab,ti.
88. nutrition.ab,ti.
89. vegetarian diet/
90. vegetarian?.ti,ab.
91. vegan$.ti,ab.
92. macrobiotic diet/
93. macrobiotic?.ti,ab.
94. food/
95. food$.ab,ti.
96. feed.ab,ti.
97. feeding.ab,ti.
98. cereal$.ab,ti.
99. grain$.ab,ti.
100. granary.ab,ti.
101. wholegrain.ab,ti.
102. wholewheat.ab,ti.
103. whole wheat.ab,ti.
104. wheat.ab,ti.
105. wheatgerm.ab,ti.
106. rye.ab,ti.

107. barley.ab,ti.
108. oat?.ab,ti.
109. exp cereal/
110. root?.ti,ab.
111. tuber?.ti,ab.
112. exp vegetable/
113. vegetable$.ab,ti.
114. onion$.ab,ti.
115. spinach.ab,ti.
116. chard.ab,ti.
117. tomato$.ab,ti.
118. pepper$.ab,ti.
119. carrot$.ab,ti.
120. beetroot.ab,ti.
121. asparagus.ab,ti.
122. garlic.ab,ti.
123. pumpkin.ab,ti.
124. sprouts.ab,ti.
125. broccoli.ab,ti.
126. cabbage$.ab,ti.
127. celery.ab,ti.
128. ginger.ab,ti.
129. potato$.ab,ti.
130. crisps.ab,ti.
131. fries.ab,ti.
132. syrup.ab,ti.
133. honey.ab,ti.
134. honey/
135. fruit/
136. fruit$.ab,ti.
137. apple?.ab,ti.
138. pear?.ab,ti.
139. banana?.ab,ti.
140. orange?.ab,ti.
141. grape?.ab,ti.
142. kiwi?.ab,ti.
143. citrus.ab,ti.

144. grapefruit?.ab,ti.
145. pulses.ab,ti.
146. beans.ab,ti.
147. lentil?.ab,ti.
148. chickpea?.ab,ti.
149. legume?.ab,ti.
150. lupin?.ab,ti.
151. soy.ab,ti.
152. soya.ab,ti.
153. nut?.ab,ti.
154. almond?.ab,ti.
155. peanut?.ab,ti.
156. groundnut?.ab,ti.
157. exp nut/
158. seed?.ti,ab.
159. sesame.ti,ab.
160. mustard.ti,ab.
161. plant seed/
162. meat/
163. meat.ab,ti.
164. beef.ab,ti.
165. pork.ab,ti.
166. lamb.ab,ti.
167. poultry.ab,ti.
168. chicken.ab,ti.
169. turkey.ab,ti.
170. duck.ab,ti.
171. fish.ab,ti.
172. fatty acid/
173. omega 3 fatty acid/
174. omega 6 fatty acid/
175. omega-3.ab,ti.
176. omega-6.ab,ti.
177. PUFA.ab,ti.
178. fat.ab,ti.
179. fats.ab,ti.
180. fatty.ab,ti.

181. egg.ab,ti.
182. eggs.ab,ti.
183. exp egg/
184. bread/
185. bread.ti,ab.
186. oil.ti,ab.
187. oils.ti,ab.
188. oily.ti,ab.
189. omega.ti,ab.
190. sea food/
191. seafood.ti,ab.
192. shellfish.ti,ab.
193. crustacean?.ti,ab.
194. mollusc?.ti,ab.
195. shellfish/
196. exp dairy product/
197. dairy.ti,ab.
198. milk/
199. milk.ti,ab.
200. artificial milk/
201. formula?.ti,ab.
202. hydrolysed.ti,ab.
203. baby food/
204. yoghurt.ab,ti.
205. probiotic.ab,ti.
206. prebiotic?.ab,ti.
207. butter.ab,ti.
208. herb?.ab,ti.
209. spice?.ab,ti.
210. chilli$.ab,ti.
211. condiment?.ab,ti.
212. exp condiment/
213. beverage/
214. beverage?.ti,ab.
215. fluid intake.ti,ab.
216. water.ti,ab.
217. drink$.ti,ab.

218. exp food preservation/
219. pickled.ab,ti.
220. bottled.ab,ti.
221. canned.ab,ti.
222. canning.ab,ti.
223. smoked.ab,ti.
224. preserved.ab,ti.
225. preservatives.ab,ti.
226. nitrosamine.ab,ti.
227. hydrogenation.ab,ti.
228. fortified.ab,ti.
229. nitrates.ab,ti.
230. nitrites.ab,ti.
231. ferment$.ab,ti.
232. processed.ab,ti.
233. antioxidant$.ab,ti.
234. genetic modif$.ab,ti.
235. genetically modif$.ab,ti.
236. cooking/
237. cooking.ab,ti.
238. cooked.ab,ti.
239. grill.ab,ti.
240. grilled.ab,ti.
241. fried.ab,ti.
242. fry.ab,ti.
243. roast.ab,ti.
244. bake.ab,ti.
245. baked.ab,ti.
246. stewing.ab,ti.
247. stewed.ab,ti.
248. casserol$.ab,ti.
249. broil.ab,ti.
250. broiled.ab,ti.
251. boiled.ab,ti.
252. poach.ab,ti.
253. poached.ab,ti.
254. steamed.ab,ti.

255. barbecue$.ab,ti.
256. chargrill$.ab,ti.
257. salt.ab,ti.
258. salting.ab,ti.
259. salted.ab,ti.
260. fiber.ab,ti.
261. fibre.ab,ti.
262. polysaccharide$.ab,ti.
263. starch.ab,ti.
264. starchy.ab,ti.
265. carbohydrate$.ab,ti.
266. lipid$.ab,ti.
267. linoleic acid$.ab,ti.
268. sugar$.ab,ti.
269. sweetener$.ab,ti.
270. saccharin$.ab,ti.
271. aspartame.ab,ti.
272. sucrose.ab,ti.
273. xylitol.ab,ti.
274. cholesterol.ab,ti.
275. hydrogenated lard.ab,ti.
276. dietary protein.ab,ti.
277. dietary proteins.ab,ti.
278. protein intake.ab,ti.
279. animal protein$.ab,ti.
280. total protein$.ab,ti.
281. vegetable protein$.ab,ti.
282. plant protein$.ab,ti.
283. carbohydrate diet/
284. carbohydrate intake/
285. fat intake/
286. dietary fiber/
287. protein intake/
288. diet supplementation/
289. food additive/
290. exp vitamin/
291. supplements.ab,ti.

292. supplement.ab,ti.
293. vitamin$.ab,ti.
294. retinol.ab,ti.
295. carotenoid$.ab,ti.
296. tocopherol.ab,ti.
297. folate$.ab,ti.
298. folic acid.ab,ti.
299. methionine.ab,ti.
300. riboflavin.ab,ti.
301. thiamine.ab,ti.
302. niacin.ab,ti.
303. pyridoxine.ab,ti.
304. cobalamin.ab,ti.
305. mineral$.ab,ti.
306. sodium.ab,ti.
307. iron.ab,ti.
308. calcium.ab,ti.
309. selenium.ab,ti.
310. iodine.ab,ti.
311. magnesium.ab,ti.
312. potassium.ab,ti.
313. zinc.ab,ti.
314. copper.ab,ti.
315. phosphorus.ab,ti.
316. manganese.ab,ti.
317. chromium.ab,ti.
318. phytochemical.ab,ti.
319. polyphenol$.ab,ti.
320. phytoestrogen$.ab,ti.
321. genistein.ab,ti.
322. saponin$.ab,ti.
323. coumarin$.ab,ti.
324. flavonoid$.ab,ti.
325. polyphenol$.ab,ti.
326. flavonol$.ab,ti.
327. flavone$.ab,ti.
328. isoflavone$.ab,ti.

329. catechin$.ab,ti.
330. ascorbic acid$.ab,ti.
331. hydroxy cholecalciferol$.ab,ti.
332. hydroxycholecalciferol$.ab,ti.
333. tocotrienol$.ab,ti.
334. carotene$.ab,ti.
335. cryptoxanthin$.ab,ti.
336. lycopene$.ab,ti.
337. lutein$.ab,ti.
338. zeaxanthin$.ab,ti.
339. selenium$.ab,ti.
340. organic diet?.ab,ti.
341. organic food/
342. 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169 or 170 or 171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181 or 182 or 183 or 184 or 185 or 186 or 187 or 188 or 189 or 190 or 191 or 192 or 193 or 194 or 195 or 196 or 197 or 198 or 199 or 200 or 201 or 202 or 203 or 204 or 205 or 206 or 207 or 208 or 209 or 210 or 211 or 212 or 213 or 214 or 215 or 216 or 217 or 218 or 219 or 220 or 221 or 222 or 223 or 224 or 225 or 226 or 227 or 228 or 229 or 230 or 231 or 232 or 233 or 234 or 235 or 236 or 237 or 238 or 239 or 240 or 241 or 242 or 243 or 244 or 245 or 246 or 247 or 248 or 249 or 250 or 251 or 252 or 253 or 254 or 255 or 256 or 257 or 258 or 259 or 260 or 261 or 262 or 263 or 264 or 265 or 266 or 267 or 268 or 269 or 270 or 271 or 272 or 273 or 274 or 275 or 276 or 277 or 278 or 279 or 280 or 281 or 282 or 283 or 284 or 285 or 286 or 287 or 288 or 289 or 290 or 291 or 292 or 293 or 294 or 295 or 296 or 297 or 298 or 299 or 300 or 301 or 302 or 303 or 304 or 305 or 306 or 307 or 308 or 309 or 310 or 311 or 312 or 313 or 314 or 315 or 316 or 317 or 318 or 319 or 320 or 321 or 322 or 323 or 324 or 325 or 326 or 327 or 328 or 329 or 330 or 331 or 332 or 333 or 334 or 335 or 336 or 337 or 338 or 339 or 340 or 341
343. allerg$.ab,ti.
344. asthma$.ab,ti.
345. wheeze.ab,ti.
346. wheezing.ab,ti.
347. bronchial hyperresponsiveness.ab,ti.

348. bronchial hyperreactivity.ab,ti.
349. Forced expiratory volume.ab,ti.
350. FEV1.ab,ti.
351. "FEV 1".ab,ti.
352. "FEV0.5".ab,ti.
353. "FEV 0.5".ab,ti.
354. Forced vital capacity.ab,ti.
355. FVC.ab,ti.
356. Peak expiratory flow rate.ab,ti.
357. PEFR.ab,ti.
358. AD.ab,ti.
359. neurodermatitis.ab,ti.
360. rhinitis.ab,ti.
361. besniers prurigo.ab,ti.
362. rhinoconjunctivitis.ab,ti.
363. hayfever.ab,ti.
364. (hay adj fever).ab,ti.
365. poll?nosis.ab,ti.
366. SAR.ab,ti.
367. (pollen adj allergy).ab,ti.
368. conjunctivitis.ab,ti.
369. immunoglobulin e.ab,ti.
370. Total IgE.ab,ti.
371. autoimmune disease?.ab,ti.
372. diabetes.ab,ti.
373. diabetic.ab,ti.
374. type 1.ab,ti.
375. c?eliac disease.ab,ti.
376. crohn$ disease.ab,ti.
377. Inflammatory Bowel Disease?.ab,ti.
378. Ulcerative colitis.ab,ti.
379. (Lympho$ adj3 thyroiditi$).ab,ti.
380. (Thyroiditi$ adj3 autoimmune).ab,ti.
381. (Hashimoto$ adj3 (syndrome? or thyroiditi$ or disease?)).ab,ti.
382. (Thyroiditi$ adj3 (post-partum or postpartum)).ab,ti.
383. Graves? disease.ab,ti.
384. Basedow$ disease.ab,ti.

385. exophthalmic goiter?.ab,ti.
386. (Still? Disease adj3 (juvenile or onset)).ab,ti.
387. (Juvenile adj3 arthriti$).ab,ti.
388. vitiligo.ab,ti.
389. Psorias?s.ab,ti.
390. (Arthriti? adj3 Psoria$).ab,ti.
391. atopic disease.ab,ti.
392. atopic dermatitis.ab,ti.
393. (food? adj3 sensiti$).ab,ti.
394. (food? adj3 toleran$).ab,ti.
395. (food? adj3 intoleran$).ab,ti.
396. ((aero or air$) adj3 allergen?).ab,ti.
397. (aeroallergen? adj3 sensiti$).ab,ti.
398. (allergen? adj3 sensiti$).ab,ti.
399. skin prick test$.ab,ti.
400. atopy.ab,ti.
401. hypersensitiv$.ab,ti.
402. exp hypersensitivity/
403. respiratory tract allergy/
404. asthma/
405. wheezing/
406. bronchus hyperreactivity/
407. forced expiratory volume/
408. forced vital capacity/
409. peak expiratory flow/
410. AD/
411. neurodermatitis/
412. rhinitis/
413. rhinoconjunctivitis/
414. hay fever/
415. pollen allergy/
416. perennial rhinitis/
417. conjunctivitis/
418. immunoglobulin E/
419. autoimmune disease/
420. diabetes mellitus/
421. insulin dependent diabetes mellitus/

422. celiac disease/
423. Crohn disease/
424. enteritis/
425. ulcerative colitis/
426. autoimmune thyroiditis/
427. Hashimoto disease/
428. postpartum thyroiditis/
429. Graves disease/
430. juvenile rheumatoid arthritis/
431. vitiligo/
432. psoriasis/
433. psoriatic arthritis/
434. atopic dermatitis/
435. nutritional intolerance/
436. 343 or 344 or 345 or 346 or 347 or 348 or 349 or 350 or 351 or 352 or 353 or 354 or 355 or 356 or 357 or 358 or 359 or 360 or 361 or 362 or 363 or 364 or 365 or 366 or 367 or 368 or 369 or 370 or 371 or 372 or 373 or 374 or 375 or 376 or 377 or 378 or 379 or 380 or 381 or 382 or 383 or 384 or 385 or 386 or 387 or 388 or 389 or 390 or 391 or 392 or 393 or 394 or 395 or 396 or 397 or 398 or 399 or 400 or 401 or 402 or 403 or 404 or 405 or 406 or 407 or 408 or 409 or 410 or 411 or 412 or 413 or 414 or 415 or 416 or 417 or 418 or 419 or 420 or 421 or 422 or 423 or 424 or 425 or 426 or 427 or 428 or 429 or 430 or 431 or 432 or 433 or 434 or 435
437. infant?.ab,ti.
438. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four" or "twenty five" or "twenty six") adj week?).ab,ti.
439. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four") adj month?).ab,ti.
440. 438 or 439
441. (old or age?).ab,ti.
442. 440 and 441
443. (("one year?" or "two year?") adj3 (old or age?)).ab,ti.
444. ((first or second or two) adj3 "year? of life").ab,ti.
445. infant/
446. newborn/
447. (maternal or pregnan$).ti,ab.

448. (lactat$).ti,ab.
449. (mother?).ti,ab.
450. 437 or 442 or 443 or 444 or 445 or 446 or 447 or 448 or 449
451. MEDLINE.tw.
452. exp systematic review/
453. systematic review.tw.
454. meta analysis/
455. intervention$.ti.
456. 451 or 452 or 453 or 454 or 455
457. 16 or 74 or 342
458. 436 and 450 and 456 and 457
459. limit 458 to yr="2011 -Current"

COCHRANE Reviews and DARE

1. “breast feeding”:ab,ti
2. breastfeeding:ab,ti
3. “breast fed”:ab,ti
4. breastfed:ab,ti
5. MeSH descriptor [Breast Feeding] this term only
6. MeSH descriptor [Milk, Human] this term only
7. formula*:ab,ti
8. hydrolysed:ab,ti
9. bottlefed:ab,ti
10. “bottle fed”:ab,ti
11. (bottle NEAR/3 feed*):ab,ti
12. MeSH descriptor [Infant Formula] this term only
13. MeSH descriptor [Bottle Feeding] this term only
14. wean*:ab,ti
15. MeSH descriptor [Weaning] this term only
16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. “complementary food*”:ab,ti
18. (introduc* NEAR/2 food*):ab,ti
19. wean*:ab,ti
20. MeSH descriptor [Weaning] this term only
21. solid*:ab,ti
22. semi-solid*:ab,ti
23. “baby food*”:ab,ti
24. MeSH descriptor [Infant Food] this term only
25. MeSH descriptor [Infant Nutritional Physiological Phenomena] this term only
26. “breast feeding”:ab,ti
27. breastfeeding:ab,ti
28. “breast fed”:ab,ti
29. breastfed:ab,ti
30. MeSH descriptor [Breast Feeding] this term only
31. MeSH descriptor [Milk, Human] this term only
32. formula*:ab,ti
33. hydrolysed:ab,ti
34. bottlefed:ab,ti
35. “bottle fed”:ab,ti

36. (bottle NEAR/3 feed*):ab,ti
37. MeSH descriptor [Infant Formula] this term only
38. MeSH descriptor [Bottle Feeding] this term only
39. liquid*:ab,ti
40. milk:ab,ti
41. MeSH descriptor [Milk] this term only
42. egg*:ab,ti
43. MeSH descriptor [Egg Proteins] this term only
44. MeSH descriptor [Egg Proteins, Dietary] this term only
45. nut*:ab,ti
46. peanut*:ab,ti
47. almond*:ab,ti
48. (brazil* NEAR/5 nut*):ab,ti
49. walnut*:ab,ti
50. pecan*:ab,ti
51. pistachio*:ab,ti
52. cashew*:ab,ti
53. hazelnut*:ab,ti
54. macadamia*:ab,ti
55. Nuts] this term only
56. MeSH descriptor [Arachis hypogaea] this term only
57. MeSH descriptor [Prunus] this term only
58. MeSH descriptor [Bertholletia] this term only
59. MeSH descriptor [Juglans] this term only
60. MeSH descriptor [Carya] this term only
61. MeSH descriptor [Pistacia] this term only
62. MeSH descriptor [Anacardium] this term only
63. MeSH descriptor [Corylus] this term only
64. MeSH descriptor [Macadamia] this term only
65. wheat:ab,ti
66. MeSH descriptor [Triticum] this term only
67. soya:ab,ti
68. MeSH descriptor [Soybeans] this term only
69. gluten*:ab,ti
70. MeSH descriptor [Glutens] this term only
71. fish:ab,ti
72. MeSH descriptor [Fishes] this term only

73. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72
74. MeSH descriptor [Diet] this term only
75. MeSH descriptor [Diet Therapy] this term only
76. MeSH descriptor [Nutritional Sciences] this term only
77. MeSH descriptor [Child Nutrition Sciences] this term only
78. diet:ab,ti
79. diets:ab,ti
80. MeSH descriptor [Diet, Mediterranean] this term only
81. “mediterranean diet*”:ab,ti
82. dietetic:ab,ti
83. dietary:ab,ti
84. eat:ab,ti
85. eating:ab,ti
86. intake:ab,ti
87. nutrient*:ab,ti
88. nutrition:ab,ti
89. MeSH descriptor [Diet, Vegetarian] this term only
90. vegetarian*:ab,ti
91. vegan*:ab,ti
92. MeSH descriptor [Diet, Macrobiotic] this term only
93. macrobiotic*:ab,ti
94. MeSH descriptor [Food] this term only
95. food*:ab,ti
96. feed:ab,ti
97. feeding:ab,ti
98. cereal*:ab,ti
99. grain*:ab,ti
100. granary:ab,ti
101. wholegrain:ab,ti
102. wholewheat:ab,ti
103. “whole wheat”:ab,ti
104. wheat:ab,ti
105. wheatgerm:ab,ti
106. rye:ab,ti

107. barley:ab,ti
108. oat*:ab,ti
109. MeSH descriptor [Cereals] explode all trees
110. root*:ab,ti
111. tuber*:ab,ti
112. MeSH descriptor [Vegetables] explode all trees
113. vegetable*:ab,ti
114. onion*:ab,ti
115. spinach:ab,ti
116. chard:ab,ti
117. tomato*:ab,ti
118. pepper*:ab,ti
119. carrot*:ab,ti
120. beetroot:ab,ti
121. asparagus:ab,ti
122. garlic:ab,ti
123. pumpkin:ab,ti
124. sprouts:ab,ti
125. broccoli:ab,ti
126. cabbage*:ab,ti
127. celery:ab,ti
128. ginger:ab,ti
129. potato*:ab,ti
130. crisps:ab,ti
131. fries:ab,ti
132. syrup:ab,ti
133. honey:ab,ti
134. MeSH descriptor [Honey] this term only
135. MeSH descriptor [Fruit] this term only
136. fruit*:ab,ti
137. apple*:ab,ti
138. pear*:ab,ti
139. banana*:ab,ti
140. orange*:ab,ti
141. grape*:ab,ti
142. kiwi*:ab,ti
143. citrus:ab,ti

144. grapefruit*:ab,ti
145. pulses:ab,ti
146. beans:ab,ti
147. lentil*:ab,ti
148. chickpea*:ab,ti
149. legume*:ab,ti
150. lupin*:ab,ti
151. soy:ab,ti
152. soya:ab,ti
153. nut*:ab,ti
154. almond*:ab,ti
155. peanut*:ab,ti
156. groundnut*:ab,ti
157. MeSH descriptor [Nuts] this term only
158. seed*:ab,ti
159. sesame:ab,ti
160. mustard:ab,ti
161. MeSH descriptor [Seeds] this term only
162. MeSH descriptor [Meat] explode all trees
163. meat:ab,ti
164. beef:ab,ti
165. pork:ab,ti
166. lamb:ab,ti
167. poultry:ab,ti
168. chicken:ab,ti
169. turkey:ab,ti
170. duck:ab,ti
171. fish:ab,ti
172. MeSH descriptor [Fatty Acids] this term only
173. MeSH descriptor [Fatty Acids, Omega-3] explode all trees
174. MeSH descriptor [Fatty Acids, Omega-6] explode all trees
175. omega-3:ab,ti
176. omega-6:ab,ti
177. PUFA:ab,ti
178. fat:ab,ti
179. fats:ab,ti
180. fatty:ab,ti

181. egg:ab,ti
182. eggs:ab,ti
183. MeSH descriptor [Eggs] explode all trees
184. MeSH descriptor [Bread] this term only
185. bread:ab,ti
186. oil:ab,ti
187. oils:ab,ti
188. oily:ab,ti
189. omega:ab,ti
190. MeSH descriptor [Seafood] explode all trees
191. seafood:ab,ti
192. shellfish:ab,ti
193. crustacean*:ab,ti
194. mollusc*:ab,ti
195. MeSH descriptor [Shellfish] this term only
196. MeSH descriptor [Dairy Products] this term only
197. dairy:ab,ti
198. MeSH descriptor [Milk] explode all trees
199. milk:ab,ti
200. MeSH descriptor [Infant Formula] this term only
201. formula*:ab,ti
202. hydrolysed:ab,ti
203. MeSH descriptor [Infant Food] this term only
204. yoghurt:ab,ti
205. probiotic:ab,ti
206. prebiotic*:ab,ti
207. butter:ab,ti
208. herb*:ab,ti
209. spice*:ab,ti
210. chilli*:ab,ti
211. condiment*:ab,ti
212. MeSH descriptor [Condiments] explode all trees
213. MeSH descriptor [Beverages] this term only
214. beverage*:ab,ti
215. “fluid intake”:ab,ti
216. water:ab,ti
217. drink*:ab,ti

218. MeSH descriptor [Food Preservation] explode all trees
219. pickled:ab,ti
220. bottled:ab,ti
221. canned:ab,ti
222. canning:ab,ti
223. smoked:ab,ti
224. preserved:ab,ti
225. preservatives:ab,ti
226. nitrosamine:ab,ti
227. hydrogenation:ab,ti
228. fortified:ab,ti
229. nitrates:ab,ti
230. nitrites:ab,ti
231. ferment*:ab,ti
232. processed:ab,ti
233. antioxidant*:ab,ti
234. “genetic modif*”:ab,ti
235. “genetically modif*”:ab,ti
236. MeSH descriptor [Cooking] this term only
237. cooking:ab,ti
238. cooked:ab,ti
239. grill:ab,ti
240. grilled:ab,ti
241. fried:ab,ti
242. fry:ab,ti
243. roast:ab,ti
244. bake:ab,ti
245. baked:ab,ti
246. stewing:ab,ti
247. stewed:ab,ti
248. casserol*:ab,ti
249. broil:ab,ti
250. broiled:ab,ti
251. boiled:ab,ti
252. poach:ab,ti
253. poached:ab,ti
254. steamed:ab,ti

255. barbecue*:ab,ti
256. chargrill*:ab,ti
257. salt:ab,ti
258. salting:ab,ti
259. salted:ab,ti
260. fiber:ab,ti
261. fibre:ab,ti
262. polysaccharide*:ab,ti
263. starch:ab,ti
264. starchy:ab,ti
265. carbohydrate*:ab,ti
266. lipid*:ab,ti
267. “linoleic acid*”:ab,ti
268. sugar*:ab,ti
269. sweetener*:ab,ti
270. saccharin*:ab,ti
271. aspartame:ab,ti
272. sucrose:ab,ti
273. xylitol:ab,ti
274. cholesterol:ab,ti
275. “hydrogenated lard”:ab,ti
276. “dietary protein”:ab,ti
277. “dietary proteins”:ab,ti
278. “protein intake”:ab,ti
279. “animal protein*”:ab,ti
280. “total protein*”:ab,ti
281. “vegetable protein*”:ab,ti
282. “plant protein*”:ab,ti
283. MeSH descriptor [Dietary Carbohydrates] explode all trees
284. MeSH descriptor [Dietary Fats] explode all trees
285. MeSH descriptor [Dietary Fiber] explode all trees
286. MeSH descriptor [Dietary Proteins] explode all trees
287. MeSH descriptor [Dietary Supplements] explode all trees
288. MeSH descriptor [Food Additives] explode all trees
289. MeSH descriptor [Vitamins] explode all trees
290. supplements:ab,ti
291. supplement:ab,ti

292. vitamin*:ab,ti
293. retinol:ab,ti
294. carotenoid*:ab,ti
295. tocopherol:ab,ti
296. folate*:ab,ti
297. “folic acid”:ab,ti
298. methionine:ab,ti
299. riboflavin:ab,ti
300. thiamine:ab,ti
301. niacin:ab,ti
302. pyridoxine:ab,ti
303. cobalamin:ab,ti
304. mineral*:ab,ti
305. sodium:ab,ti
306. iron:ab,ti
307. calcium:ab,ti
308. selenium:ab,ti
309. iodine:ab,ti
310. magnesium:ab,ti
311. potassium:ab,ti
312. zinc:ab,ti
313. copper:ab,ti
314. phosphorus:ab,ti
315. manganese:ab,ti
316. chromium:ab,ti
317. phytochemical:ab,ti
318. polyphenol*:ab,ti
319. phytoestrogen*:ab,ti
320. genistein:ab,ti
321. saponin*:ab,ti
322. coumarin*:ab,ti
323. flavonoid*:ab,ti
324. polyphenol*:ab,ti
325. flavonol*:ab,ti
326. flavone*:ab,ti
327. isoflavone*:ab,ti
328. catechin*:ab,ti

329. “ascorbic acid*”:ab,ti
330. “hydroxy cholecalciferol*”:ab,ti
331. hydroxycholecalciferol*:ab,ti
332. tocotrienol*:ab,ti
333. carotene*:ab,ti
334. cryptoxanthin*:ab,ti
335. lycopene*:ab,ti
336. lutein*:ab,ti
337. zeaxanthin*:ab,ti
338. selenium*:ab,ti
339. “organic diet*”:ab,ti
340. MeSH descriptor [Food, Organic] this term only
341. 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169 or 170 or 171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181 or 182 or 183 or 184 or 185 or 186 or 187 or 188 or 189 or 190 or 191 or 192 or 193 or 194 or 195 or 196 or 197 or 198 or 199 or 200 or 201 or 202 or 203 or 204 or 205 or 206 or 207 or 208 or 209 or 210 or 211 or 212 or 213 or 214 or 215 or 216 or 217 or 218 or 219 or 220 or 221 or 222 or 223 or 224 or 225 or 226 or 227 or 228 or 229 or 230 or 231 or 232 or 233 or 234 or 235 or 236 or 237 or 238 or 239 or 240 or 241 or 242 or 243 or 244 or 245 or 246 or 247 or 248 or 249 or 250 or 251 or 252 or 253 or 254 or 255 or 256 or 257 or 258 or 259 or 260 or 261 or 262 or 263 or 264 or 265 or 266 or 267 or 268 or 269 or 270 or 271 or 272 or 273 or 274 or 275 or 276 or 277 or 278 or 279 or 280 or 281 or 282 or 283 or 284 or 285 or 286 or 287 or 288 or 289 or 290 or 291 or 292 or 293 or 294 or 295 or 296 or 297 or 298 or 299 or 300 or 301 or 302 or 303 or 304 or 305 or 306 or 307 or 308 or 309 or 310 or 311 or 312 or 313 or 314 or 315 or 316 or 317 or 318 or 319 or 320 or 321 or 322 or 323 or 324 or 325 or 326 or 327 or 328 or 329 or 330 or 331 or 332 or 333 or 334 or 335 or 336 or 337 or 338 or 339 or 340
342. allerg*:ab,ti
343. asthma*:ab,ti
344. wheeze:ab,ti
345. wheezing:ab,ti
346. “bronchial hyperresponsiveness”:ab,ti
347. “bronchial hyperreactivity”:ab,ti

348. “Forced expiratory volume”:ab,ti
349. “FEV1”:ab,ti
350. "FEV 1":ab,ti
351. "FEV0.5":ab,ti
352. "FEV 0.5":ab,ti
353. “Forced vital capacity”:ab,ti
354. FVC:ab,ti
355. “Peak expiratory flow rate”:ab,ti
356. PEFR:ab,ti
357. AD:ab,ti
358. neurodermatitis:ab,ti
359. rhinitis:ab,ti
360. “besniers prurigo”:ab,ti
361. rhinoconjunctivitis:ab,ti
362. hayfever:ab,ti
363. “hay fever”:ab,ti
364. poll*nosis:ab,ti
365. SAR:ab,ti
366. “pollen allergy”:ab,ti
367. conjunctivitis:ab,ti
368. immunoglobulin e:ab,ti
369. Total IgE:ab,ti
370. “autoimmune disease*”:ab,ti
371. diabetes:ab,ti
372. diabetic:ab,ti
373. “type 1”:ab,ti
374. “c*eliac disease”:ab,ti
375. “crohn* disease”:ab,ti
376. “Inflammatory Bowel Disease*”:ab,ti
377. “Ulcerative colitis”:ab,ti
378. (Lympho* NEAR/3 thyroiditi*):ab,ti
379. (Thyroiditi* NEAR/3 autoimmune):ab,ti
380. (Hashimoto* NEAR/3 (syndrome* or thyroiditi* or disease*)):ab,ti
381. (Thyroiditi* NEAR/3 (post-partum or postpartum)):ab,ti
382. “Graves* disease”:ab,ti
383. “Basedow* disease”:ab,ti
384. “exophthalmic goiter*”:ab,ti

385. (“Still* Disease” NEAR/3 (juvenile or onset)):ab,ti
386. (Juvenile NEAR/3 arthriti*):ab,ti
387. vitiligo:ab,ti
388. Psorias*s:ab,ti
389. (Arthriti* NEAR/3 Psoria*):ab,ti
390. “atopic disease”:ab,ti
391. “atopic dermatitis”:ab,ti
392. (food* NEAR/3 sensiti*):ab,ti
393. (food* NEAR/3 toleran*):ab,ti
394. (food* NEAR/3 intoleran*):ab,ti
395. ((aero or air*) NEAR/3 allergen*):ab,ti
396. (aeroallergen* NEAR/3 sensiti*):ab,ti
397. (allergen* NEAR/3 sensiti*):ab,ti
398. “skin prick test*”:ab,ti
399. atopy:ab,ti
400. hypersensitiv*:ab,ti
401. MeSH descriptor [Hypersensitivity] this term only
402. MeSH descriptor [Food Hypersensitivity] explode all trees
403. MeSH descriptor [Respiratory Hypersensitivity] this term only
404. MeSH descriptor [Asthma] this term only
405. MeSH descriptor [Bronchial Hyperreactivity] this term only
406. MeSH descriptor [Forced Expiratory Volume] this term only
407. MeSH descriptor [Vital Capacity] this term only
408. MeSH descriptor [Peak Expiratory Flow Rate] this term only
409. MeSH descriptor [AD] this term only
410. MeSH descriptor [Neurodermatitis] this term only
411. MeSH descriptor [Rhinitis] this term only
412. MeSH descriptor [Rhinitis, Allergic, Perennial] this term only
413. MeSH descriptor [Rhinitis, Allergic, Seasonal] this term only
414. MeSH descriptor [Conjunctivitis] this term only
415. MeSH descriptor [Immunoglobulin E] this term only
416. MeSH descriptor [Autoimmune Diseases] this term only
417. MeSH descriptor [Diabetes Mellitus, Type 1] this term only
418. MeSH descriptor [Celiac Disease] this term only
419. MeSH descriptor [Crohn Disease] this term only
420. MeSH descriptor [Inflammatory Bowel Diseases] this term only
421. MeSH descriptor [Colitis, Ulcerative] this term only

422. MeSH descriptor [Thyroiditis, Autoimmune] this term only
423. MeSH descriptor [Hashimoto Disease] this term only
424. MeSH descriptor [Postpartum Thyroiditis] this term only
425. MeSH descriptor [Graves Disease] this term only
426. MeSH descriptor [Arthritis, Juvenile Rheumatoid] this term only
427. MeSH descriptor [Vitiligo] this term only
428. MeSH descriptor [Psoriasis] this term only
429. MeSH descriptor [Arthritis, Psoriatic] this term only
430. MeSH descriptor [Dermatitis, Atopic] this term only
431. MeSH descriptor [Hypersensitivity, Immediate] this term only
432. 342 or 343 or 344 or 345 or 346 or 347 or 348 or 349 or 350 or 351 or 352 or 353 or 354 or 355 or 356 or 357 or 358 or 359 or 360 or 361 or 362 or 363 or 364 or 365 or 366 or 367 or 368 or 369 or 370 or 371 or 372 or 373 or 374 or 375 or 376 or 377 or 378 or 379 or 380 or 381 or 382 or 383 or 384 or 385 or 386 or 387 or 388 or 389 or 390 or 391 or 392 or 393 or 394 or 395 or 396 or 397 or 398 or 399 or 400 or 401 or 402 or 403 or 404 or 405 or 406 or 407 or 408 or 409 or 410 or 411 or 412 or 413 or 414 or 415 or 416 or 417 or 418 or 419 or 420 or 421 or 422 or 423 or 424 or 425 or 426 or 427 or 428 or 429 or 430 or 431
433. infant*:ab,ti
434. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four" or "twenty five" or "twenty six") NEAR/1 week*):ab,ti
435. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four") NEAR/1 month*):ab,ti
436. 434 or 435
437. (old or age*):ab,ti
438. 436 and 437
439. (("one year*" or "two year*") NEAR/3 (old or age*)):ab,ti
440. ((first or second or two) NEAR/3 "year* of life"):ab,ti
441. MeSH descriptor [Infant] this term only
442. MeSH descriptor [Infant, Newborn] this term only
443. (maternal or pregnan*):ab,ti
444. (lactat*):ab,ti
445. (mother*):ab,ti
446. 433 or 438 or 439 or 440 or 441 or 442 or 443 or 444 or 445
447. 16 or 73 or 341

448. 432 and 446 and 447

Publication date from 2011

Appendix 2 Search Strategies for original articles on milk feeding

Medline

1. breast feeding.ab,ti.
2. breastfeeding.ab,ti.
3. breast fed.ab,ti.
4. breastfed.ab,ti.
5. Breast Feeding/
6. Milk, Human/
7. formula?.ab,ti.
8. hydrolysed.ab,ti.
9. bottlefed.ab,ti.
10. bottle fed.ab,ti.
11. (bottle adj3 feed$).ab,ti.
12. Infant Formula/
13. Bottle Feeding/
14. wean$.ab,ti.
15. Weaning/
16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. allerg$.ab,ti.
18. asthma$.ab,ti.
19. wheeze.ab,ti.
20. wheezing.ab,ti.
21. bronchial hyperresponsiveness.ab,ti.
22. bronchial hyperreactivity.ab,ti.
23. Forced expiratory volume.ab,ti.
24. FEV1.ab,ti.
25. "FEV 1".ab,ti.
26. "FEV0.5".ab,ti.
27. "FEV 0.5".ab,ti.
28. Forced vital capacity.ab,ti.
29. FVC.ab,ti.
30. Peak expiratory flow rate.ab,ti.
31. PEFR.ab,ti.
32. AD.ab,ti.
33. neurodermatitis.ab,ti.
34. rhinitis.ab,ti.
35. besniers prurigo.ab,ti.

36. rhinoconjunctivitis.ab,ti.
37. hayfever.ab,ti.
38. (hay adj fever).ab,ti.
39. poll?nosis.ab,ti.
40. SAR.ab,ti.
41. (pollen adj allergy).ab,ti.
42. conjunctivitis.ab,ti.
43. immunoglobulin e.ab,ti.
44. Total IgE.ab,ti.
45. autoimmune disease?.ab,ti.
46. diabetes.ab,ti.
47. diabetic.ab,ti.
48. type 1.ab,ti.
49. c?eliac disease.ab,ti.
50. crohn$ disease.ab,ti.
51. Inflammatory Bowel Disease?.ab,ti.
52. Ulcerative colitis.ab,ti.
53. (Lympho$ adj3 thyroiditi$).ab,ti.
54. (Thyroiditi$ adj3 autoimmune).ab,ti.
55. (Hashimoto$ adj3 (syndrome? or thyroiditi$ or disease?)).ab,ti.
56. (Thyroiditi$ adj3 (post-partum or postpartum)).ab,ti.
57. Graves? disease.ab,ti.
58. Basedow$ disease.ab,ti.
59. exophthalmic goiter?.ab,ti.
60. (Still? Disease adj3 (juvenile or onset)).ab,ti.
61. (Juvenile adj3 arthriti$).ab,ti.
62. vitiligo.ab,ti.
63. Psorias?s.ab,ti.
64. (Arthriti? adj3 Psoria$).ab,ti.
65. atopic disease.ab,ti.
66. atopic dermatitis.ab,ti.
67. (food? adj3 sensiti$).ab,ti.
68. (food? adj3 toleran$).ab,ti.
69. (food? adj3 intoleran$).ab,ti.
70. ((aero or air$) adj3 allergen?).ab,ti.
71. (aeroallergen? adj3 sensiti$).ab,ti.
72. (allergen? adj3 sensiti$).ab,ti.

73. skin prick test$.ab,ti.
74. atopy.ab,ti.
75. hypersensitiv$.ab,ti.
76. Hypersensitivity/
77. exp Food Hypersensitivity/
78. Respiratory Hypersensitivity/
79. Asthma/
80. Bronchial Hyperreactivity/
81. Forced Expiratory Volume/
82. Vital Capacity/
83. Peak Expiratory Flow Rate/
84. AD/
85. Neurodermatitis/
86. Rhinitis/
87. Rhinitis, Allergic, Perennial/
88. Rhinitis, Allergic, Seasonal/
89. Conjunctivitis/
90. Immunoglobulin E/
91. Autoimmune Diseases/
92. Diabetes Mellitus, Type 1/
93. Celiac Disease/
94. Crohn Disease/
95. Inflammatory Bowel Diseases/
96. Colitis, Ulcerative/
97. Thyroiditis, Autoimmune/
98. Hashimoto Disease/
99. Postpartum Thyroiditis/
100. Graves Disease/
101. Arthritis, Juvenile Rheumatoid/
102. Vitiligo/
103. Psoriasis/
104. Arthritis, Psoriatic/
105. Dermatitis, Atopic/
106. Hypersensitivity, Immediate/
107. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68

or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106

108. infant?.ab,ti.

109. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four" or "twenty five" or "twenty six") adj week?).ab,ti.

110. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four") adj month?).ab,ti.

111. 109 or 110

112. (old or age?).ab,ti.

113. 111 and 112

114. (("one year?" or "two year?") adj3 (old or age?)).ab,ti.

115. ((first or second or two) adj3 "year? of life").ab,ti.

116. Infant/

117. Infant, Newborn/

118. 108 or 113 or 114 or 115 or 116 or 117

119. clinical trial?.mp.

120. random$.mp.

121. factorial$.mp.

122. crossover$.mp.

123. placebo$.mp.

124. (doubl$ adj blind$).mp.

125. (singl$ adj blind$).mp.

126. assign$.mp.

127. volunteer$.mp.

128. cohort stud$.mp.

129. longitudinal$.mp.

130. follow-up.mp.

131. prospectiv$.mp.

132. retrospectiv$.mp.

133. case control.mp.

134. case referent.mp.

135. exp clinical trial/

136. Cross-Over Studies/

137. Placebos/
138. Double-Blind Method/
139. Single-Blind Method/
140. exp Cohort Studies/
141. case-control studies/
142. 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141
143. 16 and 107 and 118 and 142

Embase

1. breast feeding.ab,ti.
2. breastfeeding.ab,ti.
3. breast fed.ab,ti.
4. breastfed.ab,ti.
5. breast feeding/
6. breast milk/
7. formula?.ab,ti.
8. hydrolysed.ab,ti.
9. bottlefed.ab,ti.
10. bottle fed.ab,ti.
11. (bottle adj3 feed$).ab,ti.
12. artificial milk/
13. bottle feeding/
14. wean$.ti,ab.
15. weaning/
16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. allerg$.ab,ti.
18. asthma$.ab,ti.
19. wheeze.ab,ti.
20. wheezing.ab,ti.
21. bronchial hyperresponsiveness.ab,ti.
22. bronchial hyperreactivity.ab,ti.
23. Forced expiratory volume.ab,ti.
24. FEV1.ab,ti.
25. "FEV 1".ab,ti.
26. "FEV0.5".ab,ti.
27. "FEV 0.5".ab,ti.
28. Forced vital capacity.ab,ti.
29. FVC.ab,ti.
30. Peak expiratory flow rate.ab,ti.
31. PEFR.ab,ti.
32. AD.ab,ti.
33. neurodermatitis.ab,ti.
34. rhinitis.ab,ti.
35. besniers prurigo.ab,ti.

36. rhinoconjunctivitis.ab,ti.
37. hayfever.ab,ti.
38. (hay adj fever).ab,ti.
39. poll?nosis.ab,ti.
40. SAR.ab,ti.
41. (pollen adj allergy).ab,ti.
42. conjunctivitis.ab,ti.
43. immunoglobulin e.ab,ti.
44. Total IgE.ab,ti.
45. autoimmune disease?.ab,ti.
46. diabetes.ab,ti.
47. diabetic.ab,ti.
48. type 1.ab,ti.
49. c?eliac disease.ab,ti.
50. crohn$ disease.ab,ti.
51. Inflammatory Bowel Disease?.ab,ti.
52. Ulcerative colitis.ab,ti.
53. (Lympho$ adj3 thyroiditi$).ab,ti.
54. (Thyroiditi$ adj3 autoimmune).ab,ti.
55. (Hashimoto$ adj3 (syndrome? or thyroiditi$ or disease?)).ab,ti.
56. (Thyroiditi$ adj3 (post-partum or postpartum)).ab,ti.
57. Graves? disease.ab,ti.
58. Basedow$ disease.ab,ti.
59. exophthalmic goiter?.ab,ti.
60. (Still? Disease adj3 (juvenile or onset)).ab,ti.
61. (Juvenile adj3 arthriti$).ab,ti.
62. vitiligo.ab,ti.
63. Psorias?s.ab,ti.
64. (Arthriti? adj3 Psoria$).ab,ti.
65. atopic disease.ab,ti.
66. atopic dermatitis.ab,ti.
67. (food? adj3 sensiti$).ab,ti.
68. (food? adj3 toleran$).ab,ti.
69. (food? adj3 intoleran$).ab,ti.
70. ((aero or air$) adj3 allergen?).ab,ti.
71. (aeroallergen? adj3 sensiti$).ab,ti.
72. (allergen? adj3 sensiti$).ab,ti.

73. skin prick test$.ab,ti.
74. atopy.ab,ti.
75. hypersensitiv$.ab,ti.
76. exp hypersensitivity/
77. respiratory tract allergy/
78. asthma/
79. wheezing/
80. bronchus hyperreactivity/
81. forced expiratory volume/
82. forced vital capacity/
83. peak expiratory flow/
84. AD/
85. neurodermatitis/
86. rhinitis/
87. rhinoconjunctivitis/
88. hay fever/
89. pollen allergy/
90. perennial rhinitis/
91. conjunctivitis/
92. immunoglobulin E/
93. autoimmune disease/
94. diabetes mellitus/
95. insulin dependent diabetes mellitus/
96. celiac disease/
97. Crohn disease/
98. enteritis/
99. ulcerative colitis/
100. autoimmune thyroiditis/
101. Hashimoto disease/
102. postpartum thyroiditis/
103. Graves disease/
104. juvenile rheumatoid arthritis/
105. vitiligo/
106. psoriasis/
107. psoriatic arthritis/
108. atopic dermatitis/
109. nutritional intolerance/

110. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109
111. infant?.ab,ti.
112. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four" or "twenty five" or "twenty six") adj week?).ab,ti.
113. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four") adj month?).ab,ti.
114. 112 or 113
115. (old or age?).ab,ti.
116. 114 and 115
117. (("one year?" or "two year?") adj3 (old or age?)).ab,ti.
118. ((first or second or two) adj3 "year? of life").ab,ti.
119. infant/
120. newborn/
121. 111 or 116 or 117 or 118 or 119 or 120
122. clinical trial?.mp.
123. random$.mp.
124. factorial$.mp.
125. crossover$.mp.
126. placebo$.mp.
127. (doubl$ adj blind$).mp.
128. (singl$ adj blind$).mp.
129. assign$.mp.
130. volunteer$.mp.
131. cohort stud$.mp.
132. longitudinal$.mp.
133. follow-up.mp.
134. prospectiv$.mp.
135. retrospectiv$.mp.
136. case control.mp.

137. case referent.mp.
138. exp clinical trial/
139. crossover procedure/
140. placebo/
141. double blind procedure/
142. single blind procedure/
143. cohort analysis/
144. longitudinal study/
145. follow up/
146. prospective study/
147. retrospective study/
148. exp case control study/
149. 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148
150. 16 and 110 and 121 and 149

LILACS

(tw:((breast feeding) or breastfeeding or (breast fed) or breastfed or formula* or hydrolysed or bottlefed or (bottle fed) or (bottle feed*) or wean*)

AND

(tw:(allerg* or asthma* or wheez* or (bronchial hyperresponsiveness) or (bronchial hyperreactivity) or (Forced expiratory volume) or FEV1 or (FEV 1) or FEV0.5 or (FEV 0.5) or (Forced vital capacity) or FVC or (Peak expiratory flow rate) or PEFR or AD or neurodermatitis or rhinitis or (besniers prurigo) or rhinoconjunctivitis or hayfever or (hay fever) or poll?nosis or SAR or (pollen allergy) or conjunctivitis or (immunoglobulin e) or (Total IgE) or (autoimmune disease*) or diabetes or diabetic or (type 1) or (c?eliac disease) or (crohn* disease) or (Inflammatory Bowel Disease*) or (Ulcerative colitis) or (Lympho* thyroiditi*) or (Thyroiditi* autoimmune) or (Hashimoto* syndrome*) or (Hashimoto* thyroiditis*) or (Hashimoto* disease*) or (Thyroiditi* post-partum) or (Thyroiditi* postpartum) or (Graves* Disease) or (Basedow* disease) or (exophthalmic goiter*) or (Still's Disease) or (Stills disease) or (Juvenile arthriti*) or vitiligo or Psorias?s or (Arthriti* Psoria*) or (atopic disease) or (atopic dermatitis) or (food* sensiti*) or (food* toleran*) or (food* intoleran*) or (aero allergen*) or (air* allergen*) or (aeroallergen* sensiti*) or (allergen* sensiti*) or (skin prick test*) or atopy or hypersensitive*)

AND

db:("LILACS")

AND

type_of_study:("clinical_trials" or "case_control" or "cohort" or "systematic_reviews")

AND

limit:("infant" or "newborn" or "preschool" or "child")

COCHRANE Library

1. “breast feeding”:ab,ti
2. breastfeeding:ab,ti
3. “breast fed”:ab,ti
4. breastfed:ab,ti
5. MeSH descriptor [Breast Feeding] this term only
6. MeSH descriptor [Milk, Human] this term only
7. formula*:ab,ti
8. hydrolysed:ab,ti
9. bottlefed:ab,ti
10. “bottle fed”:ab,ti
11. (bottle NEAR/3 feed*):ab,ti
12. MeSH descriptor [Infant Formula] this term only
13. MeSH descriptor [Bottle Feeding] this term only
14. wean*:ab,ti
15. MeSH descriptor [Weaning] this term only
16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. allerg*:ab,ti
18. asthma*:ab,ti
19. wheeze:ab,ti
20. wheezing:ab,ti
21. “bronchial hyperresponsiveness”:ab,ti
22. “bronchial hyperreactivity”:ab,ti
23. “Forced expiratory volume”:ab,ti
24. “FEV1”:ab,ti
25. "FEV 1":ab,ti
26. "FEV0.5":ab,ti
27. "FEV 0.5":ab,ti
28. “Forced vital capacity”:ab,ti
29. FVC:ab,ti
30. “Peak expiratory flow rate”:ab,ti
31. PEFR:ab,ti
32. AD:ab,ti
33. neurodermatitis:ab,ti
34. rhinitis:ab,ti
35. “besniers prurigo”:ab,ti

36. rhinoconjunctivitis:ab,ti
37. hayfever:ab,ti
38. “hay fever”:ab,ti
39. poll*nosis:ab,ti
40. SAR:ab,ti
41. “pollen allergy”:ab,ti
42. conjunctivitis:ab,ti
43. “immunoglobulin e”:ab,ti
44. “Total IgE”:ab,ti
45. “autoimmune disease*”:ab,ti
46. diabetes:ab,ti
47. diabetic:ab,ti
48. “type 1”:ab,ti
49. “c*eliac disease”:ab,ti
50. “crohn* disease”:ab,ti
51. “Inflammatory Bowel Disease*”:ab,ti
52. “Ulcerative colitis”:ab,ti
53. (Lympho* NEAR/3 thyroiditi*):ab,ti
54. (Thyroiditi* NEAR/3 autoimmune):ab,ti
55. (Hashimoto* NEAR/3 (syndrome* or thyroiditi* or disease*)):ab,ti
56. (Thyroiditi* NEAR/3 (post-partum or postpartum)):ab,ti
57. “Graves* disease”:ab,ti
58. “Basedow* disease”:ab,ti
59. “exophthalmic goiter*”:ab,ti
60. (Still* Disease NEAR/3 (juvenile or onset)):ab,ti
61. (Juvenile NEAR/3 arthriti*):ab,ti
62. vitiligo:ab,ti
63. Psorias*s:ab,ti
64. (Arthriti* NEAR/3 Psoria*):ab,ti
65. “atopic disease”:ab,ti
66. “atopic dermatitis”:ab,ti
67. (food* NEAR/3 sensiti*):ab,ti
68. (food* NEAR/3 toleran*):ab,ti
69. (food* NEAR/3 intoleran*):ab,ti
70. ((aero or air*) NEAR/3 allergen*):ab,ti
71. (aeroallergen* NEAR/3 sensiti*):ab,ti
72. (allergen* NEAR/3 sensiti*):ab,ti

73. “skin prick test*”:ab,ti
74. atopy:ab,ti
75. hypersensitiv*:ab,ti
76. MeSH descriptor [Hypersensitivity] this term only
77. MeSH descriptor [Food Hypersensitivity] explode all trees
78. MeSH descriptor [Respiratory Hypersensitivity] this term only
79. MeSH descriptor [Asthma] this term only
80. MeSH descriptor [Bronchial Hyperreactivity] this term only
81. MeSH descriptor [Forced Expiratory Volume] this term only
82. MeSH descriptor [Vital Capacity] this term only
83. MeSH descriptor [Peak Expiratory Flow Rate] this term only
84. MeSH descriptor [AD] this term only
85. MeSH descriptor [Neurodermatitis] this term only
86. MeSH descriptor [Rhinitis] this term only
87. MeSH descriptor [Rhinitis, Allergic, Perennial] this term only
88. MeSH descriptor [Rhinitis, Allergic, Seasonal] this term only
89. MeSH descriptor [Conjunctivitis] this term only
90. MeSH descriptor [Immunoglobulin E] this term only
91. MeSH descriptor [Autoimmune Diseases] this term only
92. MeSH descriptor [Diabetes Mellitus, Type 1] this term only
93. MeSH descriptor [Celiac Disease] this term only
94. MeSH descriptor [Crohn Disease] this term only
95. MeSH descriptor [Inflammatory Bowel Diseases] this term only
96. MeSH descriptor [Colitis, Ulcerative] this term only
97. MeSH descriptor [Thyroiditis, Autoimmune] this term only
98. MeSH descriptor [Hashimoto Disease] this term only
99. MeSH descriptor [Postpartum Thyroiditis] this term only
100. MeSH descriptor [Graves Disease] this term only
101. MeSH descriptor [Arthritis, Juvenile Rheumatoid] this term only
102. MeSH descriptor [Vitiligo] this term only
103. MeSH descriptor [Psoriasis] this term only
104. MeSH descriptor [Arthritis, Psoriatic] this term only
105. MeSH descriptor [Dermatitis, Atopic] this term only
106. MeSH descriptor [Hypersensitivity, Immediate] this term only
107. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68

or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106

108. infant*:ab,ti

109. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four" or "twenty five" or "twenty six") NEAR/1 week*):ab,ti

110. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four") NEAR/1 month*):ab,ti

111. 109 or 110

112. (old or age*):ab,ti

113. 111 and 112

114. (("one year*" or "two year*") NEAR/3 (old or age*)):ab,ti

115. ((first or second or two) NEAR/3 "year* of life"):ab,ti

116. MeSH descriptor [Infant] this term only

117. MeSH descriptor [Infant, Newborn] this term only

118. 108 or 113 or 114 or 115 or 116 or 117

119. “clinical trial*”

120. random*

121. factorial*

122. crossover*

123. placebo*

124. “doubl* blind*”

125. “singl* blind*”

126. assign*

127. volunteer*

128. “cohort stud*”

129. longitudinal*

130. follow-up

131. prospectiv*

132. retrospectiv*

133. “case control”

134. “case referent”

135. MeSH descriptor [clinical trial] explode all trees

136. MeSH descriptor [Cross-Over Studies] this term only

137. MeSH descriptor [Placebos] this term only
138. MeSH descriptor [Double-Blind Method] this term only
139. MeSH descriptor [Single-Blind Method] this term only
140. MeSH descriptor [Cohort Studies] explode all trees
141. MeSH descriptor [case-control studies] this term only
142. 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141
143. 16 and 107 and 118 and 142

Web of Science

1. TOPIC = (“breast feeding” or breastfeeding or “breast fed” or breastfed or formula$ or hydrolysed or bottlefed or “bottle fed” or (bottle NEAR/3 feed*) or wean*)
2. TOPIC = (allerg* or asthma* or wheeze or wheezing or “bronchial hyperresponsiveness” or “bronchial hyperreactivity” or “Forced expiratory volume” or “FEV1” or "FEV 1" or "FEV0.5" or "FEV 0.5" or “Forced vital capacity” or FVC or “Peak expiratory flow rate” or PEFR or AD or neurodermatitis or rhinitis or “besniers prurigo” or rhinoconjunctivitis or hayfever or “hay fever” or poll$nosis or SAR or “pollen allergy” or conjunctivitis or “immunoglobulin e” or “Total IgE” or “autoimmune disease$” or diabetes or diabetic or “type 1” or “c$eliac disease” or “crohn* disease” or “Inflammatory Bowel Disease$” or “Ulcerative colitis” or (Lympho* NEAR/3 thyroiditi*) or (Thyroiditi* NEAR/3 autoimmune) or (Hashimoto* NEAR/3 (syndrome$ or thyroiditis* or disease$)) or (Thyroiditi* NEAR/3 (post-partum or postpartum)) or “Graves$ Disease” or “Basedow* disease” or “exophthalmic goiter$” or (“Still$ Disease” NEAR/3 (juvenile or onset)) or (Juvenile NEAR/3 arthriti*) or vitiligo or Psorias$s or (Arthriti$ NEAR/3 Psoria*) or “atopic disease” or “atopic dermatitis” or (food$ NEAR/3 sensiti*) or (food$ NEAR/3 toleran*) or (food$ NEAR/3 intoleran*) or ((aero or air*) NEAR/3 allergen$) or (aeroallergen$ NEAR/3 sensiti*) or (allergen$ NEAR/3 sensiti*) or “skin prick test*” or atopy or hypersensitive*)
3. TOPIC = (infant$ or (("one year$" or "two year$") NEAR/3 (old or age$)) or ((first or second or two) NEAR/3 "year$ of life"))
4. TOPIC = ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four" or "twenty five" or "twenty six") NEAR/1 week$)
5. TOPIC = ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four") NEAR/1 month$)
6. 4 or 5
7. TOPIC = ((old or age$))
8. 7 and 6
9. 8 or 3
10. TOPIC = (“clinical trial$” or random* or factorial* or crossover* or placebo* or “doubl* blind*” or “singl* blind*” or assign* or volunteer* or “cohort stud*” or longitudinal* or follow-up or prospective* or retrospective* or “case control” or “case referent”)
11. 1 and 2 and 9 and 10

Appendix 3 Search Strategies for original articles on other maternal or infant dietary exposures

Medline

1. Diet/
2. Diet Therapy/
3. Nutritional Sciences/
4. Child Nutrition Sciences/
5. diet.ab,ti.
6. diets.ab,ti.
7. Diet, Mediterranean/
8. mediterranean diet$.ab,ti.
9. dietetic.ab,ti.
10. dietary.ab,ti.
11. eat.ab,ti.
12. eating.ab,ti.
13. intake.ab,ti.
14. nutrient?.ab,ti.
15. nutrition.ab,ti.
16. Diet, Vegetarian/
17. vegetarian?.ab,ti.
18. vegan$.ab,ti.
19. Diet, Macrobiotic/
20. macrobiotic?.ab,ti.
21. Food/
22. food$.ab,ti.
23. feed.ab,ti.
24. feeding.ab,ti.
25. cereal$.ab,ti.
26. grain$.ab,ti.
27. granary.ab,ti.
28. wholegrain.ab,ti.
29. wholewheat.ab,ti.
30. whole wheat.ab,ti.
31. wheat.ab,ti.
32. wheatgerm.ab,ti.
33. rye.ab,ti.
34. barley.ab,ti.

35. oat?.ab,ti.
36. exp Cereals/
37. root?.ab,ti.
38. tuber?.ab,ti.
39. exp Vegetables/
40. vegetable$.ab,ti.
41. onion$.ab,ti.
42. spinach.ab,ti.
43. chard.ab,ti.
44. tomato$.ab,ti.
45. pepper$.ab,ti.
46. carrot$.ab,ti.
47. beetroot.ab,ti.
48. asparagus.ab,ti.
49. garlic.ab,ti.
50. pumpkin.ab,ti.
51. sprouts.ab,ti.
52. broccoli.ab,ti.
53. cabbage$.ab,ti.
54. celery.ab,ti.
55. ginger.ab,ti.
56. potato$.ab,ti.
57. crisps.ab,ti.
58. fries.ab,ti.
59. syrup.ab,ti.
60. honey.ab,ti.
61. Honey/
62. Fruit/
63. fruit$.ab,ti.
64. apple?.ab,ti.
65. pear?.ab,ti.
66. banana?.ab,ti.
67. orange?.ab,ti.
68. grape?.ab,ti.
69. kiwi?.ab,ti.
70. citrus.ab,ti.
71. grapefruit?.ab,ti.

72. pulses.ab,ti.
73. beans.ab,ti.
74. lentil?.ab,ti.
75. chickpea?.ab,ti.
76. legume?.ab,ti.
77. lupin?.ab,ti.
78. soy.ab,ti.
79. soya.ab,ti.
80. nut?.ab,ti.
81. almond?.ab,ti.
82. peanut?.ab,ti.
83. groundnut?.ab,ti.
84. Nuts/
85. seed?.ab,ti.
86. sesame.ab,ti.
87. mustard.ab,ti.
88. Seeds/
89. exp Meat/
90. meat.ab,ti.
91. beef.ab,ti.
92. pork.ab,ti.
93. lamb.ab,ti.
94. poultry.ab,ti.
95. chicken.ab,ti.
96. turkey.ab,ti.
97. duck.ab,ti.
98. fish.ab,ti.
99. Fatty Acids/
100. exp Fatty Acids, Omega-3/
101. exp Fatty Acids, Omega-6/
102. omega-3.ab,ti.
103. omega-6.ab,ti.
104. PUFA.ab,ti.
105. fat.ab,ti.
106. fats.ab,ti.
107. fatty.ab,ti.
108. egg.ab,ti.

109. eggs.ab,ti.
110. exp Eggs/
111. Bread/
112. bread.ab,ti.
113. oil.ab,ti.
114. oils.ab,ti.
115. oily.ab,ti.
116. omega.ab,ti.
117. exp Seafood/
118. seafood.ab,ti.
119. shellfish.ab,ti.
120. crustacean?.ab,ti.
121. mollusc?.ab,ti.
122. Shellfish/
123. Dairy Products/
124. dairy.ab,ti.
125. exp Milk/
126. milk.ab,ti.
127. Infant Formula/
128. formula?.ab,ti.
129. hydrolysed.ab,ti.
130. Infant Food/
131. yoghurt.ab,ti.
132. probiotic.ab,ti.
133. prebiotic?.ab,ti.
134. butter.ab,ti.
135. herb?.ab,ti.
136. spice?.ab,ti.
137. chilli$.ab,ti.
138. condiment?.ab,ti.
139. exp Condiments/
140. Beverages/
141. beverage?.ab,ti.
142. fluid intake.ab,ti.
143. water.ab,ti.
144. drink$.ab,ti.
145. exp Food Preservation/

146. pickled.ab,ti.
147. bottled.ab,ti.
148. canned.ab,ti.
149. canning.ab,ti.
150. smoked.ab,ti.
151. preserved.ab,ti.
152. preservatives.ab,ti.
153. nitrosamine.ab,ti.
154. hydrogenation.ab,ti.
155. fortified.ab,ti.
156. nitrates.ab,ti.
157. nitrites.ab,ti.
158. ferment$.ab,ti.
159. processed.ab,ti.
160. antioxidant$.ab,ti.
161. genetic modif$.ab,ti.
162. genetically modif$.ab,ti.
163. Cooking/
164. cooking.ab,ti.
165. cooked.ab,ti.
166. grill.ab,ti.
167. grilled.ab,ti.
168. fried.ab,ti.
169. fry.ab,ti.
170. roast.ab,ti.
171. bake.ab,ti.
172. baked.ab,ti.
173. stewing.ab,ti.
174. stewed.ab,ti.
175. casserol$.ab,ti.
176. broil.ab,ti.
177. broiled.ab,ti.
178. boiled.ab,ti.
179. poach.ab,ti.
180. poached.ab,ti.
181. steamed.ab,ti.
182. barbecue$.ab,ti.

183. chargrill$.ab,ti.
184. salt.ab,ti.
185. salting.ab,ti.
186. salted.ab,ti.
187. fiber.ab,ti.
188. fibre.ab,ti.
189. polysaccharide$.ab,ti.
190. starch.ab,ti.
191. starchy.ab,ti.
192. carbohydrate$.ab,ti.
193. lipid$.ab,ti.
194. linoleic acid$.ab,ti.
195. sugar$.ab,ti.
196. sweetener$.ab,ti.
197. saccharin$.ab,ti.
198. aspartame.ab,ti.
199. sucrose.ab,ti.
200. xylitol.ab,ti.
201. cholesterol.ab,ti.
202. hydrogenated lard.ab,ti.
203. dietary protein.ab,ti.
204. dietary proteins.ab,ti.
205. protein intake.ab,ti.
206. animal protein$.ab,ti.
207. total protein$.ab,ti.
208. vegetable protein$.ab,ti.
209. plant protein$.ab,ti.
210. exp Dietary Carbohydrates/
211. exp Dietary Fats/
212. exp Dietary Fiber/
213. exp Dietary Proteins/
214. exp Dietary Supplements/
215. exp Food Additives/
216. exp Vitamins/
217. supplements.ab,ti.
218. supplement.ab,ti.
219. vitamin$.ab,ti.

220. retinol.ab,ti.
221. carotenoid$.ab,ti.
222. tocopherol.ab,ti.
223. folate$.ab,ti.
224. folic acid.ab,ti.
225. methionine.ab,ti.
226. riboflavin.ab,ti.
227. thiamine.ab,ti.
228. niacin.ab,ti.
229. pyridoxine.ab,ti.
230. cobalamin.ab,ti.
231. mineral$.ab,ti.
232. sodium.ab,ti.
233. iron.ab,ti.
234. calcium.ab,ti.
235. selenium.ab,ti.
236. iodine.ab,ti.
237. magnesium.ab,ti.
238. potassium.ab,ti.
239. zinc.ab,ti.
240. copper.ab,ti.
241. phosphorus.ab,ti.
242. manganese.ab,ti.
243. chromium.ab,ti.
244. phytochemical.ab,ti.
245. polyphenol$.ab,ti.
246. phytoestrogen$.ab,ti.
247. genistein.ab,ti.
248. saponin$.ab,ti.
249. coumarin$.ab,ti.
250. flavonoid$.ab,ti.
251. polyphenol$.ab,ti.
252. flavonol$.ab,ti.
253. flavone$.ab,ti.
254. isoflavone$.ab,ti.
255. catechin$.ab,ti.
256. ascorbic acid$.ab,ti.

257. hydroxy cholecalciferol$.ab,ti.
258. hydroxycholecalciferol$.ab,ti.
259. tocotrienol$.ab,ti.
260. carotene$.ab,ti.
261. cryptoxanthin$.ab,ti.
262. lycopene$.ab,ti.
263. lutein$.ab,ti.
264. zeaxanthin$.ab,ti.
265. selenium$.ab,ti.
266. organic diet?.ab,ti.
267. Food, Organic/
268. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169 or 170 or 171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181 or 182 or 183 or 184 or 185 or 186 or 187 or 188 or 189 or 190 or 191 or 192 or 193 or 194 or 195 or 196 or 197 or 198 or 199 or 200 or 201 or 202 or 203 or 204 or 205 or 206 or 207 or 208 or 209 or 210 or 211 or 212 or 213 or 214 or 215 or 216 or 217 or 218 or 219 or 220 or 221 or 222 or 223 or 224 or 225 or 226 or 227 or 228 or 229 or 230 or 231 or 232 or 233 or 234 or 235 or 236 or 237 or 238 or 239 or 240 or 241 or 242 or 243 or 244 or 245 or 246 or 247 or 248 or 249 or 250 or 251 or 252 or 253 or 254 or 255 or 256 or 257 or 258 or 259 or 260 or 261 or 262 or 263 or 264 or 265 or 266 or 267
269. allerg$.ab,ti.
270. asthma$.ab,ti.
271. wheeze.ab,ti.
272. wheezing.ab,ti.
273. bronchial hyperresponsiveness.ab,ti.
274. bronchial hyperreactivity.ab,ti.
275. Forced expiratory volume.ab,ti.
276. FEV1.ab,ti.

277. "FEV 1".ab,ti.
278. "FEV0.5".ab,ti.
279. "FEV 0.5".ab,ti.
280. Forced vital capacity.ab,ti.
281. FVC.ab,ti.
282. Peak expiratory flow rate.ab,ti.
283. PEFR.ab,ti.
284. AD.ab,ti.
285. neurodermatitis.ab,ti.
286. rhinitis.ab,ti.
287. besniers prurigo.ab,ti.
288. rhinoconjunctivitis.ab,ti.
289. hayfever.ab,ti.
290. (hay adj fever).ab,ti.
291. poll?nosis.ab,ti.
292. SAR.ab,ti.
293. (pollen adj allergy).ab,ti.
294. conjunctivitis.ab,ti.
295. immunoglobulin e.ab,ti.
296. Total IgE.ab,ti.
297. autoimmune disease?.ab,ti.
298. diabetes.ab,ti.
299. diabetic.ab,ti.
300. type 1.ab,ti.
301. c?eliac disease.ab,ti.
302. crohn$ disease.ab,ti.
303. Inflammatory Bowel Disease?.ab,ti.
304. Ulcerative colitis.ab,ti.
305. (Lympho$ adj3 thyroiditi$).ab,ti.
306. (Thyroiditi$ adj3 autoimmune).ab,ti.
307. (Hashimoto$ adj3 (syndrome? or thyroiditi$ or disease?)).ab,ti.
308. (Thyroiditi$ adj3 (post-partum or postpartum)).ab,ti.
309. Graves? disease.ab,ti.
310. Basedow$ disease.ab,ti.
311. exophthalmic goiter?.ab,ti.
312. (Still? Disease adj3 (juvenile or onset)).ab,ti.
313. (Juvenile adj3 arthriti$).ab,ti.

314. vitiligo.ab,ti.
315. Psorias?s.ab,ti.
316. (Arthriti? adj3 Psoria$).ab,ti.
317. atopic disease.ab,ti.
318. atopic dermatitis.ab,ti.
319. (food? adj3 sensiti$).ab,ti.
320. (food? adj3 toleran$).ab,ti.
321. (food? adj3 intoleran$).ab,ti.
322. ((aero or air$) adj3 allergen?).ab,ti.
323. (aeroallergen? adj3 sensiti$).ab,ti.
324. (allergen? adj3 sensiti$).ab,ti.
325. skin prick test$.ab,ti.
326. atopy.ab,ti.
327. hypersensitiv$.ab,ti.
328. Hypersensitivity/
329. exp Food Hypersensitivity/
330. Respiratory Hypersensitivity/
331. Asthma/
332. Bronchial Hyperreactivity/
333. Forced Expiratory Volume/
334. Vital Capacity/
335. Peak Expiratory Flow Rate/
336. AD/
337. Neurodermatitis/
338. Rhinitis/
339. Rhinitis, Allergic, Perennial/
340. Rhinitis, Allergic, Seasonal/
341. Conjunctivitis/
342. Immunoglobulin E/
343. Autoimmune Diseases/
344. Diabetes Mellitus, Type 1/
345. Celiac Disease/
346. Crohn Disease/
347. Inflammatory Bowel Diseases/
348. Colitis, Ulcerative/
349. Thyroiditis, Autoimmune/
350. Hashimoto Disease/

351. Postpartum Thyroiditis/
352. Graves Disease/
353. Arthritis, Juvenile Rheumatoid/
354. Vitiligo/
355. Psoriasis/
356. Arthritis, Psoriatic/
357. Dermatitis, Atopic/
358. Hypersensitivity, Immediate/
359. 269 or 270 or 271 or 272 or 273 or 274 or 275 or 276 or 277 or 278 or 279 or 280 or 281 or 282 or 283 or 284 or 285 or 286 or 287 or 288 or 289 or 290 or 291 or 292 or 293 or 294 or 295 or 296 or 297 or 298 or 299 or 300 or 301 or 302 or 303 or 304 or 305 or 306 or 307 or 308 or 309 or 310 or 311 or 312 or 313 or 314 or 315 or 316 or 317 or 318 or 319 or 320 or 321 or 322 or 323 or 324 or 325 or 326 or 327 or 328 or 329 or 330 or 331 or 332 or 333 or 334 or 335 or 336 or 337 or 338 or 339 or 340 or 341 or 342 or 343 or 344 or 345 or 346 or 347 or 348 or 349 or 350 or 351 or 352 or 353 or 354 or 355 or 356 or 357 or 358
360. infant?.ab,ti.
361. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four" or "twenty five" or "twenty six") adj week?).ab,ti.
362. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four") adj month?).ab,ti.
363. 361 or 362
364. (old or age?).ab,ti.
365. 363 and 364
366. (("one year?" or "two year?") adj3 (old or age?)).ab,ti.
367. ((first or second or two) adj3 "year? of life").ab,ti.
368. Infant/
369. Infant, Newborn/
370. (maternal or pregnan$).ab,ti.
371. (lactat$).ab,ti.
372. (mother?).ab,ti.
373. 360 or 365 or 366 or 367 or 368 or 369 or 370 or 371 or 372
374. clinical trial?.mp.
375. random$.mp.
376. factorial$.mp.

377. crossover$.mp.
378. placebo$.mp.
379. (doubl$ adj blind$).mp.
380. (singl$ adj blind$).mp.
381. assign$.mp.
382. volunteer$.mp.
383. cohort stud$.mp.
384. longitudinal$.mp.
385. follow-up.mp.
386. prospectiv$.mp.
387. retrospectiv$.mp.
388. case control.mp.
389. case referent.mp.
390. exp clinical trial/
391. Cross-Over Studies/
392. Placebos/
393. Double-Blind Method/
394. Single-Blind Method/
395. exp Cohort Studies/
396. case-control studies/
397. 374 or 375 or 376 or 377 or 378 or 379 or 380 or 381 or 382 or 383 or 384 or 385 or 386 or 387 or 388 or 389 or 390 or 391 or 392 or 393 or 394 or 395 or 396
398. 268 and 359 and 373 and 397

Embase

1. diet/
2. diet therapy/
3. nutritional science/
4. diet.ti,ab.
5. diets.ti,ab.
6. Mediterranean diet/
7. mediterranean diet$.ab,ti.
8. dietetic.ab,ti.
9. dietary.ab,ti.
10. eat.ab,ti.
11. eating.ab,ti.
12. intake.ab,ti.
13. nutrient?.ab,ti.
14. nutrition.ab,ti.
15. vegetarian diet/
16. vegetarian?.ti,ab.
17. vegan$.ti,ab.
18. macrobiotic diet/
19. macrobiotic?.ti,ab.
20. food/
21. food$.ab,ti.
22. feed.ab,ti.
23. feeding.ab,ti.
24. cereal$.ab,ti.
25. grain$.ab,ti.
26. granary.ab,ti.
27. wholegrain.ab,ti.
28. wholewheat.ab,ti.
29. whole wheat.ab,ti.
30. wheat.ab,ti.
31. wheatgerm.ab,ti.
32. rye.ab,ti.
33. barley.ab,ti.
34. oat?.ab,ti.
35. exp cereal/

36. root?.ti,ab.
37. tuber?.ti,ab.
38. exp vegetable/
39. vegetable$.ab,ti.
40. onion$.ab,ti.
41. spinach.ab,ti.
42. chard.ab,ti.
43. tomato$.ab,ti.
44. pepper$.ab,ti.
45. carrot$.ab,ti.
46. beetroot.ab,ti.
47. asparagus.ab,ti.
48. garlic.ab,ti.
49. pumpkin.ab,ti.
50. sprouts.ab,ti.
51. broccoli.ab,ti.
52. cabbage$.ab,ti.
53. celery.ab,ti.
54. ginger.ab,ti.
55. potato$.ab,ti.
56. crisps.ab,ti.
57. fries.ab,ti.
58. syrup.ab,ti.
59. honey.ab,ti.
60. honey/
61. fruit/
62. fruit$.ab,ti.
63. apple?.ab,ti.
64. pear?.ab,ti.
65. banana?.ab,ti.
66. orange?.ab,ti.
67. grape?.ab,ti.
68. kiwi?.ab,ti.
69. citrus.ab,ti.
70. grapefruit?.ab,ti.
71. pulses.ab,ti.
72. beans.ab,ti.

73. lentil?.ab,ti.
74. chickpea?.ab,ti.
75. legume?.ab,ti.
76. lupin?.ab,ti.
77. soy.ab,ti.
78. soya.ab,ti.
79. nut?.ab,ti.
80. almond?.ab,ti.
81. peanut?.ab,ti.
82. groundnut?.ab,ti.
83. exp nut/
84. seed?.ti,ab.
85. sesame.ti,ab.
86. mustard.ti,ab.
87. plant seed/
88. meat/
89. meat.ab,ti.
90. beef.ab,ti.
91. pork.ab,ti.
92. lamb.ab,ti.
93. poultry.ab,ti.
94. chicken.ab,ti.
95. turkey.ab,ti.
96. duck.ab,ti.
97. fish.ab,ti.
98. fatty acid/
99. omega 3 fatty acid/
100. omega 6 fatty acid/
101. omega-3.ab,ti.
102. omega-6.ab,ti.
103. PUFA.ab,ti.
104. fat.ab,ti.
105. fats.ab,ti.
106. fatty.ab,ti.
107. egg.ab,ti.
108. eggs.ab,ti.
109. exp egg/

110. bread/
111. bread.ti,ab.
112. oil.ti,ab.
113. oils.ti,ab.
114. oily.ti,ab.
115. omega.ti,ab.
116. sea food/
117. seafood.ti,ab.
118. shellfish.ti,ab.
119. crustacean?.ti,ab.
120. mollusc?.ti,ab.
121. shellfish/
122. exp dairy product/
123. dairy.ti,ab.
124. milk/
125. milk.ti,ab.
126. artificial milk/
127. formula?.ti,ab.
128. hydrolysed.ti,ab.
129. baby food/
130. yoghurt.ab,ti.
131. probiotic.ab,ti.
132. prebiotic?.ab,ti.
133. butter.ab,ti.
134. herb?.ab,ti.
135. spice?.ab,ti.
136. chilli$.ab,ti.
137. condiment?.ab,ti.
138. exp condiment/
139. beverage/
140. beverage?.ti,ab.
141. fluid intake.ti,ab.
142. water.ti,ab.
143. drink$.ti,ab.
144. exp food preservation/
145. pickled.ab,ti.
146. bottled.ab,ti.

147. canned.ab,ti.
148. canning.ab,ti.
149. smoked.ab,ti.
150. preserved.ab,ti.
151. preservatives.ab,ti.
152. nitrosamine.ab,ti.
153. hydrogenation.ab,ti.
154. fortified.ab,ti.
155. nitrates.ab,ti.
156. nitrites.ab,ti.
157. ferment$.ab,ti.
158. processed.ab,ti.
159. antioxidant$.ab,ti.
160. genetic modif$.ab,ti.
161. genetically modif$.ab,ti.
162. cooking/
163. cooking.ab,ti.
164. cooked.ab,ti.
165. grill.ab,ti.
166. grilled.ab,ti.
167. fried.ab,ti.
168. fry.ab,ti.
169. roast.ab,ti.
170. bake.ab,ti.
171. baked.ab,ti.
172. stewing.ab,ti.
173. stewed.ab,ti.
174. casserol$.ab,ti.
175. broil.ab,ti.
176. broiled.ab,ti.
177. boiled.ab,ti.
178. poach.ab,ti.
179. poached.ab,ti.
180. steamed.ab,ti.
181. barbecue$.ab,ti.
182. chargrill$.ab,ti.
183. salt.ab,ti.

184. salting.ab,ti.
185. salted.ab,ti.
186. fiber.ab,ti.
187. fibre.ab,ti.
188. polysaccharide$.ab,ti.
189. starch.ab,ti.
190. starchy.ab,ti.
191. carbohydrate$.ab,ti.
192. lipid$.ab,ti.
193. linoleic acid$.ab,ti.
194. sugar$.ab,ti.
195. sweetener$.ab,ti.
196. saccharin$.ab,ti.
197. aspartame.ab,ti.
198. sucrose.ab,ti.
199. xylitol.ab,ti.
200. cholesterol.ab,ti.
201. hydrogenated lard.ab,ti.
202. dietary protein.ab,ti.
203. dietary proteins.ab,ti.
204. protein intake.ab,ti.
205. animal protein$.ab,ti.
206. total protein$.ab,ti.
207. vegetable protein$.ab,ti.
208. plant protein$.ab,ti.
209. carbohydrate diet/
210. carbohydrate intake/
211. fat intake/
212. dietary fiber/
213. protein intake/
214. diet supplementation/
215. food additive/
216. exp vitamin/
217. supplements.ab,ti.
218. supplement.ab,ti.
219. vitamin$.ab,ti.
220. retinol.ab,ti.

221. carotenoid$.ab,ti.
222. tocopherol.ab,ti.
223. folate$.ab,ti.
224. folic acid.ab,ti.
225. methionine.ab,ti.
226. riboflavin.ab,ti.
227. thiamine.ab,ti.
228. niacin.ab,ti.
229. pyridoxine.ab,ti.
230. cobalamin.ab,ti.
231. mineral$.ab,ti.
232. sodium.ab,ti.
233. iron.ab,ti.
234. calcium.ab,ti.
235. selenium.ab,ti.
236. iodine.ab,ti.
237. magnesium.ab,ti.
238. potassium.ab,ti.
239. zinc.ab,ti.
240. copper.ab,ti.
241. phosphorus.ab,ti.
242. manganese.ab,ti.
243. chromium.ab,ti.
244. phytochemical.ab,ti.
245. polyphenol$.ab,ti.
246. phytoestrogen$.ab,ti.
247. genistein.ab,ti.
248. saponin$.ab,ti.
249. coumarin$.ab,ti.
250. flavonoid$.ab,ti.
251. polyphenol$.ab,ti.
252. flavonol$.ab,ti.
253. flavone$.ab,ti.
254. isoflavone$.ab,ti.
255. catechin$.ab,ti.
256. ascorbic acid$.ab,ti.
257. hydroxy cholecalciferol$.ab,ti.

258. hydroxycholecalciferol$.ab,ti.
259. tocotrienol$.ab,ti.
260. carotene$.ab,ti.
261. cryptoxanthin$.ab,ti.
262. lycopene$.ab,ti.
263. lutein$.ab,ti.
264. zeaxanthin$.ab,ti.
265. selenium$.ab,ti.
266. organic diet?.ab,ti.
267. organic food/
268. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169 or 170 or 171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181 or 182 or 183 or 184 or 185 or 186 or 187 or 188 or 189 or 190 or 191 or 192 or 193 or 194 or 195 or 196 or 197 or 198 or 199 or 200 or 201 or 202 or 203 or 204 or 205 or 206 or 207 or 208 or 209 or 210 or 211 or 212 or 213 or 214 or 215 or 216 or 217 or 218 or 219 or 220 or 221 or 222 or 223 or 224 or 225 or 226 or 227 or 228 or 229 or 230 or 231 or 232 or 233 or 234 or 235 or 236 or 237 or 238 or 239 or 240 or 241 or 242 or 243 or 244 or 245 or 246 or 247 or 248 or 249 or 250 or 251 or 252 or 253 or 254 or 255 or 256 or 257 or 258 or 259 or 260 or 261 or 262 or 263 or 264 or 265 or 266 or 267
269. allerg$.ab,ti.
270. asthma$.ab,ti.
271. wheeze.ab,ti.
272. wheezing.ab,ti.
273. bronchial hyperresponsiveness.ab,ti.
274. bronchial hyperreactivity.ab,ti.
275. Forced expiratory volume.ab,ti.
276. FEV1.ab,ti.
277. "FEV 1".ab,ti.

278. "FEV0.5".ab,ti.
279. "FEV 0.5".ab,ti.
280. Forced vital capacity.ab,ti.
281. FVC.ab,ti.
282. Peak expiratory flow rate.ab,ti.
283. PEFR.ab,ti.
284. AD.ab,ti.
285. neurodermatitis.ab,ti.
286. rhinitis.ab,ti.
287. besniers prurigo.ab,ti.
288. rhinoconjunctivitis.ab,ti.
289. hayfever.ab,ti.
290. (hay adj fever).ab,ti.
291. poll?nosis.ab,ti.
292. SAR.ab,ti.
293. (pollen adj allergy).ab,ti.
294. conjunctivitis.ab,ti.
295. immunoglobulin e.ab,ti.
296. Total IgE.ab,ti.
297. autoimmune disease?.ab,ti.
298. diabetes.ab,ti.
299. diabetic.ab,ti.
300. type 1.ab,ti.
301. c?eliac disease.ab,ti.
302. crohn$ disease.ab,ti.
303. Inflammatory Bowel Disease?.ab,ti.
304. Ulcerative colitis.ab,ti.
305. (Lympho$ adj3 thyroiditi$).ab,ti.
306. (Thyroiditi$ adj3 autoimmune).ab,ti.
307. (Hashimoto$ adj3 (syndrome? or thyroiditi$ or disease?)).ab,ti.
308. (Thyroiditi$ adj3 (post-partum or postpartum)).ab,ti.
309. Graves? disease.ab,ti.
310. Basedow$ disease.ab,ti.
311. exophthalmic goiter?.ab,ti.
312. (Still? Disease adj3 (juvenile or onset)).ab,ti.
313. (Juvenile adj3 arthriti$).ab,ti.
314. vitiligo.ab,ti.

315. Psorias?s.ab,ti.
316. (Arthriti? adj3 Psoria$).ab,ti.
317. atopic disease.ab,ti.
318. atopic dermatitis.ab,ti.
319. (food? adj3 sensiti$).ab,ti.
320. (food? adj3 toleran$).ab,ti.
321. (food? adj3 intoleran$).ab,ti.
322. ((aero or air$) adj3 allergen?).ab,ti.
323. (aeroallergen? adj3 sensiti$).ab,ti.
324. (allergen? adj3 sensiti$).ab,ti.
325. skin prick test$.ab,ti.
326. atopy.ab,ti.
327. hypersensitiv$.ab,ti.
328. exp hypersensitivity/
329. respiratory tract allergy/
330. asthma/
331. wheezing/
332. bronchus hyperreactivity/
333. forced expiratory volume/
334. forced vital capacity/
335. peak expiratory flow/
336. AD/
337. neurodermatitis/
338. rhinitis/
339. rhinoconjunctivitis/
340. hay fever/
341. pollen allergy/
342. perennial rhinitis/
343. conjunctivitis/
344. immunoglobulin E/
345. autoimmune disease/
346. diabetes mellitus/
347. insulin dependent diabetes mellitus/
348. celiac disease/
349. Crohn disease/
350. enteritis/
351. ulcerative colitis/

352. autoimmune thyroiditis/
353. Hashimoto disease/
354. postpartum thyroiditis/
355. Graves disease/
356. juvenile rheumatoid arthritis/
357. vitiligo/
358. psoriasis/
359. psoriatic arthritis/
360. atopic dermatitis/
361. nutritional intolerance/
362. 269 or 270 or 271 or 272 or 273 or 274 or 275 or 276 or 277 or 278 or 279 or 280 or 281 or 282 or 283 or 284 or 285 or 286 or 287 or 288 or 289 or 290 or 291 or 292 or 293 or 294 or 295 or 296 or 297 or 298 or 299 or 300 or 301 or 302 or 303 or 304 or 305 or 306 or 307 or 308 or 309 or 310 or 311 or 312 or 313 or 314 or 315 or 316 or 317 or 318 or 319 or 320 or 321 or 322 or 323 or 324 or 325 or 326 or 327 or 328 or 329 or 330 or 331 or 332 or 333 or 334 or 335 or 336 or 337 or 338 or 339 or 340 or 341 or 342 or 343 or 344 or 345 or 346 or 347 or 348 or 349 or 350 or 351 or 352 or 353 or 354 or 355 or 356 or 357 or 358 or 359 or 360 or 361
363. infant?.ab,ti.
364. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four" or "twenty five" or "twenty six") adj week?).ab,ti.
365. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four") adj month?).ab,ti.
366. 364 or 365
367. (old or age?).ab,ti.
368. 366 and 367
369. (("one year?" or "two year?") adj3 (old or age?)).ab,ti.
370. ((first or second or two) adj3 "year? of life").ab,ti.
371. infant/
372. newborn/
373. (maternal or pregnan$).ti,ab.
374. (lactat$).ti,ab.
375. (mother?).ti,ab.
376. 363 or 368 or 369 or 370 or 371 or 372 or 373 or 374 or 375
377. clinical trial?.mp.

378. random$.mp.
379. factorial$.mp.
380. crossover$.mp.
381. placebo$.mp.
382. (doubl$ adj blind$).mp.
383. (singl$ adj blind$).mp.
384. assign$.mp.
385. volunteer$.mp.
386. cohort stud$.mp.
387. longitudinal$.mp.
388. follow-up.mp.
389. prospectiv$.mp.
390. retrospectiv$.mp.
391. case control.mp.
392. case referent.mp.
393. exp clinical trial/
394. crossover procedure/
395. placebo/
396. double blind procedure/
397. single blind procedure/
398. cohort analysis/
399. longitudinal study/
400. follow up/
401. prospective study/
402. retrospective study/
403. exp case control study/
404. 377 or 378 or 379 or 380 or 381 or 382 or 383 or 384 or 385 or 386 or 387 or 388 or 389 or 390 or 391 or 392 or 393 or 394 or 395 or 396 or 397 or 398 or 399 or 400 or 401 or 402 or 403
405. 268 and 362 and 376 and 404

LILACS

(tw:((breast feeding) or breastfeeding or (breast fed) or breastfed or formula* or hydrolysed or bottlefed or (bottle fed) or (bottle feed*) or wean*)

AND

(tw:(allerg* or asthma* or wheez* or (bronchial hyperresponsiveness) or (bronchial hyperreactivity) or (Forced expiratory volume) or FEV1 or (FEV 1) or FEV0.5 or (FEV 0.5) or (Forced vital capacity) or FVC or (Peak expiratory flow rate) or PEFR or AD or neurodermatitis or rhinitis or (besniers prurigo) or rhinoconjunctivitis or hayfever or (hay fever) or poll?nosis or SAR or (pollen allergy) or conjunctivitis or (immunoglobulin e) or (Total IgE) or (autoimmune disease*) or diabetes or diabetic or (type 1) or (c?eliac disease) or (crohn* disease) or (Inflammatory Bowel Disease*) or (Ulcerative colitis) or (Lympho* thyroiditi*) or (Thyroiditi* autoimmune) or (Hashimoto* syndrome*) or (Hashimoto* thyroiditis*) or (Hashimoto* disease*) or (Thyroiditi* post-partum) or (Thyroiditi* postpartum) or (Graves* Disease) or (Basedow* disease) or (exophthalmic goiter*) or (Still's Disease) or (Stills disease) or (Juvenile arthriti*) or vitiligo or Psorias?s or (Arthriti* Psoria*) or (atopic disease) or (atopic dermatitis) or (food* sensiti*) or (food* toleran*) or (food* intoleran*) or (aero allergen*) or (air* allergen*) or (aeroallergen* sensiti*) or (allergen* sensiti*) or (skin prick test*) or atopy or hypersensitive*)

AND

db:("LILACS")

AND

type_of_study:("clinical_trials" or "case_control" or "cohort" or "systematic_reviews")

AND

limit:("infant" or "newborn" or "preschool" or "child")

COCHRANE Library

1. MeSH descriptor: [Diet] this term only
2. MeSH descriptor: [Diet Therapy] this term only
3. MeSH descriptor: [Nutritional Sciences] this term only
4. MeSH descriptor: [Child Nutrition Sciences] this term only
5. diet:ab,ti
6. diets:ab,ti
7. MeSH descriptor: [Diet, Mediterranean] this term only
8. “mediterranean diet*”:ab,ti
9. dietetic:ab,ti
10. dietary:ab,ti
11. eat:ab,ti
12. eating:ab,ti
13. intake:ab,ti
14. nutrient*:ab,ti
15. nutrition:ab,ti
16. MeSH descriptor: [Diet, Vegetarian] this term only
17. vegetarian*:ab,ti
18. vegan*:ab,ti
19. MeSH descriptor: [Diet, Macrobiotic] this term only
20. macrobiotic*:ab,ti
21. MeSH descriptor: [Food] this term only
22. food*:ab,ti
23. feed:ab,ti
24. feeding:ab,ti
25. cereal*:ab,ti
26. grain*:ab,ti
27. granary:ab,ti
28. wholegrain:ab,ti
29. wholewheat:ab,ti
30. “whole wheat”:ab,ti
31. wheat:ab,ti
32. wheatgerm:ab,ti
33. rye:ab,ti
34. barley:ab,ti
35. oat*:ab,ti

36. MeSH descriptor: [Cereals] explode all trees
37. root*:ab,ti
38. tuber*:ab,ti
39. MeSH descriptor: [Vegetables] explode all trees
40. vegetable*:ab,ti
41. onion*:ab,ti
42. spinach:ab,ti
43. chard:ab,ti
44. tomato*:ab,ti
45. pepper*:ab,ti
46. carrot*:ab,ti
47. beetroot:ab,ti
48. asparagus:ab,ti
49. garlic:ab,ti
50. pumpkin:ab,ti
51. sprouts:ab,ti
52. broccoli:ab,ti
53. cabbage*:ab,ti
54. celery:ab,ti
55. ginger:ab,ti
56. potato*:ab,ti
57. crisps:ab,ti
58. fries:ab,ti
59. syrup:ab,ti
60. honey:ab,ti
61. MeSH descriptor: [Honey] this term only
62. MeSH descriptor: [Fruit] this term only
63. fruit*:ab,ti
64. apple*:ab,ti
65. pear*:ab,ti
66. banana*:ab,ti
67. orange*:ab,ti
68. grape*:ab,ti
69. kiwi*:ab,ti
70. citrus:ab,ti
71. grapefruit*:ab,ti
72. pulses:ab,ti

73. beans:ab,ti
74. lentil*:ab,ti
75. chickpea*:ab,ti
76. legume*:ab,ti
77. lupin*:ab,ti
78. soy:ab,ti
79. soya:ab,ti
80. nut*:ab,ti
81. almond*:ab,ti
82. peanut*:ab,ti
83. groundnut*:ab,ti
84. MeSH descriptor: [Nuts] this term only
85. seed*:ab,ti
86. sesame:ab,ti
87. mustard:ab,ti
88. MeSH descriptor: [Seeds] this term only
89. MeSH descriptor: [Meat] explode all trees
90. meat:ab,ti
91. beef:ab,ti
92. pork:ab,ti
93. lamb:ab,ti
94. poultry:ab,ti
95. chicken:ab,ti
96. turkey:ab,ti
97. duck:ab,ti
98. fish:ab,ti
99. MeSH descriptor: [Fatty Acids] this term only
100. MeSH descriptor: [Fatty Acids, Omega-3] explode all trees
101. MeSH descriptor: [Fatty Acids, Omega-6] explode all trees
102. omega-3:ab,ti
103. omega-6:ab,ti
104. PUFA:ab,ti
105. fat:ab,ti
106. fats:ab,ti
107. fatty:ab,ti
108. egg:ab,ti
109. eggs:ab,ti

110. MeSH descriptor: [Eggs] explode all trees
111. MeSH descriptor: [Bread] this term only
112. bread:ab,ti
113. oil:ab,ti
114. oils:ab,ti
115. oily:ab,ti
116. omega:ab,ti
117. MeSH descriptor: [Seafood] explode all trees
118. seafood:ab,ti
119. shellfish:ab,ti
120. crustacean*:ab,ti
121. mollusc*:ab,ti
122. MeSH descriptor: [Shellfish] this term only
123. MeSH descriptor: [Dairy Products] this term only
124. dairy:ab,ti
125. MeSH descriptor: [Milk] explode all trees
126. milk:ab,ti
127. MeSH descriptor: [Infant Formula] this term only
128. formula*:ab,ti
129. hydrolysed:ab,ti
130. MeSH descriptor: [Infant Food] this term only
131. yoghurt:ab,ti
132. probiotic:ab,ti
133. prebiotic*:ab,ti
134. butter:ab,ti
135. herb*:ab,ti
136. spice*:ab,ti
137. chilli*:ab,ti
138. condiment*:ab,ti
139. MeSH descriptor: [Condiments] explode all trees
140. MeSH descriptor: [Beverages] this term only
141. beverage*:ab,ti
142. “fluid intake”:ab,ti
143. water:ab,ti
144. drink*:ab,ti
145. MeSH descriptor: [Food Preservation] explode all trees
146. pickled:ab,ti

147. bottled:ab,ti
148. canned:ab,ti
149. canning:ab,ti
150. smoked:ab,ti
151. preserved:ab,ti
152. preservatives:ab,ti
153. nitrosamine:ab,ti
154. hydrogenation:ab,ti
155. fortified:ab,ti
156. nitrates:ab,ti
157. nitrites:ab,ti
158. ferment*:ab,ti
159. processed:ab,ti
160. antioxidant*:ab,ti
161. “genetic modif*”:ab,ti
162. “genetically modif*”:ab,ti
163. MeSH descriptor: [Cooking] this term only
164. cooking:ab,ti
165. cooked:ab,ti
166. grill:ab,ti
167. grilled:ab,ti
168. fried:ab,ti
169. fry:ab,ti
170. roast:ab,ti
171. bake:ab,ti
172. baked:ab,ti
173. stewing:ab,ti
174. stewed:ab,ti
175. casserol*:ab,ti
176. broil:ab,ti
177. broiled:ab,ti
178. boiled:ab,ti
179. poach:ab,ti
180. poached:ab,ti
181. steamed:ab,ti
182. barbecue*:ab,ti
183. chargrill*:ab,ti

184. salt:ab,ti
185. salting:ab,ti
186. salted:ab,ti
187. fiber:ab,ti
188. fibre:ab,ti
189. polysaccharide*:ab,ti
190. starch:ab,ti
191. starchy:ab,ti
192. carbohydrate*:ab,ti
193. lipid*:ab,ti
194. “linoleic acid*”:ab,ti
195. sugar*:ab,ti
196. sweetener*:ab,ti
197. saccharin*:ab,ti
198. aspartame:ab,ti
199. sucrose:ab,ti
200. xylitol:ab,ti
201. cholesterol:ab,ti
202. “hydrogenated lard”:ab,ti
203. “dietary protein”:ab,ti
204. “dietary proteins”:ab,ti
205. “protein intake”:ab,ti
206. “animal protein*”:ab,ti
207. “total protein*”:ab,ti
208. “vegetable protein*”:ab,ti
209. “plant protein*”:ab,ti
210. MeSH descriptor: [Dietary Carbohydrates] explode all trees
211. MeSH descriptor: [Dietary Fats] explode all trees
212. MeSH descriptor: [Dietary Fiber] explode all trees
213. MeSH descriptor: [Dietary Proteins] explode all trees
214. MeSH descriptor: [Dietary Supplements] explode all trees
215. MeSH descriptor: [Food Additives] explode all trees
216. MeSH descriptor: [Vitamins] explode all trees
217. supplements:ab,ti
218. supplement:ab,ti
219. vitamin*:ab,ti
220. retinol:ab,ti

221. carotenoid*:ab,ti
222. tocopherol:ab,ti
223. folate*:ab,ti
224. “folic acid”:ab,ti
225. methionine:ab,ti
226. riboflavin:ab,ti
227. thiamine:ab,ti
228. niacin:ab,ti
229. pyridoxine:ab,ti
230. cobalamin:ab,ti
231. mineral*:ab,ti
232. sodium:ab,ti
233. iron:ab,ti
234. calcium:ab,ti
235. selenium:ab,ti
236. iodine:ab,ti
237. magnesium:ab,ti
238. potassium:ab,ti
239. zinc:ab,ti
240. copper:ab,ti
241. phosphorus:ab,ti
242. manganese:ab,ti
243. chromium:ab,ti
244. phytochemical:ab,ti
245. polyphenol*:ab,ti
246. phytoestrogen*:ab,ti
247. genistein:ab,ti
248. saponin*:ab,ti
249. coumarin*:ab,ti
250. flavonoid*:ab,ti
251. polyphenol*:ab,ti
252. flavonol*:ab,ti
253. flavone*:ab,ti
254. isoflavone*:ab,ti
255. catechin*:ab,ti
256. “ascorbic acid*”:ab,ti
257. “hydroxy cholecalciferol*”:ab,ti

258. hydroxycholecalciferol*:ab,ti
259. tocotrienol*:ab,ti
260. carotene*:ab,ti
261. cryptoxanthin*:ab,ti
262. lycopene*:ab,ti
263. lutein*:ab,ti
264. zeaxanthin*:ab,ti
265. selenium*:ab,ti
266. “organic diet*”:ab,ti
267. MeSH descriptor: [Food, Organic] this term only
268. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169 or 170 or 171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181 or 182 or 183 or 184 or 185 or 186 or 187 or 188 or 189 or 190 or 191 or 192 or 193 or 194 or 195 or 196 or 197 or 198 or 199 or 200 or 201 or 202 or 203 or 204 or 205 or 206 or 207 or 208 or 209 or 210 or 211 or 212 or 213 or 214 or 215 or 216 or 217 or 218 or 219 or 220 or 221 or 222 or 223 or 224 or 225 or 226 or 227 or 228 or 229 or 230 or 231 or 232 or 233 or 234 or 235 or 236 or 237 or 238 or 239 or 240 or 241 or 242 or 243 or 244 or 245 or 246 or 247 or 248 or 249 or 250 or 251 or 252 or 253 or 254 or 255 or 256 or 257 or 258 or 259 or 260 or 261 or 262 or 263 or 264 or 265 or 266 or 267
269. allerg*:ab,ti
270. asthma*:ab,ti
271. wheeze:ab,ti
272. wheezing:ab,ti
273. “bronchial hyperresponsiveness”:ab,ti
274. “bronchial hyperreactivity”:ab,ti
275. “Forced expiratory volume”:ab,ti
276. “FEV1”:ab,ti
277. "FEV 1":ab,ti

278. "FEV0.5":ab,ti
279. "FEV 0.5":ab,ti
280. “Forced vital capacity”:ab,ti
281. FVC:ab,ti
282. “Peak expiratory flow rate”:ab,ti
283. PEFR:ab,ti
284. AD:ab,ti
285. neurodermatitis:ab,ti
286. rhinitis:ab,ti
287. “besniers prurigo”:ab,ti
288. rhinoconjunctivitis:ab,ti
289. hayfever:ab,ti
290. “hay fever”:ab,ti
291. poll*nosis:ab,ti
292. SAR:ab,ti
293. “pollen allergy”:ab,ti
294. conjunctivitis:ab,ti
295. “immunoglobulin e”:ab,ti
296. “Total IgE”:ab,ti
297. “autoimmune disease*”:ab,ti
298. diabetes:ab,ti
299. diabetic:ab,ti
300. “type 1”:ab,ti
301. “c*eliac disease”:ab,ti
302. “crohn* disease”:ab,ti
303. “Inflammatory Bowel Disease*”:ab,ti
304. “Ulcerative colitis”:ab,ti
305. (Lympho* NEAR/3 thyroiditi*):ab,ti
306. (Thyroiditi* NEAR/3 autoimmune):ab,ti
307. (Hashimoto* NEAR/3 (syndrome* or thyroiditi* or disease*)):ab,ti
308. (Thyroiditi* NEAR/3 (post-partum or postpartum)):ab,ti
309. “Graves* disease”:ab,ti
310. “Basedow* disease”:ab,ti
311. “exophthalmic goiter*”:ab,ti
312. (Still* Disease NEAR/3 (juvenile or onset)):ab,ti
313. (Juvenile NEAR/3 arthriti*):ab,ti
314. vitiligo:ab,ti

315. Psorias*s:ab,ti
316. (Arthriti* NEAR/3 Psoria*):ab,ti
317. “atopic disease”:ab,ti
318. “atopic dermatitis”:ab,ti
319. (food* NEAR/3 sensiti*):ab,ti
320. (food* NEAR/3 toleran*):ab,ti
321. (food* NEAR/3 intoleran*):ab,ti
322. ((aero or air*) NEAR/3 allergen*):ab,ti
323. (aeroallergen* NEAR/3 sensiti*):ab,ti
324. (allergen* NEAR/3 sensiti*):ab,ti
325. “skin prick test*”:ab,ti
326. atopy:ab,ti
327. hypersensitiv*:ab,ti
328. MeSH descriptor: [Hypersensitivity] this term only
329. MeSH descriptor: [Food Hypersensitivity] explode all trees
330. MeSH descriptor: [Respiratory Hypersensitivity] this term only
331. MeSH descriptor: [Asthma] this term only
332. MeSH descriptor: [Bronchial Hyperreactivity] this term only
333. MeSH descriptor: [Forced Expiratory Volume] this term only
334. MeSH descriptor: [Vital Capacity] this term only
335. MeSH descriptor: [Peak Expiratory Flow Rate] this term only
336. MeSH descriptor: [AD] this term only
337. MeSH descriptor: [Neurodermatitis] this term only
338. MeSH descriptor: [Rhinitis] this term only
339. MeSH descriptor: [Rhinitis, Allergic, Perennial] this term only
340. MeSH descriptor: [Rhinitis, Allergic, Seasonal] this term only
341. MeSH descriptor: [Conjunctivitis] this term only
342. MeSH descriptor: [Immunoglobulin E] this term only
343. MeSH descriptor: [Autoimmune Diseases] this term only
344. MeSH descriptor: [Diabetes Mellitus, Type 1] this term only
345. MeSH descriptor: [Celiac Disease] this term only
346. MeSH descriptor: [Crohn Disease] this term only
347. MeSH descriptor: [Inflammatory Bowel Diseases] this term only
348. MeSH descriptor: [Colitis, Ulcerative] this term only
349. MeSH descriptor: [Thyroiditis, Autoimmune] this term only
350. MeSH descriptor: [Hashimoto Disease] this term only
351. MeSH descriptor: [Postpartum Thyroiditis] this term only

352. MeSH descriptor: [Graves Disease] this term only
353. MeSH descriptor: [Arthritis, Juvenile Rheumatoid] this term only
354. MeSH descriptor: [Vitiligo] this term only
355. MeSH descriptor: [Psoriasis] this term only
356. MeSH descriptor: [Arthritis, Psoriatic] this term only
357. MeSH descriptor: [Dermatitis, Atopic] this term only
358. MeSH descriptor: [Hypersensitivity, Immediate] this term only
359. 269 or 270 or 271 or 272 or 273 or 274 or 275 or 276 or 277 or 278 or 279 or 280 or 281 or 282 or 283 or 284 or 285 or 286 or 287 or 288 or 289 or 290 or 291 or 292 or 293 or 294 or 295 or 296 or 297 or 298 or 299 or 300 or 301 or 302 or 303 or 304 or 305 or 306 or 307 or 308 or 309 or 310 or 311 or 312 or 313 or 314 or 315 or 316 or 317 or 318 or 319 or 320 or 321 or 322 or 323 or 324 or 325 or 326 or 327 or 328 or 329 or 330 or 331 or 332 or 333 or 334 or 335 or 336 or 337 or 338 or 339 or 340 or 341 or 342 or 343 or 344 or 345 or 346 or 347 or 348 or 349 or 350 or 351 or 352 or 353 or 354 or 355 or 356 or 357 or 358
360. infant*:ab,ti
361. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four" or "twenty five" or "twenty six") NEAR/1 week*):ab,ti
362. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four") NEAR/1 month*):ab,ti
363. 361 or 362
364. (old or age*):ab,ti
365. 363 and 364
366. (("one year*" or "two year*") NEAR/3 (old or age*)):ab,ti
367. ((first or second or two) NEAR/3 "year* of life"):ab,ti
368. MeSH descriptor: [Infant] this term only
369. MeSH descriptor: [Infant, Newborn] this term only
370. (maternal or pregnan*):ab,ti
371. (lactat*):ab,ti
372. (mother*):ab,ti
373. 360 or 365 or 366 or 367 or 368 or 369 or 370 or 371 or 372
374. “clinical trial*”
375. random*
376. factorial*
377. crossover*

378. placebo*
379. “doubl* blind*”
380. “singl* blind*”
381. assign*
382. volunteer*
383. “cohort stud*”
384. longitudinal*
385. follow-up
386. prospectiv*
387. retrospectiv*
388. “case control”
389. “case referent”
390. MeSH descriptor: [clinical trial] explode all trees
391. MeSH descriptor: [Cross-Over Studies] this term only
392. MeSH descriptor: [Placebos] this term only
393. MeSH descriptor: [Double-Blind Method] this term only
394. MeSH descriptor: [Single-Blind Method] this term only
395. MeSH descriptor: [Cohort Studies] explode all trees
396. MeSH descriptor: [case-control studies] this term only
397. 374 or 375 or 376 or 377 or 378 or 379 or 380 or 381 or 382 or 383 or 384 or 385 or 386 or 387 or 388 or 389 or 390 or 391 or 392 or 393 or 394 or 395 or 396
398. 268 and 359 and 373 and 397

Web of Science

1. TOPIC = (diet$ or “mediterranean diet*” or dietetic or dietary or eat or eating or intake or nutrient$ or nutrition or vegetarian$ or vegan$ or macrobiotic$ or food$ or feed or feeding or cereal$ or grain$ or granary or wholegrain or wholewheat or “whole wheat” or wheat or wheatgerm or rye or barley or oat$ or root$ or tuber$ or vegetable$ or onion$ or spinach or chard or tomato* or pepper$ or carrot$ or beetroot or asparagus or garlic or pumpkin or sprouts or broccoli or cabbage$ or celery or ginger or potato* or crisps or fries or syrup or honey or fruit$ or apple$ or pear$ or banana$ or orange$ or grape$ or kiwi$ or citrus or grapefruit$ or pulses or bean$ or lentil$ or chickpea$ or legume$ or lupin$ or soy or soya or nut$ or almond$ or peanut$ or groundnut$ or seed$ or sesame or mustard or meat$ or beef or pork or lamb or poultry or chicken or turkey or duck or fish* or omega-3 or omega-6 or PUFA or fat$ or fatty or egg$ or bread or oil$ or omega or seafood or shellfish or crustacean$ or mollusc$ or dairy or milk or formula$ or hydrolysed or yoghurt or probiotic$ or prebiotic$ or butter or herb$ or spice$ or chilli* or condiment$ or beverage$ or “fluid intake” or water or drink* or pickled or bottled or canned or canning or smoked or preserved or preservative$ or nitrosamine or hydrogenation or fortified or nitrates or nitrites or ferment* or processed or antioxidant$ or “genetic modif*” or “genetically modif*” or cooking or cooked or grill or grilled or fried or fry or roast or bake or baked or stewing or stewed or casserole* or broil or broiled or boiled or poach or poached or steamed or barbecue$ or chargrill* or salt or salting or salted or fiber or fibre or polysaccharide$ or starch or starchy or carbohydrate$ or lipid$ or “linoleic acid$” or sugar$ or sweetener$ or saccharin$ or aspartame or sucrose or xylitol or cholesterol or “hydrogenated lard” or “dietary protein$” or “protein intake” or “animal protein$” or “total protein$” or “vegetable protein$” or “plant protein$” or supplement$ or vitamin$ or retinol or carotenoid$ or tocopherol or folate$ or “folic acid” or methionine or riboflavin or thiamine or niacin or pyridoxine or cobalamin or mineral$ or sodium or iron or calcium or selenium or iodine or magnesium or potassium or zinc or copper or phosphorus or manganese or chromium or phytochemical or polyphenol$ or phytoestrogen$ or genistein or saponin$ or coumarin$ or flavonoid$ or polyphenol$ or flavonol$ or flavone$ or isoflavone$ or catechin$ or “ascorbic acid$” or “hydroxy cholecalciferol$” or “hydroxycholecalciferol$” or tocotrienol$ or carotene$ or cryptoxanthin$ or lycopene$ or lutein$ or zeaxanthin$ or selenium$ or “organic diet$”)

2. TOPIC = (allerg* or asthma* or wheeze or wheezing or “bronchial hyperresponsiveness” or “bronchial hyperreactivity” or “Forced expiratory volume” or “FEV1” or "FEV 1" or "FEV0.5" or "FEV 0.5" or “Forced vital capacity” or FVC or “Peak expiratory flow rate” or PEFR or AD or neurodermatitis or rhinitis or “besniers prurigo” or rhinoconjunctivitis or hayfever or “hay fever” or poll$nosis or SAR or “pollen allergy” or conjunctivitis or “immunoglobulin e” or “Total IgE” or “autoimmune disease$” or diabetes or diabetic or “type 1” or “c$eliac disease” or “crohn* disease” or “Inflammatory Bowel Disease$” or “Ulcerative colitis” or (Lympho* NEAR/3 thyroiditi*) or (Thyroiditi* NEAR/3 autoimmune) or (Hashimoto* NEAR/3 (syndrome$ or thyroiditis* or disease$))

or (Thyroiditi* NEAR/3 (post-partum or postpartum)) or “Graves$ Disease” or “Basedow* disease” or “exophthalmic goiter$” or (“Still$ Disease” NEAR/3 (juvenile or onset)) or (Juvenile NEAR/3 arthriti*) or vitiligo or Psorias$s or (Arthriti$ NEAR/3 Psoria*) or “atopic disease” or “atopic dermatitis” or (food$ NEAR/3 sensiti*) or (food$ NEAR/3 toleran*) or (food$ NEAR/3 intoleran*) or ((aero or air*) NEAR/3 allergen$) or (aeroallergen$ NEAR/3 sensiti*) or (allergen$ NEAR/3 sensiti*) or “skin prick test*” or atopy or hypersensitive*)

3. TOPIC = (infant$ or (("one year$" or "two year$") NEAR/3 (old or age$)) or ((first or second or two) NEAR/3 "year$ of life") or (maternal) or (pregnan*) or (lactat*) or (mother$))

4. TOPIC = ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four" or "twenty five" or "twenty six") NEAR/1 week$)

5. TOPIC = ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four") NEAR/1 month$)

6. 4 or 5

7. TOPIC = ((old or age$))

8. 7 and 6

9. 8 or 3

10. TOPIC = (“clinical trial$” or random* or factorial* or crossover* or placebo* or “doubl* blind*” or “singl* blind*” or assign* or volunteer* or “cohort stud*” or longitudinal* or follow-up or prospective* or retrospective* or “case control” or “case referent”)

11. 1 and 2 and 9 and 10

REVIEW OF SCIENTIFIC PUBLISHED LITERATURE ON INFANT FEEDING AND DEVELOPMENT OF ATOPIC AND AUTOIMMUNE DISEASE

REVIEW A: DURATION OF TOTAL AND EXCLUSIVE BREASTFEEDING, AND TIMING OF SOLID FOOD INTRODUCTION

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Exhibition Road,

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1. Introduction

This is one of 4 reports resulting from a comprehensive review of the scientific literature on infant feeding and the development of atopic and autoimmune diseases, commissioned by the UK Food Standards Agency. Atopic conditions such as asthma, eczema, rhinoconjunctivitis and food allergy appear to have increased in prevalence in recent decades in many countries, and are now the leading causes of chronic illness in children and young adults living in the UK [1, 2 3 4 5]. The apparently rapid changes in disease prevalence, combined with data from migration studies, suggest that early-life environmental factors may be important modulators of atopic disease risk. Similar findings apply to the autoimmune diseases type I diabetes mellitus and Crohn's disease, which appear to have increased in prevalence in some countries [6]. Significant attention has focussed on early-life dietary exposures in relation to these atopic and autoimmune diseases due to the rapid changes in the human diet in recent decades, and the potential effects of such changes on the intestinal and systemic immune development [7]. The gut associated lymphoid tissue is our largest collection of immune tissue, and our most mature immune organ at the time of birth [8]. Hence enteral exposures in infancy are likely to be especially potent modulators of immune development and risk of immune-mediated disease. Although there are a large number of observational studies, some intervention trials and several systematic reviews in this area, they tend to focus on one specific area of diet and a limited number of immune outcomes. The purpose of this project is to assess comprehensively and systematically the existing literature regarding the relationship between dietary exposures during pregnancy, lactation and infancy, and a child's risk of developing any of the common atopic and/or autoimmune diseases.

This project consists of a series of systematic reviews which together have very broad inclusion criteria and were registered as 3 separate review protocols on the International

Prospective Register of Systematic Reviews (PROSPERO references CRD42013003802 – REVIEW A; CRD42013004239 – REVIEW B; CRD42013004252 – REVIEW C; www.crd.york.ac.uk/Prospero) on the 5th August 2013. The overall purpose of the work is to inform UK Government feeding guidance for mothers and their infants. The outcomes of this project will be summarised in 4 separate reports, with a distinct set of dietary exposures examined in each report:

1. REVIEW A: DURATION OF TOTAL AND EXCLUSIVE BREASTFEEDING, AND TIMING OF SOLID FOOD INTRODUCTION
2. REVIEW B: TIMING OF INTRODUCTION OF ALLERGENIC FOODS INTO THE INFANT DIET
3. REVIEW C PART I: HYDROLYSED FORMULA IN PLACE OF STANDARD UNHYDROLYSED COW'S MILK BASED INFANT FORMULA, OR BREAST MILK
4. REVIEW C PART II: OTHER MATERNAL AND INFANT DIETARY EXPOSURES

The specific outcomes of interest for all of these reviews, chosen due to their high prevalence in the UK population, and described in more detail below, are:

Atopic disorders: Food allergy, Eczema, Asthma, Allergic rhinitis, Allergic conjunctivitis, Allergic sensitisation

Autoimmune disorders: Type 1 diabetes mellitus, Coeliac disease, Inflammatory bowel disease, Autoimmune thyroid disease, Juvenile rheumatoid arthritis, Vitiligo, Psoriasis.

1.1. REVIEW A: Duration of total and exclusive breastfeeding, and timing of solid food introduction

This first review focuses on the relationship between breastfeeding and risk of atopic/autoimmune diseases. Human breast milk is the main nutritional exposure during infancy, and usually the sole exposure during the critical early months of immune maturation. Cow's milk based infant formula has a very different composition to human breast milk, and is deficient in the high concentrations of IgG and IgA antibodies and growth factors, cellular components, cytokines and other immune active factors that influence infant immunity [9]. The introduction of non-human formula milk, and the introduction of non-milk feeds (here called 'solid food') are both associated with significant changes in the intestinal microbiome and gastrointestinal physiology, which in turn influence infant immune development [10]. Through their impact on immune development, the exposures assessed in this report may in theory be able to influence a developing child's risk of atopic or autoimmune disorders both during feeding and through the life course. Thus this first report addresses the question whether duration of total or exclusive breastfeeding, and/or timing of solid food introduction influence the development of atopic or autoimmune disorders.

1.2. Specific review questions addressed in Review A

A1. Does the total duration of breastfeeding up to 2 years, influence children's future risk of atopic disease, allergic sensitisation or autoimmune disease?

A2. Does the duration of exclusive/predominant breastfeeding during the first year of life, influence children's future risk of atopic disease, allergic sensitisation or autoimmune disease?

A3. Does the timing of introduction of solid food during the first year of life, influence children's future risk of atopic disease, allergic sensitisation or autoimmune disease?

1.3. Glossary of key terms

Allergic sensitisation: production of specific IgE antibodies directed against harmless environmental antigens such as pollens, mites, milk, egg or peanut; or production of increased serum total IgE levels. Allergic sensitisation is strongly associated with Atopic disease.

Atopic disease: chronic health conditions associated with (but not always directly caused by) the production of IgE antibodies to harmless environmental antigens.

Exclusive breastfeeding duration (EBF): age at which another food other than human breast milk (but excluding oral rehydration solution, vitamins, minerals or medications) is introduced into the infant diet.

Predominant breastfeeding duration: age at which another food other than human breast milk (but excluding oral rehydration solution, vitamins, minerals, medications, water, water-based drinks or fruit juice) is introduced into the infant diet.

Solid food introduction: time at which the first non-milk food is introduced into the infant diet eg rice cereal, pureed vegetables or fruits.

Total breastfeeding duration (TBF): time until all breastfeeding has ceased.

GRADE evaluation of evidence: grade of evidence in this report is assigned using the GRADE system, which has 4 categories HIGH, MODERATE, LOW or VERY LOW. Evidence is initially assigned as HIGH if coming from a randomised trial; LOW from observational studies; VERY LOW from other evidence. The grade of evidence is then reduced if there are serious (-1) or very serious (-2) limitations to study quality or uncertainties about directness of association; important inconsistency (-1), imprecise or sparse data (-1) or a high probability of reporting bias (-1). Grade of evidence is increased if strong evidence of association is seen (eg RR >2 or <0.5) from ≥2 observational studies with no plausible confounders (+1) or very strong direct evidence (RR >5 or <0.2) with no major threats to validity (+2); if there is evidence of a dose-response gradient (+1) or if all plausible confounders would have reduced the effect/association seen (+1). The interpretation of GRADE evidence assessments is that for HIGH level evidence further research is very unlikely to change our confidence in the estimate of effect; for MODERATE evidence further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; for LOW level evidence further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; and for VERY LOW level evidence any estimate of effect is very uncertain. Further detailed explanation of GRADE can be found at:

http://www.gradeworkinggroup.org/publications/Grading_evidence_and_recommendations_BMJ.pdf

2. Executive Summary

The key findings of this review are summarised below, in relation to each of 7 outcome domains of interest – wheeze (including asthma and lung function), eczema, rhino-conjunctivitis, allergic sensitisation, food allergy, type 1 diabetes mellitus, and all other autoimmune diseases. We used the GRADE approach to assessing the strength of evidence, and specify in the text of the Executive Summary where judgements have been made that result in lower or higher grade evidence [11].

This is followed by a summary of the Methods used to identify studies, extract, analyse and appraise data, and a Discussion of the main findings in the context of existing literature. The 7 separate systematic reviews which provide the basis for this Executive Summary and constitute the substance of REVIEW A, can be accessed from Table 1 below.

Table 1 Individual study reports in relation to 7 outcome domains of interest.

Outcome	Report
Wheeze	
Eczema	
Rhino-conjunctivitis	
Food Allergy	
Allergic Sensitisation	
Type 1 Diabetes Mellitus	
Other Autoimmune Diseases	

2.1 Duration of TBF and EBF, or timing of solid food introduction, and Wheeze

Data from over 500,000 participants in 100 studies contributed to this report. In the single randomised controlled trial (RCT) of a breastfeeding promotion intervention, there was no evidence for an effect on wheeze at age 1 year or 6.5 years. In the observational studies, there was an association between increased TBF duration and reduced risk of wheeze (TBF ever vs never at age 5-14, and TBF ≥3-4 months at age 15+), and recurrent wheeze (TBF ≥3-4 months at age 0-4; TBF ever vs never, ≥3-4, ≥18 months at age 5-14). There was no evidence for reduced risk at other cut-offs and ages. There was evidence of publication bias for TBF and wheeze/recurrent wheeze at aged 5-14 (GRADE -1; reporting bias). EBF ≥0-2 months was associated with reduced wheeze at ages 0-4 and 5-14, but not recurrent wheeze, and no consistent relationships were seen with other EBF durations. Some EBF analyses had high statistical heterogeneity, and some evidence of publication bias (GRADE -2; inconsistency, reporting bias). We did not find evidence for an association between timing of solid food introduction and asthma/wheeze. There was no consistent evidence that increased TBF and EBF duration are associated with bronchial hyper-reactivity or measures of lung function.

Conclusion:

Increased TBF duration may be associated with reduced risk of recurrent wheeze at age 5-14.

Grade of evidence: VERY LOW.

There is no evidence for an association between TBF or EBF duration, or timing of solid food introduction, and other measures of wheezing, bronchial hyper-reactivity or lung function.

2.2 Duration of TBF and EBF, or timing of solid food introduction, and Eczema

Data from over 250,000 participants in 90 studies contributed to this report. Some analyses were limited by small numbers of studies reporting relevant data, especially for EBF and timing of solid food introduction. One RCT of a breastfeeding promotion intervention found reduced eczema at age 1 year (OR 0.54 95% CI 0.31, 0.95; GRADE -2; imprecision, inconsistency) but not at age 6.5 years. . From the observational studies, we found no consistent evidence that duration of TBF or EBF, or timing of solid food introduction, are associated with risk of eczema. Some analyses suggested an association in the opposite direction i.e. increased duration of TBF and EBF were associated with increased eczema risk at age 0-4 (TBF ever vs never), at age 5-14 (TBF ≥1-2, ≥3-4, ≥5-7 and ≥8-12 months; EBF ≥0-2 months) and at age 15+ (TBF ≥3-4 months; EBF ≥0-2 months). Several of these analyses were dominated by one study, albeit one with low risk of bias. Other analyses showed either no evidence of association, or reduced eczema risk with increased breastfeeding duration (for EBF≥3-4 months only, and eczema at age 0-4). These associations were not seen in studies which couldn't be included in meta-analysis, and subgroup analysis for TBF found no association in studies with low risk of bias (GRADE -2; inconsistency, study quality). Finally, very few studies failed to make allowance in their analyses for the possibility of reverse causation ie prolonged TBF/EBF when infants develop eczema, due to concerns about associated food allergy. We found no association between timing of solid food introduction and eczema risk.

Conclusion:

A breastfeeding promotion intervention may reduce risk of eczema in the first year.

Grade of evidence: LOW.

There is no consistent evidence from observational studies, for an association between TBF and EBF duration, or timing of solid food introduction, and risk of developing eczema.

2.3 Duration of TBF and EBF, or timing of solid food introduction, and Rhino-conjunctivitis

Data from over 200,000 participants in 33 studies contributed to this report. Overall we found no evidence to support an association between duration of TBF or EBF and rhinoconjunctivitis (RC) risk at age 0-4, 5-14 or 15+. In the single RCT of a breastfeeding promotion intervention, there was no evidence for an effect on RC at age 6.5 years.. One meta-analysis of 5 observational studies (18,000 participants) found reduced RC risk at age 0-4 years associated with EBF ≥ 3-4 months (OR 0.77 95% CI 0.60, 0.99), with no statistical heterogeneity. However statistical significance was borderline, and we were unable to confirm this association using other cut-offs for EBF duration or at ages 5-14 or 15 years and older (GRADE -2 imprecision; -1 inconsistency). Data for timing of solid food introduction and disease risk were limited, but do not support an association.

Conclusion:

There is no consistent evidence for an association between TBF duration, EBF duration or timing of solid food introduction and RC.

2.4 Duration of TBF and EBF, or timing of solid food introduction, and Allergic Sensitisation

Data from over 30,000 participants in over 40 studies contributed to this report. Overall we found no clear evidence to support an association between TBF, EBF or timing of solid food introduction and allergic sensitisation. In the single RCT of a breastfeeding promotion intervention, there was no evidence for an effect on RC at age 6.5 years. From the observational studies, one meta-analysis of 3 prospective cohort studies (2000 participants) found increased risk of food AS associated with EBF ≥0-2 months with no statistical heterogeneity, and one study from that meta-analysis also reported increased risk of food AS with TBF ever vs never. However, there was no association seen in analysis of other age cut-offs for TBF or EBF duration and food AS, which included similar numbers of participants than the positive analyses. There was also no association between TBF/EBF and other forms of allergic sensitisation (i.e. milk, egg or peanut individually, to aeroallergens or to 'any allergen'), or in studies which could not be included in meta-analysis (GRADE -2; inconsistency, imprecision). The possibility of reverse causality was explored in one of the 3 positive studies, and one negative study, with no evidence found that the outcome was influencing the exposure however reverse causality cannot be excluded in the other studies.

Conclusion:

There is no evidence for an association between TBF and EBF duration, or timing of solid food introduction, and risk of developing allergic sensitisation.

2.5 Duration of TBF and EBF, or timing of solid food introduction, and Food Allergy

Data from over 70,000 participants in 29 studies contributed to this report. Food allergy was defined using medical assessments with allergy testing and clinical history in most cases, using oral food challenges in some, and parental report of food allergic reaction(s) alone in others. No intervention trial was identified, which evaluated food allergy as an outcome. From the observational studies we found some evidence to support an association between TBF ever vs never and increased risk of food allergy, but the data were mainly unadjusted, associations were not seen in other analyses of TBF, and this finding is vulnerable to reverse causation, since the 2 included studies did not undertake restricted analysis excluding cases of food allergy which arose during the breastfeeding period (GRADE -2; inconsistency, study quality).

The available data did not suggest any association between EBF duration or timing of solid food introduction and food allergy.

Conclusion:

There is no evidence for an association between TBF and EBF duration, or timing of solid food introduction, and risk of developing food allergy.

The evidence is limited by small numbers of studies and participants, often without appropriate statistical adjustments, so that important associations cannot be confidently excluded for this outcome.

2.6 Duration of TBF and EBF, or timing of solid food introduction, and Type 1 Diabetes Mellitus

Data from over 15,000 participants in over 60 studies contributed to this report. Most studies were case-control studies, some of which were nested in prospective cohorts. Overall we found evidence that longer duration of TBF at all ages from birth to 1 year, and longer duration of EBF at all ages from birth to 4 months, is associated with reduced diabetes risk. For TBF duration there was moderate/high statistical heterogeneity, and for both TBF and EBF a stronger association was seen between breastfeeding duration and TIDM risk in the retrospective studies (GRADE -1; inconsistency). Prospective studies often used surrogate serological diagnosis of TIDM at an early age, but recall bias in the retrospective studies must also be considered as an explanation for the difference in findings between prospective and retrospective studies. We found no evidence for differences between adjusted and unadjusted data, and plausible confounders such as socioeconomic status would be expected to lead to an association between longer duration of breastfeeding and *increased* TIDM risk, since both are associated with higher socioeconomic status in many settings (GRADE +1; confounding). So we consider that the risk of the association between TIDM and breastfeeding duration being due to hidden confounding is low. We found no association between timing of solid food introduction and diabetes risk.

Conclusion:

Total and exclusive breastfeeding duration are associated with reduced TIDM risk.

Grade of evidence: LOW.

There is no evidence for that timing of solid food introduction influences TIDM risk.

2.7 Duration of TBF and EBF, or timing of solid food introduction, and Other Autoimmune Diseases

Data from over 250,000 participants in 12 studies contributed to assessment of coeliac disease; 13,000 participants/ 13 studies inflammatory bowel disease; 1200 participants/ 3 studies juvenile rheumatoid arthritis; 189 participants/ 1 study thyroid disease. We did not identify studies for vitiligo/psoriasis. Most included studies were case-control design. We found shorter TBF or EBF duration in those with coeliac disease, but data were often unadjusted, and there was high statistical heterogeneity due to differences between the 2 prospective studies (100 cases) with no association, and 6 retrospective studies (1100 cases) which found reduced coeliac disease with longer TBF or EBF (GRADE -2; inconsistency, study quality). A further 1 prospective (50 cases) and 3 retrospective studies (220 cases) found no association but could not be included in meta-analyses due to the way the data were reported.

Two retrospective studies (570 cases) reporting unadjusted data found reduced risk of Crohn's disease with TBF ≥5-7 months and ≥3-4 months. There was no association at ≥1-2 months, or ever vs never; nor with EBF or solid food introduction, and no association between Ulcerative colitis and TBF/EBF or solid food introduction. Data for arthritis and thyroid disease were non-significant, but limited by low study/participant numbers.

Conclusion:

There is no evidence for an association between TBF and EBF duration, or timing of solid food introduction, and risk of autoimmune diseases.

3. Methods

3.1. Inclusion Criteria

3.1.1. Types of study included

We included recent high quality systematic reviews published from 2011 until the search date (25th July 2013; updated on 26th February 2017). Older systematic reviews were not included, due to the likelihood of being out of date. We quality assessed eligible systematic reviews using the revised AMSTAR criteria [12] and extracted data from systematic reviews with revised AMSTAR score ≥32. A summary of the identified reviews is included at the end of this report, and relevant review findings are included in each of the 7 individual systematic reviews that comprise Review A, as appropriate.

We included other research studies published at any time prior to the search date (25th July 2013; updated on 26th February 2017for intervention trials only). Original studies eligible for inclusion were randomised controlled trials (RCT), quasi RCT (RCT where the allocation sequence was predictable but not thought likely to lead to imbalance), controlled clinical trials (CCT where the allocation sequence was predictable, and thought likely to lead to significant imbalance between groups in important risk factors for the outcome(s) of interest), prospective cohort or longitudinal studies, retrospective cohort studies, nested case-control studies, other case control studies and cross-sectional surveys. We took a hierarchical approach to study design, such that where data were absent or limited from systematic reviews or intervention trials, we included observational study data. Where a large number of intervention trials were identified, we did not analyse data from observations studies that assessed the same intervention/exposure. We did not include non-comparative studies, or non-human studies.

3.1.2. Participants/population

Inclusion criteria: Infants between birth and the end of their 12th post-partum month (questions A2 and A3) or birth and the end of the 24th post-partum month (question A1). The reason for this is that the primary focus of the review is the first year of life, which encompasses food introduction and the end of exclusive breastfeeding in most circumstances, but total breastfeeding duration is recommended to be at least 2 years by the World Health Organisation (WHO). If infants were characterised as high or normal/low risk for atopic or autoimmune disease based on family history or genotype, this information was be recorded so that it could be used for the planned subgroup analysis by disease risk.

Exclusion criteria: We excluded studies in which participants were defined by a disease state - e.g. pregnant women with specific nutritional deficiencies, infants born prematurely (<31 weeks gestation) or other groups clearly representing <5% of the UK population, since the results of this review should apply to the general UK population. We did not exclude studies on the basis of including specific ethnic groups, studies of high risk infants, since this applies to many UK-born infants for allergic disease, and it is difficult to undertake studies of autoimmune disease prevention in the general population without stratifying by genetic/family risk due to the relatively low prevalence of autoimmune diseases.

3.1.3. Interventions/ exposures

3.1.3.1. Review question A1

Timing of the total duration of breastfeeding (i.e. time to complete cessation of breastfeeding). We extracted data for total breastfeeding duration when reported either as a continuous variable, and when reported categorically.

3.1.3.2. Review question A2

Timing of the transition from exclusive/predominant breastfeeding (as defined by WHO), to partial or no breastfeeding (i.e. introduction of a complementary food including infant formula). We extracted data for exclusive breastfeeding duration reported either as a continuous or categorical variable. Where possible, we planned to characterise studies as defining exclusive/predominant breastfeeding according to the WHO definition, or not, so that this information could be used for the planned subgroup analysis by breastfeeding definition.

Exclusive breastfeeding is defined by WHO as 'no other food or drink, not even water, except breast milk (including milk expressed or from a wet nurse) other than oral rehydration solution, and drops/syrups (vitamins, minerals and medicines)'.

Predominant breastfeeding is defined by WHO as meaning 'the infant's predominant source of nourishment is breast milk (as defined above), but they may also receive liquids (water and water-based drinks, fruit juice) and ritual fluids in addition to those permitted under exclusive breastfeeding.'

The vast majority of studies define exclusive breastfeeding as the period where the main source of feeding is breast milk without other milk feed or complementary food. Thus, in this report the term exclusive breastfeeding is the equivalent of predominant breastfeeding as defined by WHO. Where possible, we planned to characterise studies as defining predominant breastfeeding according to the WHO definition, or not, so that this information could be used for the planned subgroup analysis by breastfeeding.

3.1.3.3. Review question A3

Timing of the transition from liquid infant milk feed (i.e. breast milk and/or infant formula) to the introduction of other complementary foods. We extracted data for this exposure, termed 'solid food' when reported either as a continuous variable, or categorically.

3.2. Search strategy

The search strategies included both text terms and subject heading terms where appropriate. The search strategies were initially developed for use on the MEDLINE database and then adapted for use on other databases. We searched the following databases, with no specified start date:

- The Cochrane Library (2013, Issue 7)
- EMBASE (1947 to July 2013)
- LILACS (1982 to July 2013)
- MEDLINE (1946 to July 2013)
- Web of Science (1970 to July 2013)

The search was run on 25th July 2013 and included all studies published up to that date, and was updated on 26th February 2017for intervention trials and systematic reviews. We included peer reviewed publications, and abstract publications if they contained data that had not subsequently been published as a peer reviewed publication. We reviewed the bibliography of eligible studies for possible additional publications, and included all eligible publications, regardless of the language. We did not contact the authors of eligible or potentially eligible studies to request original data. The search strategies were extensively piloted and refined to optimise sensitivity, comparing search results with those of other high

quality published systematic reviews. The final search strategies for review A are listed at the end of this document, as *Appendices*.

The search for existing systematic reviews which cover any of the same exposure(s)/outcome(s) as the original studies was limited to publications from 1st January 2011 to 25th July 2013 in the original search, and to 26th February 2017in the update. The search strategy was partly based on the search strategies used for Review A, Review B and Review C but included a search filter for retrieving systematic reviews (Lee et al., 2012). Open Grey was searched using the terms '(breast OR lactation OR formula) AND (allergy OR autoimmune OR asthma OR eczema OR rhinitis OR conjunctivitis OR food allergy OR vitiligo OR psoriasis OR arthritisi OR thyroiditis OR atopy OR IgE OR diabetes OR coeliac OR inflammatory bowel disease)' for studies relevant to Review A; the terms '(wean OR peanut OR egg OR milk OR soya OR nut OR fish OR wheat) AND (allergy OR autoimmune OR asthma OR eczema OR rhinitis OR conjunctivitis OR food allergy OR vitiligo OR psoriasis OR arthritisi OR thyroiditis OR atopy OR IgE OR diabetes OR coeliac OR inflammatory bowel disease)' for studies relevant to review B; the terms '(lactation OR pregnancy OR infant OR mother) AND (allergy OR autoimmune OR asthma OR eczema OR rhinitis OR conjunctivitis OR food allergy OR vitiligo OR psoriasis OR arthritisi OR thyroiditis OR atopy OR IgE OR diabetes OR coeliac OR inflammatory bowel disease)' for studies relevant to review C.

The International Prospective Register of Systematic Reviews (PROSPERO) database was also searched for relevant systematic reviews. Due to the limited functionality of this resource individual keywords with date limits were used to search PROSPERO: we searched for titles containing 'breast OR infant OR lactation OR wean OR infant' for studies relevant to review A; 'nut OR wheat OR egg OR food OR diet' for studies relevant to review B; 'pregnant OR infant OR diet OR nutrition OR supplement' for studies relevant to review C.

The citations identified in searches were imported into Endnote libraries for de-duplication and title screening.

3.3. Study Outcomes

We selected atopic and autoimmune outcomes on the basis of their population prevalence in children and young adults in the UK. We included diseases with a prevalence of at least 1 in 1000, in children/adolescents or young adults (aged <40 years), but did not include rarer diseases [13]. We did not include pernicious anaemia or adult-onset rheumatoid arthritis despite a high prevalence in middle aged or elderly people, because their prevalence in young people is lower than 1 in 1000, and prospective studies of infant feeding in relation to diseases of older adults are unlikely to have been undertaken. We did not specifically exclude rare manifestations of food allergy such as eosinophilic oesophagitis, if they were reported as part of a food allergy definition, but did exclude them if they were reported as a unique outcome measure since their prevalence is less than 1 in 1000. For atopic outcomes, age at assessment was grouped as 1-4 years, 5-14 years, 15-24 years, 25-44 years, 45-64 years and ≥65 years. Due to a paucity of studies in adults, we pooled all age groups ≥ 15 years for almost all reports. For autoimmune outcomes, we did not stratify analyses by age at outcome assessment. Where studies reported the same outcome at different timepoints within one of these frames, we used the timepoint with the most complete dataset ie lowest percentage of missing data, as the primary assessment point for inclusion in meta-analysis. Where possible we chose a timepoint for outcome assessment that did not fall within the relevant exposure period i.e. first 1 year for A2 and A3, first 2 years for A1. For each outcome measure in this review, there is more than one possible method of assessment. We therefore included our preferred method of assessment for each outcome, which is the *a priori* 'primary outcome measure', assessed at the optimal age as defined above.

3.3.1. Atopic outcomes:

1. *Asthma/Wheeze* - defined as either 'asthma', 'infantile wheeze' or similar, using parent/self-report, doctor diagnosis, a validated questionnaire, scoring system or objective measure such as bronchial hyper-reactivity, forced vital capacity, peak expiratory flow rate or reversible airways obstruction using forced expiratory volume in 1 second. We included data for 'atopic' asthma/wheeze i.e. wheeze associated with allergic sensitisation, and for recurrent wheezing and atopic recurrent wheezing. We did not include different wheezing entities based on the timing of onset/resolution of the disease such as 'early transient wheeze' or 'persistent wheeze' due to heterogeneity in definition between studies. We did not include outcomes such as 'bronchitis' or 'bronchiolitis' which included some subjects with wheezing but others without wheezing.
2. *Eczema* – defined using parent/self-report, doctor diagnosis, a validated questionnaire, scoring system or objective measure. We included data for 'atopic' eczema i.e. eczema associated with allergic sensitisation. We did not include reports of rashes which were likely to have included other cutaneous problems, such as nappy rash, contact dermatitis 'rash', 'skin problem' etc, but did include reports of 'recurrent itchy rash in infancy' or similar descriptions which were likely to represent eczema.
3. *Allergic Rhinoconjunctivitis* – defined using parent/self-report, doctor diagnosis, a validated questionnaire, scoring system or objective measure. We included data for 'atopic' rhinoconjunctivitis i.e. rhinoconjunctivitis associated with allergic sensitisation. We included data for 'allergic rhinitis', 'allergic conjunctivitis' or 'allergic rhinoconjunctivitis' and planned to analyse 'allergic conjunctivitis' separately where data were reported separately.
4. *Food allergy* - defined by double blind placebo controlled food challenge, by open food challenge, by medical diagnosis or by self/parent report. We included reports of 'any food

allergy', and specific food allergies to cow's milk, egg or peanut. We did not include reports of 'food intolerance' that we judged were unlikely to meet current definitions of food allergy [14].

6. *Allergic sensitisation* – to an inhalant, an ingestant, or both – defined as positive skin prick test and/or specific IgE test to the relevant allergen using recognised methodologies and scoring criteria [15]. We combined data for skin prick and specific IgE testing due to limited numbers of studies available for each meta-analysis, and assessed 'any allergic sensitisation', 'food allergic sensitisation', 'aeroallergen sensitisation', 'cow's milk sensitisation', 'egg sensitisation' and 'peanut sensitisation' separately. We included Total IgE data when measured using a recognised technology such as ImmunoCAP (ThermoFisher, Massachusets).

3.3.2. Autoimmune outcomes:

1. *Type I diabetes mellitus* – defined as a medical diagnosis e.g. using the 1999 WHO recommendations for diagnosis and classification of diabetes mellitus [16], or a surrogate marker such as autoantibodies against insulin, GAD65, IA-2 or the ZnT8 transporter in the first 3 years of life. We did not include reports where the outcome was stated as 'diabetes' and thought likely to include some cases of type II diabetes mellitus or other disease entities.
2. *Coeliac disease* – defined by characteristic histological features (intraepithelial lymphocytes, crypt hyperplasia and villous atrophy) with improvement in symptoms and histology after institution of a gluten free diet, a medical diagnosis, or a surrogate marker such as IgA tissue transglutaminase or IgA endomysial antibodies.

3. *Inflammatory bowel disease* (Crohn's disease or Ulcerative colitis) – defined as a medical diagnosis.
4. *Autoimmune thyroid disease* (Graves' disease or Hashimoto's thyroiditis) - defined as a medical diagnosis.
5. *Juvenile rheumatoid arthritis* – defined as a medical diagnosis eg using the 2001 revised International League of Associations for Rheumatology (ILAR) classification criteria [17].
6. *Vitiligo* - defined as a medical diagnosis.

Primary assessment: medical diagnosis using the Vitiligo European Task Force 2007 criteria or similar [18].

7. *Psoriasis* - defined as a medical diagnosis.

3.4. Study selection and data extraction

3.4.1. Study selection

Title and abstract screening was undertaken in duplicate by a team of 7 researchers (RB, VGL, DI, NG, KJ, JC, ZR). Two researchers undertook title screening independently, and met to agree included and excluded titles. Their screening was checked by a third member of the team, and uncertainties were brought to a full team meeting for discussion. This procedure took place between February and April 2014, with weekly team meetings to discuss uncertainties about study eligibility, and again in April 2017. The full text of all potentially eligible studies was reviewed, and where electronic copies were not available, hard copies of articles were ordered from the British Library.

3.4.2. Data extraction

An Excel data extraction form was developed, piloted and refined by DI, VGL, RB and JL-B – separate forms were used for intervention studies, cohort studies and case control studies. Data extraction was undertaken in duplicate by a team of 8 researchers (DI, RB, UN, SC, VGL, NT-M, NG, EA). Disagreements and uncertainties about data coding were discussed within the team with leads as follows - RB (clinical queries), VGLA (dietetic queries), DI (analysis and coding queries) and JL-B (study design and statistics queries). For foreign language studies, data were extracted by VGL together with a native speaker of the relevant language (see Acknowledgements section). We extracted all relevant data from included studies, including data that could not (not appropriately reported) or would not (see 'data cleaning below) be included in meta-analysis, text information such as 'no significant association found', and information that adjusted or unadjusted analyses were performed but not reported.

3.4.3. Data cleaning and coding

Data were extensively cleaned and coded for analysis with further data checks to identify publications related to the same parent study, and to identify the most appropriate output for inclusion in meta-analysis from studies reporting multiple assessments of closely related exposures/outcomes at the same age in the same population. Data cleaning was undertaken by DI, NG and RJB. Data on duration of breastfeeding and timing of solid food introduction were extracted independent of exposure cut-offs used in the studies. However, in order to have homogeneous exposure reference group(s), data were only included in meta-analysis where the reference group (cut-off) of breastfeeding duration (or timing of solid food introduction) was complete i.e. 'less than' a certain duration, or in some cases 'never breast fed'. Studies evaluating timing of cow's milk or other specific food introduction into the

infant diet, or comparing different types of infant formula milk, are included in separate reports – REVIEWS B, REVIEW C PART I, AND REVIEW C PART II.

Where more than one exposure group was compared with the reference group (≤ than a specific cut-off) in relation to the same outcome at the same age, we chose the exposure furthest from the cut-off point. For example, a study reporting the relationship between total breastfeeding duration and wheeze at age 2 years, with data for ≤4 versus 5-7 and ≤4 versus >7 months duration, we would include the comparison ≤4 versus >7 months. This would be grouped for meta-analysis with studies comparing ≤4 versus >4 months duration. We used the following exposure cut-offs for total duration of breastfeeding, which were selected based on the distribution of the data presented in published reports so as to maximise our ability to undertake meta-analysis: never vs. any (and where possible a dose response of never vs. short (≥1-3 months)/ never vs. intermediate (≥4-6 months) / never vs. long (≥7-12 months) duration); ≤ 1-2 vs. >1-2; ≤3-4 vs >3-4; ≤5-7 vs.>5-7 ; ≤8-12 vs. >8-12 and ≤ 12-24 vs. >12-24 months duration. For duration of exclusive breastfeeding and timing of solid food introduction we again grouped studies according to the distribution of data presented in study reports - using groupings of ≤0-2 vs. >0-2; ≤3-4 vs >3-4 and ≤5 vs >5 months duration for exclusive breastfeeding, and ≤3-4 vs >3-4 months for timing of solid food introduction. Data that could not fit in any group were not included in meta-analysis, but were reported narratively. The outcomes of both meta-analysed and narratively reported studies were considered together when interpreting data and making conclusions.

From individual studies reporting more than one measure for the same outcome, we selected data for analysis reporting time to event (hazard ratio) in preference to cumulative incidence or lifetime prevalence i.e. ‘disease ever’, in turn in preference to point prevalence data i.e. ‘disease in the last 12 months’ for all binary outcomes with the exception of the non-clinical

outcomes allergic sensitisation and lung function, where point prevalence was analysed in preference to cumulative measures.

For allergic outcomes we grouped studies reporting outcome at ages 0-4, 5-15 and 15+ years. If a study reported associations (within or between publications) at more than one age within the same age group (i.e. age 1 and 3 years), we selected data for analysis within specific age groups that were most complete i.e. had the largest number of participants assessed. We also included data from longitudinal models (e.g. generalised estimating equation), and they were grouped according to the last age included in the model. Where appropriate we also considered the outcomes reported at other ages which were not included in meta-analysis, in our interpretation of the data. Age groups were not used for autoimmune diseases. Where different methods of outcome assessment were used within a study we prioritised validated and patient-centred outcomes – for example we prioritised clinical diagnosis of diabetes over diabetes-associated autoantibody detection; we prioritised patient or parent-reported wheeze using a validated instrument such as the ISAAC questionnaire, over doctor diagnosis of wheeze or study physician assessment. Again, where appropriate the impact of these decisions was taken into account in our interpretation of findings.

For included studies which did not report numerical data in a form that could be included in meta-analysis, for example medians, or means without a standard deviation or standard error, or 'no significant difference' statements, we summarised the findings in a 'narrative table'. Each of the 7 systematic reviews contains a single narrative table for each of the 3 exposures of interest – A1. Total breastfeeding duration; A2. Exclusive (predominant) breastfeeding duration; A3. Solid food introduction.

3.5. Risk of bias (quality) assessment

3.5.1. Review level bias

Publication bias was assessed using funnel plots and Egger's test, for those meta-analyses with ≥10 studies included. Possible causes for asymmetry other than publication bias (e.g. between study heterogeneity, small study effects) were also considered. We also took into consideration both the outcomes of meta-analyses and the findings of studies not included in meta-analysis, when interpreting systematic review outcomes.

3.5.2. Study level bias

The risk of bias in included intervention studies was assessed using a modified version of the Cochrane Collaboration Risk of Bias tool, which assessed sequence generation and allocation concealment (Selection Bias), blinding of outcome assessors and validity of outcome assessment tool (Assessment Bias), incomplete outcome data (Attrition Bias – considered high where <70% of randomised participants had outcome data available) [19]. RCTs were considered at low overall risk of bias where the risk of bias was judged to be low for all 3 key domains selection, assessment and attrition bias. The risk of bias in included cohort and case control studies was assessed using a modified version of the National Institute for Clinical Excellence methodological checklist for cohort and case-control studies respectively [20]. Key domains were Selection Bias (low if cases and controls were selected from similar populations, if the participation rate was ≥80%, or <80% but investigators explored and adjusted for characteristic differences between participants and non-participants), Assessment Bias (low if validated and reliable tools were used to assess exposure and/or outcome), and Confounding Bias (low if most likely confounders are identified and taken into account in study design and analysis). Observational studies were considered at low overall risk of bias where the risk of bias was judged to be low for all 3 key domains selection, assessment and

confounding bias. For assessment of Confounding Bias, factors that we expected to be adjusted for within studies of allergic outcomes were: siblings (parity or birth order or family size); gender; age at outcome assessment; disease risk based on family history; maternal or household smoking (asthma/wheeze outcomes); maternal age; maternal education or socioeconomic status; mode of delivery. For studies on autoimmune outcomes we expected matching and/or adjusting for gender, age, address, socioeconomic status, smoking and disease risk. For all studies we also assessed possible Conflict of Interest, judged as low where there was no evidence of industry involvement in study design, analysis, interpretation or publication, and no evidence that study authors receive remuneration from relevant industry partners for other activities. For all study reports, we created a summary Table of Study Characteristics with key study features, and a separate summary Risk of Bias Figure showing the risk of bias for all included studies – whether included in meta-analyses or reported in the narrative table.

3.6. Strategy for data synthesis

Meta-analysis was undertaken where ≥2 studies reported the same outcome for a given exposure. Where meta-analysis was deemed inappropriate due to differences in population, exposure/intervention or outcome; or where meta-analysis was not possible due to the nature of the data reported - individual study results were summarised in a narrative table at the end of each report. Separate analyses were undertaken for each disease outcome, for each (age) group of similar outcome assessment methods for any given disease, and for each intervention/exposure (group). In general our approach to meta-analysis was inclusive, with data pooled for maximum statistical power, but explored for important sources of statistical or clinical heterogeneity. Results for randomised or quasi-randomised controlled trials were

pooled separately from controlled clinical trials, and observational studies were pooled with a planned subgroup analysis of those with prospective (cohort or nested case control) or retrospective (other case control or cross-sectional) design.

3.6.1. Data extraction

Data were extracted either using raw frequencies, crude estimates of effect (including odds ratios, risk ratios, incidence rate ratios, hazard ratios, mean differences) or as adjusted estimates of effect. Adjusted estimates of effect were used in preference for primary analyses, where available. Random effect meta-analyses were performed to allow for heterogeneity between studies.

3.6.2. Heterogeneity

Heterogeneity was quantified using I^2. We explored reasons for heterogeneity using subgroup analyses based on study level factors. We classified heterogeneity as low (I^2<25%), moderate (I^2 25-50%), high (I^2 50-75%) or extreme (I^2>75%). For single study analyses, and where I^2 exceeded 80% we did not pool data in meta-analysis but presented studies in a forest plot without a pooled effect shown. Individual patient data analysis was not undertaken in this review, and study authors were not contacted to clarify data queries or request further participant data.

3.7. Data analysis

Pooled results for binary outcomes from intervention studies are presented as Risk ratios calculated from the frequencies given in the study; for observational studies as odds ratios – both with 95% confidence intervals as the vast majority of cohorts, case controls and cross sectional studies reported this measure of effect. Data from individual studies were pooled using the generic inverse variance method for pooled OR and Mantel-Haenszel method (with continuity correction of 0.5 in studies with zero cell frequencies) or inverse variance method

for single studies calculation of pooled RR in the statistical programme R version 3.1.0 (2014-04-10). Pooled results for continuous outcomes measured using similar scales are presented as mean differences with 95% confidence intervals. Where different scales are pooled across studies, we planned to report results using standardised mean differences. Where the only information given in the study was mean (SD) exposure in diseased and non diseased children, those were used for calculating pooled mean differences between cases and controls. We planned to present key findings from intervention trials in Summary of Findings tables similar to those used by the Cochrane Collaboration [21].

3.7.1. Planned subgroup analyses

We planned certain subgroup and stratified analyses prior to running our search. Subgroup analysis was undertaken for all meta-analyses with ≥ 6 studies included. We planned and undertook stratified analysis according to *type of data* - unadjusted versus adjusted data. Adjusted data were used preferentially in primary analyses. Stratified analysis was undertaken of all unadjusted data available and all adjusted data available separately to help understand the potential influence of confounding on analysis results. We also undertook planned subgroup analyses according to:

1. *Risk of bias* – studies with low, versus unclear/high overall risk of bias based on the criteria described above.
2. *Disease risk* - studies of populations at increased risk for atopic or autoimmune disease, versus those at normal or low risk of disease.
3. *Clear definition of breastfeeding status* - studies which used definitions of exclusive/predominant breastfeeding which conform to WHO definitions versus those which did not report having used such definitions.

4. *Exclusive breastfeeding* – we planned to separately analyse data for 'exclusive' versus 'predominant' breastfeeding duration as defined by WHO. However, we did not identify relevant data for this analysis since studies very rarely used WHO definitions of exclusive or predominant breastfeeding.
5. *Study design* – due to controversy about the value of combining case-control and cohort studies in the same meta-analysis, we also included a subgroup analysis for prospective versus retrospective study design in all reports.

For some reports, further specific subgroup analyses were undertaken appropriate to the outcome of interest – for example in type 1 diabetes (TIDM) meta-analyses we planned a subgroup analysis of serological versus clinical TIDM as an outcome measure, and in the Allergic Sensitisation meta-analyses we planned a subgroup of specific IgE versus Skin Prick Test as outcome measure.

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3.7.2. Graphical exploration of heterogeneity

Studies were ordered by year of publication in forest plots, in order to be able to assess any cohort effect, since human breast milk composition may have changed over time due to changing diet, and therefore have different effects on child health at different times. Due to insufficient information in included studies, it was not possible to order forest plots by year of birth for the study population or year of assessment.

3.8. Review registration

The protocol for this systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO CRD42013003802; CRD42013004239; CRD42013004252; www.crd.york.ac.uk/Prospero) on the 5th August 2013, prior to title

screening or selecting any studies from the search results. The protocol was revised following detailed review by the UK Food Standards Agency, the UK Scientific Advisory Committee on Nutrition, independent experts Professor Graham Devereux and Dr Carina Venter, and the Lancet peer review service, prior to being registered on PROSPERO.

3.9. Differences between the protocol and the review

Following external statistical review of preliminary reports, a decision was made to not undertake pooled meta-analysis where statistical heterogeneity was ≥80%. Due to insufficient data in included studies, we did not order forest plots by participant year of birth or year of outcome assessment. Instead we ordered by year of publication. New authors joined the review team due to the high workload of title screening and data extraction – NT-M, SC, UN, NG, ZR, JC, KJ, EA.

4. Results

4.1. Overview of recent high quality systematic reviews

Our search results are summarised in the PRISMA flow chart Figure 1.



PRISMA for Existing Systematic Reviews.pd

We identified 469 titles after removing duplicates, of which 33 were considered to be a report from a relevant or potentially relevant systematic review after title and abstract screening. All these studies underwent full text review and revised AMSTAR scoring by 2 authors independently (VGL, RJB) – Table 1 summarises the AMSTAR scores. Two studies were only available in Chinese, and these were scored by a native Chinese speaker Dr Sze-Chin Tan, Consultant Allergist from Tan Tock Seng Hospital Singapore, who was trained in the revised AMSTAR scoring procedure prior to undertaking this task. Of the 33 scored studies, and a further 10 review identified in the update search in February 2017, 11 were eligible for inclusion in the project overall, of which 3 are relevant to Review A. Fifteen studies were excluded due to low AMSTAR score. One study was not a systematic review. Six studies were excluded because they were either protocols for a systematic review (n=2) or were abstract publications with insufficient detail to establish the AMSTAR score or sufficient detail regarding study outcomes (n=4). One of these has subsequently been published, that is relevant to Review A, but R-AMSTAR scoring excluded the review from our report based on the quality of the systematic review [5]. Eight systematic reviews were excluded because they were only relevant to REVIEWS B or C. The updated search on 26th February 2017 identified a total of 3 systematic reviews relevant to Review A, but AMSTAR scores were below 32. A summary of R-AMSTAR scores for existing systematic reviews is shown in Table 2, and a summary of the 3 included reviews is shown in Table 3. The 3 included reviews are reviews

of observational data on breastfeeding and atopic outcomes (n=2) and breastfeeding and coeliac disease (n=1). Data from these prior systematic reviews are included in the relevant sections of this report (Table 1).

4.2. Systematic review of original studies

Our search results are summarised in the PRISMA flow chart Figure 2.



PRISMA for Original Studies.pdf

We identified 1 relevant intervention trial, 134 cohort studies, 11 nested case control studies and 114 case control or cross-sectional studies for inclusion in Review A. No further eligible intervention trials were identified from the updated search on 26th February 2017. Detailed findings, analyses and discussion for the 7 separate systematic reviews are shown in the attached reports (Table 1), and summarised in the Executive Summary.

5. **Discussion**

In these systematic reviews of mainly observational data regarding breastfeeding duration, timing of solid food introduction and atopic and autoimmune diseases, we did not find strong and consistent evidence of a relationship between the exposures and atopic outcomes, however for most analyses we were unable to confidently exclude clinically important effects due to wide confidence intervals.

We identified a single RCT of a breastfeeding promotion intervention, which resulted in increased TBF, increased EBF and delayed SF introduction. We classified the RCT under TBF, as this was arguably the major intervention of the trial – however the trial initiative was the widely-used UNICEF Baby Friendly Initiative which advises EBF to 6 months and continued TBF to at least 2 years, consistent with WHO guidance [22]. This trial found LOW certainty evidence that a breastfeeding promotion intervention reduces odds of eczema during the first year of life. We did also identify the Enquiring About Tolerance (EAT) trial, which randomised exclusively breastfed infants to SF introduction at 3 months versus 6 months – however results from this trial were included in Review B regarding timing of allergenic food introduction, since the solid foods were specific allergenic foods in this trial [23]. EAT did not identify a clear effect of SF introduction on allergic outcomes other than food allergy and food sensitisation, which are discussed in detail in Review B.

From the observational studies we found VERY LOW certainty evidence that longer TBF duration is associated with reduced risk of recurrent wheezing at age 5-14.

A recent systematic review found that increased duration of breastfeeding may be associated with reduced risk of wheeze/asthma[24]. We found a similar association, but there was significant evidence of publication bias, leading to our conclusion that there is only VERY

LOW evidence for an association between longer total or exclusive breastfeeding duration and reduced risk of wheeze or recurrent wheeze at age 5-14. The intervention trial did not support an effect of breastfeeding promotion on risk of wheeze/asthma. In contrast with a recent separate systematic review, we found no consistent evidence for an association between longer total or exclusive breastfeeding and increased lung function [25].

We found LOW and VERY LOW grade evidence that longer EBF and TBF duration respectively are associated with reduced Type 1 Diabetes Mellitus risk. One hypothesis for this association is that bovine insulin, which is present in cow's milk formula, leads to immune sensitisation in the formula fed infant, which in turn increases the risk of an autoimmune response directed against human insulin and associated antibodies, the cause of TIDM. However, a recent large randomised controlled trial comparing cow's milk with, and without (extensively hydrolysed) bovine insulin failed to confirm any difference in risk of serological TIDM [26]. Our systematic reviews of timing of cow's milk introduction to the infant diet (REVIEW B), and of hydrolysed infant formula (REVIEW C Part I), also failed to support a relationship between cow's milk or bovine insulin exposure and risk of TIDM. An alternative hypothesis is that TIDM is triggered by enterovirus infection, and the association between longer EBF/TBF and reduced TIDM risk may therefore be explained by the reduction in gastrointestinal infection seen with longer breastfeeding duration, in part attributable to the high levels of antibodies present in human milk.[27 9]

There was more mixed evidence for an association between breastfeeding duration and reduced risk of other autoimmune diseases, with no clear conclusions – but this is an area which requires further study.

6. **Conclusions**

These findings are not of sufficient strength to make new recommendations about the timing of solid food introduction in infancy, but they do support existing recommendations that breastfeeding is the optimal mode of infant feeding, and should be continued for at least 2 years since we found VERY LOW evidence that increased TBF is associated with reduced TIDM, and this association continued through to the second year of life. We found LOW certainty evidence that EBF duration of <3-4 months compared with ≥3-4 months may increase risk of Type 1 Diabetes Mellitus, but we did not find evidence of a relationship between longer EBF duration than this and TIDM risk – for EBF duration ≥ 5-9 months, 1 retrospective study found reduced TIDM risk, and one prospective study found no association. Duration of exclusive breastfeeding is largely determined by timing of cow's milk formula introduction, and to a lesser extent timing of solid food introduction, in the UK. The available evidence for timing of solid food introduction and TIDM risk was inconclusive due to extreme heterogeneity, and data for timing of cow's milk formula introduction and risk of TIDM, reported in REVIEW B, found no consistent evidence for an association. Further work is needed to understand possible effects of longer breastfeeding duration on risk of TIDM, and risk of childhood eczema and asthma.

7. Acknowledgements

We are grateful to the independent expert peer reviewers Professor Graham Devereux and Dr Carina Venter, and to members of the UK Food Standards Agency, the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT), and the UK Scientific Advisory Committee on Nutrition for their comments on the study protocol and previous versions of this report. We are grateful to Dr Marialena Trivella and Professor Doug Altman for advice on statistical analysis. We are grateful to Dr Yujie Zhao, Mr Szymon Mikolajewski, Dr Andre Amaral, Dr Mari Kihara, Dr Christian Nielsen, Mr Radoslav Latinovic, Dr Stephanie MacNeill, Dr Andreas Forsters, Dr Daniel Munblit, Dr Sze-Chin Tan, and Dr Claudia Gore for their assistance with translation of foreign language reports. We are grateful to Jackie Cousins of the St. Mary's library at Imperial College London for assistance with literature search training.

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Table 2 Quality assessment of recent or ongoing overlapping systematic reviews using R-AMSTAR scoring.

Author/Reference	VGL Score	BB Score	CONSENSUS
Antico [28]	19	14	Exclude
Braeger [29]	30	29	Exclude
Brew [30]	**35**	**37**	Include – Review A
Cardwell [31]	31	25	Exclude
Christesen [32]	24	25	Exclude
De Silva [5]	26	29	Exclude
Dick [33]	22	19	Exclude
Doege [34]	28	21	Exclude
Flohr [35]	19	19	Exclude
Foolad [36]	18	22	Exclude
Gunaratne [37, 38]	Protocol and Abstract publication only		
Henricksson [39]	18	24	Exclude
Kheirkhah [40]	Abstract publication only		
Klemens [41]	**36**	**35**	Exclude – Review C
Kramer [27]	**38**	**40**	Include – Review A
Kramer [42]	**37**	**40**	Exclude – Review C
Kremmyda [43]	21	20	Exclude
Middleton [44]	Abstract publication only		
Osborne [45]	Abstract publication only		
Osborne [46]	**38**	**40**	Exclude – Review C
Pelucci [47]	**33**	**36**	Exclude – Review C
Patelarou [48]	23	24	Exclude
Schindler [49]	Protocol only		
Schmitt [50]	Not a systematic review		
Szajeweska [51]	**36**	**35**	Include – Reviews A and B
Tang [52]	**34***		Exclude – Review C
Waidyatillake [25]	24	25	Exclude
Wang [53]	31*		Exclude

A score of ≥32 was required for inclusion; * Chinese language, scored by Dr Sze-Chin Tan

Table 3 Characteristics of included systematic reviews

Study Relevant SR	**Databases searched**	**No. studies No. (range) participants**	**Study designs included**	**Population**	**Intervention/ Exposure(s) Comparator(s)**	**Outcomes relevant to the project**	**Subgroup analyses relevant to project**
Brew [30] Review A	MEDLINE, EMBASE 01/2000 - 06/2010	31 studies 417,880 (180 – 168,330) participants	16 Birth cohort 6 Case-control 9 Cross-sectional	• Birth cohort, cross-sectional, case-control study • Age 5-18 years at follow-up	Exclusive BF for ≥3-4 months vs. less	'Current wheezing illness', defined in various ways, but usually including wheezing in last 12 months	• Study design • Definition of asthma/wheeze • Adjustment for relevant confounders • Study participation/ retention rate •Age at assessment
Kramer [27] Review A	MEDLINE EMBASE CENTRAL 2011, Issue 6 CINAHL BIOSIS African Index Medicus IMEMR LILACS 06/2011	23 studies 11,299 (30 – 3,483) participants Relevant outcomes reported in 3 studies with 4128 (135 – 3483) participants	1 Prospective cohort 2 Prospective cohorts nested within a RCT	Lactating mothers and their healthy, term, singleton infants exclusively or predominantly breast fed for at least 3 months	Continued exclusive/ predominant breast feeding to 6-7 months, versus introduction of other liquids or complementary foods at 3-4 months	• Wheezing/asthma • Eczema • Rhinoconjunctivitis (hayfever) • Allergic sensitisation • Food allergy	Nil

Szajeweska [51] Review A Review B	CENTRAL, MEDLINE, EMBASE (up to July 2012)	12 studies 266,728 participants	3 cohort studies 8 case control studies 1 RCT Data	Infants at population risk or increased risk of developing Coeliac disease (defined by HLA status, first-degree relative with celiac disease or type 1 diabetes mellitus)	• Duration of breastfeeding	• Coeliac disease • Coeliac autoantibodies (anti-TG2 or EMA)	Nil

RCT: Randomised controlled trial, BF: Breast feeding

Appendix 1 Search Strategies for other systematic reviews

These search strategies were used to identify recent SRs relevant to Reviews A, B or C

1.1. Medline

1. breast feeding.ab,ti.
2. breastfeeding.ab,ti.
3. breast fed.ab,ti.
4. breastfed.ab,ti.
5. Breast Feeding/
6. Milk, Human/
7. formula?.ab,ti.
8. hydrolysed.ab,ti.
9. bottlefed.ab,ti.
10. bottle fed.ab,ti.
11. (bottle adj3 feed$).ab,ti.
12. Infant Formula/
13. Bottle Feeding/
14. wean$.ab,ti.
15. Weaning/
16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. complementary food?.ab,ti.
18. (introduc$ adj2 food?).ab,ti.
19. wean$.ab,ti.
20. Weaning/
21. solid?.ab,ti.
22. semi-solid?.ab,ti.
23. baby food?.ab,ti.
24. Infant Food/
25. Infant Nutritional Physiological Phenomena/
26. breast feeding.ab,ti.
27. breastfeeding.ab,ti.
28. breast fed.ab,ti.
29. breastfed.ab,ti.
30. Breast Feeding/
31. Milk, Human/
32. formula?.ab,ti.
33. hydrolysed.ab,ti.
34. bottlefed.ab,ti.
35. bottle fed.ab,ti.
36. (bottle adj3 feed$).ab,ti.
37. Infant Formula/
38. Bottle Feeding/
39. liquid?.ab,ti.
40. milk.ab,ti.
41. Milk/
42. egg?.ab,ti.

43. Egg Proteins/
44. Egg Proteins, Dietary/
45. nut?.ab,ti.
46. peanut?.ab,ti.
47. almond?.ab,ti.
48. (brazil? adj5 nut?).ab,ti.
49. walnut?.ab,ti.
50. pecan?.ab,ti.
51. pistachio?.ab,ti.
52. cashew?.ab,ti.
53. hazelnut?.ab,ti.
54. macadamia?.ab,ti.
55. Nuts/
56. Arachis hypogaea/
57. Prunus/
58. Bertholletia/
59. Juglans/
60. Carya/
61. Pistacia/
62. Anacardium/
63. Corylus/
64. Macadamia/
65. wheat.ab,ti.
66. Triticum/
67. soya.ab,ti.
68. Soybeans/
69. gluten$.ab,ti.
70. Glutens/
71. fish.ab,ti.
72. Fishes/
73. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72
74. Diet/
75. Diet Therapy/
76. Nutritional Sciences/
77. Child Nutrition Sciences/
78. diet.ab,ti.
79. diets.ab,ti.
80. Diet, Mediterranean/
81. mediterranean diet$.ab,ti.
82. dietetic.ab,ti.
83. dietary.ab,ti.
84. eat.ab,ti.
85. eating.ab,ti.
86. intake.ab,ti.
87. nutrient?.ab,ti.
88. nutrition.ab,ti.

89. Diet, Vegetarian/
90. vegetarian?.ab,ti.
91. vegan$.ab,ti.
92. Diet, Macrobiotic/
93. macrobiotic?.ab,ti.
94. Food/
95. food$.ab,ti.
96. feed.ab,ti.
97. feeding.ab,ti.
98. cereal$.ab,ti.
99. grain$.ab,ti.
100. granary.ab,ti.
101. wholegrain.ab,ti.
102. wholewheat.ab,ti.
103. whole wheat.ab,ti.
104. wheat.ab,ti.
105. wheatgerm.ab,ti.
106. rye.ab,ti.
107. barley.ab,ti.
108. oat?.ab,ti.
109. exp Cereals/
110. root?.ab,ti.
111. tuber?.ab,ti.
112. exp Vegetables/
113. vegetable$.ab,ti.
114. onion$.ab,ti.
115. spinach.ab,ti.
116. chard.ab,ti.
117. tomato$.ab,ti.
118. pepper$.ab,ti.
119. carrot$.ab,ti.
120. beetroot.ab,ti.
121. asparagus.ab,ti.
122. garlic.ab,ti.
123. pumpkin.ab,ti.
124. sprouts.ab,ti.
125. broccoli.ab,ti.
126. cabbage$.ab,ti.
127. celery.ab,ti.
128. ginger.ab,ti.
129. potato$.ab,ti.
130. crisps.ab,ti.
131. fries.ab,ti.
132. syrup.ab,ti.
133. honey.ab,ti.
134. Honey/
135. Fruit/
136. fruit$.ab,ti.
137. apple?.ab,ti.

138. pear?.ab,ti.
139. banana?.ab,ti.
140. orange?.ab,ti.
141. grape?.ab,ti.
142. kiwi?.ab,ti.
143. citrus.ab,ti.
144. grapefruit?.ab,ti.
145. pulses.ab,ti.
146. beans.ab,ti.
147. lentil?.ab,ti.
148. chickpea?.ab,ti.
149. legume?.ab,ti.
150. lupin?.ab,ti.
151. soy.ab,ti.
152. soya.ab,ti.
153. nut?.ab,ti.
154. almond?.ab,ti.
155. peanut?.ab,ti.
156. groundnut?.ab,ti.
157. Nuts/
158. seed?.ab,ti.
159. sesame.ab,ti.
160. mustard.ab,ti.
161. Seeds/
162. exp Meat/
163. meat.ab,ti.
164. beef.ab,ti.
165. pork.ab,ti.
166. lamb.ab,ti.
167. poultry.ab,ti.
168. chicken.ab,ti.
169. turkey.ab,ti.
170. duck.ab,ti.
171. fish.ab,ti.
172. Fatty Acids/
173. exp Fatty Acids, Omega-3/
174. exp Fatty Acids, Omega-6/
175. omega-3.ab,ti.
176. omega-6.ab,ti.
177. PUFA.ab,ti.
178. fat.ab,ti.
179. fats.ab,ti.
180. fatty.ab,ti.
181. egg.ab,ti.
182. eggs.ab,ti.
183. exp Eggs/
184. Bread/
185. bread.ab,ti.
186. oil.ab,ti.

187. oils.ab,ti.
188. oily.ab,ti.
189. omega.ab,ti.
190. exp Seafood/
191. seafood.ab,ti.
192. shellfish.ab,ti.
193. crustacean?.ab,ti.
194. mollusc?.ab,ti.
195. Shellfish/
196. Dairy Products/
197. dairy.ab,ti.
198. exp Milk/
199. milk.ab,ti.
200. Infant Formula/
201. formula?.ab,ti.
202. hydrolysed.ab,ti.
203. Infant Food/
204. yoghurt.ab,ti.
205. probiotic.ab,ti.
206. prebiotic?.ab,ti.
207. butter.ab,ti.
208. herb?.ab,ti.
209. spice?.ab,ti.
210. chilli$.ab,ti.
211. condiment?.ab,ti.
212. exp Condiments/
213. Beverages/
214. beverage?.ab,ti.
215. fluid intake.ab,ti.
216. water.ab,ti.
217. drink$.ab,ti.
218. exp Food Preservation/
219. pickled.ab,ti.
220. bottled.ab,ti.
221. canned.ab,ti.
222. canning.ab,ti.
223. smoked.ab,ti.
224. preserved.ab,ti.
225. preservatives.ab,ti.
226. nitrosamine.ab,ti.
227. hydrogenation.ab,ti.
228. fortified.ab,ti.
229. nitrates.ab,ti.
230. nitrites.ab,ti.
231. ferment$.ab,ti.
232. processed.ab,ti.
233. antioxidant$.ab,ti.
234. genetic modif$.ab,ti.
235. genetically modif$.ab,ti.

236. Cooking/
237. cooking.ab,ti.
238. cooked.ab,ti.
239. grill.ab,ti.
240. grilled.ab,ti.
241. fried.ab,ti.
242. fry.ab,ti.
243. roast.ab,ti.
244. bake.ab,ti.
245. baked.ab,ti.
246. stewing.ab,ti.
247. stewed.ab,ti.
248. casserol$.ab,ti.
249. broil.ab,ti.
250. broiled.ab,ti.
251. boiled.ab,ti.
252. poach.ab,ti.
253. poached.ab,ti.
254. steamed.ab,ti.
255. barbecue$.ab,ti.
256. chargrill$.ab,ti.
257. salt.ab,ti.
258. salting.ab,ti.
259. salted.ab,ti.
260. fiber.ab,ti.
261. fibre.ab,ti.
262. polysaccharide$.ab,ti.
263. starch.ab,ti.
264. starchy.ab,ti.
265. carbohydrate$.ab,ti.
266. lipid$.ab,ti.
267. linoleic acid$.ab,ti.
268. sugar$.ab,ti.
269. sweetener$.ab,ti.
270. saccharin$.ab,ti.
271. aspartame.ab,ti.
272. sucrose.ab,ti.
273. xylitol.ab,ti.
274. cholesterol.ab,ti.
275. hydrogenated lard.ab,ti.
276. dietary protein.ab,ti.
277. dietary proteins.ab,ti.
278. protein intake.ab,ti.
279. animal protein$.ab,ti.
280. total protein$.ab,ti.
281. vegetable protein$.ab,ti.
282. plant protein$.ab,ti.
283. exp Dietary Carbohydrates/
284. exp Dietary Fats/

285. exp Dietary Fiber/
286. exp Dietary Proteins/
287. exp Dietary Supplements/
288. exp Food Additives/
289. exp Vitamins/
290. supplements.ab,ti.
291. supplement.ab,ti.
292. vitamin$.ab,ti.
293. retinol.ab,ti.
294. carotenoid$.ab,ti.
295. tocopherol.ab,ti.
296. folate$.ab,ti.
297. folic acid.ab,ti.
298. methionine.ab,ti.
299. riboflavin.ab,ti.
300. thiamine.ab,ti.
301. niacin.ab,ti.
302. pyridoxine.ab,ti.
303. cobalamin.ab,ti.
304. mineral$.ab,ti.
305. sodium.ab,ti.
306. iron.ab,ti.
307. calcium.ab,ti.
308. selenium.ab,ti.
309. iodine.ab,ti.
310. magnesium.ab,ti.
311. potassium.ab,ti.
312. zinc.ab,ti.
313. copper.ab,ti.
314. phosphorus.ab,ti.
315. manganese.ab,ti.
316. chromium.ab,ti.
317. phytochemical.ab,ti.
318. polyphenol$.ab,ti.
319. phytoestrogen$.ab,ti.
320. genistein.ab,ti.
321. saponin$.ab,ti.
322. coumarin$.ab,ti.
323. flavonoid$.ab,ti.
324. polyphenol$.ab,ti.
325. flavonol$.ab,ti.
326. flavone$.ab,ti.
327. isoflavone$.ab,ti.
328. catechin$.ab,ti.
329. ascorbic acid$.ab,ti.
330. hydroxy cholecalciferol$.ab,ti.
331. hydroxycholecalciferol$.ab,ti.
332. tocotrienol$.ab,ti.
333. carotene$.ab,ti.

334. cryptoxanthin$.ab,ti.
335. lycopene$.ab,ti.
336. lutein$.ab,ti.
337. zeaxanthin$.ab,ti.
338. selenium$.ab,ti.
339. organic diet?.ab,ti.
340. Food, Organic/
341. 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169 or 170 or 171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181 or 182 or 183 or 184 or 185 or 186 or 187 or 188 or 189 or 190 or 191 or 192 or 193 or 194 or 195 or 196 or 197 or 198 or 199 or 200 or 201 or 202 or 203 or 204 or 205 or 206 or 207 or 208 or 209 or 210 or 211 or 212 or 213 or 214 or 215 or 216 or 217 or 218 or 219 or 220 or 221 or 222 or 223 or 224 or 225 or 226 or 227 or 228 or 229 or 230 or 231 or 232 or 233 or 234 or 235 or 236 or 237 or 238 or 239 or 240 or 241 or 242 or 243 or 244 or 245 or 246 or 247 or 248 or 249 or 250 or 251 or 252 or 253 or 254 or 255 or 256 or 257 or 258 or 259 or 260 or 261 or 262 or 263 or 264 or 265 or 266 or 267 or 268 or 269 or 270 or 271 or 272 or 273 or 274 or 275 or 276 or 277 or 278 or 279 or 280 or 281 or 282 or 283 or 284 or 285 or 286 or 287 or 288 or 289 or 290 or 291 or 292 or 293 or 294 or 295 or 296 or 297 or 298 or 299 or 300 or 301 or 302 or 303 or 304 or 305 or 306 or 307 or 308 or 309 or 310 or 311 or 312 or 313 or 314 or 315 or 316 or 317 or 318 or 319 or 320 or 321 or 322 or 323 or 324 or 325 or 326 or 327 or 328 or 329 or 330 or 331 or 332 or 333 or 334 or 335 or 336 or 337 or 338 or 339 or 340
342. allerg$.ab,ti.
343. asthma$.ab,ti.
344. wheeze.ab,ti.
345. wheezing.ab,ti.
346. bronchial hyperresponsiveness.ab,ti.
347. bronchial hyperreactivity.ab,ti.
348. Forced expiratory volume.ab,ti.
349. FEV1.ab,ti.
350. "FEV 1".ab,ti.
351. "FEV0.5".ab,ti.
352. "FEV 0.5".ab,ti.
353. Forced vital capacity.ab,ti.
354. FVC.ab,ti.
355. Peak expiratory flow rate.ab,ti.
356. PEFR.ab,ti.
357. eczema.ab,ti.
358. neurodermatitis.ab,ti.
359. rhinitis.ab,ti.
360. besniers prurigo.ab,ti.
361. rhinoconjunctivitis.ab,ti.
362. hayfever.ab,ti.

363. (hay adj fever).ab,ti.
364. poll?nosis.ab,ti.
365. SAR.ab,ti.
366. (pollen adj allergy).ab,ti.
367. conjunctivitis.ab,ti.
368. immunoglobulin e.ab,ti.
369. Total IgE.ab,ti.
370. autoimmune disease?.ab,ti.
371. diabetes.ab,ti.
372. diabetic.ab,ti.
373. type 1.ab,ti.
374. c?eliac disease.ab,ti.
375. crohn$ disease.ab,ti.
376. Inflammatory Bowel Disease?.ab,ti.
377. Ulcerative colitis.ab,ti.
378. (Lympho$ adj3 thyroiditi$).ab,ti.
379. (Thyroiditi$ adj3 autoimmune).ab,ti.
380. (Hashimoto$ adj3 (syndrome? or thyroiditi$ or disease?)).ab,ti.
381. (Thyroiditi$ adj3 (post-partum or postpartum)).ab,ti.
382. Graves? disease.ab,ti.
383. Basedow$ disease.ab,ti.
384. exophthalmic goiter?.ab,ti.
385. (Still? Disease adj3 (juvenile or onset)).ab,ti.
386. (Juvenile adj3 arthriti$).ab,ti.
387. vitiligo.ab,ti.
388. Psorias?s.ab,ti.
389. (Arthriti? adj3 Psoria$).ab,ti.
390. atopic disease.ab,ti.
391. atopic dermatitis.ab,ti.
392. (food? adj3 sensiti$).ab,ti.
393. (food? adj3 toleran$).ab,ti.
394. (food? adj3 intoleran$).ab,ti.
395. ((aero or air$) adj3 allergen?).ab,ti.
396. (aeroallergen? adj3 sensiti$).ab,ti.
397. (allergen? adj3 sensiti$).ab,ti.
398. skin prick test$.ab,ti.
399. atopy.ab,ti.
400. hypersensitiv$.ab,ti.
401. Hypersensitivity/
402. exp Food Hypersensitivity/
403. Respiratory Hypersensitivity/
404. Asthma/
405. Bronchial Hyperreactivity/
406. Forced Expiratory Volume/
407. Vital Capacity/
408. Peak Expiratory Flow Rate/
409. Eczema/
410. Neurodermatitis/
411. Rhinitis/

412. Rhinitis, Allergic, Perennial/
413. Rhinitis, Allergic, Seasonal/
414. Conjunctivitis/
415. Immunoglobulin E/
416. Autoimmune Diseases/
417. Diabetes Mellitus, Type 1/
418. Celiac Disease/
419. Crohn Disease/
420. Inflammatory Bowel Diseases/
421. Colitis, Ulcerative/
422. Thyroiditis, Autoimmune/
423. Hashimoto Disease/
424. Postpartum Thyroiditis/
425. Graves Disease/
426. Arthritis, Juvenile Rheumatoid/
427. Vitiligo/
428. Psoriasis/
429. Arthritis, Psoriatic/
430. Dermatitis, Atopic/
431. Hypersensitivity, Immediate/
432. 342 or 343 or 344 or 345 or 346 or 347 or 348 or 349 or 350 or 351 or 352 or 353 or 354 or 355 or 356 or 357 or 358 or 359 or 360 or 361 or 362 or 363 or 364 or 365 or 366 or 367 or 368 or 369 or 370 or 371 or 372 or 373 or 374 or 375 or 376 or 377 or 378 or 379 or 380 or 381 or 382 or 383 or 384 or 385 or 386 or 387 or 388 or 389 or 390 or 391 or 392 or 393 or 394 or 395 or 396 or 397 or 398 or 399 or 400 or 401 or 402 or 403 or 404 or 405 or 406 or 407 or 408 or 409 or 410 or 411 or 412 or 413 or 414 or 415 or 416 or 417 or 418 or 419 or 420 or 421 or 422 or 423 or 424 or 425 or 426 or 427 or 428 or 429 or 430 or 431
433. infant?.ab,ti.
434. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four" or "twenty five" or "twenty six") adj week?).ab,ti.
435. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four") adj month?).ab,ti.
436. 434 or 435
437. (old or age?).ab,ti.
438. 436 and 437
439. (("one year?" or "two year?") adj3 (old or age?)).ab,ti.
440. ((first or second or two) adj3 "year? of life").ab,ti.
441. Infant/
442. Infant, Newborn/
443. (maternal adj7 pregnan$).ab,ti.
444. (maternal adj7 lactat$).ab,ti.
445. (mother? adj7 pregnan$).ab,ti.
446. 433 or 438 or 439 or 440 or 441 or 442 or 443 or 444 or 445
447. MEDLINE.tw.
448. systematic review.tw.
449. meta-analysis.pt.

450. intervention$.ti.
451. 447 or 448 or 449 or 450
452. 16 or 73 or 341
453. 432 and 446 and 451 and 452
454. limit 453 to yr="2011 -Current"

1.2. Embase

1. breast feeding.ab,ti.
2. breastfeeding.ab,ti.
3. breast fed.ab,ti.
4. breastfed.ab,ti.
5. breast feeding/
6. breast milk/
7. formula?.ab,ti.
8. hydrolysed.ab,ti.
9. bottlefed.ab,ti.
10. bottle fed.ab,ti.
11. (bottle adj3 feed$).ab,ti.
12. artificial milk/
13. bottle feeding/
14. wean$.ti,ab.
15. weaning/
16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. complementary food?.ab,ti.
18. (introduc$ adj2 food?).ab,ti.
19. wean$.ab,ti.
20. weaning/
21. solid?.ab,ti.
22. semi-solid?.ab,ti.
23. baby food?.ab,ti.
24. baby food/
25. infant nutrition/
26. breast feeding.ab,ti.
27. breastfeeding.ab,ti.
28. breast fed.ab,ti.
29. breastfed.ab,ti.
30. breast feeding/
31. breast milk/
32. formula?.ab,ti.
33. hydrolysed.ab,ti.
34. bottlefed.ab,ti.
35. bottle fed.ab,ti.
36. (bottle adj3 feed$).ab,ti.
37. artificial milk/
38. bottle feeding/
39. liquid?.ti,ab.
40. milk.ti,ab.
41. milk/
42. egg?.ti,ab.
43. egg/
44. egg protein/
45. nut?.ab,ti.
46. peanut?.ab,ti.

47. almond?.ab,ti.
48. (brazil? adj5 nut?).ab,ti.
49. walnut?.ab,ti.
50. pecan?.ab,ti.
51. pistachio?.ab,ti.
52. cashew?.ab,ti.
53. hazelnut?.ab,ti.
54. macadamia?.ab,ti.
55. nut/
56. peanut/
57. almond/
58. Brazil nut/
59. exp walnut/
60. pecan/
61. pistachio/
62. cashew nut/
63. hazelnut/
64. Corylus avellana/
65. Macadamia/
66. wheat.ti,ab.
67. exp wheat/
68. soya.ti,ab.
69. soybean/
70. gluten$.ti,ab.
71. gluten/
72. fish$.ti,ab.
73. fish/
74. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73
75. diet/
76. diet therapy/
77. nutritional science/
78. diet.ti,ab.
79. diets.ti,ab.
80. Mediterranean diet/
81. mediterranean diet$.ab,ti.
82. dietetic.ab,ti.
83. dietary.ab,ti.
84. eat.ab,ti.
85. eating.ab,ti.
86. intake.ab,ti.
87. nutrient?.ab,ti.
88. nutrition.ab,ti.
89. vegetarian diet/
90. vegetarian?.ti,ab.
91. vegan$.ti,ab.
92. macrobiotic diet/

93. macrobiotic?.ti,ab.
94. food/
95. food$.ab,ti.
96. feed.ab,ti.
97. feeding.ab,ti.
98. cereal$.ab,ti.
99. grain$.ab,ti.
100. granary.ab,ti.
101. wholegrain.ab,ti.
102. wholewheat.ab,ti.
103. whole wheat.ab,ti.
104. wheat.ab,ti.
105. wheatgerm.ab,ti.
106. rye.ab,ti.
107. barley.ab,ti.
108. oat?.ab,ti.
109. exp cereal/
110. root?.ti,ab.
111. tuber?.ti,ab.
112. exp vegetable/
113. vegetable$.ab,ti.
114. onion$.ab,ti.
115. spinach.ab,ti.
116. chard.ab,ti.
117. tomato$.ab,ti.
118. pepper$.ab,ti.
119. carrot$.ab,ti.
120. beetroot.ab,ti.
121. asparagus.ab,ti.
122. garlic.ab,ti.
123. pumpkin.ab,ti.
124. sprouts.ab,ti.
125. broccoli.ab,ti.
126. cabbage$.ab,ti.
127. celery.ab,ti.
128. ginger.ab,ti.
129. potato$.ab,ti.
130. crisps.ab,ti.
131. fries.ab,ti.
132. syrup.ab,ti.
133. honey.ab,ti.
134. honey/
135. fruit/
136. fruit$.ab,ti.
137. apple?.ab,ti.
138. pear?.ab,ti.
139. banana?.ab,ti.
140. orange?.ab,ti.
141. grape?.ab,ti.

142. kiwi?.ab,ti.
143. citrus.ab,ti.
144. grapefruit?.ab,ti.
145. pulses.ab,ti.
146. beans.ab,ti.
147. lentil?.ab,ti.
148. chickpea?.ab,ti.
149. legume?.ab,ti.
150. lupin?.ab,ti.
151. soy.ab,ti.
152. soya.ab,ti.
153. nut?.ab,ti.
154. almond?.ab,ti.
155. peanut?.ab,ti.
156. groundnut?.ab,ti.
157. exp nut/
158. seed?.ti,ab.
159. sesame.ti,ab.
160. mustard.ti,ab.
161. plant seed/
162. meat/
163. meat.ab,ti.
164. beef.ab,ti.
165. pork.ab,ti.
166. lamb.ab,ti.
167. poultry.ab,ti.
168. chicken.ab,ti.
169. turkey.ab,ti.
170. duck.ab,ti.
171. fish.ab,ti.
172. fatty acid/
173. omega 3 fatty acid/
174. omega 6 fatty acid/
175. omega-3.ab,ti.
176. omega-6.ab,ti.
177. PUFA.ab,ti.
178. fat.ab,ti.
179. fats.ab,ti.
180. fatty.ab,ti.
181. egg.ab,ti.
182. eggs.ab,ti.
183. exp egg/
184. bread/
185. bread.ti,ab.
186. oil.ti,ab.
187. oils.ti,ab.
188. oily.ti,ab.
189. omega.ti,ab.
190. sea food/

191. seafood.ti,ab.
192. shellfish.ti,ab.
193. crustacean?.ti,ab.
194. mollusc?.ti,ab.
195. shellfish/
196. exp dairy product/
197. dairy.ti,ab.
198. milk/
199. milk.ti,ab.
200. artificial milk/
201. formula?.ti,ab.
202. hydrolysed.ti,ab.
203. baby food/
204. yoghurt.ab,ti.
205. probiotic.ab,ti.
206. prebiotic?.ab,ti.
207. butter.ab,ti.
208. herb?.ab,ti.
209. spice?.ab,ti.
210. chilli$.ab,ti.
211. condiment?.ab,ti.
212. exp condiment/
213. beverage/
214. beverage?.ti,ab.
215. fluid intake.ti,ab.
216. water.ti,ab.
217. drink$.ti,ab.
218. exp food preservation/
219. pickled.ab,ti.
220. bottled.ab,ti.
221. canned.ab,ti.
222. canning.ab,ti.
223. smoked.ab,ti.
224. preserved.ab,ti.
225. preservatives.ab,ti.
226. nitrosamine.ab,ti.
227. hydrogenation.ab,ti.
228. fortified.ab,ti.
229. nitrates.ab,ti.
230. nitrites.ab,ti.
231. ferment$.ab,ti.
232. processed.ab,ti.
233. antioxidant$.ab,ti.
234. genetic modif$.ab,ti.
235. genetically modif$.ab,ti.
236. cooking/
237. cooking.ab,ti.
238. cooked.ab,ti.
239. grill.ab,ti.

240. grilled.ab,ti.
241. fried.ab,ti.
242. fry.ab,ti.
243. roast.ab,ti.
244. bake.ab,ti.
245. baked.ab,ti.
246. stewing.ab,ti.
247. stewed.ab,ti.
248. casserol$.ab,ti.
249. broil.ab,ti.
250. broiled.ab,ti.
251. boiled.ab,ti.
252. poach.ab,ti.
253. poached.ab,ti.
254. steamed.ab,ti.
255. barbecue$.ab,ti.
256. chargrill$.ab,ti.
257. salt.ab,ti.
258. salting.ab,ti.
259. salted.ab,ti.
260. fiber.ab,ti.
261. fibre.ab,ti.
262. polysaccharide$.ab,ti.
263. starch.ab,ti.
264. starchy.ab,ti.
265. carbohydrate$.ab,ti.
266. lipid$.ab,ti.
267. linoleic acid$.ab,ti.
268. sugar$.ab,ti.
269. sweetener$.ab,ti.
270. saccharin$.ab,ti.
271. aspartame.ab,ti.
272. sucrose.ab,ti.
273. xylitol.ab,ti.
274. cholesterol.ab,ti.
275. hydrogenated lard.ab,ti.
276. dietary protein.ab,ti.
277. dietary proteins.ab,ti.
278. protein intake.ab,ti.
279. animal protein$.ab,ti.
280. total protein$.ab,ti.
281. vegetable protein$.ab,ti.
282. plant protein$.ab,ti.
283. carbohydrate diet/
284. carbohydrate intake/
285. fat intake/
286. dietary fiber/
287. protein intake/
288. diet supplementation/

289. food additive/
290. exp vitamin/
291. supplements.ab,ti.
292. supplement.ab,ti.
293. vitamin$.ab,ti.
294. retinol.ab,ti.
295. carotenoid$.ab,ti.
296. tocopherol.ab,ti.
297. folate$.ab,ti.
298. folic acid.ab,ti.
299. methionine.ab,ti.
300. riboflavin.ab,ti.
301. thiamine.ab,ti.
302. niacin.ab,ti.
303. pyridoxine.ab,ti.
304. cobalamin.ab,ti.
305. mineral$.ab,ti.
306. sodium.ab,ti.
307. iron.ab,ti.
308. calcium.ab,ti.
309. selenium.ab,ti.
310. iodine.ab,ti.
311. magnesium.ab,ti.
312. potassium.ab,ti.
313. zinc.ab,ti.
314. copper.ab,ti.
315. phosphorus.ab,ti.
316. manganese.ab,ti.
317. chromium.ab,ti.
318. phytochemical.ab,ti.
319. polyphenol$.ab,ti.
320. phytoestrogen$.ab,ti.
321. genistein.ab,ti.
322. saponin$.ab,ti.
323. coumarin$.ab,ti.
324. flavonoid$.ab,ti.
325. polyphenol$.ab,ti.
326. flavonol$.ab,ti.
327. flavone$.ab,ti.
328. isoflavone$.ab,ti.
329. catechin$.ab,ti.
330. ascorbic acid$.ab,ti.
331. hydroxy cholecalciferol$.ab,ti.
332. hydroxycholecalciferol$.ab,ti.
333. tocotrienol$.ab,ti.
334. carotene$.ab,ti.
335. cryptoxanthin$.ab,ti.
336. lycopene$.ab,ti.
337. lutein$.ab,ti.

338. zeaxanthin$.ab,ti.
339. selenium$.ab,ti.
340. organic diet?.ab,ti.
341. organic food/
342. 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169 or 170 or 171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181 or 182 or 183 or 184 or 185 or 186 or 187 or 188 or 189 or 190 or 191 or 192 or 193 or 194 or 195 or 196 or 197 or 198 or 199 or 200 or 201 or 202 or 203 or 204 or 205 or 206 or 207 or 208 or 209 or 210 or 211 or 212 or 213 or 214 or 215 or 216 or 217 or 218 or 219 or 220 or 221 or 222 or 223 or 224 or 225 or 226 or 227 or 228 or 229 or 230 or 231 or 232 or 233 or 234 or 235 or 236 or 237 or 238 or 239 or 240 or 241 or 242 or 243 or 244 or 245 or 246 or 247 or 248 or 249 or 250 or 251 or 252 or 253 or 254 or 255 or 256 or 257 or 258 or 259 or 260 or 261 or 262 or 263 or 264 or 265 or 266 or 267 or 268 or 269 or 270 or 271 or 272 or 273 or 274 or 275 or 276 or 277 or 278 or 279 or 280 or 281 or 282 or 283 or 284 or 285 or 286 or 287 or 288 or 289 or 290 or 291 or 292 or 293 or 294 or 295 or 296 or 297 or 298 or 299 or 300 or 301 or 302 or 303 or 304 or 305 or 306 or 307 or 308 or 309 or 310 or 311 or 312 or 313 or 314 or 315 or 316 or 317 or 318 or 319 or 320 or 321 or 322 or 323 or 324 or 325 or 326 or 327 or 328 or 329 or 330 or 331 or 332 or 333 or 334 or 335 or 336 or 337 or 338 or 339 or 340 or 341
343. allerg$.ab,ti.
344. asthma$.ab,ti.
345. wheeze.ab,ti.
346. wheezing.ab,ti.
347. bronchial hyperresponsiveness.ab,ti.
348. bronchial hyperreactivity.ab,ti.
349. Forced expiratory volume.ab,ti.
350. FEV1.ab,ti.
351. "FEV 1".ab,ti.
352. "FEV0.5".ab,ti.
353. "FEV 0.5".ab,ti.
354. Forced vital capacity.ab,ti.
355. FVC.ab,ti.
356. Peak expiratory flow rate.ab,ti.
357. PEFR.ab,ti.
358. eczema.ab,ti.
359. neurodermatitis.ab,ti.
360. rhinitis.ab,ti.
361. besniers prurigo.ab,ti.
362. rhinoconjunctivitis.ab,ti.
363. hayfever.ab,ti.
364. (hay adj fever).ab,ti.
365. poll?nosis.ab,ti.
366. SAR.ab,ti.

367. (pollen adj allergy).ab,ti.
368. conjunctivitis.ab,ti.
369. immunoglobulin e.ab,ti.
370. Total IgE.ab,ti.
371. autoimmune disease?.ab,ti.
372. diabetes.ab,ti.
373. diabetic.ab,ti.
374. type 1.ab,ti.
375. c?eliac disease.ab,ti.
376. crohn$ disease.ab,ti.
377. Inflammatory Bowel Disease?.ab,ti.
378. Ulcerative colitis.ab,ti.
379. (Lympho$ adj3 thyroiditi$).ab,ti.
380. (Thyroiditi$ adj3 autoimmune).ab,ti.
381. (Hashimoto$ adj3 (syndrome? or thyroiditi$ or disease?)).ab,ti.
382. (Thyroiditi$ adj3 (post-partum or postpartum)).ab,ti.
383. Graves? disease.ab,ti.
384. Basedow$ disease.ab,ti.
385. exophthalmic goiter?.ab,ti.
386. (Still? Disease adj3 (juvenile or onset)).ab,ti.
387. (Juvenile adj3 arthriti$).ab,ti.
388. vitiligo.ab,ti.
389. Psorias?s.ab,ti.
390. (Arthriti? adj3 Psoria$).ab,ti.
391. atopic disease.ab,ti.
392. atopic dermatitis.ab,ti.
393. (food? adj3 sensiti$).ab,ti.
394. (food? adj3 toleran$).ab,ti.
395. (food? adj3 intoleran$).ab,ti.
396. ((aero or air$) adj3 allergen?).ab,ti.
397. (aeroallergen? adj3 sensiti$).ab,ti.
398. (allergen? adj3 sensiti$).ab,ti.
399. skin prick test$.ab,ti.
400. atopy.ab,ti.
401. hypersensitiv$.ab,ti.
402. exp hypersensitivity/
403. respiratory tract allergy/
404. asthma/
405. wheezing/
406. bronchus hyperreactivity/
407. forced expiratory volume/
408. forced vital capacity/
409. peak expiratory flow/
410. eczema/
411. neurodermatitis/
412. rhinitis/
413. rhinoconjunctivitis/
414. hay fever/
415. pollen allergy/

416. perennial rhinitis/
417. conjunctivitis/
418. immunoglobulin E/
419. autoimmune disease/
420. diabetes mellitus/
421. insulin dependent diabetes mellitus/
422. celiac disease/
423. Crohn disease/
424. enteritis/
425. ulcerative colitis/
426. autoimmune thyroiditis/
427. Hashimoto disease/
428. postpartum thyroiditis/
429. Graves disease/
430. juvenile rheumatoid arthritis/
431. vitiligo/
432. psoriasis/
433. psoriatic arthritis/
434. atopic dermatitis/
435. nutritional intolerance/
436. 343 or 344 or 345 or 346 or 347 or 348 or 349 or 350 or 351 or 352 or 353 or 354 or 355 or 356 or 357 or 358 or 359 or 360 or 361 or 362 or 363 or 364 or 365 or 366 or 367 or 368 or 369 or 370 or 371 or 372 or 373 or 374 or 375 or 376 or 377 or 378 or 379 or 380 or 381 or 382 or 383 or 384 or 385 or 386 or 387 or 388 or 389 or 390 or 391 or 392 or 393 or 394 or 395 or 396 or 397 or 398 or 399 or 400 or 401 or 402 or 403 or 404 or 405 or 406 or 407 or 408 or 409 or 410 or 411 or 412 or 413 or 414 or 415 or 416 or 417 or 418 or 419 or 420 or 421 or 422 or 423 or 424 or 425 or 426 or 427 or 428 or 429 or 430 or 431 or 432 or 433 or 434 or 435
437. infant?.ab,ti.
438. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four" or "twenty five" or "twenty six") adj week?).ab,ti.
439. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four") adj month?).ab,ti.
440. 438 or 439
441. (old or age?).ab,ti.
442. 440 and 441
443. (("one year?" or "two year?") adj3 (old or age?)).ab,ti.
444. ((first or second or two) adj3 "year? of life").ab,ti.
445. infant/
446. newborn/
447. (maternal adj7 pregnan$).ti,ab.
448. (maternal adj7 lactat$).ti,ab.
449. (mother? adj7 pregnan$).ti,ab.
450. 437 or 442 or 443 or 444 or 445 or 446 or 447 or 448 or 449
451. MEDLINE.tw.
452. exp systematic review/

453. systematic review.tw.
454. meta analysis/
455. intervention$.ti.
456. 451 or 452 or 453 or 454 or 455
457. 16 or 74 or 342
458. 436 and 450 and 456 and 457
459. limit 458 to yr="2011 -Current"

1.3. COCHRANE Reviews and DARE

1. “breast feeding”:ab,ti
2. breastfeeding:ab,ti
3. “breast fed”:ab,ti
4. breastfed:ab,ti
5. MeSH descriptor [Breast Feeding] this term only
6. MeSH descriptor [Milk, Human] this term only
7. formula*:ab,ti
8. hydrolysed:ab,ti
9. bottlefed:ab,ti
10. “bottle fed”:ab,ti
11. (bottle NEAR/3 feed*):ab,ti
12. MeSH descriptor [Infant Formula] this term only
13. MeSH descriptor [Bottle Feeding] this term only
14. wean*:ab,ti
15. MeSH descriptor [Weaning] this term only
16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. “complementary food*”:ab,ti
18. (introduc* NEAR/2 food*):ab,ti
19. wean*:ab,ti
20. MeSH descriptor [Weaning] this term only
21. solid*:ab,ti
22. semi-solid*:ab,ti
23. “baby food*”:ab,ti
24. MeSH descriptor [Infant Food] this term only
25. MeSH descriptor [Infant Nutritional Physiological Phenomena] this term only
26. “breast feeding”:ab,ti
27. breastfeeding:ab,ti
28. “breast fed”:ab,ti
29. breastfed:ab,ti
30. MeSH descriptor [Breast Feeding] this term only
31. MeSH descriptor [Milk, Human] this term only
32. formula*:ab,ti
33. hydrolysed:ab,ti
34. bottlefed:ab,ti
35. “bottle fed”:ab,ti
36. (bottle NEAR/3 feed*):ab,ti
37. MeSH descriptor [Infant Formula] this term only
38. MeSH descriptor [Bottle Feeding] this term only
39. liquid*:ab,ti
40. milk:ab,ti
41. MeSH descriptor [Milk] this term only
42. egg*:ab,ti
43. MeSH descriptor [Egg Proteins] this term only
44. MeSH descriptor [Egg Proteins, Dietary] this term only
45. nut*:ab,ti
46. peanut*:ab,ti

47. almond*:ab,ti
48. (brazil* NEAR/5 nut*):ab,ti
49. walnut*:ab,ti
50. pecan*:ab,ti
51. pistachio*:ab,ti
52. cashew*:ab,ti
53. hazelnut*:ab,ti
54. macadamia*:ab,ti
55. Nuts] this term only
56. MeSH descriptor [Arachis hypogaea] this term only
57. MeSH descriptor [Prunus] this term only
58. MeSH descriptor [Bertholletia] this term only
59. MeSH descriptor [Juglans] this term only
60. MeSH descriptor [Carya] this term only
61. MeSH descriptor [Pistacia] this term only
62. MeSH descriptor [Anacardium] this term only
63. MeSH descriptor [Corylus] this term only
64. MeSH descriptor [Macadamia] this term only
65. wheat:ab,ti
66. MeSH descriptor [Triticum] this term only
67. soya:ab,ti
68. MeSH descriptor [Soybeans] this term only
69. gluten*:ab,ti
70. MeSH descriptor [Glutens] this term only
71. fish:ab,ti
72. MeSH descriptor [Fishes] this term only
73. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72
74. MeSH descriptor [Diet] this term only
75. MeSH descriptor [Diet Therapy] this term only
76. MeSH descriptor [Nutritional Sciences] this term only
77. MeSH descriptor [Child Nutrition Sciences] this term only
78. diet:ab,ti
79. diets:ab,ti
80. MeSH descriptor [Diet, Mediterranean] this term only
81. “mediterranean diet*”:ab,ti
82. dietetic:ab,ti
83. dietary:ab,ti
84. eat:ab,ti
85. eating:ab,ti
86. intake:ab,ti
87. nutrient*:ab,ti
88. nutrition:ab,ti
89. MeSH descriptor [Diet, Vegetarian] this term only
90. vegetarian*:ab,ti
91. vegan*:ab,ti
92. MeSH descriptor [Diet, Macrobiotic] this term only

93. macrobiotic*:ab,ti
94. MeSH descriptor [Food] this term only
95. food*:ab,ti
96. feed:ab,ti
97. feeding:ab,ti
98. cereal*:ab,ti
99. grain*:ab,ti
100. granary:ab,ti
101. wholegrain:ab,ti
102. wholewheat:ab,ti
103. “whole wheat”:ab,ti
104. wheat:ab,ti
105. wheatgerm:ab,ti
106. rye:ab,ti
107. barley:ab,ti
108. oat*:ab,ti
109. MeSH descriptor [Cereals] explode all trees
110. root*:ab,ti
111. tuber*:ab,ti
112. MeSH descriptor [Vegetables] explode all trees
113. vegetable*:ab,ti
114. onion*:ab,ti
115. spinach:ab,ti
116. chard:ab,ti
117. tomato*:ab,ti
118. pepper*:ab,ti
119. carrot*:ab,ti
120. beetroot:ab,ti
121. asparagus:ab,ti
122. garlic:ab,ti
123. pumpkin:ab,ti
124. sprouts:ab,ti
125. broccoli:ab,ti
126. cabbage*:ab,ti
127. celery:ab,ti
128. ginger:ab,ti
129. potato*:ab,ti
130. crisps:ab,ti
131. fries:ab,ti
132. syrup:ab,ti
133. honey:ab,ti
134. MeSH descriptor [Honey] this term only
135. MeSH descriptor [Fruit] this term only
136. fruit*:ab,ti
137. apple*:ab,ti
138. pear*:ab,ti
139. banana*:ab,ti
140. orange*:ab,ti
141. grape*:ab,ti

142. kiwi*:ab,ti
143. citrus:ab,ti
144. grapefruit*:ab,ti
145. pulses:ab,ti
146. beans:ab,ti
147. lentil*:ab,ti
148. chickpea*:ab,ti
149. legume*:ab,ti
150. lupin*:ab,ti
151. soy:ab,ti
152. soya:ab,ti
153. nut*:ab,ti
154. almond*:ab,ti
155. peanut*:ab,ti
156. groundnut*:ab,ti
157. MeSH descriptor [Nuts] this term only
158. seed*:ab,ti
159. sesame:ab,ti
160. mustard:ab,ti
161. MeSH descriptor [Seeds] this term only
162. MeSH descriptor [Meat] explode all trees
163. meat:ab,ti
164. beef:ab,ti
165. pork:ab,ti
166. lamb:ab,ti
167. poultry:ab,ti
168. chicken:ab,ti
169. turkey:ab,ti
170. duck:ab,ti
171. fish:ab,ti
172. MeSH descriptor [Fatty Acids] this term only
173. MeSH descriptor [Fatty Acids, Omega-3] explode all trees
174. MeSH descriptor [Fatty Acids, Omega-6] explode all trees
175. omega-3:ab,ti
176. omega-6:ab,ti
177. PUFA:ab,ti
178. fat:ab,ti
179. fats:ab,ti
180. fatty:ab,ti
181. egg:ab,ti
182. eggs:ab,ti
183. MeSH descriptor [Eggs] explode all trees
184. MeSH descriptor [Bread] this term only
185. bread:ab,ti
186. oil:ab,ti
187. oils:ab,ti
188. oily:ab,ti
189. omega:ab,ti
190. MeSH descriptor [Seafood] explode all trees

191. seafood:ab,ti
192. shellfish:ab,ti
193. crustacean*:ab,ti
194. mollusc*:ab,ti
195. MeSH descriptor [Shellfish] this term only
196. MeSH descriptor [Dairy Products] this term only
197. dairy:ab,ti
198. MeSH descriptor [Milk] explode all trees
199. milk:ab,ti
200. MeSH descriptor [Infant Formula] this term only
201. formula*:ab,ti
202. hydrolysed:ab,ti
203. MeSH descriptor [Infant Food] this term only
204. yoghurt:ab,ti
205. probiotic:ab,ti
206. prebiotic*:ab,ti
207. butter:ab,ti
208. herb*:ab,ti
209. spice*:ab,ti
210. chilli*:ab,ti
211. condiment*:ab,ti
212. MeSH descriptor [Condiments] explode all trees
213. MeSH descriptor [Beverages] this term only
214. beverage*:ab,ti
215. “fluid intake”:ab,ti
216. water:ab,ti
217. drink*:ab,ti
218. MeSH descriptor [Food Preservation] explode all trees
219. pickled:ab,ti
220. bottled:ab,ti
221. canned:ab,ti
222. canning:ab,ti
223. smoked:ab,ti
224. preserved:ab,ti
225. preservatives:ab,ti
226. nitrosamine:ab,ti
227. hydrogenation:ab,ti
228. fortified:ab,ti
229. nitrates:ab,ti
230. nitrites:ab,ti
231. ferment*:ab,ti
232. processed:ab,ti
233. antioxidant*:ab,ti
234. “genetic modif*”:ab,ti
235. “genetically modif*”:ab,ti
236. MeSH descriptor [Cooking] this term only
237. cooking:ab,ti
238. cooked:ab,ti
239. grill:ab,ti

240. grilled:ab,ti
241. fried:ab,ti
242. fry:ab,ti
243. roast:ab,ti
244. bake:ab,ti
245. baked:ab,ti
246. stewing:ab,ti
247. stewed:ab,ti
248. casserol*:ab,ti
249. broil:ab,ti
250. broiled:ab,ti
251. boiled:ab,ti
252. poach:ab,ti
253. poached:ab,ti
254. steamed:ab,ti
255. barbecue*:ab,ti
256. chargrill*:ab,ti
257. salt:ab,ti
258. salting:ab,ti
259. salted:ab,ti
260. fiber:ab,ti
261. fibre:ab,ti
262. polysaccharide*:ab,ti
263. starch:ab,ti
264. starchy:ab,ti
265. carbohydrate*:ab,ti
266. lipid*:ab,ti
267. “linoleic acid*”:ab,ti
268. sugar*:ab,ti
269. sweetener*:ab,ti
270. saccharin*:ab,ti
271. aspartame:ab,ti
272. sucrose:ab,ti
273. xylitol:ab,ti
274. cholesterol:ab,ti
275. “hydrogenated lard”:ab,ti
276. “dietary protein”:ab,ti
277. “dietary proteins”:ab,ti
278. “protein intake”:ab,ti
279. “animal protein*”:ab,ti
280. “total protein*”:ab,ti
281. “vegetable protein*”:ab,ti
282. “plant protein*”:ab,ti
283. MeSH descriptor [Dietary Carbohydrates] explode all trees
284. MeSH descriptor [Dietary Fats] explode all trees
285. MeSH descriptor [Dietary Fiber] explode all trees
286. MeSH descriptor [Dietary Proteins] explode all trees
287. MeSH descriptor [Dietary Supplements] explode all trees
288. MeSH descriptor [Food Additives] explode all trees

289. MeSH descriptor [Vitamins] explode all trees
290. supplements:ab,ti
291. supplement:ab,ti
292. vitamin*:ab,ti
293. retinol:ab,ti
294. carotenoid*:ab,ti
295. tocopherol:ab,ti
296. folate*:ab,ti
297. "folic acid":ab,ti
298. methionine:ab,ti
299. riboflavin:ab,ti
300. thiamine:ab,ti
301. niacin:ab,ti
302. pyridoxine:ab,ti
303. cobalamin:ab,ti
304. mineral*:ab,ti
305. sodium:ab,ti
306. iron:ab,ti
307. calcium:ab,ti
308. selenium:ab,ti
309. iodine:ab,ti
310. magnesium:ab,ti
311. potassium:ab,ti
312. zinc:ab,ti
313. copper:ab,ti
314. phosphorus:ab,ti
315. manganese:ab,ti
316. chromium:ab,ti
317. phytochemical:ab,ti
318. polyphenol*:ab,ti
319. phytoestrogen*:ab,ti
320. genistein:ab,ti
321. saponin*:ab,ti
322. coumarin*:ab,ti
323. flavonoid*:ab,ti
324. polyphenol*:ab,ti
325. flavonol*:ab,ti
326. flavone*:ab,ti
327. isoflavone*:ab,ti
328. catechin*:ab,ti
329. "ascorbic acid*":ab,ti
330. "hydroxy cholecalciferol*":ab,ti
331. hydroxycholecalciferol*:ab,ti
332. tocotrienol*:ab,ti
333. carotene*:ab,ti
334. cryptoxanthin*:ab,ti
335. lycopene*:ab,ti
336. lutein*:ab,ti
337. zeaxanthin*:ab,ti

338. selenium*:ab,ti
339. “organic diet*”:ab,ti
340. MeSH descriptor [Food, Organic] this term only
341. 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169 or 170 or 171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181 or 182 or 183 or 184 or 185 or 186 or 187 or 188 or 189 or 190 or 191 or 192 or 193 or 194 or 195 or 196 or 197 or 198 or 199 or 200 or 201 or 202 or 203 or 204 or 205 or 206 or 207 or 208 or 209 or 210 or 211 or 212 or 213 or 214 or 215 or 216 or 217 or 218 or 219 or 220 or 221 or 222 or 223 or 224 or 225 or 226 or 227 or 228 or 229 or 230 or 231 or 232 or 233 or 234 or 235 or 236 or 237 or 238 or 239 or 240 or 241 or 242 or 243 or 244 or 245 or 246 or 247 or 248 or 249 or 250 or 251 or 252 or 253 or 254 or 255 or 256 or 257 or 258 or 259 or 260 or 261 or 262 or 263 or 264 or 265 or 266 or 267 or 268 or 269 or 270 or 271 or 272 or 273 or 274 or 275 or 276 or 277 or 278 or 279 or 280 or 281 or 282 or 283 or 284 or 285 or 286 or 287 or 288 or 289 or 290 or 291 or 292 or 293 or 294 or 295 or 296 or 297 or 298 or 299 or 300 or 301 or 302 or 303 or 304 or 305 or 306 or 307 or 308 or 309 or 310 or 311 or 312 or 313 or 314 or 315 or 316 or 317 or 318 or 319 or 320 or 321 or 322 or 323 or 324 or 325 or 326 or 327 or 328 or 329 or 330 or 331 or 332 or 333 or 334 or 335 or 336 or 337 or 338 or 339 or 340
342. allerg*:ab,ti
343. asthma*:ab,ti
344. wheeze:ab,ti
345. wheezing:ab,ti
346. “bronchial hyperresponsiveness”:ab,ti
347. “bronchial hyperreactivity”:ab,ti
348. “Forced expiratory volume”:ab,ti
349. “FEV1”:ab,ti
350. "FEV 1":ab,ti
351. "FEV0.5":ab,ti
352. "FEV 0.5":ab,ti
353. “Forced vital capacity”:ab,ti
354. FVC:ab,ti
355. “Peak expiratory flow rate”:ab,ti
356. PEFR:ab,ti
357. eczema:ab,ti
358. neurodermatitis:ab,ti
359. rhinitis:ab,ti
360. “besniers prurigo”:ab,ti
361. rhinoconjunctivitis:ab,ti
362. hayfever:ab,ti
363. “hay fever”:ab,ti
364. poll*nosis:ab,ti
365. SAR:ab,ti
366. “pollen allergy”:ab,ti

367. conjunctivitis:ab,ti
368. immunoglobulin e:ab,ti
369. Total IgE:ab,ti
370. “autoimmune disease*”:ab,ti
371. diabetes:ab,ti
372. diabetic:ab,ti
373. “type 1”:ab,ti
374. “c*eliac disease”:ab,ti
375. “crohn* disease”:ab,ti
376. “Inflammatory Bowel Disease*”:ab,ti
377. “Ulcerative colitis”:ab,ti
378. (Lympho* NEAR/3 thyroiditi*):ab,ti
379. (Thyroiditi* NEAR/3 autoimmune):ab,ti
380. (Hashimoto* NEAR/3 (syndrome* or thyroiditi* or disease*)):ab,ti
381. (Thyroiditi* NEAR/3 (post-partum or postpartum)):ab,ti
382. “Graves* disease”:ab,ti
383. “Basedow* disease”:ab,ti
384. “exophthalmic goiter*”:ab,ti
385. (“Still* Disease” NEAR/3 (juvenile or onset)):ab,ti
386. (Juvenile NEAR/3 arthriti*):ab,ti
387. vitiligo:ab,ti
388. Psorias*s:ab,ti
389. (Arthriti* NEAR/3 Psoria*):ab,ti
390. “atopic disease”:ab,ti
391. “atopic dermatitis”:ab,ti
392. (food* NEAR/3 sensiti*):ab,ti
393. (food* NEAR/3 toleran*):ab,ti
394. (food* NEAR/3 intoleran*):ab,ti
395. ((aero or air*) NEAR/3 allergen*):ab,ti
396. (aeroallergen* NEAR/3 sensiti*):ab,ti
397. (allergen* NEAR/3 sensiti*):ab,ti
398. “skin prick test*”:ab,ti
399. atopy:ab,ti
400. hypersensitiv*:ab,ti
401. MeSH descriptor [Hypersensitivity] this term only
402. MeSH descriptor [Food Hypersensitivity] explode all trees
403. MeSH descriptor [Respiratory Hypersensitivity] this term only
404. MeSH descriptor [Asthma] this term only
405. MeSH descriptor [Bronchial Hyperreactivity] this term only
406. MeSH descriptor [Forced Expiratory Volume] this term only
407. MeSH descriptor [Vital Capacity] this term only
408. MeSH descriptor [Peak Expiratory Flow Rate] this term only
409. MeSH descriptor [Eczema] this term only
410. MeSH descriptor [Neurodermatitis] this term only
411. MeSH descriptor [Rhinitis] this term only
412. MeSH descriptor [Rhinitis, Allergic, Perennial] this term only
413. MeSH descriptor [Rhinitis, Allergic, Seasonal] this term only
414. MeSH descriptor [Conjunctivitis] this term only
415. MeSH descriptor [Immunoglobulin E] this term only

416. MeSH descriptor [Autoimmune Diseases] this term only
417. MeSH descriptor [Diabetes Mellitus, Type 1] this term only
418. MeSH descriptor [Celiac Disease] this term only
419. MeSH descriptor [Crohn Disease] this term only
420. MeSH descriptor [Inflammatory Bowel Diseases] this term only
421. MeSH descriptor [Colitis, Ulcerative] this term only
422. MeSH descriptor [Thyroiditis, Autoimmune] this term only
423. MeSH descriptor [Hashimoto Disease] this term only
424. MeSH descriptor [Postpartum Thyroiditis] this term only
425. MeSH descriptor [Graves Disease] this term only
426. MeSH descriptor [Arthritis, Juvenile Rheumatoid] this term only
427. MeSH descriptor [Vitiligo] this term only
428. MeSH descriptor [Psoriasis] this term only
429. MeSH descriptor [Arthritis, Psoriatic] this term only
430. MeSH descriptor [Dermatitis, Atopic] this term only
431. MeSH descriptor [Hypersensitivity, Immediate] this term only
432. 342 or 343 or 344 or 345 or 346 or 347 or 348 or 349 or 350 or 351 or 352 or 353 or 354 or 355 or 356 or 357 or 358 or 359 or 360 or 361 or 362 or 363 or 364 or 365 or 366 or 367 or 368 or 369 or 370 or 371 or 372 or 373 or 374 or 375 or 376 or 377 or 378 or 379 or 380 or 381 or 382 or 383 or 384 or 385 or 386 or 387 or 388 or 389 or 390 or 391 or 392 or 393 or 394 or 395 or 396 or 397 or 398 or 399 or 400 or 401 or 402 or 403 or 404 or 405 or 406 or 407 or 408 or 409 or 410 or 411 or 412 or 413 or 414 or 415 or 416 or 417 or 418 or 419 or 420 or 421 or 422 or 423 or 424 or 425 or 426 or 427 or 428 or 429 or 430 or 431
433. infant*:ab,ti
434. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four" or "twenty five" or "twenty six") NEAR/1 week*):ab,ti
435. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four") NEAR/1 month*):ab,ti
436. 434 or 435
437. (old or age*):ab,ti
438. 436 and 437
439. (("one year*" or "two year*") NEAR/3 (old or age*)):ab,ti
440. ((first or second or two) NEAR/3 "year* of life"):ab,ti
441. MeSH descriptor [Infant] this term only
442. MeSH descriptor [Infant, Newborn] this term only
443. (maternal NEAR/7 pregnan*):ab,ti
444. (maternal NEAR/7 lactat*):ab,ti
445. (mother* NEAR/7 pregnan*):ab,ti
446. 433 or 438 or 439 or 440 or 441 or 442 or 443 or 444 or 445
447. 16 or 73 or 341
448. 432 and 446 and 447
Publication date from 2011

Appendix 2 Search Strategies for original articles (Review A)

2.1. Medline

1. breast feeding.ab,ti.
2. breastfeeding.ab,ti.
3. breast fed.ab,ti.
4. breastfed.ab,ti.
5. Breast Feeding/
6. Milk, Human/
7. formula?.ab,ti.
8. hydrolysed.ab,ti.
9. bottlefed.ab,ti.
10. bottle fed.ab,ti.
11. (bottle adj3 feed$).ab,ti.
12. Infant Formula/
13. Bottle Feeding/
14. wean$.ab,ti.
15. Weaning/
16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. allerg$.ab,ti.
18. asthma$.ab,ti.
19. wheeze.ab,ti.
20. wheezing.ab,ti.
21. bronchial hyperresponsiveness.ab,ti.
22. bronchial hyperreactivity.ab,ti.
23. Forced expiratory volume.ab,ti.
24. FEV1.ab,ti.
25. "FEV 1".ab,ti.
26. "FEV0.5".ab,ti.
27. "FEV 0.5".ab,ti.
28. Forced vital capacity.ab,ti.
29. FVC.ab,ti.
30. Peak expiratory flow rate.ab,ti.
31. PEFR.ab,ti.
32. eczema.ab,ti.
33. neurodermatitis.ab,ti.
34. rhinitis.ab,ti.
35. besniers prurigo.ab,ti.
36. rhinoconjunctivitis.ab,ti.
37. hayfever.ab,ti.
38. (hay adj fever).ab,ti.
39. poll?nosis.ab,ti.
40. SAR.ab,ti.
41. (pollen adj allergy).ab,ti.
42. conjunctivitis.ab,ti.
43. immunoglobulin e.ab,ti.

44. Total IgE.ab,ti.
45. autoimmune disease?.ab,ti.
46. diabetes.ab,ti.
47. diabetic.ab,ti.
48. type 1.ab,ti.
49. c?eliac disease.ab,ti.
50. crohn$ disease.ab,ti.
51. Inflammatory Bowel Disease?.ab,ti.
52. Ulcerative colitis.ab,ti.
53. (Lympho$ adj3 thyroiditi$).ab,ti.
54. (Thyroiditi$ adj3 autoimmune).ab,ti.
55. (Hashimoto$ adj3 (syndrome? or thyroiditi$ or disease?)).ab,ti.
56. (Thyroiditi$ adj3 (post-partum or postpartum)).ab,ti.
57. Graves? disease.ab,ti.
58. Basedow$ disease.ab,ti.
59. exophthalmic goiter?.ab,ti.
60. (Still? Disease adj3 (juvenile or onset)).ab,ti.
61. (Juvenile adj3 arthriti$).ab,ti.
62. vitiligo.ab,ti.
63. Psorias?s.ab,ti.
64. (Arthriti? adj3 Psoria$).ab,ti.
65. atopic disease.ab,ti.
66. atopic dermatitis.ab,ti.
67. (food? adj3 sensiti$).ab,ti.
68. (food? adj3 toleran$).ab,ti.
69. (food? adj3 intoleran$).ab,ti.
70. ((aero or air$) adj3 allergen?).ab,ti.
71. (aeroallergen? adj3 sensiti$).ab,ti.
72. (allergen? adj3 sensiti$).ab,ti.
73. skin prick test$.ab,ti.
74. atopy.ab,ti.
75. hypersensitiv$.ab,ti.
76. Hypersensitivity/
77. exp Food Hypersensitivity/
78. Respiratory Hypersensitivity/
79. Asthma/
80. Bronchial Hyperreactivity/
81. Forced Expiratory Volume/
82. Vital Capacity/
83. Peak Expiratory Flow Rate/
84. Eczema/
85. Neurodermatitis/
86. Rhinitis/
87. Rhinitis, Allergic, Perennial/
88. Rhinitis, Allergic, Seasonal/
89. Conjunctivitis/
90. Immunoglobulin E/
91. Autoimmune Diseases/
92. Diabetes Mellitus, Type 1/

93. Celiac Disease/
94. Crohn Disease/
95. Inflammatory Bowel Diseases/
96. Colitis, Ulcerative/
97. Thyroiditis, Autoimmune/
98. Hashimoto Disease/
99. Postpartum Thyroiditis/
100. Graves Disease/
101. Arthritis, Juvenile Rheumatoid/
102. Vitiligo/
103. Psoriasis/
104. Arthritis, Psoriatic/
105. Dermatitis, Atopic/
106. Hypersensitivity, Immediate/
107. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106
108. infant?.ab,ti.
109. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four" or "twenty five" or "twenty six") adj week?).ab,ti.
110. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four") adj month?).ab,ti.
111. 109 or 110
112. (old or age?).ab,ti.
113. 111 and 112
114. (("one year?" or "two year?") adj3 (old or age?)).ab,ti.
115. ((first or second or two) adj3 "year? of life").ab,ti.
116. Infant/
117. Infant, Newborn/
118. 108 or 113 or 114 or 115 or 116 or 117
119. clinical trial?.mp.
120. random$.mp.
121. factorial$.mp.
122. crossover$.mp.
123. placebo$.mp.
124. (doubl$ adj blind$).mp.
125. (singl$ adj blind$).mp.
126. assign$.mp.
127. volunteer$.mp.
128. cohort stud$.mp.
129. longitudinal$.mp.
130. follow-up.mp.
131. prospectiv$.mp.

132. retrospectiv$.mp.
133. case control.mp.
134. case referent.mp.
135. exp clinical trial/
136. Cross-Over Studies/
137. Placebos/
138. Double-Blind Method/
139. Single-Blind Method/
140. exp Cohort Studies/
141. case-control studies/
142. 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141
143. 16 and 107 and 118 and 142

2.2. Embase

1. breast feeding.ab,ti.
2. breastfeeding.ab,ti.
3. breast fed.ab,ti.
4. breastfed.ab,ti.
5. breast feeding/
6. breast milk/
7. formula?.ab,ti.
8. hydrolysed.ab,ti.
9. bottlefed.ab,ti.
10. bottle fed.ab,ti.
11. (bottle adj3 feed$).ab,ti.
12. artificial milk/
13. bottle feeding/
14. wean$.ti,ab.
15. weaning/
16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. allerg$.ab,ti.
18. asthma$.ab,ti.
19. wheeze.ab,ti.
20. wheezing.ab,ti.
21. bronchial hyperresponsiveness.ab,ti.
22. bronchial hyperreactivity.ab,ti.
23. Forced expiratory volume.ab,ti.
24. FEV1.ab,ti.
25. "FEV 1".ab,ti.
26. "FEV0.5".ab,ti.
27. "FEV 0.5".ab,ti.
28. Forced vital capacity.ab,ti.
29. FVC.ab,ti.
30. Peak expiratory flow rate.ab,ti.
31. PEFR.ab,ti.
32. eczema.ab,ti.
33. neurodermatitis.ab,ti.
34. rhinitis.ab,ti.
35. besniers prurigo.ab,ti.
36. rhinoconjunctivitis.ab,ti.
37. hayfever.ab,ti.
38. (hay adj fever).ab,ti.
39. poll?nosis.ab,ti.
40. SAR.ab,ti.
41. (pollen adj allergy).ab,ti.
42. conjunctivitis.ab,ti.
43. immunoglobulin e.ab,ti.
44. Total IgE.ab,ti.
45. autoimmune disease?.ab,ti.
46. diabetes.ab,ti.

47. diabetic.ab,ti.
48. type 1.ab,ti.
49. c?eliac disease.ab,ti.
50. crohn$ disease.ab,ti.
51. Inflammatory Bowel Disease?.ab,ti.
52. Ulcerative colitis.ab,ti.
53. (Lympho$ adj3 thyroiditi$).ab,ti.
54. (Thyroiditi$ adj3 autoimmune).ab,ti.
55. (Hashimoto$ adj3 (syndrome? or thyroiditi$ or disease?)).ab,ti.
56. (Thyroiditi$ adj3 (post-partum or postpartum)).ab,ti.
57. Graves? disease.ab,ti.
58. Basedow$ disease.ab,ti.
59. exophthalmic goiter?.ab,ti.
60. (Still? Disease adj3 (juvenile or onset)).ab,ti.
61. (Juvenile adj3 arthriti$).ab,ti.
62. vitiligo.ab,ti.
63. Psorias?s.ab,ti.
64. (Arthriti? adj3 Psoria$).ab,ti.
65. atopic disease.ab,ti.
66. atopic dermatitis.ab,ti.
67. (food? adj3 sensiti$).ab,ti.
68. (food? adj3 toleran$).ab,ti.
69. (food? adj3 intoleran$).ab,ti.
70. ((aero or air$) adj3 allergen?).ab,ti.
71. (aeroallergen? adj3 sensiti$).ab,ti.
72. (allergen? adj3 sensiti$).ab,ti.
73. skin prick test$.ab,ti.
74. atopy.ab,ti.
75. hypersensitiv$.ab,ti.
76. exp hypersensitivity/
77. respiratory tract allergy/
78. asthma/
79. wheezing/
80. bronchus hyperreactivity/
81. forced expiratory volume/
82. forced vital capacity/
83. peak expiratory flow/
84. eczema/
85. neurodermatitis/
86. rhinitis/
87. rhinoconjunctivitis/
88. hay fever/
89. pollen allergy/
90. perennial rhinitis/
91. conjunctivitis/
92. immunoglobulin E/
93. autoimmune disease/
94. diabetes mellitus/
95. insulin dependent diabetes mellitus/

96. celiac disease/
97. Crohn disease/
98. enteritis/
99. ulcerative colitis/
100. autoimmune thyroiditis/
101. Hashimoto disease/
102. postpartum thyroiditis/
103. Graves disease/
104. juvenile rheumatoid arthritis/
105. vitiligo/
106. psoriasis/
107. psoriatic arthritis/
108. atopic dermatitis/
109. nutritional intolerance/
110. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109
111. infant?.ab,ti.
112. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four" or "twenty five" or "twenty six") adj week?).ab,ti.
113. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four") adj month?).ab,ti.
114. 112 or 113
115. (old or age?).ab,ti.
116. 114 and 115
117. (("one year?" or "two year?") adj3 (old or age?)).ab,ti.
118. ((first or second or two) adj3 "year? of life").ab,ti.
119. infant/
120. newborn/
121. 111 or 116 or 117 or 118 or 119 or 120
122. clinical trial?.mp.
123. random$.mp.
124. factorial$.mp.
125. crossover$.mp.
126. placebo$.mp.
127. (doubl$ adj blind$).mp.
128. (singl$ adj blind$).mp.
129. assign$.mp.
130. volunteer$.mp.
131. cohort stud$.mp.
132. longitudinal$.mp.
133. follow-up.mp.
134. prospectiv$.mp.

135. retrospectiv$.mp.
136. case control.mp.
137. case referent.mp.
138. exp clinical trial/
139. crossover procedure/
140. placebo/
141. double blind procedure/
142. single blind procedure/
143. cohort analysis/
144. longitudinal study/
145. follow up/
146. prospective study/
147. retrospective study/
148. exp case control study/
149. 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148
150. 16 and 110 and 121 and 149

2.3. LILACS

(tw:((breast feeding) or breastfeeding or (breast fed) or breastfed or formula* or hydrolysed or bottlefed or (bottle fed) or (bottle feed*) or wean*)
AND
(tw:(allerg* or asthma* or wheez* or (bronchial hyperresponsiveness) or (bronchial hyperreactivity) or (Forced expiratory volume) or FEV1 or (FEV 1) or FEV0.5 or (FEV 0.5) or (Forced vital capacity) or FVC or (Peak expiratory flow rate) or PEFR or eczema or neurodermatitis or rhinitis or (besniers prurigo) or rhinoconjunctivitis or hayfever or (hay fever) or poll?nosis or SAR or (pollen allergy) or conjunctivitis or (immunoglobulin e) or (Total IgE) or (autoimmune disease*) or diabetes or diabetic or (type 1) or (c?eliac disease) or (crohn* disease) or (Inflammatory Bowel Disease*) or (Ulcerative colitis) or (Lympho* thyroiditi*) or (Thyroiditi* autoimmune) or (Hashimoto* syndrome*) or (Hashimoto* thyroiditis*) or (Hashimoto* disease*) or (Thyroiditi* post-partum) or (Thyroiditi* postpartum) or (Graves* Disease) or (Basedow* disease) or (exophthalmic goiter*) or (Still's Disease) or (Stills disease) or (Juvenile arthriti*) or vitiligo or Psorias?s or (Arthriti* Psoria*) or (atopic disease) or (atopic dermatitis) or (food* sensiti*) or (food* toleran*) or (food* intoleran*) or (aero allergen*) or (air* allergen*) or (aeroallergen* sensiti*) or (allergen* sensiti*) or (skin prick test*) or atopy or hypersensitive*)
AND
db:("LILACS")
AND
type_of_study:("clinical_trials" or "case_control" or "cohort" or "systematic_reviews")
AND
limit:("infant" or "newborn" or "preschool" or "child")

2.4. COCHRANE Library

1. “breast feeding”:ab,ti
2. breastfeeding:ab,ti
3. “breast fed”:ab,ti
4. breastfed:ab,ti
5. MeSH descriptor [Breast Feeding] this term only
6. MeSH descriptor [Milk, Human] this term only
7. formula*:ab,ti
8. hydrolysed:ab,ti
9. bottlefed:ab,ti
10. “bottle fed”:ab,ti
11. (bottle NEAR/3 feed*):ab,ti
12. MeSH descriptor [Infant Formula] this term only
13. MeSH descriptor [Bottle Feeding] this term only
14. wean*:ab,ti
15. MeSH descriptor [Weaning] this term only
16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. allerg*:ab,ti
18. asthma*:ab,ti
19. wheeze:ab,ti
20. wheezing:ab,ti
21. “bronchial hyperresponsiveness”:ab,ti
22. “bronchial hyperreactivity”:ab,ti
23. “Forced expiratory volume”:ab,ti
24. “FEV1”:ab,ti
25. "FEV 1":ab,ti
26. "FEV0.5":ab,ti
27. "FEV 0.5":ab,ti
28. “Forced vital capacity”:ab,ti
29. FVC:ab,ti
30. “Peak expiratory flow rate”:ab,ti
31. PEFR:ab,ti
32. eczema:ab,ti
33. neurodermatitis:ab,ti
34. rhinitis:ab,ti
35. “besniers prurigo”:ab,ti
36. rhinoconjunctivitis:ab,ti
37. hayfever:ab,ti
38. “hay fever”:ab,ti
39. poll*nosis:ab,ti
40. SAR:ab,ti
41. “pollen allergy”:ab,ti
42. conjunctivitis:ab,ti
43. “immunoglobulin e”:ab,ti
44. “Total IgE”:ab,ti
45. “autoimmune disease*”:ab,ti
46. diabetes:ab,ti

47. diabetic:ab,ti
48. “type 1”:ab,ti
49. “c*eliac disease”:ab,ti
50. “crohn* disease”:ab,ti
51. “Inflammatory Bowel Disease*”:ab,ti
52. “Ulcerative colitis”:ab,ti
53. (Lympho* NEAR/3 thyroiditi*):ab,ti
54. (Thyroiditi* NEAR/3 autoimmune):ab,ti
55. (Hashimoto* NEAR/3 (syndrome* or thyroiditi* or disease*)):ab,ti
56. (Thyroiditi* NEAR/3 (post-partum or postpartum)):ab,ti
57. “Graves* disease”:ab,ti
58. “Basedow* disease”:ab,ti
59. “exophthalmic goiter*”:ab,ti
60. (Still* Disease NEAR/3 (juvenile or onset)):ab,ti
61. (Juvenile NEAR/3 arthriti*):ab,ti
62. vitiligo:ab,ti
63. Psorias*s:ab,ti
64. (Arthriti* NEAR/3 Psoria*):ab,ti
65. “atopic disease”:ab,ti
66. “atopic dermatitis”:ab,ti
67. (food* NEAR/3 sensiti*):ab,ti
68. (food* NEAR/3 toleran*):ab,ti
69. (food* NEAR/3 intoleran*):ab,ti
70. ((aero or air*) NEAR/3 allergen*):ab,ti
71. (aeroallergen* NEAR/3 sensiti*):ab,ti
72. (allergen* NEAR/3 sensiti*):ab,ti
73. “skin prick test*”:ab,ti
74. atopy:ab,ti
75. hypersensitiv*:ab,ti
76. MeSH descriptor [Hypersensitivity] this term only
77. MeSH descriptor [Food Hypersensitivity] explode all trees
78. MeSH descriptor [Respiratory Hypersensitivity] this term only
79. MeSH descriptor [Asthma] this term only
80. MeSH descriptor [Bronchial Hyperreactivity] this term only
81. MeSH descriptor [Forced Expiratory Volume] this term only
82. MeSH descriptor [Vital Capacity] this term only
83. MeSH descriptor [Peak Expiratory Flow Rate] this term only
84. MeSH descriptor [Eczema] this term only
85. MeSH descriptor [Neurodermatitis] this term only
86. MeSH descriptor [Rhinitis] this term only
87. MeSH descriptor [Rhinitis, Allergic, Perennial] this term only
88. MeSH descriptor [Rhinitis, Allergic, Seasonal] this term only
89. MeSH descriptor [Conjunctivitis] this term only
90. MeSH descriptor [Immunoglobulin E] this term only
91. MeSH descriptor [Autoimmune Diseases] this term only
92. MeSH descriptor [Diabetes Mellitus, Type 1] this term only
93. MeSH descriptor [Celiac Disease] this term only
94. MeSH descriptor [Crohn Disease] this term only
95. MeSH descriptor [Inflammatory Bowel Diseases] this term only

96. MeSH descriptor [Colitis, Ulcerative] this term only
97. MeSH descriptor [Thyroiditis, Autoimmune] this term only
98. MeSH descriptor [Hashimoto Disease] this term only
99. MeSH descriptor [Postpartum Thyroiditis] this term only
100. MeSH descriptor [Graves Disease] this term only
101. MeSH descriptor [Arthritis, Juvenile Rheumatoid] this term only
102. MeSH descriptor [Vitiligo] this term only
103. MeSH descriptor [Psoriasis] this term only
104. MeSH descriptor [Arthritis, Psoriatic] this term only
105. MeSH descriptor [Dermatitis, Atopic] this term only
106. MeSH descriptor [Hypersensitivity, Immediate] this term only
107. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106
108. infant*:ab,ti
109. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four" or "twenty five" or "twenty six") NEAR/1 week*):ab,ti
110. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four") NEAR/1 month*):ab,ti
111. 109 or 110
112. (old or age*):ab,ti
113. 111 and 112
114. (("one year*" or "two year*") NEAR/3 (old or age*)):ab,ti
115. ((first or second or two) NEAR/3 "year* of life"):ab,ti
116. MeSH descriptor [Infant] this term only
117. MeSH descriptor [Infant, Newborn] this term only
118. 108 or 113 or 114 or 115 or 116 or 117
119. “clinical trial*”
120. random*
121. factorial*
122. crossover*
123. placebo*
124. “doubl* blind*”
125. “singl* blind*”
126. assign*
127. volunteer*
128. “cohort stud*”
129. longitudinal*
130. follow-up
131. prospectiv*
132. retrospectiv*
133. “case control”

134. "case referent"
135. MeSH descriptor [clinical trial] explode all trees
136. MeSH descriptor [Cross-Over Studies] this term only
137. MeSH descriptor [Placebos] this term only
138. MeSH descriptor [Double-Blind Method] this term only
139. MeSH descriptor [Single-Blind Method] this term only
140. MeSH descriptor [Cohort Studies] explode all trees
141. MeSH descriptor [case-control studies] this term only
142. 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141
143. 16 and 107 and 118 and 142

2.5. Web of Science

1. TOPIC = (“breast feeding” or breastfeeding or “breast fed” or breastfed or formula$ or hydrolysed or bottlefed or “bottle fed” or (bottle NEAR/3 feed*) or wean*)
2. TOPIC = (allerg* or asthma* or wheeze or wheezing or “bronchial hyperresponsiveness” or “bronchial hyperreactivity” or “Forced expiratory volume” or “FEV1” or "FEV 1" or "FEV0.5" or "FEV 0.5" or “Forced vital capacity” or FVC or “Peak expiratory flow rate” or PEFR or eczema or neurodermatitis or rhinitis or “besniers prurigo” or rhinoconjunctivitis or hayfever or “hay fever” or poll$nosis or SAR or “pollen allergy” or conjunctivitis or “immunoglobulin e” or “Total IgE” or “autoimmune disease$” or diabetes or diabetic or “type 1” or “c$eliac disease” or “crohn* disease” or “Inflammatory Bowel Disease$” or “Ulcerative colitis” or (Lympho* NEAR/3 thyroiditi*) or (Thyroiditi* NEAR/3 autoimmune) or (Hashimoto* NEAR/3 (syndrome$ or thyroiditis* or disease$)) or (Thyroiditi* NEAR/3 (post-partum or postpartum)) or “Graves$ Disease” or “Basedow* disease” or “exophthalmic goiter$” or (“Still$ Disease” NEAR/3 (juvenile or onset)) or (Juvenile NEAR/3 arthriti*) or vitiligo or Psorias$s or (Arthriti$ NEAR/3 Psoria*) or “atopic disease” or “atopic dermatitis” or (food$ NEAR/3 sensiti*) or (food$ NEAR/3 toleran*) or (food$ NEAR/3 intoleran*) or ((aero or air*) NEAR/3 allergen$) or (aeroallergen$ NEAR/3 sensiti*) or (allergen$ NEAR/3 sensiti*) or “skin prick test*” or atopy or hypersensitive*)
3. TOPIC = (infant$ or (("one year$" or "two year$") NEAR/3 (old or age$)) or ((first or second or two) NEAR/3 "year$ of life"))
4. TOPIC = ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four" or "twenty five" or "twenty six") NEAR/1 week$)
5. TOPIC = ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four") NEAR/1 month$)
6. 4 or 5
7. TOPIC = ((old or age$))
8. 7 and 6
9. 8 or 3
10. TOPIC = (“clinical trial$” or random* or factorial* or crossover* or placebo* or “doubl* blind*” or “singl* blind*” or assign* or volunteer* or “cohort stud*” or longitudinal* or follow-up or prospective* or retrospective* or “case control” or “case referent”)
11. 1 and 2 and 9 and 10

Dietary Exposures during Pregnancy, Lactation and/or Infancy for Reducing Risk of Allergic or Autoimmune Outcomes: a systematic review and meta-analysis (Review C Part II).

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I. Background

Review C Part II is one of 4 reports resulting from a comprehensive review of the scientific literature on infant feeding and the development of atopic and autoimmune diseases, commissioned by the UK Food Standards Agency. Atopic conditions such as asthma, eczema, rhinoconjunctivitis and food allergy appear to have increased in prevalence in recent decades in many countries, and are some of the commonest causes of chronic illness in children and young adults living in the UK (1,2)(3)(4)(5). An apparent increase in disease prevalence, combined with data from migration studies, suggests that early-life environmental factors may be important modulators of atopic disease risk. Similarly the autoimmune diseases type I diabetes mellitus and Crohn's disease appear to have increased in some countries (6). Significant attention has focussed on early-life dietary exposures in relation to these atopic and autoimmune diseases, due to recent changes in the human diet, and the potential effects of such changes on intestinal and systemic immune development (7). The gut associated lymphoid tissue is the largest collection of immune tissue in humans, and is the most mature immune organ at the time of birth (8). So enteral exposures in infancy are likely to be especially potent modulators of immune development and risk of immune-mediated disease. Although there is a large number of observational studies, some intervention trials and several systematic reviews in this area, they tend to focus on one specific area of diet and a limited number of immune outcomes. The purpose of this project is to assess comprehensively and systematically the existing literature regarding the relationship between dietary exposures during pregnancy, lactation and infancy, and a child's risk of developing any of the common atopic and autoimmune diseases.

This project consists of a series of systematic reviews which together have very broad inclusion criteria and were registered as 3 separate review protocols on the International Prospective Register of Systematic Reviews (PROSPERO references CRD42013003802 – REVIEW A; CRD42013004239 – REVIEW B; CRD42013004252 – REVIEW C; www.crd.york.ac.uk/Prospero) on the 5th August 2013. The overall purpose of the work is to inform UK Government feeding guidance for mothers and their infants.

The outcomes of this project will be summarised in 4 separate reports, with a distinct set of dietary exposures examined in each report:

1. REVIEW A: DURATION OF TOTAL AND EXCLUSIVE BREASTFEEDING, AND TIMING OF SOLID FOOD INTRODUCTION
2. REVIEW B: TIMING OF INTRODUCTION OF ALLERGENIC FOODS INTO THE INFANT DIET
3. REVIEW C PART I: HYDROLYSED FORMULA IN PLACE OF STANDARD UNHYDROLYSED COW'S MILK BASED INFANT FORMULA, OR BREAST MILK
4. REVIEW C PART II: OTHER MATERNAL AND INFANT DIETARY EXPOSURES (INTERVENTION TRIALS AND OBSERVATIONAL STUDIES)

The specific outcomes of interest for all of these reviews, chosen due to their high prevalence in the UK population, and described in more detail below, are:

Atopic disorders: Food allergy, Eczema, Asthma/Wheeze, Allergic rhinitis, Allergic conjunctivitis, Allergic sensitisation

Autoimmune diseases: Type 1 diabetes mellitus, Coeliac disease, Inflammatory bowel disease, Autoimmune thyroid disease, Juvenile rheumatoid arthritis, Vitiligo, Psoriasis.

1. Review C Part II: other maternal (pregnancy/ lactation) and/or infant dietary exposures

Review C includes all dietary interventions and exposures not captured elsewhere in the review, ie dietary patterns, specific food or food group intake, dietary supplements and micro/macronutrient intake. The review includes supplements given directly to infants, either alone, as part of a more complex intervention, or given to infants indirectly via maternal supplementation during pregnancy and/or lactation. In this report we present data from intervention studies as well as from observational studies.

1.1. Specific questions addressed in Review C

Review C addresses 2 key research questions, to help understand the potential role of dietary exposures during pregnancy/ lactation and infancy for reducing an infant's risk of atopic or autoimmune disease:

a) does exposure to specific dietary patterns, food groups or nutrients during the first year of life, influence a child's future risk of developing atopic disease, allergic sensitisation or autoimmune disease.

b) does maternal exposure to specific dietary patterns, food groups or nutrients during pregnancy or lactation, influence a child's future risk of developing atopic disease, allergic sensitisation or autoimmune disease.

1.2. Glossary of key terms

Allergic sensitisation: production of specific IgE antibodies directed against harmless environmental antigens such as pollens, mites, milk, egg or peanut; and sometimes associated with increased serum total IgE levels. Allergic sensitisation is strongly associated with atopic disease. Although there are also other forms of allergic sensitisation which do not involve IgE, these are poorly characterised in the context of food allergy and have not been included in this review.

Atopic disease: chronic health conditions associated with the production of IgE antibodies to harmless environmental antigens.

Atopy: a predisposition to mount IgE antibody responses

Case control study: a retrospective study that compares people with an outcome of interest (cases) with people without the outcome (controls), in relation to specific risk factor(s).

Controlled clinical trial: An intervention trial which used a predicatable allocation sequence, thought likely to lead to unbalanced treatment groups in relation to an important risk factor for the outcome(s) of interest.

Extensively hydrolysed formula: cow's milk formula described in original publication as extensively hydrolysed.

GRADE evaluation of evidence: grade of evidence in this report is assigned using the GRADE system, which has 4 categories HIGH, MODERATE, LOW or VERY LOW. Evidence is initially assigned as HIGH if coming from a randomised trial; LOW from observational studies; VERY LOW from other evidence. The grade of evidence is then reduced if there are serious (-1) or very serious (-2) limitations to study quality or uncertainties about directness of association; important inconsistency (-1), imprecise or sparse data (-1) or a high probability of reporting bias (-1). Grade of evidence is increased if strong evidence of association is seen (eg RR >2 or <0.5) from ≥2 observational studies with no plausible confounders (+1) or very strong direct evidence (RR >5 or <0.2) with no major threats to validity (+2); if there is evidence of a dose-response gradient (+1) or if all plausible confounders would have reduced the effect/association seen (+1). The interpretation of GRADE evidence assessments is that for HIGH level evidence further research is very unlikely to change our confidence in the estimate of effect; for MODERATE evidence further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; for LOW level evidence further research is very likely to have an

important impact on our confidence in the estimate of effect and is likely to change the estimate; and for VERY LOW level evidence any estimate of effect is very uncertain. Further detailed explanation of GRADE can be found at :
http://www.gradeworkinggroup.org/publications/Grading_evidence_and_recommendations_BMJ.pdf

Maternal allergenic food avoidance: avoidance of one or more of the following foods during any part of pregnancy and/or lactation - cow's milk, soya, egg, peanut, tree nuts, wheat, fish, seafood, which are the 'major food allergens' as defined by the US Food Allergen Labeling and consumer Protection Act of 2004.

Multifaceted interventions: an intervention which includes more than one category of dietary intervention that was eligible for inclusion in this FSA/COT systematic review project. Many such interventions also include environmental control measures such as house dust mite reduction and tobacco smoke avoidance.

Nested case control study: a case control study in which cases and controls are identified from within a larger prospective cohort study

Prospective cohort study: a study in which people are followed over time to determine whether they develop an outcome of interest, and exposure data are collected prior to outcome data.

Prebiotic: selectively fermented ingredient (typically oligosaccharides), that allows specific changes in the composition and/or activity of the gastrointestinal microflora, and thereby confer a health benefit.

Probiotic: live microorganisms which, when administered in adequate amounts, confer a health benefit on the host.

PUFA: polyunsaturated fatty acids – n-3 or n-6 fatty acids, including essential and also some non-essential fatty acids.

RCT: Randomised controlled trial. An intervention trial which reported that a random method of treatment allocation was used.

Retrospective cohort study: a special type of cohort study in which the outcome of interest has already occurred at the time when participants are categorised by exposure status.

Synbiotic: a combination of probiotic and prebiotic administered to the same individual.

1.3. Executive summary

The key findings of this review are summarised below, in relation to each of 9 reports – intervention trials of probiotics, prebiotics, polyunsaturated fatty acids (PUFAs), maternal allergenic food avoidance, and multifaceted interventions; observational studies of fruits and vegetables, fats and fatty acids and 'other dietary exposures'; and a report on vitamin and mineral exposures which includes both intervention and observational studies. We used the GRADE approach to assessing the strength of evidence, and specify in the text of the Executive Summary section of each individual report where judgements have been made that result in lower or higher grade evidence (9).

This is followed by a summary of the Methods used to identify studies, extract, analyse and appraise data, and a Discussion of the main findings in the context of existing literature. The 9 separate systematic reviews which provide the basis for this Executive Summary and constitute the substance of REVIEW C, can be accessed from Table 1 below.

Table 1 Individual study reports in relation to 9 exposure groups of interest

Dietary exposure	Report
Probiotic supplementation intervention trials	
Prebiotic supplementation intervention trials	
PUFA supplementation intervention trials	
Maternal allergenic food avoidance intervention trials	
Multifaceted interventions intervention trials	
Vitamins and minerals intervention and observational studies	
Fruits and vegetables Observational studies	
Dietary sources of fatty acids observational studies	
Other foods observational studies	

1.3.1.

1.3.2. Probiotic supplementation

Data from over 6000 participants in 28 intervention trials contributed to this report. We found MODERATE level evidence (-1 inconsistency) that probiotics can prevent atopic AD ie AD with associated positive skin prick test or specific IgE test (11 studies, 12 interventions; 3000 participants RR 0.78; 95% CI 0.65 to 0.92; I^2=0%). We found MODERATE level evidence (-1 inconsistency) that probiotics can prevent *all* atopic dermatitis (AD) (19 studies; 4500 participants; RR 0.78; 95% CI 0.68 to 0.90; I^2=61%) in children ≤ 4 years old. The majority of the evidence in these positive meta-analyses came from studies of high risk infants ie those with a positive family history of atopic disease (10 of 12 interventions for atopic AD; 16 of 19 trials for *all* AD). In subgroup analyses we found some evidence that probiotic supplementation during pregnancy and lactation, rather than just given directly to infants, is important for efficacy. Approximately half of the trials evaluating AD as an outcome used *Lactobacillus rhamnosus* strains either alone or in combination with others. We found no evidence that probiotics reduce risk of AD at age 5-14 (11 studies; 2500 participants; RR 0.87; 95% CI 0.74, 1.02; I^2=39%). We found LOW level evidence
(-1 indirect outcome; -1 inconsistency) that probiotics can prevent allergic sensitisation to cow's milk in high risk infants, but no evidence that probiotics prevent allergic sensitisation to other allergens or prevent clinical cow's milk allergy. We found no evidence that probiotics prevent wheezing, allergic rhinitis or food allergy, but we found no studies reporting data for allergic conjunctivitis or autoimmune outcomes.

Conclusion:

Probiotics during pregnancy/lactation/infancy reduce risk of AD in high risk infants at age ≤4 years.

Grade of evidence: MODERATE.

Probiotics during pregnancy/lactation/infancy reduce risk of allergic sensitisation to cow's milk in high risk infants.

Grade of evidence: LOW.

There is no evidence that probiotics influence risk of wheeze, allergic rhinitis, food allergy, or other forms of allergic sensitisation. Further research is needed to understand whether probiotics influence risk of autoimmune diseases.

1.3.3. Prebiotic supplementation

Data from almost 4000 participants in 10 intervention trials contributed to this report. For all analyses data were either sparse or inconsistent, and carried a significant risk of conflict of interest, and of overall bias, especially attrition bias. The findings have largely resulted from industry-sponsored studies undertaken in populations of infants with very limited or no breastfeeding, and often with significant post-randomisation losses/exclusions. Given the very high levels of prebiotics naturally present in human breast milk, the role of prebiotics in infant nutrition is likely to be as an additive to formula milk in formula-fed infants, rather than as a supplement for all infants.

We found no evidence that probiotics reduce risk of wheezing, allergic sensitisation, AD, food allergy or allergic rhinitis.

Conclusion:

There is no evidence that prebiotics influence risk of wheeze, AD, allergic rhinitis, allergic sensitisation or food allergy. Further research is needed to confirm these findings, and we did not identify any studies reporting prebiotic effects on allergic conjunctivitis or autoimmune diseases.

1.3.4. PUFA supplementation

Data from over 14,000 participants in 19 intervention trials contributed to this report. Overall the quality of evidence was moderate - there was a low or unclear risk of bias and risk of conflict of interest in most studies. Half of the trials studied infants at high risk of allergic outcomes due to family history of allergic disease, half studied 'normal risk' populations.

We found MODERATE level evidence (-1 indirectness of outcome measure) that n-3 supplementation using fish oil during pregnancy +/- lactation, reduces allergic sensitisation to egg in high risk infants (6 studies; 1800 participants; RR 0.69; 95% CI 0.53, 0.90; I^2=15%). No effect was seen for allergic sensitisation to other allergens, and no studies evaluated this outcome in a 'normal risk' population.

There was no evidence for any effect of n-3 supplementation on the other allergic outcomes reported – AD, AR, wheeze or food allergy, but data were sparse and inconclusive for n-3 supplementation and risk of food allergy, suggesting a need for further research. Data were also sparse and inconclusive for n-6 supplementation and allergic outcomes. We did not find any studies reporting effects of PUFA supplementation on autoimmune outcomes.

Conclusion:
Fish oil supplementation during pregnancy +/- lactation in high risk infants reduces risk of allergic sensitisation to eggs.
Grade of evidence: MODERATE.

There is no evidence that fish oil or other n-3 polyunsaturated fatty acid sources influence risk of wheezing, AD or allergic rhinitis, and further work is needed to assess whether the effect on egg sensitisation leads to an effect on food allergy. We did not identify any reports of PUFA supplementation on risk of autoimmune diseases.

1.3.5. Maternal allergenic food avoidance

Data from over 1900 participants in 12 intervention trials (9 RCT, 3 CCT) contributed to this report. Overall the quality of evidence was low - there was a high or unclear risk of bias in all studies, and data were sparse for all outcomes, especially TIDM, food allergy and allergic rhinitis. No reports of other autoimmune outcomes were identified. All studies evaluated participants at high risk of allergic outcomes. There was a low risk of conflict of interest in most studies.

Two studies intervened in pregnancy only, 6 during lactation and 4 during both periods of time. Seven studies were single intervention (AFA), 5 were multifaceted (typically both maternal and infant dietary interventions, with environmental control measures to reduce allergen/ irritant exposure). The foods excluded were: milk alone (2), egg alone (1), milk and egg (3), or multiple other food groups (6), the latter usually including milk and egg as well.

We found no evidence that maternal allergenic food avoidance during pregnancy and/or lactation reduces risk of allergic disease or TIDM development.

Conclusion:

There is no evidence that maternal allergenic food avoidance reduces risk of allergic or autoimmune outcomes. Data are sparse, and high quality adequately-powered studies are needed to confidently exclude a beneficial effect. Data are lacking for ‘normal risk’ populations, and for autoimmune diseases other than TIDM.

1.3.6. Multifaceted interventions

Data from over 2000 participants in 9 intervention trials contributed to this report. Overall the quality of evidence was mixed. There was an unclear risk of bias in most studies, largely due to insufficient details about the randomisation process (selection bias). All the trials studied infants at high risk of allergic outcomes due to family history of allergic disease. Data were generally sparse, such that clinically significant effects could not be confidently excluded.

We found LOW level evidence that multifaceted interventions reduce risk of AR at age ≤ 4 years (-1 indirect intervention; -1 imprecision). Two studies, 613 participants, RR 0.61 95% CI 0.44, 0.84; I^2=0%. We found no evidence for an effect on AC, or on AR at age 5-14.

We found LOW level evidence (-1 indirect intervention; -1 imprecision) that multifaceted interventions reduce risk of wheeze (2 studies, 500 participants, RR 0.57 95% CI 0.41, 0.81; I^2=0%) or recurrent wheeze (4 studies, 730 participants, RR 0.77 95% CI 0.61, 0.97; I^2=0%) at age 5-14 years. We found no evidence for an effect on lung function, or on wheeze at age ≤ 4 years.

Conclusion:
Multifaceted interventions reduce risk of AR in high risk infants, at age ≤4.
Grade of evidence: LOW.

Multifaceted interventions prevent wheeze/recurrent wheeze in high risk children at age 5-14.
Grade of evidence: LOW.

There is no evidence that multifaceted interventions reduce risk of food allergy, allergic sensitisation, allergic conjunctivitis or AD, but data were sparse such that clinically significant effects cannot be confidently excluded. We found no data for autoimmune outcomes, nor for 'normal risk' populations.

1.3.7. Vitamins and minerals

Intervention trials: Data from over 15,000 participants in 11 intervention trials contributed to this report. Five of the 11 studies were at high risk of bias due to high attrition bias. Opportunities for meta-analysis were limited due to differing interventions and outcome measures. Two studies used vitamin A in infants; one vitamin A/beta carotene in pregnancy; 2 studies used vitamin C +/- E during pregnancy; 3 used vitamin D during pregnancy, one vitamin D during pregnancy and infancy and 2 multivitamins during pregnancy. One trial found evidence that vitamin A supplementation during pregnancy increases lung function in offspring; but this was downgraded to no evidence, due to inconsistency, indirectness of the study population and imprecision. We found no evidence for other effects, and no reports of autoimmune outcomes.

Observational studies: We identified 50 observational studies which reported the association between infant, maternal or combined intake of vitamins and minerals and allergic or autoimmune outcomes. Of these, 32 were prospective cohorts, 4 were nested case-control studies, and 14 were case-control studies. The main dietary exposures studied were antioxidant vitamins A, C, E, and their precursors, vitamin D and folic acid.
We found no consistent evidence that vitamin or mineral exposures influence allergic or autoimmune outcomes.

Conclusion:
There is no evidence that vitamin or mineral supplementation reduces risk of allergic outcomes, but data were sparse and heterogeneous such that clinically significant effects cannot be confidently excluded. We found no data for autoimmune outcomes.

1.3.8. Fruits and vegetables – observational studies

A total of 35 observational studies reported the association between infant and/or maternal intake of fruit and vegetable and allergic or autoimmune diseases. Of these studies, 27 were prospective cohort studies, 6 case-controls, and 2 nested case control studies. Nineteen studies investigated the association between risk of AD and fruit or vegetable intake, nine studies investigated food allergy (FA), 1 study investigated lung function (LF), 19 studied wheeze, seven studied rhino-conjunctivitis (RC), 15 studied allergenic sensitisation, nine

studied type 1 diabetes mellitus (T1DM) and one investigated inflammatory bowel disease (IBD).

Risk of bias was generally low, and opportunities for meta-analysis were very limited due to heterogeneity in reporting of associations.

Overall, we found no consistent evidence to suggest that intake of fruits and vegetables early in life influences risk of other allergic or autoimmune diseases.

Conclusion:

There is no evidence that maternal or infant fruit or vegetable intake or introduction is associated with risk of allergic or autoimmune outcomes.

1.3.9. Fats and fatty acids – observational studies

A total of 26 studies investigated intake of fats and risk of allergic or autoimmune diseases. Twenty were prospective cohort studies, 1 nested case-control, 1 retrospective cohort, 3 case-control and 1 cross-sectional study. Outcomes studied were atopic dermatitis (AD) (n=13), food allergy (FA) (n=3), wheeze (n=13), lung function (LF) (n=1), allergic sensitisation (AS) (n=6), type 1 diabetes mellitus (T1DM) (n=3) and juvenile idiopathic arthritis (JIA) (n=1).

Risk of bias was generally low, and opportunities for meta-analysis were very limited due to heterogeneity in reporting of associations.

We found inconsistent evidence regarding infant fish intake and risk of later AD or RC, with one study finding increased infant fish intake associated with reduced AD or RC, but other studies failing to support this association.

In our report of intervention trials for fish/fish oil supplementation we identified studies of fish oil supplementation during infancy, which did not show a protective effect on allergic outcomes – however we did not identify any intervention trials of fish supplementation in infancy.

We found no evidence for an association between other measures of maternal or infant fat and fatty acid intake, and risk of allergic outcomes or autoimmune disease.

Conclusion:

We found no evidence for associations between infant fish, fat or fatty acid intake, or maternal fish, fat or fatty acid intake during pregnancy or lactation, and risk of allergic or autoimmune outcomes.

1.3.10. 'Other dietary exposures' – observational studies

We identified a total of 47 observational studies that investigated the association between other infant or maternal dietary exposures, and allergic or autoimmune diseases. 27 studies were prospective cohorts (PC), 4 were nested case-controls (NCC), 12 were case-controls (CC), and 4 cross-sectional studies (CS). 22 studies included atopic dermatitis (AD) as outcome; 2 studied food allergy (FA); 2 lung function (LF); 21 wheeze; 7 rhino-conjunctivitis (RC); 10 allergic sensitisation (AS); 10 type 1 diabetes mellitus (T1DM); one studied juvenile idiopathic arthritis (JIA), and one studied inflammatory bowel disease (IBD).).

Risk of bias was generally low, and opportunities for meta-analysis were very limited due to heterogeneity in reporting of associations. We found no consistent evidence for associations between other maternal or infant dietary exposures and allergic or autoimmune outcomes.

Conclusion:
Overall we did not find consistent evidence for associations between other maternal or infant dietary exposures, and allergic or autoimmune outcomes in this report.

2. Methodology

The systematic review was undertaken according to PRISMA guidelines for intervention trial evidence.The systematic review protocol was registered on PROSPERO. Studies included in the review were those relevant to maternal dietary exposures during pregnancy and/or lactation, and allergic and autoimmune outcomes as described in more detail below.

2.1. Inclusion Criteria

2.1.1. Types of study included

We included recent high quality systematic reviews published from 2011 until the search date (25th July 2013; updated on 26th February 2017). Older systematic reviews were not included, due to the likelihood of being out of date. We quality assessed eligible systematic reviews using the revised AMSTAR criteria (10) and extracted data from systematic reviews with revised AMSTAR score ≥32. A summary of the identified reviews and data is included in the General Conclusions section at the end of this report.

We included original research studies published at any time prior to the search date (25th July 2013; updated on 26th February 2017for intervention trials only). Original studies eligible for inclusion were randomised controlled trials (RCT), quasi RCT (RCT where the allocation sequence was predictable but not thought likely to lead to imbalance), controlled clinical trials (CCT where the allocation sequence was predictable, and thought likely to lead to significant imbalance between groups in important risk factors for the outcome(s) of interest), prospective cohort or longitudinal studies, retrospective cohort studies, nested case-control studies, other case control studies and cross-sectional surveys. We took a hierarchical approach to study design, such that where data were absent or limited from systematic reviews or intervention trials, we included observational study data. Where a significant number of intervention trials were identified, we did not analyse data from observational studies that assessed the same intervention/exposure. We did not include non-comparative studies, or non-human studies.

2.1.2. Participants/population

Inclusion criteria: Infants between birth and the end of their 12th post-partum month, and their mothers during pregnancy and lactation up to the end of the 24th month postnatally. If infants were characterised as high or normal/low risk for atopic or autoimmune disease based on family history or genotype, this information was recorded so that it could be used for the planned subgroup analysis by disease risk.

Exclusion criteria: We excluded studies in which participants were defined by a disease state - eg pregnant women with specific nutritional deficiencies, infants born prematurely (<31 weeks gestation) or other groups clearly representing <5% of the UK population, since the results of this review should apply to the general UK population. We did not exclude studies on the basis of including specific ethnic groups, studies of high risk infants, since this applies to many UK-born infants for allergic disease, and it is difficult to undertake studies of autoimmune disease prevention in the general population without stratifying by genetic/family risk due to the relatively low prevalence of autoimmune diseases.

2.1.3. Interventions/Exposures

Dietary Interventions and Exposures of interest in this report were any nutritional intervention, from dietary pattern to specific micronutrient supplementation.

Comparators of interest were no intervention/exposure, or any control intervention or control level of exposure.

2.1.4. Study outcomes

We selected atopic and autoimmune outcomes on the basis of their population prevalence in children and young adults in the UK. We included diseases with a prevalence of at least 1 in 1000, in children/adolescents or young adults (aged <40 years), but did not include rarer diseases (11). We did not include pernicious anaemia or adult-onset rheumatoid arthritis despite a high prevalence in middle aged or elderly people, because their prevalence in young people is lower than 1 in 1000, and prospective studies of infant feeding in relation to diseases of older adults are unlikely to have been undertaken. We did not specifically exclude rare manifestations of food allergy such as eosinophilic oesophagitis, if they were reported as part of a food allergy definition, but did exclude them if they were reported as a unique outcome measure since their prevalence is less than 1 in 1000. For atopic outcomes, age at

assessment was grouped as 1-4 years, 5-14 years, 15-24 years, 25-44 years, 45-64 years and ≥65 years. Due to a paucity of studies in adults, we pooled all age groups ≥ 15 years for almost all reports. For autoimmune outcomes, we did not stratify analyses by age at outcome assessment. Where studies reported the same outcome at different timepoints within one of these frames, we used the timepoint with the most complete dataset ie lowest percentage of missing data, as the primary assessment point for inclusion in meta-analysis. Where possible we chose a timepoint for outcome assessment that did not fall within the relevant exposure period ie the first year of life. For each outcome measure in this review, there is more than one possible method of assessment. We therefore included our preferred methods of assessment for each outcome as below *a priori*. In general where multiple measures of the same outcome were reported we selected outcomes that included the most complete data, used a published or validated assessment tool, and were meaningful for patients eg patient/parent-reported measures.

2.1.5. Atopic outcomes:

1. *Asthma/Wheeze* - defined as either 'asthma', 'infantile wheeze' or similar, using parent/self-report, doctor diagnosis, a validated questionnaire, scoring system or objective measure such as bronchial hyper-reactivity, forced vital capacity, peak expiratory flow rate or reversible airways obstruction using forced expiratory volume in 1 second. We included data for 'atopic' asthma/wheeze ie wheeze associated with allergic sensitisation, and for recurrent wheezing. For all asthma/wheeze outcomes, data were analysed as 'wheeze', 'atopic wheeze' or 'recurrent wheeze' depending on the definition of wheeze/asthma used in the original publication. We did not include different wheezing entities based on the timing of onset/resolution of the disease such as 'early transient wheeze' or 'persistent wheeze' due to heterogeneity in definition between studies. We did not include outcomes such as 'bronchitis' or 'bronchiolitis' which included some subjects with wheezing but others without wheezing.
2. *Eczema* – defined using parent/self-report, doctor diagnosis, a validated questionnaire, scoring system or objective measure. We also included data for 'atopic' eczema ie eczema associated with allergic sensitisation. We did not include reports of rashes which were likely to have included other cutaneous problems, such as nappy rash, contact dermatitis,

'rash', 'skin problem' etc, but did include reports of 'recurrent itchy rash in infancy' or similar descriptions which were likely to represent eczema.

3. *Allergic Rhinoconjunctivitis* – defined using parent/self-report, doctor diagnosis, a validated questionnaire, scoring system or objective measure. We included data for 'atopic' rhinoconjunctivitis ie rhinoconjunctivitis associated with allergic sensitisation. We included data for 'allergic rhinitis', 'allergic conjunctivitis' or 'allergic rhinoconjunctivitis' and planned to analyse 'allergic conjunctivitis' separately where data were reported separately.
4. *Food allergy* - defined by double blind placebo controlled food challenge, by open food challenge, by medical diagnosis or by self/parent report. We included reports of 'any food allergy', and specific food allergies to cow's milk, egg or peanut. We did not include reports of 'food intolerance' that we judged were unlikely to meet current definitions of food allergy (12).
6. *Allergic sensitisation* – to an inhalant, an ingestant, or both – defined as positive skin prick test and/or specific IgE test to the relevant allergen using recognised methodologies and scoring criteria (13). We combined data for skin prick and specific IgE testing (using SPT where both were reported in the same study) due to limited numbers of studies available for each meta-analysis, and assessed 'any allergic sensitisation', 'food allergic sensitisation', 'aeroallergen sensitisation', 'cow's milk sensitisation', 'egg sensitisation' and 'peanut sensitisation' separately. We included Total IgE data when measured using a recognised technology such as ImmunoCAP (ThermoFisher, Massachusets).

2.1.6. Autoimmune outcomes:

1. *Type I diabetes mellitus* – defined as a medical diagnosis eg using the 1999 WHO recommendations for diagnosis and classification of diabetes mellitus (14), or a surrogate marker such as autoantibodies against insulin, GAD65, IA-2 or the ZnT8 transporter in the first 3 years of life. We did not include reports where the outcome was stated as 'diabetes' and thought likely to include some cases of type II diabetes mellitus or other disease entities.
2. *Coeliac disease* – defined by characteristic histological features (intraepithelial lymphocytes, crypt hyperplasia and villous atrophy) with improvement in symptoms and histology after institution of a gluten free diet, a medical diagnosis, or a surrogate marker such as IgA tissue transglutaminase or IgA endomysial antibodies.

3. *Inflammatory bowel disease* (Crohn's disease or ulcerative colitis) – defined as a medical diagnosis.
4. *Autoimmune thyroid disease* (Graves' disease or Hashimoto's thyroiditis) - defined as a medical diagnosis.
5. *Juvenile rheumatoid arthritis* – defined as a medical diagnosis eg using the 2001 revised International League of Associations for Rheumatology (ILAR) classification criteria (15).
6. *Vitiligo* - defined as a medical diagnosis.

Primary assessment: medical diagnosis using the Vitiligo European Task Force 2007 criteria or similar (16).

7. *Psoriasis* - defined as a medical diagnosis.

2.2. Search strategy

The search strategies included both text terms and subject heading terms where appropriate. The search strategies were initially developed for use on the MEDLINE database and then adapted for use on other databases. We searched the following databases, with no specified start date:

- The Cochrane Library (2013, Issue 7)
- EMBASE (1947 to July 2013)
- LILACS (1982 to July 2013)
- MEDLINE (1946 to July 2013)
- Web of Science (1970 to July 2013)

The search was run on 25th July 2013 and included all studies published up to that date, and was updated on 26th February 2017 for intervention trials and systematic reviews. We included peer reviewed publications, and abstract publications if they contained data that had not subsequently been published as a peer reviewed publication. We reviewed the bibliography of eligible studies for possible additional publications, and included all eligible publications, regardless of the language. We did not contact the authors of eligible or potentially eligible studies to request original data. The search strategies were extensively piloted and refined to optimise sensitivity, comparing search results with those of other high quality published systematic reviews. The final search strategies for review C are included at the end of this report as *Appendices*.

The search for existing systematic reviews which cover any of the same exposure(s)/outcome(s) as the original studies was limited to publications from 1st January 2011 to 25th July 2013 in the original search, and to 26th February 2017 in the update. The search strategy was partly based on the search strategies used for Review A, Review B and Review C but included a search filter for retrieving systematic reviews (17). Open Grey was searched using the terms '(breast OR lactation OR formula) AND (allergy OR autoimmune OR asthma OR eczema OR rhinitis OR conjunctivitis OR food allergy OR vitiligo OR psoriasis OR arthritisi OR thyroiditis OR atopy OR IgE OR diabetes OR coeliac OR inflammatory bowel disease)' for studies relevant to Review A; the terms '(wean OR peanut OR egg OR milk OR soya OR nut OR fish OR wheat) AND (allergy OR autoimmune OR asthma OR eczema OR rhinitis OR conjunctivitis OR food allergy OR vitiligo OR psoriasis OR arthritisi OR thyroiditis OR atopy OR IgE OR diabetes OR coeliac OR inflammatory bowel disease)' for studies relevant to review B; the terms '(lactation OR pregnancy OR infant OR mother) AND (allergy OR autoimmune OR asthma OR eczema OR rhinitis OR conjunctivitis OR food allergy OR vitiligo OR psoriasis OR arthritisi OR thyroiditis OR atopy OR IgE OR diabetes OR coeliac OR inflammatory bowel disease)' for studies relevant to review C.

The International Prospective Register of Systematic Reviews (PROSPERO) database was also searched for relevant systematic reviews. Due to the limited functionality of this resource individual keywords with date limits were used to search PROSPERO: we searched for titles containing 'breast OR infant OR lactation OR wean OR infant' for studies relevant to review A; 'nut OR wheat OR egg OR food OR diet' for studies relevant to review B; 'pregnant OR infant OR diet OR nutrition OR supplement' for studies relevant to review C.

The citations identified in searches were imported into Endnote libraries for de-duplication and title screening.

2.3. Study selection, data extraction and analysis

2.3.1. Study selection

Title and abstract screening was undertaken in duplicate by a team of 7 researchers (RB, VGL, DI, NG, KJ, JC, ZR). Two researchers undertook title screening independently, and met to agree included and excluded titles. Their screening was checked by a third member of the team, and uncertainties were brought to a full team meeting for discussion. This procedure took place between February and April 2014, with weekly team meetings to

discuss uncertainties about study eligibility, and again in April 2017. The full text of all potentially eligible studies was reviewed, and where electronic copies were not available, hard copies of articles were ordered from the British Library.

2.3.2. Data extraction

An Excel data extraction form was developed, piloted and refined by DI, VGL, RB and JL-B – separate forms were used for intervention studies, cohort studies and case control studies. Data extraction was undertaken in duplicate by a team of 10 researchers (DI, RB, UN, SC, VGL, NT-M, NG, EA, AR, PD). Disagreements and uncertainties about data coding were discussed within the team with leads as follows - RB (clinical queries), VGLA (dietetic queries), DI (analysis and coding queries) and JL-B (study design and statistics queries). For foreign language studies, data were extracted by VGL together with a native speaker of the relevant language (see Acknowledgements section). We extracted all relevant data from included studies, including data that could not (not appropriately reported) or would not (see 'data cleaning' below) be included in meta-analysis, text information such as 'no significant association found', and information that adjusted or unadjusted analyses were performed but not reported.

2.3.3. Data cleaning and coding

Data were extensively cleaned and coded for analysis with further data checks to identify publications related to the same parent study, and to identify the most appropriate output for inclusion in meta-analysis from studies reporting multiple assessments of closely related exposures/outcomes at the same age in the same population. In general from individual studies reporting more than one measure for the same outcome, we selected data for analysis reporting time to event (hazard ratio) in preference to cumulative incidence or lifetime prevalence ie 'disease ever', in turn in preference to point prevalence data ie 'disease in the last 12 months' for all binary outcomes with the exception of the non-clinical outcomes allergic sensitisation and lung function, where point prevalence was analysed in preference to cumulative measures. Data cleaning was undertaken by DI, VGL and RJB. The outcomes of both meta-analysed and narratively reported studies were considered together when interpreting data and making conclusions.

For allergic outcomes we grouped studies reporting outcome at ages 0-4, 5-15 and 15+ years. If a study reported associations (within or between publications) at more than one age within

the same age group (eg age 1 and 3 years), we selected data for analysis within specific age groups that were most complete ie had the largest number of participants assessed. We also included data from longitudinal models (eg generalised estimating equation), and they were grouped according to the last age included in the model. Where appropriate we also considered the outcomes reported at other ages which were not included in meta-analysis, in our interpretation of the data. Age groups were not used for autoimmune diseases. Where different methods of outcome assessment were used within a study we prioritised validated and patient-centred outcomes – for example we prioritised clinical diagnosis of diabetes over diabetes-associated autoantibody detection; we prioritised patient or parent-reported wheeze using a validated instrument such as the ISAAC questionnaire, over doctor diagnosis of wheeze or study physician assessment. Again where appropriate the impact of these decisions was taken into account in our interpretation of findings.

For included studies which did not report numerical data in a form that could be included in meta-analysis, for example medians, or means without a standard deviation or standard error, or 'no significant difference' statements, we summarised the findings narratively in the text or tables of the review.

2.3.4. Risk of bias assessment

a) Review level bias

Publication bias was assessed using funnel plots and Egger's test, for those meta-analyses with ≥10 studies included. Possible causes for asymmetry other than publication bias (eg between study heterogeneity, small study effects) were also considered. We also took into consideration both the outcomes of meta-analyses and the findings of studies not included in meta-analysis, when interpreting systematic review outcomes.

b) Study level bias

The risk of bias in included intervention studies was assessed using a modified version of the Cochrane Collaboration Risk of Bias tool, which assessed sequence generation and allocation concealment (Selection Bias), blinding of outcome assessors and validity of outcome assessment tool (Assessment Bias), incomplete outcome data (Attrition Bias – considered high where <70% of randomised participants had outcome data available). RCTs were considered at low overall risk of bias where the risk of bias was judged to be low for all 3 key

domains selection, assessment and attrition bias. We assessed risk of Conflict of Interest as low where there was no evidence of industry involvement in study design, analysis, interpretation or publication, and no evidence that study authors receive remuneration from relevant industry partners for other activities. The summary Risk of Bias Figures show the risk of bias for all studies reporting the relevant outcome, whether or not their data could be included in meta-analyses.

The risk of bias in included cohort and case control studies was assessed using a modified version of the National Institute for Clinical Excellence methodological checklist for cohort and case-control studies respectively [25]. Key domains were Selection Bias (low if cases and controls were selected from similar populations, if the participation rate was ≥80%, or <80% but investigators explored and adjusted for characteristic differences between participants and non-participants), Assessment Bias (low if validated and reliable tools were used to assess exposure and/or outcome), and Confounding Bias (low if most likely confounders are identified and taken into account in study design and analysis). Observational studies were considered at low overall risk of bias where the risk of bias was judged to be low for all 3 key domains selection, assessment and confounding bias. For assessment of Confounding Bias, factors that we expected to be adjusted for within studies of allergic outcomes were: siblings (parity or birth order or family size); gender; age at outcome assessment; disease risk based on family history; maternal or household smoking (asthma/wheeze outcomes); maternal age; maternal education or socioeconomic status; mode of delivery. For studies on autoimmune outcomes we expected matching and/or adjusting for gender, age, address, socioeconomic status, smoking and disease risk. For all studies we also assessed possible Conflict of Interest, judged as low where there was no evidence of industry involvement in study design, analysis, interpretation or publication, and no evidence that study authors receive remuneration from relevant industry partners for other activities. For all study reports, we created a summary Table of Study Characteristics with key study features, and a separate summary Risk of Bias Figure showing the risk of bias for all included studies – whether included in meta-analyses or reported in the narrative table.

2.3.5. Strategy for data synthesis

Meta-analysis was undertaken where ≥2 studies reported the same outcome for a given exposure. Where meta-analysis was deemed inappropriate due to differences in population, exposure/intervention or outcome; or where meta-analysis was not possible due to the nature

of the data reported - individual study results were summarised in a narrative table at the end of each report. Separate analyses were undertaken for each disease outcome, for each (age) group of similar outcome assessment methods for any given disease, and for each intervention/exposure (group). In general our approach to meta-analysis was inclusive, with data pooled for maximum statistical power, but explored for important sources of statistical or clinical heterogeneity. Results for randomised or quasi-randomised controlled trials were pooled separately from controlled clinical trials.

a) Data extraction

Where studies reported data at multiple timepoints within one of our pre-defined age groupings, we extracted the most complete dataset available, beyond the intervention period (ie from 1 year of age onwards). This is the dataset with the largest denominator, or where the denominator is identical for multiple time points then the largest numerator (number of events) is used. We planned to undertake subgroup/stratified analyses for meta-analyses which contained a total of >5 studies, and to assess publication bias using Funnel plots and Egger's test where there were ≥10 studies in a meta-analysis.

b) Heterogeneity

Heterogeneity was quantified using I^2. We explored reasons for heterogeneity using subgroup analyses based on study level factors. We classified heterogeneity as low (I^2<25%), moderate (I^2 25-50%), high (I^2 50-75%) or extreme (I^2>75%). For single study analyses, and where I^2 exceeded 80% we did not pool data in meta-analysis but presented studies in a forest plot without a pooled effect shown. Individual patient data analysis was not undertaken in this review, and study authors were not contacted to clarify data queries or request further participant data.

c) Data analysis

Pooled results for binary outcomes from intervention studies are presented as RR calculated from the frequencies given in the study. Data from individual studies were pooled using the generic inverse variance method for pooled RR and Mantel-Haenszel method (with continuity correction of 0.5 in studies with zero cell frequencies) or inverse variance method for single studies calculation of pooled RR in the statistical programme R version 3.1.0

(www.r-project.org). Pooled results for continuous outcomes measured using similar scales are presented as mean differences with 95% confidence intervals.

d) Planned subgroup analyses

We planned certain subgroup and stratified analyses prior to running our search. Subgroup analysis was undertaken for all meta-analyses with >5 studies included, since subgroup analysis was unlikely to yield clear subgroup differences where the total number of studies was ≤5. We undertook planned subgroup analyses according to:

1. *Risk of bias* – studies with low, versus unclear/high overall risk of bias based on the criteria described above.
2. *Disease risk* - studies of populations at increased risk for atopic or autoimmune disease, versus those at normal or low risk of disease.
3. *Study design* – we also included a subgroup analysis for qRCT versus RCT.

In the Allergic Sensitisation meta-analyses we planned a subgroup analysis of specific IgE (sIgE) versus Skin Prick Test (SPT) as outcome measure, and in type 1 diabetes mellitus meta-analyses for clinical versus serological diabetes. For all analyses we planned subgroup analyses according to timing of the intervention used (ie pre/postnatal, and postnatal to infant alone or mother +/- infant). For probiotics and prebiotics we planned a subgroup analysis for those studies which used a symbiotic, versus those which used just probiotic or prebiotic alone; and for probiotics we planned a subgroup analysis for the specific species used (*L. rhamnosus* vs others).

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e) Graphical exploration of heterogeneity

Studies were ordered by year of publication in forest plots, in order to be able to assess any cohort effect, since the composition of infant formula and the prevalence of allergic and autoimmune diseases appear to have changed over time. Due to insufficient information in included studies, it was not possible to order forest plots by year of birth for the study population or year of assessment.

2.4. Review registration

The protocol for this systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO CRD42013003802; CRD42013004239;

CRD42013004252; www.crd.york.ac.uk/Prospero) on the 5th August 2013, prior to title screening or selecting any studies from the search results. The protocol was revised following detailed review by the UK Food Standards Agency, the UK Scientific Advisory Committee on Nutrition, independent experts Professor Graham Devereux and Dr Carina Venter, and the Lancet peer review service, prior to being registered on PROSPERO.

2.5. Differences between the protocol and review

Following external statistical review of preliminary reports, a decision was made to not undertake pooled meta-analysis where statistical heterogeneity was ≥80%. Due to insufficient data in included studies, we did not order forest plots by participant year of birth or year of outcome assessment. Instead we ordered by year of publication. New authors joined the review team due to the high workload of title screening and data extraction – TA, TK, SC, NG, ZR, JC, KJ, EA, AR, PD.

3. Results of the Searches

3.1. Systematic reviews identified

Our search results are summarised in the PRISMA flow chart Figure 1.



PRISMA for Existing Systematic Reviews.pd

We identified 469 titles after removing duplicates, of which 33 were considered to be a report from a relevant or potentially relevant systematic review after title and abstract screening. All these studies underwent full text review and revised AMSTAR scoring by 2 authors independently (VGL, RJB) – Table 1 summarises the AMSTAR scores. Two studies were only available in Chinese, and these were scored by a native Chinese speaker Dr Sze-Chin Tan, Consultant Allergist from Tan Tock Seng Hospital Singapore, who was trained in the revised AMSTAR scoring procedure prior to undertaking this task. Of the 33 scored studies, and a further 10 review identified in the update search in February 2017, 11 were eligible for inclusion in the project overall, of which 5 were relevant to Review C. Fifteen studies were excluded due to low AMSTAR score. One study was not a systematic review. Six studies were excluded because they were either protocols for a systematic review (n=2) or were abstract publications with insufficient detail to establish the AMSTAR score or sufficient detail regarding study outcomes (n=4). Six high-quality systematic reviews were excluded because they were only relevant to REVIEWS A or B. A summary of R-AMSTAR scores for existing systematic reviews identified in the original search is shown in Table 2, and a summary of the 5 included reviews from the original search is shown in Table 3. The 11 systematic reviews are reviews of probiotics (n=5), prebiotics (n=1), maternal allergenic food avoidance (n=1), vitamin D (n=2), dietary patterns (n=1) and maternal fatty acid supplementation (n=1). Data from these prior systematic reviews are included in the relevant reports where appropriate (Table 1).

3.2. Original studies identified

Our search results are summarised in the PRISMA flow chart Figure 2.



PRISMA for Original Studies.pdf

We identified 80 relevant intervention trials for inclusion in Review C part II. A small number of identified trials were included in more than one report, due to use of a synbiotic intervention (included in both probiotic and prebiotic reports) or due to use of a multifaceted intervention which included maternal allergenic food avoidance (included in both multifaceted, and maternal allergenic food avoidance reports). We identified 92 observational studies - several observational studies were included in more than one report, due to multiple exposures assessed in the same study population.

Detailed findings, analyses and discussion for the 9 separate systematic reviews are shown in the attached reports (Table 1), and summarised in the Executive Summary.

4. General Conclusions

In these systematic reviews of intervention trial data regarding nutritional exposures during pregnancy, lactation and infancy, we found evidence that nutritional exposures can influence allergic disease development, at least in populations at high risk of allergic disease based on family history. We did not find evidence for effects on risk of autoimmune diseases, but data for these outcomes were either lacking or very sparse in all cases.

Specifically we found MODERATE evidence that probiotics can reduce risk of AD; LOW evidence that multifaceted interventions can reduce risk of wheezing and allergic rhinitis; MODERATE evidence that n-3 PUFA can reduce risk of allergic sensitisation to egg; and LOW level evidence that probiotics can reduce risk of allergic sensitisation to cow's milk..

From the observational studies we found no consistent evidence for associations between maternal or infant dietary exposures and allergic or autoimmune outcome. While single case-control studies reported significant associations in some cases, we did not consider such findings to be significant evidence, in the absence of replication.

Taken together our analyses support recent international recommendations to use probiotics in people at high risk of developing AD, and suggest the need for further trials of maternal n-3 PUFA supplementation.

Acknowlegements

We are grateful to the independent expert peer reviewers Professor Graham Devereux and Dr Carina Venter, and to members of the UK Food Standards Agency, the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT), and the UK Scientific Advisory Committee on Nutrition for their comments on the study protocol and previous versions of this report. We are grateful to Dr Yujie Zhao, Mr Szymon Mikolajewski, Dr Andre Amaral, Dr Mari Kihara, Dr Christian Nielsen, Mr Radoslav Latinovic, Dr Stephanie MacNeill, Dr Andreas Forsters, Dr Daniel Munblit, Dr Sze-Chin Tan, and Dr Claudia Gore for their assistance with translation of foreign language reports. We are grateful to Jackie Cousins of the St. Mary's library at Imperial College London for assistance with literature search training.

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Appendix 1 Tables

Table 2 Quality assessment of recent SRs using R-AMSTAR scoring

Author/Reference	VGL Score	BB Score	CONSENSUS
Antico (18)	19	14	Exclude
Braeger (19)	30	29	Exclude
Brew (20)	**35**	**37**	Exclude – Review A
Cardwell (21)	31	25	Exclude
Christesen (22)	24	25	Exclude
De Silva (5)	26	29	Exclude
Dick (23)	22	19	Exclude
Doege (24)	28	21	Exclude
Flohr (25)	19	19	Exclude
Foolad (26)	18	22	Exclude
Gunaratne (27, 28)	Protocol and Abstract publication only		
Henricksson (29)	18	24	Exclude
Kheirkhah (30)	Abstract publication only		
Klemens (31)	**36**	**35**	Include – Review C
Kramer (32)	**38**	**40**	Exclude – Review A
Kramer (33)	**37**	**40**	Include – Review C
Kremmyda (34)	21	20	Exclude
Middleton (35)	Abstract publication only		
Osborn (36)	Abstract publication only		
Osborn (37)	**38**	**40**	Include – Review C
Pelucci (38)	**33**	**36**	Include – Review C
Patelarou (39)	23	24	Exclude
Schindler (40)	Protocol only		
Schmitt (41)	Not a systematic review		
Szajeweska (42)	**36**	**35**	Exclude – Reviews A and B
Tang (43)	**34***		Include – Review C
Waidyatillake (44)	24	25	Exclude
Wang (45)	31*		Exclude

A score of ≥32 was required for inclusion; * Chinese language, scored by Dr Sze-Chin Tan

Table 3 Characteristics of included systematic reviews

Study Relevant SR	**Databases searched**	**No. studies No. (range) participants**	**Study designs included**	**Population**	**Intervention/ Exposure(s) Comparator(s)**	**Outcomes relevant to the project**	**Subgroup analyses relevant to project**
Klemens (31) Review C	MEDLINE, EBM reviews, ACP Journal Club, DARE, CCTR, CMR, HTA, NHSEED (1950 – 10/2010)	5 studies 949 (98 -402) participants	All RCTs	• Pregnant or lactating women and their offspring • Two high risk and 3 normal risk studies	Supplementation of pregnant or lactating women with n-3 PUFA, versus olive oil (3), placebo not described (1) or soya oil (1)	• Asthma • Eczema • Food allergy in infancy or childhood • Egg sensitisation in infancy	Nil
Kramer (33) Review C	Cochrane Pregnancy and childbirth Group's Trials Register* 07/2012	5 studies 925 (19 – 497) participants	All RCTs	Pregnant or lactating women at high risk for having an atopic child	Exclusion or reduced intake of potentially allergenic foods such as cow milk, egg, peanuts, fish, versus no exclusion	• Eczema • Wheezing • Rhinoconjunctivitis, • Positive skin prick test to egg, milk and peanut • Cord blood IgE	Nil
Osborn (37) Review C	CENTRAL 2012; Issue 8 MEDLINE (1948 -8/2012) EMBASE (1974-8/ 2012)	4 studies 1,428 (113-830) participants	All RCTs	Infants in the first six months of life without clinical evidence of allergy, both with and without risk factors for allergic disease	Prebiotics added to human milk or infant formula, compared to control (placebo or no treatment) or a different prebiotic	• Asthma/wheeze • Eczema • Rhinitis [no data] • Food allergy [no data]	• High risk of allergic disease based on family history • Breastfeeding status • Age – infant (under 2), child (2-10), adolescent (10-18), adult • Study quality [no data – all high risk of bias]

Pelucci (38) Review C	MEDLINE, EMBASE, the Cochrane Library (reviews only) 10/2011	14 studies 1,417 (12-368) participants	All RCTs	Pregnant women, lactating women and their infants	Any probiotic or combination of probiotics, compared with no probiotic	Eczema or IgE-associated eczema, up to age 12	• High risk of allergic disease • Treatment in pregnancy/ lactation/ infancy • Method of diagnosis
Tang (43)† Review C	PUBMED, MEDLINE, SPRINGER LINK, HIGHWIRE, COCHRANE, VIP, WANFANG DATA, CKNI (09/2011)	11 studies 1007 participants	All RCTs	Infants at high risk of atopic disease (first degree relative with any atopic disease including asthma, allergic rhinitis, atopic eczema, food allergy etc) and their mothers	Prenatal and/or postnatal probiotic use versus no probiotic use	• Eczema* • Asthma* • Food sensitisation (positive SPT and/or specific IgE to a food)	Nil

SR: Systematic reviews, RCT: Randomised controlled trial, PUFA: Polyunsaturated fatty acid

Table 4 Summary of findings from intervention trials

GRADE of evidence assessment							Summary of findings		Absolute Risk Reduction*	
No of studies and design	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Other considerations**	**Relative risk**	**GRADE of evidence**	**Control Risk Cases per 1000 population**	**Risk Difference Cases per 1000 population**
Intervention: Maternal or infant probiotic vs no probiotic Outcome: Eczema at age 0-4 Study design: RCT										
1 RCT Eczema	Not Serious Unblinded outcome assessmen t	Serious No effect seen at age 6-7 years. No association seen in observational studies	No	Serious Wide confidence intervals	No	No association found between exclusive breastfeeding duration of and eczema in an observational analyslis of this trial	**OR 0.54 95% CI 0.31, 0.95**	⊗⊗○○ **Low**	**200 (low risk) 300 (high risk) 400 (very high risk)**	**81 cases 95% CI 8 to 128 112 cases 95% CI 11 to 183 135 cases 95% CI 12 to 229**
Intervention: Maternal or infant probiotic vs no probiotic Outcome: Eczema, atopic eczema or cow's milk sensitisation at age 0-4 Study design: RCT										
23 RCT (19 in meta-analysis) 1 CCT Eczema	Not Serious <20% of studies had a high risk of bias	Serious I^2=61% Eczema Study estimates vary from 0.14 to 1.34; subgroup analysis suggests greatest effect if postnatal component includes maternal supplementation	No	No	No	Most RCTs were undertaken in populations at high risk of eczema due to family history of allergic disease. No evidence of an effect on eczema beyond age 0-4.	**RR = 0.78 (0.68, 0.90)**	⊗⊗⊗○ **Moderate**	**200 (low risk) 300 (high risk) 400 (very high risk)**	**44 cases 95% CI 20 to 64 66 cases 95% CI 30 to 96 88 cases 95% CI 40 to 128**

GRADE of evidence assessment							Summary of findings		Absolute Risk Reduction*	
No of studies and design	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Other considerations**	**Relative risk**	**GRADE of evidence**	**Control Risk Cases per 1000 population**	**Risk Difference Cases per 1000 population**
11 RCT Atopic Eczema	Not Serious <20% of studies had a high risk of bias	Serious I^2=0% Study estimates from 0.47 to 1.36. No effect at age 5-14 years RR 0.99 (0.80, 1.22; I^2=0%)	No	No	No Egger's P=0.70	Most RCTs were undertaken in populations at high risk of eczema due to family history of allergic disease.	**RR = 0.78 (0.65, 0.92)**	⊗⊗⊗○ **Moderate**	**100 (low risk)** **150 (high risk)** **200 (very high risk)**	**22 cases 95% CI 8 to 35** **33 cases 95% CI 12 to 53** **44 cases 95% CI 16 to 70**
9 RCT (8 in meta-analysis) Cow's milk sensitisation	Not Serious <20% of studies had a high risk of bias	Not Serious I^2=0% Study estimates vary from 0.14 to 0.98. No beneficial effect seen for allergic sensitisation to other allergens.	Serious Sensitisation is a surrogate measure of clinical food allergy. No effect of intervention on food allergy	Serious Low event numbers and borderline statistical significance	Not tested (n<10) No evidence of publication bias in Funnel plots for other forms of allergic sensitisation	Most RCTs were undertaken in populations at high risk of eczema due to family history of allergic disease	**RR = 0.60 (0.37, 0.96)**	⊗⊗○○ **Low**	**30 (low risk)** **100 (high risk)** **300 (very high risk)**	**12 cases 95% CI 1 to 19** **40 cases 95% CI 4 to 63** **120 cases 95% CI 12 to 189**
Intervention: Infant prebiotic versus no prebiotic **Outcome: Eczema at age 0-4** **Study design: RCT**										
9 RCT (7 in meta-analysis) Eczema	Serious 4 studies with high risk of attrition bias, 5 with high risk of conflict of interest	Serious I^2=57% Study estimates vary from 0.14 to 1.64	Serious 6 studies restricted inclusion to infants fully formula fed from birth, 3 days, < 2 weeks, <6 weeks (n=2) and <8 weeks; 3 other studies used co-interventions – hydrolysed formula and probiotics	Serious Wide confidence intervals, borderline statistical significance	Not tested (n<10)	3 RCTs were undertaken in populations at high risk due to family history of allergic disease, 4 at normal risk, and 1 at low risk due to absence of family history of allergic disease. All studies used galactooligosaccharides, usually combined with other oligosaccharides; 2 studies combined the intervention with probiotic(s)	**RR = 0.75 (0.56, 1.01)**	○○○○ **No evidence**	**-**	**-**

GRADE of evidence assessment							Summary of findings		Absolute Risk Reduction*	
No of studies and design	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Other considerations**	**Relative risk**	**GRADE of evidence**	**Control Risk Cases per 1000 population**	**Risk Difference Cases per 1000 population**
Intervention: Maternal fish oil (n-3 PUFA) vs no fish oil **Outcome: Allergic sensitisation to egg** **Study design: RCT**										
6 RCT Allergic sensitisation to egg	Not Serious 2 studies with unclear overall risk of bias, and 2 studies with unclear risk of conflict of interest	Not Serious I^2=15% Study estimates vary from 0.45 to 1.02. No significant effect seen for allergic sensitisation to other allergens, but direction of effect is not inconsistent with that seen for egg	Serious Egg sensitisation is a surrogate measure of clinical food allergy. No effect of the intervention was seen on clinical food allergy.	Not serious Limits of 95% CI are all important effects at a population level.	Not tested (n<10)	All RCTs were undertaken in populations at high risk of allergy due to family history of allergic disease. Subgroup analysis suggests effect is greatest if treatment is given during pregnancy.	**RR = 0.69 (0.53, 0.90)**	⊗⊗⊗○ **Moderate**	**100 (low risk)** **150 (high risk)** **200 (very high risk)**	**31 cases 95% CI 10 to 47** **46 cases 95% CI 15 to 71** **62 cases 95% CI 20 to 94**
Intervention: Multifaceted interventions vs control **Outcome: Allergic rhinitis at age 0-4** **Study design: RCT**										
3 RCT (2 in meta-analysis) Allergic rhinitis	Not serious No study with high risk of bias or high risk of conflict of interest	Not serious I^2=0% Study estimates vary from 0.58 to 0.61	Serious Both studies in meta-analysis included environmental control measures such as dust mite and tobacco smoke avoidance	Serious Sparse data, inconsistent with data for age 5-14, where no effect was seen. Study not included in meta-analysis found no effect	Not tested (n<10)	All RCTs were undertaken in populations at high risk due to family history of allergic disease. All studies included delayed introduction of allergenic foods and maternal allergenic food avoidance	**RR = 0.61 (0.44, 0.84)**	⊗⊗○○ **Low**	**50 (low risk)** **100 (high risk)** **150 (very high risk)**	**20 cases 95% CI 8 to 28** **39 cases 95% CI 16 to 56** **59 cases 95% CI 24 to 84**

GRADE of evidence assessment							Summary of findings		Absolute Risk Reduction*	
No of studies and design	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Other considerations**	**Relative risk**	**GRADE of evidence**	**Control Risk Cases per 1000 population**	**Risk Difference Cases per 1000 population**
Intervention: Multifaceted interventions vs control **Outcome: Wheeze or recurrent wheeze at age 5-14** **Study design: RCT**										
2 RCT Wheeze	Not serious No study with high risk of attrition bias or high risk of conflict of interest	Not serious I^2=0% Study estimates vary from 0.50 to 0.59	Serious Both studies included environmental control measures such as dust mite and tobacco smoke avoidance, which are known to reduce respiratory symptoms	Serious Sparse data, inconsistent with data for age 0-4 and lung function data, where no effect was seen	Not tested (n<10)	All RCTs were undertaken in populations at high risk due to family history of allergic disease. Both studies included delayed introduction of allergenic foods and maternal allergenic food avoidance	**RR = 0.57 (0.41, 0.81)**	⊗⊗○○ **Low**	**100 (low risk)** **150 (high risk)** **200 (very high risk)**	**43 cases 95% CI 19 to 59** **65 cases 95% CI 29 to 89** **86 cases 95% CI 38 to 118**
4 RCT Recurrent wheeze	Not serious 1 study high risk of attrition bias, and no study with high risk of conflict of interest	Not serious I^2=0% Study estimates vary from 0.64 to 1.41	Serious 3 studies included environmental control measures such as dust mite and tobacco smoke avoidance, which are known to reduce respiratory symptoms	Serious Sparse data, inconsistent with data for age 0-4 and lung function data, where no effect was seen	Not tested (n<10)	All RCTs were undertaken in populations at high risk due to family history of allergic disease. All studies included delayed introduction of allergenic foods; three also included maternal allergenic food avoidance	**RR = 0.77 (0.61, 0.97)**	⊗⊗○○ **Low**	**50 (low risk)** **100 (high risk)** **150 (very high risk)**	**12 cases 95% CI 2 to 20** **23 cases 95% CI 3 to 39** **35 cases 95% CI 5 to 59**

GRADE of evidence assessment							Summary of findings		Absolute Risk Reduction*	
No of studies and design	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Other considerations**	**Relative risk**	**GRADE of evidence**	**Control Risk Cases per 1000 population**	**Risk Difference Cases per 1000 population**
Intervention: Maternal vitamin A vs no vitamin A **Outcome: Lung function at age 11 years** **Study design: RCT**										
1 RCT Lung function	Not serious Low risk of bias	Very serious Supplementation with the vitamin A precursor beta carotene in the same trial had no effect on lung function. Neither vtamin A nor beta carotene had an effect on risk of wheeze. Separate trial with similar design but lower vitamin A dose as part of a multivitamin intervention found no effect on FEV1 or FVC at age 8	Serious Study population was a poor rural Nepalese population at risk of vitamin A deficiency	Serious Single study, with wide confidence intervals	Not tested (n<10)	Dose response relationship between maternal postpartum serum retinol levels and lung function outcomes	**Mean Difference** **FEV_1 46mls (6, 86)** **FVC 46mls (8, 84)**	○○○○ **No evidence**	**-**	**-**

Appendix 2 Search Strategies for other systematic reviews

These search strategies were used to identify recent SRs relevant to Reviews A, B or C

Medline

1. breast feeding.ab,ti.
2. breastfeeding.ab,ti.
3. breast fed.ab,ti.
4. breastfed.ab,ti.
5. Breast Feeding/
6. Milk, Human/
7. formula?.ab,ti.
8. hydrolysed.ab,ti.
9. bottlefed.ab,ti.
10. bottle fed.ab,ti.
11. (bottle adj3 feed$).ab,ti.
12. Infant Formula/
13. Bottle Feeding/
14. wean$.ab,ti.
15. Weaning/
16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. complementary food?.ab,ti.
18. (introduc$ adj2 food?).ab,ti.
19. wean$.ab,ti.
20. Weaning/
21. solid?.ab,ti.
22. semi-solid?.ab,ti.
23. baby food?.ab,ti.
24. Infant Food/
25. Infant Nutritional Physiological Phenomena/
26. breast feeding.ab,ti.
27. breastfeeding.ab,ti.
28. breast fed.ab,ti.
29. breastfed.ab,ti.
30. Breast Feeding/
31. Milk, Human/
32. formula?.ab,ti.
33. hydrolysed.ab,ti.
34. bottlefed.ab,ti.
35. bottle fed.ab,ti.
36. (bottle adj3 feed$).ab,ti.
37. Infant Formula/
38. Bottle Feeding/
39. liquid?.ab,ti.
40. milk.ab,ti.
41. Milk/
42. egg?.ab,ti.
43. Egg Proteins/
44. Egg Proteins, Dietary/

45. nut?.ab,ti.
46. peanut?.ab,ti.
47. almond?.ab,ti.
48. (brazil? adj5 nut?).ab,ti.
49. walnut?.ab,ti.
50. pecan?.ab,ti.
51. pistachio?.ab,ti.
52. cashew?.ab,ti.
53. hazelnut?.ab,ti.
54. macadamia?.ab,ti.
55. Nuts/
56. Arachis hypogaea/
57. Prunus/
58. Bertholletia/
59. Juglans/
60. Carya/
61. Pistacia/
62. Anacardium/
63. Corylus/
64. Macadamia/
65. wheat.ab,ti.
66. Triticum/
67. soya.ab,ti.
68. Soybeans/
69. gluten$.ab,ti.
70. Glutens/
71. fish.ab,ti.
72. Fishes/
73. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72
74. Diet/
75. Diet Therapy/
76. Nutritional Sciences/
77. Child Nutrition Sciences/
78. diet.ab,ti.
79. diets.ab,ti.
80. Diet, Mediterranean/
81. mediterranean diet$.ab,ti.
82. dietetic.ab,ti.
83. dietary.ab,ti.
84. eat.ab,ti.
85. eating.ab,ti.
86. intake.ab,ti.
87. nutrient?.ab,ti.
88. nutrition.ab,ti.
89. Diet, Vegetarian/
90. vegetarian?.ab,ti.
91. vegan$.ab,ti.

92. Diet, Macrobiotic/
93. macrobiotic?.ab,ti.
94. Food/
95. food$.ab,ti.
96. feed.ab,ti.
97. feeding.ab,ti.
98. cereal$.ab,ti.
99. grain$.ab,ti.
100. granary.ab,ti.
101. wholegrain.ab,ti.
102. wholewheat.ab,ti.
103. whole wheat.ab,ti.
104. wheat.ab,ti.
105. wheatgerm.ab,ti.
106. rye.ab,ti.
107. barley.ab,ti.
108. oat?.ab,ti.
109. exp Cereals/
110. root?.ab,ti.
111. tuber?.ab,ti.
112. exp Vegetables/
113. vegetable$.ab,ti.
114. onion$.ab,ti.
115. spinach.ab,ti.
116. chard.ab,ti.
117. tomato$.ab,ti.
118. pepper$.ab,ti.
119. carrot$.ab,ti.
120. beetroot.ab,ti.
121. asparagus.ab,ti.
122. garlic.ab,ti.
123. pumpkin.ab,ti.
124. sprouts.ab,ti.
125. broccoli.ab,ti.
126. cabbage$.ab,ti.
127. celery.ab,ti.
128. ginger.ab,ti.
129. potato$.ab,ti.
130. crisps.ab,ti.
131. fries.ab,ti.
132. syrup.ab,ti.
133. honey.ab,ti.
134. Honey/
135. Fruit/
136. fruit$.ab,ti.
137. apple?.ab,ti.
138. pear?.ab,ti.
139. banana?.ab,ti.
140. orange?.ab,ti.
141. grape?.ab,ti.

142. kiwi?.ab,ti.
143. citrus.ab,ti.
144. grapefruit?.ab,ti.
145. pulses.ab,ti.
146. beans.ab,ti.
147. lentil?.ab,ti.
148. chickpea?.ab,ti.
149. legume?.ab,ti.
150. lupin?.ab,ti.
151. soy.ab,ti.
152. soya.ab,ti.
153. nut?.ab,ti.
154. almond?.ab,ti.
155. peanut?.ab,ti.
156. groundnut?.ab,ti.
157. Nuts/
158. seed?.ab,ti.
159. sesame.ab,ti.
160. mustard.ab,ti.
161. Seeds/
162. exp Meat/
163. meat.ab,ti.
164. beef.ab,ti.
165. pork.ab,ti.
166. lamb.ab,ti.
167. poultry.ab,ti.
168. chicken.ab,ti.
169. turkey.ab,ti.
170. duck.ab,ti.
171. fish.ab,ti.
172. Fatty Acids/
173. exp Fatty Acids, Omega-3/
174. exp Fatty Acids, Omega-6/
175. omega-3.ab,ti.
176. omega-6.ab,ti.
177. PUFA.ab,ti.
178. fat.ab,ti.
179. fats.ab,ti.
180. fatty.ab,ti.
181. egg.ab,ti.
182. eggs.ab,ti.
183. exp Eggs/
184. Bread/
185. bread.ab,ti.
186. oil.ab,ti.
187. oils.ab,ti.
188. oily.ab,ti.
189. omega.ab,ti.
190. exp Seafood/
191. seafood.ab,ti.

192. shellfish.ab,ti.
193. crustacean?.ab,ti.
194. mollusc?.ab,ti.
195. Shellfish/
196. Dairy Products/
197. dairy.ab,ti.
198. exp Milk/
199. milk.ab,ti.
200. Infant Formula/
201. formula?.ab,ti.
202. hydrolysed.ab,ti.
203. Infant Food/
204. yoghurt.ab,ti.
205. probiotic.ab,ti.
206. prebiotic?.ab,ti.
207. butter.ab,ti.
208. herb?.ab,ti.
209. spice?.ab,ti.
210. chilli$.ab,ti.
211. condiment?.ab,ti.
212. exp Condiments/
213. Beverages/
214. beverage?.ab,ti.
215. fluid intake.ab,ti.
216. water.ab,ti.
217. drink$.ab,ti.
218. exp Food Preservation/
219. pickled.ab,ti.
220. bottled.ab,ti.
221. canned.ab,ti.
222. canning.ab,ti.
223. smoked.ab,ti.
224. preserved.ab,ti.
225. preservatives.ab,ti.
226. nitrosamine.ab,ti.
227. hydrogenation.ab,ti.
228. fortified.ab,ti.
229. nitrates.ab,ti.
230. nitrites.ab,ti.
231. ferment$.ab,ti.
232. processed.ab,ti.
233. antioxidant$.ab,ti.
234. genetic modif$.ab,ti.
235. genetically modif$.ab,ti.
236. Cooking/
237. cooking.ab,ti.
238. cooked.ab,ti.
239. grill.ab,ti.
240. grilled.ab,ti.
241. fried.ab,ti.

242. fry.ab,ti.
243. roast.ab,ti.
244. bake.ab,ti.
245. baked.ab,ti.
246. stewing.ab,ti.
247. stewed.ab,ti.
248. casserol$.ab,ti.
249. broil.ab,ti.
250. broiled.ab,ti.
251. boiled.ab,ti.
252. poach.ab,ti.
253. poached.ab,ti.
254. steamed.ab,ti.
255. barbecue$.ab,ti.
256. chargrill$.ab,ti.
257. salt.ab,ti.
258. salting.ab,ti.
259. salted.ab,ti.
260. fiber.ab,ti.
261. fibre.ab,ti.
262. polysaccharide$.ab,ti.
263. starch.ab,ti.
264. starchy.ab,ti.
265. carbohydrate$.ab,ti.
266. lipid$.ab,ti.
267. linoleic acid$.ab,ti.
268. sugar$.ab,ti.
269. sweetener$.ab,ti.
270. saccharin$.ab,ti.
271. aspartame.ab,ti.
272. sucrose.ab,ti.
273. xylitol.ab,ti.
274. cholesterol.ab,ti.
275. hydrogenated lard.ab,ti.
276. dietary protein.ab,ti.
277. dietary proteins.ab,ti.
278. protein intake.ab,ti.
279. animal protein$.ab,ti.
280. total protein$.ab,ti.
281. vegetable protein$.ab,ti.
282. plant protein$.ab,ti.
283. exp Dietary Carbohydrates/
284. exp Dietary Fats/
285. exp Dietary Fiber/
286. exp Dietary Proteins/
287. exp Dietary Supplements/
288. exp Food Additives/
289. exp Vitamins/
290. supplements.ab,ti.
291. supplement.ab,ti.

292. vitamin$.ab,ti.
293. retinol.ab,ti.
294. carotenoid$.ab,ti.
295. tocopherol.ab,ti.
296. folate$.ab,ti.
297. folic acid.ab,ti.
298. methionine.ab,ti.
299. riboflavin.ab,ti.
300. thiamine.ab,ti.
301. niacin.ab,ti.
302. pyridoxine.ab,ti.
303. cobalamin.ab,ti.
304. mineral$.ab,ti.
305. sodium.ab,ti.
306. iron.ab,ti.
307. calcium.ab,ti.
308. selenium.ab,ti.
309. iodine.ab,ti.
310. magnesium.ab,ti.
311. potassium.ab,ti.
312. zinc.ab,ti.
313. copper.ab,ti.
314. phosphorus.ab,ti.
315. manganese.ab,ti.
316. chromium.ab,ti.
317. phytochemical.ab,ti.
318. polyphenol$.ab,ti.
319. phytoestrogen$.ab,ti.
320. genistein.ab,ti.
321. saponin$.ab,ti.
322. coumarin$.ab,ti.
323. flavonoid$.ab,ti.
324. polyphenol$.ab,ti.
325. flavonol$.ab,ti.
326. flavone$.ab,ti.
327. isoflavone$.ab,ti.
328. catechin$.ab,ti.
329. ascorbic acid$.ab,ti.
330. hydroxy cholecalciferol$.ab,ti.
331. hydroxycholecalciferol$.ab,ti.
332. tocotrienol$.ab,ti.
333. carotene$.ab,ti.
334. cryptoxanthin$.ab,ti.
335. lycopene$.ab,ti.
336. lutein$.ab,ti.
337. zeaxanthin$.ab,ti.
338. selenium$.ab,ti.
339. organic diet?.ab,ti.
340. Food, Organic/

341. 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169 or 170 or 171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181 or 182 or 183 or 184 or 185 or 186 or 187 or 188 or 189 or 190 or 191 or 192 or 193 or 194 or 195 or 196 or 197 or 198 or 199 or 200 or 201 or 202 or 203 or 204 or 205 or 206 or 207 or 208 or 209 or 210 or 211 or 212 or 213 or 214 or 215 or 216 or 217 or 218 or 219 or 220 or 221 or 222 or 223 or 224 or 225 or 226 or 227 or 228 or 229 or 230 or 231 or 232 or 233 or 234 or 235 or 236 or 237 or 238 or 239 or 240 or 241 or 242 or 243 or 244 or 245 or 246 or 247 or 248 or 249 or 250 or 251 or 252 or 253 or 254 or 255 or 256 or 257 or 258 or 259 or 260 or 261 or 262 or 263 or 264 or 265 or 266 or 267 or 268 or 269 or 270 or 271 or 272 or 273 or 274 or 275 or 276 or 277 or 278 or 279 or 280 or 281 or 282 or 283 or 284 or 285 or 286 or 287 or 288 or 289 or 290 or 291 or 292 or 293 or 294 or 295 or 296 or 297 or 298 or 299 or 300 or 301 or 302 or 303 or 304 or 305 or 306 or 307 or 308 or 309 or 310 or 311 or 312 or 313 or 314 or 315 or 316 or 317 or 318 or 319 or 320 or 321 or 322 or 323 or 324 or 325 or 326 or 327 or 328 or 329 or 330 or 331 or 332 or 333 or 334 or 335 or 336 or 337 or 338 or 339 or 340
342. allerg$.ab,ti.
343. asthma$.ab,ti.
344. wheeze.ab,ti.
345. wheezing.ab,ti.
346. bronchial hyperresponsiveness.ab,ti.
347. bronchial hyperreactivity.ab,ti.
348. Forced expiratory volume.ab,ti.
349. FEV1.ab,ti.
350. "FEV 1".ab,ti.
351. "FEV0.5".ab,ti.
352. "FEV 0.5".ab,ti.
353. Forced vital capacity.ab,ti.
354. FVC.ab,ti.
355. Peak expiratory flow rate.ab,ti.
356. PEFR.ab,ti.
357. eczema.ab,ti.
358. neurodermatitis.ab,ti.
359. rhinitis.ab,ti.
360. besniers prurigo.ab,ti.
361. rhinoconjunctivitis.ab,ti.
362. hayfever.ab,ti.
363. (hay adj fever).ab,ti.
364. poll?nosis.ab,ti.
365. SAR.ab,ti.
366. (pollen adj allergy).ab,ti.
367. conjunctivitis.ab,ti.
368. immunoglobulin e.ab,ti.
369. Total IgE.ab,ti.
370. autoimmune disease?.ab,ti.

371. diabetes.ab,ti.
372. diabetic.ab,ti.
373. type 1.ab,ti.
374. c?eliac disease.ab,ti.
375. crohn$ disease.ab,ti.
376. Inflammatory Bowel Disease?.ab,ti.
377. Ulcerative colitis.ab,ti.
378. (Lympho$ adj3 thyroiditi$).ab,ti.
379. (Thyroiditi$ adj3 autoimmune).ab,ti.
380. (Hashimoto$ adj3 (syndrome? or thyroiditi$ or disease?)).ab,ti.
381. (Thyroiditi$ adj3 (post-partum or postpartum)).ab,ti.
382. Graves? disease.ab,ti.
383. Basedow$ disease.ab,ti.
384. exophthalmic goiter?.ab,ti.
385. (Still? Disease adj3 (juvenile or onset)).ab,ti.
386. (Juvenile adj3 arthriti$).ab,ti.
387. vitiligo.ab,ti.
388. Psorias?s.ab,ti.
389. (Arthriti? adj3 Psoria$).ab,ti.
390. atopic disease.ab,ti.
391. atopic dermatitis.ab,ti.
392. (food? adj3 sensiti$).ab,ti.
393. (food? adj3 toleran$).ab,ti.
394. (food? adj3 intoleran$).ab,ti.
395. ((aero or air$) adj3 allergen?).ab,ti.
396. (aeroallergen? adj3 sensiti$).ab,ti.
397. (allergen? adj3 sensiti$).ab,ti.
398. skin prick test$.ab,ti.
399. atopy.ab,ti.
400. hypersensitiv$.ab,ti.
401. Hypersensitivity/
402. exp Food Hypersensitivity/
403. Respiratory Hypersensitivity/
404. Asthma/
405. Bronchial Hyperreactivity/
406. Forced Expiratory Volume/
407. Vital Capacity/
408. Peak Expiratory Flow Rate/
409. Eczema/
410. Neurodermatitis/
411. Rhinitis/
412. Rhinitis, Allergic, Perennial/
413. Rhinitis, Allergic, Seasonal/
414. Conjunctivitis/
415. Immunoglobulin E/
416. Autoimmune Diseases/
417. Diabetes Mellitus, Type 1/
418. Celiac Disease/
419. Crohn Disease/
420. Inflammatory Bowel Diseases/

421. Colitis, Ulcerative/
422. Thyroiditis, Autoimmune/
423. Hashimoto Disease/
424. Postpartum Thyroiditis/
425. Graves Disease/
426. Arthritis, Juvenile Rheumatoid/
427. Vitiligo/
428. Psoriasis/
429. Arthritis, Psoriatic/
430. Dermatitis, Atopic/
431. Hypersensitivity, Immediate/
432. 342 or 343 or 344 or 345 or 346 or 347 or 348 or 349 or 350 or 351 or 352 or 353 or 354 or 355 or 356 or 357 or 358 or 359 or 360 or 361 or 362 or 363 or 364 or 365 or 366 or 367 or 368 or 369 or 370 or 371 or 372 or 373 or 374 or 375 or 376 or 377 or 378 or 379 or 380 or 381 or 382 or 383 or 384 or 385 or 386 or 387 or 388 or 389 or 390 or 391 or 392 or 393 or 394 or 395 or 396 or 397 or 398 or 399 or 400 or 401 or 402 or 403 or 404 or 405 or 406 or 407 or 408 or 409 or 410 or 411 or 412 or 413 or 414 or 415 or 416 or 417 or 418 or 419 or 420 or 421 or 422 or 423 or 424 or 425 or 426 or 427 or 428 or 429 or 430 or 431
433. infant?.ab,ti.
434. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four" or "twenty five" or "twenty six") adj week?).ab,ti.
435. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four") adj month?).ab,ti.
436. 434 or 435
437. (old or age?).ab,ti.
438. 436 and 437
439. (("one year?" or "two year?") adj3 (old or age?)).ab,ti.
440. ((first or second or two) adj3 "year? of life").ab,ti.
441. Infant/
442. Infant, Newborn/
443. (maternal adj7 pregnan$).ab,ti.
444. (maternal adj7 lactat$).ab,ti.
445. (mother? adj7 pregnan$).ab,ti.
446. 433 or 438 or 439 or 440 or 441 or 442 or 443 or 444 or 445
447. MEDLINE.tw.
448. systematic review.tw.
449. meta-analysis.pt.
450. intervention$.ti.
451. 447 or 448 or 449 or 450
452. 16 or 73 or 341
453. 432 and 446 and 451 and 452
454. limit 453 to yr="2011 -Current"

Embase

1. breast feeding.ab,ti.
2. breastfeeding.ab,ti.
3. breast fed.ab,ti.
4. breastfed.ab,ti.
5. breast feeding/
6. breast milk/
7. formula?.ab,ti.
8. hydrolysed.ab,ti.
9. bottlefed.ab,ti.
10. bottle fed.ab,ti.
11. (bottle adj3 feed$).ab,ti.
12. artificial milk/
13. bottle feeding/
14. wean$.ti,ab.
15. weaning/
16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. complementary food?.ab,ti.
18. (introduc$ adj2 food?).ab,ti.
19. wean$.ab,ti.
20. weaning/
21. solid?.ab,ti.
22. semi-solid?.ab,ti.
23. baby food?.ab,ti.
24. baby food/
25. infant nutrition/
26. breast feeding.ab,ti.
27. breastfeeding.ab,ti.
28. breast fed.ab,ti.
29. breastfed.ab,ti.
30. breast feeding/
31. breast milk/
32. formula?.ab,ti.
33. hydrolysed.ab,ti.
34. bottlefed.ab,ti.
35. bottle fed.ab,ti.
36. (bottle adj3 feed$).ab,ti.
37. artificial milk/
38. bottle feeding/
39. liquid?.ti,ab.
40. milk.ti,ab.
41. milk/
42. egg?.ti,ab.
43. egg/
44. egg protein/
45. nut?.ab,ti.
46. peanut?.ab,ti.
47. almond?.ab,ti.
48. (brazil? adj5 nut?).ab,ti.
49. walnut?.ab,ti.

50. pecan?.ab,ti.
51. pistachio?.ab,ti.
52. cashew?.ab,ti.
53. hazelnut?.ab,ti.
54. macadamia?.ab,ti.
55. nut/
56. peanut/
57. almond/
58. Brazil nut/
59. exp walnut/
60. pecan/
61. pistachio/
62. cashew nut/
63. hazelnut/
64. Corylus avellana/
65. Macadamia/
66. wheat.ti,ab.
67. exp wheat/
68. soya.ti,ab.
69. soybean/
70. gluten$.ti,ab.
71. gluten/
72. fish$.ti,ab.
73. fish/
74. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73
75. diet/
76. diet therapy/
77. nutritional science/
78. diet.ti,ab.
79. diets.ti,ab.
80. Mediterranean diet/
81. mediterranean diet$.ab,ti.
82. dietetic.ab,ti.
83. dietary.ab,ti.
84. eat.ab,ti.
85. eating.ab,ti.
86. intake.ab,ti.
87. nutrient?.ab,ti.
88. nutrition.ab,ti.
89. vegetarian diet/
90. vegetarian?.ti,ab.
91. vegan$.ti,ab.
92. macrobiotic diet/
93. macrobiotic?.ti,ab.
94. food/
95. food$.ab,ti.
96. feed.ab,ti.

97. feeding.ab,ti.
98. cereal$.ab,ti.
99. grain$.ab,ti.
100. granary.ab,ti.
101. wholegrain.ab,ti.
102. wholewheat.ab,ti.
103. whole wheat.ab,ti.
104. wheat.ab,ti.
105. wheatgerm.ab,ti.
106. rye.ab,ti.
107. barley.ab,ti.
108. oat?.ab,ti.
109. exp cereal/
110. root?.ti,ab.
111. tuber?.ti,ab.
112. exp vegetable/
113. vegetable$.ab,ti.
114. onion$.ab,ti.
115. spinach.ab,ti.
116. chard.ab,ti.
117. tomato$.ab,ti.
118. pepper$.ab,ti.
119. carrot$.ab,ti.
120. beetroot.ab,ti.
121. asparagus.ab,ti.
122. garlic.ab,ti.
123. pumpkin.ab,ti.
124. sprouts.ab,ti.
125. broccoli.ab,ti.
126. cabbage$.ab,ti.
127. celery.ab,ti.
128. ginger.ab,ti.
129. potato$.ab,ti.
130. crisps.ab,ti.
131. fries.ab,ti.
132. syrup.ab,ti.
133. honey.ab,ti.
134. honey/
135. fruit/
136. fruit$.ab,ti.
137. apple?.ab,ti.
138. pear?.ab,ti.
139. banana?.ab,ti.
140. orange?.ab,ti.
141. grape?.ab,ti.
142. kiwi?.ab,ti.
143. citrus.ab,ti.
144. grapefruit?.ab,ti.
145. pulses.ab,ti.
146. beans.ab,ti.

147. lentil?.ab,ti.
148. chickpea?.ab,ti.
149. legume?.ab,ti.
150. lupin?.ab,ti.
151. soy.ab,ti.
152. soya.ab,ti.
153. nut?.ab,ti.
154. almond?.ab,ti.
155. peanut?.ab,ti.
156. groundnut?.ab,ti.
157. exp nut/
158. seed?.ti,ab.
159. sesame.ti,ab.
160. mustard.ti,ab.
161. plant seed/
162. meat/
163. meat.ab,ti.
164. beef.ab,ti.
165. pork.ab,ti.
166. lamb.ab,ti.
167. poultry.ab,ti.
168. chicken.ab,ti.
169. turkey.ab,ti.
170. duck.ab,ti.
171. fish.ab,ti.
172. fatty acid/
173. omega 3 fatty acid/
174. omega 6 fatty acid/
175. omega-3.ab,ti.
176. omega-6.ab,ti.
177. PUFA.ab,ti.
178. fat.ab,ti.
179. fats.ab,ti.
180. fatty.ab,ti.
181. egg.ab,ti.
182. eggs.ab,ti.
183. exp egg/
184. bread/
185. bread.ti,ab.
186. oil.ti,ab.
187. oils.ti,ab.
188. oily.ti,ab.
189. omega.ti,ab.
190. sea food/
191. seafood.ti,ab.
192. shellfish.ti,ab.
193. crustacean?.ti,ab.
194. mollusc?.ti,ab.
195. shellfish/
196. exp dairy product/

197. dairy.ti,ab.
198. milk/
199. milk.ti,ab.
200. artificial milk/
201. formula?.ti,ab.
202. hydrolysed.ti,ab.
203. baby food/
204. yoghurt.ab,ti.
205. probiotic.ab,ti.
206. prebiotic?.ab,ti.
207. butter.ab,ti.
208. herb?.ab,ti.
209. spice?.ab,ti.
210. chilli$.ab,ti.
211. condiment?.ab,ti.
212. exp condiment/
213. beverage/
214. beverage?.ti,ab.
215. fluid intake.ti,ab.
216. water.ti,ab.
217. drink$.ti,ab.
218. exp food preservation/
219. pickled.ab,ti.
220. bottled.ab,ti.
221. canned.ab,ti.
222. canning.ab,ti.
223. smoked.ab,ti.
224. preserved.ab,ti.
225. preservatives.ab,ti.
226. nitrosamine.ab,ti.
227. hydrogenation.ab,ti.
228. fortified.ab,ti.
229. nitrates.ab,ti.
230. nitrites.ab,ti.
231. ferment$.ab,ti.
232. processed.ab,ti.
233. antioxidant$.ab,ti.
234. genetic modif$.ab,ti.
235. genetically modif$.ab,ti.
236. cooking/
237. cooking.ab,ti.
238. cooked.ab,ti.
239. grill.ab,ti.
240. grilled.ab,ti.
241. fried.ab,ti.
242. fry.ab,ti.
243. roast.ab,ti.
244. bake.ab,ti.
245. baked.ab,ti.
246. stewing.ab,ti.

247. stewed.ab,ti.
248. casserol$.ab,ti.
249. broil.ab,ti.
250. broiled.ab,ti.
251. boiled.ab,ti.
252. poach.ab,ti.
253. poached.ab,ti.
254. steamed.ab,ti.
255. barbecue$.ab,ti.
256. chargrill$.ab,ti.
257. salt.ab,ti.
258. salting.ab,ti.
259. salted.ab,ti.
260. fiber.ab,ti.
261. fibre.ab,ti.
262. polysaccharide$.ab,ti.
263. starch.ab,ti.
264. starchy.ab,ti.
265. carbohydrate$.ab,ti.
266. lipid$.ab,ti.
267. linoleic acid$.ab,ti.
268. sugar$.ab,ti.
269. sweetener$.ab,ti.
270. saccharin$.ab,ti.
271. aspartame.ab,ti.
272. sucrose.ab,ti.
273. xylitol.ab,ti.
274. cholesterol.ab,ti.
275. hydrogenated lard.ab,ti.
276. dietary protein.ab,ti.
277. dietary proteins.ab,ti.
278. protein intake.ab,ti.
279. animal protein$.ab,ti.
280. total protein$.ab,ti.
281. vegetable protein$.ab,ti.
282. plant protein$.ab,ti.
283. carbohydrate diet/
284. carbohydrate intake/
285. fat intake/
286. dietary fiber/
287. protein intake/
288. diet supplementation/
289. food additive/
290. exp vitamin/
291. supplements.ab,ti.
292. supplement.ab,ti.
293. vitamin$.ab,ti.
294. retinol.ab,ti.
295. carotenoid$.ab,ti.
296. tocopherol.ab,ti.

297. folate$.ab,ti.
298. folic acid.ab,ti.
299. methionine.ab,ti.
300. riboflavin.ab,ti.
301. thiamine.ab,ti.
302. niacin.ab,ti.
303. pyridoxine.ab,ti.
304. cobalamin.ab,ti.
305. mineral$.ab,ti.
306. sodium.ab,ti.
307. iron.ab,ti.
308. calcium.ab,ti.
309. selenium.ab,ti.
310. iodine.ab,ti.
311. magnesium.ab,ti.
312. potassium.ab,ti.
313. zinc.ab,ti.
314. copper.ab,ti.
315. phosphorus.ab,ti.
316. manganese.ab,ti.
317. chromium.ab,ti.
318. phytochemical.ab,ti.
319. polyphenol$.ab,ti.
320. phytoestrogen$.ab,ti.
321. genistein.ab,ti.
322. saponin$.ab,ti.
323. coumarin$.ab,ti.
324. flavonoid$.ab,ti.
325. polyphenol$.ab,ti.
326. flavonol$.ab,ti.
327. flavone$.ab,ti.
328. isoflavone$.ab,ti.
329. catechin$.ab,ti.
330. ascorbic acid$.ab,ti.
331. hydroxy cholecalciferol$.ab,ti.
332. hydroxycholecalciferol$.ab,ti.
333. tocotrienol$.ab,ti.
334. carotene$.ab,ti.
335. cryptoxanthin$.ab,ti.
336. lycopene$.ab,ti.
337. lutein$.ab,ti.
338. zeaxanthin$.ab,ti.
339. selenium$.ab,ti.
340. organic diet?.ab,ti.
341. organic food/
342. 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or

144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169 or 170 or 171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181 or 182 or 183 or 184 or 185 or 186 or 187 or 188 or 189 or 190 or 191 or 192 or 193 or 194 or 195 or 196 or 197 or 198 or 199 or 200 or 201 or 202 or 203 or 204 or 205 or 206 or 207 or 208 or 209 or 210 or 211 or 212 or 213 or 214 or 215 or 216 or 217 or 218 or 219 or 220 or 221 or 222 or 223 or 224 or 225 or 226 or 227 or 228 or 229 or 230 or 231 or 232 or 233 or 234 or 235 or 236 or 237 or 238 or 239 or 240 or 241 or 242 or 243 or 244 or 245 or 246 or 247 or 248 or 249 or 250 or 251 or 252 or 253 or 254 or 255 or 256 or 257 or 258 or 259 or 260 or 261 or 262 or 263 or 264 or 265 or 266 or 267 or 268 or 269 or 270 or 271 or 272 or 273 or 274 or 275 or 276 or 277 or 278 or 279 or 280 or 281 or 282 or 283 or 284 or 285 or 286 or 287 or 288 or 289 or 290 or 291 or 292 or 293 or 294 or 295 or 296 or 297 or 298 or 299 or 300 or 301 or 302 or 303 or 304 or 305 or 306 or 307 or 308 or 309 or 310 or 311 or 312 or 313 or 314 or 315 or 316 or 317 or 318 or 319 or 320 or 321 or 322 or 323 or 324 or 325 or 326 or 327 or 328 or 329 or 330 or 331 or 332 or 333 or 334 or 335 or 336 or 337 or 338 or 339 or 340 or 341
343. allerg$.ab,ti.
344. asthma$.ab,ti.
345. wheeze.ab,ti.
346. wheezing.ab,ti.
347. bronchial hyperresponsiveness.ab,ti.
348. bronchial hyperreactivity.ab,ti.
349. Forced expiratory volume.ab,ti.
350. FEV1.ab,ti.
351. "FEV 1".ab,ti.
352. "FEV0.5".ab,ti.
353. "FEV 0.5".ab,ti.
354. Forced vital capacity.ab,ti.
355. FVC.ab,ti.
356. Peak expiratory flow rate.ab,ti.
357. PEFR.ab,ti.
358. eczema.ab,ti.
359. neurodermatitis.ab,ti.
360. rhinitis.ab,ti.
361. besniers prurigo.ab,ti.
362. rhinoconjunctivitis.ab,ti.
363. hayfever.ab,ti.
364. (hay adj fever).ab,ti.
365. poll?nosis.ab,ti.
366. SAR.ab,ti.
367. (pollen adj allergy).ab,ti.
368. conjunctivitis.ab,ti.
369. immunoglobulin e.ab,ti.
370. Total IgE.ab,ti.
371. autoimmune disease?.ab,ti.
372. diabetes.ab,ti.
373. diabetic.ab,ti.
374. type 1.ab,ti.
375. c?eliac disease.ab,ti.
376. crohn$ disease.ab,ti.

377. Inflammatory Bowel Disease?.ab,ti.
378. Ulcerative colitis.ab,ti.
379. (Lympho$ adj3 thyroiditi$).ab,ti.
380. (Thyroiditi$ adj3 autoimmune).ab,ti.
381. (Hashimoto$ adj3 (syndrome? or thyroiditi$ or disease?)).ab,ti.
382. (Thyroiditi$ adj3 (post-partum or postpartum)).ab,ti.
383. Graves? disease.ab,ti.
384. Basedow$ disease.ab,ti.
385. exophthalmic goiter?.ab,ti.
386. (Still? Disease adj3 (juvenile or onset)).ab,ti.
387. (Juvenile adj3 arthriti$).ab,ti.
388. vitiligo.ab,ti.
389. Psorias?s.ab,ti.
390. (Arthriti? adj3 Psoria$).ab,ti.
391. atopic disease.ab,ti.
392. atopic dermatitis.ab,ti.
393. (food? adj3 sensiti$).ab,ti.
394. (food? adj3 toleran$).ab,ti.
395. (food? adj3 intoleran$).ab,ti.
396. ((aero or air$) adj3 allergen?).ab,ti.
397. (aeroallergen? adj3 sensiti$).ab,ti.
398. (allergen? adj3 sensiti$).ab,ti.
399. skin prick test$.ab,ti.
400. atopy.ab,ti.
401. hypersensitiv$.ab,ti.
402. exp hypersensitivity/
403. respiratory tract allergy/
404. asthma/
405. wheezing/
406. bronchus hyperreactivity/
407. forced expiratory volume/
408. forced vital capacity/
409. peak expiratory flow/
410. eczema/
411. neurodermatitis/
412. rhinitis/
413. rhinoconjunctivitis/
414. hay fever/
415. pollen allergy/
416. perennial rhinitis/
417. conjunctivitis/
418. immunoglobulin E/
419. autoimmune disease/
420. diabetes mellitus/
421. insulin dependent diabetes mellitus/
422. celiac disease/
423. Crohn disease/
424. enteritis/
425. ulcerative colitis/
426. autoimmune thyroiditis/

427. Hashimoto disease/
428. postpartum thyroiditis/
429. Graves disease/
430. juvenile rheumatoid arthritis/
431. vitiligo/
432. psoriasis/
433. psoriatic arthritis/
434. atopic dermatitis/
435. nutritional intolerance/
436. 343 or 344 or 345 or 346 or 347 or 348 or 349 or 350 or 351 or 352 or 353 or 354 or 355 or 356 or 357 or 358 or 359 or 360 or 361 or 362 or 363 or 364 or 365 or 366 or 367 or 368 or 369 or 370 or 371 or 372 or 373 or 374 or 375 or 376 or 377 or 378 or 379 or 380 or 381 or 382 or 383 or 384 or 385 or 386 or 387 or 388 or 389 or 390 or 391 or 392 or 393 or 394 or 395 or 396 or 397 or 398 or 399 or 400 or 401 or 402 or 403 or 404 or 405 or 406 or 407 or 408 or 409 or 410 or 411 or 412 or 413 or 414 or 415 or 416 or 417 or 418 or 419 or 420 or 421 or 422 or 423 or 424 or 425 or 426 or 427 or 428 or 429 or 430 or 431 or 432 or 433 or 434 or 435
437. infant?.ab,ti.
438. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four" or "twenty five" or "twenty six") adj week?).ab,ti.
439. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four") adj month?).ab,ti.
440. 438 or 439
441. (old or age?).ab,ti.
442. 440 and 441
443. (("one year?" or "two year?") adj3 (old or age?)).ab,ti.
444. ((first or second or two) adj3 "year? of life").ab,ti.
445. infant/
446. newborn/
447. (maternal adj7 pregnan$).ti,ab.
448. (maternal adj7 lactat$).ti,ab.
449. (mother? adj7 pregnan$).ti,ab.
450. 437 or 442 or 443 or 444 or 445 or 446 or 447 or 448 or 449
451. MEDLINE.tw.
452. exp systematic review/
453. systematic review.tw.
454. meta analysis/
455. intervention$.ti.
456. 451 or 452 or 453 or 454 or 455
457. 16 or 74 or 342
458. 436 and 450 and 456 and 457
459. limit 458 to yr="2011 -Current"

COCHRANE Reviews and DARE

1. “breast feeding”:ab,ti
2. breastfeeding:ab,ti
3. “breast fed”:ab,ti
4. breastfed:ab,ti
5. MeSH descriptor [Breast Feeding] this term only
6. MeSH descriptor [Milk, Human] this term only
7. formula*:ab,ti
8. hydrolysed:ab,ti
9. bottlefed:ab,ti
10. “bottle fed”:ab,ti
11. (bottle NEAR/3 feed*):ab,ti
12. MeSH descriptor [Infant Formula] this term only
13. MeSH descriptor [Bottle Feeding] this term only
14. wean*:ab,ti
15. MeSH descriptor [Weaning] this term only
16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. “complementary food*”:ab,ti
18. (introduc* NEAR/2 food*):ab,ti
19. wean*:ab,ti
20. MeSH descriptor [Weaning] this term only
21. solid*:ab,ti
22. semi-solid*:ab,ti
23. “baby food*”:ab,ti
24. MeSH descriptor [Infant Food] this term only
25. MeSH descriptor [Infant Nutritional Physiological Phenomena] this term only
26. “breast feeding”:ab,ti
27. breastfeeding:ab,ti
28. “breast fed”:ab,ti
29. breastfed:ab,ti
30. MeSH descriptor [Breast Feeding] this term only
31. MeSH descriptor [Milk, Human] this term only
32. formula*:ab,ti
33. hydrolysed:ab,ti
34. bottlefed:ab,ti
35. “bottle fed”:ab,ti
36. (bottle NEAR/3 feed*):ab,ti
37. MeSH descriptor [Infant Formula] this term only
38. MeSH descriptor [Bottle Feeding] this term only
39. liquid*:ab,ti
40. milk:ab,ti
41. MeSH descriptor [Milk] this term only
42. egg*:ab,ti
43. MeSH descriptor [Egg Proteins] this term only
44. MeSH descriptor [Egg Proteins, Dietary] this term only
45. nut*:ab,ti
46. peanut*:ab,ti
47. almond*:ab,ti
48. (brazil* NEAR/5 nut*):ab,ti
49. walnut*:ab,ti

50. pecan*:ab,ti
51. pistachio*:ab,ti
52. cashew*:ab,ti
53. hazelnut*:ab,ti
54. macadamia*:ab,ti
55. Nuts] this term only
56. MeSH descriptor [Arachis hypogaea] this term only
57. MeSH descriptor [Prunus] this term only
58. MeSH descriptor [Bertholletia] this term only
59. MeSH descriptor [Juglans] this term only
60. MeSH descriptor [Carya] this term only
61. MeSH descriptor [Pistacia] this term only
62. MeSH descriptor [Anacardium] this term only
63. MeSH descriptor [Corylus] this term only
64. MeSH descriptor [Macadamia] this term only
65. wheat:ab,ti
66. MeSH descriptor [Triticum] this term only
67. soya:ab,ti
68. MeSH descriptor [Soybeans] this term only
69. gluten*:ab,ti
70. MeSH descriptor [Glutens] this term only
71. fish:ab,ti
72. MeSH descriptor [Fishes] this term only
73. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72
74. MeSH descriptor [Diet] this term only
75. MeSH descriptor [Diet Therapy] this term only
76. MeSH descriptor [Nutritional Sciences] this term only
77. MeSH descriptor [Child Nutrition Sciences] this term only
78. diet:ab,ti
79. diets:ab,ti
80. MeSH descriptor [Diet, Mediterranean] this term only
81. “mediterranean diet*”:ab,ti
82. dietetic:ab,ti
83. dietary:ab,ti
84. eat:ab,ti
85. eating:ab,ti
86. intake:ab,ti
87. nutrient*:ab,ti
88. nutrition:ab,ti
89. MeSH descriptor [Diet, Vegetarian] this term only
90. vegetarian*:ab,ti
91. vegan*:ab,ti
92. MeSH descriptor [Diet, Macrobiotic] this term only
93. macrobiotic*:ab,ti
94. MeSH descriptor [Food] this term only
95. food*:ab,ti
96. feed:ab,ti

97. feeding:ab,ti
98. cereal*:ab,ti
99. grain*:ab,ti
100. granary:ab,ti
101. wholegrain:ab,ti
102. wholewheat:ab,ti
103. “whole wheat”:ab,ti
104. wheat:ab,ti
105. wheatgerm:ab,ti
106. rye:ab,ti
107. barley:ab,ti
108. oat*:ab,ti
109. MeSH descriptor [Cereals] explode all trees
110. root*:ab,ti
111. tuber*:ab,ti
112. MeSH descriptor [Vegetables] explode all trees
113. vegetable*:ab,ti
114. onion*:ab,ti
115. spinach:ab,ti
116. chard:ab,ti
117. tomato*:ab,ti
118. pepper*:ab,ti
119. carrot*:ab,ti
120. beetroot:ab,ti
121. asparagus:ab,ti
122. garlic:ab,ti
123. pumpkin:ab,ti
124. sprouts:ab,ti
125. broccoli:ab,ti
126. cabbage*:ab,ti
127. celery:ab,ti
128. ginger:ab,ti
129. potato*:ab,ti
130. crisps:ab,ti
131. fries:ab,ti
132. syrup:ab,ti
133. honey:ab,ti
134. MeSH descriptor [Honey] this term only
135. MeSH descriptor [Fruit] this term only
136. fruit*:ab,ti
137. apple*:ab,ti
138. pear*:ab,ti
139. banana*:ab,ti
140. orange*:ab,ti
141. grape*:ab,ti
142. kiwi*:ab,ti
143. citrus:ab,ti
144. grapefruit*:ab,ti
145. pulses:ab,ti
146. beans:ab,ti

147. lentil*:ab,ti
148. chickpea*:ab,ti
149. legume*:ab,ti
150. lupin*:ab,ti
151. soy:ab,ti
152. soya:ab,ti
153. nut*:ab,ti
154. almond*:ab,ti
155. peanut*:ab,ti
156. groundnut*:ab,ti
157. MeSH descriptor [Nuts] this term only
158. seed*:ab,ti
159. sesame:ab,ti
160. mustard:ab,ti
161. MeSH descriptor [Seeds] this term only
162. MeSH descriptor [Meat] explode all trees
163. meat:ab,ti
164. beef:ab,ti
165. pork:ab,ti
166. lamb:ab,ti
167. poultry:ab,ti
168. chicken:ab,ti
169. turkey:ab,ti
170. duck:ab,ti
171. fish:ab,ti
172. MeSH descriptor [Fatty Acids] this term only
173. MeSH descriptor [Fatty Acids, Omega-3] explode all trees
174. MeSH descriptor [Fatty Acids, Omega-6] explode all trees
175. omega-3:ab,ti
176. omega-6:ab,ti
177. PUFA:ab,ti
178. fat:ab,ti
179. fats:ab,ti
180. fatty:ab,ti
181. egg:ab,ti
182. eggs:ab,ti
183. MeSH descriptor [Eggs] explode all trees
184. MeSH descriptor [Bread] this term only
185. bread:ab,ti
186. oil:ab,ti
187. oils:ab,ti
188. oily:ab,ti
189. omega:ab,ti
190. MeSH descriptor [Seafood] explode all trees
191. seafood:ab,ti
192. shellfish:ab,ti
193. crustacean*:ab,ti
194. mollusc*:ab,ti
195. MeSH descriptor [Shellfish] this term only
196. MeSH descriptor [Dairy Products] this term only

197. dairy:ab,ti
198. MeSH descriptor [Milk] explode all trees
199. milk:ab,ti
200. MeSH descriptor [Infant Formula] this term only
201. formula*:ab,ti
202. hydrolysed:ab,ti
203. MeSH descriptor [Infant Food] this term only
204. yoghurt:ab,ti
205. probiotic:ab,ti
206. prebiotic*:ab,ti
207. butter:ab,ti
208. herb*:ab,ti
209. spice*:ab,ti
210. chilli*:ab,ti
211. condiment*:ab,ti
212. MeSH descriptor [Condiments] explode all trees
213. MeSH descriptor [Beverages] this term only
214. beverage*:ab,ti
215. “fluid intake”:ab,ti
216. water:ab,ti
217. drink*:ab,ti
218. MeSH descriptor [Food Preservation] explode all trees
219. pickled:ab,ti
220. bottled:ab,ti
221. canned:ab,ti
222. canning:ab,ti
223. smoked:ab,ti
224. preserved:ab,ti
225. preservatives:ab,ti
226. nitrosamine:ab,ti
227. hydrogenation:ab,ti
228. fortified:ab,ti
229. nitrates:ab,ti
230. nitrites:ab,ti
231. ferment*:ab,ti
232. processed:ab,ti
233. antioxidant*:ab,ti
234. “genetic modif*”:ab,ti
235. “genetically modif*”:ab,ti
236. MeSH descriptor [Cooking] this term only
237. cooking:ab,ti
238. cooked:ab,ti
239. grill:ab,ti
240. grilled:ab,ti
241. fried:ab,ti
242. fry:ab,ti
243. roast:ab,ti
244. bake:ab,ti
245. baked:ab,ti
246. stewing:ab,ti

247. stewed:ab,ti
248. casserol*:ab,ti
249. broil:ab,ti
250. broiled:ab,ti
251. boiled:ab,ti
252. poach:ab,ti
253. poached:ab,ti
254. steamed:ab,ti
255. barbecue*:ab,ti
256. chargrill*:ab,ti
257. salt:ab,ti
258. salting:ab,ti
259. salted:ab,ti
260. fiber:ab,ti
261. fibre:ab,ti
262. polysaccharide*:ab,ti
263. starch:ab,ti
264. starchy:ab,ti
265. carbohydrate*:ab,ti
266. lipid*:ab,ti
267. “linoleic acid*”:ab,ti
268. sugar*:ab,ti
269. sweetener*:ab,ti
270. saccharin*:ab,ti
271. aspartame:ab,ti
272. sucrose:ab,ti
273. xylitol:ab,ti
274. cholesterol:ab,ti
275. “hydrogenated lard”:ab,ti
276. “dietary protein”:ab,ti
277. “dietary proteins”:ab,ti
278. “protein intake”:ab,ti
279. “animal protein*”:ab,ti
280. “total protein*”:ab,ti
281. “vegetable protein*”:ab,ti
282. “plant protein*”:ab,ti
283. MeSH descriptor [Dietary Carbohydrates] explode all trees
284. MeSH descriptor [Dietary Fats] explode all trees
285. MeSH descriptor [Dietary Fiber] explode all trees
286. MeSH descriptor [Dietary Proteins] explode all trees
287. MeSH descriptor [Dietary Supplements] explode all trees
288. MeSH descriptor [Food Additives] explode all trees
289. MeSH descriptor [Vitamins] explode all trees
290. supplements:ab,ti
291. supplement:ab,ti
292. vitamin*:ab,ti
293. retinol:ab,ti
294. carotenoid*:ab,ti
295. tocopherol:ab,ti
296. folate*:ab,ti

297. “folic acid”:ab,ti
298. methionine:ab,ti
299. riboflavin:ab,ti
300. thiamine:ab,ti
301. niacin:ab,ti
302. pyridoxine:ab,ti
303. cobalamin:ab,ti
304. mineral*:ab,ti
305. sodium:ab,ti
306. iron:ab,ti
307. calcium:ab,ti
308. selenium:ab,ti
309. iodine:ab,ti
310. magnesium:ab,ti
311. potassium:ab,ti
312. zinc:ab,ti
313. copper:ab,ti
314. phosphorus:ab,ti
315. manganese:ab,ti
316. chromium:ab,ti
317. phytochemical:ab,ti
318. polyphenol*:ab,ti
319. phytoestrogen*:ab,ti
320. genistein:ab,ti
321. saponin*:ab,ti
322. coumarin*:ab,ti
323. flavonoid*:ab,ti
324. polyphenol*:ab,ti
325. flavonol*:ab,ti
326. flavone*:ab,ti
327. isoflavone*:ab,ti
328. catechin*:ab,ti
329. “ascorbic acid*”:ab,ti
330. “hydroxy cholecalciferol*”:ab,ti
331. hydroxycholecalciferol*:ab,ti
332. tocotrienol*:ab,ti
333. carotene*:ab,ti
334. cryptoxanthin*:ab,ti
335. lycopene*:ab,ti
336. lutein*:ab,ti
337. zeaxanthin*:ab,ti
338. selenium*:ab,ti
339. “organic diet*”:ab,ti
340. MeSH descriptor [Food, Organic] this term only
341. 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or

156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169 or 170 or 171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181 or 182 or 183 or 184 or 185 or 186 or 187 or 188 or 189 or 190 or 191 or 192 or 193 or 194 or 195 or 196 or 197 or 198 or 199 or 200 or 201 or 202 or 203 or 204 or 205 or 206 or 207 or 208 or 209 or 210 or 211 or 212 or 213 or 214 or 215 or 216 or 217 or 218 or 219 or 220 or 221 or 222 or 223 or 224 or 225 or 226 or 227 or 228 or 229 or 230 or 231 or 232 or 233 or 234 or 235 or 236 or 237 or 238 or 239 or 240 or 241 or 242 or 243 or 244 or 245 or 246 or 247 or 248 or 249 or 250 or 251 or 252 or 253 or 254 or 255 or 256 or 257 or 258 or 259 or 260 or 261 or 262 or 263 or 264 or 265 or 266 or 267 or 268 or 269 or 270 or 271 or 272 or 273 or 274 or 275 or 276 or 277 or 278 or 279 or 280 or 281 or 282 or 283 or 284 or 285 or 286 or 287 or 288 or 289 or 290 or 291 or 292 or 293 or 294 or 295 or 296 or 297 or 298 or 299 or 300 or 301 or 302 or 303 or 304 or 305 or 306 or 307 or 308 or 309 or 310 or 311 or 312 or 313 or 314 or 315 or 316 or 317 or 318 or 319 or 320 or 321 or 322 or 323 or 324 or 325 or 326 or 327 or 328 or 329 or 330 or 331 or 332 or 333 or 334 or 335 or 336 or 337 or 338 or 339 or 340
342. allerg*:ab,ti
343. asthma*:ab,ti
344. wheeze:ab,ti
345. wheezing:ab,ti
346. “bronchial hyperresponsiveness”:ab,ti
347. “bronchial hyperreactivity”:ab,ti
348. “Forced expiratory volume”:ab,ti
349. “FEV1”:ab,ti
350. "FEV 1":ab,ti
351. "FEV0.5":ab,ti
352. "FEV 0.5":ab,ti
353. “Forced vital capacity”:ab,ti
354. FVC:ab,ti
355. “Peak expiratory flow rate”:ab,ti
356. PEFR:ab,ti
357. eczema:ab,ti
358. neurodermatitis:ab,ti
359. rhinitis:ab,ti
360. “besniers prurigo”:ab,ti
361. rhinoconjunctivitis:ab,ti
362. hayfever:ab,ti
363. “hay fever”:ab,ti
364. poll*nosis:ab,ti
365. SAR:ab,ti
366. “pollen allergy”:ab,ti
367. conjunctivitis:ab,ti
368. immunoglobulin e:ab,ti
369. Total IgE:ab,ti
370. “autoimmune disease*”:ab,ti
371. diabetes:ab,ti
372. diabetic:ab,ti
373. “type 1”:ab,ti
374. “c*eliac disease”:ab,ti
375. “crohn* disease”:ab,ti
376. “Inflammatory Bowel Disease*”:ab,ti

377. “Ulcerative colitis”:ab,ti
378. (Lympho* NEAR/3 thyroiditi*):ab,ti
379. (Thyroiditi* NEAR/3 autoimmune):ab,ti
380. (Hashimoto* NEAR/3 (syndrome* or thyroiditi* or disease*)):ab,ti
381. (Thyroiditi* NEAR/3 (post-partum or postpartum)):ab,ti
382. “Graves* disease”:ab,ti
383. “Basedow* disease”:ab,ti
384. “exophthalmic goiter*”:ab,ti
385. (“Still* Disease” NEAR/3 (juvenile or onset)):ab,ti
386. (Juvenile NEAR/3 arthriti*):ab,ti
387. vitiligo:ab,ti
388. Psorias*s:ab,ti
389. (Arthriti* NEAR/3 Psoria*):ab,ti
390. “atopic disease”:ab,ti
391. “atopic dermatitis”:ab,ti
392. (food* NEAR/3 sensiti*):ab,ti
393. (food* NEAR/3 toleran*):ab,ti
394. (food* NEAR/3 intoleran*):ab,ti
395. ((aero or air*) NEAR/3 allergen*):ab,ti
396. (aeroallergen* NEAR/3 sensiti*):ab,ti
397. (allergen* NEAR/3 sensiti*):ab,ti
398. “skin prick test*”:ab,ti
399. atopy:ab,ti
400. hypersensitiv*:ab,ti
401. MeSH descriptor [Hypersensitivity] this term only
402. MeSH descriptor [Food Hypersensitivity] explode all trees
403. MeSH descriptor [Respiratory Hypersensitivity] this term only
404. MeSH descriptor [Asthma] this term only
405. MeSH descriptor [Bronchial Hyperreactivity] this term only
406. MeSH descriptor [Forced Expiratory Volume] this term only
407. MeSH descriptor [Vital Capacity] this term only
408. MeSH descriptor [Peak Expiratory Flow Rate] this term only
409. MeSH descriptor [Eczema] this term only
410. MeSH descriptor [Neurodermatitis] this term only
411. MeSH descriptor [Rhinitis] this term only
412. MeSH descriptor [Rhinitis, Allergic, Perennial] this term only
413. MeSH descriptor [Rhinitis, Allergic, Seasonal] this term only
414. MeSH descriptor [Conjunctivitis] this term only
415. MeSH descriptor [Immunoglobulin E] this term only
416. MeSH descriptor [Autoimmune Diseases] this term only
417. MeSH descriptor [Diabetes Mellitus, Type 1] this term only
418. MeSH descriptor [Celiac Disease] this term only
419. MeSH descriptor [Crohn Disease] this term only
420. MeSH descriptor [Inflammatory Bowel Diseases] this term only
421. MeSH descriptor [Colitis, Ulcerative] this term only
422. MeSH descriptor [Thyroiditis, Autoimmune] this term only
423. MeSH descriptor [Hashimoto Disease] this term only
424. MeSH descriptor [Postpartum Thyroiditis] this term only
425. MeSH descriptor [Graves Disease] this term only
426. MeSH descriptor [Arthritis, Juvenile Rheumatoid] this term only

427. MeSH descriptor [Vitiligo] this term only
428. MeSH descriptor [Psoriasis] this term only
429. MeSH descriptor [Arthritis, Psoriatic] this term only
430. MeSH descriptor [Dermatitis, Atopic] this term only
431. MeSH descriptor [Hypersensitivity, Immediate] this term only
432. 342 or 343 or 344 or 345 or 346 or 347 or 348 or 349 or 350 or 351 or 352 or 353 or 354 or 355 or 356 or 357 or 358 or 359 or 360 or 361 or 362 or 363 or 364 or 365 or 366 or 367 or 368 or 369 or 370 or 371 or 372 or 373 or 374 or 375 or 376 or 377 or 378 or 379 or 380 or 381 or 382 or 383 or 384 or 385 or 386 or 387 or 388 or 389 or 390 or 391 or 392 or 393 or 394 or 395 or 396 or 397 or 398 or 399 or 400 or 401 or 402 or 403 or 404 or 405 or 406 or 407 or 408 or 409 or 410 or 411 or 412 or 413 or 414 or 415 or 416 or 417 or 418 or 419 or 420 or 421 or 422 or 423 or 424 or 425 or 426 or 427 or 428 or 429 or 430 or 431
433. infant*:ab,ti
434. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four" or "twenty five" or "twenty six") NEAR/1 week*):ab,ti
435. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four") NEAR/1 month*):ab,ti
436. 434 or 435
437. (old or age*):ab,ti
438. 436 and 437
439. (("one year*" or "two year*") NEAR/3 (old or age*)):ab,ti
440. ((first or second or two) NEAR/3 "year* of life"):ab,ti
441. MeSH descriptor [Infant] this term only
442. MeSH descriptor [Infant, Newborn] this term only
443. (maternal NEAR/7 pregnan*):ab,ti
444. (maternal NEAR/7 lactat*):ab,ti
445. (mother* NEAR/7 pregnan*):ab,ti
446. 433 or 438 or 439 or 440 or 441 or 442 or 443 or 444 or 445
447. 16 or 73 or 341
448. 432 and 446 and 447
Publication date from 2011

Appendix 3 Search Strategies for original articles (Review C)

Medline

1. Diet/
2. Diet Therapy/
3. Nutritional Sciences/
4. Child Nutrition Sciences/
5. diet.ab,ti.
6. diets.ab,ti.
7. Diet, Mediterranean/
8. mediterranean diet$.ab,ti.
9. dietetic.ab,ti.
10. dietary.ab,ti.
11. eat.ab,ti.
12. eating.ab,ti.
13. intake.ab,ti.
14. nutrient?.ab,ti.
15. nutrition.ab,ti.
16. Diet, Vegetarian/
17. vegetarian?.ab,ti.
18. vegan$.ab,ti.
19. Diet, Macrobiotic/
20. macrobiotic?.ab,ti.
21. Food/
22. food$.ab,ti.
23. feed.ab,ti.
24. feeding.ab,ti.
25. cereal$.ab,ti.
26. grain$.ab,ti.
27. granary.ab,ti.
28. wholegrain.ab,ti.
29. wholewheat.ab,ti.
30. whole wheat.ab,ti.
31. wheat.ab,ti.
32. wheatgerm.ab,ti.
33. rye.ab,ti.
34. barley.ab,ti.
35. oat?.ab,ti.
36. exp Cereals/
37. root?.ab,ti.
38. tuber?.ab,ti.
39. exp Vegetables/
40. vegetable$.ab,ti.
41. onion$.ab,ti.
42. spinach.ab,ti.
43. chard.ab,ti.
44. tomato$.ab,ti.
45. pepper$.ab,ti.

46. carrot$.ab,ti.
47. beetroot.ab,ti.
48. asparagus.ab,ti.
49. garlic.ab,ti.
50. pumpkin.ab,ti.
51. sprouts.ab,ti.
52. broccoli.ab,ti.
53. cabbage$.ab,ti.
54. celery.ab,ti.
55. ginger.ab,ti.
56. potato$.ab,ti.
57. crisps.ab,ti.
58. fries.ab,ti.
59. syrup.ab,ti.
60. honey.ab,ti.
61. Honey/
62. Fruit/
63. fruit$.ab,ti.
64. apple?.ab,ti.
65. pear?.ab,ti.
66. banana?.ab,ti.
67. orange?.ab,ti.
68. grape?.ab,ti.
69. kiwi?.ab,ti.
70. citrus.ab,ti.
71. grapefruit?.ab,ti.
72. pulses.ab,ti.
73. beans.ab,ti.
74. lentil?.ab,ti.
75. chickpea?.ab,ti.
76. legume?.ab,ti.
77. lupin?.ab,ti.
78. soy.ab,ti.
79. soya.ab,ti.
80. nut?.ab,ti.
81. almond?.ab,ti.
82. peanut?.ab,ti.
83. groundnut?.ab,ti.
84. Nuts/
85. seed?.ab,ti.
86. sesame.ab,ti.
87. mustard.ab,ti.
88. Seeds/
89. exp Meat/
90. meat.ab,ti.
91. beef.ab,ti.
92. pork.ab,ti.
93. lamb.ab,ti.
94. poultry.ab,ti.
95. chicken.ab,ti.

96. turkey.ab,ti.
97. duck.ab,ti.
98. fish.ab,ti.
99. Fatty Acids/
100. exp Fatty Acids, Omega-3/
101. exp Fatty Acids, Omega-6/
102. omega-3.ab,ti.
103. omega-6.ab,ti.
104. PUFA.ab,ti.
105. fat.ab,ti.
106. fats.ab,ti.
107. fatty.ab,ti.
108. egg.ab,ti.
109. eggs.ab,ti.
110. exp Eggs/
111. Bread/
112. bread.ab,ti.
113. oil.ab,ti.
114. oils.ab,ti.
115. oily.ab,ti.
116. omega.ab,ti.
117. exp Seafood/
118. seafood.ab,ti.
119. shellfish.ab,ti.
120. crustacean?.ab,ti.
121. mollusc?.ab,ti.
122. Shellfish/
123. Dairy Products/
124. dairy.ab,ti.
125. exp Milk/
126. milk.ab,ti.
127. Infant Formula/
128. formula?.ab,ti.
129. hydrolysed.ab,ti.
130. Infant Food/
131. yoghurt.ab,ti.
132. probiotic.ab,ti.
133. prebiotic?.ab,ti.
134. butter.ab,ti.
135. herb?.ab,ti.
136. spice?.ab,ti.
137. chilli$.ab,ti.
138. condiment?.ab,ti.
139. exp Condiments/
140. Beverages/
141. beverage?.ab,ti.
142. fluid intake.ab,ti.
143. water.ab,ti.
144. drink$.ab,ti.
145. exp Food Preservation/

146. pickled.ab,ti.
147. bottled.ab,ti.
148. canned.ab,ti.
149. canning.ab,ti.
150. smoked.ab,ti.
151. preserved.ab,ti.
152. preservatives.ab,ti.
153. nitrosamine.ab,ti.
154. hydrogenation.ab,ti.
155. fortified.ab,ti.
156. nitrates.ab,ti.
157. nitrites.ab,ti.
158. ferment$.ab,ti.
159. processed.ab,ti.
160. antioxidant$.ab,ti.
161. genetic modif$.ab,ti.
162. genetically modif$.ab,ti.
163. Cooking/
164. cooking.ab,ti.
165. cooked.ab,ti.
166. grill.ab,ti.
167. grilled.ab,ti.
168. fried.ab,ti.
169. fry.ab,ti.
170. roast.ab,ti.
171. bake.ab,ti.
172. baked.ab,ti.
173. stewing.ab,ti.
174. stewed.ab,ti.
175. casserol$.ab,ti.
176. broil.ab,ti.
177. broiled.ab,ti.
178. boiled.ab,ti.
179. poach.ab,ti.
180. poached.ab,ti.
181. steamed.ab,ti.
182. barbecue$.ab,ti.
183. chargrill$.ab,ti.
184. salt.ab,ti.
185. salting.ab,ti.
186. salted.ab,ti.
187. fiber.ab,ti.
188. fibre.ab,ti.
189. polysaccharide$.ab,ti.
190. starch.ab,ti.
191. starchy.ab,ti.
192. carbohydrate$.ab,ti.
193. lipid$.ab,ti.
194. linoleic acid$.ab,ti.
195. sugar$.ab,ti.

196. sweetener$.ab,ti.
197. saccharin$.ab,ti.
198. aspartame.ab,ti.
199. sucrose.ab,ti.
200. xylitol.ab,ti.
201. cholesterol.ab,ti.
202. hydrogenated lard.ab,ti.
203. dietary protein.ab,ti.
204. dietary proteins.ab,ti.
205. protein intake.ab,ti.
206. animal protein$.ab,ti.
207. total protein$.ab,ti.
208. vegetable protein$.ab,ti.
209. plant protein$.ab,ti.
210. exp Dietary Carbohydrates/
211. exp Dietary Fats/
212. exp Dietary Fiber/
213. exp Dietary Proteins/
214. exp Dietary Supplements/
215. exp Food Additives/
216. exp Vitamins/
217. supplements.ab,ti.
218. supplement.ab,ti.
219. vitamin$.ab,ti.
220. retinol.ab,ti.
221. carotenoid$.ab,ti.
222. tocopherol.ab,ti.
223. folate$.ab,ti.
224. folic acid.ab,ti.
225. methionine.ab,ti.
226. riboflavin.ab,ti.
227. thiamine.ab,ti.
228. niacin.ab,ti.
229. pyridoxine.ab,ti.
230. cobalamin.ab,ti.
231. mineral$.ab,ti.
232. sodium.ab,ti.
233. iron.ab,ti.
234. calcium.ab,ti.
235. selenium.ab,ti.
236. iodine.ab,ti.
237. magnesium.ab,ti.
238. potassium.ab,ti.
239. zinc.ab,ti.
240. copper.ab,ti.
241. phosphorus.ab,ti.
242. manganese.ab,ti.
243. chromium.ab,ti.
244. phytochemical.ab,ti.
245. polyphenol$.ab,ti.

246. phytoestrogen$.ab,ti.
247. genistein.ab,ti.
248. saponin$.ab,ti.
249. coumarin$.ab,ti.
250. flavonoid$.ab,ti.
251. polyphenol$.ab,ti.
252. flavonol$.ab,ti.
253. flavone$.ab,ti.
254. isoflavone$.ab,ti.
255. catechin$.ab,ti.
256. ascorbic acid$.ab,ti.
257. hydroxy cholecalciferol$.ab,ti.
258. hydroxycholecalciferol$.ab,ti.
259. tocotrienol$.ab,ti.
260. carotene$.ab,ti.
261. cryptoxanthin$.ab,ti.
262. lycopene$.ab,ti.
263. lutein$.ab,ti.
264. zeaxanthin$.ab,ti.
265. selenium$.ab,ti.
266. organic diet?.ab,ti.
267. Food, Organic/
268. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169 or 170 or 171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181 or 182 or 183 or 184 or 185 or 186 or 187 or 188 or 189 or 190 or 191 or 192 or 193 or 194 or 195 or 196 or 197 or 198 or 199 or 200 or 201 or 202 or 203 or 204 or 205 or 206 or 207 or 208 or 209 or 210 or 211 or 212 or 213 or 214 or 215 or 216 or 217 or 218 or 219 or 220 or 221 or 222 or 223 or 224 or 225 or 226 or 227 or 228 or 229 or 230 or 231 or 232 or 233 or 234 or 235 or 236 or 237 or 238 or 239 or 240 or 241 or 242 or 243 or 244 or 245 or 246 or 247 or 248 or 249 or 250 or 251 or 252 or 253 or 254 or 255 or 256 or 257 or 258 or 259 or 260 or 261 or 262 or 263 or 264 or 265 or 266 or 267
269. allerg$.ab,ti.
270. asthma$.ab,ti.
271. wheeze.ab,ti.
272. wheezing.ab,ti.
273. bronchial hyperresponsiveness.ab,ti.
274. bronchial hyperreactivity.ab,ti.
275. Forced expiratory volume.ab,ti.
276. FEV1.ab,ti.
277. "FEV 1".ab,ti.

278. "FEV0.5".ab,ti.
279. "FEV 0.5".ab,ti.
280. Forced vital capacity.ab,ti.
281. FVC.ab,ti.
282. Peak expiratory flow rate.ab,ti.
283. PEFR.ab,ti.
284. eczema.ab,ti.
285. neurodermatitis.ab,ti.
286. rhinitis.ab,ti.
287. besniers prurigo.ab,ti.
288. rhinoconjunctivitis.ab,ti.
289. hayfever.ab,ti.
290. (hay adj fever).ab,ti.
291. poll?nosis.ab,ti.
292. SAR.ab,ti.
293. (pollen adj allergy).ab,ti.
294. conjunctivitis.ab,ti.
295. immunoglobulin e.ab,ti.
296. Total IgE.ab,ti.
297. autoimmune disease?.ab,ti.
298. diabetes.ab,ti.
299. diabetic.ab,ti.
300. type 1.ab,ti.
301. c?eliac disease.ab,ti.
302. crohn$ disease.ab,ti.
303. Inflammatory Bowel Disease?.ab,ti.
304. Ulcerative colitis.ab,ti.
305. (Lympho$ adj3 thyroiditi$).ab,ti.
306. (Thyroiditi$ adj3 autoimmune).ab,ti.
307. (Hashimoto$ adj3 (syndrome? or thyroiditi$ or disease?)).ab,ti.
308. (Thyroiditi$ adj3 (post-partum or postpartum)).ab,ti.
309. Graves? disease.ab,ti.
310. Basedow$ disease.ab,ti.
311. exophthalmic goiter?.ab,ti.
312. (Still? Disease adj3 (juvenile or onset)).ab,ti.
313. (Juvenile adj3 arthriti$).ab,ti.
314. vitiligo.ab,ti.
315. Psorias?s.ab,ti.
316. (Arthriti? adj3 Psoria$).ab,ti.
317. atopic disease.ab,ti.
318. atopic dermatitis.ab,ti.
319. (food? adj3 sensiti$).ab,ti.
320. (food? adj3 toleran$).ab,ti.
321. (food? adj3 intoleran$).ab,ti.
322. ((aero or air$) adj3 allergen?).ab,ti.
323. (aeroallergen? adj3 sensiti$).ab,ti.
324. (allergen? adj3 sensiti$).ab,ti.
325. skin prick test$.ab,ti.
326. atopy.ab,ti.
327. hypersensitiv$.ab,ti.

328. Hypersensitivity/
329. exp Food Hypersensitivity/
330. Respiratory Hypersensitivity/
331. Asthma/
332. Bronchial Hyperreactivity/
333. Forced Expiratory Volume/
334. Vital Capacity/
335. Peak Expiratory Flow Rate/
336. Eczema/
337. Neurodermatitis/
338. Rhinitis/
339. Rhinitis, Allergic, Perennial/
340. Rhinitis, Allergic, Seasonal/
341. Conjunctivitis/
342. Immunoglobulin E/
343. Autoimmune Diseases/
344. Diabetes Mellitus, Type 1/
345. Celiac Disease/
346. Crohn Disease/
347. Inflammatory Bowel Diseases/
348. Colitis, Ulcerative/
349. Thyroiditis, Autoimmune/
350. Hashimoto Disease/
351. Postpartum Thyroiditis/
352. Graves Disease/
353. Arthritis, Juvenile Rheumatoid/
354. Vitiligo/
355. Psoriasis/
356. Arthritis, Psoriatic/
357. Dermatitis, Atopic/
358. Hypersensitivity, Immediate/
359. 269 or 270 or 271 or 272 or 273 or 274 or 275 or 276 or 277 or 278 or 279 or 280 or 281 or 282 or 283 or 284 or 285 or 286 or 287 or 288 or 289 or 290 or 291 or 292 or 293 or 294 or 295 or 296 or 297 or 298 or 299 or 300 or 301 or 302 or 303 or 304 or 305 or 306 or 307 or 308 or 309 or 310 or 311 or 312 or 313 or 314 or 315 or 316 or 317 or 318 or 319 or 320 or 321 or 322 or 323 or 324 or 325 or 326 or 327 or 328 or 329 or 330 or 331 or 332 or 333 or 334 or 335 or 336 or 337 or 338 or 339 or 340 or 341 or 342 or 343 or 344 or 345 or 346 or 347 or 348 or 349 or 350 or 351 or 352 or 353 or 354 or 355 or 356 or 357 or 358
360. infant?.ab,ti.
361. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four" or "twenty five" or "twenty six") adj week?).ab,ti.
362. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four") adj month?).ab,ti.
363. 361 or 362
364. (old or age?).ab,ti.
365. 363 and 364
366. (("one year?" or "two year?") adj3 (old or age?)).ab,ti.

367. ((first or second or two) adj3 "year? of life").ab,ti.
368. Infant/
369. Infant, Newborn/
370. (maternal adj7 pregnan$).ab,ti.
371. (maternal adj7 lactat$).ab,ti.
372. (mother? adj7 pregnan$).ab,ti.
373. 360 or 365 or 366 or 367 or 368 or 369 or 370 or 371 or 372
374. clinical trial?.mp.
375. random$.mp.
376. factorial$.mp.
377. crossover$.mp.
378. placebo$.mp.
379. (doubl$ adj blind$).mp.
380. (singl$ adj blind$).mp.
381. assign$.mp.
382. volunteer$.mp.
383. cohort stud$.mp.
384. longitudinal$.mp.
385. follow-up.mp.
386. prospectiv$.mp.
387. retrospectiv$.mp.
388. case control.mp.
389. case referent.mp.
390. exp clinical trial/
391. Cross-Over Studies/
392. Placebos/
393. Double-Blind Method/
394. Single-Blind Method/
395. exp Cohort Studies/
396. case-control studies/
397. 374 or 375 or 376 or 377 or 378 or 379 or 380 or 381 or 382 or 383 or 384 or 385 or 386 or 387 or 388 or 389 or 390 or 391 or 392 or 393 or 394 or 395 or 396
398. 268 and 359 and 373 and 397

Embase

1. diet/
2. diet therapy/
3. nutritional science/
4. diet.ti,ab.
5. diets.ti,ab.
6. Mediterranean diet/
7. mediterranean diet$.ab,ti.
8. dietetic.ab,ti.
9. dietary.ab,ti.
10. eat.ab,ti.
11. eating.ab,ti.
12. intake.ab,ti.
13. nutrient?.ab,ti.
14. nutrition.ab,ti.
15. vegetarian diet/
16. vegetarian?.ti,ab.
17. vegan$.ti,ab.
18. macrobiotic diet/
19. macrobiotic?.ti,ab.
20. food/
21. food$.ab,ti.
22. feed.ab,ti.
23. feeding.ab,ti.
24. cereal$.ab,ti.
25. grain$.ab,ti.
26. granary.ab,ti.
27. wholegrain.ab,ti.
28. wholewheat.ab,ti.
29. whole wheat.ab,ti.
30. wheat.ab,ti.
31. wheatgerm.ab,ti.
32. rye.ab,ti.
33. barley.ab,ti.
34. oat?.ab,ti.
35. exp cereal/
36. root?.ti,ab.
37. tuber?.ti,ab.
38. exp vegetable/
39. vegetable$.ab,ti.
40. onion$.ab,ti.
41. spinach.ab,ti.
42. chard.ab,ti.
43. tomato$.ab,ti.
44. pepper$.ab,ti.
45. carrot$.ab,ti.
46. beetroot.ab,ti.
47. asparagus.ab,ti.
48. garlic.ab,ti.

49. pumpkin.ab,ti.
50. sprouts.ab,ti.
51. broccoli.ab,ti.
52. cabbage$.ab,ti.
53. celery.ab,ti.
54. ginger.ab,ti.
55. potato$.ab,ti.
56. crisps.ab,ti.
57. fries.ab,ti.
58. syrup.ab,ti.
59. honey.ab,ti.
60. honey/
61. fruit/
62. fruit$.ab,ti.
63. apple?.ab,ti.
64. pear?.ab,ti.
65. banana?.ab,ti.
66. orange?.ab,ti.
67. grape?.ab,ti.
68. kiwi?.ab,ti.
69. citrus.ab,ti.
70. grapefruit?.ab,ti.
71. pulses.ab,ti.
72. beans.ab,ti.
73. lentil?.ab,ti.
74. chickpea?.ab,ti.
75. legume?.ab,ti.
76. lupin?.ab,ti.
77. soy.ab,ti.
78. soya.ab,ti.
79. nut?.ab,ti.
80. almond?.ab,ti.
81. peanut?.ab,ti.
82. groundnut?.ab,ti.
83. exp nut/
84. seed?.ti,ab.
85. sesame.ti,ab.
86. mustard.ti,ab.
87. plant seed/
88. meat/
89. meat.ab,ti.
90. beef.ab,ti.
91. pork.ab,ti.
92. lamb.ab,ti.
93. poultry.ab,ti.
94. chicken.ab,ti.
95. turkey.ab,ti.
96. duck.ab,ti.
97. fish.ab,ti.
98. fatty acid/

99. omega 3 fatty acid/
100. omega 6 fatty acid/
101. omega-3.ab,ti.
102. omega-6.ab,ti.
103. PUFA.ab,ti.
104. fat.ab,ti.
105. fats.ab,ti.
106. fatty.ab,ti.
107. egg.ab,ti.
108. eggs.ab,ti.
109. exp egg/
110. bread/
111. bread.ti,ab.
112. oil.ti,ab.
113. oils.ti,ab.
114. oily.ti,ab.
115. omega.ti,ab.
116. sea food/
117. seafood.ti,ab.
118. shellfish.ti,ab.
119. crustacean?.ti,ab.
120. mollusc?.ti,ab.
121. shellfish/
122. exp dairy product/
123. dairy.ti,ab.
124. milk/
125. milk.ti,ab.
126. artificial milk/
127. formula?.ti,ab.
128. hydrolysed.ti,ab.
129. baby food/
130. yoghurt.ab,ti.
131. probiotic.ab,ti.
132. prebiotic?.ab,ti.
133. butter.ab,ti.
134. herb?.ab,ti.
135. spice?.ab,ti.
136. chilli$.ab,ti.
137. condiment?.ab,ti.
138. exp condiment/
139. beverage/
140. beverage?.ti,ab.
141. fluid intake.ti,ab.
142. water.ti,ab.
143. drink$.ti,ab.
144. exp food preservation/
145. pickled.ab,ti.
146. bottled.ab,ti.
147. canned.ab,ti.
148. canning.ab,ti.

149. smoked.ab,ti.
150. preserved.ab,ti.
151. preservatives.ab,ti.
152. nitrosamine.ab,ti.
153. hydrogenation.ab,ti.
154. fortified.ab,ti.
155. nitrates.ab,ti.
156. nitrites.ab,ti.
157. ferment$.ab,ti.
158. processed.ab,ti.
159. antioxidant$.ab,ti.
160. genetic modif$.ab,ti.
161. genetically modif$.ab,ti.
162. cooking/
163. cooking.ab,ti.
164. cooked.ab,ti.
165. grill.ab,ti.
166. grilled.ab,ti.
167. fried.ab,ti.
168. fry.ab,ti.
169. roast.ab,ti.
170. bake.ab,ti.
171. baked.ab,ti.
172. stewing.ab,ti.
173. stewed.ab,ti.
174. casserol$.ab,ti.
175. broil.ab,ti.
176. broiled.ab,ti.
177. boiled.ab,ti.
178. poach.ab,ti.
179. poached.ab,ti.
180. steamed.ab,ti.
181. barbecue$.ab,ti.
182. chargrill$.ab,ti.
183. salt.ab,ti.
184. salting.ab,ti.
185. salted.ab,ti.
186. fiber.ab,ti.
187. fibre.ab,ti.
188. polysaccharide$.ab,ti.
189. starch.ab,ti.
190. starchy.ab,ti.
191. carbohydrate$.ab,ti.
192. lipid$.ab,ti.
193. linoleic acid$.ab,ti.
194. sugar$.ab,ti.
195. sweetener$.ab,ti.
196. saccharin$.ab,ti.
197. aspartame.ab,ti.
198. sucrose.ab,ti.

199. xylitol.ab,ti.
200. cholesterol.ab,ti.
201. hydrogenated lard.ab,ti.
202. dietary protein.ab,ti.
203. dietary proteins.ab,ti.
204. protein intake.ab,ti.
205. animal protein$.ab,ti.
206. total protein$.ab,ti.
207. vegetable protein$.ab,ti.
208. plant protein$.ab,ti.
209. carbohydrate diet/
210. carbohydrate intake/
211. fat intake/
212. dietary fiber/
213. protein intake/
214. diet supplementation/
215. food additive/
216. exp vitamin/
217. supplements.ab,ti.
218. supplement.ab,ti.
219. vitamin$.ab,ti.
220. retinol.ab,ti.
221. carotenoid$.ab,ti.
222. tocopherol.ab,ti.
223. folate$.ab,ti.
224. folic acid.ab,ti.
225. methionine.ab,ti.
226. riboflavin.ab,ti.
227. thiamine.ab,ti.
228. niacin.ab,ti.
229. pyridoxine.ab,ti.
230. cobalamin.ab,ti.
231. mineral$.ab,ti.
232. sodium.ab,ti.
233. iron.ab,ti.
234. calcium.ab,ti.
235. selenium.ab,ti.
236. iodine.ab,ti.
237. magnesium.ab,ti.
238. potassium.ab,ti.
239. zinc.ab,ti.
240. copper.ab,ti.
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242. manganese.ab,ti.
243. chromium.ab,ti.
244. phytochemical.ab,ti.
245. polyphenol$.ab,ti.
246. phytoestrogen$.ab,ti.
247. genistein.ab,ti.
248. saponin$.ab,ti.

249. coumarin$.ab,ti.
250. flavonoid$.ab,ti.
251. polyphenol$.ab,ti.
252. flavonol$.ab,ti.
253. flavone$.ab,ti.
254. isoflavone$.ab,ti.
255. catechin$.ab,ti.
256. ascorbic acid$.ab,ti.
257. hydroxy cholecalciferol$.ab,ti.
258. hydroxycholecalciferol$.ab,ti.
259. tocotrienol$.ab,ti.
260. carotene$.ab,ti.
261. cryptoxanthin$.ab,ti.
262. lycopene$.ab,ti.
263. lutein$.ab,ti.
264. zeaxanthin$.ab,ti.
265. selenium$.ab,ti.
266. organic diet?.ab,ti.
267. organic food/
268. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169 or 170 or 171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181 or 182 or 183 or 184 or 185 or 186 or 187 or 188 or 189 or 190 or 191 or 192 or 193 or 194 or 195 or 196 or 197 or 198 or 199 or 200 or 201 or 202 or 203 or 204 or 205 or 206 or 207 or 208 or 209 or 210 or 211 or 212 or 213 or 214 or 215 or 216 or 217 or 218 or 219 or 220 or 221 or 222 or 223 or 224 or 225 or 226 or 227 or 228 or 229 or 230 or 231 or 232 or 233 or 234 or 235 or 236 or 237 or 238 or 239 or 240 or 241 or 242 or 243 or 244 or 245 or 246 or 247 or 248 or 249 or 250 or 251 or 252 or 253 or 254 or 255 or 256 or 257 or 258 or 259 or 260 or 261 or 262 or 263 or 264 or 265 or 266 or 267
269. allerg$.ab,ti.
270. asthma$.ab,ti.
271. wheeze.ab,ti.
272. wheezing.ab,ti.
273. bronchial hyperresponsiveness.ab,ti.
274. bronchial hyperreactivity.ab,ti.
275. Forced expiratory volume.ab,ti.
276. FEV1.ab,ti.
277. "FEV 1".ab,ti.
278. "FEV0.5".ab,ti.
279. "FEV 0.5".ab,ti.
280. Forced vital capacity.ab,ti.

281. FVC.ab,ti.
282. Peak expiratory flow rate.ab,ti.
283. PEFR.ab,ti.
284. eczema.ab,ti.
285. neurodermatitis.ab,ti.
286. rhinitis.ab,ti.
287. besniers prurigo.ab,ti.
288. rhinoconjunctivitis.ab,ti.
289. hayfever.ab,ti.
290. (hay adj fever).ab,ti.
291. poll?nosis.ab,ti.
292. SAR.ab,ti.
293. (pollen adj allergy).ab,ti.
294. conjunctivitis.ab,ti.
295. immunoglobulin e.ab,ti.
296. Total IgE.ab,ti.
297. autoimmune disease?.ab,ti.
298. diabetes.ab,ti.
299. diabetic.ab,ti.
300. type 1.ab,ti.
301. c?eliac disease.ab,ti.
302. crohn$ disease.ab,ti.
303. Inflammatory Bowel Disease?.ab,ti.
304. Ulcerative colitis.ab,ti.
305. (Lympho$ adj3 thyroiditi$).ab,ti.
306. (Thyroiditi$ adj3 autoimmune).ab,ti.
307. (Hashimoto$ adj3 (syndrome? or thyroiditi$ or disease?)).ab,ti.
308. (Thyroiditi$ adj3 (post-partum or postpartum)).ab,ti.
309. Graves? disease.ab,ti.
310. Basedow$ disease.ab,ti.
311. exophthalmic goiter?.ab,ti.
312. (Still? Disease adj3 (juvenile or onset)).ab,ti.
313. (Juvenile adj3 arthriti$).ab,ti.
314. vitiligo.ab,ti.
315. Psorias?s.ab,ti.
316. (Arthriti? adj3 Psoria$).ab,ti.
317. atopic disease.ab,ti.
318. atopic dermatitis.ab,ti.
319. (food? adj3 sensiti$).ab,ti.
320. (food? adj3 toleran$).ab,ti.
321. (food? adj3 intoleran$).ab,ti.
322. ((aero or air$) adj3 allergen?).ab,ti.
323. (aeroallergen? adj3 sensiti$).ab,ti.
324. (allergen? adj3 sensiti$).ab,ti.
325. skin prick test$.ab,ti.
326. atopy.ab,ti.
327. hypersensitiv$.ab,ti.
328. exp hypersensitivity/
329. respiratory tract allergy/
330. asthma/

331. wheezing/
332. bronchus hyperreactivity/
333. forced expiratory volume/
334. forced vital capacity/
335. peak expiratory flow/
336. eczema/
337. neurodermatitis/
338. rhinitis/
339. rhinoconjunctivitis/
340. hay fever/
341. pollen allergy/
342. perennial rhinitis/
343. conjunctivitis/
344. immunoglobulin E/
345. autoimmune disease/
346. diabetes mellitus/
347. insulin dependent diabetes mellitus/
348. celiac disease/
349. Crohn disease/
350. enteritis/
351. ulcerative colitis/
352. autoimmune thyroiditis/
353. Hashimoto disease/
354. postpartum thyroiditis/
355. Graves disease/
356. juvenile rheumatoid arthritis/
357. vitiligo/
358. psoriasis/
359. psoriatic arthritis/
360. atopic dermatitis/
361. nutritional intolerance/
362. 269 or 270 or 271 or 272 or 273 or 274 or 275 or 276 or 277 or 278 or 279 or 280 or 281 or 282 or 283 or 284 or 285 or 286 or 287 or 288 or 289 or 290 or 291 or 292 or 293 or 294 or 295 or 296 or 297 or 298 or 299 or 300 or 301 or 302 or 303 or 304 or 305 or 306 or 307 or 308 or 309 or 310 or 311 or 312 or 313 or 314 or 315 or 316 or 317 or 318 or 319 or 320 or 321 or 322 or 323 or 324 or 325 or 326 or 327 or 328 or 329 or 330 or 331 or 332 or 333 or 334 or 335 or 336 or 337 or 338 or 339 or 340 or 341 or 342 or 343 or 344 or 345 or 346 or 347 or 348 or 349 or 350 or 351 or 352 or 353 or 354 or 355 or 356 or 357 or 358 or 359 or 360 or 361
363. infant?.ab,ti.
364. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four" or "twenty five" or "twenty six") adj week?).ab,ti.
365. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four") adj month?).ab,ti.
366. 364 or 365
367. (old or age?).ab,ti.
368. 366 and 367

369. (("one year?" or "two year?") adj3 (old or age?)).ab,ti.
370. ((first or second or two) adj3 "year? of life").ab,ti.
371. infant/
372. newborn/
373. (maternal adj7 pregnan$).ti,ab.
374. (maternal adj7 lactat$).ti,ab.
375. (mother? adj7 pregnan$).ti,ab.
376. 363 or 368 or 369 or 370 or 371 or 372 or 373 or 374 or 375
377. clinical trial?.mp.
378. random$.mp.
379. factorial$.mp.
380. crossover$.mp.
381. placebo$.mp.
382. (doubl$ adj blind$).mp.
383. (singl$ adj blind$).mp.
384. assign$.mp.
385. volunteer$.mp.
386. cohort stud$.mp.
387. longitudinal$.mp.
388. follow-up.mp.
389. prospectiv$.mp.
390. retrospectiv$.mp.
391. case control.mp.
392. case referent.mp.
393. exp clinical trial/
394. crossover procedure/
395. placebo/
396. double blind procedure/
397. single blind procedure/
398. cohort analysis/
399. longitudinal study/
400. follow up/
401. prospective study/
402. retrospective study/
403. exp case control study/
404. 377 or 378 or 379 or 380 or 381 or 382 or 383 or 384 or 385 or 386 or 387 or 388 or 389 or 390 or 391 or 392 or 393 or 394 or 395 or 396 or 397 or 398 or 399 or 400 or 401 or 402 or 403
405. 268 and 362 and 376 and 404

2.3. LILACS

(tw:((breast feeding) or breastfeeding or (breast fed) or breastfed or formula* or hydrolysed or bottlefed or (bottle fed) or (bottle feed*) or wean*)
AND
(tw:(allerg* or asthma* or wheez* or (bronchial hyperresponsiveness) or (bronchial hyperreactivity) or (Forced expiratory volume) or FEV1 or (FEV 1) or FEV0.5 or (FEV 0.5) or (Forced vital capacity) or FVC or (Peak expiratory flow rate) or PEFR or eczema or neurodermatitis or rhinitis or (besniers prurigo) or rhinoconjunctivitis or hayfever or (hay fever) or poll?nosis or SAR or (pollen allergy) or conjunctivitis or (immunoglobulin e) or (Total IgE) or (autoimmune disease*) or diabetes or diabetic or (type 1) or (c?eliac disease) or (crohn* disease) or (Inflammatory Bowel Disease*) or (Ulcerative colitis) or (Lympho* thyroiditi*) or (Thyroiditi* autoimmune) or (Hashimoto* syndrome*) or (Hashimoto* thyroiditis*) or (Hashimoto* disease*) or (Thyroiditi* post-partum) or (Thyroiditi* postpartum) or (Graves* Disease) or (Basedow* disease) or (exophthalmic goiter*) or (Still's Disease) or (Stills disease) or (Juvenile arthriti*) or vitiligo or Psorias?s or (Arthriti* Psoria*) or (atopic disease) or (atopic dermatitis) or (food* sensiti*) or (food* toleran*) or (food* intoleran*) or (aero allergen*) or (air* allergen*) or (aeroallergen* sensiti*) or (allergen* sensiti*) or (skin prick test*) or atopy or hypersensitive*)
AND
db:("LILACS")
AND
type_of_study:("clinical_trials" or "case_control" or "cohort" or "systematic_reviews")
AND
limit:("infant" or "newborn" or "preschool" or "child")

COCHRANE Library

1. MeSH descriptor: [Diet] this term only
2. MeSH descriptor: [Diet Therapy] this term only
3. MeSH descriptor: [Nutritional Sciences] this term only
4. MeSH descriptor: [Child Nutrition Sciences] this term only
5. diet:ab,ti
6. diets:ab,ti
7. MeSH descriptor: [Diet, Mediterranean] this term only
8. “mediterranean diet*”:ab,ti
9. dietetic:ab,ti
10. dietary:ab,ti
11. eat:ab,ti
12. eating:ab,ti
13. intake:ab,ti
14. nutrient*:ab,ti
15. nutrition:ab,ti
16. MeSH descriptor: [Diet, Vegetarian] this term only
17. vegetarian*:ab,ti
18. vegan*:ab,ti
19. MeSH descriptor: [Diet, Macrobiotic] this term only
20. macrobiotic*:ab,ti
21. MeSH descriptor: [Food] this term only
22. food*:ab,ti
23. feed:ab,ti
24. feeding:ab,ti
25. cereal*:ab,ti
26. grain*:ab,ti
27. granary:ab,ti
28. wholegrain:ab,ti
29. wholewheat:ab,ti
30. “whole wheat”:ab,ti
31. wheat:ab,ti
32. wheatgerm:ab,ti
33. rye:ab,ti
34. barley:ab,ti
35. oat*:ab,ti
36. MeSH descriptor: [Cereals] explode all trees
37. root*:ab,ti
38. tuber*:ab,ti
39. MeSH descriptor: [Vegetables] explode all trees
40. vegetable*:ab,ti
41. onion*:ab,ti
42. spinach:ab,ti
43. chard:ab,ti
44. tomato*:ab,ti
45. pepper*:ab,ti
46. carrot*:ab,ti
47. beetroot:ab,ti
48. asparagus:ab,ti
49. garlic:ab,ti

50. pumpkin:ab,ti
51. sprouts:ab,ti
52. broccoli:ab,ti
53. cabbage*:ab,ti
54. celery:ab,ti
55. ginger:ab,ti
56. potato*:ab,ti
57. crisps:ab,ti
58. fries:ab,ti
59. syrup:ab,ti
60. honey:ab,ti
61. MeSH descriptor: [Honey] this term only
62. MeSH descriptor: [Fruit] this term only
63. fruit*:ab,ti
64. apple*:ab,ti
65. pear*:ab,ti
66. banana*:ab,ti
67. orange*:ab,ti
68. grape*:ab,ti
69. kiwi*:ab,ti
70. citrus:ab,ti
71. grapefruit*:ab,ti
72. pulses:ab,ti
73. beans:ab,ti
74. lentil*:ab,ti
75. chickpea*:ab,ti
76. legume*:ab,ti
77. lupin*:ab,ti
78. soy:ab,ti
79. soya:ab,ti
80. nut*:ab,ti
81. almond*:ab,ti
82. peanut*:ab,ti
83. groundnut*:ab,ti
84. MeSH descriptor: [Nuts] this term only
85. seed*:ab,ti
86. sesame:ab,ti
87. mustard:ab,ti
88. MeSH descriptor: [Seeds] this term only
89. MeSH descriptor: [Meat] explode all trees
90. meat:ab,ti
91. beef:ab,ti
92. pork:ab,ti
93. lamb:ab,ti
94. poultry:ab,ti
95. chicken:ab,ti
96. turkey:ab,ti
97. duck:ab,ti
98. fish:ab,ti
99. MeSH descriptor: [Fatty Acids] this term only

100. MeSH descriptor: [Fatty Acids, Omega-3] explode all trees
101. MeSH descriptor: [Fatty Acids, Omega-6] explode all trees
102. omega-3:ab,ti
103. omega-6:ab,ti
104. PUFA:ab,ti
105. fat:ab,ti
106. fats:ab,ti
107. fatty:ab,ti
108. egg:ab,ti
109. eggs:ab,ti
110. MeSH descriptor: [Eggs] explode all trees
111. MeSH descriptor: [Bread] this term only
112. bread:ab,ti
113. oil:ab,ti
114. oils:ab,ti
115. oily:ab,ti
116. omega:ab,ti
117. MeSH descriptor: [Seafood] explode all trees
118. seafood:ab,ti
119. shellfish:ab,ti
120. crustacean*:ab,ti
121. mollusc*:ab,ti
122. MeSH descriptor: [Shellfish] this term only
123. MeSH descriptor: [Dairy Products] this term only
124. dairy:ab,ti
125. MeSH descriptor: [Milk] explode all trees
126. milk:ab,ti
127. MeSH descriptor: [Infant Formula] this term only
128. formula*:ab,ti
129. hydrolysed:ab,ti
130. MeSH descriptor: [Infant Food] this term only
131. yoghurt:ab,ti
132. probiotic:ab,ti
133. prebiotic*:ab,ti
134. butter:ab,ti
135. herb*:ab,ti
136. spice*:ab,ti
137. chilli*:ab,ti
138. condiment*:ab,ti
139. MeSH descriptor: [Condiments] explode all trees
140. MeSH descriptor: [Beverages] this term only
141. beverage*:ab,ti
142. “fluid intake”:ab,ti
143. water:ab,ti
144. drink*:ab,ti
145. MeSH descriptor: [Food Preservation] explode all trees
146. pickled:ab,ti
147. bottled:ab,ti
148. canned:ab,ti
149. canning:ab,ti

150. smoked:ab,ti
151. preserved:ab,ti
152. preservatives:ab,ti
153. nitrosamine:ab,ti
154. hydrogenation:ab,ti
155. fortified:ab,ti
156. nitrates:ab,ti
157. nitrites:ab,ti
158. ferment*:ab,ti
159. processed:ab,ti
160. antioxidant*:ab,ti
161. “genetic modif*”:ab,ti
162. “genetically modif*”:ab,ti
163. MeSH descriptor: [Cooking] this term only
164. cooking:ab,ti
165. cooked:ab,ti
166. grill:ab,ti
167. grilled:ab,ti
168. fried:ab,ti
169. fry:ab,ti
170. roast:ab,ti
171. bake:ab,ti
172. baked:ab,ti
173. stewing:ab,ti
174. stewed:ab,ti
175. casserol*:ab,ti
176. broil:ab,ti
177. broiled:ab,ti
178. boiled:ab,ti
179. poach:ab,ti
180. poached:ab,ti
181. steamed:ab,ti
182. barbecue*:ab,ti
183. chargrill*:ab,ti
184. salt:ab,ti
185. salting:ab,ti
186. salted:ab,ti
187. fiber:ab,ti
188. fibre:ab,ti
189. polysaccharide*:ab,ti
190. starch:ab,ti
191. starchy:ab,ti
192. carbohydrate*:ab,ti
193. lipid*:ab,ti
194. “linoleic acid*”:ab,ti
195. sugar*:ab,ti
196. sweetener*:ab,ti
197. saccharin*:ab,ti
198. aspartame:ab,ti
199. sucrose:ab,ti

200. xylitol:ab,ti
201. cholesterol:ab,ti
202. “hydrogenated lard”:ab,ti
203. “dietary protein”:ab,ti
204. “dietary proteins”:ab,ti
205. “protein intake”:ab,ti
206. “animal protein*”:ab,ti
207. “total protein*”:ab,ti
208. “vegetable protein*”:ab,ti
209. “plant protein*”:ab,ti
210. MeSH descriptor: [Dietary Carbohydrates] explode all trees
211. MeSH descriptor: [Dietary Fats] explode all trees
212. MeSH descriptor: [Dietary Fiber] explode all trees
213. MeSH descriptor: [Dietary Proteins] explode all trees
214. MeSH descriptor: [Dietary Supplements] explode all trees
215. MeSH descriptor: [Food Additives] explode all trees
216. MeSH descriptor: [Vitamins] explode all trees
217. supplements:ab,ti
218. supplement:ab,ti
219. vitamin*:ab,ti
220. retinol:ab,ti
221. carotenoid*:ab,ti
222. tocopherol:ab,ti
223. folate*:ab,ti
224. “folic acid”:ab,ti
225. methionine:ab,ti
226. riboflavin:ab,ti
227. thiamine:ab,ti
228. niacin:ab,ti
229. pyridoxine:ab,ti
230. cobalamin:ab,ti
231. mineral*:ab,ti
232. sodium:ab,ti
233. iron:ab,ti
234. calcium:ab,ti
235. selenium:ab,ti
236. iodine:ab,ti
237. magnesium:ab,ti
238. potassium:ab,ti
239. zinc:ab,ti
240. copper:ab,ti
241. phosphorus:ab,ti
242. manganese:ab,ti
243. chromium:ab,ti
244. phytochemical:ab,ti
245. polyphenol*:ab,ti
246. phytoestrogen*:ab,ti
247. genistein:ab,ti
248. saponin*:ab,ti
249. coumarin*:ab,ti

250. flavonoid*:ab,ti
251. polyphenol*:ab,ti
252. flavonol*:ab,ti
253. flavone*:ab,ti
254. isoflavone*:ab,ti
255. catechin*:ab,ti
256. “ascorbic acid*”:ab,ti
257. “hydroxy cholecalciferol*”:ab,ti
258. hydroxycholecalciferol*:ab,ti
259. tocotrienol*:ab,ti
260. carotene*:ab,ti
261. cryptoxanthin*:ab,ti
262. lycopene*:ab,ti
263. lutein*:ab,ti
264. zeaxanthin*:ab,ti
265. selenium*:ab,ti
266. “organic diet*”:ab,ti
267. MeSH descriptor: [Food, Organic] this term only
268. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169 or 170 or 171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181 or 182 or 183 or 184 or 185 or 186 or 187 or 188 or 189 or 190 or 191 or 192 or 193 or 194 or 195 or 196 or 197 or 198 or 199 or 200 or 201 or 202 or 203 or 204 or 205 or 206 or 207 or 208 or 209 or 210 or 211 or 212 or 213 or 214 or 215 or 216 or 217 or 218 or 219 or 220 or 221 or 222 or 223 or 224 or 225 or 226 or 227 or 228 or 229 or 230 or 231 or 232 or 233 or 234 or 235 or 236 or 237 or 238 or 239 or 240 or 241 or 242 or 243 or 244 or 245 or 246 or 247 or 248 or 249 or 250 or 251 or 252 or 253 or 254 or 255 or 256 or 257 or 258 or 259 or 260 or 261 or 262 or 263 or 264 or 265 or 266 or 267
269. allerg*:ab,ti
270. asthma*:ab,ti
271. wheeze:ab,ti
272. wheezing:ab,ti
273. “bronchial hyperresponsiveness”:ab,ti
274. “bronchial hyperreactivity”:ab,ti
275. “Forced expiratory volume”:ab,ti
276. “FEV1”:ab,ti
277. "FEV 1":ab,ti
278. "FEV0.5":ab,ti
279. "FEV 0.5":ab,ti
280. “Forced vital capacity”:ab,ti
281. FVC:ab,ti

282. “Peak expiratory flow rate”:ab,ti
283. PEFR:ab,ti
284. eczema:ab,ti
285. neurodermatitis:ab,ti
286. rhinitis:ab,ti
287. “besniers prurigo”:ab,ti
288. rhinoconjunctivitis:ab,ti
289. hayfever:ab,ti
290. “hay fever”:ab,ti
291. poll*nosis:ab,ti
292. SAR:ab,ti
293. “pollen allergy”:ab,ti
294. conjunctivitis:ab,ti
295. “immunoglobulin e”:ab,ti
296. “Total IgE”:ab,ti
297. “autoimmune disease*”:ab,ti
298. diabetes:ab,ti
299. diabetic:ab,ti
300. “type 1”:ab,ti
301. “c*eliac disease”:ab,ti
302. “crohn* disease”:ab,ti
303. “Inflammatory Bowel Disease*”:ab,ti
304. “Ulcerative colitis”:ab,ti
305. (Lympho* NEAR/3 thyroiditi*):ab,ti
306. (Thyroiditi* NEAR/3 autoimmune):ab,ti
307. (Hashimoto* NEAR/3 (syndrome* or thyroiditi* or disease*)):ab,ti
308. (Thyroiditi* NEAR/3 (post-partum or postpartum)):ab,ti
309. “Graves* disease”:ab,ti
310. “Basedow* disease”:ab,ti
311. “exophthalmic goiter*”:ab,ti
312. (Still* Disease NEAR/3 (juvenile or onset)):ab,ti
313. (Juvenile NEAR/3 arthriti*):ab,ti
314. vitiligo:ab,ti
315. Psorias*s:ab,ti
316. (Arthriti* NEAR/3 Psoria*):ab,ti
317. “atopic disease”:ab,ti
318. “atopic dermatitis”:ab,ti
319. (food* NEAR/3 sensiti*):ab,ti
320. (food* NEAR/3 toleran*):ab,ti
321. (food* NEAR/3 intoleran*):ab,ti
322. ((aero or air*) NEAR/3 allergen*):ab,ti
323. (aeroallergen* NEAR/3 sensiti*):ab,ti
324. (allergen* NEAR/3 sensiti*):ab,ti
325. “skin prick test*”:ab,ti
326. atopy:ab,ti
327. hypersensitiv*:ab,ti
328. MeSH descriptor: [Hypersensitivity] this term only
329. MeSH descriptor: [Food Hypersensitivity] explode all trees
330. MeSH descriptor: [Respiratory Hypersensitivity] this term only
331. MeSH descriptor: [Asthma] this term only

332. MeSH descriptor: [Bronchial Hyperreactivity] this term only
333. MeSH descriptor: [Forced Expiratory Volume] this term only
334. MeSH descriptor: [Vital Capacity] this term only
335. MeSH descriptor: [Peak Expiratory Flow Rate] this term only
336. MeSH descriptor: [Eczema] this term only
337. MeSH descriptor: [Neurodermatitis] this term only
338. MeSH descriptor: [Rhinitis] this term only
339. MeSH descriptor: [Rhinitis, Allergic, Perennial] this term only
340. MeSH descriptor: [Rhinitis, Allergic, Seasonal] this term only
341. MeSH descriptor: [Conjunctivitis] this term only
342. MeSH descriptor: [Immunoglobulin E] this term only
343. MeSH descriptor: [Autoimmune Diseases] this term only
344. MeSH descriptor: [Diabetes Mellitus, Type 1] this term only
345. MeSH descriptor: [Celiac Disease] this term only
346. MeSH descriptor: [Crohn Disease] this term only
347. MeSH descriptor: [Inflammatory Bowel Diseases] this term only
348. MeSH descriptor: [Colitis, Ulcerative] this term only
349. MeSH descriptor: [Thyroiditis, Autoimmune] this term only
350. MeSH descriptor: [Hashimoto Disease] this term only
351. MeSH descriptor: [Postpartum Thyroiditis] this term only
352. MeSH descriptor: [Graves Disease] this term only
353. MeSH descriptor: [Arthritis, Juvenile Rheumatoid] this term only
354. MeSH descriptor: [Vitiligo] this term only
355. MeSH descriptor: [Psoriasis] this term only
356. MeSH descriptor: [Arthritis, Psoriatic] this term only
357. MeSH descriptor: [Dermatitis, Atopic] this term only
358. MeSH descriptor: [Hypersensitivity, Immediate] this term only
359. 269 or 270 or 271 or 272 or 273 or 274 or 275 or 276 or 277 or 278 or 279 or 280 or 281 or 282 or 283 or 284 or 285 or 286 or 287 or 288 or 289 or 290 or 291 or 292 or 293 or 294 or 295 or 296 or 297 or 298 or 299 or 300 or 301 or 302 or 303 or 304 or 305 or 306 or 307 or 308 or 309 or 310 or 311 or 312 or 313 or 314 or 315 or 316 or 317 or 318 or 319 or 320 or 321 or 322 or 323 or 324 or 325 or 326 or 327 or 328 or 329 or 330 or 331 or 332 or 333 or 334 or 335 or 336 or 337 or 338 or 339 or 340 or 341 or 342 or 343 or 344 or 345 or 346 or 347 or 348 or 349 or 350 or 351 or 352 or 353 or 354 or 355 or 356 or 357 or 358
360. infant*:ab,ti
361. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four" or "twenty five" or "twenty six") NEAR/1 week*):ab,ti
362. ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four") NEAR/1 month*):ab,ti
363. 361 or 362
364. (old or age*):ab,ti
365. 363 and 364
366. (("one year*" or "two year*") NEAR/3 (old or age*)):ab,ti
367. ((first or second or two) NEAR/3 "year* of life"):ab,ti
368. MeSH descriptor: [Infant] this term only
369. MeSH descriptor: [Infant, Newborn] this term only

370. (maternal NEAR/7 pregnan*):ab,ti
371. (maternal NEAR/7 lactat*):ab,ti
372. (mother* NEAR/7 pregnan*):ab,ti
373. 360 or 365 or 366 or 367 or 368 or 369 or 370 or 371 or 372
374. “clinical trial*”
375. random*
376. factorial*
377. crossover*
378. placebo*
379. “doubl* blind*”
380. “singl* blind*”
381. assign*
382. volunteer*
383. “cohort stud*”
384. longitudinal*
385. follow-up
386. prospectiv*
387. retrospectiv*
388. “case control”
389. “case referent”
390. MeSH descriptor: [clinical trial] explode all trees
391. MeSH descriptor: [Cross-Over Studies] this term only
392. MeSH descriptor: [Placebos] this term only
393. MeSH descriptor: [Double-Blind Method] this term only
394. MeSH descriptor: [Single-Blind Method] this term only
395. MeSH descriptor: [Cohort Studies] explode all trees
396. MeSH descriptor: [case-control studies] this term only
397. 374 or 375 or 376 or 377 or 378 or 379 or 380 or 381 or 382 or 383 or 384 or 385 or 386 or 387 or 388 or 389 or 390 or 391 or 392 or 393 or 394 or 395 or 396
398. 268 and 359 and 373 and 397

Web of Science

1. TOPIC = (diet$ or “mediterranean diet*” or dietetic or dietary or eat or eating or intake or nutrient$ or nutrition or vegetarian$ or vegan$ or macrobiotic$ or food$ or feed or feeding or cereal$ or grain$ or granary or wholegrain or wholewheat or “whole wheat” or wheat or wheatgerm or rye or barley or oat$ or root$ or tuber$ or vegetable$ or onion$ or spinach or chard or tomato* or pepper$ or carrot$ or beetroot or asparagus or garlic or pumpkin or sprouts or broccoli or cabbage$ or celery or ginger or potato* or crisps or fries or syrup or honey or fruit$ or apple$ or pear$ or banana$ or orange$ or grape$ or kiwi$ or citrus or grapefruit$ or pulses or bean$ or lentil$ or chickpea$ or legume$ or lupin$ or soy or soya or nut$ or almond$ or peanut$ or groundnut$ or seed$ or sesame or mustard or meat$ or beef or pork or lamb or poultry or chicken or turkey or duck or fish* or omega-3 or omega-6 or PUFA or fat$ or fatty or egg$ or bread or oil$ or omega or seafood or shellfish or crustacean$ or mollusc$ or dairy or milk or formula$ or hydrolysed or yoghurt or probiotic$ or prebiotic$ or butter or herb$ or spice$ or chilli* or condiment$ or beverage$ or “fluid intake” or water or drink* or pickled or bottled or canned or canning or smoked or preserved or preservative$ or nitrosamine or hydrogenation or fortified or nitrates or nitrites or ferment* or processed or antioxidant$ or “genetic modif*” or “genetically modif*” or cooking or cooked or grill or grilled or fried or fry or roast or bake or baked or stewing or stewed or casserole* or broil or broiled or boiled or poach or poached or steamed or barbecue$ or chargrill* or salt or salting or salted or fiber or fibre or polysaccharide$ or starch or starchy or carbohydrate$ or lipid$ or “linoleic acid$” or sugar$ or sweetener$ or saccharin$ or aspartame or sucrose or xylitol or cholesterol or “hydrogenated lard” or “dietary protein$” or “protein intake” or “animal protein$” or “total protein$” or “vegetable protein$” or “plant protein$” or supplement$ or vitamin$ or retinol or carotenoid$ or tocopherol or folate$ or “folic acid” or methionine or riboflavin or thiamine or niacin or pyridoxine or cobalamin or mineral$ or sodium or iron or calcium or selenium or iodine or magnesium or potassium or zinc or copper or phosphorus or manganese or chromium or phytochemical or polyphenol$ or phytoestrogen$ or genistein or saponin$ or coumarin$ or flavonoid$ or polyphenol$ or flavonol$ or flavone$ or isoflavone$ or catechin$ or “ascorbic acid$” or “hydroxy cholecalciferol$” or “hydroxycholecalciferol$” or tocotrienol$ or carotene$ or cryptoxanthin$ or lycopene$ or lutein$ or zeaxanthin$ or selenium$ or “organic diet$”)
2. TOPIC = (allerg* or asthma* or wheeze or wheezing or “bronchial hyperresponsiveness” or “bronchial hyperreactivity” or “Forced expiratory volume” or “FEV1” or "FEV 1" or "FEV0.5" or "FEV 0.5" or “Forced vital capacity” or FVC or “Peak expiratory flow rate” or PEFR or eczema or neurodermatitis or rhinitis or “besniers prurigo” or rhinoconjunctivitis or hayfever or “hay fever” or poll$nosis or SAR or “pollen allergy” or conjunctivitis or “immunoglobulin e” or “Total IgE” or “autoimmune disease$” or diabetes or diabetic or “type 1” or “c$eliac disease” or “crohn* disease” or “Inflammatory Bowel Disease$” or “Ulcerative colitis” or (Lympho* NEAR/3 thyroiditi*) or (Thyroiditi* NEAR/3 autoimmune) or (Hashimoto* NEAR/3 (syndrome$ or thyroiditis* or disease$)) or (Thyroiditi* NEAR/3 (post-partum or postpartum)) or “Graves$ Disease” or “Basedow* disease” or “exophthalmic goiter$” or (“Still$ Disease” NEAR/3 (juvenile or onset)) or (Juvenile NEAR/3 arthriti*) or vitiligo or Psorias$s or (Arthriti$ NEAR/3 Psoria*) or “atopic disease” or “atopic dermatitis” or (food$ NEAR/3 sensiti*) or (food$ NEAR/3 toleran*) or (food$ NEAR/3 intoleran*) or ((aero or air*) NEAR/3 allergen$) or (aeroallergen$ NEAR/3 sensiti*) or (allergen$ NEAR/3 sensiti*) or “skin prick test*” or atopy or hypersensitive*)
3. TOPIC = (infant$ or (("one year$" or "two year$") NEAR/3 (old or age$)) or ((first or second or two) NEAR/3 "year$ of life") or (maternal NEAR/7 pregnan*) or (maternal NEAR/7 lactat*) or (mother$ NEAR/7 pregnan*))

4. TOPIC = ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four" or "twenty five" or "twenty six") NEAR/1 week$)
5. TOPIC = ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or nineteen or twenty or "twenty one" or "twenty two" or "twenty three" or "twenty four") NEAR/1 month$)
6. 4 or 5
7. TOPIC = ((old or age$))
8. 7 and 6
9. 8 or 3
10. TOPIC = (“clinical trial$” or random* or factorial* or crossover* or placebo* or “doubl* blind*” or “singl* blind*” or assign* or volunteer* or “cohort stud*” or longitudinal* or follow-up or prospective* or retrospective* or “case control” or “case referent”)
11. 1 and 2 and 9 and 10

BREASTFEEDING, SOLID FOOD INTRODUCTION AND RHINOCONJUNCTIVITIS

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1 Total breastfeeding and rhinoconjunctivitis

1.1 Overall characteristics of studies, risk of bias and summary of results

Table 1 describes the main characteristics of the studies that assessed total breastfeeding duration (TBF) in relation to rhinoconjunctivitis (RC) risk. A total of 1 cluster randomised controlled trial and 21 observational studies, reported the association between TBF and RC. Of these, 16 were prospective cohort studies, 5 cross-sectional studies. The majority of studies (n=17) are from Europe – others are from North America (n=2) and Japan (n=2). Overall, valid data on TBF duration in the first 2 years of life and RC risk were available from over 200,000 subjects. Information on RC was obtained solely from a medical assessment in 8 studies, and mainly via parental report in 13 studies. With regards to time of outcome diagnosis, 4 studies explored the association between TBF duration and RC at age 0-4, where allergic RC can be most difficult to distinguish from infectious RC, 10 at ages 5-14, and 7 at ages up to and beyond 15 years. Four studies used an interview, one parent diaries, and one a medical records review; in one study the method of exposure assessment was unclear and in all others a questionnaire method was used.

Risk of bias was assessed using the NICE Methodological checklists for cohort and case-control studies. Figure 1 illustrates the distribution of bias across the five main methodological areas of the studies. Over half of studies had a high risk of bias, most commonly due to lack of adjustment for confounding bias i.e. no adjusted data presented, but also in some cases due to high risk of selection bias. Risk of conflict of interest was generally assessed as low.

Where data were available, five levels of comparison were used to assess the risk of RC according to TBF duration, namely ‘ever vs. never’, ‘≥1-2 months vs. <1-2 months’, ‘≥3-4 months vs. <3-4 months’, ‘≥5-7 months vs. <5-7 months’, and ‘≥8-12 months vs. <8-12 months’.

Main Findings

In the single intervention trial there was no evidence of a relationship between breastfeeding promotion and risk of allergic rhinoconjunctivitis. For observational studies, across all cut-offs where data were available, there was no clear evidence of a relationship between risk of

RC and initiation or prolongation of BF. In general there were only small numbers of studies with available data for individual meta-analyses, although the number of participants in some of the relevant studies was large. For RC at age 0-4 there was a trend to reduced risk with TBF ever and ≥5-7 months, but this was not statistically significant. For RC at older ages the large study sizes mean that we can be more confident of having excluded at least a large reduction in RC risk with increased initiation or duration of TBF.

Table 1 Characteristics of included studies evaluating TBF duration and rhinoconjunctivitis

First Author & Publication Year	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Kramer, 2001 (1); Kramer, 2007 (2)	8865/8181	Cluster RCT	Belarus	-	SPT-Aero	6.5	Breastfeeding promotion program based on the WHO/UNICEF baby friendly hospital initiative, versus standard local breastfeeding policies
Kull, 2002 (3)	3790/262	PC	Sweden	Q	Parent reported RC symptoms	2	BAMSE study. Population based cohort of children born between 1994-1996
Butland, 1997 (BCS58 and BCS70) (4)	20582/3631	PC	UK	I	Parent reported current AR	16	British Cohort Study (two samples): infants born in England, Wales, and Scotland in 1958 and 1970
Taylor, 1983 (BSC70) (5)	10781/452	PC	UK	I	Parent reported RC	5	CHES study. Population based cohort of children born in England, Scotland, and Wales in 1970
Burr, 1993 (6)	453/117	PC	UK	Q	Parent reported AR	7	Infants with family history of allergy born in 1982

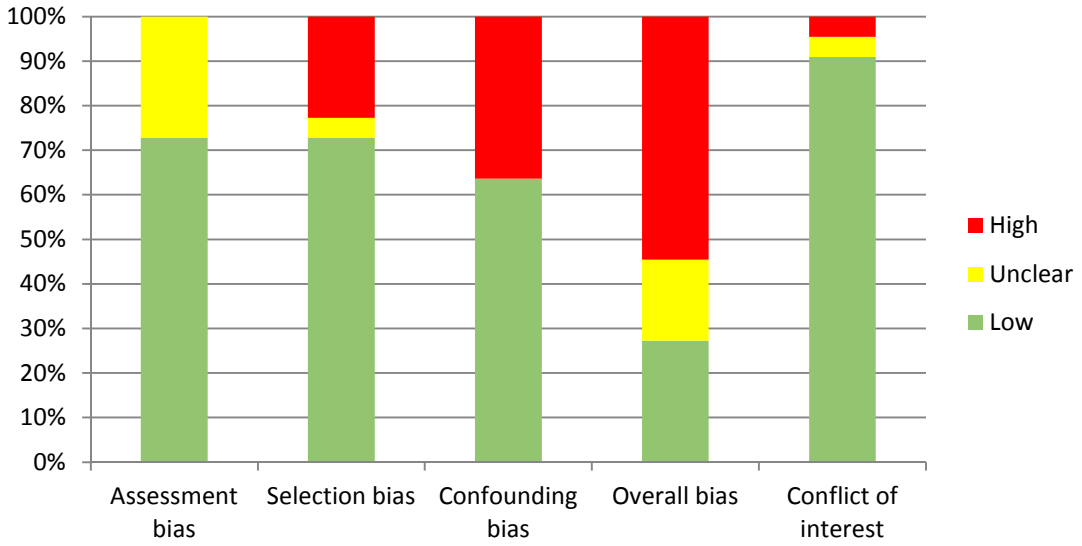
First Author & Publication Year	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Businco, 1987 (7)	244/3	PC	Italy	I	Physician assessment	8	Infants of atopic parents recruited from hospital and born in 1985-1988
Larsson, 2008 (8)	4779/573 (in 2000), 975 (in 2005)	PC	Sweden	Q	DD; ISAAC - current AR	9	DBH study. Preschool children aged 1–6 years surveyed in 2000 and 2005
Devereux, 2006 (9)	1253/54	PC	UK	Q	ISAAC	5	Population based birth cohort of infants born in 1998
Virtanen, 2010 (10)	1288/185	PC	Finland	Q	Modified ISAAC questionnaire	5	DIPP study. Infants at high risk (HLA) for TIDM born between 1996-2004 invited to the allergy study 1998-2000
Farooqi, 1998 (11)	1453	PC	UK	R	DD	16	Representative sample of general practice born in 1975-84
Gruskay 1982 (12)	908/22	PC	USA	Unclear	Parent reported AR	3, 5, 15	Children born in 1961-1966 seen in a private pediatric practice
Marini, 1996	359/	PC	Italy	Q	Physician	3	Infants with family history of

First Author & Publication Year	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
(13)					assessment		allergy who participated in an allergy prevention program
Miskelly, 1988 (14)	468/204	PC	UK	D	Physician assessment	1	Infants from antenatal clinics with family history of allergy enrolled in a dietary intervention trial
Strachan, 1996 (15)	11765/1932	PC	UK	I	DD	16	Population based cohort born in 1975
Hide, 1981 (16)	843/198	PC	UK	D/Q	Parent reported rhinitis symptoms	1	Isle of Wight study: infants born in 1977-1978
Wright, 1994 (17)	747/313	PC	USA	Q	Parent reported AR	6	Tuscon Children's Respiratory Study: recruited from local health maintenance organisation born in 1980-1984
Bergmann, 2000; Kulig, 2000(18, 19)	587/88	PC	Germany	Q/I	Physician assessment; Parent reported AR ever	6, 7	MAS study. Atopic risk enriched cohort of infants born in 1990 in 5 German cities

First Author & Publication Year	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Björkstén, 2011 (20)	103716/unclear	CS	Worldwide	Q	ISAAC - AR ever	7	ISAAC Phase 3: Schoolchildren age 6-7 from different countries
Miyake, 2003 (21)	5614/1340	CS	Japan	Q	ISAAC - current AR	15	12-15 year old children from all public junior high schools in Suita, Japan
Karino, 2008 (22)	9615/4038	CS	Japan	Q	DD	18	University students aged 18–19 years enrolled from 2003-2005
Kurt, 2007 (23)	25843/4618	CS	Turkey	Q	Parent reported current AR	6-15	Prevalence and Risk Factors of Allergies in Turkey. Representative sample of children aged 6-15
Selcuk, 1997(24)	5412/271	CS	Turkey	Q	Parent reported RC ever	7-12	Children aged 7-12 at 18 primary schools

Q: questionnaire, I: interview, R: medical records, D: diary, PC: prospective cohort, NCC: nested case control, CS: Cross-sectional, CC: case control, DD: doctor diagnosis of RC, in contrast to 'Physician assessment' where RC diagnosis was always made by a study physician as part of the study protocol.

Figure 1 Risk of bias in studies of TBF duration and rhino conjunctitis



1.2 TBF and rhinoconjunctivitis

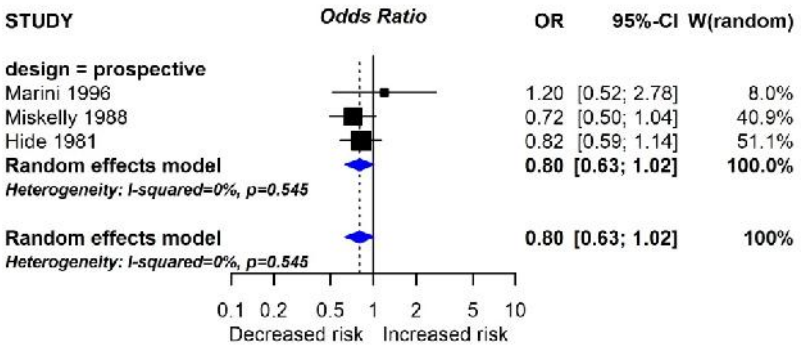
The single intervention trial of a breastfeeding promotion intervention was rated as having a low risk of bias on all domains, and a low risk of conflict of interest. Kramer found no significant difference in odds of ever having hayfever by the age of 6.5 years – cluster adjusted odds ratio 1.1 (95% CI 0.6, 1.9), or hayfever in the past 12 months at the same age OR 1.0 (0.6, 1.8). All other evidence was derived from observational studies.

1.2.1 TBF duration and risk of RC in children aged 0-4 years

1.2.1.1 TBF Ever vs. Never

Figure 2 shows the outcomes of 3 eligible observational studies including over 600 children with RC. The data show reduced odds of RC in breastfed infants, but do not reach statistical significance. There is no statistical heterogeneity (I^2=0%). All three studies are prospective cohort studies – the study of Marini reported adjusted data at age 3 and had overall unclear risk of bias due to unclear assessment bias; the other two studies reported unadjusted data at age 1, and are therefore at high risk of confounding bias. Thus the data do not show strong evidence of a relationship between breastfeeding ever and risk of RC.

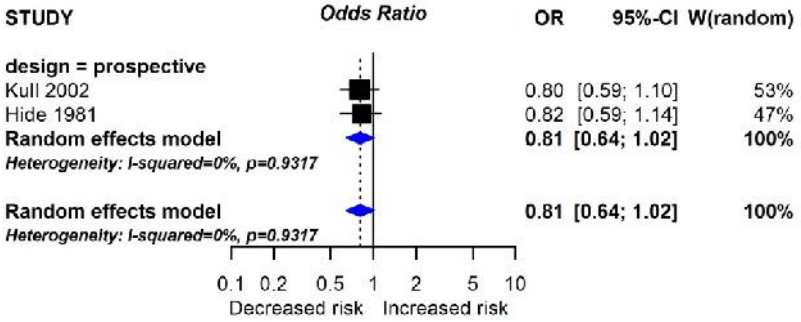
Figure 2 TBF Ever vs. Never and RC at age 0-4 years



1.2.1.2 TBF ≥5-7 months vs. <5-7 months

Two prospective cohort studies reported data that could be used to calculate OR for RC at age 0-4 with TBF ≥ 6 months compared to <6 months and found reduced odds of RC with longer breastfeeding duration, which did not reach statistical significance. There was no statistical heterogeneity (I^2=0%). The study of Hide assessed infants at 1 year and reported unadjusted data, so carries a high risk of bias. The study of Kull assessed infants at 2 years and reported adjusted data – there was unclear risk of assessment bias but low risk of bias on other parameters.

Figure 3 TBF ≥5-7 months vs. <5-7 months and risk of RC at age 0-4 years



1.2.2 TBF duration and risk of RC in children aged 5-14 years

1.2.2.1 TBF Ever vs. Never

Four prospective cohort studies and two cross-sectional surveys reported data that could be used to calculate OR for RC at age 5-14 with TBF ever vs. never and found no association between breastfeeding duration and odds of RC (Figure 4). There was high statistical heterogeneity (I^2=72.2%). The studies of Selcuk and Bjorksten reported adjusted data and were judged to be at low overall risk of bias. Other studies reported unadjusted data and were therefore at high risk of confounding bias. Subgroup analyses (Table 2) did not identify a

clear explanation for the statistical heterogeneity between studies, but there was no heterogeneity between the two studies reporting adjusted data.

Analysis of 'dose response' using a reference group of 'never BF' with comparison groups of short TBF (≥1-3; Figure 5), medium TBF (≥4-6; Figure 6) and long TBF (≥7-12; Figure 7) were limited by small numbers of eligible studies reporting only unadjusted data, and did not show evidence of a dose response relationship.

Figure 4 TBF Ever vs. Never and risk of RC at age 5-14 years

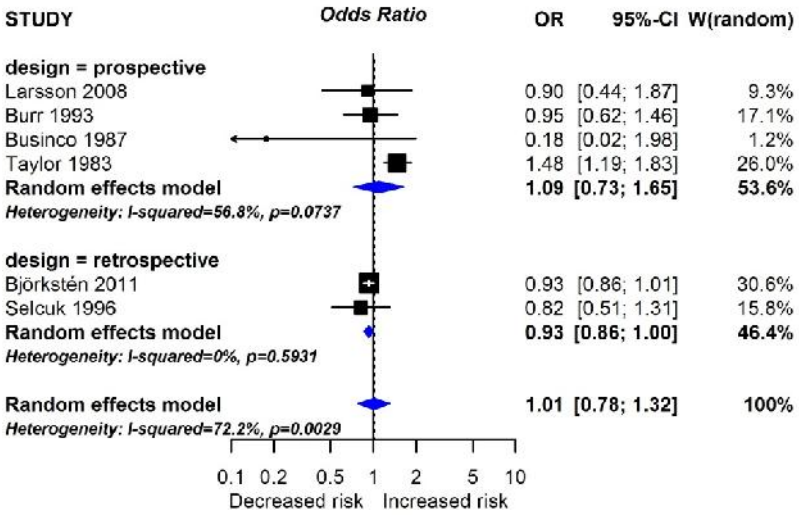


Figure 5 TBF short duration (≥1-3 months) vs. never and risk of RC at age 5-14 years

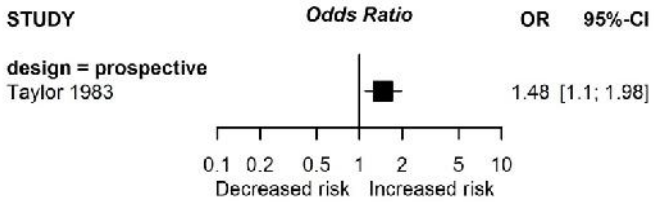


Figure 6 TBF medium duration (≥4-6 months) vs. never and risk of RC at age 5-14 years

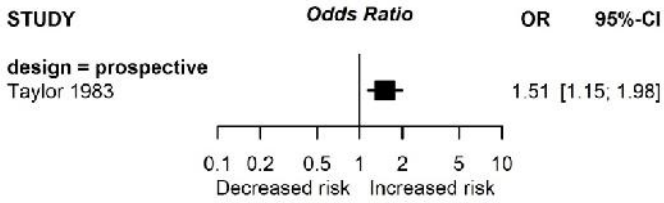


Figure 7 TBF long duration (≥7-12 months) vs. never and risk of RC at age 5-14 years

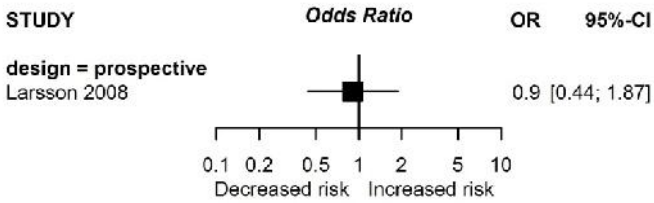


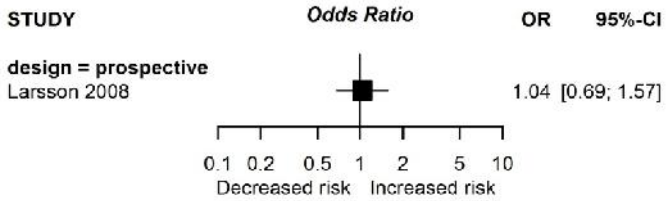
Table 2 Subgroup Analyses of risk of RC and TBF ever vs. never in children aged 5-14 years

	Number of studies	OR [95% CI]	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted value used)				
Adjusted	2	0.93 [0.86; 1.00]	0.00	Not tested
Unadjusted	4	1.10 [0.73; 1.65]	56.8	
Study Design – Prospective	4	1.00 [0.62; 1.62]	58.6	0.44
Study Design – Retrospective	2	0.93 [0.86; 1.00]	0.00	
Risk of disease – High	2	0.64 [0.16; 2.59]	44.7	0.50
Risk of disease – Normal	4	1.00 [0.76; 1.43]	81.3	
Risk of bias – Low	4	1.00 [0.76; 1.43]	81.3	0.50
Risk of bias – High/Unclear	2	0.64 [0.16; 2.59]	44.7	

1.2.2.2 TBF ≥3-4 Months vs. <3-4 months

One prospective cohort study reported data that could be used to calculate an OR for this comparison, shown in Figure 8. Unadjusted data, with a high risk of confounding bias, showed no significant association between TBF duration and risk of RC at age 5-14.

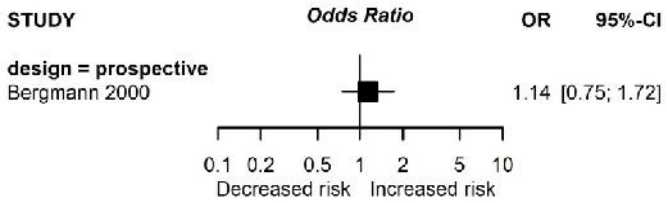
Figure 8 TBF ≥3-4 months vs. <3-4 months and RC risk at age 5-14 years



1.2.2.3 TBF ≥5-7 Months vs. <5-7 months

One prospective cohort study reported data that could be used to calculate an OR for this comparison, shown in Figure 9. Adjusted data showed no significant association between TBF duration and risk of RC at age 5-14. There was a high risk of selection bias due to loss to follow up of 33% of participants when assessed at age 6 years.

Figure 9 TBF ≥5-7 months vs. <5-7 months and risk of RC at age 5-14 years



1.2.3 TBF duration and the risk of RC in children aged 15+ years

1.2.3.1 TBF Ever vs. Never

Two cross-sectional and four prospective cohort studies reported data that could be used to calculate an OR for this comparison. Pooled data showed increased risk of RC in breastfed children at age 15+, but this did not reach statistical significance and there was high statistical heterogeneity (Figure 10). The cross-sectional studies of Miyake and Kurt, and the prospective study of Butland, reported adjusted data. The studies of Strachan and Farooqi reported unadjusted data and were therefore at high risk of confounding bias. It was not possible to identify a clear cause for the statistical heterogeneity seen in this analysis. Analysis of 'dose response' using a reference group of 'never BF' with comparison groups of short TBF (≥1-3; Figure 11) and medium TBF (≥4-6; Figure 12) were limited by small numbers of eligible studies and did not show evidence of a dose response relationship.

Figure 10 TBF Ever vs. Never and risk of RC at age 15+ years

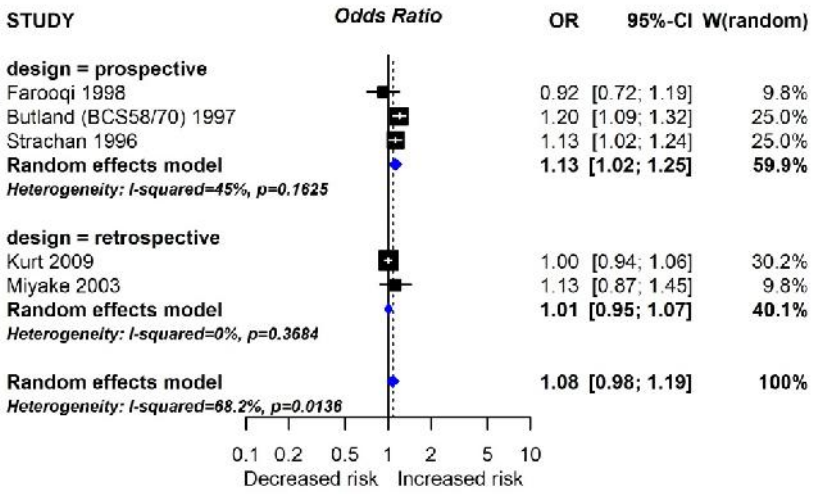


Figure 11 TBF short duration (≥1-3 months) vs. never and risk of RC at age 15+ years

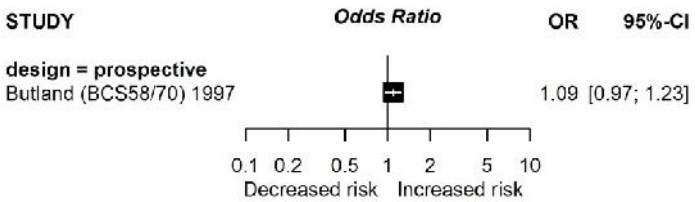
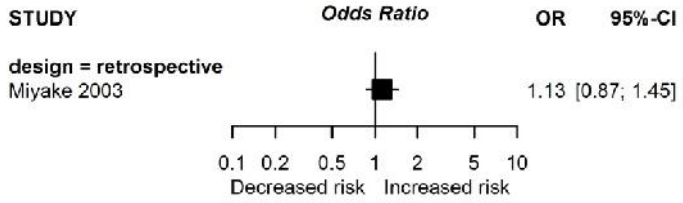


Figure 12TBF medium duration (≥4-6 months) vs. never and risk of RC at age 15+ years



1.3 TBF and Atopic RC

We also assessed the outcome 'atopic RC', where participants have the outcome if they are reported as having RC, and also have evidence of specific allergic sensitisation through skin prick or sIgE testing. This may be a more reliable measure of allergic rhinoconjunctivitis than RC alone, since infective rhinitis and conjunctivitis can be difficult to distinguish from allergic forms especially when patient or parent report is used for outcome assessment.

A single study was identified which reported TBF and atopic RC data that could be used to calculate ORs. In the study of Gruskay 6 of 782 formula fed children had RC at age 3, compared with none of 126 children who had been breastfed. At age five OR 3.51 (0.63, 19.61), at age 15 OR 1.71 (0.18, 15.80) there was no association found between TBF and atopic RC.

1.4 Data for TBF duration and RC that couldn't be meta-analysed

Meta-analyses included 10 studies, reporting data on at least 13,000 participants with RC. A further 5 studies reported relevant data which could not be reported in meta-analysis, in relation to at least 4500 participants with RC. These studies are summarised in Table 3. In all studies and analyses reported there was no association found.

Table 3 Studies investigating the association between TBF and RC which were not eligible for meta-analysis

Study	Design	Age	N/n	Data	Measure	Outcome (s)	P
Wright, 1994 (17)	PC	6	747/313	Continuous	No significant difference between groups in breastfeeding duration		
Kulig, 2000 (19)	PC	7	587/88	Continuous	No significant difference between groups in breastfeeding duration (P=0.91; adjusted)		
Devereux, 2006	PC	5	1253/54	Categorical	No significant relationship between BF ever and RC (adjusted)		
Virtanen, 2010 (10)	PC	5	1288/185	Categorical	aHR (95%CI) 1.1 (0.6-1.9) for TBF <5 vs. >9.5 months		
				Categorical	aHR (95%CI) 1.1 (0.6-1.6) for TBF 5-9 vs. >9.5 months		
Karino, 2008 (22)	CS	18	9615/4038	Categorical	BF duration not associated with RC when classified as never/ever; more/less than 1 month, 3 months or 6 months (unadjusted)		

2 Exclusive breastfeeding and rhinoconjunctivitis

2.1 Overall characteristics of studies, risk of bias and summary of results

Table 4 describes the main characteristics of the studies analysed in this report. A total of 1 systematic review which included 1 RCT analysed as a cohort study and 1 other prospective cohort study, and 13 observational studies, reported the association between duration of exclusive breastfeeding (EBF) and risk of RC. Of these, 10 were prospective cohort studies and 3 cross-sectional studies. Over half of the studies (n=9) are from Europe – others are from Australasia (n=4), and the Middle East (n=1). Overall, valid data on EBF duration and RC risk were available from over 29,000 subjects. Information on RC was obtained mainly from a medical assessment in 6 studies, via parental report in 8 studies. With regards to time of outcome diagnosis, 5 studies explored the association between EBF duration and RC at age 0-4, where allergic RC can be difficult to distinguish from infective RC, 5 evaluated RC at age 5-14, and 4 at age 15+. Most studies used a questionnaire to assess the exposure (EBF), one study used a diary and three used an interview.

Risk of bias for the observational studies is shown in Figure 13. Over half of studies had a high risk of bias, due to lack of adjustment for confounding bias i.e. no adjusted data presented. Risk of conflict of interest was generally assessed as low. All included studies reported data which could be analysed as odds ratios and presented using forest plots.

Where data were available, three levels of comparison were used to assess the risk of RC according to EBF duration, namely ≥0-2 months vs. <0-2 months; ≥3-4 months vs. <3-4 months; ≥5-9 months vs. <5-9 months.

Main Findings

There was no consistent evidence of an association between EBF and risk of RC. In general there were only small numbers of studies with available data for each analysis, and several analyses were restricted to studies with high risk of bias. Two prospective RCT showed inconsistent and non-significant findings. We did find some evidence from observational studies that EBF ≥3-4 months may reduce odds of RC at age 0-4 OR 0.77 (0.60, 0.99) with no statistical heterogeneity (I^2=0%), but this was not supported by other data. One large

cohort study suggested increased odds of hayfever by age 44 in those EBF ≥3 months however such an effect was not supported by shorter term observations in intervention studies or cohort studies.

Table 4 Characteristics of included studies evaluating EBF duration and rhinoconjunctivitis

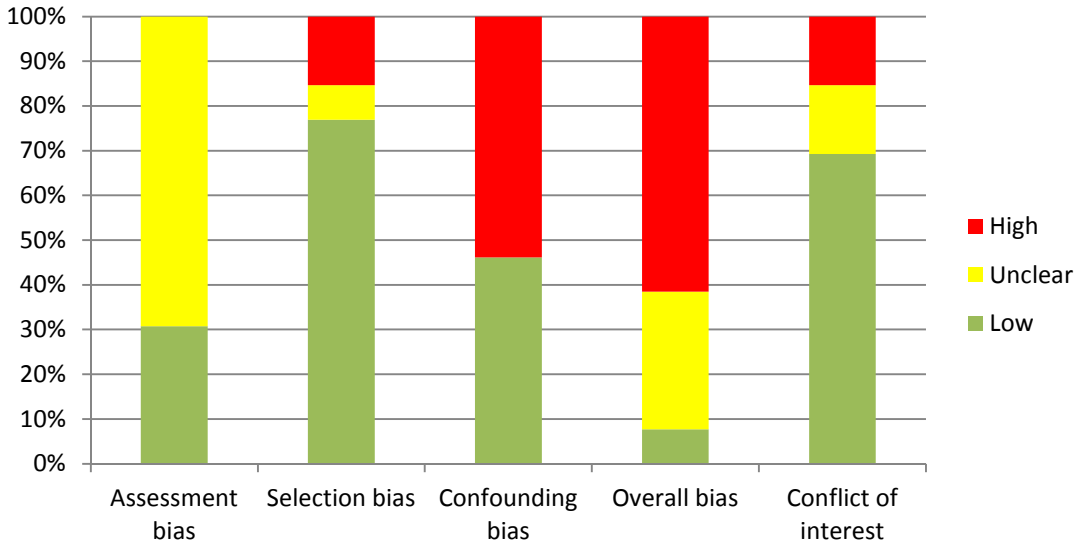
Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Kramer (25)	3584	SR of PC nested in RCTs	Finland/Belarus	-	ISAAC – current AR	5-7	Study #1: Infants of atopic parents Study #2: Healthy, term, breastfed newborns participating in a breastfeeding promotion trial.
Kajosaari, 1991(26)	135	PC	Finland		Parent report of pollen allergy	5	Solid food introduction at 6 months versus 3 months, in exclusively breastfed infants
Kellberger, 2012 (27)	3785/314	PC	Germany	Q	ISAAC - ever AR	9-18	SOLAR. Community based random sample of all pupils aged 9-11 years in 1995-1996 as part of ISAAC study, with follow-up survey 2002-2003
Kull, 2002 (3)	3791/263	PC	Sweden	Q	Parent reported RC symptoms	2	BAMSE. Population based cohort of children born between 1994-1996
Kramer, 2009 (28)	13889/455	PC nested in RCT	Belarus	I	ISAAC - current AR	6.5	PROBIT. Born 1996-1997
Siltanen,2003 (29)	285/53	PC	Finland	Q	Physician assessment	4	Infants recruited from maternal hospital born in 1994-1995

Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Strachan, 1996 (15)	11765/1932	PC	UK	I	DD	16	Population representative sample born in 1975
Matheson, 2007 (30)	5729/2610	PC	Australia	Q	Physician assessment	44	Tasmanian Asthma Study: population based cohort born in 1961
Van Asperen, 1983 (31)	79/44	PC	Australia	I	Physician assessment	1	Cohort recruited from medical service, born in 1980-1981 with family history of atopy
Arshad, 1992 (32)	1167/38	PC	UK	D/Q	Physician assessment	1	Isle of Wight Study. Population based birth cohort of infants born in semi-rural areas between 1989 and 1990
Marini, 1996 (13)	359	PC	Italy	Q	Physician assessment	3	Infants with family history of allergy whose mother agreed to participate in an allergy prevention program
Erkkola, 2012 (33)	2441/359	PC	Finland	D	ISAAC - current AR	5	DIPP study. Infants at high risk (HLA) for TIDM born between 1996-2004 invited to the allergy study 1998-2000
Ehlayel, 2008 (34)	1278	CS	Qatar	Q	ISAAC - AR ever	5	Children 0-5 years old attending primary healthcare centers for routine immunisation

Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Liu 2012 (35)	8733/397	CS	China	Q	ATS questionnaire	8	Sample of children from kindergarten and elementary schools in Shenyang
Miyake, 2003 (21)	6845/1340	CS	Japan	Q	ISAAC - current AR	15	12-15 year old children from all public junior high schools in Suita, Japan

Q: questionnaire, I: interview, R: medical records, D: diary, PC: prospective cohort, NCC: nested case control, CS: Cross-sectional, CC: case control, DD: doctor diagnosis of RC, in contrast to 'Physician assessment' where RC diagnosis was always made by a study physician as part of the study protocol.

Figure 13 Risk of bias in studies of EBF duration and rhinoconjunctivitis



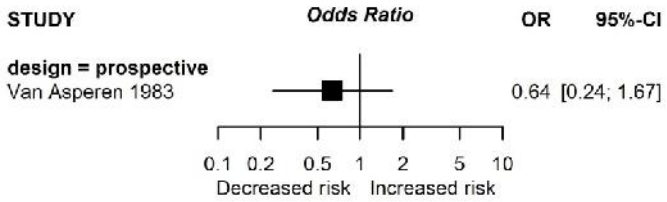
2.2 EBF duration and risk of rhinoconjunctivitis

2.3 EBF duration and risk of RC in children aged 0-4 years

2.3.1.1 EBF ≥0-2 months vs. <0-2 months

One prospective cohort study reported data that could be used to calculate OR for RC in the first year, in infants with EBF for ≥2 months vs. <2 months duration and is shown in Figure 14. The study found no significant association. The data are unadjusted, so carry a high risk of bias.

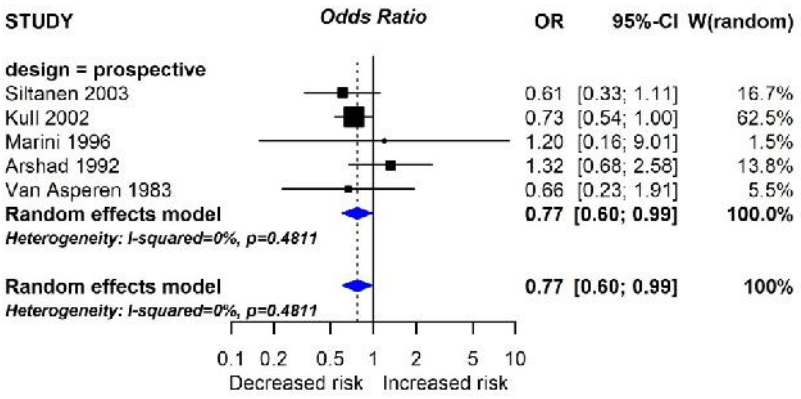
Figure 14 EBF ≥0-2 months vs. <0-2 months and RC risk at age 0-4



2.3.1.2 EBF ≥3-4 months vs. <3-4 months

Five prospective cohort studies reported data that could be used to calculate OR for RC at age 0-4, in infants with EBF for ≥3-4 months vs. <3-4 months duration and are shown in Figure 15. They show reduced odds of RC with longer EBF duration, with no statistical heterogeneity. The data from Arshad, Marini and Van Asperen are unadjusted, so carry a high risk of bias, but the data of Kull and Siltanen are adjusted.

Figure 15 EBF ≥3-4 months vs. <3-4 months and risk of RC at age 0-4 years



2.3.2 EBF and risk of RC in children aged 5-14 years

2.3.2.1 Systematic reviews and intervention trials

As shown in Table 5, the single systematic review found no evidence that increased duration of exclusive/predominant breastfeeding influences risk of RC at 6.5 years, although there was heterogeneity in findings, with one small study finding borderline evidence for reduced risk of RC RR 0.53 (0.28, 1.01), and a larger study showing no evidence of association.

Table 5 Promotion of increased EBF duration and risk of RC

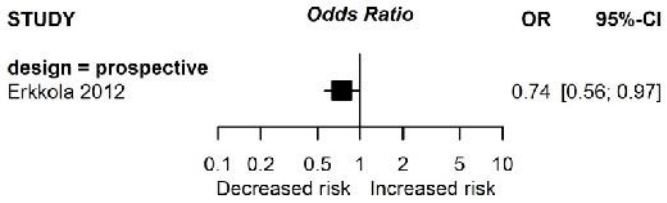
Study	Outcome measure	No. participants (studies)	Outcome (95% CI)
Kajosaari 1991 (26)	Pollen allergy at 5 years	113 (1)	RR 0.5 (0.3, 1.0)
Kramer 2007 (2)	Allergic rhinoconjunctivitis at age 6.5 years using ISAAC questionnaire	17,046 (1)	RR 1.1 (0.6, 1.9)

Data for Kajosaari 1991 are taken from the systematic review of Kramer 2012 (25).

2.3.2.2 EBF ≥0-2 months vs. <0-2 months

One prospective cohort study reported data that could be used to calculate OR for RC at age 5-14, in infants with EBF for ≥0-2 months vs. <0-2 months duration and is shown in Figure 16. The study found reduced odds of RC with EBF duration of >3months vs. <1 month (Figure 18) and a trend to reduced RC with longer EBF when all 3 categories (<1 month, 1-3 months, >3 months) were considered (P=0.093). The data carry a high risk of bias because they are unadjusted.

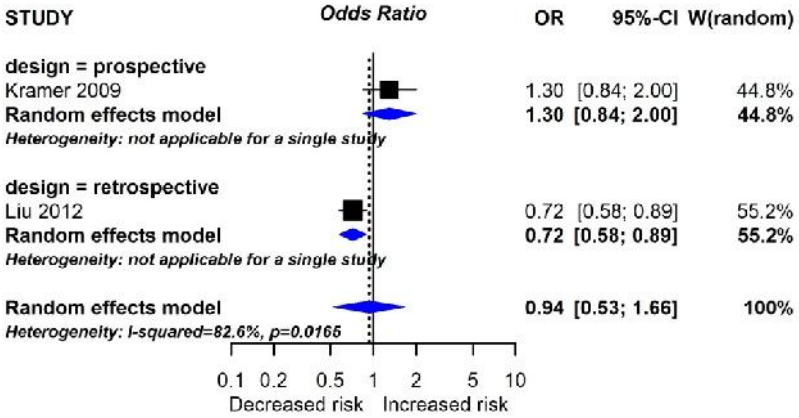
Figure 16 EBF ≥0-2 months vs. <0-2 months and risk of RC at age 5-14 years



2.3.2.3 EBF ≥3-4 months vs. <3-4 months

Two observational studies reported data that could be used to calculate OR for RC at age 5-14, in infants with EBF for ≥3-4 months vs. <3-4 months duration are shown in Figure 17. Data were not pooled due to extreme statistical heterogeneity (I^2 >80%). The cross-sectional study of Liu found reduced odds of RC with EBF duration of >3months vs. <3 months but data were unadjusted so carry a high risk of bias. The prospective cohort study of Kramer presented adjusted data showing no association when comparing EBF for >6 months with <3 months (data shown in Figure 17) but found increased odds of RC with EBF 3-6 months vs <3 months (OR 1.3 95%CI 1.1, 1.5).

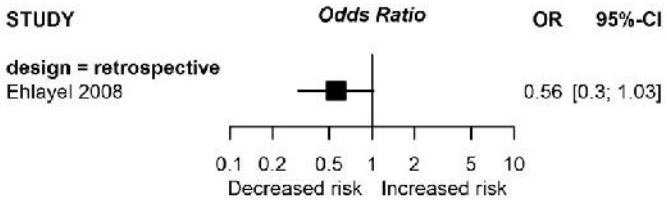
Figure 17 EBF ≥3-4 months vs. <3-4 months and risk of RC at age 5-14 years



2.3.2.4 EBF ≥5-7 months vs. <5-7 months

One cross-sectional study reported OR for RC at age 5, in children EBF for ≥6 months vs. <6 months duration and is shown in Figure 18. There were reduced odds of RC with prolonged EBF duration, but this did not reach statistical significance. The study reported unadjusted data, and therefore carries a high risk of bias.

Figure 18 EBF ≥5-7 months vs. <5-7 months and risk of RC at age 5-14 years

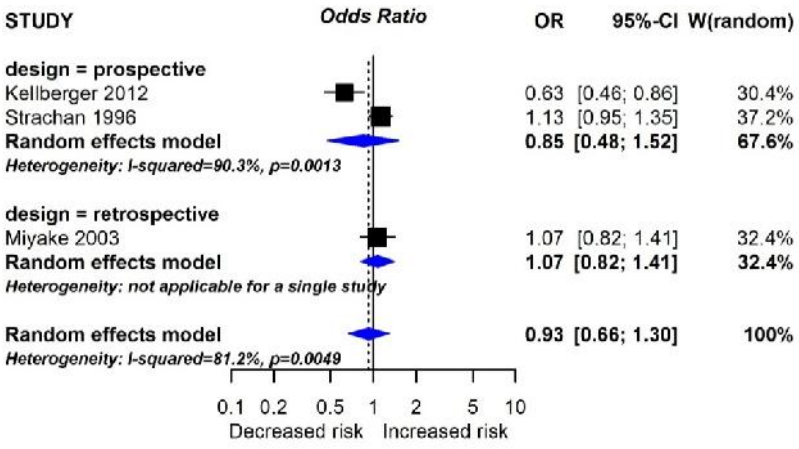


2.3.3 EBF and risk of RC in children aged 15+ years

2.3.3.1 EBF ≥0-2 months vs. <0-2 months

Two prospective cohort studies (Strachan, Kellberger) and one cross-sectional study reported OR for RC at age 15+, in infants with EBF for ≥0-2 months vs. <0-2 months duration and are shown in Figure 19. Data were not pooled due to extreme heterogeneity (I^2 >80%). The study of Kellberger reported adjusted data showing reduced odds of RC with prolonged EBF beyond 2 months; the studies of Miyake and Strachan reported adjusted and unadjusted data respectively, showing no association between EBF duration and RC risk.

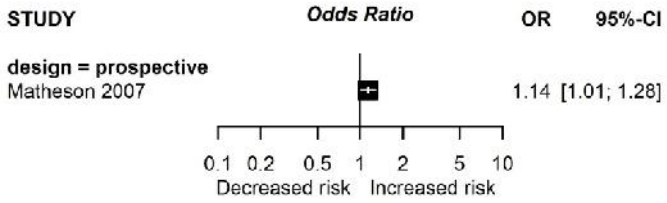
Figure 19 EBF ≥0-2 months vs. <0-2 months and risk of RC in children aged 15+ years



2.3.3.2 EBF ≥3-4 months vs. <3-4 months

One prospective cohort study reported data that could be used to calculate OR for RC at age 44, in infants with EBF ≥3-4 months vs. <3-4 months duration and is shown in Figure 20. There were significantly increased odds of self-reported hayfever in adults who had received longer duration of EBF. The data were appropriately adjusted, but the study was considered at unclear risk of bias due to inadequate definition of EBF, which was assessed retrospectively through parental report at aged 7 years.

Figure 20 EBF ≥3-4 months vs. <3-4 months and risk of RC at age 15+ years



2.4 Data for EBF duration and RC that couldn't be meta-analysed

All included studies reported OR that have been presented as forest plots – there were no further data of note for EBF duration and RC risk.

3 Solid Food Introduction and Rhinoconjunctivitis

3.1 Overall characteristics of studies, risk of bias and summary of results

Table 6 describes the main characteristics of the studies analysed in this report. A total of 6 prospective cohort studies and no intervention studies, reported the association between timing of solid food introduction (SF) and risk of RC. The studies were from Europe (n=4), USA (n=1) and Australia (n=1). Overall, valid data on SF and RC risk were available from over 8000 subjects. Information on RC was obtained from a medical assessment in 3 studies, via parental report in 3 studies. With regards to time of outcome diagnosis, 3 studies explored the association between SF and RC in the first 4 years of life, when allergic RC can be difficult to distinguish from infectious RC, and 3 studies assessed at age 5-14. Five studies used a questionnaire +/- diary to assess the exposure (SF), 1 used an interview.

Risk of bias is summarised in Figure 21. Half of studies had a high risk of bias, due to lack of adjustment for confounding bias i.e. no adjusted data presented. Four of six studies had unclear risk of assessment bias. Risk of conflict of interest was generally assessed as low.

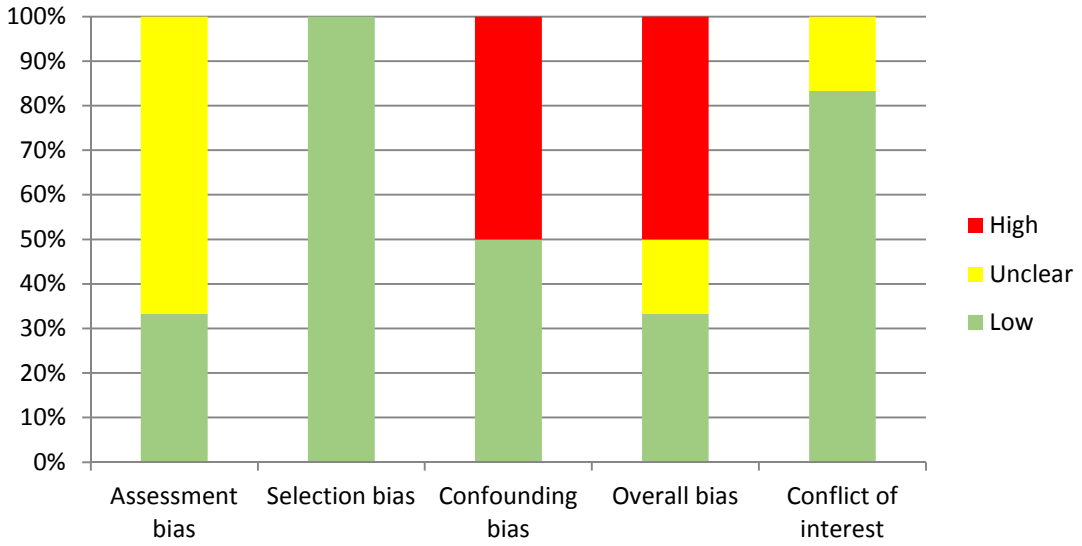
The risk of RC according to SF was categorised as ≥3-4 months vs. <3-4 months. Overall the evidence base was limited due to small numbers of included studies. We found no evidence that the timing of solid food introduction is associated with risk of RC, based on the available data.

Table 6 Characteristics of included studies evaluating SF introduction and rhinoconjunctivitis

Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Larsson, 2008 (8)	4779/573 (in 2000), 975(in 2005)	PC	Sweden	Q	ISAAC - current AR	9	DBH study. Preschool children aged 1–6 years surveyed in 2000 and 2005.
Zutavern, 2008 (36)	2073/83	PC	Germany	Q	DD	6	LISA study. Population based birth cohort of infants born 1997-1999 at selected maternity hospitals in 4 German cities
Marini, 1996 (13)	359	PC	Italy	Q	Physician assessment	3	Infants with family history of allergy whose mother agreed to participate in an allergy prevention program
Hide, 1981 (16)	843/198	PC	UK	D/Q	Parent reported rhinitis symptoms	1	The Isle of Wight study: born in 1977-1978
Wright, 1994 (17)	747/313	PC	USA	Q	Parent reported AR	6	Tuscon Children's Respiratory Study: Healthy newborn infants recruited from local health maintenance organisation born in 1980-1984
Van Asperen, 1983 (31)	79/44	PC	Australia	I	Physician assessment	1.3	Cohort recruited from medical service, born in 1980-1981 with family history of atopy

Q: questionnaire, I: interview, R: medical records, D: diary, PC: prospective cohort, NCC: nested case control, CS: Cross-sectional, CC: case control, DD: doctor diagnosis of RC, in contrast to 'Physician assessment' where RC diagnosis was always made by a study physician as part of the study protocol.

Figure 21 Risk of bias in studies of SF introduction and rhinoconjunctivitis

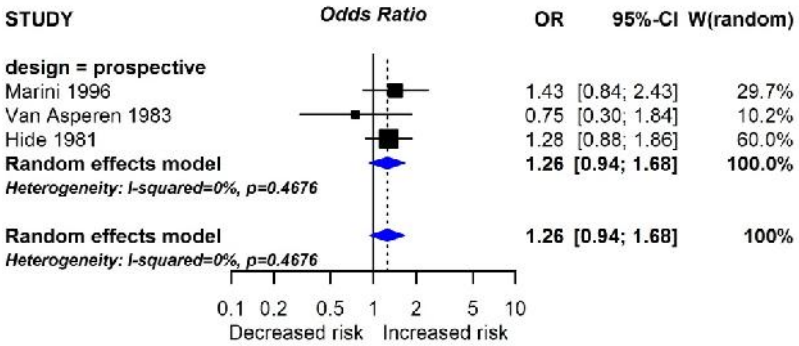


3.2 SF introduction and risk of rhinoconjunctivitis

3.2.1 SF introduction and risk of RC in children aged 0-4 years

Three prospective cohort studies reported OR for RC at age 0-4, in infants with SF ≥3-4 months vs. <3-4 months and are shown in Figure 22. There was no significant association found. The study of Marini reported adjusted data at age 3 and had overall unclear risk of bias due to unclear assessment bias; the other two studies reported unadjusted data at age 1, and are therefore at high risk of confounding bias.

Figure 22 SF ≥3-4 months vs. <3-4 months and RC risk at age 0-4

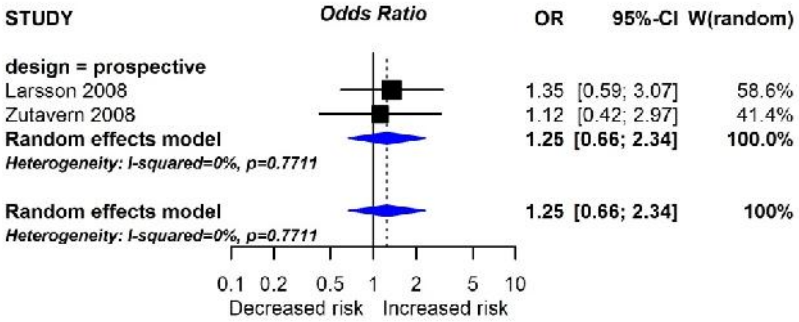


3.2.2 SF introduction and risk of RC in children aged 5-14 years

Two prospective cohort studies reported OR for RC at age 5-14, in infants with SF ≥3-4 months vs. <3-4 months and is shown in Figure 23. There was no significant association found. The study of Zutavern reported adjusted data at age 6 and had overall low risk of bias;

the study of Larsson reported unadjusted data but also stated that there was no significant relationship between SF introduction and RC in adjusted analyses, and had overall low risk of bias.

Figure 23 SF ≥3-4 months vs. <3-4 months and RC risk at age 5-14 years



3.3 Data for SF introduction and RC that couldn't be meta-analysed

Meta-analyses included 5 studies, reporting data on ~ 900 participants with RC. One further study reporting RC in over 300 participants reported no relationship between timing of SF introduction and RC (Table 7).

Table 7 Studies of SF introduction and RC which were not eligible for meta-analysis

Study	Design	Age	N/n cases	Data	Measure	TBF in no AR	TBF in AR	P
Wright, 1994 (17)	PC	6	747/313	Continuous	No relationship between timing of solid food introduction and RC			

4 Conclusion

This report summarises the results of 26 studies investigation the association between total and exclusive breastfeeding duration, timing of solid food introduction and risk of rhinoconjunctivitis. The majority of studies were prospective cohort studies, with one systematic review and one intervention trial. Overall we found no clear evidence to support an association between TBF duration, and RC risk at any age. The data from the intervention trial showed no evidence that promotion of longer TBF duration influences risk of RC – OR 1.1 (95% CI 0.6, 1.9),.One meta-analysis of observational studies found reduced risk of RC at ages 0-4 years associated with EBF ≥3-4 months vs <3-4 months with no statistical heterogeneity, based largely on 2 prospective cohort studies reporting adjusted data. However, statistical significance was borderline, and we were unable to confirm this association using other cutoffs for EBF duration. At other ages there was no association between EBF duration and RC risk. Data for timing of SF introduction and RC risk were limited, but the available data do not support an association between timing of SF introduction and RC.

The possible relationship between EBF duration and RC risk at age 0-4 years makes some physiological sense, and is consistent with findings from the systematic review of Kramer, who evaluated EBF duration in relation to a range of child health outcomes and found some evidence for reduced nasal symptoms with longer EBF duration (25). Most RC in this age group is infective rather than allergic in origin and distinction of the two can be difficult in epidemiological studies. Breastfeeding duration is known to be associated with reduced risk of respiratory and gastrointestinal infections during infancy, so the possible association here may reflect a protective effect of human breast milk through the high immunoglobulin content which is thought to mediate the effects on other infections. The quality of data was limited, especially for analysis of timing of solid food introduction in relation to RC, and more research is needed to clarify whether there is an effect of different infant feeding regimens on upper airway and ocular health.

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BREASTFEEDING, SOLID FOOD INTRODUCTION AND RISK OF ECZEMA

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1 Total breastfeeding duration and eczema

1.1 Overall characteristics of studies, risk of bias and summary of results

Table 1 describes the main characteristics of the studies that assessed total breastfeeding duration (TBF) in relation to eczema/atopic dermatitis (AD) risk. In this report AD or eczema refers to any eczema/atopic dermatitis, and 'atopic AD' refers to eczema in association with evidence of IgE sensitisation to dietary or inhalant allergens. A total of 1 cluster randomised controlled trial and 57 observational studies, reported the association between TBF and AD. Of these, 43 were prospective cohort studies, 1 retrospective cohort study, 1 nested case-control study, 3 case control studies, and 9 cross-sectional studies. The majority of studies (n=40) are from Europe – others are from Asia (n=7), North America (n=3) and Australasia (n=3), Africa (n=1), Middle East (n=1) and worldwide (n=2). Overall, valid data on TBF duration in the first 2 years of life and AD risk were available from over 250,000 subjects. Information on AD was obtained from a medical assessment (n=23), parental report (n=15), Hanifin and Rajka criteria or modifications of these (n=8), the ISAAC questionnaire (n=9), self-report (n=1) and unclear methodology (n=1). With regards to time of outcome diagnosis, 33 studies explored the association between TBF duration and AD at age 0-4, 18 at ages 5-14, and six at age 15 and over. For assessment of TBF duration, 10 studies used an interview, 8 parent diaries, and 4 a medical records review; in one study the method of exposure assessment was unclear and in all others (n=24) a questionnaire method was used.

Risk of bias was assessed using the NICE Methodological checklists for cohort and case-control studies. Figure 1 illustrates the distribution of bias across the five main methodological areas of the studies. Approximately 30% of studies had a high risk of bias due to lack of adjustment for confounding bias i.e. no adjusted data presented, and a further 10-15% had a high risk of selection bias. Risk of conflict of interest was generally assessed as low.

Where data were available, five levels of comparison were used to assess the risk of AD according to TBF duration, namely 'ever vs. never', '≥1-2 months vs. <1-2 months', '≥3-4 months vs. <3-4 months', '≥5-7 months vs. <5-7 months', and '≥8-12 months vs. <8-12 months'.

Main Findings

In the single intervention trial there was LOW certainty evidence (-1 imprecision; -1 inconsistency) of a relationship between breastfeeding promotion and reduced risk of AD in the first year of life; OR 0.54 (95% CI 0.31, 0.95). This effect was not seen at later follow up at age 6-7 years. For observational studies, across all cut-offs where data were available, there was no consistent evidence of a relationship between risk of AD and initiation or prolongation of BF. There was weak evidence that ever BF may be associated with increased AD risk at age 0-4 years; OR 1.15 (1.00, 1.32; I^2=57%). This was not the case in the subgroup of studies with low risk of bias, prospective study design, or adjusted data analysis. Studies which could not be included in meta-analysis, which represented over 16,000 participants in 16 studies, almost universally found no evidence of a relationship between TBF duration and AD.

Table 1 Characteristics of included studies evaluating TBF duration and eczema

Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Kramer, 2001 (1); Kramer, 2007 (2)	8865/ 8181	Cluster RCT	Belarus	-	SPT-Aero	6.5	Breastfeeding promotion program based on the WHO/UNICEF baby friendly hospital initiative, versus standard local breastfeeding policies
Hesselmar, 2010 (3)	184	PC	Sweden	I	UK Working Party Criteria	1.5	ALLERGYFLORA study. Population based study of babies selected from antenatal clinics between 1998 and 2003 - mainly high risk of allergic disease
Abd, 2012 (4)	Unclear	PC	UK	Q	Visible flexural dermatitis; Parent reported eczema	3.5, 7.5	ALSPAC study. Population based cohort of children born 1991-1992.
Purvis, 2005(5)	550	PC	New Zealand	Q	UK Working Party Criteria	3.5	Auckland Birthweight Collaborative study. Birth cohort with representative sample of babies born in 1996-1997
Kull, 2002(6)	3790	PC	Sweden	Q	Parent reported OR DD eczema	2	BAMSE study. Population based cohort of children born between 1994-1996
Berth-Jones, 1997 (7)	413	PC	UK	Q	Physician assessment	1	Infants born in 1992 and registered with the two major Leicester obstetric units
Taylor, 1984 (8)	14498	PC	UK	I/Q	Parent reported eczema	5, 6, 7	British Cohort Studies of children born in England and Wales in 1946; England, Scotland and Wales in 1958 and 1970

Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Taylor, 1983 (9)	10886	PC	UK	I	Parent reported eczema	5	CHES study. Population based cohort of children born in England, Scotland, and Wales in 1970
Burr, 1989; Burr, 1993; Burr, 1993 (b) (10-12)	483	PC	UK	D, Q	Physician assessment	1, 7	Infants with family history of allergic diseases in South Wales
Businco, 1987(13)	244	PC	Italy	I	Physician assessment	8	Infants of atopic parents recruited from hospital and born in 1985-1988
Mihrshahi, 2007 (14)	516	PC	Australia	I	Visible flexural dermatitis OR DD eczema	5	CAPS study. Infants born in 1997-1999 with family history of asthma or wheezing
Bisgaard, 2009 (15)	354	PC	Denmark	Q	Hanifin and Rajka criteria	3	COPSAC study. Infants of mothers with a history of doctor-diagnosed asthma, recruited from August 1998 to December 2001.
Larsson, 2008 (16)	4779	PC	Sweden	Q	ISAAC	9	DBH study. Preschool children aged 1–6 years surveyed in 2000 and 2005.
Devereux, 2006 (17)	1704	PC	UK	Q	ISAAC	5	Population based birth cohort of infants born in 1998
Nwaru, 2013(18)	3109	PC	Finland	D	ISAAC	0.5	DIPP study. Infants at high risk (HLA) for TIDM born between 1996-2004 invited to the allergy study between 1998 and 2000

Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Farooqi, 1998 (19)	1453	PC	UK	R	DD	16	Representative sample of general practice born in 1975-84
Forster, 1990(20)	145	PC	Germany	Q	Parental report	1.5	Babies hospitalised in 1985
Harris, 2001(21)	622	PC	UK	I	UK Working Party Criteria	2	Population based birth cohort of children born between 1993 and 1995 in three general practices in Ashford
Hikino, 2001(22)	21766	PC	Japan	Q	Physician assessment	1.5	All children born in 1993-1995 attending Well-baby check-ups funded by Fukuoka City
Howie, 1990(23)	618	PC	UK	R/D	Physician assessment	1	Population based birth cohort of infants born between 1983 and 1986 in Dundee
Gruskay, 1982 (24)	908	PC	USA	Q	Physician assessment	3, 5, 15	Children born in 1961-1966 in a private paediatric practice
Alm, 2008 (25)	4941	PC	Sweden	Q	Parent reported eczema	1	Infants of Western Sweden. Population birth cohort of infants born in 2003
Morales, 2012 (26)	467	PC	Spain	Q/I	Parent reported eczema	1	INMA project. Population based birth cohort of infants born 2004-2006

Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Kemeny, 1991(27)	180	PC	UK	Unclear	Unclear	1	Population based birth cohort of infants born at Dulwich and King's College Hospitals in London
Snijders, 2007; Snijders, 2008(28, 29)	2510/ 783	PC	Netherlands	Q	Parent reported eczema	2	KOALA study. Population based birth cohort of infants born between 2000-2002 (conventional and anthroposophic lifestyle)
Wetzig, 2000(30)	475	PC	Germany	Q	Physician assessment	1	LARS study. High allergy risk or low birth weight children born within one year in the City and District of Leipzig
Marini, 1996 (31)	279	PC	Italy	Q	Physician assessment	1	Infants with family history of allergy whose mother were proposed to participate in an allergy prevention program
Miskelly, 1988(32)	482	PC	UK	D	Physician assessment	1	Infants from antenatal clinics with family history of allergy randomised into a dietary intervention program
Moore, 1985(33)	475	PC	UK	D/I	Physician assessment	0.25	Infants born in a hospital in 1979-1980 with family history of eczema or asthma, participating in a dietary intervention program
Morgan, 2004; Morgan, 2004 (b) (34, 35)	257	PC	UK	I	Parent reported eczema; Physician assessment	1, 1.5	Infants from five prospective randomised dietary trials conducted in the UK between 1993 and 1997. One LBW, 2 premature and 2 appropriate weight/gestation cohorts
Bergmann, 2000; Bergmann,	1314	PC	Germany	Q/I	Physician assessment; Hanifin and Rajka criteria	6, 7	MAS study. Atopic risk enriched cohort of infants born in 1990 in 5 German cities

Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
2002(36, 37)							
Silvers, 2009 (38)	987	PC	New Zealand	Q	Parent reported eczema	1	New Zealand Asthma and Allergy Cohort Study. Population based birth cohort of infants born between 1997 and 2001
Miyake, 2009(39)	763	PC	Japan	Q	Physician assessment	2	OMCHS study. Population based birth cohort of infants born in 2002-2003
Kerkhof, 2003(40)	304	PC	Netherlands	Q	UK Working Party Criteria	1	PIAMA: population-based born in 1996-1997 (normal risk of disease)
Porch, 1998(41)	130	PC	USA	D	ISAAC - current AD	1	Infants recruited from prenatal services with family history of allergy (high risk of disease)
Pratt, 1984(42)	198	PC	UK	D/I	DD; Physician assessment	4.5, 5	Recruited in antenatal clinics, normal risk of disease
Rothenbacher, 2005(43)	803	PC	Germany	Q/I	DD	2	Recruited from university service, born in 2000-2001 (normal risk of disease)
Ruiz 1992(44)	39	PC	UK	Unclear	Hanifin and Rajka criteria	1	Recruited from hospital and family history of atopy (high risk of disease)

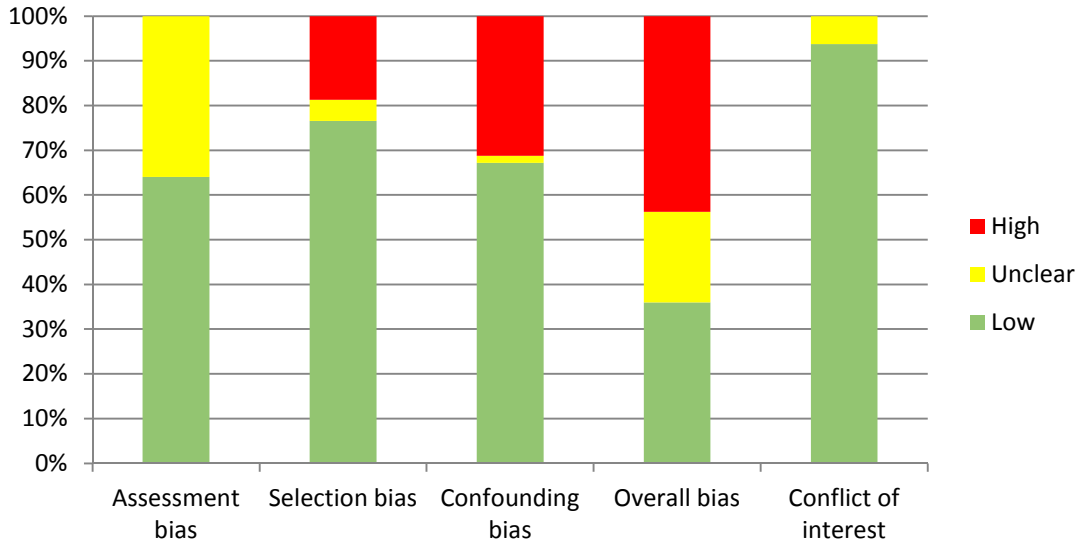
Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Saarinen, 1995(45)	150	PC	Finland	R	Parent reported OR DD eczema	5, 17	Recruited from hospital and born in 1975 (normal risk of disease)
Chuang, 2011(46)	18773	PC	Taiwan	R/I	Physician assessment	1.5	Taiwan Birth Cohort Study: population representative sample born in 1995 (normal risk of disease)
Hide, 1981(47)	843	PC	UK	D/Q	DD	1	The Isle of Wight study: born in 1977-1978 (normal risk of disease)
Wang, 2007(48)	1760	PC	Taiwan	Q	DD	0.5	Tiawan National Birth Cohort Study: population representative sample born in 2003 (normal risk of disease)
Zutavern, 2004(48)	604	PC	UK	I	DD	5.5	Cohort recruited from general practices and born in 1993-1995 (normal risk of disease)
Hagendorens, 2005; Sariachvili, 2007(49, 50)	976	PC	Belgium	Q	Parent reported eczema	1	PIPO study: recruited from university service, born 1997-2001 (normal risk of disease)
Sariachvili 2010 (51)	557	NCC	Belgium	Q	ISAAC	4	PIPO: nested case control study within the PIPO cohort
Monego, 1989(52)	144	RC	Italy	D	DD	4	144 Italian infants retrospectively followed to examine association between breastfeeding and allergic diseases

Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Kramer, 1981 (53)	470	CC	Canada	I	Hanifin and Lobitz criteria	<20	Cases and controls were1 month to 20 years old children attending dermatology clinics visits
Ghaderi, 2014 (54)	200	CC	Iran	I	DD	5	Unclear source of population. Sex and age matched controls
Haileamlak, 2005 (55)	732	CC	Ethiopia	I	ISAAC	5	Children age 1- 5 years. Cases were defined according to the ISAAC criteria for AD and confirmed by clinical examination
Flohr, 2011 (56)	51, 119	CS	Worldwide	Q	Parent reported eczema	12	ISAAC Phase 2. Schoolchildren aged 8–12 years from 27 centres in 21 affluent and nonaffluent countries
Civelek, 2001(57)	1533	CS	Turkey	Q	ISAAC	11	Representative sample of schoolchildren in 5 cities
Nakamura, 1999(58)	3850	CS	Japan	Q	DD	3	All 3 year old children participating in a health check-up in 1997
Tanaka, 2009(59)	1957	CS	Japan	Q	ISAAC - current AD	3	Fukuoka Child Health Study. All 3-year old children examined at public public health centre's in Fukuoka city
Girolomoni,2003(60)	1369	CS	Italy	Q	UK Working Party Criteria	9	Representative sample of children attending the fourth grade at elementary school

Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Björkstén, 2011(61)	103716	CS	Worldwide	Q	ISAAC - AD ever	7	ISAAC Phase 3: Schoolchildren aged 6-7 years from different countries and geographic regions
Karino, 2008(62)	9615	CS	Japan	Q	Self-reported AD	18	University students aged 18–19 years enrolled from 2003 through 2005.
Kurt, 2007 (63)	25843	CS	Turkey	Q	Parent reported current eczema	15	Prevalence and Risk Factors of Allergies in Turkey (PARFAIT): population representative sample of children aged 9-15 years old (normal risk of disease0
Selcuk, 1997 (64)	5412	CS	Turkey	Q	Parent reported current eczema	12	Children 7-12 yrs. from 18 primary schools (normal risk of disease)

Q: questionnaire, I: interview, R: medical records, D: diary, PC: prospective cohort, RC: retrospective cohort, NCC: nested case-control, CC: case-control, CS: Cross-sectional, AD: eczema, DD: doctor diagnosis of AD, in contrast to 'Physician assessment' where AD diagnosis was always made by a study physician as part of the study protocol.

Figure 1 Risk of bias in studies of TBF duration and eczema



1.2 Total breastfeeding duration and eczema

The single intervention trial of a breastfeeding promotion intervention was rated as having a low risk of bias on all domains, and a low risk of conflict of interest. Kramer found reduced odds of AD at age 1 year – cluster adjusted odds ratio 0.54 (95% CI 0.31, 0.95). This outcome was an unblinded assessment of AD by study paediatricians, and the authors reported poor agreement between sites in the outcome measure. The effect on AD was not seen at later follow-up in the same trial at age 6.5 years (OR 1.0 95% CI 0.50, 1.80). Certainty of evidence was downgraded for imprecision (wide confidence intervals) and for inconsistency with later outcome data and with the findings of observational studies. All other evidence was derived from observational studies.

1.2.1 TBF and risk of eczema in children aged 0-4 years

1.2.1.1 TBF Ever vs. Never

Figure 2 shows the outcomes of 20 eligible observational studies reporting OR for TBF never vs ever and AD. The pooled data show increased risk of AD in breastfed infants, with borderline statistical significance and high heterogeneity (I^2=57%). The outlier study of Purvis had very few participants in the reference group of never breastfed (n=26, including just 3 cases of AD), which may account for the extreme OR and wide confidence intervals.

A Funnel plot to explore publication bias is shown in

Figure 3, and shows no clear evidence of publication bias.

Subgroup analyses are shown in Table 2. Here we did not find clear subgroup differences, but there was a trend to different outcome according to risk of allergic disease. Those children with no increased risk of allergic disease (i.e. not selected for family history of allergic problems) had the strongest association between TBF initiation and increased AD. Heterogeneity was high (I^2=53%).

Analysis of dose-response relationship, using studies with short, medium or long duration/cut-off for the exposed group, with 'never BF' as reference group, showed some evidence of a dose-response relationship between TBF and AD although with moderate to high heterogeneity in each analysis (Figure 4 and 5).

Figure 2 TBF Ever vs. Never and risk of eczema at age 0-4 years

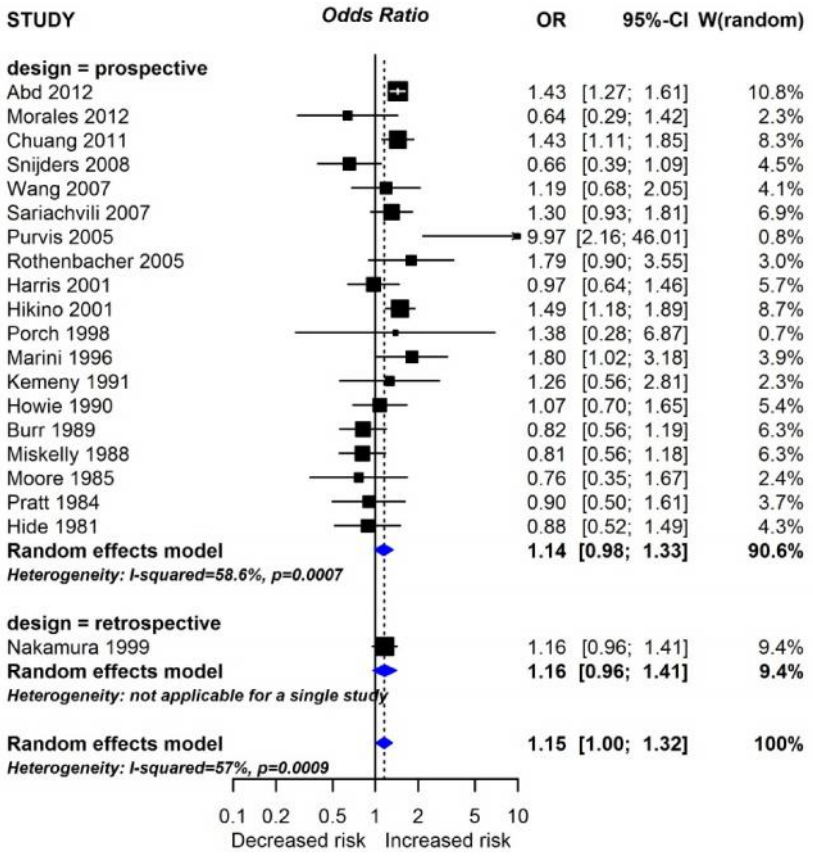
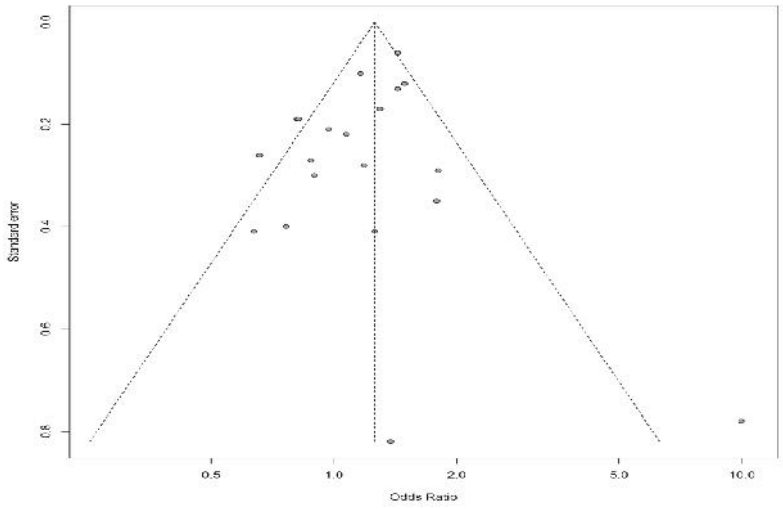


Figure 3 Risk of publication bias in studies investigating TBF Ever vs. Never and risk of eczema in children aged 0-4 years



Egger's test p-value = 0.116

Table 2 Subgroup Analyses of risk of atopic dermatitis and TBF Ever vs. Never in children aged 0-4 years

	Number of studies	OR [95% CI]	I^2 (%)	P-value for between group difference
Overall	20	1.15 [1.00; 1.32]	57.0	
Adjusted	7	1.17 [0.87; 1.57]	70.1	Not tested
Unadjusted	19	1.78 [1.03; 1.35]	58.3	
Study Design – Prospective	19	1.14 [0.98; 1.33]	58.6	0.90
Study Design – Retrospective	1	1.16 [0.96; 1.41]	-	
Risk of disease – High	5	0.97 [0.70; 1.34]	40.0	0.22
Risk of disease – Normal	15	1.21 [1.05; 1.39]	53.0	
Risk of bias – Low	7	1.02 [0.80; 1.32]	55.8	0.23
Risk of bias – High/Unclear	13	1.22 [1.04; 1.44]	54.3	

Figure 4 TBF short duration (1-3 months) vs. never and risk of eczema at age 0-4 years

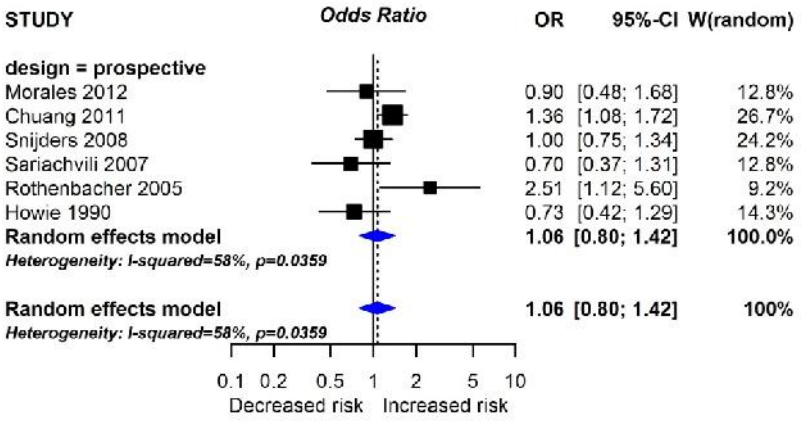


Figure 5 TBF medium duration (4-6 months) and risk of eczema at age 0-4 years

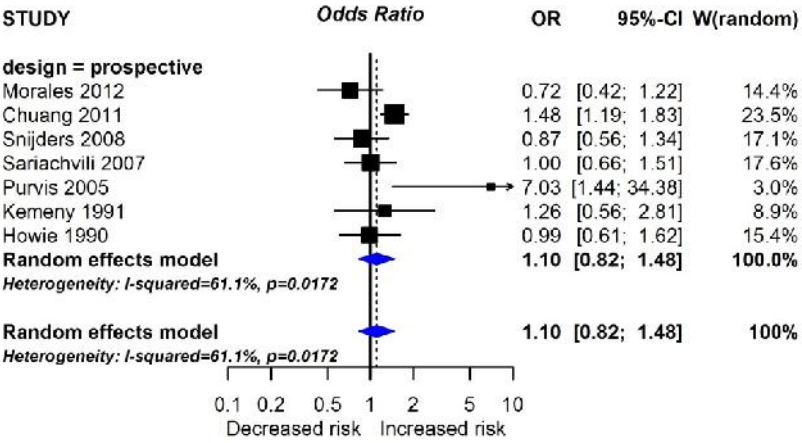
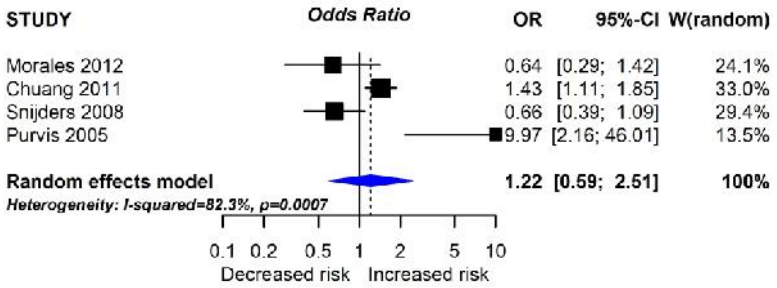


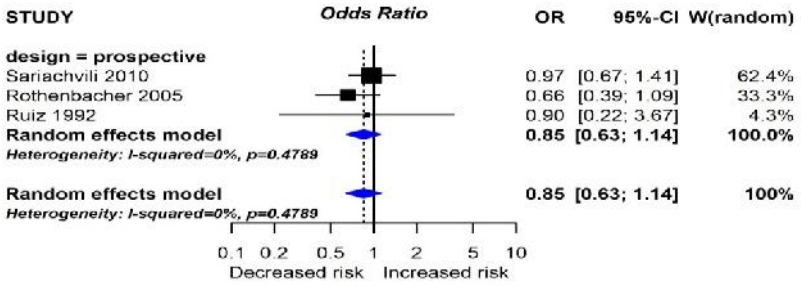
Figure 6 TBF long duration (≥7-12 months) and risk of eczema at age 0-4 years



1.2.1.2 TBF ≥3-4 months vs. <3-4 months

One nested case control study and two prospective cohort studies reported data that could be pooled to calculate OR for AD, in infants with TBF for ≥3-4 months vs. <3-4 months duration and are shown in Figure 7. They show no evidence of association between TBF and AD risk, with low statistical heterogeneity. All studies report unadjusted data, so carry a high risk of confounding bias.

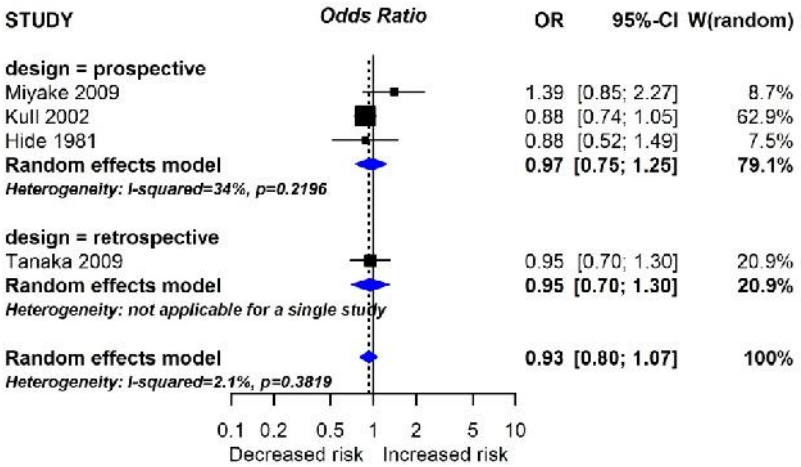
Figure 7 TBF ≥3-4 months vs. <3-4 months and risk of eczema at age 0-4 years



1.2.1.3 TBF ≥5-7 months vs. <5-7 months

One cross-sectional and three prospective cohort studies reported data that could be pooled to calculate OR for AD, in infants with TBF for ≥5-7 months vs. <5-7 months duration and are shown in Figure 8. They show no evidence of association between TBF and AD risk, with low statistical heterogeneity. Three of the four studies report adjusted data, and the study of Hide reported unadjusted data.

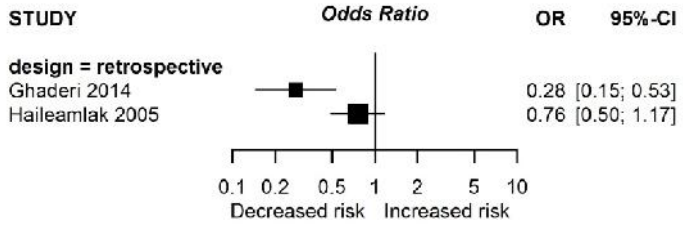
Figure 8 TBF ≥5-7 months vs. <5-7 months and risk of eczema at age 0-4 years



1.2.1.4 TBF ≥8-12 months vs. <8-12 months

Two case-control studies reported data that could be pooled to calculate OR for AD, in infants with TBF for ≥12 months vs. <12 months duration and are shown in Figure 9. Due to extreme statistical heterogeneity (I^2= 84.6%) we did not undertake pooled analysis. The study of Haileamlak reported adjusted data, and the study of Ghaderi reported unadjusted data.

Figure 9 TBF ≥8-12 months vs. <8-12 months and risk of eczema at age 0-4 years



1.2.2 TBF and risk of eczema in children aged 5-14 years

1.2.2.1 TBF Ever vs. Never

Figure 10 shows the outcomes of 13 eligible observational studies reporting OR for TBF never vs ever and AD at age 5-14 years. The pooled data show association between breastfeeding and risk of AD, but with extreme statistical heterogeneity (I^2=79%). The analysis was dominated by the ISAAC phase II and III surveys published in 2011, and the British Birth Cohorts published in 1984. A Funnel plot to explore publication bias is shown in Figure 11. There is no asymmetry, and Egger's test does not suggest clear evidence of publication bias.

Subgroup analyses are shown in Table 3. Here we did not find clear subgroup differences, but of note the studies at low overall risk of bias, using prospective study design and reporting adjusted data found least evidence of an association between TBF any vs never and AD risk, compared with studies at high risk of bias, with retrospective design or reporting unadjusted data. However all subgroup analyses had moderate, high or extreme levels of statistical heterogeneity.

Analysis of dose response, with forest plots for never versus short, medium and long duration/cut-off of TBF showed no evidence of a dose-response relationship between TBF duration and risk of AD at age 5-14 years (Figure 12, Figure 13, and Figure 14).

Figure 10 TBF Ever vs. Never and risk of eczema at age 5-14 years

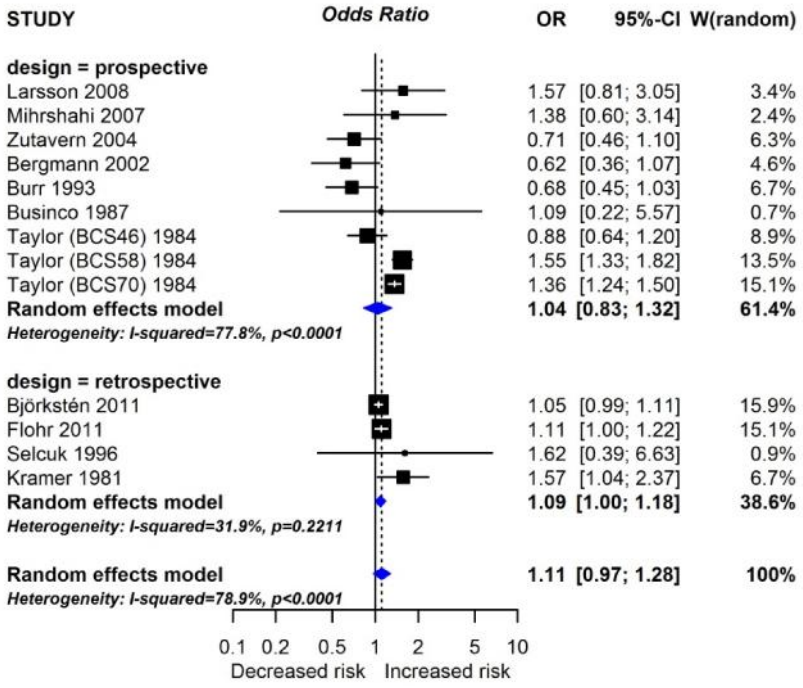
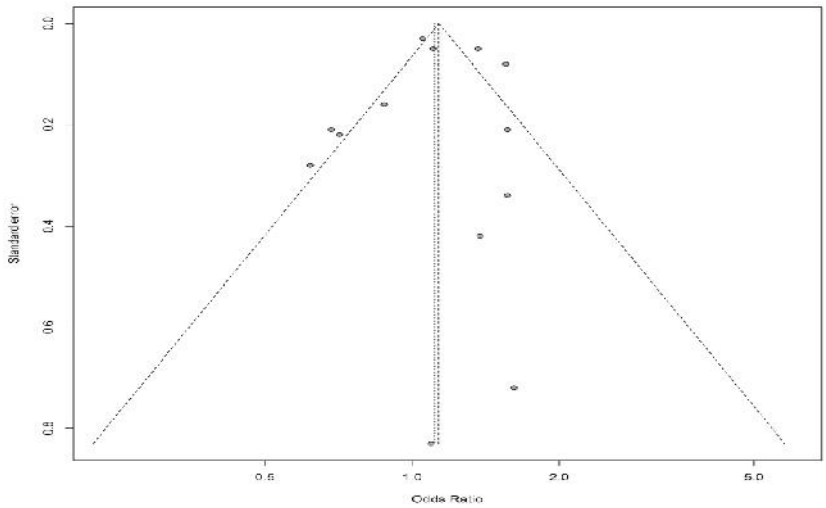


Figure 11 Risk of publication bias in studies investigating TBF and risk of eczema in children aged 5-14 years



Egger's test p-value = 0.139

Table 3 Subgroup analyses of risk of eczema and TBF Ever vs. Never in children aged 5-14 years

	Number of studies	OR [95% CI]*	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted used)	13	1.11 [0.97; 1.28]	78.9	
Adjusted	6	1.04 [0.93; 1.15]	40.9	Not tested
Unadjusted	9	1.17 [0.94; 1.44]	75.6	
Study Design – Prospective	9	1.04 [0.83; 1.31]	77.8	0.72
Study Design – Retrospective	4	1.09 [1.00; 1.18]	31.9	
Risk of disease – High	3	0.84 [0.54; 1.31]	15.7	0.20
Risk of disease – Normal	10	1.14 [1.00; 1.32]	82.3	
Risk of bias – Low	7	0.95 [0.79; 1.17]	39.6	0.057
Risk of bias – High/Unclear	6	1.24 [1.03; 1.50]	80.6	

Figure 12 TBF short duration (1-3 months) vs. never and risk of eczema at age 5-14 years

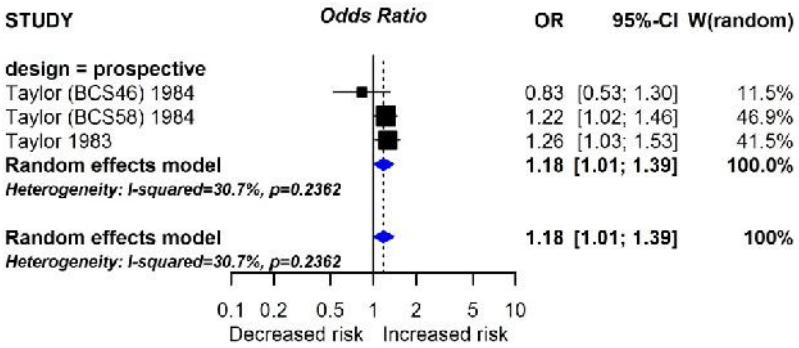


Figure 13 TBF medium duration (4-6 months) vs. never and risk of eczema at age 5-14 years

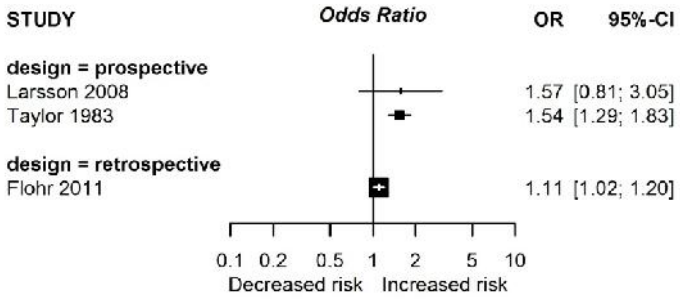
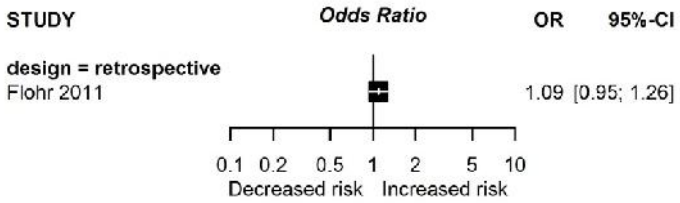


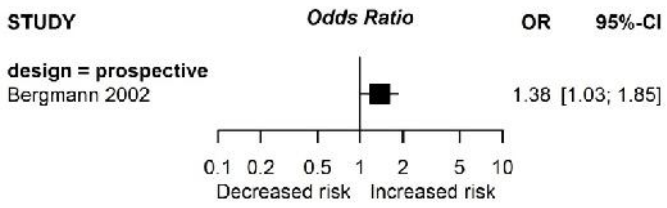
Figure 14 TBF long duration (7-12 months) vs. never and risk of eczema at age 5-14 years



1.2.2.2 TBF ≥1-2 months vs. <1-2 months

One study reported data for TBF ≥1-2 months vs. <1-2 months duration and risk of AD at age 5-14 years, and is shown in Figure 15. The study suggests increased AD risk with increased TBF duration. This is a prospective cohort study with low risk of bias in all domains, which reported adjusted data for several TBF cut-offs and found an overall significant association between increased TBF duration and increased AD risk - OR 1.03 (1.00, 1.06) for each additional month TBF P=0.034.

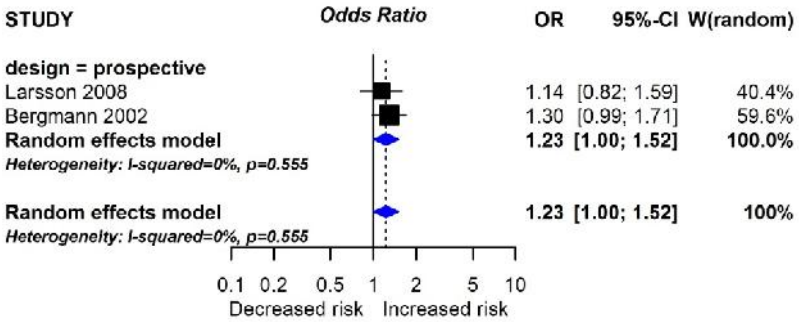
Figure 15 TBF ≥1-2 months vs. <1-2 months and risk of eczema at age 5-14 years



1.2.2.3 TBF ≥3-4 months vs. <3-4 months

Two studies reported data for TBF ≥3-4 months vs. <3-4 months duration and risk of AD at age 5-14 years, and are shown in Figure 16. They show borderline significant increase risk of AD with prolonged breastfeeding (≥3-4 months), without statistical heterogeneity. Both studies are prospective cohort studies in a normal risk population, with low risk of bias in all domains, reporting adjusted OR.

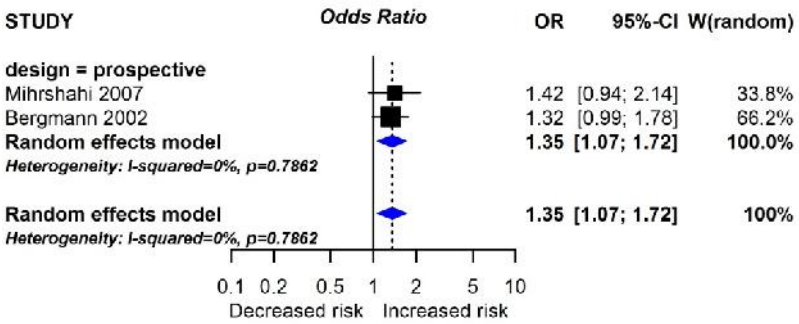
Figure 16 TBF ≥3-4 months vs. <3-4 months and risk of eczema at age 5-14 years



1.2.2.4 TBF ≥5-7 months vs. <5-7 months

Two studies reported data for TBF ≥5-7 months vs. <5-7 months duration and risk of AD at age 5-14 years and are shown in Figure 17. They show increased risk of AD with longer TBF, with no statistical heterogeneity. Both studies are prospective cohort studies with low risk of bias in all domains, reporting adjusted OR.

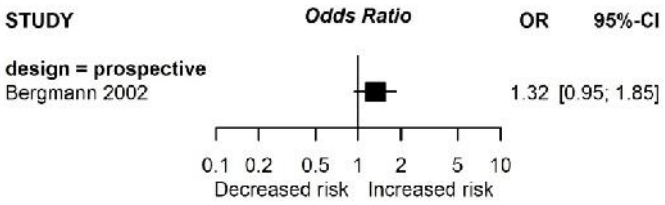
Figure 17 TBF for ≥5-7 months vs. <5-7 months and risk of eczema at age 5-14 years



1.2.2.5 TBF ≥8-12 months vs. <8-12 months

One study reported data for TBF ≥8-12 months vs. <8-12 months duration and risk of AD at age 5-14 years, and is shown in Figure 18. The study found no significant association using this cut-off. As mentioned above, the authors found an overall significant association between increased TBF duration and increased AD risk in this study.

Figure 18 TBF for ≥8-12 months vs. <8-12 months and risk of eczema at age 5-14 years

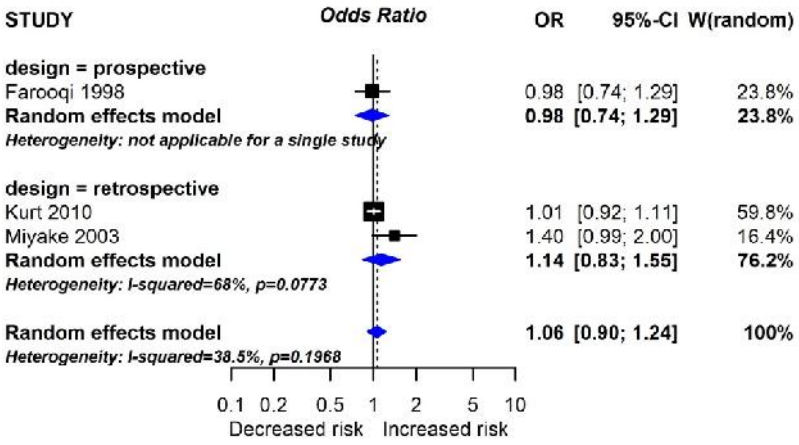


1.2.3 TBF and risk of eczema in children aged 15+ years

1.2.3.1 TBF Never vs. Any

Figure 19 shows the outcomes of 3 eligible observational studies reporting OR for TBF never vs ever and AD at age 15+ years. The pooled data show no association between breastfeeding and risk of AD, but with moderate statistical heterogeneity (I^2=38%). The studies of Miyake and Kurt report adjusted data from cross-sectional surveys; the study of Farooqi reports unadjusted data from a prospective cohort study – they do state in the manuscript that adjusted analysis showed no significant association between TBF and AD. The study of Kurt was assessed as at low risk of bias on all domains, the other two studies as at high risk of bias overall. These differences may be relevant to the statistical heterogeneity seen in the meta-analysis.

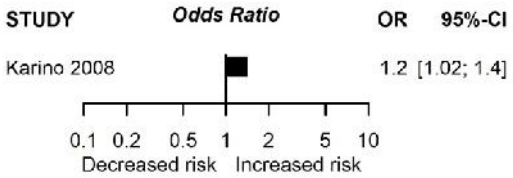
Figure 19 TBF Never vs. Any and risk of eczema at age 15+ years



1.2.3.2 TBF ≥3-4 months vs. <3-4 months

One study reported data for TBF ≥3-4 months vs. <3-4 months duration and risk of AD by age 18 years in a cross sectional survey reporting adjusted data. As shown in Figure 20, there was an association between longer TBF duration and increased risk of AD, with borderline statistical significance.

Figure 20 TBF ≥3-4 months vs. <3-4 months and risk of eczema at age 15+ years



1.3 Data for TBF and risk of eczema that couldn't be analysed

A further 14 prospective cohort studies and 2 cross-sectional studies reported relevant data from over 16000 study participants, which could not be included in meta-analysis. These studies are summarised in Table 4. In one small prospective cohort study there was reduced AD associated with TBF ≥5 months. In all other studies and analyses reported there was no association found between TBF and AD.

Table 4 Studies investigating the association between TBF duration and eczema which were not eligible for meta-analysis

Study	Design	Outcome	Age	N/n	Data	Measure	TBF in AD	TBF in No AD	P
Berth-Jones, 1997 (7)	PC	AD	1	413	Continuous	Average	6.2	5.7	NS
Hesselmar, 2010 (3)	PC	AD	1.5	184	Continuous	Median (IQR)	6.7 (6, 9)	7.2 (4, 10)	0.82
Forster, 1990 (20)	PC	AD	1.5	145	Continuous	No significant association between TBF duration and AD risk			
Alm, 2008 (25)	PC	AD	1	4941	Continuous	No significant association between TBF duration and AD risk			
Morgan, 2004 (35)	PC	AD	1	257	Continuous/ Categorical	No significant association between TBF duration and AD risk			
Kerkhof, 2003 (40)	PC	AD	1	304	Continuous	No significant association between TBF duration and AD risk			
Nwaru, 2013 (18)	PC	AD	5	3109 / 476	Continuous	No significant association between TBF duration either as a categorical or continuous variable in adjusted analyses, and risk of AD up to age 5. Median TBF 7 (4, 11) AD; 7 (4, 11) no AD. P=0.57			

Study	Design	Outcome	Age	N/n	Data	Measure	TBF in AD	TBF in No AD	P
Silvers, 2009 (38)	PC	AD	1	987	Continuous	No significant association between TBF duration and AD. Adjusted OR 1 (0.98-1.03) per month increase in TBF. P=0.79			
Bisgaard, 2009 (15)	PC	AD	3	354	Continuous	No significant association between TBF duration and AD. Adjusted OR 2.8 (0.9-9.0) per year increase in TBF. P=0.10			
Hagendorens, 2005 (49)	PC	AD	1	669	Categorical	No significant association between TBF ever vs never, and AD. OR>1, data in graphical form. NS			
Monego 1989 (52)	PC	AD	4	144	Categorical	No significant association between TBF duration >1 month and AD.			
Wetzig, 2000(30)	PC	AD	1	323	Categorical	Significantly reduced risk of AD with TBF >5 vs <5 months			
Civelek, 2001(57)	CS	AD	11	1533 /743	Continuous	No significant association between TBF duration and AD risk. Mean duration 11.0 months AD, 11.7 months No AD			
Devereux 2006 (17)	PC	AD	5	1704	Categorical	No significant relationship between TBF ever vs never and AD risk			
Girolomoni,2003 (60)	CS	AD	9	1369	Categorical	No significant relationship between TBF ever vs never and AD risk			

Study	Design	Outcome	Age	N/n	Data	Measure	TBF in AD	TBF in No AD	P
Saarinen, 1995(45)	PC	AD	5	150	>1	No significant relationship between TBF <1 month, 1-6 months, >6 months and AD at 5 or 17 years			

2 Exclusive Breastfeeding Duration and Eczema

2.1 Overall characteristics of studies, risk of bias and summary of results

Table 5 describes the main characteristics of the studies analysed in this report. A total of 1 systematic review, which included 1 RCT analysed as a cohort study and 1 other prospective cohort study, and 45 observational studies, reported the association between duration of exclusive breastfeeding (EBF) and risk of AD. Of these, 37 were prospective cohort studies, 3 case-control studies and 5 cross-sectional studies. Most studies (n=30) are from Europe – others are from Australasia (n=6), Asia (n=5), North America (n=3), Middle East (n=2) and worldwide (n=1). Overall, valid data on EBF duration and AD risk were available from over 100,000 subjects. Information on AD was obtained mainly from a medical assessment in 21 studies, using Hanifin and Rajka criteria or adaptations of these (n=12), via parental report (n=7), using the ISAAC questionnaire (n=5), and by unclear methodology in 2 studies. With regards to time of outcome diagnosis, 25 studies explored the association between EBF duration and AD at age 0-4 years, when most AD begins, 17 evaluated AD at age 5-14 years, and five at age 15-44 years. Most studies used a questionnaire to assess the exposure (EBF), 11 used an interview, 6 used a diary, one medical records and in 3 studies the method was unclear.

Risk of bias is shown in Figure 21. Over half of studies had a high risk of bias, most commonly due to lack of adjustment for confounding bias i.e. no adjusted data presented. Over half of studies had unclear risk of assessment bias, mainly due to unclear method for assessing/classifying EBF duration. Risk of conflict of interest was generally assessed as low.

Where data were available, three levels of comparison were used to assess the risk of AD according to EBF duration, namely ≥0-2 months vs. <0-2 months; ≥3-4 months vs. <3-4 months; ≥5-9 months vs. <5-9 months. Across all cut-offs there was no consistent evidence of a lower risk of AD if EBF was prolonged. In general, there were only small numbers of studies with available data in each analysis, and a significant number of studies and participants could only be analysed in narrative form due to the way the data were presented (Table 9). The relatively large number of observational studies and participants did not suggest that there is likely to be an association between EBF duration and AD risk. We did

however find some evidence for gene-environment interaction in the relationship between EBF duration and AD risk.

Table 5 Characteristics of included studies evaluating EBF duration and eczema

Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Kramer 2012 (65)	3618	SR of PC	Finland/Belarus	-	#1 Hanifin and Rajka #2 ISAAC	1, 5-6.5	Study #1: Infants of atopic parents Study #2: Healthy, term, breastfed newborns participating in a breastfeeding promotion intervention trial
Kajosaari, 1991 (66)	135	PC	Finland	Unclear	Hanifin and Rajka	1, 5	Solid food introduction at 6 months versus 3 months, in exclusively breastfed infants
Ludvigsson, 2005 (67)	8346	PC	Sweden	Q	Parent reported eczema	1	ABIS study. Population based study of babies born between Oct 1997 and Oct 1999.
Hesselmar 2010 (3)	184	PC	Sweden	I	UK Working Party Criteria	1.5	ALLERGYFLORA study. Population based study of babies selected from antenatal clinics between 1998 and 2003 - mainly high risk of allergic disease
Purvis, 2005 (5)	550	PC	New Zealand	Q	UK Working Party Criteria	3.5	Auckland Birthweight Collaborative study. Birth cohort with representative sample of babies born in 1996-1997
Kull, 2002; Kull, 2005; Kull, 2009 (6, 68, 69)	3791	PC	Sweden	Q	Parent report OR DD eczema (+/- sIgE)	2, 4, 8	BAMSE study. Population based cohort of children born between 1994-1996

Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Besednjak-Kocijancic, 2010 (70)	408	PC	Slovenia	Unclear	Unclear	1, 5	Infants with a positive history of parental allergy
Peters, 1987 (71)	11920	PC	UK	Q	Parent reported eczema	5	British Cohort Study: sample of all infants born in 1970 in Britain
Mihrshahi, 2007 (14)	516	PC	Australia	I	Visible flexural dermatitis OR DD eczema	5	CAPS study. Infants born in 1997-1999 with family history of asthma or wheezing
Fergusson, 1982; Fergusson 1990 (72)	1175	PC	New Zealand	R/D/I	DD eczema; DD eczema for >=3 years needing medication	1, 10	Christchurch Child Development Study. Population based cohort of infants born in 1977 in the Christchurch urban region
Cogswell, 1987 (73)	73	PC	UK	D	Physician assessment (+ SPT)	5	Birth cohort of infants with family history of hay fever or asthma
Giwercman, 2010 (74)	306	PC	Denmark	I	Hanifin and Rajka criteria	2	COPSAC study. Infants of mothers with a history of doctor-diagnosed asthma, recruited from August 1998 to December 2001.
Benn, 2004; Linneberg, 2006 (75, 76)	34793	PC	Denmark	Q/I	Physician assessment; Parent reported eczema	1.5	DNBC. Population based birth cohort of children born between 1997-2002

Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Nwaru, 2013 (18)	3109	PC	Finland	D	ISAAC	5	DIPP study. Infants at high risk (HLA) for TIDM born between 1996-2004 invited to the allergy study 1998 - 2000
Laubereau, 2003 (77)	2251	PC	Germany	I	DD	3	GINI study. Term newborn infants born 1995-8 were recruited from 2 regions of Germany to participate into an intervention program
Arshad, 1992 (78)	1167	PC	UK	D/Q	Physician assessment	1	Isle of Wight Study. Population based birth cohort of infants born in semi-rural areas between 1989 and 1990
Jedrychowski, 2011 (79)	469	PC	USA and Poland	I	Physician assessment	1	Birth cohort of full-term infants born between 2001 and 2004
Kemeny, 1991 (27)	180	PC	UK	Unclear	Unclear	1	Population based birth cohort of infants born at Dulwich and King's College Hospitals in London
Kitz, 2006 (80)	131	PC	Germany	D	Hanifin and Rajka criteria	1	Birth cohort of infants at increased risk for atopy participate in RCT on infant feeding intervention
Marini, 1996 (31)	359	PC	Italy	Q	Physician assessment	1	Infants with family history of allergy whose mother were proposed to participate in an allergy prevention program
Midwinter, 1987 (81)	455	PC	UK	Unclear	DD	5	Children born to parents with a family history of atopy in 1979-1981

Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Gruber 2010 (82)	300	PC	Netherlands, Austria, Switzerland, Italy, Germany	Q	Hanifin and Rajka criteria	1	MIPS-1 study. Infants born in 2006 without family history of allergy, randomised to intervention if fully formula fed < 8 weeks
Moore, 1985 (33)	475	PC	UK	D/I	Physician assessment	0.25	Infants born in a hospital in 1979-1980 with family history of eczema or asthma (high risk of disease)
Nentwich, 2009 (83)	121	PC	Germany	Q/I	DD	0.5	Newborns with a hereditary risk for atopy
Silvers, 2009 (38)	987	PC	New Zealand	Q	Parent reported eczema	1	New Zealand Asthma and Allergy Cohort Study. Population based birth cohort of infants born between 1997 and 2001
Miyake, 2009 (39)	763	PC	Japan	Q	Physician assessment	2	OMCHS study. Population based birth cohort of infants born in 2002-2003
Pesonen, 2006 (84)	160	PC	Finland	I	Physician assessment	5, 20	Population based birth cohort of infants born in 1981
Kerkhof, 2003 (40)	304	PC	Netherlands	Q	UK Working Party Criteria	1	PIAMA: population-based born in 1996-1997 (normal risk of disease)
Pratt, 1984 (42)	198	PC	UK	D/I	Physician assessment	5	Recruited in antenatal clinics, normal risk of disease

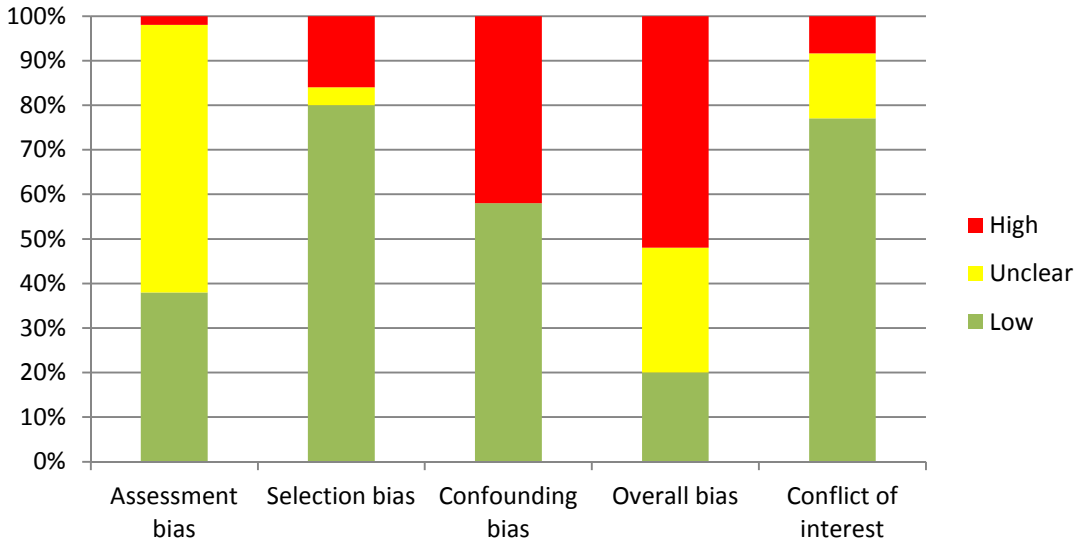
Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Kramer, 2003; Kramer, 2009 (85, 86)	2951	PC	Belarus	I	Physician assessment// ISAAC	1, 6.5	PROBIT study: recruited in hospitals , born 1996-1997 (normal risk of disease)
Moore, 2004 (87)	1005	PC	USA	Q	DD	0.5, 6.5	PROJECT VIVA: hospital based and born 1998-2002 (normal risk of disease)
Saarinen, 1979 (88)	177	PC	Finland	Q	Physician assessment	1	Recruited from hospital and born in 1975 (normal risk of disease)
Siltanen,2003 (89)	285	PC	Finland	Q	Hanifin and Rajka criteria	4	Infants recruited from maternal hospital born in 1994-1995 (normal risk of disease)
Shohet, 1985 (90)	368	PC	Israel	I	Hanifin and Lobitz criteria	0.5	Cohort born in 1980 (normal risk of disease)
Dunlop, 2006 (91)	1326	PC	Slovakia	Q	Physician assessment	1	Recruited from hospital, born 1997-1999 (normal risk of disease)
Matheson, 2007 (92)	5729	PC	Tasmania	Q	Parent reported eczema	44	Tasmanian ASTHMA Study: population based born in 1961 (normal risk of disease)
Wang, 2007 (48)	1760	PC	Taiwan	Q	DD	0.5	Tiawan National Birth Cohort Study: population representative sample born in 2003 (normal risk of disease)
Van Asperen, 1983 (48)	79	PC	Australia	I	Physician assessment	1	Cohort recruited from medical service, born in 1980-1981 with family history of atopy (high risk of

Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
							disease)
Zutavern 2004 (93)	604	PC	UK	I	DD	5.5	Cohort recruited from general practices and born in 1993-1995 (normal risk of disease)
Amri 2012 (94)	343	CC	Saudi Arabia	Q	Hanifin and Rajka criteria	<15	Cases from hospital, source of control unknown
Sahakyan, 2006 (95)	240	CC	Armenia	Q	UK Working Party Criteria	7	Hospital-based study with matched controls (low risk of disease)
Kramer, 1981 (31)	142	CC	Canada	I	Hanifin and Lobitz criteria	<20	Cases and controls were1 month to 20 years old children attending dermatology clinics visits
Tanaka, 2009 (59)	1957	CS	Japan	Q	ISAAC - current AD	3	Fukuoka Child Health Study. All 3-year old children examined at public health centres in Fukuoka city
Civelek, 2001 (57)	1533	CS	Turkey	Q	ISAAC	11	Representative sample of schoolchildren in 5 cities
Ehlayel, 2008 (96)	1278	CS	Qatar	Q	Parent reported eczema	5	Children 0-5 years old attending primary healthcare centres for routine immunisation
Flohr,2011(56)	51 119	CS	Worldwide	Q	Parent reported eczema	12	ISAAC Phase 2. Schoolchildren aged 8–12 years from 27 centres in 21 affluent and nonaffluent countries

Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Miyake, 2003 (97)	6845	CS	Japan	Q	ISAAC - current AD	15	12-15 years old children from all public junior high schools in Suita, Japan.

Q: questionnaire, I: interview, R: medical records, D: diary, PC: prospective cohort, RC: retrospective cohort, NCC: nested case-control, CC: case-control, CS: Cross-sectional, AD: eczema, DD: doctor diagnosis of AD, in contrast to 'Physician assessment' where AD diagnosis was always made by a study physician as part of the study protocol.

Figure 21 Risk of bias in studies of exclusive breastfeeding duration and eczema



2.2 Exclusive breastfeeding duration and eczema

2.2.1 EBF duration and risk of eczema in children aged 0-4 years

2.2.1.1 EBF ≥0-2 months vs. <0-2

Seven prospective cohort studies reported data that could be pooled to calculate OR for AD, in infants with EBF for ≥0-2 months vs. <0-2 months duration and are shown in Figure 20. They show no association between EBF duration and AD risk, with high statistical heterogeneity. Most studies in this meta-analysis were at high risk of bias due to reporting unadjusted data, including those with most extreme OR, which may account for some of the statistical heterogeneity. Subgroup analysis (Table 6) did not identify significant differences by subgroup in this outcome.

Figure 22 EBF ≥0-2 months vs. <0-2 months and risk of eczema at age 0-4 years

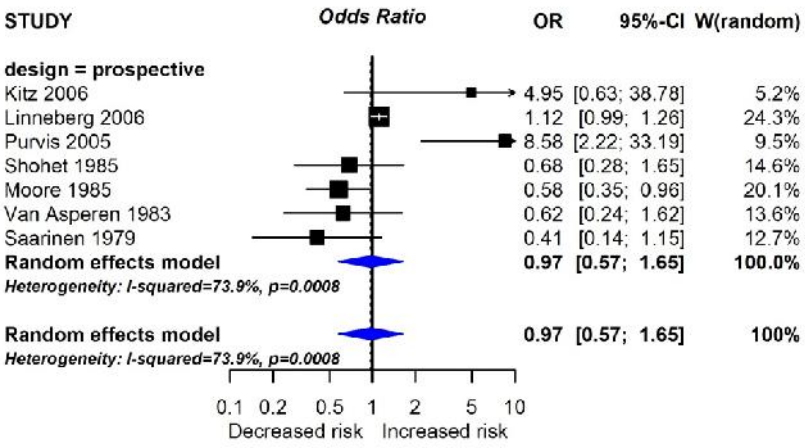


Table 6 Subgroup Analyses EBF duration ≥0-2 vs. <0-2 months and risk of AD at 0-4 years

	Number of studies	OR [95% CI]	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted used)	7	0.97 [0.57; 1.65]	73.9	
Adjusted	1	1.12 [0.99; 1.26]	--	Not tested
Unadjusted	6	1.01 [0.47; 2.19]	72.6	
Study Design – Prospective	7	0.97 [0.57; 1.65]	73.9	1.00
Study Design – Retrospective	0	-	-	
Risk of disease – High	3	0.77 [0.35; 1.72]	49.5	0.51
Risk of disease – Normal	4	1.14 [0.50; 2.60]	77.9	
Risk of bias – Low	1	0.58 [0.35; 0.96]	--	0.11
Risk of bias – High/Unclear	6	1.13 [0.59; 2.17]	70.6	

2.2.1.2 EBF ≥3-4 months vs. <3-4 months

1.1.1.1 Systematic reviews and intervention trials

As shown in Table 7, the single systematic review found no evidence that exclusive/predominant breastfeeding for 6 months, compared with exclusive/predominant breastfeeding for 3 months, influenced risk of AD at 1 or 5 years. There was evidence of reduced AD at 1 year with prolonged EBF, from the study of Kajosaari, but the study of Kramer found no relationship, yielding significant statistical heterogeneity between the 2 studies. Of note, the study of Kramer separately reported reduced AD at 12 months in centres randomised to a breastfeeding promotion programme (OR 0.54 95% CI 0.30, 0.95), as discussed under 'TBF' in this report. The study of Kajosaari reported no effect on AD at age 5 years (Table 7), and the study of Kramer separately reported no effect on AD at age 6.5 years (OR 1.0 95% CI 0.50, 1.80).

Table 7 EBF for 6 months versus 3 months and risk of RC

Study	Outcome measure	No. participants (studies)	Outcome (95% CI)
Kramer 2012 (98) Kajosaari (66) Kramer 2007 (2)	AD at 1 year	3618 (2)	RR 0.73 (0.49, 1.08) I^2=78%
Kramer 2012 (98) Kajosaari (66)	AD at 5 years	3584 (2)	RR 0.97 (0.50, 1.89)

Data shown are from analyses of the trials of Kramer and Kajosaari in the 2012 Cochrane review of Kramer (98).

1.1.1.2 Observational studies

Eighteen observational studies reported data that could be pooled to calculate OR for AD, in infants with EBF for ≥3-4 months vs. <3-4 months duration and are shown in Figure 22. They show reduced risk of AD with increased EBF duration, of borderline statistical significance, with moderate statistical heterogeneity. The Funnel plot (Figure 24) was not symmetrical, but Egger's test was >0.05 suggesting no clear evidence of publication bias. Subgroup analyses (Table 8) suggested that the statistical heterogeneity may be explained by family disease risk – children at high risk of allergic disease had less AD where EBF ≥3-4 months, whereas for children without high risk of allergic disease there was no association. It is notable that two other large observational studies reported effect modification by family history, for EBF and AD, whereby children from non-allergic families had increased AD with increased EBF duration, but this was not seen from children from allergic families (75, 76, 97). Other studies have suggested important gene environment interactions between EBF duration and allergic sensitisation, at least to foods (99).

Figure 23 EBF for ≥3-4 months vs. <3-4 months and risk of eczema at age 0-4 years

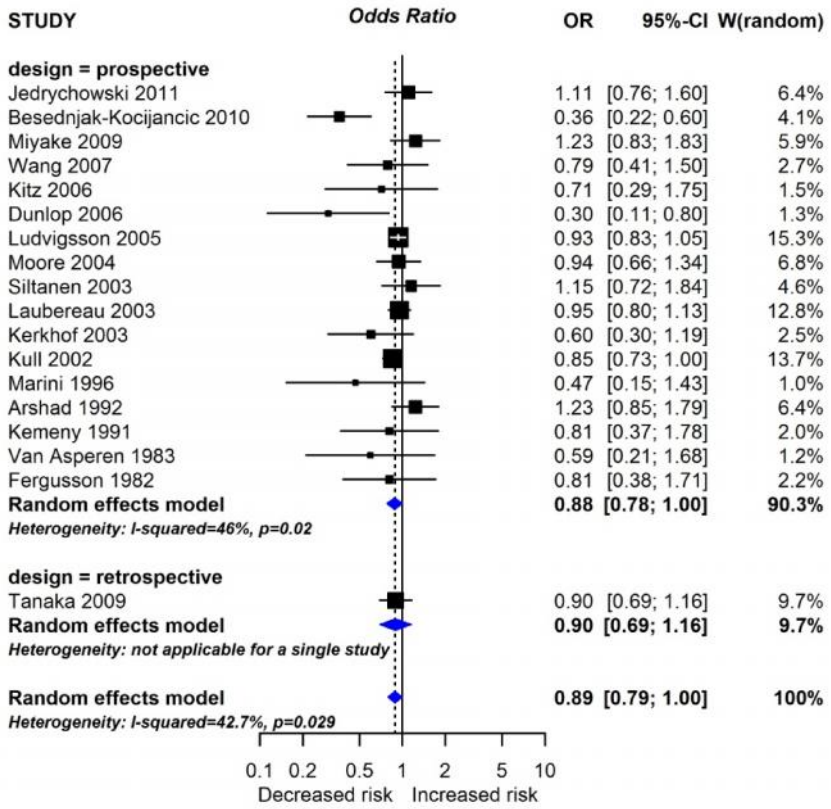
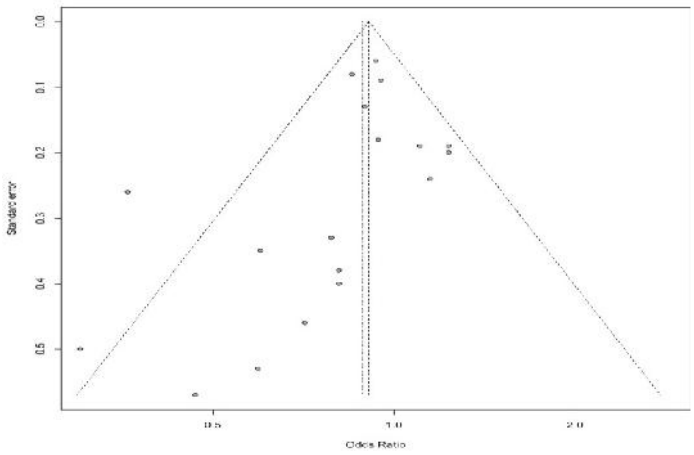


Figure 24 Risk of publication bias in studies investigating EBF duration for ≥3-4 months vs. <3-4 months and risk of eczema in children aged 0-4 years



Egger's test p-value = 0.141

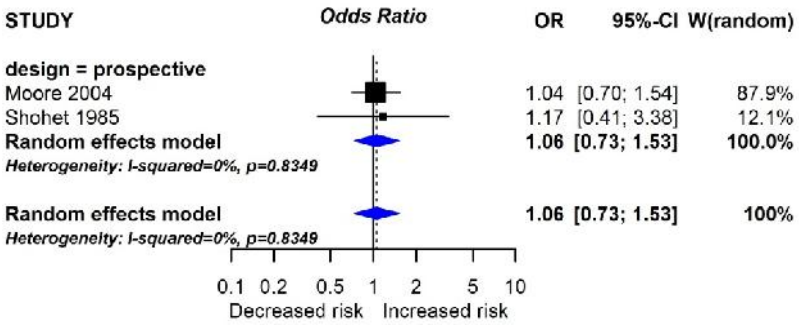
Table 8 Subgroup Analyses of risk of atopic dermatitis and EBF duration ≥3-4 months vs. <3-4 months in children aged 0-4 years

	Number of studies	OR [95% CI]*	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted used)	18	0.89 [0.79; 1.00]	42.7	
Adjusted	6	0.92 [0.85; 0.99]	0	Not tested
Unadjusted	16	0.89 [0.78; 1.03]	47.8	
Study Design – Prospective	17	0.88 [0.78; 1.00]	46	0.92
Study Design – Retrospective	1	0.90 [0.69; 1.16]	--	
Risk of disease – High	4	0.45 [0.31; 0.66]	0	0.00
Risk of disease – Normal	14	0.93 [0.86; 1.01]	9.2	
Risk of bias – Low	1	0.95 [0.80; 1.14]	--	0.45
Risk of bias – High/Unclear	17	0.87 [0.76; 1.00]	45.5	

2.2.1.3 EBF for ≥5-9 months vs. <5-9 months

Three prospective cohort studies reported data that could be pooled to calculate OR for AD, in infants with EBF for ≥5-9 months vs. <5-9 months duration and are shown in Figure 25. They show no association between EBF duration and AD risk, with no statistical heterogeneity.

Figure 25 EBF ≥5 -9months vs. <5-9 months and risk of eczema at age 0-4 years

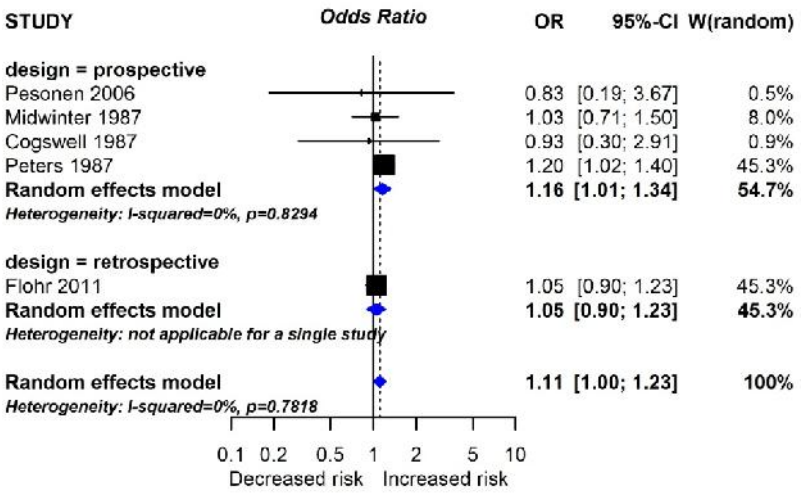


2.2.2 EBF duration and the risk of eczema in children aged 5-14 years

2.2.2.1 EBF ≥0-2 months vs. <0-2 months

Four prospective cohort studies and one cross-sectional study reported data that could be pooled to calculate OR for AD, in infants with EBF for ≥0-2 months vs. <0-2 months duration and are shown in Figure 26. They show increased AD with increasing duration of EBF, with borderline statistical significance but no statistical heterogeneity (I^2=0%). Two of the studies presented adjusted data including the cross-sectional study of Flohr, and three presented unadjusted data including the significant study of Peters.

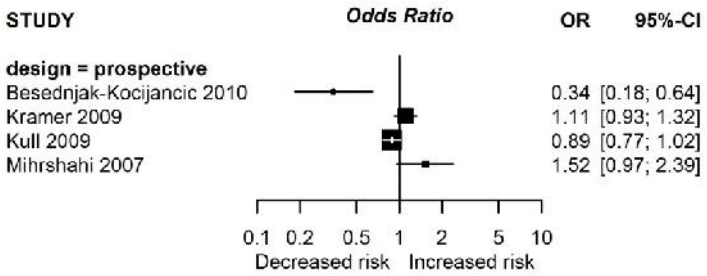
Figure 26 EBF ≥0-2 months vs. <0-2 months and risk of eczema at age 5-14 years



2.2.2.2 EBF ≥3-4 months vs. <3-4 months

Four prospective cohort studies reported OR for AD, in infants with EBF for ≥0-2 months vs. <0-2 months duration and are shown in Figure 27. The studies could not be pooled due to extreme statistical heterogeneity (I^2=83%). The studies of Mihrshahi and Besednjak-Kocijancic were in populations at high risk of allergic outcomes, the latter study reported unadjusted data; the former adjusted. The studies of Kramer and Kull were in normal risk populations and reported adjusted data. Overall the data do not support an association between EBF ≥0-2 months vs. <0-2 months duration and altered AD risk.

Figure 27 EBF for ≥3-4 months vs. <3-4 months and risk of eczema at age 5-14 years

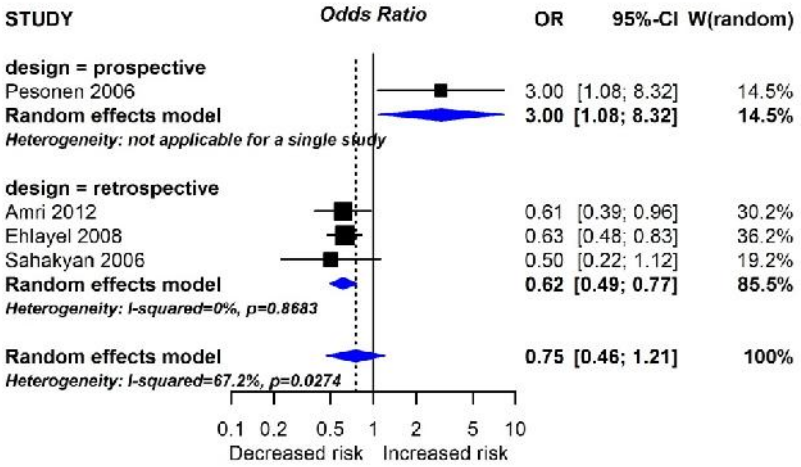


2.2.2.3 EBF ≥5-9 months vs. <5-9 months

Four observational studies reported OR for AD, in infants with EBF for ≥5-9 months vs. <5-9 months duration and are shown in Figure 28. The pooled OR show no association, with high statistical heterogeneity (I^2=67%). The studies of Amri and Ehlayel were retrospective studies reporting unadjusted data and thus carry a high risk of confounding bias. The study of Pesonen compared EBF duration ≥9 vs <9 months which is an unusual duration of EBF and

this analysis included relatively small numbers hence the wide confidence intervals. The study of Sahakya is a case-control study which reported adjusted OR and was judged as low or unclear risk of bias in all domains.

Figure 28 EBF for ≥5 months vs. <5 months and risk of eczema at age 5-14 years

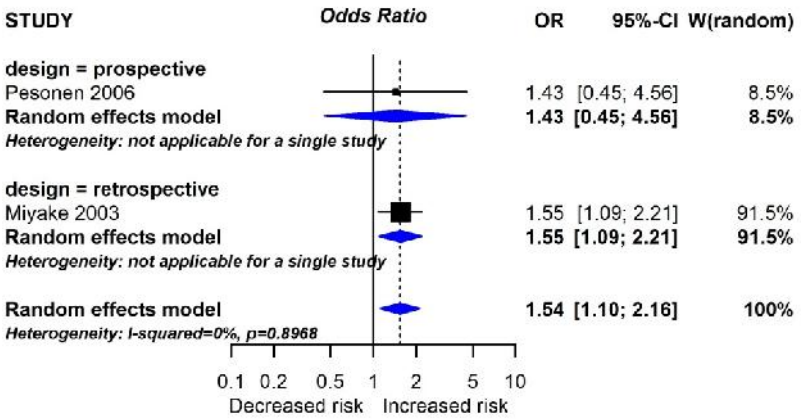


2.2.3 EBF duration and risk of eczema in children aged 15+ years

2.2.3.1 EBF ≥0-2 months vs. <0-2 months

Two observational studies reported data that could be pooled to calculate OR for AD, in people aged 15+ years with EBF for ≥0-2 months vs. <0-2 months duration and are shown in Figure 29. They show increased AD with increasing duration of EBF, with no statistical heterogeneity (I^2=0%). The study of Pesonen compared EBF duration ≥9 vs <9 months which is an unusual duration of EBF and this analysis included relatively small numbers hence the wide confidence intervals. The study of Miyake is a cross-sectional survey using the ISAAC questionnaire, which reported adjusted data. The same authors found a similar effect for partial BF in the first 3 months, as for EBF.

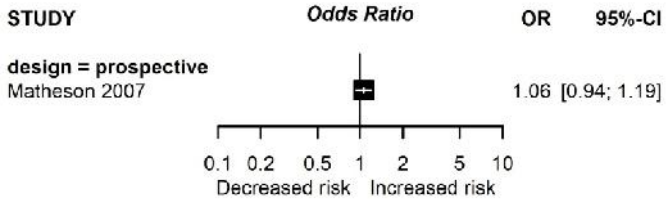
Figure 29 EBF for ≥0-2 months vs. <0-2 months and risk of eczema at age 15+ years



2.2.3.2 EBF ≥3-4 months vs. <3-4 months

One prospective cohort study reported OR for AD, in adults aged 44 years with EBF for ≥3-4 months vs. <3-4 months duration and is shown in Figure 30. There was no evidence of an association.

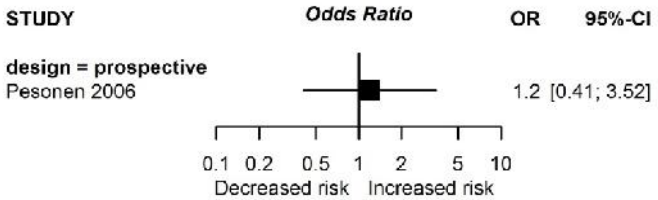
Figure 30 EBF ≥3-4 months vs. <3-4 months and risk of eczema at age 15+ years



2.2.3.3 EBF 5-9 months vs. <5-9 months

One prospective cohort study reported OR for AD, in adults aged 44 years with EBF for ≥5-9 months vs. <5-9 months duration and is shown in Figure 31. There was no evidence of an association.

Figure 31 EBF ≥5 months vs. <5 months and risk of eczema at age 15+ years



2.3 Exclusive breastfeeding duration and atopic eczema

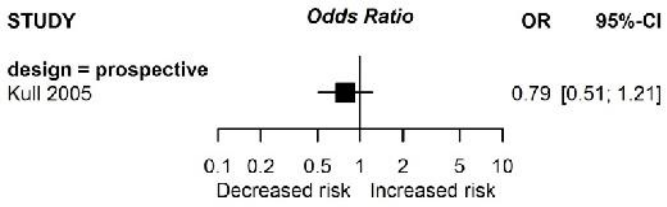
We also evaluated associations between EBF duration and eczema associated with atopy (i.e. a positive SPT or sIgE test). Relatively few included studies reported this outcome.

2.3.1 EBF and atopic eczema in children aged 0-4 years

2.3.1.1 EBF ≥3-4 months vs. <3-4 months

One prospective cohort study reported OR for atopic-AD, in infants with EBF for ≥3-4 months vs. <3-4 months duration and is shown in Figure 32. There was no evidence of an association.

Figure 32 EBF ≥3-4 months vs. <3-4 months and risk of atopic eczema at age 0-4 years

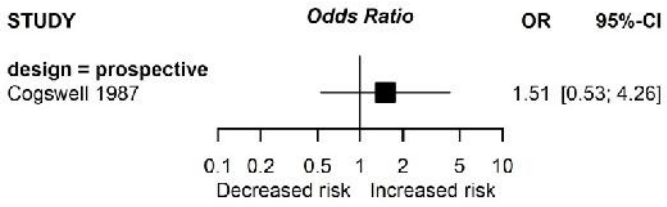


2.3.2 EBF and atopic eczema in children aged 5-14 years

2.3.2.1 EBF ≥0-2 months vs. <0-2 months

One large cross-sectional study reported separately for affluent and non-affluent countries, calculated OR for atopic-AD, in children with EBF for ≥0-2 months vs. <0-2 months duration and is shown in Figure 33. There was no evidence of an association, with low statistical heterogeneity.

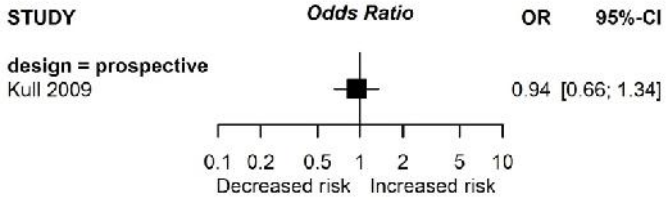
Figure 33 EBF ≥0-2 months vs. <0-2 months and risk of atopic eczema at age 5-14 years



2.3.2.2 EBF ≥3-4 months vs. <3-4 months

One prospective cohort study reported OR for atopic-AD, in children with EBF for ≥3-4 months vs. <3-4 months duration and is shown in Figure 34. There was no evidence of an association.

Figure 34 EBF for ≥3-4 months vs. <3-4 months and risk of atopic eczema at age 5-14 years



2.4 Data for TBF and risk of eczema that couldn't be analysed

A further 11 prospective cohort studies, 1 case-control and 1 cross-sectional study reported relevant data from over 35000 study participants, which could not be included in meta-analysis. These studies are summarised in Table 9. In one prospective cohort study there was increased AD associated with increased EBF duration. In all other studies reported there was no association found between EBF and AD.

Table 9 Studies investigating the association between EBF duration and eczema which were not eligible for meta-analysis

Study	Design	Outcome	Age	N/n cases	Data	Measure	EBF in AD	EBF in no AD	P
Hesselmar, 2010 (3)	PC	AD	1.5	184	Continuous	Median (IQR)	4 (3.2, 4.5)	4 (3.9, 4.5)	0.63
Giwercman, 2010 (74)	PC	AD	2	306	Categorical	Risk of AD increased with increasing duration of EBF in analyses adjusted for allergy risk factors and filaggrin genotype HR 2.1 (1.2-3.8) P=0.016			
Gruber, 2010 (82)	PC	AD	1	543/47	Categorical	Cumulative incidence 7.3% (SE1.6%) with EBF>2 months vs 9.7% (SE1.5%) with EBF <2 months. Not adjusted. No statistical comparison.			
Ludvigsson, 2005 (67)	PC	AD	1	8346/ unclear	Categorical	Cumulative incidence of AD to 1 year in EBF ≥4 vs <4 months was not significantly different. Adjusted HR 1.0 (0.95, 1.06)			
Kramer, 2003 (86)	PC	AD	1	3483/96	Categorical	Cumulative incidence of AD to 1 year in EBF ≥6 vs 3-5 months was not significantly different. Adjusted OR 1.1 (0.65, 2.0)			
Benn, 2004 (75)	PC	AD	1.5	15430	Categorical	Cumulative incidence of AD to 1.5 years in EBF ≥4 vs <4 months was not significantly different. Adjusted HR 1.1 (0.98-1.28) NB The authors found significantly increased AD with EBF ≥4 months where there was no parental allergy, but not if parents were allergic			
Nentwich, (83)	PC	AD	2	106	Categorical	At 2 and 6 months of age there were more atopic symptoms in EBF group, but differences disappeared after 6 months			

Study	Design	Outcome	Age	N/n cases	Data	Measure	EBF in AD	EBF in no AD	P
Silvers, 2009 (38)	PC	AD	1	987	Categorical	No association between duration of EBF and AD to 1 year. Adjusted OR 0.96 (0.9-1.03)			
Nwaru, 2013 (18)	PC	AD	5	3109	Categorical; Continuous	No significant association between EBF duration either as a categorical or continuous variable in adjusted analyses, and risk of AD up to age 5. Median EBF 1.8 (0.2, 3.5) AD; 1.5 (0.2, 3.5) no AD			
Kramer, 1981 (53)	CC	AD	<20	142/ unclear	Categorical	No significant association between EBF >2 months and AD risk			
Zutavern, 2004 (93)	PC	AD	5.5	604	Categorical	No significant association between EBF ≥2 months and AD risk, in adjusted analysis			
Fergusson, 1990 (72)	PC	AD	10	1067	Categorical	No significant association between EBF ≥4 months and AD risk, in adjusted analysis. P>0.80			
Civelek, 2001 (57)	CS	AD	11	1533/743	Continuous	No significant association between EBF duration and AD risk, in adjusted analysis			

3 Solid food introduction and atopic eczema

3.1 Overall characteristics of studies, risk of bias and summary of results

Table 10 describes the main characteristics of the studies analysed in this section of the report. A total of 25 observational studies including 21 prospective cohort studies, 1 retrospective cohort study, 1 nested case-control study and 2 case-control studies, reported the association between timing of solid food introduction (SF) and risk of AD. The studies were mainly from Europe (n=17), but also Australasia (n=3), Asia (n=3), USA (n=1) and Africa (n=1). Overall, valid data on SF and AD risk were available from over 45,000 subjects. Information on AD was obtained from a medical assessment in 11 studies, via parental report in 6 studies, using Hanifin and Rajka criteria or modified versions of the criteria in 4 studies, and ISAAC questionnaire in 4 studies. With regards to time of outcome diagnosis, 19 studies explored the association between SF and AD in the first 4 years of life, and 6 studies assessed at age 5-14 years. Eleven studies used a questionnaire to assess the exposure (SF), 3 diary, 10 interview and 1 used medical record review.

Risk of bias is summarised in Figure 35. Just over 40% of studies had a high risk of bias, most commonly due to lack of adjustment for confounding bias i.e. no adjusted data presented. Risk of conflict of interest was generally assessed as low.

The risk of AD according to SF was categorised as ≥3-4 months vs. <3-4 months. Overall the evidence base was limited by some unexplained statistical heterogeneity in both meta-analyses, but the available data do not suggest any relationship between timing of solid food introduction and AD risk.

Table 10 Characteristics of included studies evaluating solid food introduction and eczema

Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Hesselmar, 2010 (3)	184	PC	Sweden	I	UK Working Party Criteria	1.5	ALLERGYFLORA study. Population based study of babies selected from antenatal clinics between 1998 and 2003 - mainly high risk of allergic disease
Mihrshahi, 2007 (14)	516	PC	Australia	I	Visible flexural dermatitis OR DD eczema	5	CAPS study. Infants born in 1997-1999 with family history of asthma or wheezing
Fergusson, 1981 (100); Fergusson, 1982 (100)	1175	PC	New Zealand	R/I	DD	1, 2	Christchurch Child Development Study. Population based cohort of infants born in 1977 in the Christchurch urban region
Larsson, 2008 (16)	4779	PC	Sweden	Q	ISAAC	9	DBH study. Preschool children aged 1–6 years surveyed in 2000 and 2005.
Forsyth, 1993 (101)	455	PC	UK	D/I	Parent reported eczema	2	Dundee infant feeding study. Population based cohort of infants born between 1983-1986
Filipiak, 2007; Schoetzau, 2002 (102-104)	4753	PC	Germany	Q, D	DD; Physician assessment	1, 4	GINI study. Term newborn infants born 1995-8 in 2 regions of Germany referred to an intervention program according to risk of allergy
Harris, 2001 (21)	622	PC	UK	I	UK Working Party Criteria	2	Population based birth cohort of children born between 1993 and 1995 in three general practices in Ashford

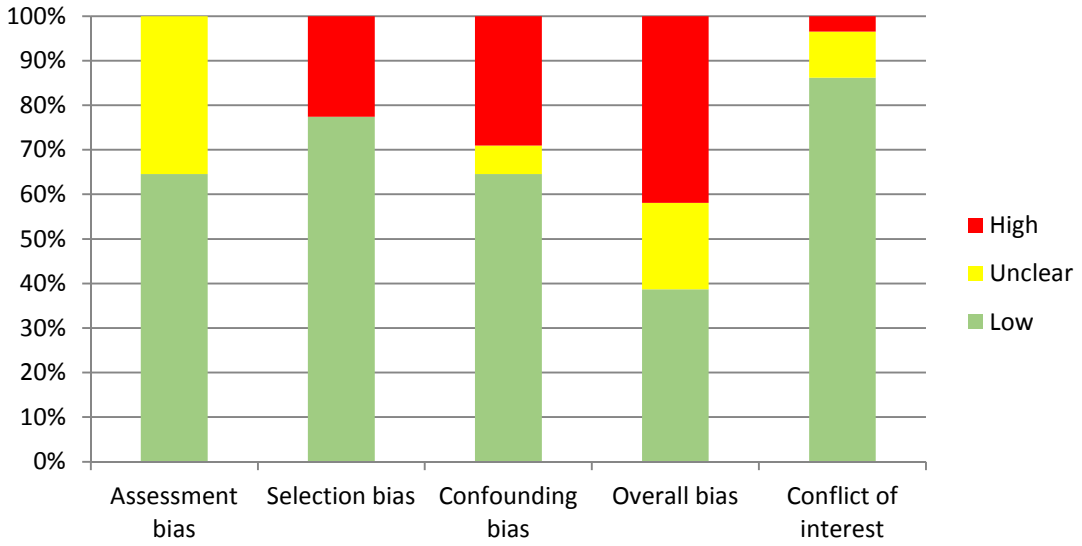
Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Huang, 2013 (105)	684	PC	China	Q	ISAAC	2	Mother-infant pairs registered in Putuo District, Changzheng Town Community Health Service Center Child Health Clinic, 2008
Alm, 2008 (25)	4941	PC	Sweden	Q	Parent reported eczema	1	Infants of Western Sweden. Population birth cohort of infants born in 2003
Snijders, 2008 (28)	822	PC	Netherlands	Q	Parent reported eczema	2	KOALA study. Population based birth cohort of infants born 2000-2002 (including a cohort with anthroposophic lifestyle)
Brockow, 2008; Zutavern 2006 ; Zutavern, 2008 (106-108)	2474	PC	Germany	I, Q	DD; Parent reported eczema	2, 6	LISA study. Population based birth cohort of infants born between 1997-9 at selected maternity hospitals in 4 German cities
Marini, 1996 (31)	359	PC	Italy	Q	Physician assessment	1	Infants with family history of allergy whose mother were proposed to participate in an allergy prevention program
Moore, 1985 (33)	470	PC	UK	D/I	Physician assessment	1.0	Infants born in a hospital in 1979-1980 with family history of eczema or asthma (high risk of disease)
Morgan, 2004; Morgan, 2004 (b) (34, 35)	257	PC	UK	I	Parent reported eczema; Physician assessment	1, 1.5	Infants from five prospective randomised dietary trials conducted in the UK 1993-7. Two term infants, one LBW infants, two premature infants

Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Ruiz, 1992 (44)	39	PC	UK	I	Hanifin and Rajka criteria	1	Recruited from hospital and family history of atopy (high risk of disease)
Dunlop, 2006 (91)	1326	PC	Slovakia	Q	Physician assessment	1	Recruited from hospital, born 1997-1999 (normal risk of disease)
Chuang, 2011 (46)	18773/ 1050	PC	Taiwan	R/I	Physician assessment	1.5	TaiwanBirth Cohort Study: population representative sample born in 1995 (normal risk of disease)
Joseph, 2011 (109)	594	PC	USA	I	DD	3	WHEALS STUDY: Recruited from hospital prenatal care and born in 2005 (normal risk of disease)
Zutavern, 2004 (93)	604	PC	UK	I	DD	5.5	Cohort recruited from general practices and born in 1993-1995 (normal risk of disease)
Hide, 1981 (47)	843	PC	UK	D/Q	DD	1	The Isle of Wight study: born in 1977-1978 (normal risk of disease)
Van Asperen, 1983 (110)	79	PC	Australia	I	Physician assessment	1.3	Cohort recruited from medical service, born in 1980-1981 with family history of atopy (high risk of disease)
Sariachvili, 2010 (51)	557	NCC	Belgium	Q	ISAAC	4	PIPO COHORT: population representative sample, participants born in 1997-2001 (normal risk of disease)
von Geburstsreif , 1990 (20)	145	RC	Germany	Q	Parental report	1.5	Incident cases from diabetes registry and controls from schools (normal risk of disease)

Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Haileamlak, 2005 (55)	732	CC	Ethiopia	I	ISAAC	5	Children age 1- 5 years. Cases were defined according to the ISAAC criteria for AD and confirmed by clinical examination
Sahakyan, 2006 (95)	240	CC	Armenia	Q	UK Working Party Criteria	7	Hospital-based study with matched controls (normal risk of disease)

Q: questionnaire, I: interview, R: medical records, D: diary, PC: prospective cohort, RC: retrospective cohort, NCC: nested case-control, CC: case-control, CS: Cross-sectional, AD: eczema, DD: doctor diagnosis of AD, in contrast to 'Physician assessment' where AD diagnosis was always made by a study physician as part of the study protocol.

Figure 35 Risk of bias in studies of solid food introduction and eczema



3.1.1 SF introduction and risk of eczema in children aged 0-4 years

3.1.1.1 SF ≥3-4 months vs. <3-4 months

Figure 36 shows the outcomes of 14 eligible observational studies evaluating SF ≥3-4 months vs. <3-4 months and risk of AD at age 0-4 years. The data show no significant relationship, with high statistical heterogeneity (I^2=70%). Chuang also reported no relationship between SF introduction at >6 months and AD, in their prospective cohort study with low overall risk of bias in a normal risk population evaluated at age 1.5 years aOR 1.08 (0.74-1.57). In an analysis of a subset of the GINI dataset reported by Filipiak, Schoetzao also found no association between SF introduction at >6 months and risk of AD in the first year – unadjusted OR 1.8 (0.8-1.7). Funnel plot is shown in Figure 37, and does not suggest obvious publication bias. In the study of Snijders a cutoff of >7 versus 3 months was used.

Subgroup analyses are shown in Table 11 and do not identify important subgroup differences or explanations for the statistical heterogeneity.

Figure 36 SF ≥3-4 months vs. <3-4 months and risk of atopic eczema at age 0-4 years

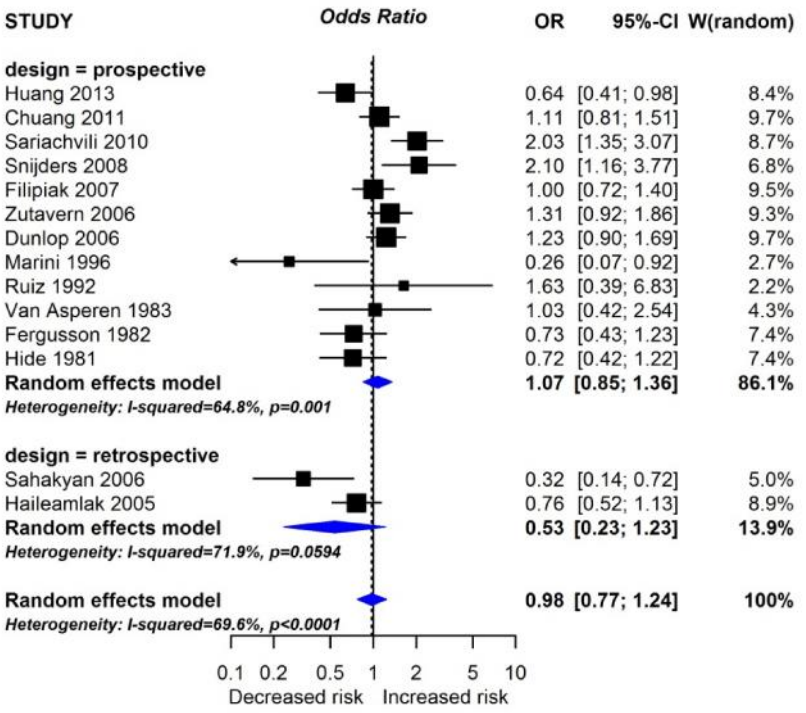
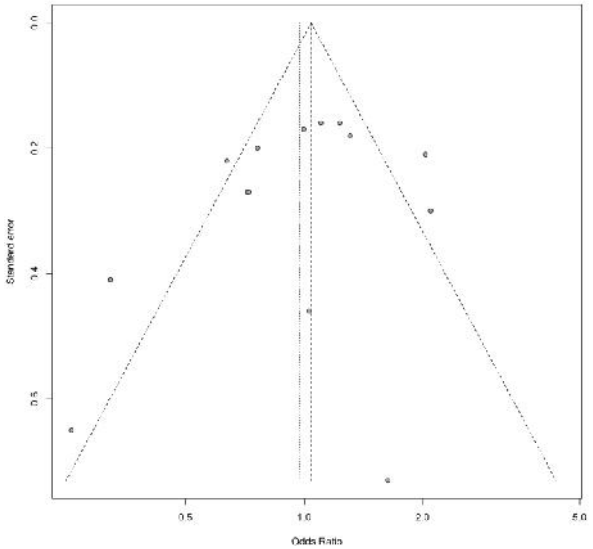


Figure 37 Risk of publication bias in studies investigating SF introduction ≥3-4 months vs. <3-4 months and risk of eczema in children aged 0-4 years



Egger's test p-value = 0.241

Table 11 Subgroup Analyses of risk of atopic dermatitis and SF ≥3-4 months vs. <3-4 months in children aged 0-4 years

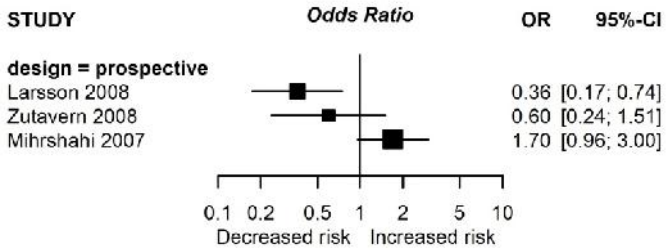
	Number of studies	OR [95% CI]	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted used)	14	0.98 [0.77; 1.24]	69.6	
Adjusted	8	1.03 [0.73; 1.46]	77.9	Not tested
Unadjusted	9	1.10 [0.84; 1.43]	63.3	
Study Design – Prospective	12	1.07 [0.85; 1.36]	64.8	0.11
Study Design – Retrospective	2	0.54 [0.23; 1.23]	71.9	
Risk of disease – High	3	0.76 [0.28; 2.07]	53.6	0.60
Risk of disease – Normal	11	1.00 [0.78; 1.28]	73.5	
Risk of bias – Low	6	1.20 [0.84; 1.71]	76.8	0.09
Risk of bias – High/Unclear	8	0.81 [0.62; 1.06]	44.0	

3.1.2 SF introduction and risk of eczema in children aged 5-14 years

3.1.2.1 SF ≥3-4 months vs <3-4 months

Three observational studies reported OR for SF at ≥3-4 months vs <3-4 months and risk of AD at age 5-14 years. Data were not pooled due to extreme statistical heterogeneity (I^2=83%). All 3 studies had a low risk of bias on all domains, and reported adjusted data – Zutavern at aged 6 in a normal risk population using parental report of eczema, Mihrshahi at aged 5 in a high risk population using doctor diagnosis, Larsson at aged 9 in a normal risk population using ISAAC. In the study of Larsson, there was no significant association between SF 3-6 months versus >6 months and AD OR 0.99 (0.77, 1.27). However, there was a significant association between SF >6 months vs <3 months and AD (data shown in Figure 38). We were unable to identify an explanation for the statistical heterogeneity seen between studies.

Figure 38 SF ≥3-4 months vs. <3-4 months and risk of eczema at age 5-14 years



3.2 Data for SF and risk of eczema that couldn't be analysed

A further 7 prospective cohort studies reported relevant data from over 7500 study participants, which could not be included in meta-analysis. This was due to the way the studies presented the data, either as simply a narrative in the Results section, or with estimates that were not comparable. Their characteristics and results are summarised in Table 12. The studies show no evidence of an association between SF and AD.

Table 12 Studies investigating the association between solid food introduction and eczema which were not eligible for meta-analysis

Study	Design	Outcome	Age	N/n cases	Data	Measure	SF in AD	SF in no AD	P
Hesselmar 2010 (3)	PC	AD	1.5	184/ unclear	Continuous	Median (IQR)	4 (4, 5)	4 (4, 4.6)	0.97
Moore, 1985 (33)	PC	AD	1	470	Categorical		No significant association between SF >3 vs <3 and risk of AD (adjusted analysis)		
Joseph 2011 (109)	PC	AD	3	594	Categorical		No significant association between SF >4 vs <4 and risk of AD P=0.76		
Forsyth, 1993 (101)	PC	AD	2	455	Categorical		SF >3 had less AD (8.3%) than SF 2-3 (17.0%) but more than SF <2 (5.4%) P<0.05. Adjusted analysis		
Morgan, 2004 (35)	PC	AD	1.5	257	Categorical		No significant association between SF >3 vs <3 and risk of AD (adjusted analysis)		
Alm, 2008 (25)	PC	AD	1	4941/ unclear	Categorical		No significant association between SF and risk of AD		
Harris, 2001 (21)	PC	AD	2	622/ 283	Categorical		No significant association between SF and risk of AD		

4 Conclusions

This report summarises the results of 57, 47, 25 studies of TBF, EBF and SF respectively, in relation to AD risk. Studies included over 250,000 people and AD is a common disease affecting 5-20% of most human populations. Thus we captured a significant dataset in which to explore the relationship between BF, SF and AD risk. Our search identified one high quality recent systematic review, which appraised 2 observational studies of EBF duration and AD and found no evidence for an association. One cluster RCT trial of a breastfeeding promotion intervention found reduced AD risk at 1 year (but not at 6.5 years) in centres randomised to the breastfeeding promotion intervention. Despite a large volume of data from observational studies, some analyses especially for EBF and solid food introduction were limited by small numbers of studies reporting relevant data. Overall we found no evidence from the observational studies that duration of TBF or EBF at any stage is associated with reduced risk of AD. Some analyses suggested an association in the opposite direction i.e. prolonged BF associated with increased AD – however these were not consistent between analyses, not robust to subgroup analysis, and not seen in studies which did not contribute to meta-analysis. The intervention trial evidence that breastfeeding promotion reduces risk of AD was graded at LOW certainty, due to imprecision and inconsistency with other sources of evidence. We found no association between timing of SF introduction and AD risk.

Our data suggest that breastfeeding promotion may reduce risk of AD, at least in the first year of life, but that the evidence for this is of LOW certainty. We did not find evidence that duration of EBF, or timing of SF introduction, influence AD risk. We did identify some evidence of gene-environment effects which were also seen in the 'Allergic Sensitisation' report – suggesting that human breast milk may be able to have an effect on AD risk, but that its composition or the genetic make-up of the infant are important effect modifiers. This is an unproven hypothesis with respect to AD, but needs exploration in future studies since our understanding of eczema pathogenesis may be enhanced by understanding the relationship between breast milk composition, maternal and infant genotype, and clinical outcome.

A previous overview of systematic reviews undertaken by the Cochrane Collaboration found no evidence of a relationship between these exposures and risk of eczema, but did highlight the single intervention trial which we also found, that reported reduced eczema risk in infants born in centres randomised to a breastfeeding promotion intervention (111). Our

comprehensive analysis of the observational studies literature has failed to strengthen support for this finding..

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BREASTFEEDING DURATION, SOLID FOOD INTRODUCTION AND RISK OF FOOD ALLERGY

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1 Total Breastfeeding Duration and Food Allergy

1.1 Overall characteristics of studies, risk of bias and summary of results

Table 1 describes the main characteristics of the studies analysed in this report. A total of 18 observational studies, and no intervention studies, reported the association between duration of breastfeeding and risk of Food Allergy (FA). Of these, 11 were prospective cohort studies, 1 nested case-control, 1 cross-sectional study and 4 case-control studies. Over half of the studies (n=12) are from Europe – others are from North America (n=2), Australasia (n=3), and Africa (n=1). Overall, valid data on Total Breastfeeding Duration in the first 2 years of life (TBF) and FA risk were available from over 72,000 subjects. Information on FA was obtained mainly from a medical assessment in 10 studies, via parental report in 4 studies and supervised oral food challenge in 4 studies. With regards to time of outcome diagnosis, 14 studies explored the association between TBF duration and FA in the first 5 years of life, where FA and anaphylaxis are most common, and 4 evaluated FA in older children or adolescents. Twelve studies used interview or questionnaire to assess the exposure (TBF), 2 studies assessed medical records only and in 3 studies the method of exposure assessment was unclear.

Risk of bias was assessed using the NICE Methodological checklists for cohort and case-control studies. Figure 1 illustrates the distribution of bias across the five main methodological areas of the studies. Over half of studies had a high risk of bias, most commonly due to lack of adjustment for confounding bias i.e. no adjusted data presented. Over a quarter of studies had an 'unclear' overall risk of bias, for varied reasons. Risk of conflict of interest was generally assessed as low.

Where data were available, five levels of comparison were used to assess the risk of FA according to TBF duration, namely 'any (including ever) vs. never', '≥1-2 months vs. <1-2 months', '≥3-4 months vs. <3-4 months', '≥5-7 months vs. <5-7 months', and '≥8-12 months vs. <8-12 months'.

Main Findings

In general there were only small numbers of studies with data available, and several analyses were restricted to studies with high risk of bias. Two large prospective studies found significantly increased risk of FA in breastfed compared to never breastfed children (Figure 2) OR 1.57 (1.28, 1.93), with high statistical heterogeneity (I^2=63%) which may be explained by appropriate adjustment for confounders in one study and not the other. Two additional studies reported data that could be used to calculate OR for peanut and/or other nut allergy in infants breastfed versus not breastfed, and found increased risk of peanut/nut FA in breastfed infants in unadjusted analyses, but not in adjusted analyses. Other studies did not support a relationship between different durations of TBF and FA, or TBF ever/never and allergy to specific foods CM, Egg or PN. However numbers of studies and participants were low for such analyses. Stratified and subgroup analyses and Funnel plots were not undertaken due to small numbers of studies in individual meta-analyses.

In summary we found weak evidence that FA may be more common in breastfed children. To our knowledge neither of the relevant studies excluded FA occurring during breastfeeding, in order to reduce the possibility that breastfeeding is prolonged due to the initiation of FA symptoms. Given the type and quality of the studies, these data provide no consistent evidence (GRADE -2; inconsistency, study quality) for a causal relationship between TBF duration and FA, and further work is needed to understand the relationship between breastfeeding and FA.

Table 1 Characteristics of included studies evaluating TBF duration and food allergy

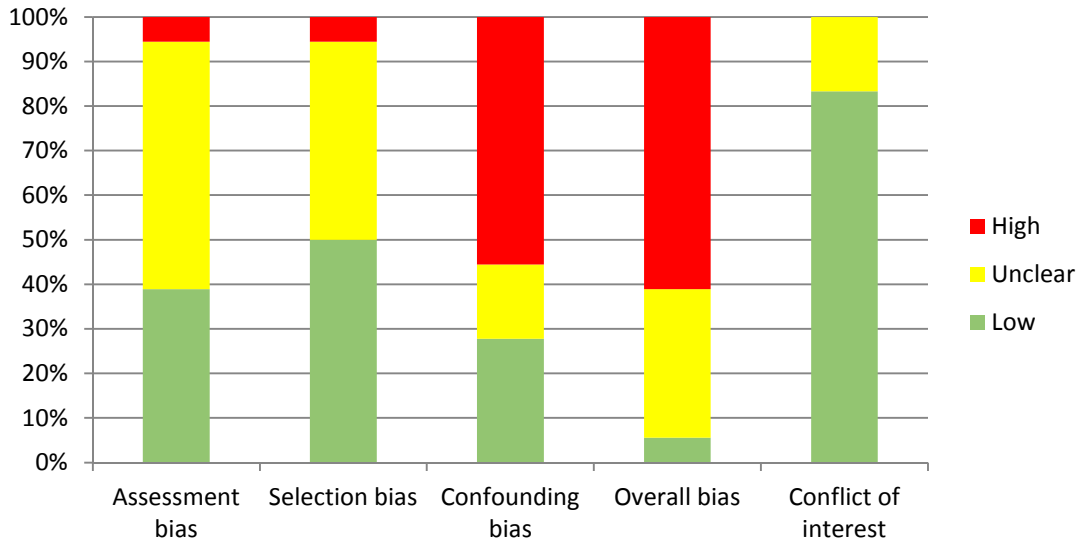
First Author & Publication Year	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Hesselmar, 2010 (1)	184/14	PC	Sweden	I	Physician assessment: history +/- investigations	0.5, 1.5	ALLERGYFLORA. Population based cohort of mainly high risk infants recruited from antenatal clinics 1998-2003
Lack, 2003 (2)	11179/ 45(21)	PC	UK	Q/I	Parent report of food reaction (DBPCFC)	5.5	ALSPAC. Population based cohort of children born 1991-1992
Kull, 2002 (3)	3790/768	PC	Sweden	Q	DD	2	BAMSE. Population based cohort of children born 1994-1996
Gustafsson, 2000 (4)	94/56	PC	Sweden	Q	Parent report of food reaction	7	Children with atopic dermatitis attending allergic clinic or referred by child welfare clinics
Koplin, 2010 (5)	2589/231	PC	Australia	Q	Open food challenge	1	HEALTHNUTS. Population based cohort of children born 2008-2010 recruited at 1 year at routine immunization clinics
Hikino, 2001 (6)	21766/23 81	PC	Japan	Q	DD	1.5	All children born in 1993-1995 attending well-baby check-ups funded by Fukuoka City
Goksor, 2011 (7)	4496/202	PC	Sweden	Unclear	DD	4.5	Infants of Western Sweden. Population birth cohort of infants born in 2003

First Author & Publication Year	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Kemeny, 1991 (8)	180/9	PC	UK	Unclear	Parent report of ≥2 food reactions	1	Population based birth cohort of infants born at Dulwich and King's College Hospitals in London
Milner, 2004 (9)	8073/396	PC	USA	Q	DD	3	National Maternal and Infant Health Survey and Longitudinal Follow Up. Representative population-based cohort born in 1988. Blacks, individuals with low socioeconomic status, and premature infants intentionally overrepresented
Saarinen, 1995 (10)	236/61 and 18	PC	Finland	R	Parent report of food reaction	5 and 17	Cohort recruited from hospital and born in 1975
Venter, 2009 (11)	891/58	PC	UK	Q	Open food challenge	3	Population based cohort recruited from antenatal clinics and born in 2001-2002
Oliver, 2010 (12)	93/31	NCC	UK	R	DBPCFC	1	EuroPrevall UK. Cases and age-matched controls selected from a population based birth cohort of infants born in 2008
DesRoches, 2010 (13)	403/202	CC	Canada	Q	Physician assessment: history +/- investigations	<1.5	Hospital based cases and controls recruited 1998-2004.
Djenouhat, 2011 (14)	450/150	CC	Algeria	Unclear	Physician assessment: history +/- investigations	0.3	Hospital based cases and family controls, born 1999-2005

First Author & Publication Year	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Fox, 2009 (15)	283/133	CC	UK	Q	Physician assessment: history +/- investigations	<4	Cases and controls were children referred for suspected FA to a large paediatric service
Ventura, 1988 (16)	339/148	CC	Italy	I	Physician assessment: history +/- investigations	<1	Italian Working Group on CMPA. Cases selected from 15 paediatric centres in Italy and age and area matched controls from well-baby clinics
Paton, 2012 (17)	15142/592	CS	Australia	Q	Parent-reported food reaction (any nut)	7	Representative primary school entrants 2006-2009
Berjon, 1987 (18)	2690/148	CS	Spain	Unclear	DD	14	Patients attending a paediatric allergy clinic in Valladolid, Spain between 1970 and 1984, with and without diagnosed food allergy

Q: questionnaire, I: interview, R: medical records, PC: prospective cohort, NCC: nested case control, CS: Cross-sectional, CC: case control, DBPCFC: double blind placebo controlled food challenge, DD: doctor diagnosis of FA, in contrast to 'Physician assessment' where FA diagnosis was always made by a study physician as part of the study protocol, NA: not available

Figure 1 Risk of bias in studies of TBF duration and food allergy



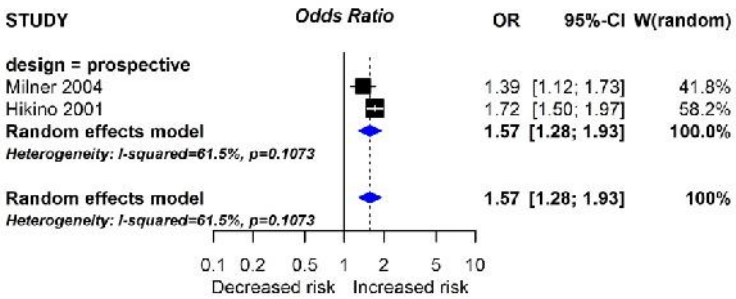
1.1 TBF and FA in children aged 0-4 years

1.1.1 Any Food Allergy in children aged 0-4 years

1.1.1.1 TBF Ever vs. Never

Figure 2 shows the pooled estimates of 2 eligible observational studies including 2777 people with FA, suggesting increased risk of FA if breastfeeding was initiated, with high heterogeneity between the two studies (I^2=62%) The prospective cohort study of Milner presents OR adjusted just for multivitamin intake, while the prospective cohort study of Hikino adjusted for birthweight, sex and gestational age. The unadjusted OR (1.44) of the latter was very similar to the OR in the study of Milner. In the study of Hikino data were also presented for FA at age 3 years, where there was high risk of selection bias due to greater loss to follow up, but there remained increased odds of FA in breastfed children - unadjusted OR 4.45 (3.42, 5.78).

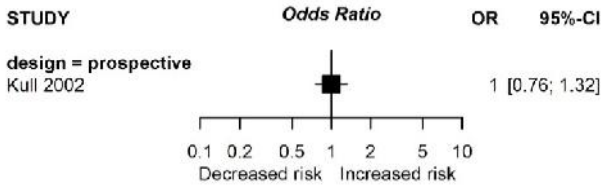
Figure 2 TBF Ever vs. Never and risk of any FA at age 0-4 years



1.1.1.2 TBF ≥ 5-7 months vs. <5-7 months

No studies reported data that could be used to calculate OR for FA with different TBF exposure/reference groups. One prospective cohort study including 768 cases of FA reported odds of diagnosed FA in children aged 2 who were breastfed for ≥ 6 months compared to <6 months and found no significant difference in adjusted analysis (Figure 3). The study risk of bias was judged as low in most domains.

Figure 3 TBF ≥5-7 months vs. <5-7 months and risk of any FA at age 0-4 years

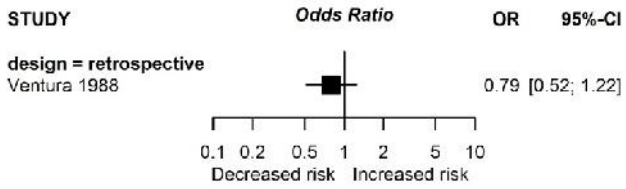


1.1.2 Cow's Milk Allergy in children aged 0-4 years

1.1.2.1 TBF Ever vs. Never

One study reported data that could be used to calculate OR for Cow's Milk Allergy (CMA) in infants breastfed versus not breastfed, and is shown in Figure 4. The data are unadjusted, and therefore carry a high risk of bias, and show no significant difference in OR for CMA in relation to breastfeeding status. In the same study, mean TBF duration was not significantly different between infants with (2.0 months) and without (1.6 months) CMA.

Figure 4 TBF Ever vs. Never and risk of FA to milk at age 0-4 years

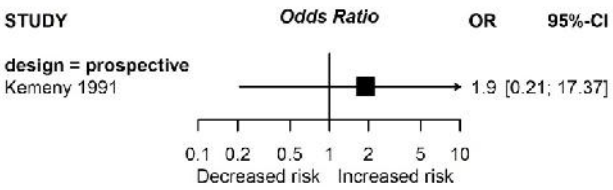


1.1.3 Egg Allergy in children aged 0-4 years

1.1.3.1 TBF Ever vs. Never

One study reported data that could be used to calculate OR for egg allergy in infants breastfed versus not breastfed, and is shown in Figure 5. The data are unadjusted and therefore carry a high risk of bias, and show no significant difference in OR for egg allergy in relation to breastfeeding status.

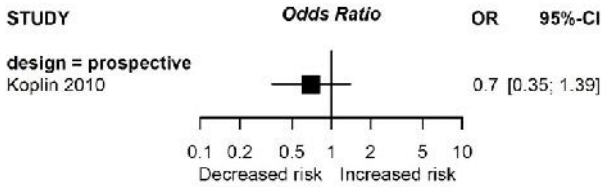
Figure 5 TBF Ever vs. Never and risk of FA to egg at age 0-4 years



1.1.3.2 TBF ≥1-2 months vs < 1-2 months

One study reported risk of egg allergy in infants breastfed longer than 1 month. The data are adjusted, the study had a low overall risk of bias, and they show no significant difference in OR for egg allergy in relation to breastfeeding status: OR 0.9 (95%CI 0.5, 2.2) for TBF 1-3 months; OR 1.1 (0.6, 2.3) 4-6 months; OR 0.9 (0.5, 1.9) 7-9 months; OR 0.9 (0.4, 1.8) 10-12 months; OR 0.7 (0.4, 1.4 for >12 months (shown in Figure 6).

Figure 6 TBF ≥1-2 months vs. <1-2 months and risk of FA to egg at age 0-4 years



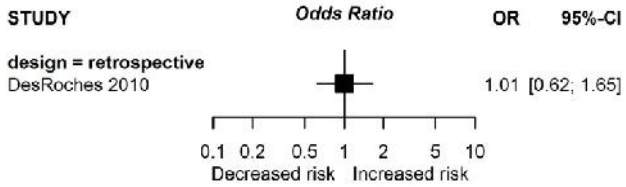
1.1.4 Peanut Allergy in children aged 0-4 years

1.1.4.1 TBF Ever vs. Never

One case control study reported data that could be used to calculate OR for peanut allergy in infants breastfed versus not breastfed, and is shown in Figure 7. The data are unadjusted and therefore carry a high risk of bias, and show no significant

difference in OR for peanut allergy in relation to breastfeeding status. In the same study, mean TBF duration was not significantly different between infants with (6.3, sd 3.8) and without (5.7, sd 3.7) peanut allergy.

Figure 7 TBF Ever vs. Never and risk of peanut allergy at age 0-4 years



1.2 TBF and FA in children aged 5-14 years

1.2.1 Peanut Allergy in children aged 5-14 years

1.2.1.1 TBF Ever vs. Never

Two studies reported data that could be used to calculate OR for peanut and/or other nut allergy in infants breastfed versus not breastfed, and are shown in Figure 8. The data on peanut allergy reported from the cohort study of Lack 2003 are unadjusted and therefore carry a high risk of bias, and Paton 2012 is a cross-sectional study which was judged as at high risk of confounding bias because data were only adjusted for age and sex and not for other factors such as family history of allergic disease and eczema which are associated with peanut and/or other nut allergy. Pooled analysis shows increased odds of peanut/nut allergy in breastfed infants OR 1.59 (1.17, 2.15) with no statistical heterogeneity. In the study of Lack 2003 unadjusted analysis showed increased odds of peanut allergy with breastfeeding duration of ≥6 months OR 2.60 (1.04, 6.53) and there was a trend to increased odds of peanut allergy with increased TBF duration (Figure 9, Figure 10, and Figure 11). Lack also reported the relationship between TBF and peanut allergy confirmed by DBPCFC in a subset of the population with reported peanut allergy. Here they found no significant association between TBF ever and peanut allergy – unadjusted OR 2.14 (0.91, 5.04). In adjusted analyses, the associations between TBF and peanut allergy were not significant.

Overall the data do not provide strong evidence for a relationship between TBF duration and peanut allergy.

Figure 8 TBF Ever vs. Never and risk of FA to nut-peanut at age 5-14 years

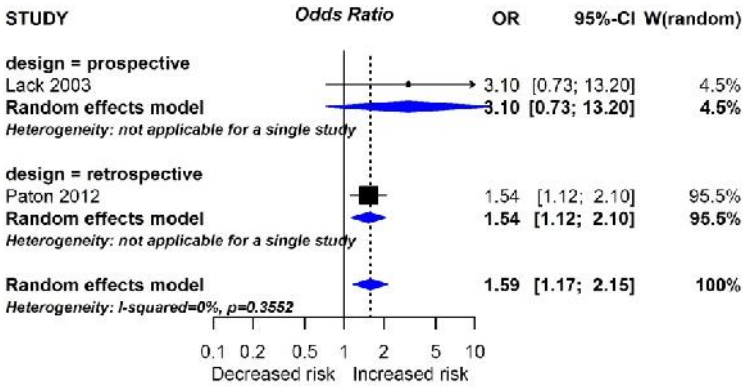


Figure 9 TBF 0-3 months vs. never and risk of FA to peanut at age 5-14 years

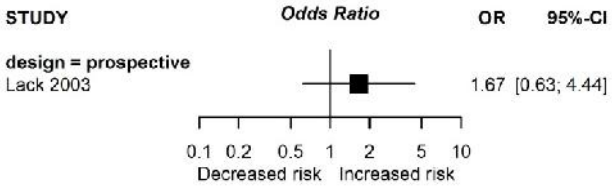


Figure 10 TBF 3-5 months vs. never and risk of FA to peanut at age 5-14 years

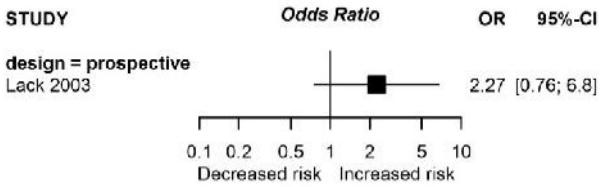
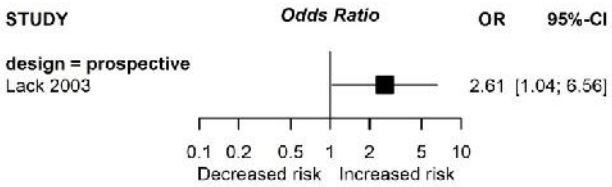


Figure 11 TBF ≥6 months vs. never and risk of FA to peanut at age 5-14 years



1.3 Data for TBF duration and FA which were not suitable for meta-analysis

Meta-analyses included 9 studies, reporting data on at least 4200 participants with FA. A further 9 studies reported relevant data which could not be reported in meta-analysis, in relation to at least 800 participants with FA. Results in these studies did not allow creating effect estimates that could be combined in a meta-analysis. Four studies used mean or median, and six provided a narrative only describing the effect observed. These studies are summarised in Table 2. TBF duration was shorter in people with CMA in one study. In all other studies and analyses reported there was no association found.

Table 2 Studies investigating the association between TBF duration and food allergy which were not eligible for meta-analysis

Study	Design	Outcome	Age	N/n cases	Data	Measure	TBF in no FA	TBF in FA	P
Hesselmar 2010 (1)	PC	FA	1.5	184/14	Continuous	Median (IQR)	7 (4.5)	8.5 (5.5)	0.25
		CMA	0.5	184/unclear	Continuous	Median (IQR)	7 (4.6)	8 (4)	0.35
Oliver 2010 (12)	NCC	FA	1	93/31	Continuous	Mean (weeks)	22	15	NS
Fox 2009 (15)	CC	Peanut Allergy	<4	293/133	Continuous	Mean (months)	8.1	8.1	NS
Berjon, 1987 (18)	CS	FA	14	2690/148	Categorical	No significant difference between those with and without food allergy in TBF ever			
Djenouhat (14) (2011)	CC	CMA	0.3	450/150	Categorical	Breastfeeding was associated with reduced CMA in adjusted analysis (abstract publication)			
Venter, 2009 (11)	PC	FA	3	891/ 58	Categorical	No significant difference between those with and without food allergy in TBF ever, >6 or >9 months (unadjusted)			

Study	Design	Outcome	Age	N/n cases	Data	Measure	TBF in no FA	TBF in FA	P
Goksor 2011 (7)	PC	FA	4.5	4496/202	Categorical	No significant association between TBF >4 months and FA ? adjusted analysis			
Gustafsson, 2000 (4)	PC	FA	8	94/56	Categorical	No significant association between TBF >1 or >6 months and FA			
Saarinen, 1995 (10)	PC	FA	5 and 17	256/61 and 18	Categorical	No significant association between TBF <1, 1-6 or >6 months and FA			

2 Exclusive Breastfeeding Duration and Food Allergy

2.1 Overall characteristics of studies, risk of bias and summary of results

Table 3 describes the main characteristics of the studies analysed in this report. A total of 1 systematic review describing 1 cohort study, and 14 observational studies, reported the association between duration of exclusive breastfeeding (EBF) and risk of Food Allergy (FA). Of these, 11 were prospective cohort studies, 1 nested case-control, 2 cross-sectional study and none case-control studies. Over half of the studies (n=10) are from Europe – others are from Australasia (n=3), and the Middle East (n=1). Overall, valid data on EBF duration and FA risk were available from over 30,000 subjects. Information on FA was obtained mainly from a medical assessment in 5 studies, via parental report in 6 studies, through supervised oral food challenge in 3 studies and not clear in 1 study. With regards to time of outcome diagnosis, 13 studies explored the association between EBF duration and FA in the first 5 years of life, where FA and anaphylaxis are most common, and 2 evaluated FA in older children or adults. Most studies used a questionnaire to assess the exposure (EBF), sometimes supplemented by a diary or medical record review, and in 2 studies the method of exposure assessment was unclear.

Risk of bias for the observational studies is shown in Figure 12. Over half of studies had a high risk of bias, due to lack of adjustment for confounding bias i.e. no adjusted data presented. The majority of studies also had 'unclear' risk of assessment bias due to inadequate definition of what was meant by EBF duration. Risk of conflict of interest was generally assessed as low.

Where data were available, three levels of comparison were used to assess the risk of FA according to EBF duration, namely ≥0-2 months vs. <0-2 months; ≥3-4 months vs. <3-4 months; ≥5-9 months vs. <5-9 months. Across all these cut-offs there was no consistent evidence of a lower risk of FA if EBF was prolonged. In general there were only small numbers of studies with data available, and several analyses were restricted to studies with high risk of bias. A single prospective RCT was underpowered and inconclusive, and the few prospective cohort studies reporting appropriately adjusted data yielded mixed and inconclusive findings.

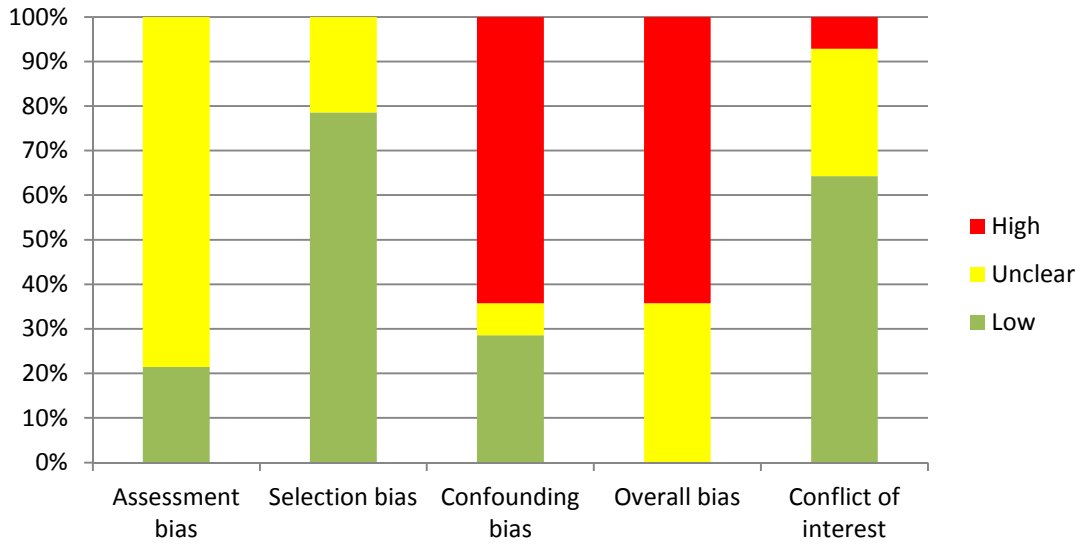
Table 3 Characteristics of included studies evaluating EBF duration and food allergy

First Author & Publication Year	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Kramer (19) Kajosaari, 1991 (20)	135	SR/PC	Finland	-	Parent reported FA and DBPCFC	1, 5	Infants of atopic parents
Hesselmar, 2010 (1)	184/14	PC	Sweden	I	Physician assessment: history +/- investigations	1.5	ALLERGYFLORA. Population based cohort of mainly high risk infants recruited from antenatal clinics 1998-2003
Kull, 2002 (3)	3791/768	PC	Sweden	Q	DD	2	BAMSE. Population based cohort of children born 1994-1996
Besednjak-Kocijancic, 2010 (21)	408/24	PC	Slovenia	Unclear	Unclear	1, 5	Infants with a positive history of parental allergy
Arshad, 1992 (22)	1167/80	PC	UK	D/Q	Parent report of ≥ 2 food reactions	1	Isle of Wight Study. Population based birth cohort of infants born in semi-rural areas between 1989 and 1990
Kemeny, 1991 (8)	180/9	PC	UK	Unclear	Parent report of ≥ 2 food reactions	1	Population based birth cohort of infants born at Dulwich and King's College Hospitals in London
Kim, 2011 (23)	1177/61	PC	Korea	Q/I	Parent report of ≥ 2 food reactions	1	Population based birth cohort of infants born in Seoul between July 2006 and August 2007

First Author & Publication Year	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Host, 1991 (24)	315/16	PC	Denmark	R/Q/I	Open food challenge	1	Population birth cohort of infants from the municipality of Odense born in 1985
Pesonen, 2006 (25)	160/19	PC	Finland	I	Parent report of ≥ 2 food reactions	5	Population based birth cohort of infants born in 1981
Saarinen, 1979 (26)	177/17	PC	Finland	Q	Physician assessment: methodology unclear	1	Recruited from hospital and born in 1975
Matheson, 2007 (27)	5729/568	PC	Australia	Q	DD	44	Tasmanian Asthma Study: population based cohort born in 1961
Venter, 2009 (11)	891/58	PC	UK	Q	Open food challenge	3	Population based cohort recruited from antenatal clinics and born in 2001-2002
Maskell, 2010 (28)	117/31	NCC	UK	D	DBPCFC	1	EuroPrevall UK. Cases and age-matched controls selected from a population based birth cohort of infants born in 2008
Paton, 2012 (17)	15142/592	CS	Australia	Q	Parent-reported reaction to any nut	7	Representative primary school entrants 2006-2009.
Ehlayel, 2008 (29)	1278/ unclear	CS	Qatar	Q	DD	5	Children 0-5 years old attending primary healthcare centres for routine immunisation

Q: questionnaire, I: interview, R: medical records, D: diary, PC: prospective cohort, NCC: nested case control, CS: Cross-sectional, CC: case control, DBPCFC: double blind placebo controlled food challenge, DD: doctor diagnosis of FA, in contrast to 'Physician assessment' where FA diagnosis was always made by a study physician as part of the study protocol.

Figure 12 Risk of bias in studies of EBF duration and food allergy



2.2 Exclusive breastfeeding duration and risk of food allergy

2.2.1 Systematic reviews and intervention trials

The single systematic review and included cohort study (Table 4) found no evidence that exclusive/predominant breastfeeding for 6 months, compared with exclusive/predominant breastfeeding for 3 months, influenced risk of challenge-proven food allergy at 1 year (RR 0.77 95%CI 0.25, 2.41) although parent reported food allergy at the same time-point in the same study was significantly reduced (30). Food allergy at 5 years was not significantly different in the same study (RR 0.61 95% CI 0.12, 3.19).

Table 4 EBF for 6 months versus 3 months and risk of food allergy

Study	Outcome measure	No. participants (studies)	Outcome (95% CI)
Kramer (19) Kajosaari (20) (30)	Parent report - 1 year	135 (1)	RR 0.19 [0.08, 0.48]
	DBPCFC - 1 year	135 (1)	RR 0.77 [0.25, 2.41]
	FA diagnosis - 5 years	113 (1)	RR 0.61 [0.12, 3.19]

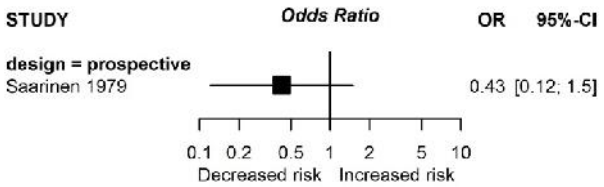
2.2.2 Observational studies of EBF duration and FA in children aged 0-4 years

2.2.2.1 Any Food Allergy in children aged 0-4 years

2.2.2.1.1 EBF ≥0-2 months vs. <0-2 months

One prospective cohort study reported data that could be used to calculate OR for FA in the first year, in infants with EBF for 6 months vs. <2 months duration and is shown in Figure 13. The study found no significant association. The data are unadjusted, so carry a high risk of bias, and the authors reported similar findings comparing 2-6 months duration with <2 months, and using the same categorisations at age 3 years.

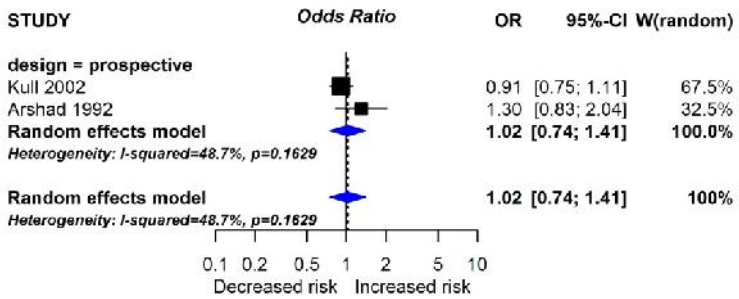
Figure 13 EBF ≥0-2 months vs. <0-2 months and risk of any FA at age 0-4 years



2.2.2.1.2 EBF ≥3-4 months vs. <3-4 months

Two prospective cohort studies reported data that could be used to calculate OR for FA at age 0-4 years, in infants with EBF for ≥3-4 months vs. <3-4 months duration and are shown in Figure 14. They show no significant association, with moderate heterogeneity. The data from Arshad 1992 are unadjusted, so carry a high risk of bias, but the data of Kull 2002 are adjusted. This may explain the statistical heterogeneity.

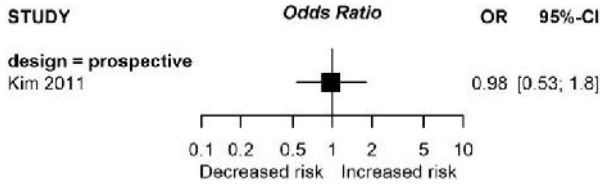
Figure 14 EBF ≥3-4 months vs. <3-4 months and risk of any FA at age 0-4 years



2.2.2.1.3 EBF ≥5-6 months vs. <5-6 months

One prospective cohort study reported data that could be used to calculate OR for FA in the first year in infants with EBF for ≥6 months vs. <6 months duration and is shown in Figure 15. The study reported adjusted data, and found no significant association.

Figure 15 EBF ≥5 months vs. <5 months and risk of any FA at age 0-4 years

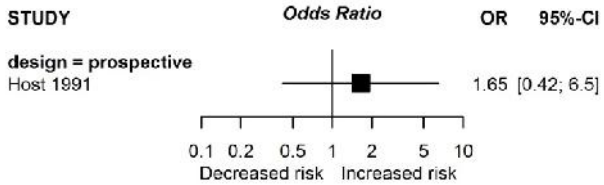


2.2.2.2 Cow's Milk Allergy in children aged 0-4 years

2.2.2.2.1 EBF ≥0-2 months vs. <0-2 months

One prospective cohort study reported data that could be used to calculate OR for CMA in the first year, in infants with EBF for >1 month vs. <1 month duration and is shown in Figure 16. The study found no significant association. The data are unadjusted, so carry a high risk of bias, and the authors reported similar insignificant findings when assessing 1-3 months vs. <1 month, and >3 months vs. <1 month.

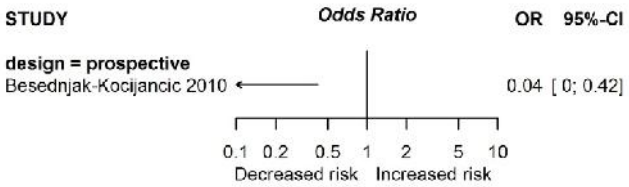
Figure 16 EBF ≥0-2 months vs. <0-2 months and risk of FA to cow's milk at age 0-4 years



2.2.2.2.2 EBF ≥3-4 months vs. <3-4 months

One prospective cohort study reported data that could be used to calculate OR for CMA in the first year, in infants with EBF for ≥3-4 months vs. <3-4 months duration and is shown in Figure 17. The study found significantly reduced risk of CMA with longer EBF. The data are unadjusted, so carry a high risk of bias.

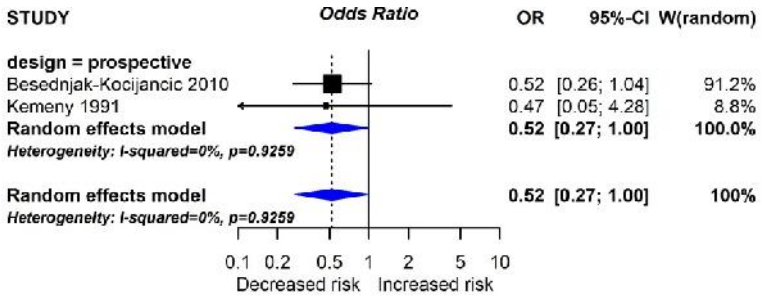
Figure 17 EBF ≥3-4 months vs. <3-4 months and risk of FA to cow's milk at age 0-4 years



2.2.2.3 Egg Allergy in children aged 0-4 years

Two prospective cohort studies reported data that could be used to calculate OR for egg allergy at age 0-4 years, in infants with EBF for ≥3-4 months vs. <3-4 months duration and are shown in Figure 18. They show reduced odds of egg allergy with longer duration of EBF, with borderline statistical significance and no statistical heterogeneity. Both studies reported unadjusted data, and are therefore at high risk of bias.

Figure 18 EBF ≥3-4 months vs. <3-4 months and risk of FA to egg at age 0-4 years



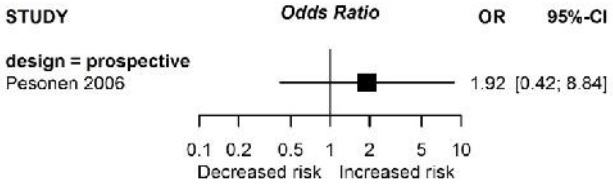
2.2.3 Observational studies of EBF duration and FA in children aged 5-14 years

2.2.3.1 Any Food Allergy in children aged 5-14 years

2.2.3.1.1 EBF ≥0-2 months vs. <0-2 months

One prospective cohort study reported data that could be used to calculate OR for FA at age 5-14 years, in infants with EBF for ≥0-2 months vs. <0-2 months duration and is shown in Figure 19. The study found no significant association, and the data carry a high risk of bias because they are unadjusted.

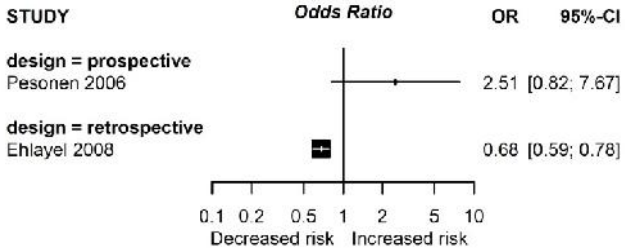
Figure 19 EBF ≥0-2 months vs. <0-2 months and risk of any FA at age 5-14 years



2.2.3.1.2 EBF ≥5 months vs. <5 months

Two prospective cohort studies reported data that could be used to calculate OR for FA at age 5-14 years, in infants with EBF for ≥5 months vs. <5 months duration and are shown in Figure 20. The data were not pooled due to extreme statistical heterogeneity. The cross-sectional study of Ethlayel 2008 reported unadjusted data, and therefore carries a high risk of bias. The prospective cohort study of Pesonen 2006 reported adjusted data, and had unclear risk of bias due to unclear method for defining EBF duration, which was categorised as ≥9 vs. <9 months, which is an unusually long duration of EBF in most human populations.

Figure 20 EBF ≥5 months vs. <5 months and risk of any FA at age 5-14 years

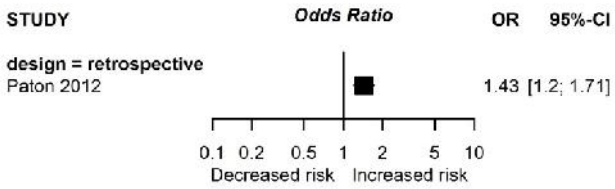


2.2.3.2 Peanut Allergy in children aged 5-14 years

2.2.3.2.1 EBF ≥5 months vs. <5 months

One cross-sectional study reported data that could be used to calculate OR for nut allergy (peanut or tree nut) at age 5-14 years, in infants with EBF for ≥5 months vs. <5 months duration and is shown in Figure 21. There were significantly increased odds of nut allergy in children who had longer duration of EBF. However the study was considered at high risk of bias due to inadequate adjustment for potential confounders – age and sex only were adjusted for.

Figure 21 EBF ≥5 months vs. <5 months and risk of FA to nut-peanut at age 5-14 years

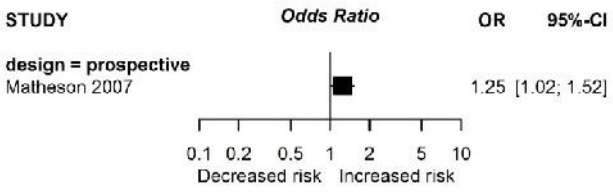


2.2.4 Observational studies of EBF duration and FA at age 15+

2.2.4.1 Any Food Allergy in children aged 15+ years

One prospective cohort study reported data that could be used to calculate OR for any food allergy at age 44 years, in adults with a history of EBF ≥3-4 months vs. <3-4 months duration and is shown in Figure 22. There were significantly increased odds of self-reported FA in adults who had received longer duration of EBF. The data were appropriately adjusted, but the study was considered at unclear risk of bias due to inadequate definition of EBF, which was assessed retrospectively through parental report at aged 7 years. In the same study, reduced odds of parent-reported allergy to foods or medicines were found with EBF ≥3-4 months at age 7; aOR 0.75 (0.62, 0.92).

Figure 22 EBF ≥3-4 months vs. <3-4 months and risk of any FA at age 15+ years



2.2.5 Data for TBF duration and FA which were not suitable for meta-analysis

Meta-analyses included 12 studies, reporting data on at least 1800 participants with FA. A further 4 studies reported relevant data which could not be reported in meta-analysis, in relation to at least 100 participants with FA. These studies are summarised in Table 5. TBF duration was shorter in people with FA in one study. In all other studies and analyses reported there was no association found.

Table 5 Studies investigating the association between EBF duration and food allergy which were not eligible for meta-analysis

Study	Design	Outcome	Age	N/n cases	Data	Measure	EBF duration with no FA	EBF duration with FA	P
Hesselmar 2010 (1)	PC	FA	1.5	184/14	Continuous	Median (IQR) in months	4 (4, 4.5)	4 (3.3, 4)	NS
Maskell 2010 (28)	NCC	FA	1	117/39	Continuous	Mean (weeks)	5.4	3.2	P=0.045
Venter, 2009 (11)	PC	FA	3	891/58	Categorical	No significant association between EBF duration of >3 months and food allergy at 1 or 3 years			
Kemeny, 1991 (8)	PC	CMA	1	180/0	Categorical	No significant association between EBF duration of >3 months and food allergy at 1 year			

3 Solid Food Introduction and Food Allergy

3.1 Overall characteristics of studies, risk of bias and summary of results

Table 6 describes the main characteristics of the studies analysed in this report. A total of 6 observational studies and no intervention studies, reported the association between timing of solid food introduction (SF) and risk of FA. Of these, 4 were prospective cohort studies, 1 nested case-control, 1 case-control study. Half of the studies (n=3) are from Europe, 2 from Australasia (n=3), and 1 North America. Overall, valid data on SF and FA risk were available from almost 3000 subjects. Information on FA was obtained mainly from a medical assessment in 2 studies, via parental report in 1 study, and through supervised oral food challenge in 3 studies. With regards to time of outcome diagnosis, all studies explored the association between SF and FA in the first 1.5 years of life. Four studies used a questionnaire to assess the exposure (SF), 1 used an interview and 1 a diary.

Risk of bias is summarised in Figure 23. Almost half of studies had a high risk of bias, due to lack of adjustment for confounding bias i.e. no adjusted data presented. In a further 25% of studies the risk of confounding bias was unclear. Risk of conflict of interest was generally assessed as low.

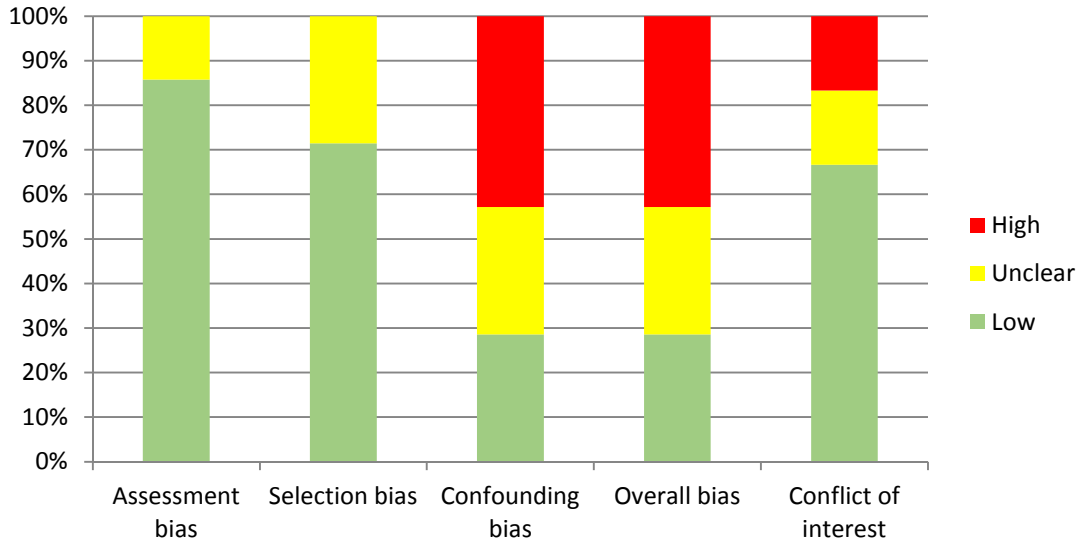
The risk of FA according to SF was categorised as ≥3-4 months vs. <3-4 months. Overall the evidence base was limited due to small numbers of studies and participants with food allergy included in analyses. We found no evidence that the timing of solid food introduction is associated with risk of FA, based on the available data.

Table 6 Characteristics of included studies evaluating SF introduction and food allergy

First Author & Publication Year	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Hesselmar, 2010 (1)	184/14	PC	Sweden	I	Physician assessment: history +/- investigations	0.5, 1.5	ALLERGYFLORA. Population based cohort of mainly high risk infants recruited from antenatal clinics 1998-2003
Koplin, 2010 (5)	2589/231	PC	Australia	Q	Open food challenge	1	HEALTHNUTS. Population based cohort of children born 2008-2010 recruited at 1 year at routine immunization clinics
Kim, 2011 (23)	1177/61	PC	Korea	Q/I	Parent report of ≥2 food reactions	1	Population based birth cohort of infants born in Seoul between July 2006 and August 2007
Venter, 2009 (11)	757/39	PC	UK	Q	Open food challenge	1	Population based cohort recruited from antenatal clinics and born in 2001-2002
Maskell, 2011; Oliver, 2010 (12, 28)	117/31	NCC	UK	D	DBPCFC	1	EuroPrevall UK. Cases and age-matched controls selected from a population based birth cohort of infants born in 2008
DesRoches, 2010 (13)	403/202	CC	Canada	Q	Physician assessment: history +/- investigations	1.5	Hospital based cases and controls recruited 1998-2004.

Q: questionnaire, I: interview, D: diary, PC: prospective cohort, NCC: nested case control, CC: case control, DBPCFC: double blind placebo controlled food challenge.

Figure 23 Risk of bias in studies of SF introduction and food allergy



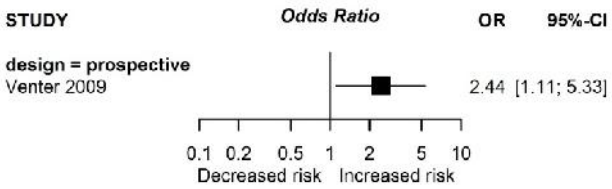
3.2 Solid food introduction and FA in children aged 0-4 years

3.2.1 SF ≥3-4 months vs. <3-4 months

3.2.1.1 Any Food Allergy in children aged 0-4 years

One prospective cohort study reported data that could be used to calculate OR for FA at age 0-4 years, in infants with SF ≥3-4 months vs. <3-4 months and is shown in Figure 24. There were significantly increased odds of FA in infants with delayed SF introduction. The data were unadjusted, so the study was considered at high risk of bias.

Figure 24 SF ≥3-4 months vs. <3-4 months and risk of any FA at age 0-4 years

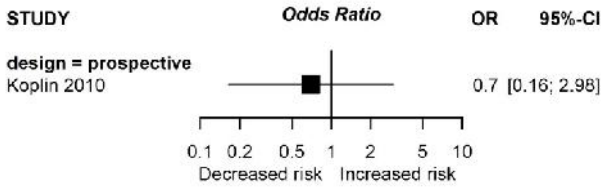


3.2.1.2 Egg Allergy in children aged 0-4 years

One prospective cohort study reported data that could be used to calculate OR for egg allergy at age 0-4 years, in infants with SF ≥3-4 months vs. <3-4 months and is shown in Figure 25. There were no association found in this analysis of SF≥6 vs <4 months. The same authors found no association between SF 4-5 vs <4 months – adjusted OR

2.1 (0.6, 7.0). The data were adjusted, and the study was considered at low overall risk of bias however confidence intervals were wide.

Figure 25 SF ≥3-4 months vs. <3-4 months and risk of FA to egg at age 0-4 years



3.2.2 Data for SF and FA reported narratively

Five other studies with 345 cases of FA reported data in a way that could not be included in the predefined meta-analyses. These studies are summarised in Table 7. No association was found between SF and FA in these studies.

Table 7 Studies investigating the association between SF introduction and food allergy which were not eligible for meta-analysis

Study	Design	Outcome	Age	N/n	Data	Measure	SF timing with no FA	SF timing with FA	P
Kim, 2011 (23)	PC	FA	1	1177/61	Categorical (>6months)	Adj.OR (95%CI)	1.4 (0.7-2.5)		NS
Hesselmar 2010 (1)	PC	FA	1.5	184/14	Continuous	Median (IQR) in months	4 (4)	4 (4)	NS
Oliver 2010 (12)	NCC	FA	1	93/31	Continuous	Mean (months)	4.2	4.2	NS
Maskell 2011 (28)	NCC	FA	1	117/39	Continuous	No significant difference in timing of solid food introduction between cases and controls			
DesRoches, 2010 (13)	CC	Peanut allergy	1.5	403/202	Continuous	Mean (SD) in months	4.5 (1.6)	4.3 (1.8)	NS

4 Conclusion

This report summarises the results of 29 studies investigation the association between total and exclusive breastfeeding duration, timing of solid food introduction and risk of food allergy. The majority of studies were prospective cohort studies. One systematic review of a single cohort study assessing EBF duration 6 months vs 3 months found evidence of reduced parent-reported food allergy at age 1 with longer EBF duration, however this effect was not seen in objective assessment of food allergy at the same age, nor in assessment of food allergy at age 5 years. From the observational studies we found weak evidence to support an association between longer TBF duration and increased risk of food allergy, but the data were not consistent. The quality and quantity of data was limited, especially for analysis of timing of solid food introduction in relation to FA. Few studies (2 in TBF, 2 in EBF and 2 in SFI) used an objective measure of food allergy (food challenge) which might contribute to the lack of evidence. Our conclusion is similar to that drawn by the EAACI Food Allergy Anaphylaxis Group, where the authors indicated that they found no evidence to suggest that breastfeeding could be protective against risk of food allergy in children (31). The available data did not suggest an association between EBF or SF and FA, and the evidence for an association between TBF and FA was weak. There is a strong, dose-response association between severity of infant eczema and risk of food allergy, and we found a similar weak association between increased TBF duration and eczema in our eczema report. Both the association between increased TBF and FA, and between increased TBF and eczema, may be influenced by mother's decision to prolong TBF when infants develop eczema or signs of food allergy. Only a minority of studies made appropriate adjustments to the analysis dataset to account for this possibility of reverse causation. Restricted analysis, excluding subjects with outcomes during breastfeeding should be undertaken in future studies of TBF/EBF and FA or eczema.

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BREASTFEEDING, SOLID FOOD INTRODUCTION AND ALLERGIC SENSITISATION

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TABLE 6 STUDIES INVESTIGATING THE ASSOCIATION BETWEEN SF INTRODUCTION AND ALLERGIC SENSITISATION WHICH WERE NOT ELIGIBLE FOR META-ANALYSIS 55

1 Total breastfeeding duration and Allergic Sensitisation

1.1 Overall characteristics of studies, risk of bias and summary of results

Table 1 describes the main characteristics of the studies that assessed total breastfeeding duration (TBF) in relation to food and aero-allergen allergic sensitisation (AS) risk. A total of 1 cluster randomised controlled trial and 35 observational studies, reported the association between TBF and AS. Of these, 30 were prospective cohort studies, 2 retrospective cohort studies and 3 cross-sectional studies. The majority of studies (n=23) are from Europe – others are from North America (n=4) and Australasia (n=5), Africa (n=1), South America (n=1) and unclear (n=1). Overall, valid data on TBF duration in the first 2 years of life and AS risk were available from over 31,000 subjects. Information on AS was obtained from skin prick testing using standard techniques in 19 studies, and by blood specific IgE testing in 16 studies. With regards to time of outcome diagnosis, 16 studies explored the association between TBF duration and AS at age 0-4, 16 at ages 5-14, and 3 at age 15 years and over. For assessment of TBF duration, 11 studies used an interview, one parent diaries, and 2 a medical records review; in 3 studies the method of exposure assessment was unclear and in all others a questionnaire method was used.

Risk of bias was assessed using the NICE Methodological checklists for cohort and case-control studies. Figure 1 illustrates the distribution of bias across the five main methodological areas of the studies. Over 40% of studies had a high risk of bias, most commonly due to lack of adjustment for confounding bias i.e. no adjusted data presented, and a similar number of studies had unclear risk of assessment bias, usually due to unclear method for determining TBF duration. Risk of conflict of interest was generally assessed as low (over 70% of studies) or unclear.

Where data were available, five levels of comparison were used to assess the risk of sensitization to allergen (food and aero-allergens) according to TBF duration, namely ‘any (including ever) vs. never’, ‘≥1-2 months vs. <1-2 months’, ‘≥3-4 months vs. <3-4 months’, ‘≥5-7 months vs. <5-7 months’, and ‘≥8-12 months vs. <8-12 months’.

Main Findings

In the single intervention trial there was no evidence of a relationship between breastfeeding promotion and risk of allergic sensitisation. For observational studies, across all cut-offs where data were available, there was no consistent evidence of a relationship between risk of AS and

initiation or prolongation of TBF. One study found food sensitisation to be increased in children who were breastfed ever, but other studies did not find a relationship between longer TBF and food sensitisation, or initiation/duration of TBF and sensitisation to specific foods cow's milk (CM), Egg and Peanut (PN). In general there were only small numbers of studies with data available for food sensitisation. The studies of aeroallergen sensitisation, or 'any' sensitisation, consistently showed no evidence of a relationship with initiation of breastfeeding. Studies of Total IgE showed no consistent relationship with TBF initiation or duration.

Studies which could not be included in meta-analysis generally found no evidence of a relationship between TBF duration and AS. Certainly there was no support for a protective effect of TBF duration against AS. In one study (Wright 1999 [1]) the authors' analysis suggested that increased TBF duration may be associated with increased Total IgE in the child when mother is atopic, but with reduced Total IgE in the child where mother is non-atopic.

Table 1 Characteristics of included studies evaluating TBF duration and allergic sensitisation

Study	N/n cases	Design	Country	Exposure assessment	Outcome	Age at outcome (years)	Population characteristics/ Intervention
Kramer, 2001 [2]; Kramer, 2007 [3]	8865/ 8181	Cluster RCT	Belarus	-	SPT-Aero	6.5	Breastfeeding promotion program based on the WHO/UNICEF baby friendly hospital initiative, versus standard local breastfeeding policies
Hesselmar, 2010 [2]	169/25	PC	Sweden	I	sIgE - FOOD	1.5	ALLERGYFLORA study. Population based study of babies selected from antenatal clinics between 1998 and 2003
Elliott, 2008 [3]	5779/ 1235	PC	UK	Q	SPT-ANY	7	ALSPAC study. Population based cohort of children born 1991-1992
Juto, 1980 [4]	56/NA	PC	Sweden	Q	Total IgE	0.25	Population based birth cohort of infants born in 1977
Hong, 2011 [5]	970/ 361	PC	USA	Q/I	sIgE-FOOD	2.5	Boston Birth Cohort. Predominantly African-American mother-infant pairs.
Burr, 1997 [6]	437/ 109	PC	UK	Unclear	sIgE-AERO/ANY	7	Infants with family history of allergic diseases in South Wales
Bruno, 1995 [7]	174	PC	Italy	I	sIgE-ANY, Total IgE	0-2, 2	Infants of atopic parents recruited from hospital and born in 1985-1988

Study	N/n cases	Design	Country	Exposure assessment	Outcome	Age at outcome (years)	Population characteristics/ Intervention
Mihrshahi, 2007 [8]	516/ 217	PC	Australia	I	SPT-ANY	5	CAPS study. Infants born in 1997-1999 with family history of asthma or wheezing
Wegienka, 2006 [9]	403/ 127	PC	USA	I	SPT-AERO	7	CAS study. Middle class mother-infant pairs enrolled in a health maintenance organisation in 1987-89
Devereux, 2006 [10]	700/ 54	PC	UK	Q	SPT-AERO	5	Population based birth cohort of infants born in 1998
Nwaru, 2010 [11]	994/ 200	PC	Finland	D	sIgE-AERO/CM/EGG/FOOD	5	DIPP study. Infants at high risk (HLA) for TIDM born between 1996-2004 invited to the allergy study between 1998 and 2000
Rowntree, 1985 [12]	80/ 20	PC	UK	I	sIgE-CM/EGG	5	Recruited from hospital and family history of atopy
Saarinen, 1979 [13]	95/NA	PC	Finland	R	sIgE-CM; Total IgE	0-1, 1	Recruited from hospital and born in 1975
Sicherer, 2010 [14]	503/ 140	PC	USA	I	sIgE-PN	1	The Consortium of Food Allergy Research: atopic children recruited from clinical services
Wright, 1999 [1]	982/ NA	PC	USA	Q/I	Total IgE	1, 6	Tuscon Children's Respiratory Study: Healthy newborn infants recruited from local health maintenance organisation born in 1980-1984

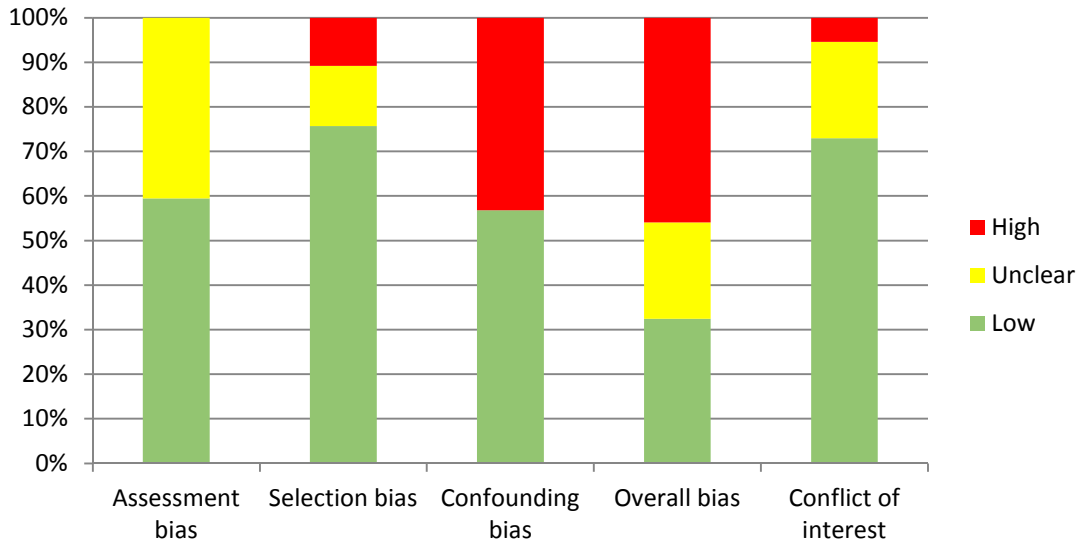
Study	N/n cases	Design	Country	Exposure assessment	Outcome	Age at outcome (years)	Population characteristics/ Intervention
Venter, 2009 [15]	891/27	PC	UK	Q	SPT-FOOD	1, 3	Recruited from antenatal clinics and born in 2001-2002
Oddy, 1999 [16]	1595/ 651	PC	Australia	D/Q	SPT-AERO	6	Western Australia Pregnancy Cohort: Recruited from antenatal clinics born in 1989-1992
Zutavern 2004 [17]	623/ 103	PC	UK	I	SPT-AERO	5.5	Cohort recruited from general practices and born in 1993-1995
Shaheen, 1996 [18]	395/44	PC	Guinea-Bissau	I	SPT-AERO	21	Young adults part of a cohort recruited for a survey of aged 0-6 year children in 1978-80 and living in a semi-rural district of Bissau
Gustafsson, 1999 [19]	94/57	PC	Sweden	Q	SPT-ANY	8	Children with atopic dermatitis attending allergic clinic or referred by child welfare clinics
Allen, 2009 [20]	310/50	PC	Australia	Q	SPT-FOOD	1	Part of the HealthNUTS study. Representative cohort of infants recruited from routine immunisation clinics 2008-2010
Hoppu, 2002 [21]	114/27	PC	Finland	I	SPT-ANY	1	Birth cohort of infants with a family history of atopy
Huurre, 2008 [22]	98/29	PC	Finland	I	SPT-ANY	1	Cohort of infants whose mother participated in a nutritional intervention trial during pregnancy

Study	N/n cases	Design	Country	Exposure assessment	Outcome	Age at outcome (years)	Population characteristics/ Intervention
Kemeny, 1991 [23]	189/11	PC	UK	Unclear	SPT and sIgE-CM/EGG; Total IgE	1	Population based birth cohort of infants born at Dulwich and King's College Hospitals in London
Snijders, 2007; Snijders, 2008 [24, 25]	776/ 218	PC	Netherlands	Q	sIgE-ANY/AERO/CM/EGG/ PN; Total IgE.	2	KOALA study. Population based birth cohort of infants born between 2000-2002
Kusel, 2005 [26]	263/ 107	PC	Australia	Unclear	SPT-ANY	5	Birth cohort of children at high risk of developing atopic disease born 1996-8
Wetzig, 2000 [27]	475/ 43	PC	Germany	Q	sIgE-CM/EGG	1	LARS study. High allergy risk or low birth weight children born within one year in Leipzig
Strachan, 1997 (BCS58 and BCS70) [28]	1369/ 730	PC	UK	I	SPT-AERO	35	British Cohort Study: infants born in England, Wales, and Scotland in 1958 and 1970
Silvers, 2009 [29]	889/ 249	PC	New Zealand	Q	SPT-ANY	1	New Zealand Asthma and Allergy Cohort Study. Population based birth cohort of infants born 1997-2001
Sears, 2002	714/ 319	PC	New Zealand	R/I	SPT-AEROALLERGEN	13	Dunedin Multidisciplinary Health and Development Research Study. Population based cohort of infants born between 1972-1973

Study	N/n cases	Design	Country	Exposure assessment	Outcome	Age at outcome (years)	Population characteristics/ Intervention
Scholtens, 2009 [30]	1553/ 427	PC	Netherlands	Q	sIgE-AERO	8	PIAMA. Population-based cohort born in 1996-1997
Hagendorens, 2005 [31]	810/ 107	PC	Belgium	Q	sIgE-ANY	1	PIPO study. Recruited from university service, born 1997-2001
Friday, 2000 [32]	94/18	RC	Unclear	Unclear	sIgE-CM	~10	Unclear
Rona, 2005 [33]	1213/ 345	RC	Chile	R	SPT-AERO	27	Infants born in a hospital in 1974-1978
Kuyucu, 2004 [34]	2774/ 570	CS	Turkey	Q	SPT-AERO	11	ISAAC Phase 2. Schoolchildren aged 8–12 years
Kucukosmanoglu, 2008 [35]	1015/ 20	CS	Turkey	Q/I	SPT-EGG	1	Hospital based selection of 8-18 months old Infants born in 2001-2002
Kuehr, 1992 [36]	1470/ 201	CS	Germany	Q	SPT-AERO	8	Schoolchildren between 6 and 8 years of age

Q: questionnaire, I: interview, R: medical records, D: diary, PC: prospective cohort, RC: retrospective cohort, CS: Cross-sectional, SPT: allergen skin prick test, sIgE: allergen-specific IgE; ANY: a panel of aero and food allergens; CM: cow's milk, PN: peanut, AERO: aeroallergen.

Figure 1 Risk of bias in observational studies of TBF duration and allergic sensitisation to foods or aero-allergens



1.2 Total breastfeeding duration and allergic sensitisation to food or aero-allergens

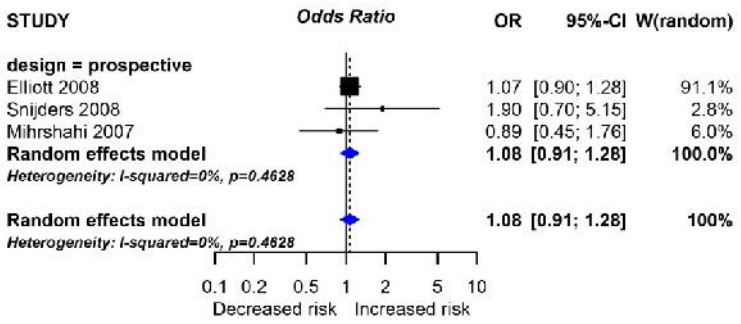
The single intervention trial of a breastfeeding promotion intervention was rated as having a low risk of bias on all domains, and a low risk of conflict of interest. Kramer found no significant difference in odds of allergic sensitisation to at least one aeroallergen at the age of 6.5 years – cluster adjusted odds ratio 1.2 (95% CI 0.5, 2.6). A sensitivity analysis excluding sites with unusually high rates of allergic sensitisation showed increased odds of allergic sensitisation in the breastfeeding promotion group – cluster adjusted odds ratio 2.0 (95% CI 1.1, 3.4). All other evidence was derived from observational studies. For assessment of TBF and AS using our pre-defined analysis strategy, most exposure/outcome meta-analyses contained either one or zero eligible studies. We therefore pooled data for studies reporting sIgE and SPT together, and pooled data from different age groups 0-4 years, 5-14 years and 15+ years. We did however take into consideration differences between study populations and AS assessment methods when interpreting the outputs from individual meta-analyses.

1.2.1 Allergic Sensitisation to Any Allergen

1.2.1.1 TBF Ever vs. Never

Figure 2 shows the outcomes of 3 eligible observational studies evaluating TBF any vs never and risk of AS to any allergen. The data show no significant relationship, with no statistical heterogeneity (I^2=0%). All three studies are prospective cohort studies at low or unclear risk of bias, reporting prospectively collected breastfeeding information and adjusted data. Elliott in a normal risk population at aged 7 years using SPT; Mihrshahi in a high risk population at age 5 using SPT; Snijders in a normal risk population at age 2 using sIgE. The Snijders study included a population within the cohort, with an anthroposophic lifestyle. There were insufficient data for a meaningful dose-response analysis.

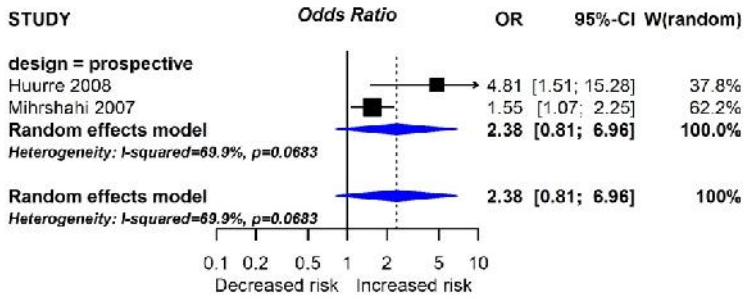
Figure 2 TBF Ever vs. Never and risk of any allergic sensitisation



1.2.1.2 TBF ≥5-7 months vs <5-7 months

Figure 3 shows the outcomes of 2 eligible observational studies evaluating TBF duration of ≥5-7 months vs <5-7 months and risk of AS to any allergen. The data show no significant relationship, with high statistical heterogeneity (I^2=70%). Mihrshahi reported adjusted data in a high risk population at age 5 years using SPT; Huurre reported adjusted data in a high risk population at age 1 using SPT. Both studies had a low risk of bias on all parameters, and the reason for the high statistical heterogeneity is not clear.

Figure 3 TBF ≥5-7 months vs. <5-7 months and risk of allergic sensitisation to any allergens

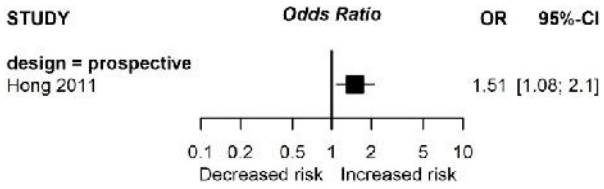


1.2.2 Allergic sensitisation to Food

1.2.2.1 Ever vs. Never

Figure 4 shows the outcome of 1 eligible observational study evaluating TBF duration of any vs never and risk of AS to any food allergen. The data show increased food sensitisation in breastfed infants. Hong reported adjusted data in a high risk population at age 5 years using SPT. The authors did not find this effect varied by family history of allergy, but it was significantly modified by certain genetic polymorphisms related to cytokines. No data were available for dose response analysis.

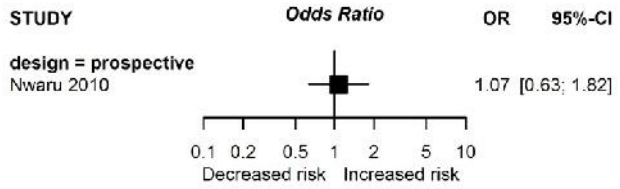
1.2.2.2 Figure 4 TBF Ever vs. Never and risk of allergic sensitisation to food



1.2.2.3 TBF ≥5-7 months vs <5-7 months

Figure 5 shows the outcome of 1 eligible observational study evaluating TBF duration of ≥5-7 months vs. <5-7 months and risk of AS to any food allergen. The data show no association between TBF and AS to any food allergen. Nwaru reported adjusted data in a normal risk population at age 5 using sIgE. The authors also reported no significant association between TBF duration and CM-AS (P=0.15) or Egg-AD (P=0.83) using sIgE at age 5 years.

Figure 5 TBF ≥5-7 months vs. <5-7 months and risk of allergic sensitisation to any food

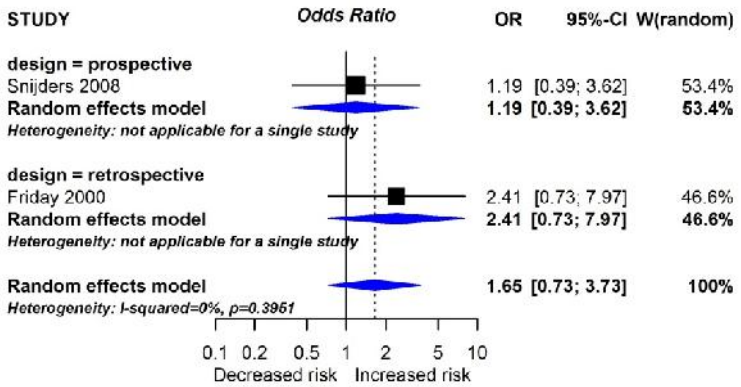


1.2.3 Allergic sensitisation to Cow's Milk (CM-AS)

1.2.3.1 TBF Ever vs. Never

Figure 6 shows the outcome of 2 eligible observational studies evaluating TBF duration of any vs never and risk of CM-AS. The data show no significant relationship, with no statistical heterogeneity. Snijders reported adjusted data in a prospective cohort study of a normal risk population at age 2 years using sIgE. The population included a population with anthroposophic lifestyle. Friday reported unadjusted data in a retrospective cohort study of a high risk population at age 10, with a consequent high risk of bias. Data from the Kemeny and Rowntree studies for CM-AS could not be meta-analysed, but show no significant association with TBF duration using different cutoffs for SPT or sIgE to CM. No data were available for meaningful dose response analysis.

Figure 6 TBF Ever vs. Never and risk of allergic sensitisation to cow's milk



1.2.3.2 CM-AS and longer TBF durations

Friday also reported CM-AS risk with TBF ≥3 months vs. <3 months (Figure 7) where there was no evidence of an association; and the same study showed data for CM-AS risk and TBF ≥6 months vs. <6 months (Figure 8) where they reported an association between prolonged TBF and increased CM-AS risk. However these unadjusted data were judged to have a high risk of confounding bias.

Figure 7 TBF ≥3-4 months vs. <3-4 months and risk of allergic sensitisation to cow's milk

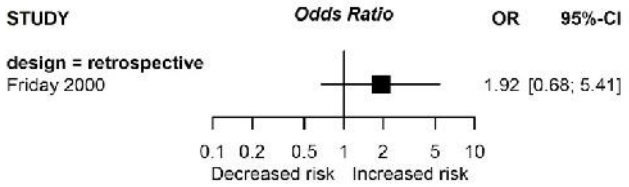
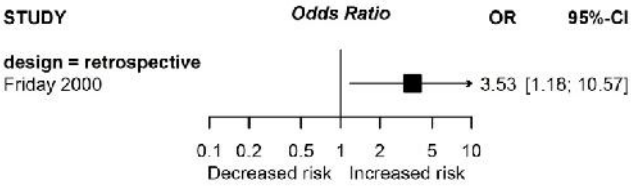


Figure 8 TBF ≥5-7 months vs. <5-7 months and risk of allergic sensitisation to cow's milk



1.2.4 Allergic Sensitisation to Egg (EGG-AS)

1.2.4.1 TBF Ever vs. Never

Figure 9 shows the outcome of 3 eligible observational studies evaluating TBF duration of ever vs never and risk of EGG-AS. The data show no significant relationship, with no statistical heterogeneity. Snijders reported adjusted data in a prospective cohort study of a normal risk population at age 2 years using sIgE. The population included a population with anthroposophic lifestyle. Kemeny and Rowntree reported unadjusted data in prospective cohort studies of normal and high risk populations, at ages 1 year and 5 years,respectively, and used both SPT and sIgE to assess AS. Both studies were judged as at high risk of confounding bias. Kemeny and Rowntree also found no difference when EGG-AS was measured as skin prick test rather than sIgE (sIgE in Figure). Dose response analysis did not show evidence of a dose response relationship (Figures 10-11).

Figure 9 TBF Ever vs. Never and risk of allergic sensitisation to Egg

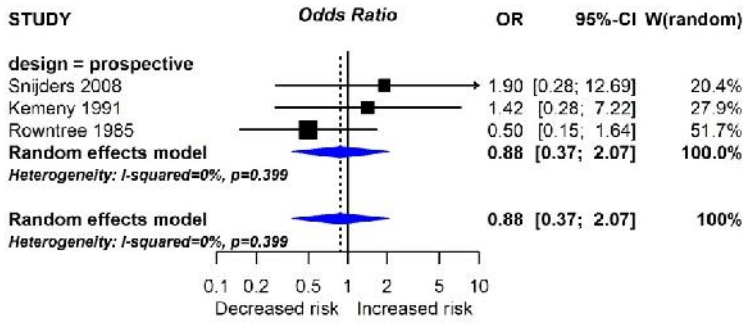


Figure 10 TBF medium duration (4-6months) vs. Never and risk of allergic sensitisation to egg

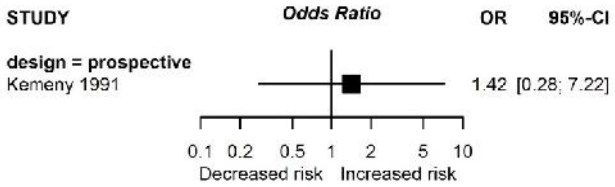
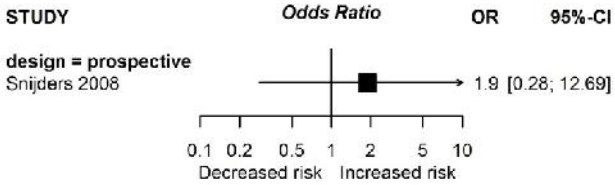


Figure 11 TBF long duration (7-12months) vs. Never and risk of allergic sensitisation to egg



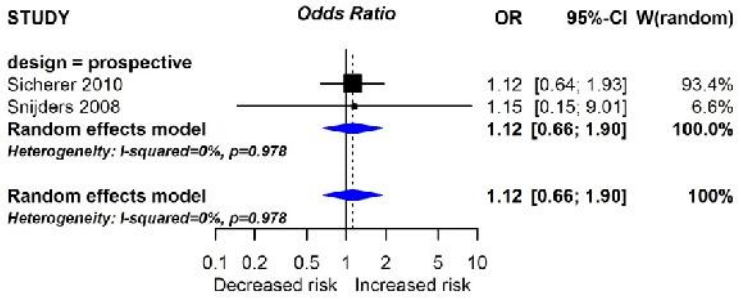
1.2.5 Allergic Sensitisation to Peanut (PN-AS)

1.2.5.1 Ever vs. Never

Figure 12 shows the outcome of 2 eligible observational studies evaluating TBF duration of any vs never and risk of PN-AS. The data show no significant relationship, with no statistical heterogeneity. Snijders reported adjusted data in a prospective cohort study of a normal risk population at age 2 using sIgE. The study included a population with anthroposophic lifestyle. Sicherer reported unadjusted data in a prospective cohort study of a high risk population at age 5 using sIgE. Adjusted

analyses in the same study showed no evidence of a relationship between BF any vs never and PN-AS. There were insufficient data for meaningful dose response analysis.

Figure 12 TBF Ever vs. Never and risk of allergic sensitisation to PN



1.2.6 Allergic Sensitisation to any Aeroallergen (AERO-AS)

1.2.6.1 Ever vs. Never

Figure 13 shows the outcome of 5 eligible observational studies evaluating TBF duration of any vs never and risk of AERO-AS. The data show no significant relationship, with low statistical heterogeneity. All studies reported adjusted data in a prospective cohort study of a normal risk population - Snijders at age 2 years using sIgE. The study included a population with anthroposophic lifestyle. Scholtens at age 8 years using sIgE; Wegienka, Strachan and Zutavern using SPT at age 7, 35 and 5.5 years respectively. These studies were generally judged to be at low risk of bias on most parameters. Dose response analysis (Figure 14 and Figure 15) did not show clear evidence of a dose response relationship between increasing duration of TBF and risk of AERO-AS when compared with never TBF.

Figure 13 TBF Ever vs. Never and risk of allergic sensitisation to aeroallergen

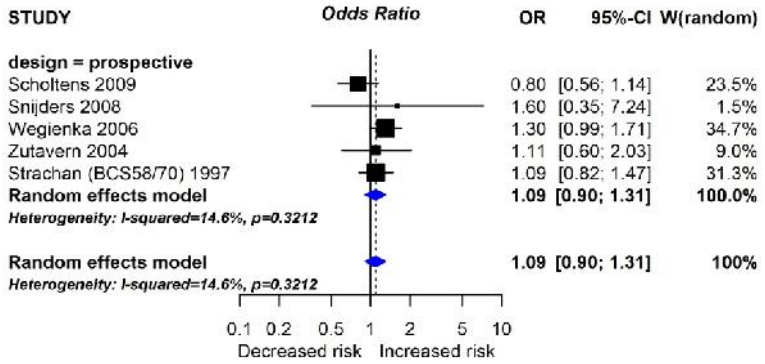


Figure 14 TBF medium duration (4-6months) vs. Never and risk of allergic sensitisation to aeroallergen

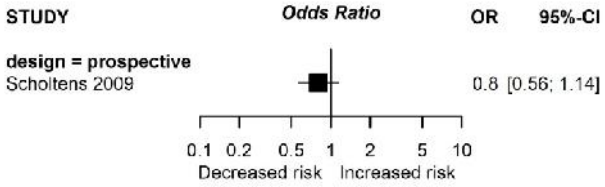
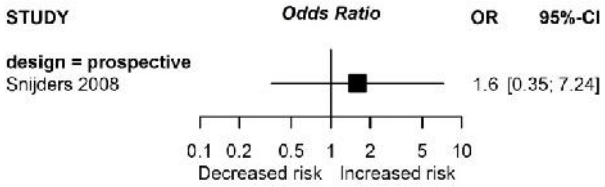


Figure 15 TBF long duration (7-12months) vs. Never and risk of allergic sensitisation to aeroallergen

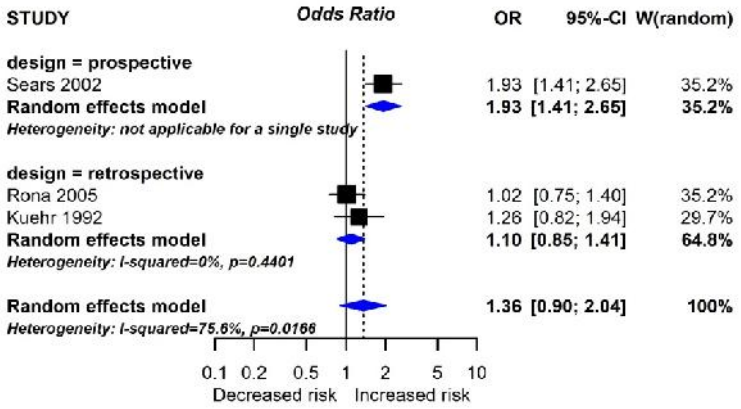


1.2.6.2 TBF ≥1-2 months vs. <1-2 months 1-2 months

Figure 16 shows the outcome of 3 eligible observational studies evaluating TBF duration of ≥1-2 months vs. <1-2 months and risk of AERO-AS. The data show no significant relationship, with extreme statistical heterogeneity (I^2 = 75.6%). The study of Kuehr was a cross sectional study which reported unadjusted data in normal risk population at age 8 using SPT. The study of Rona was a retrospective cohort study which reported adjusted data in a normal risk population at age 27 years using SPT. The study of Sears is a prospective cohort with SPT assessed at 13 years reporting adjusted estimates. Given the nature of the cross-sectional and retrospective cohort

studies, it is possible that some recall bias occurred, which might partly explain the statistical heterogeneity observed.

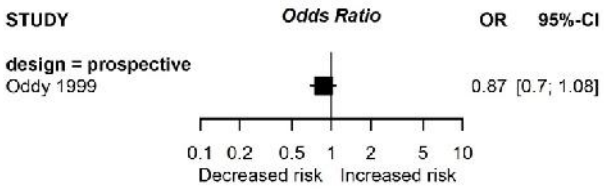
Figure 16 TBF ≥1-2 months vs. <1-2 months and risk of allergic sensitisation to aeroallergen



1.2.6.3 TBF ≥3-4 months vs. <3-4 months

Figure 17 shows the outcome of 1 eligible observational study evaluating TBF duration of ≥3-4 months vs. <3-4 months and risk of AERO-AS. The data show no significant relationship. The study of Oddy was a prospective cohort study which reported adjusted data in a normal risk population at age 6 years using SPT.

Figure 17 TBF ≥3-4 months vs. <3-4 months and risk of allergic sensitisation to aeroallergen

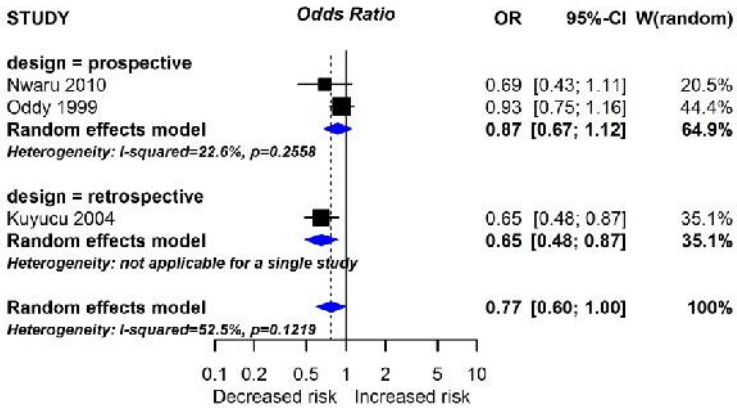


1.2.6.4 TBF ≥5-7 months vs. <5-7 months

Figure 18 shows the outcome of 3 eligible observational studies evaluating TBF duration of ≥5-7 months vs. <5-7 months and risk of AERO-AS. The data show reduced risk of sensitisation with prolonged TBF duration, with moderate statistical heterogeneity and borderline statistical significance. The study of Oddy was a

prospective cohort study which reported adjusted data in a normal risk population at age 6 years using SPT. Nwaru reported adjusted data in a normal risk population at age 5 using sIgE. Kuyucu reported adjusted data in a normal risk population at age 11 years in a cross-sectional study using SPT. Kuyucu also reported an interaction with maternal atopic status, such that children of atopic mothers with TBF ≥6 months vs. <6 months had reduced risk of a positive SPT to aeroallergen, whereas this was not the case for children of non-atopic mothers.

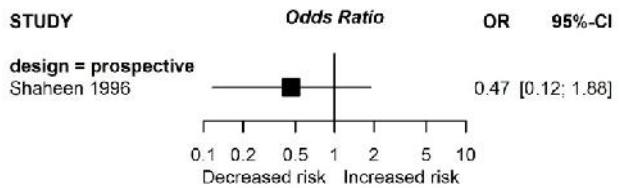
Figure 18 TBF ≥5-7 months vs. <5-7 months and risk of allergic sensitisation to aeroallergen



1.2.6.5 TBF ≥8-12 months vs. <8-12 months

Figure 19 shows the outcome of 1 eligible observational study evaluating TBF duration of ≥8-12 months vs. <8-12 months and risk of AERO-AS. The data show no significant relationship. The study of Shaheen was a prospective cohort study which reported adjusted data in a normal risk population in Guinea-Bissau at age 21 years using SPT.

Figure 19 TBF ≥8-12 months vs. <8-12 months and risk of allergic sensitisation to aeroallergen

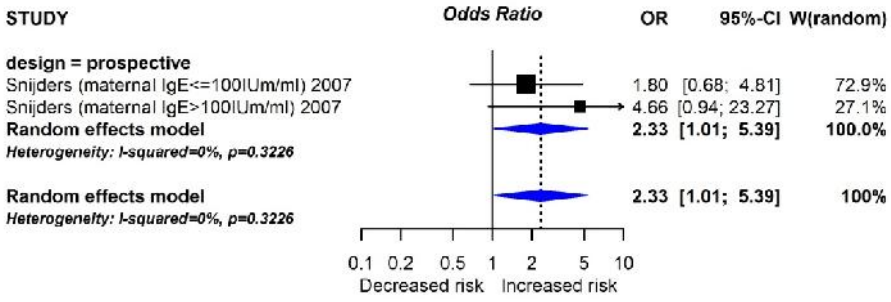


1.2.7 Total IgE

1.2.7.1 TBF any vs never and Total IgE

One study reported OR for raised total IgE (>10IU/mL) in breastfed versus not breastfed infants, and found increased total IgE in breastfed infants at the age of 2 years, with borderline statistical significance. The sample population in this study was not representative of the general population as it only included children from families who had an anthroposofic lifestyle (Figure 20).

Figure 20 TBF Ever vs. Never and risk of raised Total IgE



1.3 Data for TBF duration and AS that were not suitable for meta-analysis

Almost half of all included studies (17 of 35) did not report data that could be included in a meta-analysis, and are summarised below in Table 2. In 2 studies there was a significant positive association between TBF initiation or duration and specific AS risk; in 2 further studies there was evidence of such a relationship in some analyses, but not in the most complete analyses; in 1 study there was evidence of reduced specific AS risk associated with TBF; in 8 other studies there was no relationship between specific AS and TBF. Total IgE was reported by 5 of the narrative studies in relation to TBF. Here 4 studies (~950 participants) found no relationship between TBF initiation or duration and Total IgE; 1 study (95 participants) found increased Total IgE with TBF initiation or prolongation. In one of these studies the authors found a possible interaction between TBF and Total IgE, in relation to maternal atopic status.

Table 2 Studies investigating the association between TBF duration and allergic sensitisation which were not eligible for meta-analysis

Study	Design	Outcome	Age	N/n cases	Data	Measure	TBF in AS	TBF in No AS	P
Hoppu, 2002 [21]	PC	SPT-ANY	1	114/27	Continuous	Mean (95%CI)	7.5 (6.9, 8.2)	8.1 (6.4, 9.8)	NS
Hesselmar 2010 [2]	PC	sIgE-FOOD	1.5	169/25	Continuous	Median (IQR)	7 (4.7, 10)	7 (4, 9)	NS
Silvers, 2009 [29]	PC	SPT-ANY	1	889/249	Continuous	Average	Adjusted OR for AS, for each month increase in TBF duration was 1.03 (1, 1.06) (P=0.051)		
Hagendorens, 2005 [31]	PC	sIgE-ANY	1	810/107	Categorical	Odds ratio	Unadjusted OR for AS in ever versus never breastfed, is >1 and not statistically significant		
Bruno, 1995 [7]	PC	sIgE-ANY, Total IgE	2	174	Categorical/ Continuous		No significant difference in Total IgE according to feeding type. sIgE-ANY was significantly less common in ever versus never breastfed.		
Kemeny, 1991 [23]	PC	Total IgE	1	189/ NA	Continuous		No significant difference in Total IgE according to TBF≥3 months versus <3 months versus never		
Saarinen, 1979 [13]	PC	Total IgE; sIgE-CM	1	95/NA	Continuous/ Categorical	Adjusted geometric mean Total IgE significantly higher in ever vs. never breastfed at up to 4 months; CM-IgE not detected in never BF, rarely detected in ever BF up to 1 year			

Study	Design	Outcome	Age	N/n cases	Data	Measure	TBF in AS	TBF in No AS	P
Juto, 1980 [4]	PC	Total IgE	1	56/NA	Continuous	No significant difference			
Wetzig, 2000 [27]	PC	sIgE-CM, sIgE-Egg	1	475/43	Categorical	Infants TBF >5 months had more Egg-AS than <5 months (significant in a subgroup with high cord IgE), but no significant difference for CM-AS			
Kucukosmanoglu 2008 [35]	CS	SPT-EGG	1	1015/20	Categorical	No significant difference in Egg-AS between ever and never BF. P=0.32			
Allen, 2009 [20]	PC	SPT-FOOD	1	310/50	Categorical	Sensitised infants significantly more frequently BF at 12 months; no significant difference in ever BF (2.5% AS, 10.5% Not AS)			
Venter, 2009 [15]	PC	SPT-FOOD	1, 3	891/27	Categorical	No significant relationship between Food-AS and TBF ever/never, >/<6 months or >/<9 months at age 1 or 3			
Burr, 1997 [6]	PC	sIgE-AERO/ SPT-AERO	7	338	Categorical	AS to AEROs by SPT or sIgE not associated with TBF duration in adjusted analysis			
Devereux 2006 [10]	PC	SPT-AERO	5	700/54	Categorical	No significant relationship between BF ever and AS			

Study	Design	Outcome	Age	N/n cases	Data	Measure	TBF in AS	TBF in No AS	P
Kusel, 2005 [26]	PC	SPT-ANY	5	263/107	Continuous		Analysis of children with eczema – those with AS had longer TBF than no AS, but this was not statistically significant in adjusted analyses		
Gustafsson, 1999 [19]	PC	SPT-ANY	8	94/57	Categorical		No association between TBF >6 months, or any other duration and AS		
Wright, 1999 (All) [1]	PC	Total IgE	6	534/NA	Categorical		No association overall between TBF Never, <4 months or ≥4 months and Total IgE at 0.75, 6 or 11 years		
Wright, 1999 (low maternal IgE) [1]	PC	Total IgE	6	534/NA	Continuous		Significantly reduced Total IgE in children of mothers with low Total IgE for ever versus never. P<0.02		
Wright, 1999 (high maternal IgE) [1]	PC	Total IgE	6	534/NA	Continuous		Significantly increased Total IgE in children of mothers with high Total IgE for ≥4 vs. <4 months. P<0.005		

2 Exclusive breastfeeding duration and Allergic Sensitisation

2.1.1 Overall characteristics of studies, risk of bias and summary of results

Table 3 describes the main characteristics of the studies analysed in this report. A total of 1 systematic review which included 1 RCT analysed as a cohort study, and 1 other prospective cohort study; and 25 prospective cohort studies, reported the association between duration of exclusive breastfeeding (EBF) and risk of AS. The majority of studies were undertaken in Europe – others in Australasia (n=4), North America (n=1) and South America (n=1). Overall, valid data on EBF duration and AS risk were available from over 31,000 subjects. Information on AS was obtained using skin prick testing in 16 studies, and by blood IgE testing in 12 studies. With regards to time of outcome diagnosis, 15 studies explored the association between EBF duration and AS at age 0-4 years, and 12 at age 5-14 years. Eight studies used a questionnaire to assess the exposure (EBF), 10 used an interview, three studies used a diary, in three the method was unclear, one used medical records.

Risk of bias in both the studies included in the systematic review was assessed as 'low' on all parameters. Risk of bias for the observational studies is shown in Figure 21. Over half of studies had a high risk of bias, due to lack of adjustment for confounding bias i.e. no adjusted data presented. A similar number of studies had unclear risk of assessment bias, due to inadequate information about the method for classifying EBF duration. Risk of conflict of interest was generally assessed as low.

Where data were available, three levels of comparison were used to assess the risk of AS according to EBF duration, namely ≥0-2 months vs. <0-2 months; ≥3-4 months vs. <3-4 months; ≥5-9 months vs. <5-9 months. Across most cut-offs there was no consistent evidence of a lower risk of AS if EBF was prolonged. In general there were only small numbers of studies with available data, and several analyses were restricted to single studies with high risk of bias. We did find some evidence from one meta-analysis of 3 observational studies (Figure 25) that EBF ≥0-2 months may be associated with increased risk of AS to food OR 1.61 (1.17, 2.22) with no statistical heterogeneity (I^2=0%). This was not reflected in data for AS to specific foods, to

aeroallergens or any allergen, or at different EBF cut-offs. The studies included in this analysis did not take measures to account for the possibility that mothers of infants with symptoms associated with food sensitisation might extend the duration of EBF due to concern about symptoms. In general there was significant unexplained statistical heterogeneity in several analyses, even when restricted to studies with low risk of bias reporting adjusted data. We found evidence from one study of a gene-environment interaction affecting the relationship between EBF and Food AS, which may be relevant to some of the unexplained statistical heterogeneity between individual studies [5].

We found no evidence of a relationship between EBF duration and total IgE levels.

Table 3 Characteristics of included studies evaluating EBF duration and allergic sensitisation

Study	N/n cases	Design	Country	Exposure assessment	Outcome	Age at outcome (years)	Population characteristics
Kramer [37]	2651	SR of PC	Finland/Belarus	-	SPT-ANY	5-7	Study #1: Population based cohort study
Hesselmar, 2010 [2]	169/25	PC	Sweden	I	sIgE-FOOD	1.5	ALLERGYFLORA study. Population based study of babies selected from antenatal clinics between 1998 and 2003 - mainly high risk of allergic disease
Elliott, 2008 [3]	5095/1235	PC	UK	Q	SPT-ANY	7	ALSPAC study. Population based cohort of children born 1991-1992.
Kull, 2004; Kull, 2010 [38, 39]	2370/654	PC	Sweden	Q	sIgE-AERO/ANY/CM/EGG/FOOD/PN	4, 8	BAMSE study. Population based cohort of children born between 1994-1996
Hong, 2011 [5]	970/361	PC	USA	Q/I	sIgE-FOOD	2.5	Boston Birth Cohort. Predominantly African-American mother-infant pairs.
Bruno, 1995 [40]	107	PC	Italy	Unclear	Total IgE	5	Infants of atopic parents recruited from hospital and born in 1985-1988
Mihrshahi, 2007 [8]	516/217	PC	Australia	I	SPT-ANY	5	CAPS study. Infants born in 1997-1999 with family history of asthma or wheezing

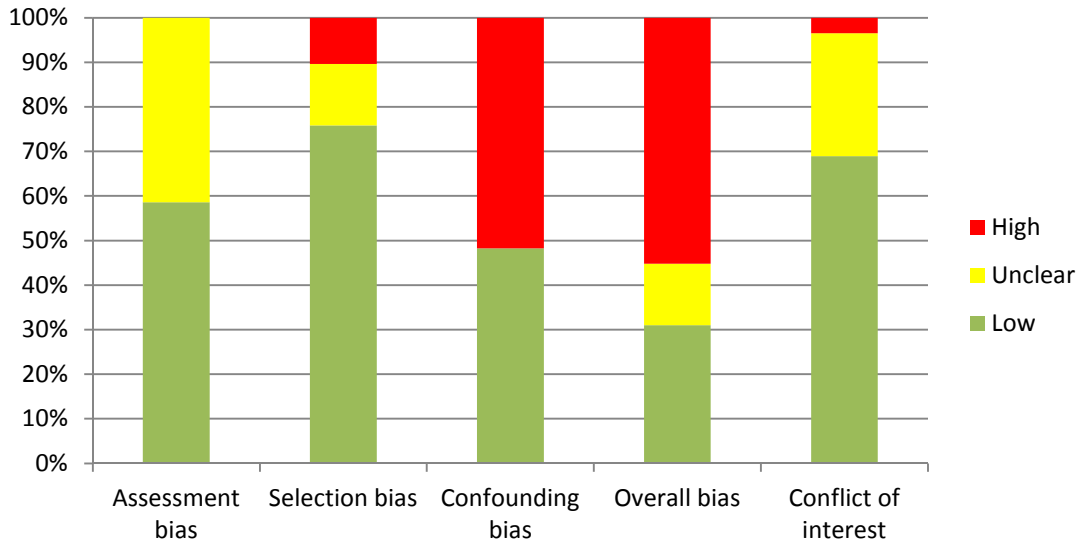
Study	N/n cases	Design	Country	Exposure assessment	Outcome	Age at outcome (years)	Population characteristics
Cogswell, 1987 [41]	73/32	PC	UK	D	SPT-ANY	5	Birth cohort of infants with family history of hay fever or asthma
Nwaru, 2010 [11]	994/ 200	PC	Finland	D	sIgE-AERO/CM/EGG/FOOD	5	DIPP study. Infants at high risk (HLA) for TIDM born between 1996-2004 invited to the allergy study between 1998 and 2000
Schoetzau, 2002 [42]	829/92	PC	Germany	D	sIgE-CM	1	GINI study. Term newborn infants born 1995-8 from 2 regions of Germany who participated in an intervention program according to risk of allergy
Hoppu, 2000 [21]	114/27	PC	Finland	I	SPT-ANY	1	Birth cohort of infants with a family history of atopy
Huurre, 2008 [22]	98/29	PC	Finland	I	SPT-ANY	1	Infants born to mothers who participated in a nutritional intervention trial during pregnancy
Arshad, 1992[43]	344/123	PC	UK	D/Q	SPT-ANY/CM/EGG	1	Isle of Wight Study. Population based birth cohort of infants born in semi-rural areas between 1989 and 1990
Kemeny, 1991 [23]	189/11	PC	UK	Unclear	SPT and sIgE-CM/EGG; SPT-CM; Total IgE	1	Population based birth cohort of infants born at Dulwich and King's College Hospitals in London
Gruber 2010 [44]	167/15	PC	Central Europe	Q	sIgE-CM/EGG; Total IgE	1	MIPS-1 study. Infants born in 2006 without family history of allergy, randomised to a prebiotic formula intervention if fully formula fed < 8 weeks

Study	N/n cases	Design	Country	Exposure assessment	Outcome	Age at outcome (years)	Population characteristics
Silvers, 2009 [29]	889/249	PC	New Zealand	Q	SPT-ANY	1	New Zealand Asthma and Allergy Cohort Study. Population based birth cohort of infants born between 1997 and 2001
Odelram, 1996 [45]	70/23	PC	Sweden and Finland	D	sIgE-CM; SPT-ANY; Total IgE	1.5	Birth cohort of infant with family history and high cord blood IgE born in 1989-1990
Poysa, 1990; Poysa, 1992 [46, 47]	120/41	PC	Finland	I	Total IgE; SPT-AERO	5,10	High risk of disease, born 1979-1980
Kramer, 2009 [48]	13888 9/3135	PC	Belarus	I	SPT-AERO	6.5	PROBIT study: recruited in hospitals , born 1996-1997
Siltanen,2003 [49]	285/75	PC	Finland	Q	sIgE-ANY; SPT-ANY; Total IgE	4	Infants recruited from maternal hospital born in 1994-5
Strassburger , 2010 [50]	325/94	PC	Brazil	I	SPT-AERO	3.5	Recruited from hospital, born 2001-2002
Van Asperen, 1983 [51]	79/13	PC	Australia	I	SPT-FOOD	1	Cohort recruited from medical service, born in 1980-1981 with family history of atopy
Vandenplas, 1988 [52]	75/9	PC	Belgium	Unclear	sIgE-CM; SPT-CM; Total IgE	0.33	Infants with family history of atopy

Study	N/n cases	Design	Country	Exposure assessment	Outcome	Age at outcome (years)	Population characteristics
Venter, 2009 [15]	891/27	PC	UK	Q	SPT-FOOD	3	Recruited from antenatal clinics and born in 2001-2002
Oddy, 2004; Oddy, 1999 [16, 53]	1595/651	PC	Australia	D/Q	SPT-AERO	6	Western Australia Pregnancy Cohort: Recruited from antenatal clinics born in 1989-1992
Zutavern, 2004 [17]	623/103	PC	UK	I	SPT-AERO	5.5	Cohort recruited from general practices and born in 1993-1995

Q: questionnaire, I: interview, R: medical records, D: diary, PC: prospective cohort, SPT: allergen skin prick test, sIgE: allergen-specific IgE; ANY: a panel of aero and food allergens; CM: cow's milk.

Figure 21 Risk of bias in studies of EBF duration and allergic sensitisation



2.2 Exclusive breastfeeding and allergic sensitisation

For assessment of EBF and AS most exposure/outcome meta-analyses contained either one or zero eligible studies. We therefore pooled data for studies reporting sIgE and SPT together, and pooled data from different age groups 0-4 years, 5-14 years and 15+ years. We did however take into consideration differences between study populations and AS assessment methods when interpreting the outputs from individual meta-analyses.

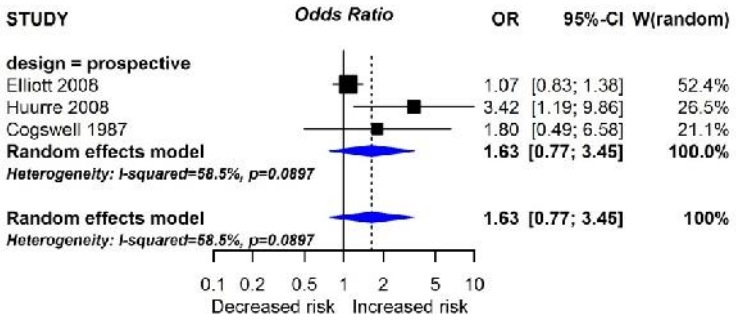
2.2.1 Allergic sensitisation to any allergen

2.2.1.1 EBF ≥0-2 months vs. <0-2 months

Three prospective cohort studies reported data that could be pooled to calculate OR for any AS, in infants with EBF for ≥0-2 months vs. <0-2 months duration and are shown in Figure 22. They show no association between EBF duration and AS risk, with high statistical heterogeneity. All three studies used skin prick testing as an outcome measure. The studies of Elliott and Huurre reported adjusted data, and the study of Cogswell reported unadjusted data. We were not able to confidently explain the heterogeneity between Huurre and Elliott results, but the data of Huurre are based on a subgroup of infants born to allergic mothers whereas Elliott reported on a large

representative population-based cohort and it is possible that EBF duration has different effects depending on the allergic status of the mother.

Figure 22 EBF ≥0-2 months vs. <0-2 months and risk of allergic sensitisation in children



2.2.1.2 EBF ≥3-4 vs. <3-4 Months

2.2.1.2.1 Systematic reviews and intervention trials

As shown in Table 4, the single systematic review found no evidence that longer exclusive/predominant breastfeeding (for 6 months vs 3 months in the systematic review) influenced risk of AS at 6-7 years. Kramer's intervention trial of breastfeeding promotion, which we have included under TBF which aimed to increase EBF duration, also found no effect on AS.

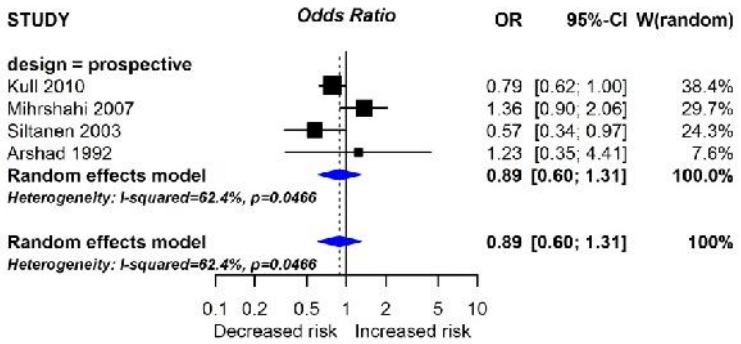
Table 4 Promotion of increased EBF duration and risk of AS

Study	Outcome measure	No. participants (studies)	Outcome (95% CI)
Kramer 2012 [37] Oddy, 1999 [16, 53]	Positive skin prick test at 6 years	331 (1)	RR 0.99 (0.73, 1.35)

2.2.1.2.2 Observational studies

Four prospective cohort studies reported data that could be pooled to calculate OR for any AS, in infants with EBF for ≥3-4 months vs. <3-4 months duration and are shown in Figure 23. They show no association between AS and EBF duration, with high statistical heterogeneity. The data from Arshad and Siltanen are unadjusted data using skin prick testing, with high risk of confounding bias. The data from Kull and Mihrshahi are adjusted data using specific IgE and skin prick testing respectively. The studies of Siltanen and Kull included normal risk infants, the studies of Arshad and Mihrshahi included high risk infants.

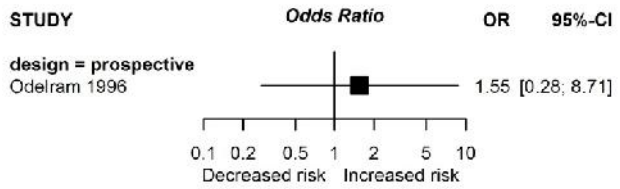
Figure 23 EBF ≥3-4 months vs. <3-4 months and risk of allergic sensitisation



2.2.1.3 EBF ≥5 months vs. <5 months

A single study reported unadjusted data regarding risk of any AS in infants EBF for at least 9 months compared with less than 9 months, and found no significant association (Figure 24).

Figure 24 EBF ≥5-9 months vs. <5-9 months and risk of allergic sensitisation

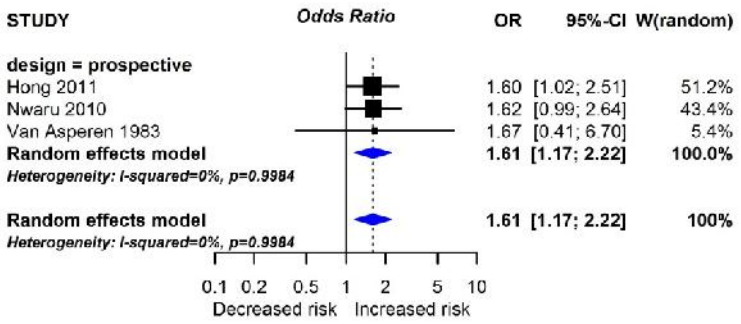


2.2.2 EBF and allergic sensitisation to Food

2.2.2.1 EBF ≥0-2 months vs. <0-2 months

Three prospective cohort studies reported data that could be pooled to calculate OR for Food AS, in infants with EBF for ≥0-2 months vs. <0-2 months duration and are shown in Figure 25. They show an association between increased EBF duration and increased risk of food sensitisation OR1.61 (1.17, 2.22), with no statistical heterogeneity. The study of Van Asperen reported unadjusted data using skin prick testing at 1 year as an outcome measure in a high risk population, the other studies reported adjusted data used specific IgE at 2.5 and 5 years in normal risk populations. The study of Nwaru separately reported no association between EBF duration and Egg allergy (P=0.30) or CMA (P=0.71). The study of Hong also excluded the occurrence of allergic symptoms during the first 4 months of infancy, and found this did not alter the study findings suggesting that reverse causality was not relevant.

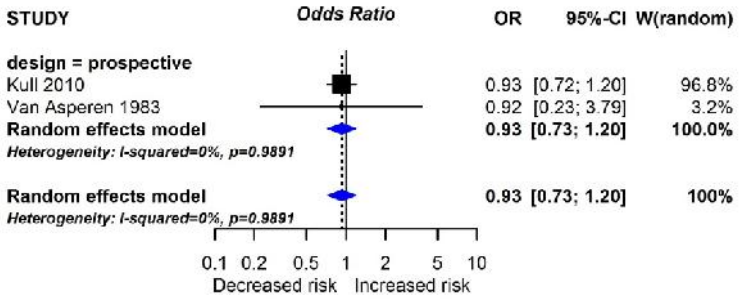
Figure 25 EBF ≥0-2 months vs. <0-2 months and risk of allergic sensitisation to food



2.2.2.2 EBF ≥3-4 months vs. <3-4 months

Two prospective cohort studies reported data that could be pooled to calculate OR for Food AS, in infants with EBF for ≥3-4 months vs. <3-4 months duration and are shown in Figure 26. They show no association between EBF duration and risk of food sensitisation, with no statistical heterogeneity. The study of Van Asperen reported unadjusted data using skin prick testing at 1 year as an outcome measure in a high risk population, the study of Kull reported adjusted data using specific IgE in a normal risk population at age 8.

Figure 26 EBF ≥3-4 months vs. <3-4 months and risk of allergic sensitisation to food in children

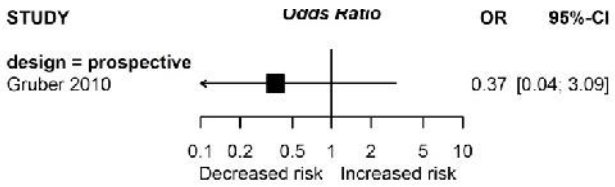


2.2.3 EBF and allergic sensitisation Cow's Milk

2.2.3.1 EBF ≥0-2 months vs. <0-2 months 0-2

One prospective cohort study reported OR for CM AS, in infants with EBF for ≥0-2 months vs. <0-2 months duration and is shown in Figure 27. There was no association found, with wide confidence intervals due to low study power, and data were unadjusted so carry a high risk of confounding bias.

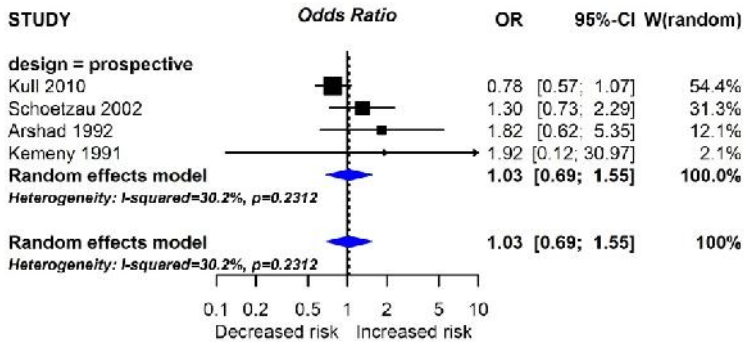
Figure 27 EBF ≥0-2 months vs. <0-2 months and risk of allergic sensitisation in children to cow's milk



2.2.3.2 EBF ≥3-4 months vs. <3-4 months 3-4

Four prospective cohort studies reported OR for CM AS, in infants with EBF for ≥3-4 months vs. <3-4 months duration and are shown in Figure 28. There was no association found, moderate statistical heterogeneity. All studies other than that of Arshad used specific IgE for assessment; all studies other than Kull assessed at 1 year age; Kull and Schoetzau reported adjusted data, Kemeny and Arshad unadjusted data. In the study of Kemeny there were no participants with positive SPT to cow's milk (sIgE data presented in Figure 28).

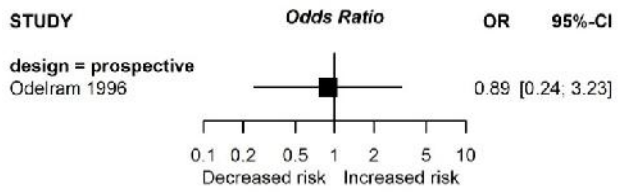
Figure 28 EBF ≥3-4 months vs. <3-4 months and risk of allergic sensitisation to cow's milk



2.2.3.3 EBF for ≥5-9 months vs. <5-9 months

One prospective cohort study reported OR for CM AS, in infants with EBF for ≥5-9 months vs. <5-9 months duration and is shown in Figure 29. There was no association found, with wide confidence intervals due to low study power, and data were unadjusted so carry a high risk of confounding bias.

Figure 29 EBF ≥5-9 months vs. <5-9 months and risk of allergic sensitisation to cow's milk

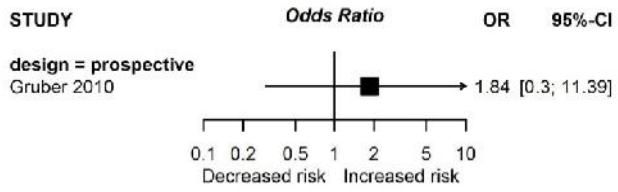


2.2.4 EBF and allergic sensitisation to Egg

2.2.4.1 EBF ≥0-2 months vs. <0-2 months

One prospective cohort study reported OR for Egg AS, in infants with EBF for ≥0-2 months vs. <0-2 months duration and is shown in Figure 30. There was no association found, with wide confidence intervals due to low study power, and data were unadjusted so carry a high risk of confounding bias

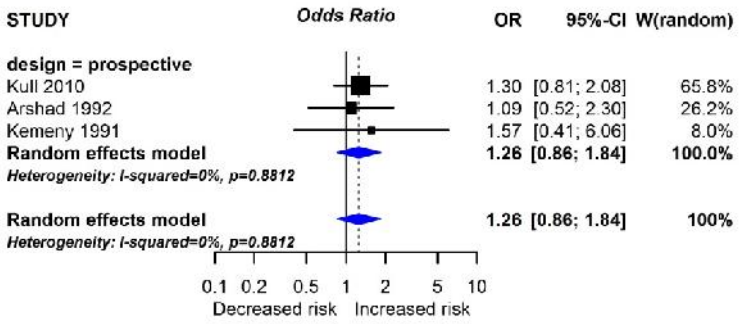
Figure 30 EBF ≥0-2 months vs. <0-2 months and risk of allergic sensitisation to Egg



2.2.4.2 EBF ≥3-4 months vs. <3-4 months

Three prospective cohort studies reported OR for Egg AS, in infants with EBF for ≥3-4 months vs. <3-4 months duration and are shown in Figure 31. There was no association found, with no statistical heterogeneity. All studies other than that of Arshad used specific IgE for assessment; all studies other than Kull assessed at 1 year age; Kull reported adjusted data, Kemeny and Arshad unadjusted data. In the study of Kemeny skin prick testing data showed very similar findings (sIgE data presented in Figure 31).

Figure 31 EBF ≥3-4 months vs. <3-4 months and risk of allergic sensitisation to Egg

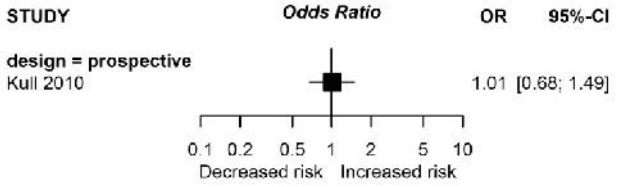


2.2.5 EBF and allergic sensitisation to Peanut

2.2.5.1 EBF ≥3-4 months vs. <3-4 months

One prospective cohort study reported OR for PN AS, in infants with EBF for ≥3-4 months vs. <3-4 months duration and is shown in Figure 32. There was no association found. This was a study with low risk of bias on all parameters, which reported adjusted data for PN sensitisation at age 8, measured using specific IgE.

Figure 32 Exclusive breastfeeding ≥3-4 months vs. <3-4 months and risk of allergic sensitisation to PN

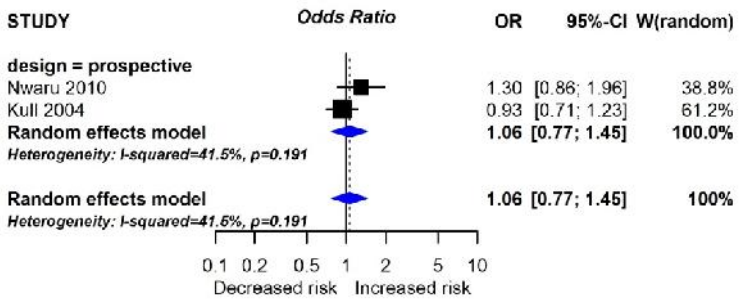


2.2.6 EBF and allergic sensitisation to aeroallergen

2.2.6.1 EBF ≥0-2 months vs. <0-2 months

Two prospective cohort studies reported OR for Aeroallergen AS, in infants with EBF for ≥0-2 months vs. <0-2 months duration and are shown in Figure 33. There was no association found, with moderate statistical heterogeneity (I^2=40%). Both studies reported adjusted data on sIgE in normal risk populations, and were considered at low risk of bias.

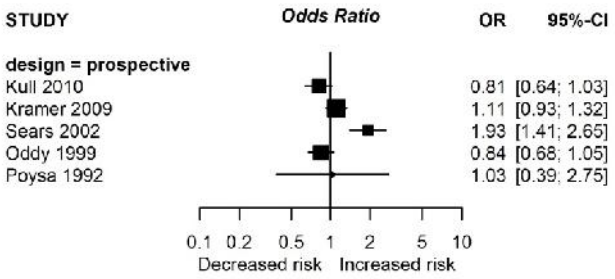
Figure 33 EBF ≥0-2 months vs. <0-2 months and risk of allergic sensitisation to aeroallergen



2.2.6.2 EBF ≥3-4 months vs. <3-4 months

Five prospective cohort studies reported OR for Aeroallergen AS, in infants with EBF for ≥3-4 months vs. <3-4 months duration and are shown in Figure 34. Data were not pooled due to extreme statistical heterogeneity (I^2=83%), largely driven by the study of Sears. Two of the studies (Oddy and Kramer) were reported in the included systematic review. All studies are prospective cohorts reporting adjusted data in normal risk populations, other than Poysa which reports unadjusted data in a high risk population. All studies used SPT other than Kull. Ages at outcome assessment ranged from 6 to 21 years.

Figure 34 EBF ≥3-4 months vs. <3-4 months and risk of allergic sensitisation to aeroallergen

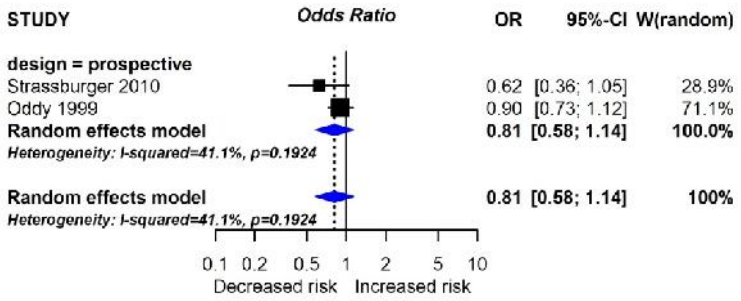


2.2.6.3 EBF ≥5-9 months vs. <5-9 months

Two prospective cohort studies reported OR for Aeroallergen AS, in infants with EBF for ≥5-7 months vs. <5-7 months duration and are shown in Figure 35. There was no association found, with moderate statistical heterogeneity. Both studies reported adjusted data in normal risk populations, and were considered at low risk of bias on

all parameters and used SPT for assessment of AS at 3.5-6 years. We were unable to explain the statistical heterogeneity.

Figure 35 EBF ≥5-7 months vs. <5-7 months and risk of allergic sensitisation to aeroallergen

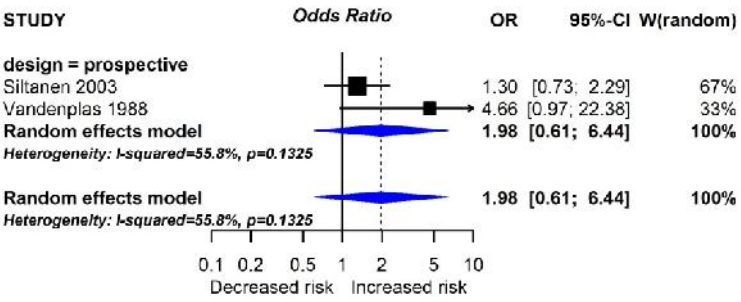


2.2.7 Total IgE

2.2.7.1 EBF ≥3-4 months vs. <3-4 months and elevated Total IgE

Two studies reported the relationship between EBF duration ≥3-4 months and risk of raised Total IgE, and are shown in Figure 36. Pooled data show no evidence of association, with high statistical heterogeneity for unexplained reasons.

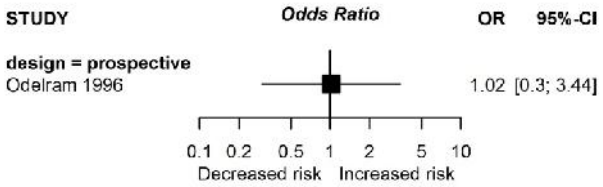
Figure 36 EBF ≥3-4 months vs. <3-4 months and risk of raised Total IgE



2.2.7.2 EBF ≥5-9 months vs. <5-9 months and elevated Total IgE

One study reported the relationship between EBF duration ≥5-9 months and risk of raised Total IgE, and is shown in Figure 37. There was no evidence of association.

Figure 37 EBF ≥5-9 months vs. <5-9 months and risk of raised Total IgE



2.3 Data for EBF duration and AS that were not suitable for meta-analysis

Nine of the 25 included studies did not report data that could be included in a meta-analysis, and are summarised below in Table 4. In 6 studies reporting EBF duration and specific AS risk there was evidence of a positive relationship in just one small study reporting unadjusted data. In all others there was no evidence of association. In 3 studies reporting EBF duration and Total IgE there was no evidence of association.

Table 5 Studies investigating the association between EBF and allergic sensitisation which were not eligible for meta-analysis

Study	Design	Outcome	Age	N/n	Data	Measure	EBF in no AS	EBF in AS	P-value
Vandenplas 1988 [52]	PC	sIgE-CM, SPT-CM, Total IgE	0.33	75/9	Categorical	Increased AS in those with longer EBF. 3/60 vs 0/15 (sIgE-CM), 7/60 vs 0/15 (SPT-CM). Unadjusted data.			
Venter, 2009 [15]	PC	SPT-FOOD	3	891/27	Categorical	No relationship between EBF duration of >3 or <3 months, and food sensitisation at 1 or 3 years			
Silvers, 2009 [29]	PC	SPT-ANY	1	889/249	Continuous	Adjusted OR for AS, for each month increase in EBF duration was 1.03 (0.96, 1.1) P=0.40			
Hoppu, 2000 [21]	PC	SPT-ANY	1	114/27	Continuous	Mean (95%C)	3.3 (3, 3.7)	3.2 (2.6, 3.8)	NS
Hesselmar 2010 [2]	PC	sIgE-FOOD	1.5	169/25	Continuous	Median (IQR)	4 (4, 4.5)	4 (2.5, 4.5)	0.58
Zutavern 2004 [17]	PC	SPT-AERO	5.5	623/103	Categorical	No significant relationship between EBF duration of >8 or <8 weeks, and food sensitisation			

Study	Design	Outcome	Age	N/n	Data	Measure	EBF in no AS	EBF in AS	P-value
Bruno, 1995 [40]	PC	Total IgE	5	107	Continuous		Geometric mean Total IgE was 8.5 in those EBF for 6 months, and 14 for shorter EBF duration. The difference was no statistically significant		
Gruber 2010 [44]	PC	Total IgE	1	167/15	Continuous		Least squares mean (kU/L) for those EBF for >2 months 10.9 (8.2, 14.5) versus <2 months 11.9 (10.2, 13.8). Not statistically significant		
Poysa, 1990 [46]	PC	Total IgE	5	91	Continuous		Total IgE not significantly different between those EBF for ≥3 versus <3 months		

3 Age at solid food introduction and allergic sensitisation

3.1.1 Overall characteristics of studies, risk of bias and summary of results

Table 5 describes the main characteristics of the studies analysed in this report. A total of 9 prospective cohort studies and one cross-sectional study, reported the association between timing of solid food introduction (SF) and risk of AS. The studies were from Europe (n=6), USA (n=2) and Australia (n=2). Overall, valid data on SF and AS risk were available from over 7000 subjects. Information on AS was obtained from a skin prick test in 5 studies, and blood IgE measurement in 5 studies. With regards to time of outcome diagnosis, 7 studies explored the association between SF and AS in the first 4 years of life, 3 studies assessed at age 5-14 years. Four studies used a questionnaire and/or interview to assess the exposure (SF), 6 used an interview alone.

Risk of bias is summarised in Figure 38. Just under half of studies had a high risk of bias, due to lack of adjustment for confounding bias i.e. no adjusted data presented. One third of studies had unclear risk of assessment bias. Risk of conflict of interest was generally assessed as low.

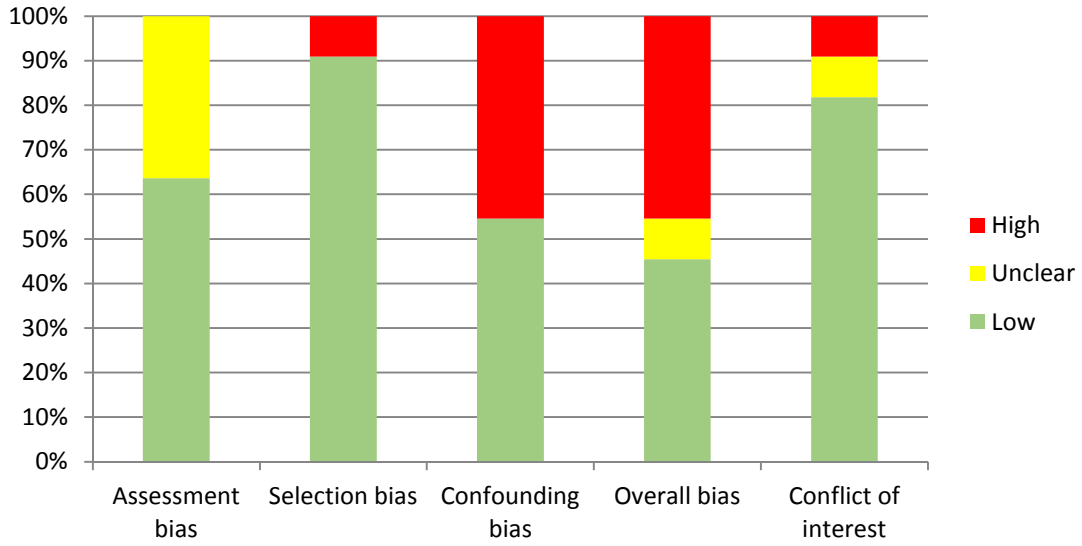
The risk of AS according to SF was categorised as ≥3-4 months vs. <3-4 months. Overall the evidence base was limited due to small numbers of included studies. We found no evidence that the timing of solid food introduction is associated with risk of AS.

Table 6 Characteristics of included studies evaluating SF introduction and allergic sensitisation

First Author & Publication Year	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Hesselmar, 2010 [2]	169/25	PC	Sweden	I	sIgE-FOOD	1.5	ALLERGYFLORA study. Population based study of babies selected from antenatal clinics between 1998 and 2003 - mainly high risk of allergic disease
Mihrshahi, 2007 [8]	516/217	PC	Australia	I	SPT-ANY	5	CAPS study. Infants born in 1997-1999 with family history of asthma or wheezing
Snijders, 2008 [24]	776/218	PC	Netherlands	Q	sIgE-AERO/ANY/CM/EGG/PN	2	KOALA study. Population based birth cohort of infants born between 2000-2002 (consisting of cohorts with conventional and alternative lifestyle)
Zutavern, 2006; Zutavern, 2008 [55, 56]	2612/258; 1123/301	PC	Germany	Q/I	sIgE-ANY/FOOD/AERO/CM/EGG/PN	2, 6	LISA study. Population based birth cohort of infants born 1997-9 at selected maternity hospitals in 4 German cities
Sicherer, 2010 [14]	503/140	PC	USA	I	sIgE-PN	1	The Consortium of Food Allergy Research: atopic children recruited from services
Van Asperen, 1983 [51]	79/13	PC	Australia	I	SPT-FOOD	1.3	Cohort recruited from medical service, born in 1980-1981 with family history of atopy
Venter, 2009 [15]	757/27	PC	UK	Q	SPT-FOOD	1, 3	Recruited from antenatal clinics and born in 2001-2002

First Author & Publication Year	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Joseph, 2011 [57]	594/178	PC	USA	I	sIgE-CM/EGG/PN	3	WHEALS STUDY: Recruited from hospital prenatal care and born in 2005
Zutavern, 2004 [17]	623/103	PC	UK	I	SPT-AERO	5.5	Cohort recruited from general practices and born in 1993-5
Kucukosmanoglu, 2008 [35]	1015/20	CS	Turkey	Q/I	SPT-EGG	1	Hospital based selection of 8-18 months old Infants born in 2001-2002

Figure 38 Risk of bias in studies of SF introduction and allergic sensitisation

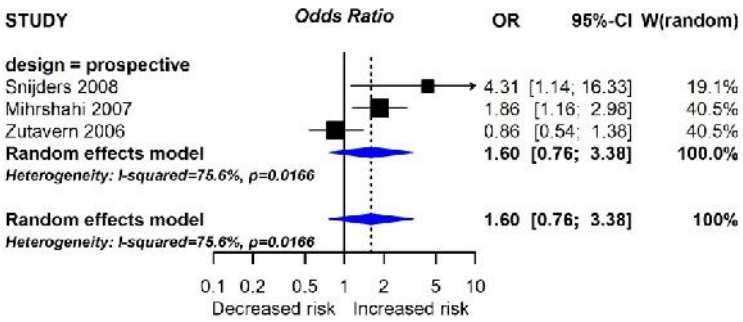


3.2 Solid food introduction and allergic sensitisation

3.2.1 SF and allergic sensitisation to any allergen

Three prospective cohort studies reported OR for AS to any allergen, in infants with SF ≥3-4 months vs. <3-4 months and are shown in Figure 39. There was no significant association found, with extreme statistical heterogeneity. All studies reported adjusted data, and were considered at low risk of bias on all domains. The study of Mihrshahi used skin prick testing for assessment at age 5, and the other studies used blood specific IgE testing for similar combined food/aeroallergen profiles at age 2 years. We were unable to confidently explain the heterogeneity between the findings of Snijders and Zutavern, however the study of Snijders included very few participants with SF introduction prior to 4 months (n=50), and included participants with an anthroposophic lifestyle (~20% of participants).

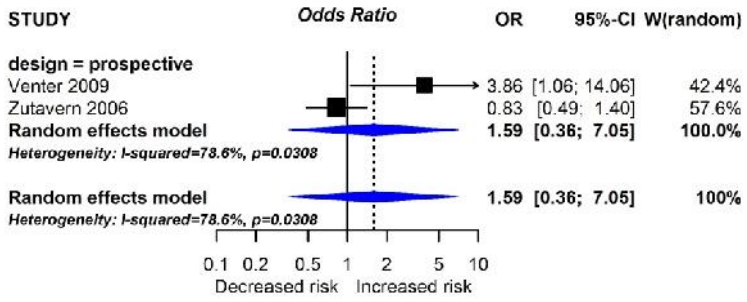
Figure 39 SF ≥3-4 months vs. <3-4 months and risk of allergic sensitisation to any allergen



3.2.2 SF and allergic sensitisation to Food

Two prospective cohort studies reported OR for AS to any food allergen at age 0-4 years, in infants with SF ≥3-4 months vs. <3-4 months and are shown in Figure 40. There was no significant association found, with extreme statistical heterogeneity. The study of Zutavern reported adjusted data using specific IgE blood testing at aged 2, and was considered at low risk of bias on all domains. The study of Venter reported unadjusted data using skin prick testing at age 1, and was therefore considered at high risk of bias. This difference in adjustment for potential confounding variables may explain the statistical heterogeneity.

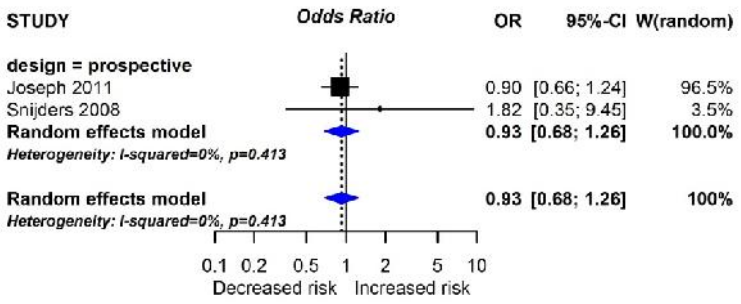
Figure 40 SF ≥3-4 months vs. <3-4 months and risk of allergic sensitisation to food



3.2.3 SF and allergic sensitisation to Cow's Milk

Two prospective cohort studies reported OR for AS to CM at age 0-4 years, in infants with SF ≥3-4 months vs. <3-4 months and are shown in Figure 41. There was no significant association found, with no statistical heterogeneity. Both studies assessed sensitisation using specific IgE blood testing at aged 2 years. The study of Snijders reported adjusted data and was considered at low risk of bias on all domains. The study of Joseph reported unadjusted data, and was therefore considered at high risk of bias.

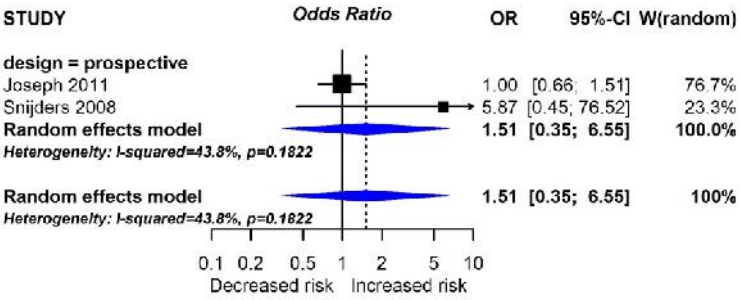
Figure 41 SF ≥3-4 months vs. <3-4 months and risk of allergic sensitisation to cow's milk



3.2.4 SF and allergic sensitisation to Egg

Two prospective cohort studies reported OR for AS to Egg at age 0-4, in infants with SF ≥3-4 months vs. <3-4 months and are shown in Figure 42. There was no significant association found, with moderate statistical heterogeneity. Both studies assessed sensitisation using specific IgE blood testing at aged 2 years. The study of Snijders reported adjusted data and was considered at low risk of bias on all domains. The study of Joseph reported unadjusted data, and was therefore considered at high risk of bias.

Figure 42 SF ≥3-4 months vs. <3-4 months and risk of allergic sensitisation to Egg

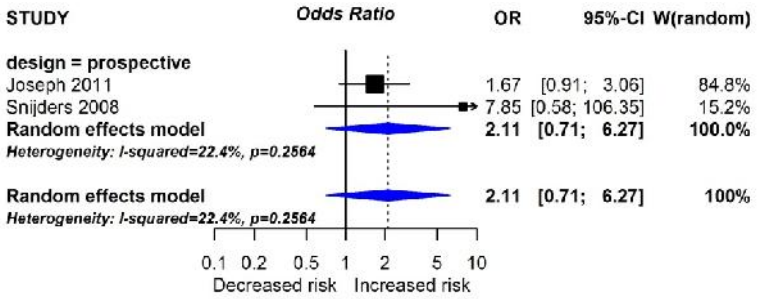


3.2.5 SF and allergic sensitisation to Peanut

Two prospective cohort studies reported OR for AS to PN at age 0-4 years, in infants with SF ≥3-4 months vs. <3-4 months and are shown in Figure 43. There was no significant association found, with low statistical heterogeneity. Both studies assessed

sensitisation using specific IgE blood testing at aged 2 years. The study of Snijders reported adjusted data and was considered at low risk of bias on all domains. The study of Joseph reported unadjusted data, and was therefore considered at high risk of bias. A third study Zutavern 2008 could only be reported in narrative form, and found increased PN sensitisation associated with later SF. A fourth study Sicherer 2010 could only be reported in narrative form, and found no association between SF and PN sensitisation.

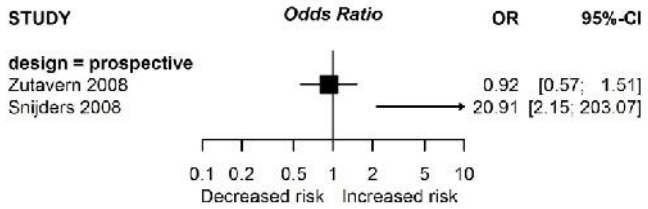
Figure 43 SF ≥3-4 months vs. <3-4 months and risk of allergic sensitisation to Peanut



3.2.6 SF and allergic sensitisation to Aeroallergen

Two prospective cohort studies reported OR for AS to any aerollergen at age 0-4 years, in infants with SF ≥3-4 months vs. <3-4 months and are shown in Figure 44. The data were not pooled due to extreme statistical heterogeneity. Both studies reported adjusted data using specific IgE testing at age 2 years, and were considered at low risk of bias on all domains. The study of Zutavern found no association; the study of Snijders found increased odds of aeroallergen sensitisation with later SF introduction. We were unable to confidently explain the heterogeneity between the findings of Snijders and Zutavern, however the study of Snijders included very few participants with SF introduction prior to 4 months (n=50), and included participants with an anthroposophic lifestyle (~20% of participants).

Figure 44 SF ≥3-4 months vs. <3-4 months and risk of allergic sensitisation to aeroallegen



3.3 Data for SF and AS that were not suitable for meta-analysis

No studies were identified for SF and Total IgE.

Six of the 10 included studies did not report data that could be included in a meta-analysis, and are summarised below in Table 6. In one study there was a significant association between delayed SF introduction and increase PN-AS (but not CM or Egg AS). In all other studies there was no association seen.

Table 7 Studies investigating the association between SF introduction and allergic sensitisation which were not eligible for meta-analysis

Study	Design	Outcome	Age	N/n	Data	Measure	SF in no AS	SF in AS	P
Hesselmar 2010 [2]	PC	sIgE-FOOD	1.5	169/25	Continuous	Median (IQR)	4 (4, 5)	4 (4, 5)	0.84
Kucukosmanoglu 2008 [35]	CS	SPT-EGG	1	1015/20	Continuous	Mean (SD)	4.11 (1.91)	4.26 (1.91)	0.77
Van Asperen, 1983 [51]	PC	SPT-FOOD	1.3	79/13	Categorical	No significant difference in food sensitisation in those with SF before and after 6 months			
Sicherer, 2010 [14]	PC	sIgE-PN	1	503/140	Categorical	No significant association between SF timing and PN sensitisation. One analysis gave OR 1.03 (0.89, 1.18) P=0.71.			
Zutavern, 2008 [56]	PC	sIgE-CM/EGG/PN	6	1123/301	Categorical	Significant association between SF >4 months and increased PN sensitisation (P<0.05), but not milk or Egg sensitisation			
Zutavern 2004 [17]	PC	SPT-AERO	5.5	623/103	Categorical	No significant relationship between SF timing and AERO sensitisation			

4 Conclusion

This report summarises the results of over 40 studies investigation the association between total and exclusive breastfeeding duration, timing of solid food introduction and risk of allergic sensitisation. The majority of studies were prospective cohort studies. We identified one systematic review and one intervention trial which found no evidence for an association between EBF duration or TBF duration respectively, and risk of AS. From the observational studies, we overall found no clear evidence to support an association between TBF or EBF duration, or SF introduction and AS. One meta-analysis found increased risk of food AS associated with EBF ≥0-2 months vs <0-2 months with no statistical heterogeneity, and one study from that meta-analysis also reported increased risk of food AS with TBF ever vs never. However there was no association seen in analysis of other cut-offs for TBF or EBF duration and food AS, no association between these exposures and other forms of allergic sensitisation (i.e. AS to milk, egg or peanut individually, AS to aeroallergens or to any allergen), or in studies which could not be included in meta-analysis. The possibility of reverse causality in those 3 studies should be considered, and was adjusted for in some studies, where they did not find evidence that early symptoms associated with food sensitisation is associated with extension of TBF or EBF duration in infancy. Overall this report has not identified evidence of a relationship between TBF, EBF, SF introduction and AS, and we did not identify any other detailed systematic review of these outcomes with which to compare our findings.

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BREASTFEEDING, SOLID FOOD INTRODUCTION AND TYPE I DIABETES MELLITUS

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1. Total breastfeeding duration and risk of TIDM

1.1. Overall characteristics of studies, risk of bias and summary of results

Table 1 describes the main characteristics of the studies analysed in this report. A total of 65 observational studies, and no intervention studies, reported the association between duration of breastfeeding and risk of TIDM. Of these, 15 were prospective cohort studies, 7 nested case-controls, 1 cross-sectional study and 42 case-control studies. Over half of the studies (n=39) are from Europe – others are from North America (n=9), South America (n=4), Asia (n=8), the Middle East (n=4) and Africa (n=1). Overall, valid data on total breastfeeding duration in the first year of life (TBF) and TIDM risk were available from almost 50,000 subjects including over 12,000 with TIDM. Information on TIDM was obtained mainly from serology (Islet auto-antibodies) in 15 prospective studies and via medical diagnosis in 50 (mainly case control) studies. With regards to time of outcome diagnosis, 12 studies explored the association between exposure to breastfeeding and TIDM in the first 5 years of life, 2 didn't report the age at outcome assessment, and others evaluated TIDM in older children or young adults. 58 studies used interview or questionnaire to assess the exposure (TBF), 7 studies assessed medical records only.

Risk of bias was assessed using the NICE Methodological checklists for cohort and case-control studies. Figure 1 illustrates the distribution of bias across the five main methodological areas of the studies. Over half of studies had a high risk of bias, most commonly due to lack of adjustment for confounding bias i.e. no adjusted data presented. Over a quarter of studies had an 'unclear' overall risk of bias, most commonly due to insufficient information to evaluate assessment bias. We undertook subgroup/stratified analyses for meta-analyses with >5 studies, and Funnel plots and Egger's test where there were ≥10 studies in a meta-analysis.

Five levels of comparison were used to assess the risk of TIDM according to total breastfeeding duration, namely 'ever vs. never', '≥1-2 months vs. <1-2 months', '≥3-4 months vs. <3-4 months', '≥5-7 months vs. <5-7 months', and '≥8-12 months vs. <8-12 months'.

Main Findings

Across all cut-offs for TBF duration, there was evidence of a lower risk of TIDM with longer duration of breastfeeding, however meta-analyses showed moderate to high statistical heterogeneity across studies. Stratified and subgroup analyses showed some evidence of risk

difference when specific risk groups and study design characteristics were analysed. Prospective studies, which often used autoantibodies at a young age as a surrogate for TIDM, and sometimes reported HR rather than OR, tended to not show a significant association between TBF and TIDM risk. In contrast, retrospective studies using clinical TIDM as an outcome tended to report an association between longer TBF and reduced TIDM risk, sometimes with low statistical heterogeneity. It is possible that the difference observed between these two groups of study design lies in the type of outcome used to measure TIDM. In general adjusted and unadjusted analyses showed similar findings. We were not able to clearly confirm the relationship between TBF and TIDM in dose-response analysis, although data were limited for this analysis - and only a small number of the 24 studies (~1/3 of TIDM cases) which could not be included in any meta-analysis found the same association between TBF and reduced TIDM risk. Thus our data must be interpreted as VERY LOW certainty evidence (GRADE -1 inconsistency) that longer duration of TBF is associated with reduced TIDM risk.

Table 1 Description of observational studies on total breastfeeding duration and Risk of TIDM

First Author & Publication Year	N/n cases	Design	Country	Exposure assessment	Specific outcome	Age at outcome (years)	Population characteristics
Couper, 1999 (1)	317/70	PC	Australia	D/Q	Islet autoantibodies	2	First degree relatives of diabetic children
Couper, 2009 (2)	548/~30	PC	Australia	D/I	Islet autoantibodies	2	First degree relatives of diabetic children
Fronczak, 2003 (3)	222/~16	PC	USA	Q	Islet autoantibodies	4	Newborn screening, or Colorado register
Holmberg, 2007 (4)	3788/~51	PC	Sweden	Q	Islet autoantibodies	6	General population
Hummel, 2000 (5)	568	PC	Germany	Q	Islet autoantibodies	2	Offspring of diabetic parents
Karlen, 2012 (6)	1409	PC	Sweden	Q	Islet autoantibodies	1	General population
Lamb 2008 (7)	642	PC	Australia	I	Islet autoantibodies	13	St. Joseph's Hospital in Denver, Colorado
Lamb, 2013 (8)	260	PC	America	I	Islet autoantibodies	Not reported	not reported
Ludvigsson, 2003 (9)	205	PC	Sweden	Q	Islet autoantibodies	2	Relatives of diabetics
Norris, 2003 (10)	1183/~733	PC	USA	I	Islet autoantibodies	4	St Joseph's Hospital, Colorado
Viner, 2008 (11)	11211/61	PC	UK	Q	Medical diagnosis	>10	not reported
Virtanen, 1998 (12)	697/43	PC	Finland	Q	Medical diagnosis, Islet autoantibodies	<25	Siblings of diabetic children
Virtanen, 2011 (13)	~4000/~160	PC	Finland	Q	Medical diagnosis or islet autoantibodies	5	Odu and Tampere University Hospitals
Wahlberg, 2006 (14)	8715/31	PC	Sweden	Q	Islet autoantibodies	2	General population

First Author & Publication Year	N/n cases	Design	Country	Exposure assessment	Specific outcome	Age at outcome (years)	Population characteristics
Ziegler, 2003 (15)	1460/~68	PC	Germany	Q	Islet autoantibodies	5	Newborn children
Jones, 1998 (16)	518/60	NCC	UK	R	Medical diagnosis	5.0-9	Hospital admission
Kimpimaki, 2001 (17)	455/65	NCC	Finland	Q	Medical diagnosis	<4	Turku, Oulu and Tampere Hospital births
Kyvik, 1992 (18)	228/76	NCC	Denmark	R	Medical diagnosis	<20	National Service Conscript records
Norris, 1996 (19)	171/18	NCC	USA	Q/R	Islet autoantibodies	<7	Siblings or offspring of Barbara Davies Centre Diabetics
Robertson, 2010 (20)	1444/361	NCC	UK	R	Medical diagnosis	<15	AMND and SSG register, hospital births
Savilahti, 2009 (21)	6209/45	NCC	Finland	R	Medical diagnosis	12	NHI database
Virtanen, 2000 (22)	287/33	NCC – nested in Virtanen, 1998 (12)	Finland	Q	Medical diagnosis	7	Siblings of previously diagnosed diabetic child
Glatthaar, 1988 (23)	946/~200	CS	Australia	Q	Medical diagnosis	<18	School register
Ahadi, 2011 (24)	202/101	CC	Iran	Q/I	Medical diagnosis	7	Hospital admission
Alves, 2012 (25)	246/123	CC	Brazil	I	Medical diagnosis	7	Siblings
Ashraf, 2010 (26)	195/128	CC	USA	Q	Medical diagnosis	<10	Children's hospital
Baruah, 2011 (27)	86/43	CC	India	I	Medical diagnosis	<18	Endocrinology ward
Bener, 2009 (28)	340	CC	Qatar	I	Medical diagnosis	<16	Endocrinology clinic and community

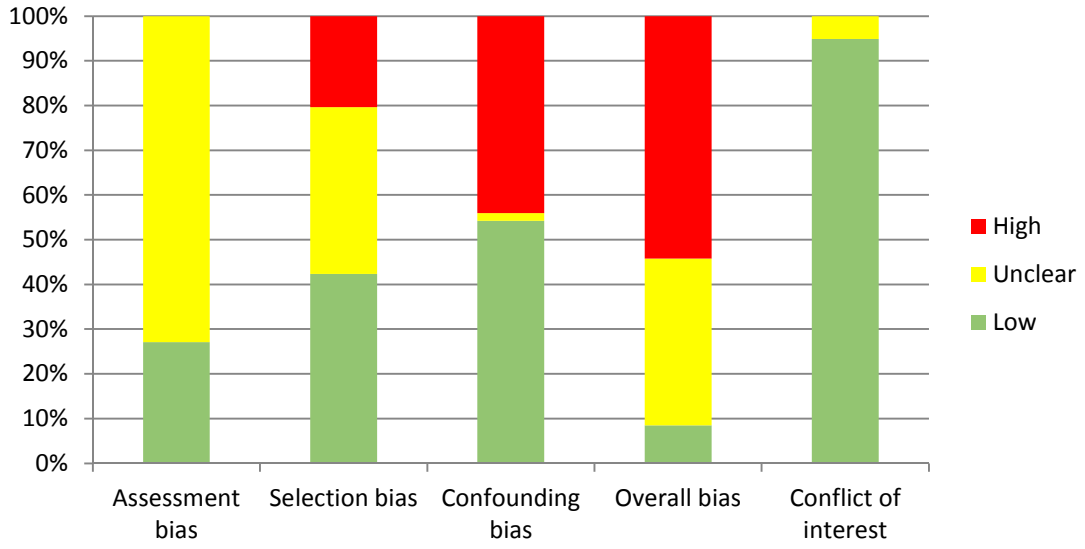
First Author & Publication Year	N/n cases	Design	Country	Exposure assessment	Specific outcome	Age at outcome (years)	Population characteristics
Blom, 1989 (29)	867/339	CC	Sweden	Q	Medical diagnosis	7	Paediatric referral and population register
Bodington, 1994 (30)	393/209	CC	UK	Q	Medical diagnosis	<15	Independent sources and population register
Borras, 2011 (31)	1530/306	CC	Spain	R	Medical diagnosis	not reported	Diabetes register and Catalonia birth register
Esfarjani, 2001 (32)	104/52	CC	Iran	Q	Medical diagnosis	<14	Endocrine clinic and paediatric OPD attendance
Dahlquist, 2002 (33)	2226/610	CC	Austria, Latvia, Lithuania, Luxembourg and UK	Q/I	Medical diagnosis	<15	Diabetes register and population register
Gimeno, 1997 (34)	626/313	CC	Brazil	Q	Medical diagnosis	<18	Juvenile Diabetes Association or hospital records
Hathout, 2006 (35)	402/102	CC	USA	Q/I	Medical diagnosis	7	Diabetes hospital care and Hospital Well Child clinics
Hypponen, 1999 (36)	821/435	CC	Finland	Q	Medical diagnosis	8	Finnish Population Registry
Kostraba, 1992 (37)	264/132-white 108/54-black	CC	USA	Q/I	Medical diagnosis	10	Alleghany Hospital diabetes register
Kostraba, 1993 (38)	306/142	CC	USA	Q	Medical diagnosis	<18	Colorado IDDM Registry and otor vehicle driver register
Majeed, 2011 (39)	310/96	CC	Iraq	Q	Medical diagnosis	<17	Hospital admission or OPD
Malcova, 2006 (40)	2334/868	CC	Czech Republic	Q	Medical diagnosis	<15	Czech Childhood Diabetes Register and diabetes clinic
Marshall, 2004 (41)	577/196	CC	UK	I	Medical diagnosis	<16	Paediatric clinic and Local Health Authority Register

First Author & Publication Year	N/n cases	Design	Country	Exposure assessment	Specific outcome	Age at outcome (years)	Population characteristics
Mayer, 1988 (42)	747/268	CC	USA	Q/I	Medical diagnosis	<18	Colorado IDDM Registry or Barbara Davies Centre
McKinney, 1999 (43)	521/196	CC	UK	I	Medical diagnosis	<16	Yorkshire Childhood Diabetes Register and Family Health Service Authority Register
Meloni, 1997 (44)	200/100	CC	Italy	Q	Medical diagnosis	<17	Paediatric clinic or hospital admission
Patterson, 1994 (45)	1548/258	CC	UK	R	Medical diagnosis	<15	Diabetes register, hospital discharge, Health Service records
Perez-Bravo, 1996 (46)	165/80	CC	Chile	Q/I	Medical diagnosis	<15	Santiago de Chile registry
Perez-Bravo, 2003 (47)	250/143	CC	Chile	Q	Medical diagnosis	8	School volunteers
Rami, 1999 (48)	609/114	CC	Austria	Q	Medical diagnosis	<15	Austrian diabetes register
Rosenbauer, 2008 (49)	2631/760	CC	Germany	Q/I	Medical diagnosis	<5	Hospital based surveillance system ESPD and local registration office records
Sadauskaite-Kuehne, 2004 (50)	1944/803	CC	Sweden/Lithuania	Q	Medical diagnosis	7	Population register and outpatients
Samuelsson, 1993 (51)	1089/297	CC	Sweden	Q/R	Medical diagnosis	<15	Paediatric department and population register
Siemiatycki, 1989 (52)	482/161	CC	Canada	I	Medical diagnosis	<17	Hospital admission
Sipetic, 2005 (53)	315/105	CC	Serbia	I	Medical diagnosis	<16	Hospital admission
Skrodeniene, 2010 (54)	1099/286	CC	Lithuania	Q	Medical diagnosis	9	Population register and outpatients
Soltesz, 1994 (55)	305/130	CC	Hungary	Q	Medical diagnosis	<14	Incidence register
Strotmeyer, 2004 (56)	485/247	CC	China	Q	Medical diagnosis	10	Diabetes register and population register

First Author & Publication Year	N/n cases	Design	Country	Exposure assessment	Specific outcome	Age at outcome (years)	Population characteristics
Tai, 1998 (57)	310/117	CC	Taiwan	I	Medical diagnosis	8	Taipei City
Telahun, 1994 (58)	129/55	CC	Ethiopia	Q	Medical diagnosis	<15	Ethio-Swedish Children's Hospital Diabetic Clinic
Tenconi, 2007 (59)	477/159	CC	Italy	R/I/Q	Medical diagnosis	16	Diabetes register or paediatric admissions
Thorsdottir, 2000 (60)	220/55	CC	Iceland	I	Medical diagnosis	12	Statistical Bureau of Iceland
Verge, 1994 (61)	475/217	CC	Australia	Q	Medical diagnosis	<15	New South Wales diabetes register and school records
Virtanen, 1992 (74) (46) (46)	852/426	CC	Finland	Q	Medical diagnosis	<14	Hospital admissions
Virtanen, 1993 (62)	1380/690	CC	Finland	Q	Medical diagnosis	14	Finnish National Population Registry
Visalli, 2003 (63)	900/150	CC	Italy	Q	Medical diagnosis	6-18	EURODIAB study register and school records
Wadsworth, 1997 (64)	639/276	CC	UK	Q	Medical diagnosis	<5	BPASU reporting system and District Health Authority Immunisation Register

Q: questionnaire, I: interview, R: medical records, PC: prospective cohort, NCC: nested case control, CS: Cross-sectional, CC: case control

Figure 1 Risk of bias in observational studies of total breastfeeding duration and TIDM



1.2. Outcomes from studies of total breastfeeding and TIDM

1.2.1. Ever vs. never breastfed

Figure 2 shows the combined effect of 32 eligible observational studies including over 6000 people with TIDM investigating the risk of TIDM according to whether infants were breastfed for any duration or never breastfed. Overall, there was a 22% (OR 0.78; 95% confidence interval [CI] 0.68, 0.89) reduction in the risk of having TIDM in infants who were ever breastfed, with high heterogeneity across studies (I^2=51.2%). Subgroup analyses are shown in Table 2. Adjusted and unadjusted analyses yielded similar findings, with high heterogeneity in each. In the small number of studies with prospective design (total 313 cases), in those which used TIDM associated antibodies rather than disease as an outcome (and recruited high risk populations; total 116 cases) and in studies with low risk of bias (total 86 cases), there was no evidence of an association between BF and TIDM. Risk of bias was commonly considered unclear, due to lack of information about blinding of outcome assessors to exposure data. We found no evidence of publication bias (Egger's test P-value=0.81) (Figure 3).

Figure 2 Breastfeeding ever vs. never and TIDM risk

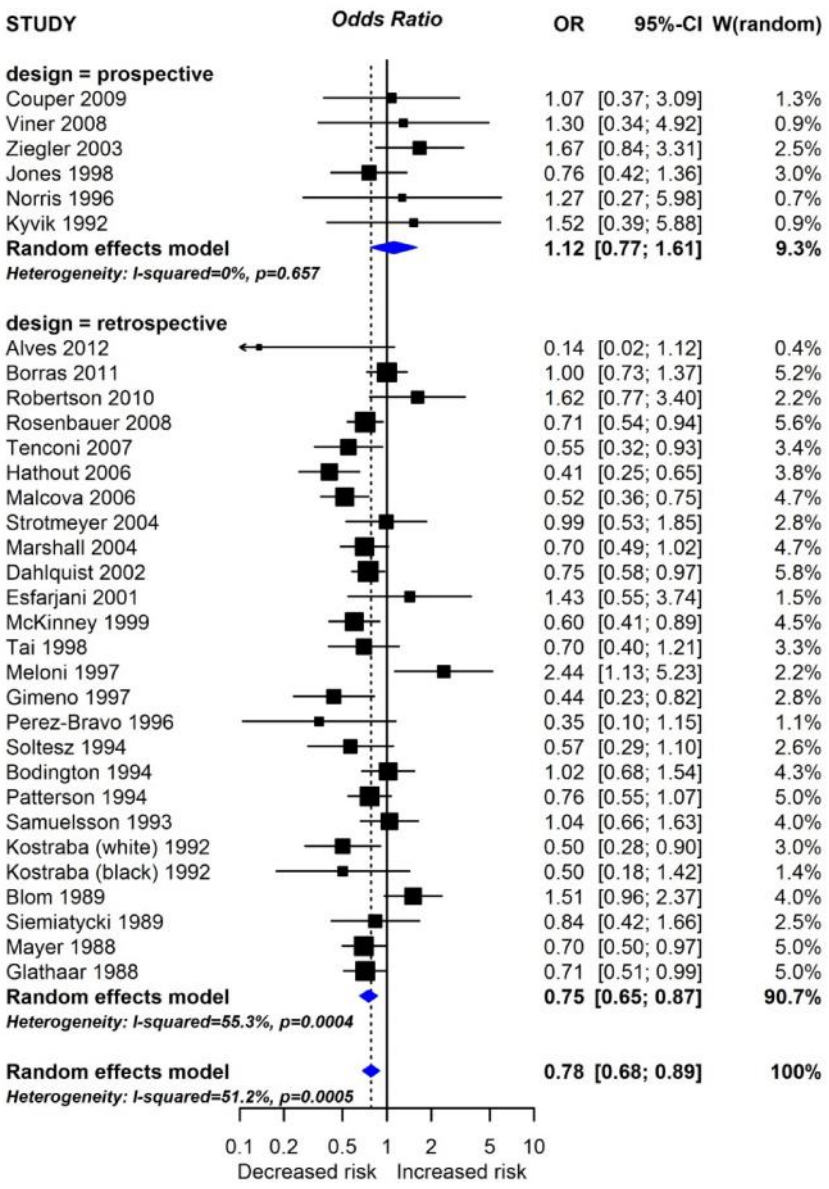
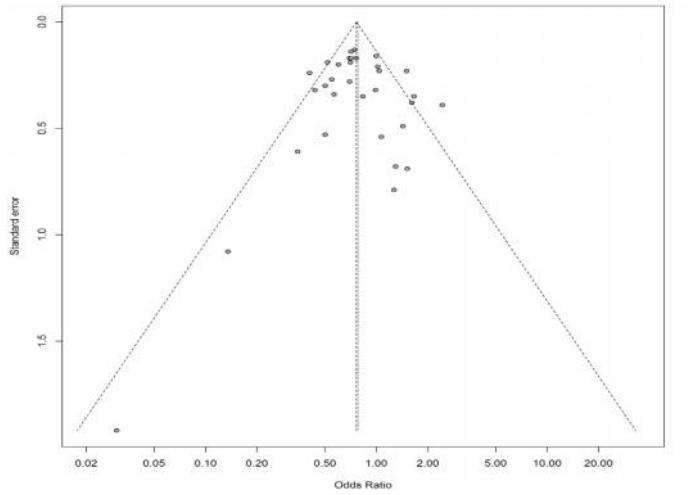


Table 2 Stratified and subgroup analyses of association between ever vs. never being breastfed and risk of TIDM

	Number of studies	OR [95% CI]*	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted value used)	32	0.78 [0.68-0.89]	51.2	
Adjusted	15	0.76 [0.64-0.91]	51.8	Not tested
Unadjusted	29	0.81 [0.70-0.94]	54.0	
Risk of disease – High	3	1.44 [0.84-2.47]	0	**0.025**
Risk of disease – Normal	29	0.76 [0.67-0.87]	51.4	
Risk of bias – Low	2	1.59 [0.85-2.98]	0	**0.025**
Risk of bias – High/Unclear	30	0.76 [0.66-0.87]	50.1	
Study Design – Prospective	6	1.15 [0.77-1.61]	0	**0.049**
Study Design - Retrospective	26	0.75 [0.65-0.87]	55.3	
Method of diagnosis – clinical	29	0.76 [0.66-0.87]	51.4	**0.025**
Method of diagnosis – serological (single or combination of antibodies)	3	1.44 [0.84-2.47]	0	

*Pooled estimate [95%CI] of meta-analysis of studies reporting Odds or Relative risk or Risk ratios

Figure 3 Risk of publication bias in observational studies investigating breastfed ever vs. never and TIDM risk

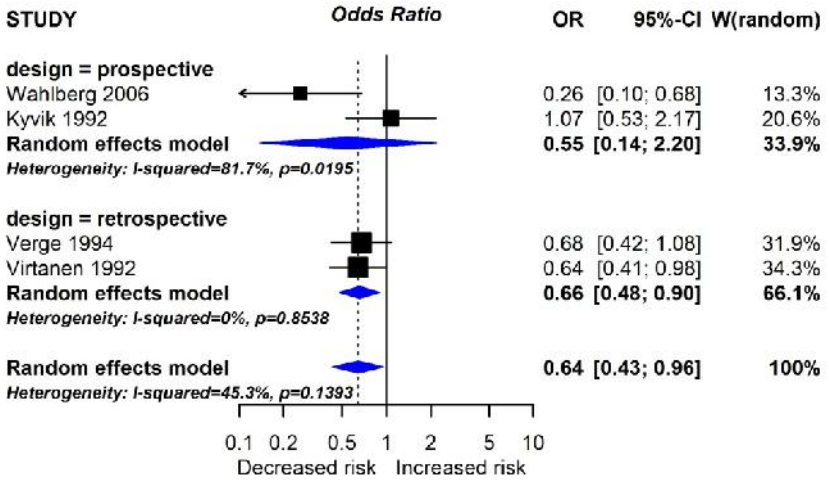


Egger's test p=0.81

1.2.2. Total breastfeeding ≥1-2 months vs. < 1-2 months

Four studies examined the risk of TIDM if infants were breastfed for over 1-2 months compared to less than this duration. Figure 4 shows that the combined risk of TIDM is 36% lower (Pooled OR 0.64; 95% CI 0.43, 0.96) if infants were breastfed for at least 1-2 months. There was moderate heterogeneity across studies (I^2=45.3%). Stratified and subgroup analyses was not performed due to the small number of studies included. The study of Kyvik presented unadjusted data from a nested case control study, considered at high risk of bias, comparing ≥5 months with 0-1 months TBF; Virtanen and Verge presented adjusted data from case control studies; Wahlberg unadjusted data from a prospective cohort study using autoantibodies as an outcome. The reason for the statistical heterogeneity is not clear, but may relate to use of autoantibodies at age 2 as an outcome in Wahlberg, and presentation of unadjusted data in Kyvik.

Figure 4 Breastfeeding for ≥1-2 months vs. < 1-2 months and TIDM risk



1.2.3. Total breastfeeding duration ≥3-4 months vs. <3-4 months

The association between breastfeeding for at least 3-4 months vs. less than this duration and risk of TIDM was examined in 10 studies. Meta-analysis showed reduced risk of TIDM (OR 0.55; 95% CI 0.39, 0.77) (Figure 5) although there was high heterogeneity across studies (I^2=61.2%). There was little evidence of different outcomes in subgroup or stratified analyses, other than a greater reduction in risk in individuals with high disease risk versus low/normal risk (Table 3). Ziegler, Fronczak and Couper presented HR from prospective studies using autoantibodies for TIDM diagnosis in young children. Holmberg also used autoantibodies in young children in a prospective study. In general heterogeneity was reduced in retrospective studies using clinical diagnosis of TIDM.

Figure 5 Breastfeeding for ≥3-4 months vs. <3-4 months and TIDM risk

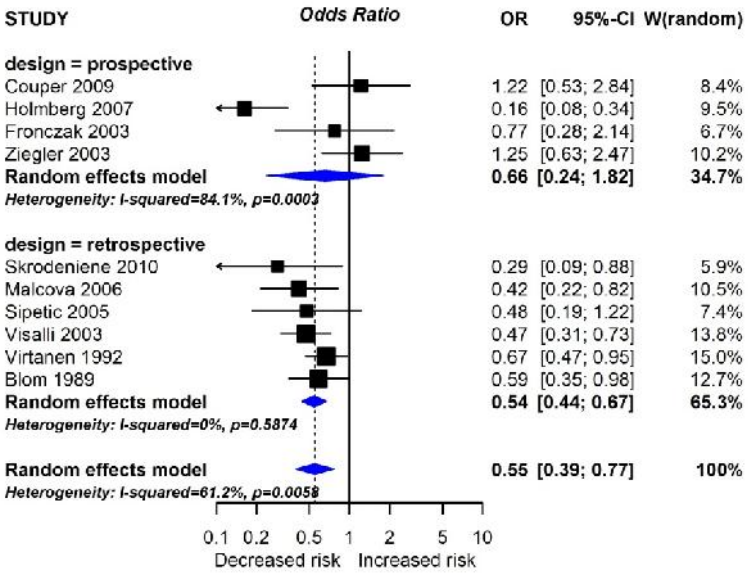
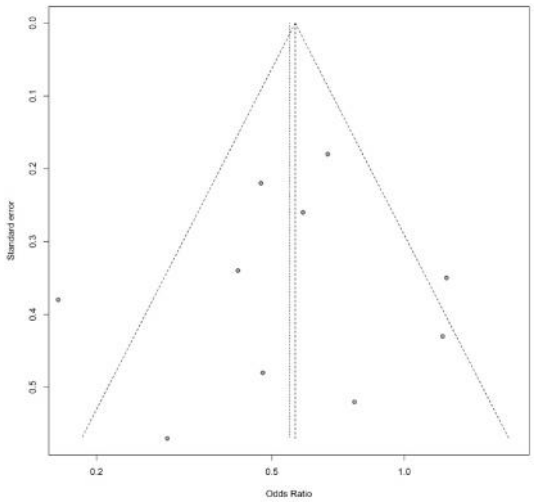


Table 3 Stratified and subgroup analyses of breastfeeding ≥3-4 months vs. <3-4 months and TIDM risk

	Number of studies	OR [95% CI]*	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted value used)	10	0.55 [0.39-0.77]	61.2	
Adjusted	5	0.58 [0.40-0.85]	53.8	Not tested
Unadjusted	7	0.63 [0.38-1.04]	74.5	
Risk of disease – High	3	1.12 [0.70-1.79]	0	**0.002**
Risk of disease – Normal	7	0.45 [0.32-0.62]	53.6	
Risk of bias – Low	2	0.85 [0.47-1.53]	59.7	0.099
Risk of bias – High/Unclear	8	0.47 [0.32-0.69]	53.7	
Study Design – Prospective	4	0.66 [0.24-1.82]	84.1	0.719
Study Design - Retrospective	6	0.54 [0.44-0.67]	0	
Method of diagnosis – clinical	6	0.54 [0.44-0.67]	0	0.719
Method of diagnosis – serological (single or combination of antibodies)	4	0.66 [0.24-1.82]	84.1	

*Pooled estimate [95%CI] of meta-analysis of studies reporting Odds or Relative risk or Risk ratios

Figure 6 Risk of publication bias in observational studies investigating TBF ≥3-4 months vs. <3-4 months and TIDM risk



Egger's test P=0.72

1.2.4. Total duration of breastfeeding ≥5-7 months vs. < 5-7 months

Six studies contributed data to meta-analysis of TBF ≥5-7 vs. <5-7 months and TIDM risk (Figure 7). There was reduced risk associated with prolonged TBF (OR 0.59; 95% CI 0.37, 0.92) but there was extreme heterogeneity across studies (I^2=76.6%). Table 4 shows subgroup and stratified analyses. There was reduced statistical heterogeneity in analysis of adjusted data. Studies of retrospective design and those with an unclear definition of breastfeeding showed a greater level of risk reduction for TIDM than prospective studies or those with clear TBF definition. Data from Majeed included in meta-analysis were unadjusted, and adjusted analysis in the same study was not statistically significant. Sensitivity analysis excluding the study by Majeed reduced heterogeneity (I^2=54.2%, OR 0.72, 95% CI 0.53, 0.98).

Figure 7 Breastfeeding for ≥5-7 months vs. <5-7 months and TIDM risk

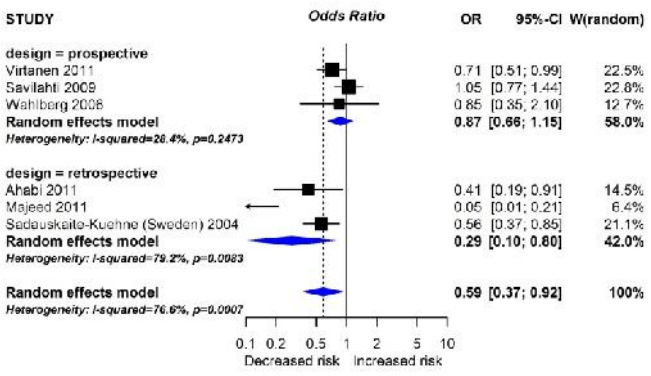


Table 4 Stratified and subgroup analyses of breastfeeding ≥5-7 months vs. <5-7 months and TIDM risk

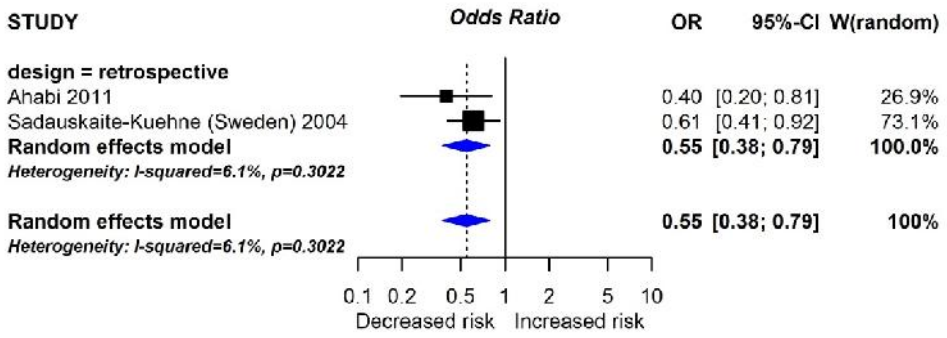
	Number of studies	OR [95% CI]*	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted value used)	6	0.59 [0.37-0.92]	76.6	
Adjusted	2	0.65 [0.50-0.84]	0	Not tested
Unadjusted	5	0.61 [0.35-1.06]	78.8	
Risk of disease – High	1	0.71[0.51-0.99]	-	0.377
Risk of disease – Normal	5	0.51 [0.27-0.97]	81.2	
Risk of bias – Low	1	0.71 [0.51-0.99]	-	0.377
Risk of bias – High/Unclear	5	0.51 [0.27-0.97]	81.2	
Study Design – Prospective	3	0.87 [0.66-1.15]	28.4	**0.042**
Study Design - Retrospective	3	0.29 [0.10-0.80]	79.2	
Method of diagnosis – clinical	4	0.45 [0.21-0.96]	85.9	0.244
Method of diagnosis – serological (single or combination of antibodies)	2	0.73 [0.53-0.99]	0	

*Pooled estimate [95%CI] of meta-analysis of studies reporting Odds or Relative risk or Risk ratios

1.2.5. Total duration of breastfeeding ≥8-12 months vs. <8-12 months

Total breastfeeding duration for ≥8-12 months showed an overall reduced risk of TIDM compared to shorter TBF duration – 2 studies, pooled OR 0.55 (95% CI 0.38, 0.79) with no significant heterogeneity (I^2=6.1%) (Figure 8). Both studies are case control studies using medical diagnosis of TIDM, one reporting adjusted and one (Ahabi) unadjusted data.

Figure 8 Breastfeeding for ≥8-12 months vs. <8-12 months and TIDM risk



1.2.6. Dose response analysis of TBF and TIDM risk

We also analysed TBF duration by grouping studies according to the exposure rather than the reference group – short (≥1-3 months), medium (≥4-6 months) and long (≥7-12 months); all compared to a reference group of never BF. These analyses are shown in Figures 9, 10 and 11. The data showed no significant difference between any time frame analysed versus never. There was low heterogeneity in the short and medium versus never analyses (I^2=0 and I^2=11.7% respectively). There was extreme heterogeneity in the long versus never breastfeeding meta-analysis (I^2=84.3%) so pooled analysis was not reported; the reason for this heterogeneity is unclear. Sensitivity analysis excluding the study by Meloni reduced heterogeneity (I^2=33.7%, OR 0.40, 95% CI 0.19, 0.84), although there appeared to be no major difference in method between studies to explain the difference in results. All 3 studies reported adjusted data from case control studies using clinical diagnosis of TIDM.

We were unable to identify a clear explanation for why dose response analysis did not mirror the positive association seen in analyses using reference groups to define the cut off. Four individual studies were included in more than one dose response analysis - they did not show a clear trend, but in general there tended to be a stronger association between TBF and reduced TIDM for longer TBF exposure (11, 42, 49, 57).

Figure 9 Breastfeeding for short duration versus never

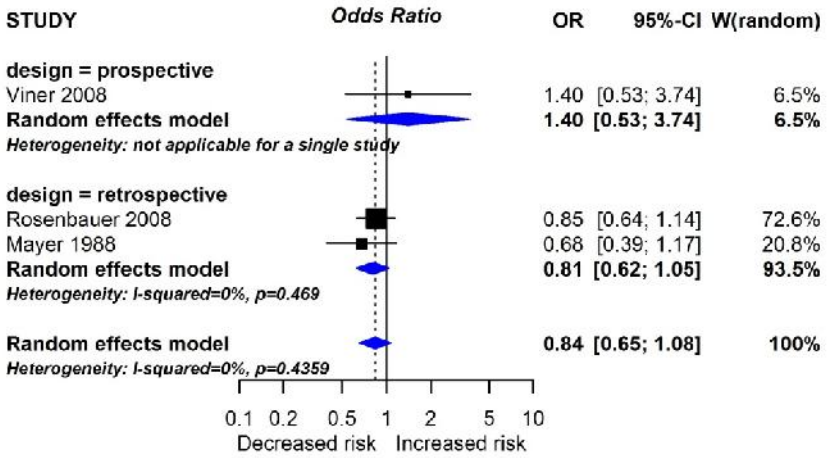


Figure 10 Breastfeeding for medium duration versus never

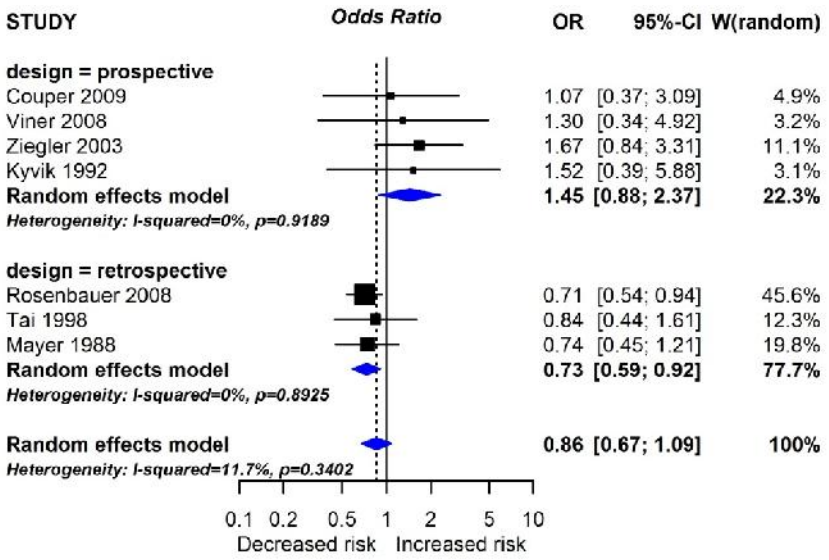
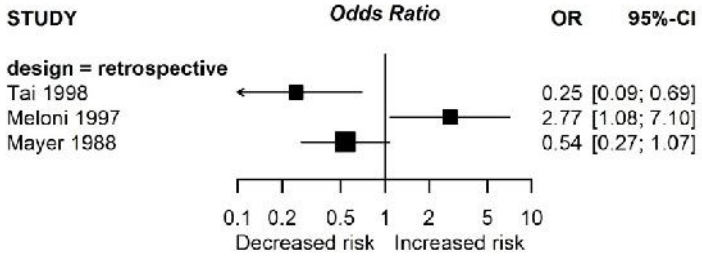


Figure 11 Breastfeeding for long duration versus never



1.2.7. Studies investigating TBF and TIDM as a continuous variable

Three studies reported OR of TIDM for each month increase in TBF duration. Meta-analysis of these data showed no significant association (pooled OR 1.01; 95 CI% 0.87, 1.18) but with extreme statistical heterogeneity (I^2=76.8%; Figure 12). Three additional studies comparing the mean duration of TBF between TIDM and unaffected subjects were meta-analysed (Figure 13). Data could not be pooled to extreme statistical heterogeneity (I^2=91.8%) which was present even when the study of Baruah (27) was excluded (I^2=92.8%). This extreme heterogeneity may be related to the non-Gaussian distribution of TBF duration in the population.

Figure 12 Risk of TIDM for each month increase in TBF duration

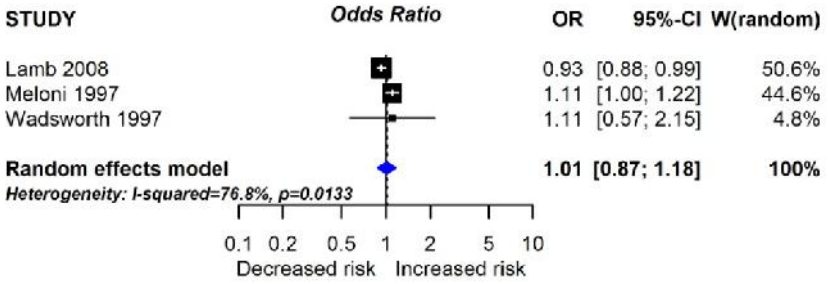
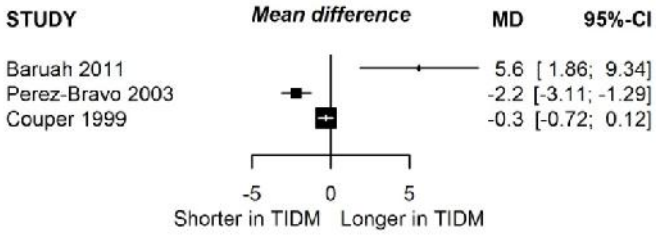


Figure 13 Difference in TBF in people with TIDM versus unaffected subjects



1.2.8 Data for TBF and TIDM which couldn't be meta-analysed

Meta-analyses included 7 cohort, 4 nested case control, 1 cross sectional and 29 case control studies in total, including at least 8221 participants with TIDM. A further 7 cohort, 3 nested case control and 14 case control studies reported relevant data which could not be included in meta-analysis, in relation to at least 3909 participants with TIDM. These studies are summarised in Table 5. Two of the case control studies (Ashraf (26), Perez-Bravo (47)) showed a significantly shorter TBF duration in TIDM compared to unaffected subjects. The other 22 studies showed no significant relationship, although TBF duration was shorter in people with TIDM in 9 of these 22 studies, longer in 4 and similar or unclear in 9. The study of Lamb 2008 (7) also reported adjusted HR 0.93 (95%CI 0.86, 0.99) for each additional month of breastfeeding.

Table 5 Other studies evaluating total breastfeeding and TIDM which couldn't be meta-analysed

First Author and Year of Publication	Design	N/n cases	Total BF duration	Units	Descriptive measure	Unaffected	TIDM	P value
Baruah, 2011 (27)	CC	86/43	continuous	Months	Mean	13	18.6	-
Kostraba, 1993 (38)	CC	306/142	continuous	Months	Mean	6.95	6.2	-
Marshall, 2004 (41)	CC	577/196	continuous	Months	Mean	4.6	3.9	-
Norris, 2003 (10)	PC	1183/~733	continuous	Months	Mean	6.1	5.9	-
Perez-Bravo, 2003 (47)	CC	250/143	continuous	Months	Mean	7.6	5.4	**<0.02**
Virtanen, 1993 (62)	CC	1380/690	continuous	Months	Mean	6.6	6.6	NS
Ashraf, 2010 (26)	CC	195/128	continuous	Months	Median(range)	3 (0-4)	1 (0-4)	**0.001**
Hummel, 2000 (mother with TIDM) (5)	PC	568	continuous	Months	Median	3	4	NS
Hummel, 2000 (father with TIDM)			continuous	Months	Median	4	2.50	0.41
Kimpimaki, 2001 (17)	NCC	455/65	continuous	Months	Median (IQR)	6.5 (3-10)	6.0 (2.9-10.5)	-
Norris, 1996 (19)	NCC	171/18	continuous	Months	Median (IQR)	8	10	-
Rami, 1999 (48)	CC	609/114	continuous	Months	Median (range)	2 (0-72)	2 (0-24)	0.54
Hypponen, 1999 (36)	CC	821/435	continuous	Months	Average			NS
Lamb, 2013 (8)	NCC	260	continuous	Months	Average			NS
Ludvigsson, 2003 (9)	PC	205	continuous	Months	Average			NS

Telahun, 1994 (58)	CC	129/55	continuous	Months	Average			NS
Lamb, 2008 (7)	PC	642	continuous	Months	aHR(95%CI)	0.93 (0.86, 0.99) per month TBF		-
Virtanen, 1998 (12)	PC	697/~43	categorical	>2 vs <2 months	aHR (95%CI)	0.53 (0.2-1.6)		-
Karlen, 2012 (6)	PC	1409	categorical	>7 vs 0-6 months	uOR (95% CI)	0.83 (0.52-1.32)		-
Wadsworth, 1997 (64)	CC	639/276	categorical	>2 vs <2 weeks	aOR (95% CI)	1.1 (0.56-2.16)		0.7
Bener, 2009 (28)	CC	340/170	categorical	Breastfed (yes)	%	97.2	95.1	-
Couper, 1999 (1)	PC	317/70	categorical	Breastfed (yes)	%	75	61	-
			continuous	Months	Mean	6.1	5.3	NS
Sadauskaite-Kuehne, 2004 (Lithuania) (50)	CC	813/286	categorical	Breastfed (yes)	%	91.6	95	NS
Strotmeyer, 2004 (56)	CC	485/247	categorical	Breastfed (yes)	%	91.1	91.0	-
Thorsdottir, 2000 (60)	CC	220/55	categorical	Breastfed (yes)	%			0.10

2. Exclusive breastfeeding duration and risk of TIDM

2.1 Overall characteristics of studies, risk of bias and summary of results

Table 6 describes the main characteristics of the studies analysed in this report. A total of 28 observational studies, and no intervention studies, reported the association between duration of exclusive breastfeeding (EBF) and risk of TIDM. Of these, 8 were prospective cohort studies, 2 nested case-control, and 18 case-control studies. Over half of the studies (n=16) are from Europe – others are from North America (n=4), South America (n=2), Asia/Pacific (n=4), and the Middle East (n=2). Overall, valid data on EBF duration and TIDM risk were available from almost 35,000 subjects and over 5300 people with TIDM. Information on TIDM was obtained mainly from Islet auto-antibodies in 8 prospective studies and via medical diagnosis in 20 (mainly case control) studies. With regards to time of outcome diagnosis, 6 studies explored the association between duration of EBF and TIDM in the first 5 years of life and 22 studies evaluated the outcome in older children or adolescents. 26 studies used interview or questionnaire to assess EBF duration, 1 study assessed medical records and 1 did not report the method of exposure assessment.

Risk of bias was assessed using the NICE Methodological checklist for cohort and case-control studies. Figure 14 illustrates the distribution of bias across the five main methodological areas of the studies. Over half of the studies had a high risk, most commonly due to lack of adjustment for confounding bias i.e., no adjusted data presented. A third of the studies had an 'unclear' overall risk of bias, most commonly due to insufficient information to assess selection and assessment bias.

Three levels of comparison were used to meta-analyse binary data for TIDM risk and EBF duration, based on the distribution of data reported in included studies: EBF duration with a cut-off in the first 2 months ('≥0-2 months vs. <0-2 months'); EBF duration '≥3-4 months vs. <3-4 months'; EBF duration '≥5-9 months vs. <5-9 months'.

Main Findings

Across all three EBF duration cut-offs there was some evidence of reduced TIDM risk with increased EBF duration. Stratified and subgroup analyses by specific risk groups and study

characteristics showed little evidence of difference. Adjusted and unadjusted analyses gave similar findings. The evidence for an association between EBF and TIDM from the 14 studies (1588 TIDM cases) which could not be included in meta-analysis was weaker as only three studies showed statistically significant associations between increased EBF duration and reduced TIDM risk and the others were inconclusive. All but one study used mean or median to present results which prevented the use of the data in the meta-analysis, and one study used a definition of breastfeeding duration that was not possible to combine with the other studies (Table 9). Overall the data suggest there is LOW certainty evidence that longer duration of EBF is associated with reduced TIDM risk, with relatively low statistical heterogeneity within individual meta-analyses, and reasonable consistency between meta-analyses.

Table 6 Characteristics of Included Studies for analysis of Exclusive Breast Feeding duration and TIDM Risk

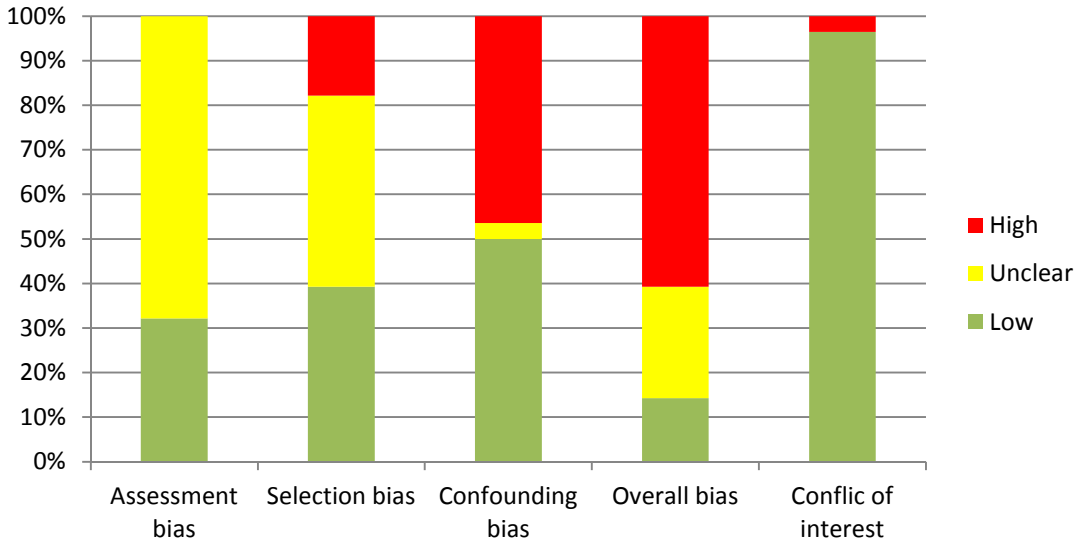
First Author & Publication Year	N/n cases	Design	Country	Exposure assessment	Specific outcome	Age at outcome (years)	Population characteristics
Couper, 1999 (1)	317/70	PC	Australia	D/Q	Islet autoantibodies	2	First degree relatives of diabetic children
Couper, 2009 (65)	548/~30	PC	Australia	D/I	Islet autoantibodies	2	First degree relatives of diabetic children
Frederikson, 2012 (abstract) (66)	1698	PC	USA	-	Medical diagnosis	<7	High risk children via HLA screening
Holmberg, 2007 (67)	3788/~51	PC	Sweden	Q	Islet autoantibodies	6	General population
Hummel, 2000 (5)	568	PC	Germany	Q	Islet autoantibodies	2	Offspring of diabetic parents
Virtanen, 2011 (13)	~4000/~160	PC	Finland	Q	Medical diagnosis or islet autoantibodies	<18	Odu and Tampere University Hospitals
Wahlberg, 2006 (15)	8715/31	PC	Sweden	Q	Islet autoantibodies	2	General population
Ziegler, 2003 (14)	1460/~68	PC	Germany	Q	Islet autoantibodies	5	Children of a mother/father withT1DM
Kimpimaki, 2001 (17)	455/65	NCC	Finland	I	Islet autoantibodies	<4	Turku, Oulu and Tampere Hospital births
Lamb, 2013 (8)	260	NCC	USA	I	Islet autoantibodies	<7	High risk children via HLA screening

First Author & Publication Year	N/n cases	Design	Country	Exposure assessment	Specific outcome	Age at outcome (years)	Population characteristics
Alves, 2012 (25)	246/123	CC	Brazil	I	Medical diagnosis	7	Endocrine clinic attendance
Baruah, 2011 (27)	86/43	CC	India	I	Medical diagnosis	<18	Endocrinology ward
Esfarjani, 2001 (32)	104/52	CC	Iran	Q	Medical diagnosis	<14	Endocrine clinic attendance
Gimeno, 1997 (45)	626/313	CC	Brazil	Q	Medical diagnosis	<18	Juvenile Diabetes Association or hospital records
Kostraba, 1992 (38)	264/132-white 108/54-Black	CC	USA	Q/I	Medical diagnosis	10	Alleghany Hospital diabetes register
Liese, 2012 (68)	709/505	CC	USA	I	Medical diagnosis	<20	SEARCH surveillance (Colorado and South Carolina research centres)
Patterson, 1994 (34)	1548/258	CC	UK	R	Medical diagnosis	<16	Diabetes register, hospital discharge, Health Service records
Rabiei 2011 (69)	300/100	CC	Iran	Q	Medical diagnosis	11	Diabetes register
Rami, 1999 (48)	609/114	CC	Austria	Q	Medical diagnosis	<15	Austrian diabetes register
Sadauskaite-Kuehne, 2004 (50)	1944/803	CC	Sweden/Lithuania	Q	Medical diagnosis	7	Hospital admissions
Samuelsson, 1993 (51)	1026/297	CC	Sweden	R/Q	Medical diagnosis	<17	Paediatric department
Soltesz, 1994 (55)	305/130	CC	Hungary	Q	Medical diagnosis	<14	Incidence register

First Author & Publication Year	N/n cases	Design	Country	Exposure assessment	Specific outcome	Age at outcome (years)	Population characteristics
Stene, 2000 (70)	1156/85	CC	Norway	Q	Medical diagnosis	<15	National Childhood Diabetes register
Stene, 2003 (71)	2213/545	CC	Norway	Q	Medical diagnosis	9	Diabetes register
Thorsdottir, 2000 (60)	220/55	CC	Iceland	I	Medical diagnosis	12	General population
Verge, 1994 (61)	475/217	CC	Australia	Q	Medical diagnosis	9	New South Wales diabetes register
Virtanen, 1992 (74)	852/426	CC	Finland	Q	Medical diagnosis	<14	Hospital admissions
Virtanen, 1993 (62)	1380/690	CC	Finland	Q	Medical diagnosis	<14	Finnish National Population Registry

PC = prospective cohort, NCC = nested case control, CC = case control, D = diary, I = interview, Q = questionnaire, R = medical records

Figure 14 Risk of bias in observational studies of exclusive breastfeeding and TIDM



1.3. Outcomes from studies of exclusive breastfeeding and TIDM

2.2.1 Exclusive breastfeeding for ≥0-2 months vs. <0-2 months

Nine studies reported the association between EBF for a duration of at least 0-2 months, compared to less than this (17, 34, 45, 50, 62). Meta-analysis showed significantly reduced TIDM risk with longer EBF duration (OR 0.74; 95% CI 0.63, 0.88) with low statistical heterogeneity (I^2=10.2%; Figure 15). There was no evidence of differences in strength of association in the stratified or subgroup analyses (Table 7). Adjusted analyses and unadjusted analyses showed similar findings, but heterogeneity was lower in the retrospective case control studies reporting clinical TIDM as an outcome, than in the prospective studies reporting autoantibodies as an outcome.

Figure 15 Exclusive breastfeeding for ≥0-2 months vs. < 0-2 months and TIDM risk

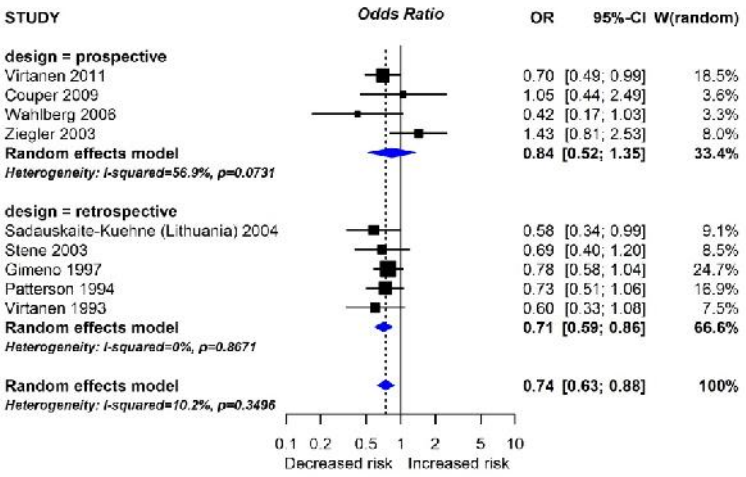


Table 7 Stratified and subgroup analyses of EBF duration ≥0-2 months vs. <0-2 months and TIDM risk

	Number of studies	OR [95% CI]*	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted used)	9	0.74 [0.63-0.88]	10.2	Not tested
Adjusted	6	0.76 [0.63-0.92]	18.8	
Unadjusted	7	0.77 [0.59-1.00]	45.8	
Risk of disease – High	3	0.97 [0.59-1.59]	57	0.221
Risk of disease – Normal/Low	6	0.70 [0.58-0.84]	0	
Overall risk of bias – Low	2	0.96 [0.48-1.95]	77.5	0.402
Overall risk of bias – High/Unclear	7	0.71 [0.59-0.84]	0	
Study Design – Prospective	4	0.84 [0.52-1.35]	56.9	0.519
Study Design – Retrospective	5	0.71 [0.59-0.86]	0	
Method of diagnosis – clinical	5	0.71 [0.59-0.86]	0	0.519
Method of diagnosis – serological	4	0.84 [0.52-1.35]	56.9	
Clear definition of exclusive breastfeeding	4	0.78 [0.54-1.13]	55.3	0.703
Unclear definition of exclusive breastfeeding	5	0.72 [0.59-0.89]	0	

*Pooled estimate [95%CI] of meta-analysis of studies reporting Odds or Relative risk or Risk ratios

2.2.2 Exclusive breastfeeding for ≥3-4 months vs < 3-4 months

Nine studies reported data which could be meta-analysed, for risk of TIDM in relation to EBF for more or less than 3-4 months (Figure 16). Pooled data showed significantly reduced risk of TIDM with longer EBF duration (OR 0.68; 95% CI 0.55, 0.83), with moderate statistical heterogeneity (I^2 =28.6%). There was no evidence of differences in strength of association in the stratified or subgroup analyses (Table 8). Adjusted analyses and unadjusted analyses showed similar findings.

Figure 16 Exclusive BF for ≥ 3-4 months vs. < 3-4 months and TIDM risk

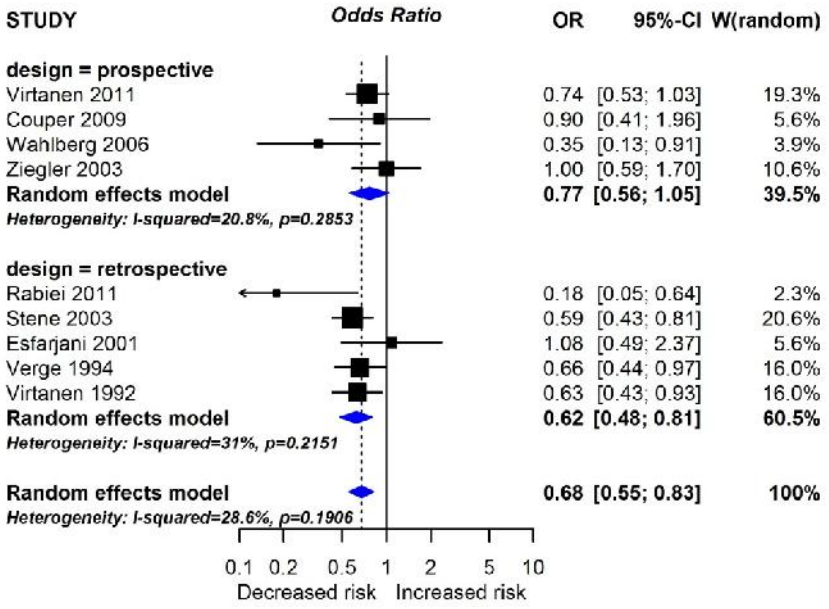


Table 8 Stratified and subgroup analyses of EBF duration ≥3-4 months vs. <3-4 months and TIDM risk

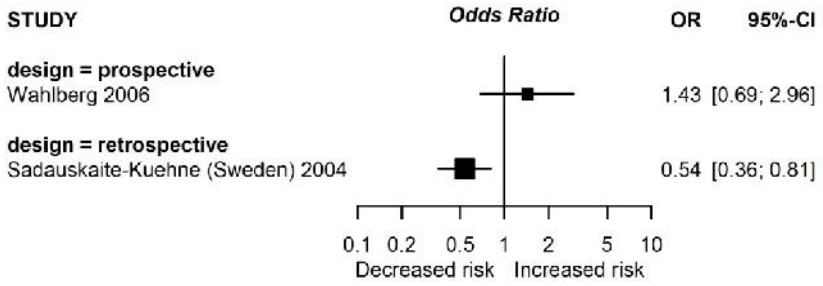
	Number of studies	OR [95% CI]*	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted used)	9	0.68 [0.55-0.83]	28.6	
Adjusted	6	0.66 [0.54-0.82]	32.6	Not tested
Unadjusted	8	0.71 [0.60-0.84]	14.8	
Risk of disease – High	3	0.82 [0.63-1.06]	0	0.104
Risk of disease – Normal/Low	6	0.60 [0.47-0.78]	30.2	
Risk of bias – Low	3	0.74 [0.59-0.93]	0	0.348
Risk of bias – High/Unclear	6	0.62 [0.45-0.85]	37.8	
Study Design – Prospective	4	0.77 [0.56-1.05]	20.8	0.326
Study Design - Retrospective	5	0.62 [0.48-0.81]	31.0	
Method of diagnosis – clinical	5	0.62 [0.48-0.81]	31.0	0.326
Method of diagnosis – serological	4	0.77 [0.56-1.05]	20.8	
Clear definition of exclusive breastfeeding	4	0.71 [0.54-0.93]	27.9	0.705
Unclear definition of exclusive breastfeeding	5	0.65 [0.47-0.90]	39.1	

*Pooled estimate [95%CI] of meta-analysis of studies reporting Odds or Relative risk or Risk ratios

2.2.3 Exclusive breastfeeding for ≥5-9 months vs. <5-9 months

Two studies reported the association between risk of TIDM and exposure to exclusive breastfeeding for ≥5-9 months. There was extreme statistical heterogeneity between studies (I^2=81.2%). The study of Wahlberg reported unadjusted OR for diabetes associated antibodies in preschool children. The study of Sadauskaite-Kuehne reported adjusted OR for clinical TIDM in 7 year old children in a case-control study. These differences in study design and outcome assessment may explain the extreme heterogeneity. One study suggested a protective effect, and one study suggested no evidence of protection (Figure 17).

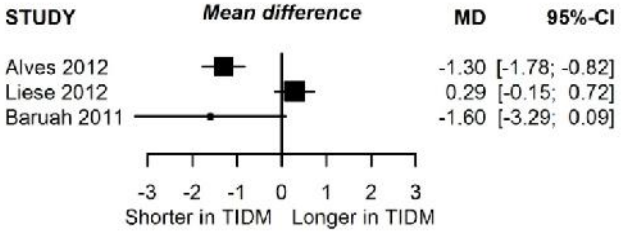
Figure 17 Exclusive breastfeeding for ≥5-9 months vs. < 5-9 months and TIDM risk



2.2.4 Studies investigating EBF as a continuous variable and risk of TIDM

Three studies reported the unadjusted relationship between EBF duration and TIDM risk, comparing the mean duration of EBF in TIDM versus unaffected subjects. There was extreme statistical heterogeneity (I^2=92%) attributable to the study of Liese, so data were not pooled (Figure 18). There was also heterogeneity *within* the study of Liese, with shorter duration of EBF in controls than TIDM in South Carolina, but longer EBF in controls in Colorado. It is not clear that EBF is normally distributed in general, so one reason for the extreme heterogeneity may be inappropriate analysis of EBF duration as arithmetic mean (sd) in these studies.

Figure 18 Difference in EBF in people with T1DM versus unaffected subjects



2.2.5 Other studies evaluating EBF and TIDM which couldn't be meta-analysed

Meta-analyses included 4 cohort and 9 case control studies in total, including at least 3733 participants with TIDM. A further 4 cohort, 2 nested case control and 8 case control studies reported relevant data which could not be included in meta-analysis, in relation to at least 1588 participants with TIDM. All but one study used mean or median to present results which prevented the use of the data in the meta-analysis, and one study used a definition of breastfeeding duration that was not possible to combine with the other studies (Table 9). Two of the case control studies (Alves (25), Baruah (27)) and one prospective cohort study (Holmberg (67)) showed a significantly shorter EBF duration in TIDM compared to unaffected subjects. The other 11 studies showed no significant relationship, although EBF duration was shorter in people with TIDM in 2 of these 11 studies, longer in 2 and similar or unclear in 7.

Table 9 Other studies evaluating exclusive breastfeeding and TIDM which couldn't be meta-analysed

First Author and Year of Publication	Design	N/n cases	Exclusive BF duration	Units	Descriptive measure	Unaffected	TIDM	P value
Alves, 2009 (25)	CC	246/123	Continuous	Months	Mean (SD)	4.6	3.3	**<0.001**
Baruah, 2011 (27)	CC	86/43	Continuous	Months	Mean (SD)	6.6	5	**<0.05**
Couper, 1999 (1)	PC	317/70	Continuous	Months	Mean (SD)	4.5	3.4	NS
Liese, 2012 (68)	CC	709/505	Continuous	Months	Mean (SD)	2.40	2.69	0.23
Samuelsson, 1993 (51) (<5y)	CC	1089/297	continuous	Months	Mean (SE)	3.0 (0.5)	4.5 (0.7)	0.17
Samuelsson, 1993 (51) (5-9y)			continuous	Months	Mean (SE)	3.6 (0.3)	3.2 (0.3)	0.34
Samuelsson, 1993 (51) (>10y)			continuous	Months	Mean (SE)	2.4 (0.1)	2.2 (0.2)	0.31
Hummel, 2000 (mother with TIDM) (4)	PC	568	continuous	Months	Median	1	2	NS
Hummel, 2000 (father with TIDM) (4)			continuous	Months	Median	3	1	0.31
Kimpimaki, 2001 (17)	NCC	455/65	continuous	Months	Median (IQR)	1.8 (0.5-3.9)	2 (1-4)	-
Rami, 1999 (48)	CC	609/114	continuous	Months	Median (range)	2 (0-18)	2 (0-7)	-
Soltesz, 1994 (55)	CC	305/130	continuous	Months	Median	2.5	2	NS
Frederikson, 2012 (66)	PC	548	continuous	Months	Average			NS

First Author and Year of Publication	Design	N/n cases	Exclusive BF duration	Units	Descriptive measure	Unaffected	TIDM	P value
Kostraba, 1992 (white) (38)	CC	302/132	continuous	Months	Average	3.3	4.5	0.40
Kostraba, 1992 (black)		106/54	continuous	Months	Average	6.8	3.3	0.16
Lamb, 2013 (8)	NCC	260	continuous	Months	Average			NS
Thorsdottir, 2000 (60)	CC	220/55	continuous	Months	Average			NS
Holmberg, 2007 (67)	PC	3788	categorical	>4 vs 1-3 months	aOR (95% CI)	0.50 (0.27-0.93)		**0.028**

3 Age at introduction of solid food and risk of TIDM

3.1. Overall characteristics of studies, risk of bias and summary of results

General characteristics of included studies are summarised in Table 10. No intervention trials were identified. Data were available from a total of 17 studies with over 4000 people with TIDM. There were 2 prospective cohort studies, 1 nested case-control studies, and 14 case-control studies evaluating timing of solid food introduction and TIDM risk. The studies were European (n=8), North American (n=3), Asia-Pacific (n=1), South American (n=2) and Middle Eastern (n=3). This analysis addresses the first introduction of non-milk feed in any form (here termed 'solid food') into the infant diet.

Two studies evaluated TIDM risk only in young children (age ≤5), and 15 studies only in older children (up to 20 years old). Other than one study which didn't describe the source of dietary exposure assessment, and another which used diary records, all studies obtained information on age of solid food introduction based on questionnaire or interview data.

Based on the distribution of data reported in included studies, meta-analysis of binary data compared TIDM risk and timing of solid food introduction ≥3-4 months vs. <3-4 months.

A summary of the risk of bias in included studies is shown in Figure 19. Just over half of studies had a high overall risk of bias, mainly due to reliance on unadjusted data, hence high risk of confounding bias. Meta-analyses showed extreme statistical heterogeneity, with no clear evidence that delaying introduction of solid food until after 3-4 months was associated with altered risk of TIDM. Studies which analysed EBF duration as a continuous variable, or could not be included in meta-analysis, also showed a mixed and unclear picture. We were not able to exclude a clinically important association, due to the small number of studies in meta-analysis and high statistical heterogeneity and confidence intervals.

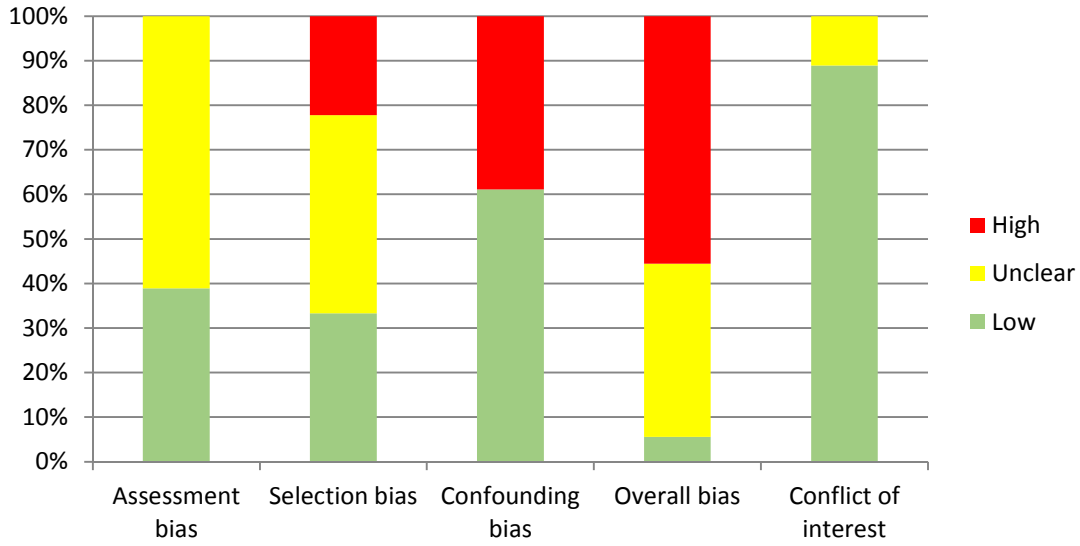
Table 10 Characteristics of studies reporting timing of solid food and TIDM risk

First Author & Publication Year	N/n cases	Country	Design	Exposure assessment	Specific outcome	Age at outcome (years)	Population characteristics
Frederiksen, 2012 (66)	1698	USA	PC	-	Medical diagnosis	<7	High risk children via HLA screening
Ziegler, 2003 (15)	1460/~68	Germany	PC	Q	Islet autoantibodies	5	Newborn children
Savilahti, 2009 (72)	6209/45	Finland	NCC	D	Medical diagnosis	12	NHI database
Alves, 2012 (25)	246/123	Brazil	CC	I	Medical diagnosis	9	Endocrinology clinic
Dahlquist, 2002 (33)	2226/610	Austria, Latvia, Lithuania, Luxembourg and UK	CC	Q/I	Medical diagnosis	<15	Diabetes register
Esfarjani, 2001 (32)	104/52	Iran	CC	Q	Medical diagnosis	<14	Endocrine clinic attendance
Hypponen, 1999 (36)	821/435	Finland	CC	Q	Medical diagnosis	8	Hospital admissions
Kostraba, 1993 (38)	309/142	USA	CC	Q	Medical diagnosis	<18	Colorado IDDM Registry
Liese, 2012 (40, 68)	709/505	USA	CC	I	Medical diagnosis	<20	SEARCH surveillance (Colorado and South Carolina research centres)
Majeed, 2011 (39)	395/96	Iraq	CC	Q	Medical diagnosis	<18	Paediatric clinic
Meloni, 1997 (44)	200/100	Italy	CC	Q/I	Medical diagnosis	<15	Paediatric clinic

First Author & Publication Year	N/n cases	Country	Design	Exposure assessment	Specific outcome	Age at outcome (years)	Population characteristics
Perez-Bravo, 1996 (73)	165/80	Chile	CC	Q	Medical diagnosis	<15	Santiago de Chile registry
Rabiei, 2011 (69)	300/100	Iran	CC	Q	Medical diagnosis	<15	Diabetes register
Rosenbauer, 2008 (49)	2631/760	Germany	CC	Q	Medical diagnosis	<5	Hospital based surveillance system ESPD
Stene, 2003 (71)	2118/545	Norway	CC	Q	Medical diagnosis	9	Diabetes register
Strotmeyer, 2004 (56)	690/247	China	CC	Q	Medical diagnosis	10	Diabetes register
Visalli, 2003 (63)	900/150	Italy	CC	Q	Medical diagnosis	12	EURODIAB register

PC = prospective cohort, NCC = nested case control, CC = case control, D = diary, I = interview, Q = questionnaire, R = medical records

Figure 19 Risk of bias in observational studies of solid food exposure and TIDM risk



3.2. Outcomes from studies of solid food introduction and TIDM

3.2.1 Solid food introduction at ≥ 3-4 months vs < 3-4 months, and risk of TIDM

Six studies examined the association between delaying introduction of solid food for longer than 3-4 and risk of TIDM (Figure 20). There was extreme statistical heterogeneity (I^2=83.5%) so data were not pooled for meta-analysis. This heterogeneity could not be attributed to a particular study. If the study of Ziegler was excluded, extreme heterogeneity (I^2=86%) remained. Frederikson and Ziegler reported adjusted HR from prospective cohort studies, Ziegler using autoantibodies and Frederikson clinical TIDM for case definition. The other studies reported adjusted (Kostraba, Stene) or unadjusted OR from case control studies using clinical TIDM for case definition. Subgroup and stratified analyses did not show important differences in strength of association and extreme heterogeneity remained in all groups (Table 11).

Figure 20 Introduction of solid food at age ≥3-4 months vs. <3-4 months and TIDM risk

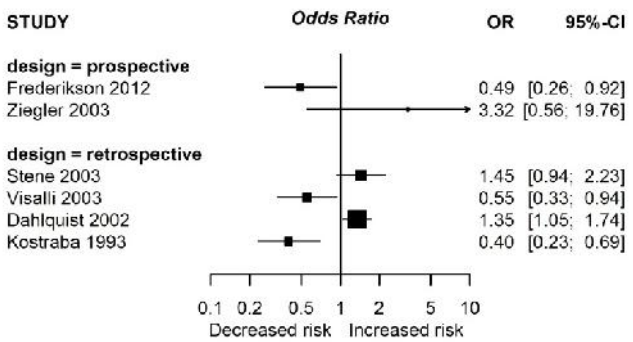


Table 11 Stratified and subgroup analyses of solid food introduction ≥3-4 months vs. <3-4 months and TIDM risk

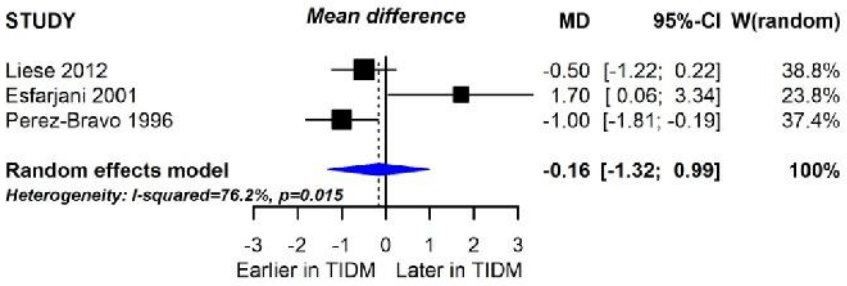
	Number of studies	OR [95% CI]*	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted used)	6	0.83 [0.49-1.40]	83.5	
Adjusted	4	0.82 [0.36-1.87]	83.5	Not tested
Unadjusted	5	0.79 [0.48-1.29]	81.0	
Risk of disease – High	2	1.06 [0.17-6.62]	74.5	0.813
Risk of disease – Normal/Low	4	0.84 [0.46-1.51]	87.2	
Risk of bias – Low	2	0.96 [0.12-7.48]	79.8	0.947
Risk of bias – High/Unclear	4	0.90 [0.54-1.50]	82.2	
Study Design – Prospective	2	1.06 [0.17-6.62]	74.5	0.813
Study Design - Retrospective	4	0.84 [0.46-1.51]	87.2	
Method of diagnosis – clinical	5	0.76 [0.44-1.30]	86.0	0.121
Method of diagnosis – serological	1	3.32 [0.56-19.76]	-	

*Pooled estimate [95%CI] of meta-analysis of studies reporting Odds or Relative risk or Risk ratios or Hazard ratios

3.2.2 Timing of solid food introduction as a continuous variable, and TIDM risk

Three studies compared the mean time of solid food introduction in subjects with T1DM versus unaffected subjects. Pooled data show no overall difference between cases and controls (MD -0.16; 95% CI -1.32, 0.99) with extreme statistical heterogeneity (I^2=76.2%) (Figure 21). All 3 studies reported unadjusted data from case control studies. Heterogeneity was attributable to the study of Esfarjani (32), for unclear reasons, but timing of SF introduction occurred later in the study of Esfarjani than the other 2 studies, and if timing of SF introduction is not normally distributed then analysis of arithmetic mean (sd) may not be appropriate and may have contributed to the heterogeneity.

Figure 21 Timing of solid food introduction as a continuous variable, and TIDM risk



3.2.3 Other studies solid food introduction and TIDM, which couldn't be meta-analysed

Meta-analyses included 1 cohort and 4 case control studies in total, including at least 2264 participants with TIDM. A further 1 nested case control and 7 case control studies reported relevant data which could not be included in meta-analysis, in relation to at least 1825 participants with TIDM. These studies are summarised in Table 12. Two of the case control studies (Kostraba (38, 49), Rosenbauer (49)) showed a significant relationship between early introduction of solid food in TIDM compared to unaffected subjects. 6 studies showed no significant relationship, although solid food introduction was earlier in people with TIDM in 3 of these 6 studies, and similar or unclear in 3.

Table 12 Other studies evaluating timing of solid food introduction and TIDM which couldn't be meta-analysed

First Author and Year of Publication	Design	N/n cases	Age at first solid food introduction	Units	Descriptive measure	Unaffected	TIDM	P value
Kostraba, 1993 (38)	CC	309/142	Continuous	Weeks	Mean	16.9	13.4	**0.01**
Savilahti, 2009 (72)	NCC	6209/45	Continuous	Months	Mean	4	3.7	0.09
Hypponen, 1999 (36)	CC	821/435	Continuous	Months	Average			NS
Majeed, 2011 (39)	CC	395/96	Categorical	>6 vs <6 months				NS
Rabiei, 2011 (69)	CC	300/100	Categorical	>6 vs <6 months	aOR (95% CI)	0.60 (0.27-1.32)		NS
Rosenbauer, 2008 (49)	CC	2631/760	Categorical	>5 vs <5 months	aOR (95% CI)	0.82 (0.64-1.05)		NS
					uOR (95% CI)	0.78 (0.65-0.93)*		**0.006**
Strotmeyer, 2004 (56)	CC	690/247	1-3 months	%		20	13	**<0.05**
			4-6 months	%		48	58	**<0.05**
			7-12 months	%		30	28	NS

* Adjusted data from this study showed no statistically significant difference

4 Conclusions

This report summarises the results of over 60 studies examining the association between total or exclusive breastfeeding duration, timing of solid food introduction and TIDM risk, including over 15,000 people with TIDM. The majority of the studies were case-control design, some of which were nested in cohort studies. Overall we found VERY LOW evidence that increased duration of TBF, and LOW evidence that increased duration of EBF, are associated with reduced risk of TIDM. We found no association between timing of SF introduction and TIDM risk.

Figure 22 Summary of Meta-Analysis findings for Duration of BF and TIDM risk

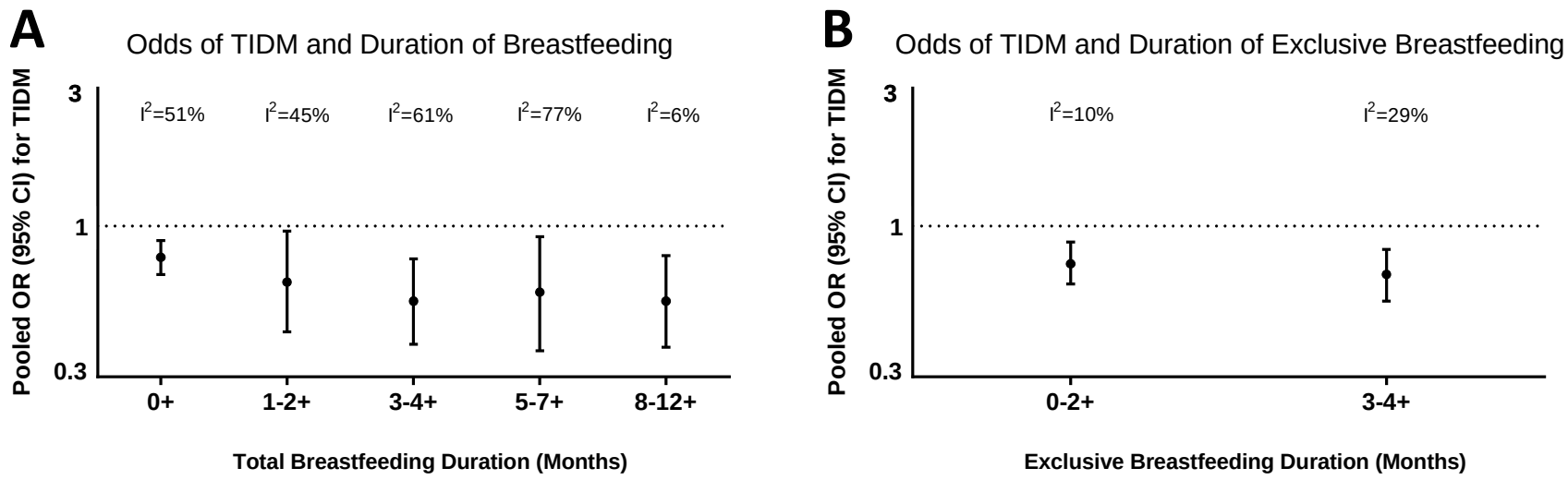


Figure 22. Pooled OR for TIDM in relation to TBF (A) and eBF (B). Bars are 95% CI; I^2 is a measure of statistical heterogeneity.

In spite of the growing number of epidemiological studies examining the association between breastfeeding, solid food introduction and risk of TIDM, there are very few systematic reviews analysing this relationship. The current report probably provides the most comprehensive description of eligible studies on breastfeeding and TIDM to date. A recent literature review by Hornell and colleagues (74) concluded that prolonged breastfeeding had a protective effect against the risk of TIDM. The authors based their conclusions on an earlier paper by Ip and colleagues (75) and on a single prospective study, also included in our report (2).

In our search for existing systematic reviews we identified two existing reviews of this area, by Patelarou et al (76) and by Cardwell et al (77). Both were scored below the recommended AMSTAR cut-off point for a high quality systematic review (24 and 31, respectively) and therefore were excluded from our Overview and we have not directly included their data in this report. Cardwell's meta-analysis of individual patient data from 43 observational studies reported no clear association between TBF for more than 2 weeks (28 studies; OR = 0.93, 95% CI 0.81 to 1.07) or for more than 3 months (29 studies; OR = 0.88, 95% CI 0.78 to 1.00) and TIDM. They found a protective effect of EBF >2 weeks on risk of TIDM albeit with very high statistical heterogeneity (17 studies; aOR = 0.78, 95% CI 0.65, 0.93; I^2=52%), but no such effect for EBF >3 months. Cardwell's analysis differs from ours because they acquired individual patient data from the majority of the 43 included studies, including confounders, so that they could do adjusted analyses where possible. Due to their methods they were able to include larger numbers of studies in individual meta-analyses of specific cut-off durations. They did not however identify as many studies as our review, so had increased risk of publication bias from the methods used. They also only explored 2 time cut-offs i.e., 2 weeks and 3 months for their analyses. For example in their analysis of EBF >2 weeks versus shorter they included 13 distinct studies in meta-analysis – of these, 1 study was not included in our review (78) because relevant data were only available through contact with the authors. In contrast we included 28 separate studies in our analysis of EBF duration, although a maximum of 6 studies could be included in meta-analysis of EBF duration and TIDM at any given time cut-off, due to lack of individual patient data. Our finding that TBF durations of ≥5-7 and 8-12 months are associated with reduced TIDM risk was not explored by Cardwell et al, and theirs was not a systematic review including all

available data but rather a details analysis of studies well known to the authors. The review by Patelarou *et al* (76) was methodologically weaker, only identifying 28 studies.

In the current report, the pooled data suggest reduced risk of TIDM is associated with increased duration of total or exclusive breastfeeding duration. Some meta-analyses showed significant statistical heterogeneity across studies, especially for TBF, which remained largely unexplained after subgroup and stratified analyses. There was no evidence for a difference between adjusted and unadjusted analyses, suggesting that confounding bias may not be a major issue for studies of TBF/EBF and TIDM. There was however reduced heterogeneity in some analyses when analysing retrospective and prospective studies separately, and in some analyses these 2 subgroups were significantly different i.e. retrospective studies showed more positive findings than prospective studies. The use of serology for outcome assessment in some of the prospective studies, often with shorter time between exposure and outcome assessment, may account for the reduced evidence for association between TBF/EBF and TIDM seen in prospective compared with retrospective studies. The relationship between serological diabetes and clinical diabetes is only moderately strong - approximately 60% of people with ≥2 diabetes-associated antibodies develop clinical TIDM over a 10 year follow up period (79).

Evidence for an association was strongest for EBF and TIDM, where both meta-analysed and non meta-analysed data suggested prolonged EBF is associated with reduced TIDM risk, with low or moderate statistical heterogeneity and no significant difference between prospective and retrospective studies. Possible explanations for this association are reduced gastrointestinal infection, an established effect of prolonged EBF duration and a proposed risk factor for TIDM; or reduced cow's milk exposure in infancy, also proposed as a risk factor for TIDM (80, 81). We found no evidence that timing of SF introduction is relevant.

Overall these data support an association between longer TBF and EBF duration and reduced risk of TIDM, and no association between delayed solid food introduction until after 3-4 months and risk of T1DM. The association seen with prolonged TIDM suggests a protective effect against infection as the most likely mechanism, rather than an adverse effect of early CM introduction, since other parts of this systematic review series have not identified a relationship between timing of CM introduction, or use of hydrolysed infant formula, and risk of TIDM.

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BREASTFEEDING, SOLID FOOD INTRODUCTION AND AUTOIMMUNE DISEASES

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1 Total breastfeeding duration and Autoimmune Diseases

1.1 Total breastfeeding duration and Coeliac Disease

1.1.1 Overall characteristics of studies, risk of bias and summary of results

Table 1 describes the main characteristics of the studies analysed in this report. A total of 1 systematic review including 11 observational studies, and 9 further observational studies reported the association between duration of breastfeeding (namely 'any vs. never', '≥1-2 months vs. <1-2 months' and '≥3-4 months vs. <3-4 months') and risk of coeliac disease. Of the original studies, 3 were prospective cohort studies and 6 were case-control studies. Most of the studies (n=7) were from Europe, with one from North America and one with origin unknown. Overall, relevant data on total breastfeeding duration in the first year of life (TBF) and coeliac disease was available from 15,108 subjects in the original studies, and over 250,000 subjects in the systematic review. Information on coeliac disease was obtained from serology (autoantibodies to transglutaminase, here termed IgA-tTG) in the 3 prospective studies and via medical diagnosis using ESPGHAN criteria in the remaining (case control) studies; method of outcome assessment was unclear in one study. With regards to time of outcome diagnosis, 5 studies explored the association between exposure to breastfeeding and coeliac disease in the first 5 years of life and others evaluated coeliac disease in older children or young adults. All studies used interview or questionnaire to assess the exposure (TBF), with 3 studies combining this with diary or medical record information.

Risk of bias in original studies was assessed using the NICE Methodological checklists for cohort and case-control studies. Figure 1 illustrates the distribution of bias across the five main methodological areas of the studies. Over 80% of studies had a high risk of bias, most commonly due to lack of adjustment for confounding bias i.e. no adjusted data presented.

Risk of coeliac disease was measured in relation to each of the three cut-offs for breastfeeding duration mentioned above. Dose response relationships were assessed by analysing risk of coeliac disease according to total breastfeeding duration 'ever vs never', 'short duration vs never', 'medium duration vs never' and 'long duration vs never'.

Main Findings

Meta-analyses in this review were characterised by significant clinical and statistical heterogeneity, and the majority of cases and studies could not be included in meta-analysis. While

some meta-analyses found an association between increased TBF duration and reduced coeliac disease risk, those studies which could not be included in meta-analysis more often reported increased TBF duration associated with increased coeliac disease risk. Thus these data must be interpreted as inconclusive, requiring further investigation. Certainly the available data have not reported a consistent relationship between TBF duration and coeliac disease, but many studies only reported unadjusted data and therefore carry a high risk of bias. So a significant association between TBF and coeliac disease cannot be confidently excluded based on the available data.

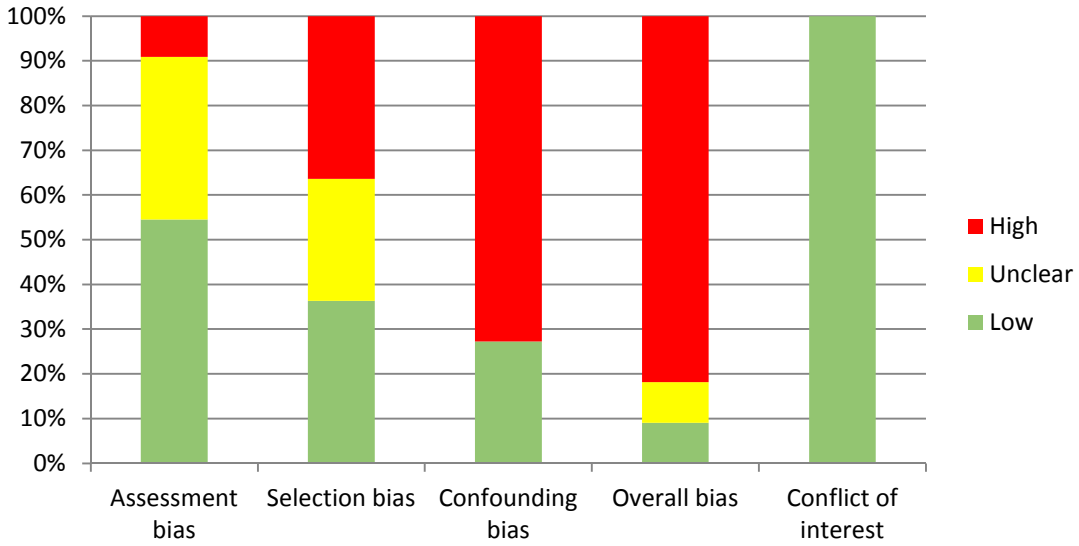
Table 1 Characteristics of included studies evaluating TBF duration and Coeliac Disease

Study	Design	N/n cases	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Welander, 2010 [1]	PC	9414/~29	D/I	IgA-tTG and biopsy	8.4	Sweden	ABIS study. Population based study of babies born between Oct 1997 and Oct 1999.
Ascher, 1997 [2]	CC	81/8	I	ESPGHAN criteria	<18	Sweden	Cases of coeliac disease were compared with the siblings at high genetic risk (DQA1*0501-DQB1*02), in whom the diagnosis was excluded
Auricchio, 1983 [3]	CC	437/190	R/I	ESPGHAN criteria	<18	Italy	Source of cases unknown, controls unaffected siblings
Roberts 2009 [4]	CC	248521/ 90	R	ICD codes 269.0 (ICD-8) or 579.0 (ICD-9) or K90.0 (ICD-10	<24	UK	Cases identified from hospital admission codes, controls the rest of the population with linked record data
Decker 2010 [5]	CC	866/123	Q	Medical diagnosis	<18	Germany	Cases from paediatric gastroenterology clinics; controls from ophthalmology and dental clinics
Norris, 2005 [6]	PC	1560	Q/I	IgA-tTG	<5	USA	DAISY study. Children at increased risk for T1DM were enrolled at birth from 1993 to 2006 and/or identified by newborn screening for HLA genotype
Falth-Magnusson, 1996 [7]	CC	336/72	R/Q	ESPGHAN criteria	<2	Sweden	Cases from paediatric department records, born in 1987-1989. Reference children were age matched from same county.

Study	Design	N/n cases	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Ziegler, 2003 [8]	PC	1460/81	Q	IgA-tTG	5	Germany	German BABYDIAB study. Offspring of mothers and/or fathers with T1DM born in Germany between 1989 and 2000
Ivarsson, 2002 [9]	CC	1272/392	Q	ESPGHAN criteria	2, 15	Sweden	Cases selected from CD Register born in 1992-1996 and sex age and area matched controls from the national population register
Pacilio, 2010 [10]	CC	278/139	Unclear	Unclear	2	Not known	Unclear source of cases and controls. Cases aged 0.5-2 years old with age matched healthy controls
Peters, 2001 [11]	CC	270/133	Q	ESPGHAN criteria	< 10	Germany	All newly diagnosed patients aged <10 years old were identified from paediatricians and a biannual meeting of the German Coeliac Disease Society in 1985–1995. Sex and aged matched control selected from population registry

Q: questionnaire, I: interview, R: medical records, PC: prospective cohort, NCC: nested case control, CS: Cross-sectional, CC: case control

Figure 1 Risk of bias in studies of TBF duration and Coeliac Disease



1.1.2 Total Breastfeeding duration and Coeliac Disease

1.1.2.1 Evidence from prior systematic reviews

Overall there was no evidence for an association between duration of exclusive/predominant breastfeeding and coeliac disease.

Szajewska et al identified 11 studies evaluating this relationship, 6 of which were previously included in a systematic review by Akobeng et al which had concluded that a short duration of breastfeeding predisposed to coeliac disease [12]. The 11 studies and their findings are summarised below – the conclusion of Szajewska is that there is no evidence of a relationship between duration of breastfeeding and risk of coeliac disease. Meta-analysis was not undertaken in either review, due to heterogeneity of studies.

All studies identified by Szajewska were identified in our review, under TBF or EBF as the exposure, and four of them could be included in at least one meta-analysis in our review, together with a more recent study which we identified in our own systematic review of original studies.

Table 4. Relationship between duration of breastfeeding and autoimmune outcomes (coeliac disease) - data from Szajewska et al 2012 [12]

Study ID	Study design	No. participants	Exposure/Comparison	Outcome
Auricchio 1983	Case control	505	Breastfed for >30 days versus less	OR 4.05 [2.20, 7.27] for CD with short duration
Ascher 1997	Case control	81	Duration of BF in CD versus controls	No association
Falth-Magnusson 1996	Case control	336	Duration of BF in CD versus controls	Median 2.5 months CD; 4 months controls P=0.003
Greco 1988*	Case control	2150	BF for >90 days versus less	OR 4.97 [3.5, 6.9] for CD with short duration
Ivarsson 2002	Case control	1272	Duration of BF in CD versus controls	Children <2 median 5 months CD; 7 months controls P <0.001 Children >2: No significant difference
Peters 2001	Case control	280	BF for >2months versus less	OR 0.37 [0.21, 0.64] for CD with long duration
Decker 2010	Case control	866	Duration of BF in CD versus controls	No difference
Norris 2005	Cohort	1560	Duration of BF in CD serology positive versus negative	Mean 8.3 months CD, 6.7 months controls NS
Roberts 2008	Cohort	248,521	Duration of BF in CD versus controls	No association
Welander 2010	Case control	9364	Duration of BF in CD versus controls	No association
Ziegler 2003	Cohort	1610	Duration of BF in CD serology positive versus negative	No association

BF breastfeeding; CD coeliac disease

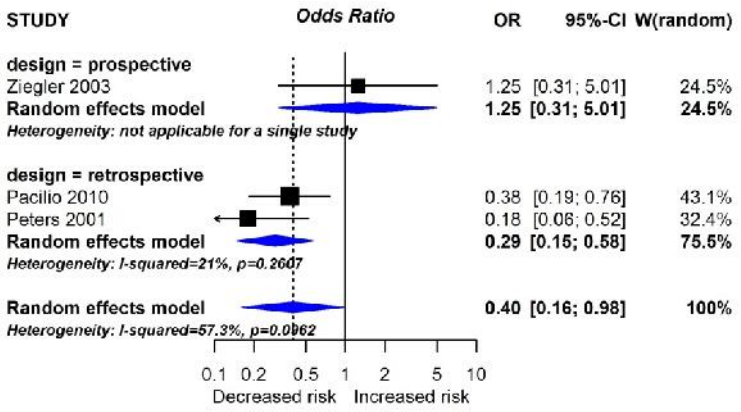
*This study is included in EBF in our analysis, because BF exposure was judged to represent EBF rather than TBF exposure

1.1.2.2 Evidence from original studies and new meta-analyses

1.1.2.2.1 TBF Any vs. Never

Figure 2 shows the combined effect of all studies investigating the association between any duration of breastfeeding versus never breastfeeding, and coeliac disease risk. Overall there was a significant reduction in risk of disease in infants who were breast fed (OR 0.40, 95% CI 0.16, 0.98) with high heterogeneity between studies (I^2=57.3%). Subgroup and stratified analyses was not performed due to the small number of studies included. Pacilio presented unadjusted data in a case control study comparing TBF ever versus never; Ziegler presented adjusted HR in a prospective cohort study of high risk participants (family history of autoimmune disease) comparing TBF 3-6 months versus never; Peters presented adjusted OR in a case-control study comparing TBF ≥7 months versus never. The high statistical heterogeneity may be explained by this heterogeneity in study design and analysis.

Figure 2 TBF any vs. never and risk of Coeliac Disease

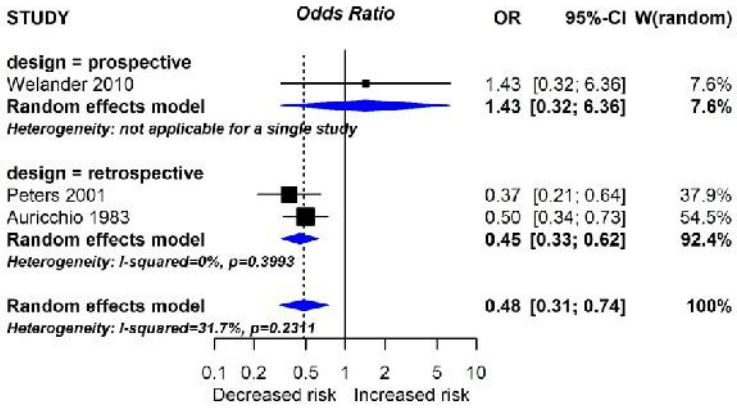


1.1.2.2.2 TBF ≥1-2 months vs. <1-2 months

Three studies examined the risk of coeliac disease in infants who were breast fed for over 1-2 months compared to less than this duration. Figure 3 shows that the combined risk of T1DM is significantly lower if infants were breastfed for at least 1-2 months, (OR 0.48, 95% CI 0.31, 074) with moderate heterogeneity between studies (I^2=31.7%). Welander presented unadjusted HR from a prospective cohort study comparing TBF ≥11-12 vs 0-2 months; Peters presented adjusted OR from a case

control study comparing TBF ≥2 vs <2 months; Auricchio presented unadjusted OR from a case control study comparing TBF ≥1 vs <1 month. The moderate statistical heterogeneity may be explained by this heterogeneity in study design and analysis.

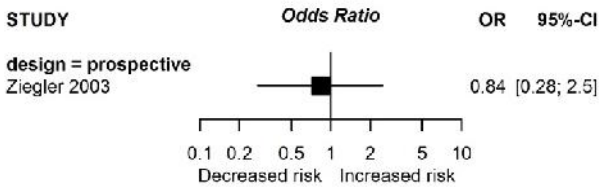
Figure 3 TBF ≥1-2 months vs. <1-2 months and risk of Coeliac Disease



1.1.2.2.3 TBF ≥3-4 months vs. <3-4 months

The association between breastfeeding for at least 3-4months versus less than this duration, and risk of coeliac disease, was examined in only one study (Figure 4). The study found no evidence of a relationship between TBF over 3-4 months and coeliac disease risk (OR 0.84, 95% CI 0.28, 2.5).

Figure 4 TBF ≥3-4 months vs. <3-4 months and risk of Coeliac Disease



1.1.2.3 Dose response analysis of TBF duration and Coeliac Disease

We also analysed TBF duration by grouping studies according to exposure duration – short (1-3 months), medium (4-6 months) and long ((≥ 6 months) in comparison with never breastfed. These results are shown in Figures 5, 6 and 7. The very small number of studies reporting relevant data limited the power of these analyses. Of note the

study of Peters [11] did report a lower OR for coeliac disease with increased TBF duration.

Figure 5 TBF short vs. never and risk of Coeliac Disease

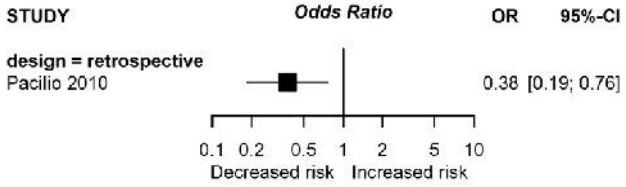


Figure 6 TBF medium vs. never and risk of Coeliac Disease

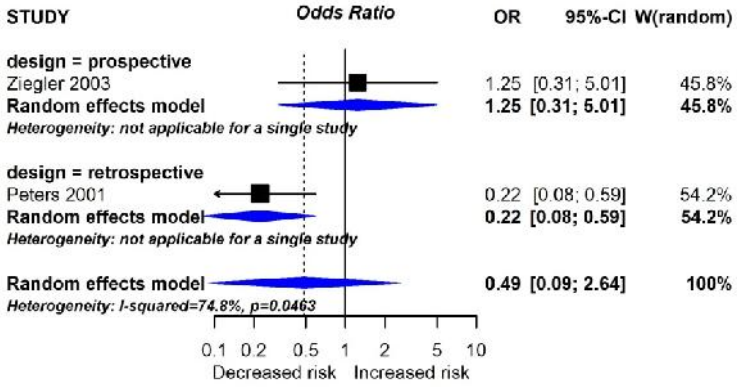
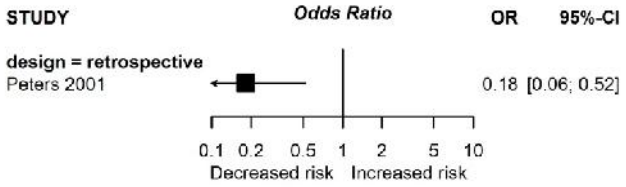


Figure 7 TBF long vs. never and risk of Coeliac Disease in children



1.1.2.4 Data for TBF duration and Coeliac Disease which were not suitable for meta-analysis

Meta-analyses included 5 studies, reporting data on at least 491 participants with coeliac disease. A further 5 case control studies and one prospective cohort study reported relevant data which could not be reported in meta-analysis, in relation to at least 850 participants with coeliac disease. The reason for exclusion from meta-analysis was the type of effect measure used, which in five of these studies was median or mean, or as in 2 studies, risk effects that could not be combined. These

studies are summarised in Table 2. TBF duration was shorter in people with coeliac disease in two studies (one significantly so), longer in three studies (not significant), and unclear in the other.

Table 2 Other studies evaluating TBF duration and coeliac disease which were not suitable for meta-analysis

First Author and year of publication	Design	N/n cases	TBF duration (months)	Descriptive measure	TBF in Unaffected	TBF in Affected	P-value
Ascher, 1997 [2]	CC	81 /8	continuous	Median (range)	5 (0-14)	6.5 (1.5-9)	NS
Falth-Magnusson 1996 [7]	CC	336 /72	continuous	Mean (range)	5.3 (0-20)	3.9 (0-9)	**<0.05**
Roberts 2009 [4]	CC	248521 /90	categorical	Unadjusted cumulative incidence rate per 100,000 births 43.2 (27.1, 65.4) no BF, 32.4 (22.9, 44.5) BF. P=0.28			
Decker 2010 [5]	CC	866 /123	categorical	Increased TBF in cases vs controls. OR 1.99 (1.12, 3.51) which was not significant in adjusted analyses			
Norris 2005 [6]	PC	1560 /51	continuous	Mean (SD)	6.7 (6.8)	8.3 (8.8)	NS
				HR of 1.02 (95% CI 0.99-1.05) for each month increase in breastfeeding			
Ivarsson 2002 (0-2 y.o) [9]	CC	1018 /392	continuous	Median (IQR)	7 (4, 9)	5 (3, 7)	**<0.001**
Ivarsson 2002 (2-14 y.o) [9]		254 /99	continuous	Median (IQR)	6 (3, 9)	6 (4, 8)	NS

1.2 Total breastfeeding duration and inflammatory bowel disease

1.2.1 Overall characteristics of studies, risk of bias and summary of results

Table 3 describes the main characteristics of the studies analysed in this report. A total of 13 observational studies, and no intervention studies, reported the association between duration of total breastfeeding (TBF) and risk of inflammatory bowel disease (IBD). Of these, 1 was a nested case-control study, and 12 were case-control studies. Over half of the studies (n=8) were from Europe – others are from North America (n=1), and Asia/Pacific (n=2). One study involved subjects from a variety of 9 countries and one did not report location. Overall, valid data on TBF duration and IBD risk were available from over 13,000 subjects. Information on IBD was obtained via medical diagnosis, using diagnostic criteria or histology. With regards to time of outcome diagnosis, no studies explored the association between duration of TBF and IBD in the first 5 years of life; studies evaluated the outcome in older children and adults up to 70 years old. All studies used interview or questionnaire to assess TBF duration, and 2 studies combined this information with data from medical records.

Risk of bias was assessed using the NICE Methodological checklist for case-control studies. Figure 8 illustrates the distribution of bias across the five main methodological areas of the studies. Almost half of the studies had a high risk, most commonly due to lack of adjustment for confounding bias i.e., no adjusted data presented. A third of the studies had an 'unclear' overall risk of bias, most commonly due to insufficient information to assess selection and assessment bias.

Where data were available, five levels of comparison were used to assess the risk of FA according to TBF duration, namely 'any (including ever) vs. never', '≥1-2 months vs. <1-2 months', '≥3-4 months vs. <3-4 months', '≥5-7 months vs. <5-7 months', and '≥8-12 months vs. <8-12 months'.

Main Findings

Overall the data show significant statistical heterogeneity, especially for Crohn's disease analysis. The heterogeneity remained unexplained after subgroup analysis, but careful review of the included studies suggests that it may be partly related to varied

methods for acquisition of exposure data, often decades following cessation of breastfeeding, with methods often carrying an unclear and variable risk of assessment bias. Based on the available data, we found no evidence for an association between TBF and IBD risk – this was most clearly the case for UC, where large protective effects of TBF seem unlikely, whereas the evidence base for Crohn's disease was more mixed, with individual studies finding an association in either direction, but inconclusive overall.

Table 3 Characteristics of included studies evaluating TBF duration and inflammatory bowel disease

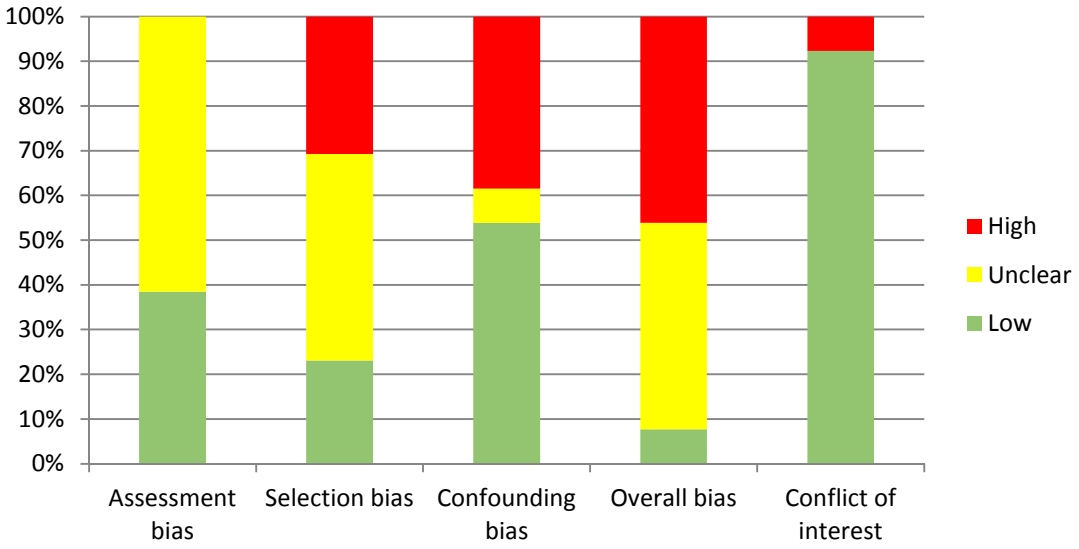
First Author & Publication Year	Design	N/n cases	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Baron, 2005 [13]	CC	444/222	I	DD	<17	France	Cases from EPIMAD registry (1988-97) with community-based sex, age, region matched controls
Gearry, 2010 [14]	CC	1253/653	R/Q	DD	>20	New Zealand	Canterbury Inflammatory Bowel Disease Project. Cases selected from patient advertising, letters to patients from their doctor, patient support groups; Community based (Electoral Roll) controls
Castiglione, 2011 [15]	CC	1030/468	Q	ECCO guideline	16-66	Italy	Cases from gastroenterology units; controls comprised from physicians, nurses, and support services professionals from the participating sites
Corrao, 1997 [16]	CC	1252/626	I	DD including histology	18-65	Italy	Cases identified in clinics with controls sex and age matched hospital-based control
Decker 2010 [5]	CC	1286/374 Crohn, 169 UC		Medical diagnosis	<18	Germany	Cases from paediatric gastroenterology clinics; controls from ophthalmology and dental clinics
Gruber, 1996 [17]	CC	144/54	Q	Unclear	<22	USA	Children diagnosed with Crohn's disease with mothers who were volunteers from the Western New York Chapter of the Crohn's and Colitis Foundation of America, Inc. with age

First Author & Publication Year	Design	N/n cases	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
							matched unrelated controls
Hansen, 2011[18]	CC	534/267	Q	Copenhagen Diagnostic Criteria	38	Denmark	All patients diagnosed with IBD in Copenhagen City and County (private and public sector) in 2003-4 with age, sex, ethnicity and area matched control with orthopaedic problems
Bergstrand, 1983 [19]	CC	616/308	Q/I	Unclear	20	Sweden	Cases were residents of Stockholm County diagnosed with Crohn's disease between 1955 and 1974 with sex, age, residence matched controls from population registry in Stockholm County
Koletzko, 1991 [20]	CC	231/93	Q	DD including histology	15	Not Available	Source of cases unclear. Sibling controls
Thompson, 1999 [21]	NCC	243/27	R/I	DD	33-43	UK	Cases and matched for gender and social class controls were selected from the 1946 National Survey of Health & Development (NSHD) and the 1958 National Child Development Study (NCDS), two on-going, longitudinal birth cohort studies in UK.
Sonntag, 2007 [22]	CC	1974/1096	Q	DD including histology	40	Germany	Cases identified from different sources and controls from partners (normal risk of disease)

First Author & Publication Year	Design	N/n cases	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Gilat, 1987 [23]	CC	1497/499	Q/I	DD	<25	9 countries: USA, Canada, UK, Sweden, Denmark, Holland, France, Italy, Israel	The International IBD Study Group: Cases and matched controls from several health centres (normal risk of disease)
Wang, 2013 [24]	CC	2616/1308	I	Chinese diagnostic guideline including histology	<70	China	Cases from several health centres and matched controls from friends or neighbours (normal risk of disease)

Q: questionnaire, I: interview, R: medical records, PC: prospective cohort, NCC: nested case control, CS: Cross-sectional, CC: case control

Figure 8 Risk of bias in studies of TBF duration and inflammatory bowel disease



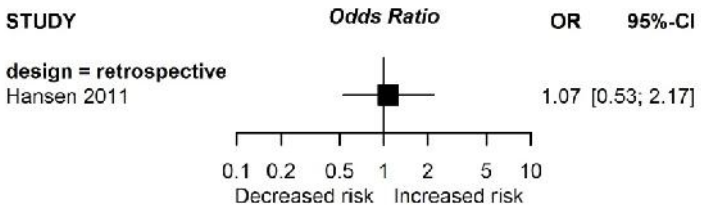
1.2.2 Total Breastfeeding duration and Inflammatory Bowel Disease

1.2.2.1 TBF duration and any IBD

1.2.2.1.1 TBF Any vs. Never

One study reported the relationship between any breastfeeding duration compared to never being breastfed, and risk of IBD (Figure 9). There was no association found in adjusted analysis (OR 1.07, 95% CI 0.53, 2.17).

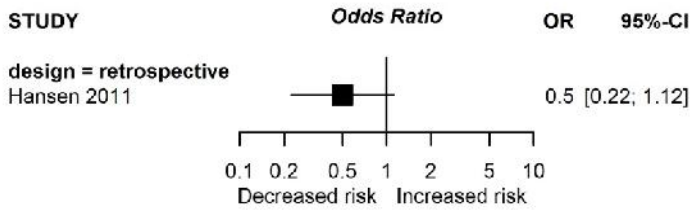
Figure 9 TBF any vs. never and risk of IBD



1.2.2.1.2 TBF ≥5-7 months vs. <5-7

Figure 10 illustrates comparison of TBF ≥6 months vs <6 months in the same study. The study reported a reduced risk of IBD with longer breastfeeding duration but this result failed to reach statistical significance (OR 0.50, 95% CI 0.22, 1.12).

Figure 10 TBF ≥5-7 months vs. <5-7 months and risk of IBD



1.2.2.2 Total Breastfeeding duration and Crohn's Disease

1.2.2.2.1 TBF Any vs. Never

Nine studies which reported the association between TBF any vs never and risk of Crohn's disease are shown in Figure 11. Crohn's disease was not association with breastfeeding initiation (OR 0.79, 95%CI 0.58, 1.08), however there was high statistical heterogeneity between studies (I^2=76.1%). Bergstrand compared short vs never and the rest of the studies compared ever vs never and risk of Crohn's disease. Thompson was the only prospective study contributing to the analysis. All of the studies were assessed as at high or unclear overall risk of bias. Excluding each study individually did not materially impact on the statistical heterogeneity. Stratified and subgroup analyses were limited by the number of studies, but showed similar findings in adjusted and unadjusted analyses. Studies used quite varied methods for assessment of breastfeeding duration, often with an unclear risk of assessment bias, and this may account for some of the statistical heterogeneity between studies.

Figure 11 TBF any vs. never and risk of Crohn's Disease

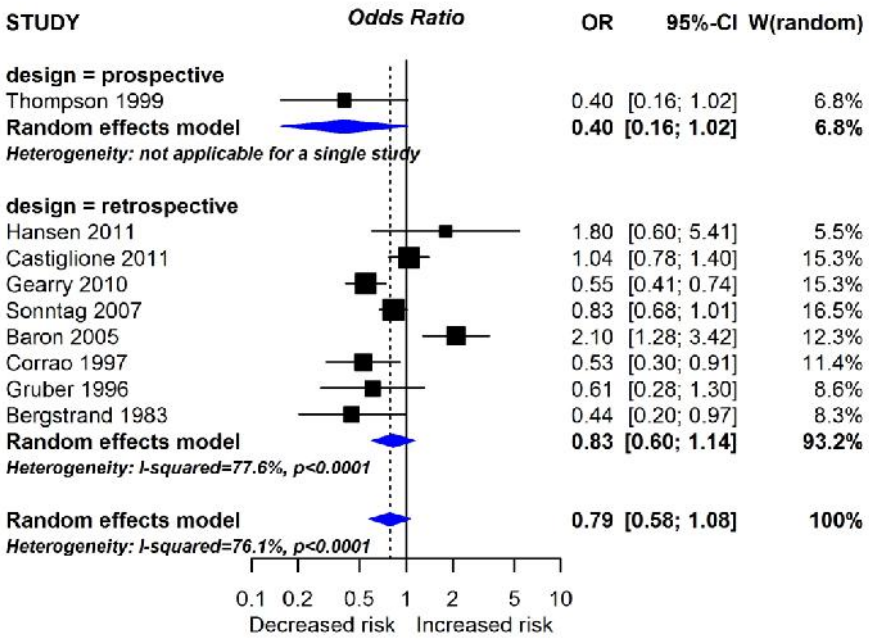


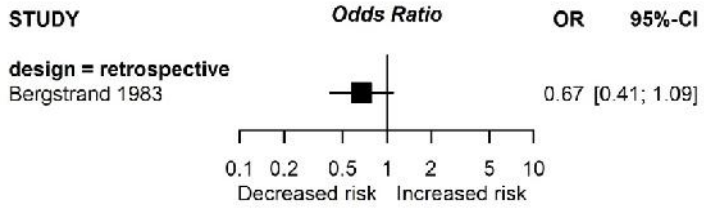
Table 4 Subgroup Analyses of risk of TBF any vs. never and the risk of Crohn's disease

	Number of studies	OR [95% CI]	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted value used)	9	0.79 [0.58; 1.10]	76.1	
Adjusted	4	0.97 [0.45; 2.06]	88.1	Not tested
Unadjusted	8	0.86 [0.64; 1.14]	63.1	
Study Design – Prospective	1	0.40 [0.16; 1.02]	-	0.14
Study Design – Retrospective	8	0.83 [0.60; 1.14]	77.6	
Risk of disease – High	0			-
Risk of disease – Normal	9	0.79 [0.58; 1.08]	77.6	
Risk of bias – Low	0			-
Risk of bias – High/Unclear	9	0.79 [0.58; 1.08]	77.6	

1.2.2.2.2 TBF ≥1-2 months vs. <1-2 months

Only one study reported unadjusted data using 1-2 months as a cut-off for Crohn's disease (Figure 12). The study by Bergstrand showed a non-significant reduction in risk with increased TBF duration (OR 0.67, 95% CI 0.41, 1.09).

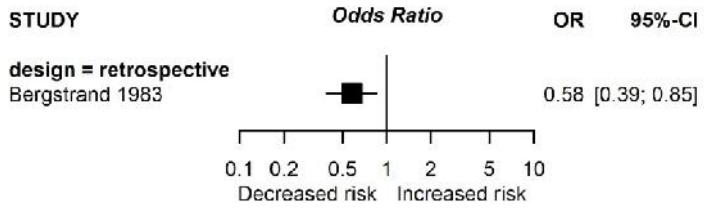
Figure 12 TBF ≥1-2 months vs. <1-2 months and risk of Crohn's Disease



1.2.2.2.3 TBF ≥3-4 months vs. <3-4 months

The same study by Bergstrand also reported the association between risk of Crohn's disease and exposure to TBF for ≥3-4 months (Figure 13). Longer duration of breastfeeding was associated with a statistically significant reduction in risk of disease in unadjusted analysis (OR 0.58, 95% CI 0.39, 0.85).

Figure 13 TBF ≥3-4 months vs. <3-4 months and risk of Crohn's Disease

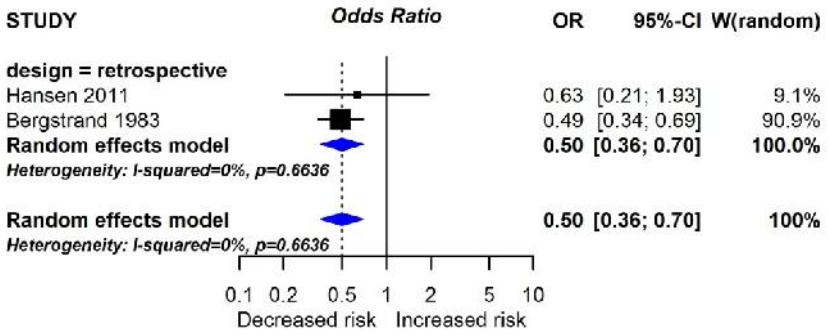


1.2.2.2.4 TBF ≥5-7 months vs. <5-7 months

Two studies assessed the effect of breastfeeding for more than 5-7 months compared to shorter durations on risk of Crohn's disease (Figure 14). There was a significantly reduced risk of disease associated with longer breastfeeding (OR 0.50, 95% CI 0.36, 0.70) with no heterogeneity

(I^2=0%). The study by Bergstrand reported an stronger association with reduced Crohn's risk, with increased duration of breastfeeding across the three cut-offs analysed. However these unadjusted data from a case control study carry a high risk of recall and confounding bias.

Figure 14 TBF ≥5-7 months vs. <5-7 months and risk of Crohn's Disease



1.2.2.3 Total Breastfeeding duration and Ulcerative Colitis

1.2.2.3.1 TBF Any vs. Never

Eight studies reported data which could be meta-analysed for risk of ulcerative colitis in relation to TBF any vs never (Figure 15). Overall, there was no association shown between exposure and outcome (OR 0.98, 95% CI 0.78, 1.23), with high heterogeneity between studies (I^2=61.63%). Stratified and subgroup analyses are shown in table 5. The highest ORs were seen in the only prospective study Thompson, and the only case control study using sibling controls Koletzko.

Figure 15 TBF any vs. never and risk and risk of ulcerative colitis

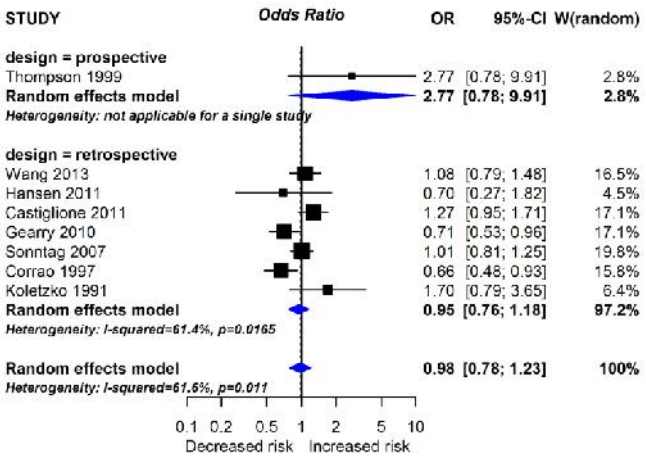


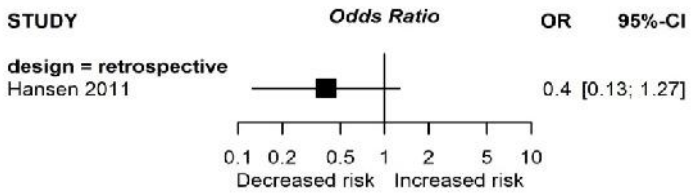
Table 5 Subgroup Analyses of risk of TBF any vs. never and the risk of ulcerative colitis

	Number of studies	OR [95% CI]	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted value used)	8	0.98 [0.78; 1.23]	61.6	
Adjusted	4	0.77 [0.57; 1.06]	40.4	Not tested
Unadjusted	6	1.00 [0.80; 1.27]	56.4	
Study Design – Prospective	1	2.77 [0.77; 9.91]	-	0.104
Study Design – Retrospective	7	0.95 [0.76; 1.18]	61.4	
Risk of disease – High	0			-
Risk of disease – Normal	8	0.98 [0.78; 1.23]	61.6	
Risk of bias – Low	1	1.70 [0.79; 3.65]	-	0.148
Risk of bias – High/Unclear	7	0.94 [0.75; 1.18]	62.1	

1.2.2.3.2 TBF ≥5-7 months vs. <5-7 months

Only one study reported data on the association between TBF for at least 5-7 months compared to less than this, in association with ulcerative colitis (Figure 16). The study found that increased duration of TBF was associated with a reduction in disease (OR 0.4) but this result was not statistically significant in adjusted analysis (95% CI 0.13, 1.27).

Figure 16 TBF ≥5-7 months vs. <5-7 months and risk of ulcerative colitis



1.2.2.4 Data for TBF duration and IBD which were not suitable for meta-analysis

Meta-analyses included 11 studies, including at least 5,122 participants with IBD. Two other studies were identified which could not be included in meta-analysis (Table 6), which contained information regarding 1042 participants with disease. These studies used different definitions for breastfeeding duration and one of them did not provide figures for the effects estimates. The data are shown below. In one study increased TBF was associated with reduced UC (but not Crohn's) risk. In the other study no association was found.

Table 6 Studies which could not be included in meta-analysis of TBF and IBD

First Author and year of publication	Design	N/n cases	TBF duration (months)	Descriptive measure	TBF in Unaffected	Exposure in Affected	P-value
Decker 2010 [5]	CC	1286/ 374 Crohn, 169 UC	continuous	Adjusted analyses showed reduced UC risk with longer TBF duration OR 0.93 (0.89, 0.98) but not for Crohn's (OR 0.99 (0.96, 1.01)			
Gilat, 1987 [23]	CC	1497/499	continuous	No significant difference in breastfeeding duration between diseased and healthy subjects			

1.3 Total breastfeeding duration and Thyroid disease

1.3.1 Overall characteristics of studies, risk of bias and summary of results

Table 7 shows the characteristics of the only study reporting data on TBF and risk of thyroid autoimmune disease. This was an American case control study reporting data on 189 subjects. Exposure data were collected by interview and outcome data included medical diagnosis of disease and auto-antibody results. The study reported narrative data, shown in Table 8.

A summary of the risk of bias of this study is shown in Figure 17. The study was categorised as having a high risk of overall bias due to reliance on unadjusted data, hence high risk of confounding bias.

Main Findings

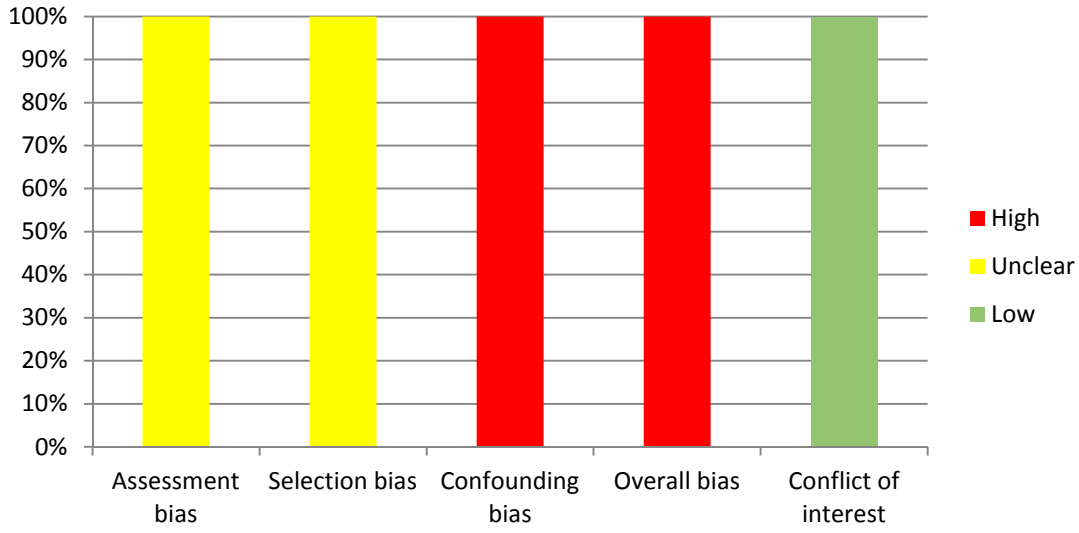
The authors found reduced TBF duration in cases compared with controls, but this was not statistically significant and overall the study was underpowered to identify an effect.

Table 7 Characteristics of included studies evaluating TBF duration and Thyroid disease

Study	Design	N/n cases	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Fort, 1990 [25]	CC	189/59	I	DD including autoantibody testing - Hashimoto and Graves	15	USA	Cases being followed up in clinics with sibling or other controls

I: interview, CC: case control

Figure 17 Risk of bias in studies of TBF duration and Thyroid disease



1.3.2 Data for TBF and thyroid disease which were not suitable for meta-analysis

The case control study by Fort et al (regarding 59 cases of thyroid disease) reported no significant difference in mean breast feeding duration between affected and unaffected subjects (Table 8).

Table 8 Study evaluating TBF duration and thyroid disease which were not suitable for meta-analysis

First Author and year of publication	Design	N/n cases	Measure	TBF in Unaffected	TBF in Affected	P-value
Fort, 1990 (Controls – siblings) [25]	CC	189/ 59	Mean (SD)	5.6 (3.2)	5.2 (3.7)	NS
Fort, 1990 (Controls – healthy controls) [25]			Mean (SD)	8.7 (4.5)	5.2 (3.7)	

1.4 Total breastfeeding duration and juvenile rheumatoid arthritis

1.4.1 Overall characteristics of studies, risk of bias and summary of results

General characteristics of included studies are summarised in Table 9. No intervention trials were identified. Data were available from a total of 3 case-control studies evaluating total breastfeeding duration ('never vs ever', 'short duration vs never' and 'medium duration vs never') and juvenile rheumatoid arthritis risk (JRA). The studies were North American (n=2) and Australian (n=1).

All studies evaluated JRA risk in children over 5 years old, and obtained information on duration of breastfeeding based on questionnaire or interview data.

Based on the distribution of data reported in included studies, meta-analysis compared JRA risk and each of the breastfeeding definitions indicated above. Separate analysis of pauciarticular and polyarticular JRA was also undertaken.

A summary of the risk of bias in included studies is shown in Figure 18. All the studies had a high overall risk of bias, due either to reliance on unadjusted data (hence high risk of confounding bias), or high/unreported inclusion rates (leading to high risk of selection bias).

Main Findings

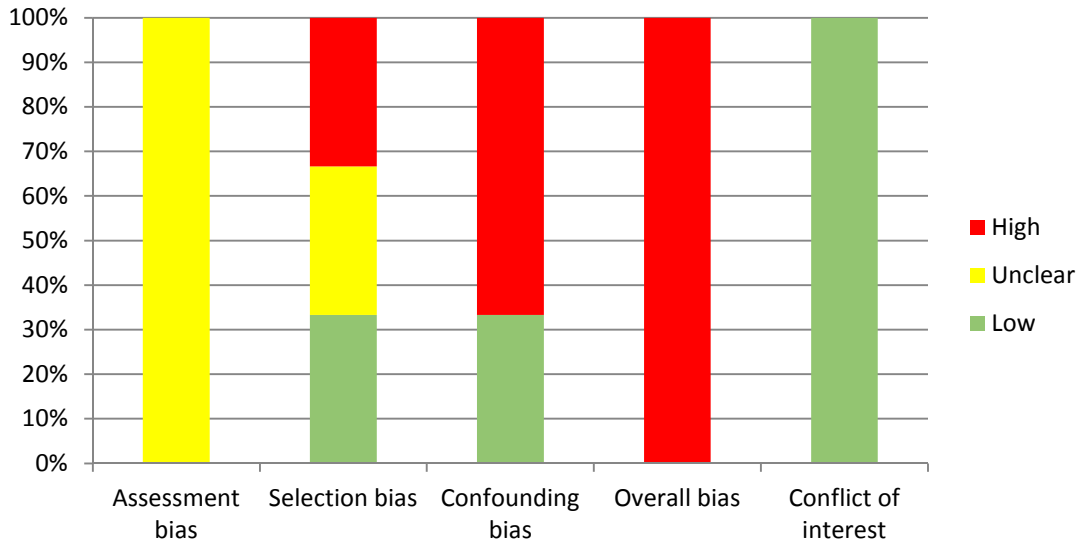
Overall the data do not provide evidence for a relationship between TBF duration and JRA risk. Interpretation of the strength of the evidence is limited by the small number of studies and the high risk of bias observed in all of them.

Table 9 Characteristics of included studies evaluating TBF duration and juvenile rheumatoid arthritis

First Author & Publication Year	Design	N/n cases	Exposure assessment	Specific outcome/Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Ellis, 2012 [26]	CC	655/246	Q/I	DD	<18	Australia	CLARITY study. Cases from paediatric rheumatology clinic; controls from pediatric surgery unit and born in the same area
Mason, 1995 [27]	CC	133/54	I	DD	6	USA	Children seen at the outpatient paediatric rheumatology clinics with playmates matched for age and race as controls
Rosenberg, 1996 [28]	CC	468/137	Q	American College of Rheumatology criteria	<18	Canada	Cases from a health service and matched control from population

Q: questionnaire, I: interview, R: medical records, PC: prospective cohort, NCC: nested case control, CS: Cross-sectional, CC: case control

Figure 18 Risk of bias in studies of TBF duration and juvenile rheumatoid arthritis

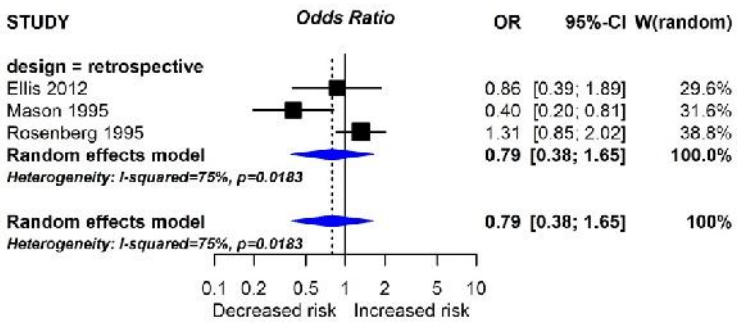


1.4.2 Total Breastfeeding duration and juvenile rheumatoid arthritis

1.4.2.1.1 TBF Any vs. Never

Figure 19 shows the results of meta-analysis of the association between any breastfeeding never vs ever and risk of JRA. Overall, there was no significant association (OR 0.79, 95% CI 0.38, 1.65), but with extreme statistical heterogeneity (I^2=75%). The study of Ellis reported adjusted data, and the other two studies unadjusted, which may account for some of the statistical heterogeneity.

Figure 19 TBF any vs. never and risk of juvenile rheumatoid arthritis



1.4.2.1.2 Any vs. never and pauciarticular and polyarticular JRA

Two studies reported the effect of any vs never breastfeeding and risk of both pauciarticular JRA and polyarticular JRA (Figure 20 and Figure 21 respectively). Studies reporting association between ever breastfeeding and pauciartiular JRA were extremely heterogeneous (I^2=88.8%) and could not be meta-analysed. There was a reduction in risk of polyarticular JRA with nil heterogeneity but this association did not reach statistical significance (OR 0.68 95% CI 0.40, 1.41).

Figure 20 TBF any vs. never and risk of pauciarticular juvenile rheumatoid arthritis

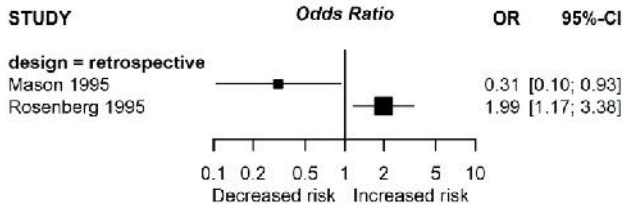
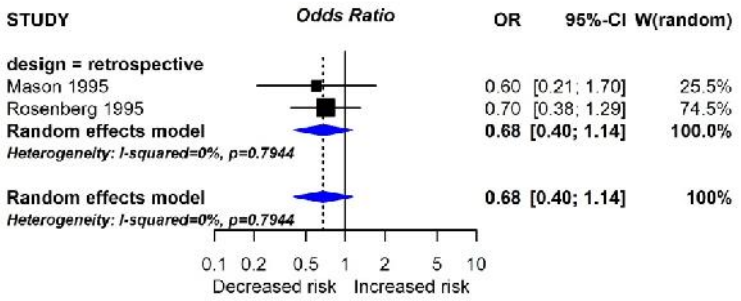


Figure 21 TBF any vs. never and risk of polyarticular juvenile rheumatoid arthritis



1.4.3 Total Breastfeeding dose-response and juvenile rheumatoid arthritis

We also analysed the dose response relationship between breastfeeding duration and JRA (Figure 22 and Figure 23). The single included study by Mason et al [27] shows an increasing protective effect with continuation of breastfeeding from short duration (0-3 months) (OR 0.56, 95% 0.28, 1.13) to medium duration (>3 months) (OR 0.28, 95% 0.12, 0.68) although these were unadjusted analyses.

Figure 22 TBF short vs never and risk of juvenile rheumatoid arthritis

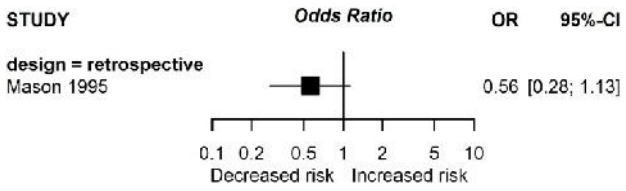
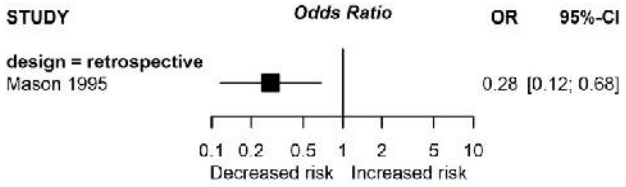


Figure 23 TBF medium vs never and risk of juvenile rheumatoid arthritis



2 Exclusive breastfeeding duration and Autoimmune Diseases

2.1 Exclusive breastfeeding duration and Coeliac Disease

2.1.1 Overall characteristics of studies, risk of bias and summary of results

Table 10 describes the main characteristics of the studies analysed in relation to exclusive breastfeeding duration and coeliac disease. A total of 4 observational studies were identified; of these, 1 was a prospective cohort studies and the remaining 3 were case-control studies. All of the studies originated in Europe. Overall, valid data on exclusive breastfeeding duration and coeliac disease risk were available from 4,216 subjects – this information was obtained by questionnaires in all studies, with two studies combining this with medical record information. Information on coeliac disease was obtained mainly from medical diagnosis using ESPGHAN criteria, although one study used serological transglutaminase auto-antibodies. With regards to time of outcome diagnosis, 3 studies explored the association between exposure to exclusive breastfeeding and coeliac disease in the first 5 years of life and one evaluated coeliac disease in older children.

Risk of bias was assessed using the NICE Methodological checklists for cohort and case-control studies. Figure 24 illustrates the distribution of bias across the five main methodological areas of the studies. Over half of studies had a high risk of bias, most commonly due to lack of adjustment for confounding bias.

Two levels of comparison were used to assess the risk of coeliac disease according to exclusive breastfeeding duration, namely '≥0-2 months vs. <0-2 months' and '≥3-4 months vs. <3-4 months'. Stratified and subgroup analyses were not performed due to the small number of studies included in analysis.

Main Findings

In total 3 case control studies found that EBF duration was associated with reduced risk of coeliac disease, and 1 prospective cohort study in a population with a paternal or maternal history of TIDM failed to confirm this relationship. This is a similar pattern to that seen with TBF and coeliac disease, and TBF/EBF and TIDM, where

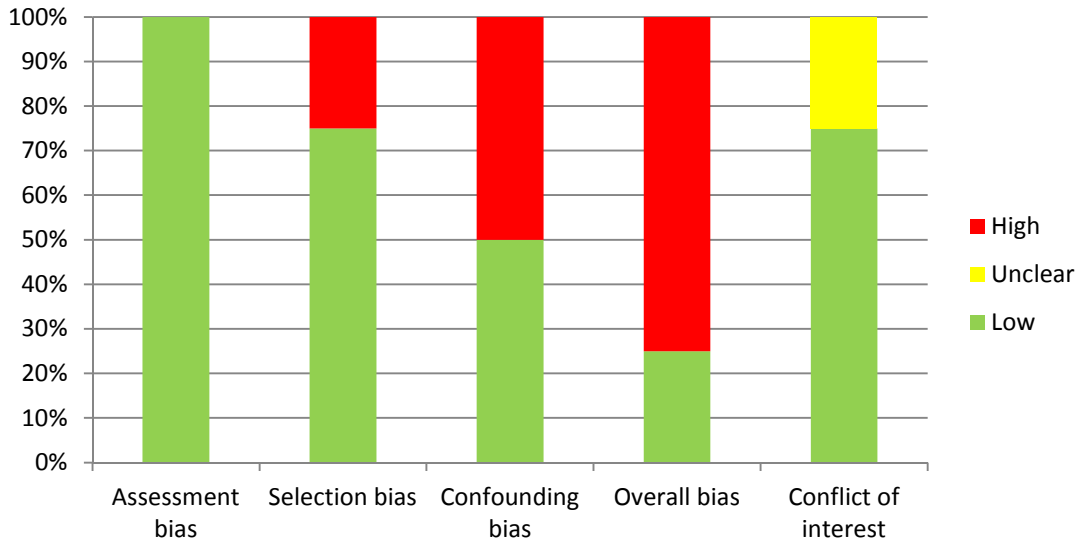
retrospective and prospective studies have discrepant findings, with retrospective studies showing a relationship but prospective studies – often with smaller numbers of cases in specific high risk populations, using surrogate outcomes for clinical disease – not finding a relationship between BF and disease.

Table 10 Characteristics of included studies evaluating EBF duration and Coeliac Disease

First Author & Publication Year	Design	N/n cases	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Falth-Magnusson, 1996 [7]	CC	336/72	R/Q	ESPGHAN criteria	<2	Sweden	Cases from paediatric department records, born in 1987-1989. Reference children were age matched from same county.
Ziegler, 2003 [8]	PC	1460/27	Q	IgA-tTG	5	Germany	German BABYDIAB study. Offspring of mothers and/or fathers with T1DM born in Germany between 1989 and 2000
Greco, 1988 [29]	CC	2150/201	R/Q	ESPGHAN criteria	2	Italy	Hospital-based cases born in 1976-1983 with age and area matched controls
Peters, 2001 [11]	CC	270/133	Q	ESPGHAN criteria	< 10	Germany	Cases born in 1985-1995 identified from registries of several hospitals and matched control from population registry (normal risk of disease)

Q: questionnaire, I: interview, R: medical records, PC: prospective cohort, NCC: nested case control, CS: Cross-sectional, CC: case control

Figure 24 Risk of bias in studies of EBF duration and coeliac disease

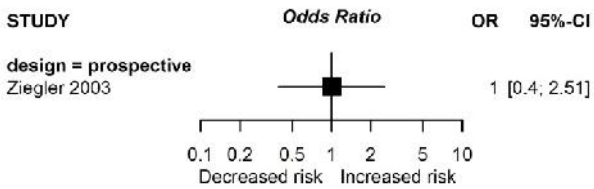


2.1.2 Exclusive breastfeeding duration and Coeliac Disease

2.1.2.1 EBF ñ0-2 months vs <0-2 months

Figure 25 shows the one study which reported the association between exclusive breastfeeding for 0-2 months or more, versus shorter durations. There was no difference in risk of disease between these exposures (OR 1.0, 95% CI 0.40, 2.51).

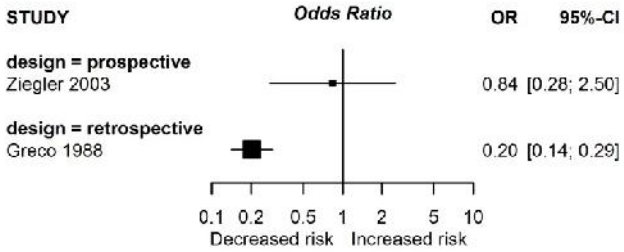
Figure 25 EBF ñ0-2 months vs <0-2 months and risk of Coeliac Disease



2.1.2.2 EBF ñ3-4 months vs <3-4 months

Two studies reported the association between exclusive breastfeeding for more than vs less than 3-4 months. Data could not be pooled due to extreme statistical heterogeneity (I^2=82.8%) between the case control study of Greco reporting unadjusted OR, and the prospective cohort study of Ziegler reporting adjusted HR.

Figure 26 EBF ñ3-4 months vs <3-4 months and risk of Coeliac Disease



2.1.2.3 Data for EBF duration and coeliac disease which were not suitable for meta-analysis

Meta-analysis involved two studies, containing information on 228 subjects with coeliac disease. A further two studies, with 205 subjects with coeliac disease, could not be meta-analysed. The reasons for exclusion from meta-analysis was the type of measurement used to report data (mean, median, or percentage), which made comparisons of effect size not possible. Details of these studies are shown in Table 11.

Both studies showed that individuals with coeliac disease had been exclusively breastfed for a significantly shorter duration than unaffected controls. The study by Peters et al [11] also reported that risk of coeliac disease was reduced by 12% for each month of exclusive breastfeeding (OR 0.88, 95% CI 0.79,0.98).

Table 11 Other studies reporting data on EBF duration and coeliac disease which couldn't be meta-analysis

First Author and year of publication	Design	N/n cases	EBF duration (months)	Descriptive measure	EBF in Unaffected	Exposure in Affected	P-value
Peters, 2001 [11]	CC	270/133	Continuous	Mean (SD)	2.7 (2.3)	2.1 (2.5)	**<0.05**
				Coeliac disease was reduced by 12% for each month of exclusive breastfeeding in adjusted analysis (OR 0.88, 95% CI 0.79,0.98)			
Falth-Magnusson 1996 [7]	CC	336/72	Continuous	Median (range)	4 (0-10)	2 (0-6)	**<0.05**

2.2 Exclusive breastfeeding duration and inflammatory bowel disease

2.2.1 Overall characteristics of studies, risk of bias and summary of results

Table 12 shows the characteristics of the studies included in analysis of exclusive breastfeeding duration and IBD. Two studies were identified: both were case control studies and included a total of 675 subjects. One study was from Europe while the origin of the second study was unknown. Exposure information was obtained by questionnaire or interview and outcome assessment used medical diagnosis. Both studies assessed children older than 5 years old.

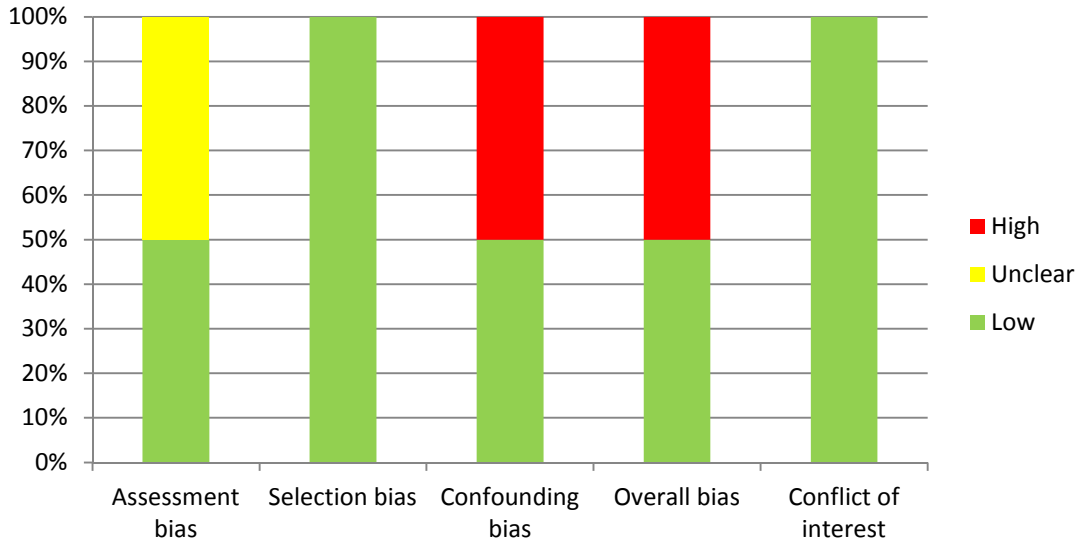
Risk of bias was assessed using the NICE Methodological checklists for case-control studies (Figure 27). One study had a high overall risk of bias due to lack of adjustment for confounding bias whereas the other study was considered to have low risk of bias. Meta-analysis was not performed due to only narrative data being reported. The limited data show no evidence of a relationship between EBF duration and risk of IBD.

Table 12 Characteristics of included studies evaluating EBF duration and inflammatory bowel disease

Study	Design	N/ cases	Exposure assessment	Outcome assessment	Age (yrs)	Country	Population characteristics
Baron, 2005 [13]	CC	444/222	I	DD	<17	France	Cases from EPIMAD registry (1988-97) with community-based sex, age, region matched controls
Koletzko, 1991[20]	CC	231/93	Q	DD including histology	15	Unclear	Source of cases unclear. Sibling controls

Q: questionnaire, I: interview, R: medical records, PC: prospective cohort, NCC: nested case control, CS: Cross-sectional, CC: case control

Figure 27 Risk of bias in studies of EBF duration and inflammatory bowel disease



2.2.2 Data for EBF duration and IBD which were not suitable for meta-analysis

There was no significant difference in EBF duration between cases and controls (Table 13), using either continuous analysis (mean) or categorical analysis (OR).

Table 13 Studies reporting data on EBF duration and IBD which were not suitable for meta-analysis

Study	Design	N/n cases	EBF duration (months)	Descriptive measure	EBF in Unaffected	Exposure in Affected	P
Koletzko, 1991 [20]	CC	231/93	>0 vs 0 months	Adj.OR			NS
Baron, 2005 [13]	CC	444/222	continuous	Mean	2	2.5	NS

3 Solid food introduction and Autoimmune Disease

3.1 Solid food introduction and Coeliac Disease

3.1.1 Overall characteristics of studies, risk of bias and summary of results

Table 14 Table 14 Characteristics of included studies evaluating solid food introduction and Coeliac Disease shows the characteristics of the only study included in analysis of timing of solid food introduction and risk of coeliac disease. This was a European prospective cohort study containing relevant information form 1219 subjects. Exposure data were collected using a questionnaire and transglutaminase auto-antibody serology was used as the outcome measure. The authors reported that neither breastfeeding or its duration nor the age of first exposure to gluten was associated with the risk of developing transglutaminase antibodies.

Risk of bias assessment is reported in Figure 27. The study was categorised as having a high overall risk of bias due to a lack of adjustment for confounders. Due to the information reported in the paper, the cut-off of solid food introduction '≥3-4 months vs <3-4 months' was chosen.

Main Findings

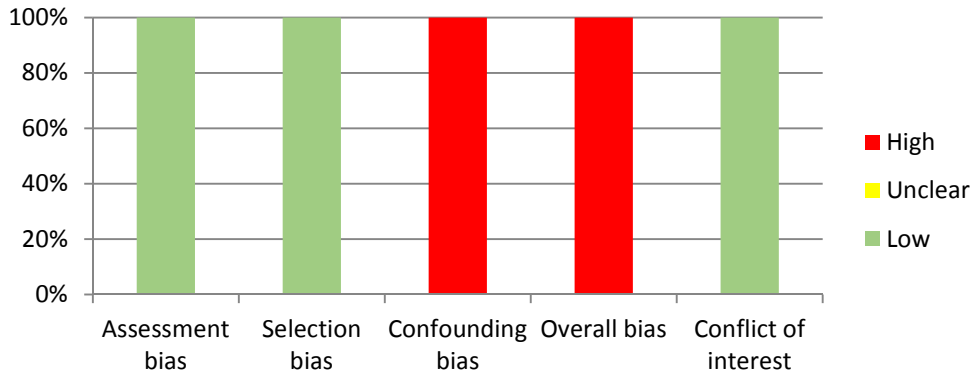
We found no evidence to support a relationship between timing of SF introduction and risk of Coeliac disease.

Table 14 Characteristics of included studies evaluating solid food introduction and Coeliac Disease

Study	Design	N/n cases	Exposure	Outcome	Age (yrs)	Country	Population characteristics
Hummel, 2007 [30]	PC	1219/27	Q	IgA-tTG	8	Germany	German BABYDIAB. Offspring of mothers and/or fathers with T1DM born in Germany between 1989 and 2000

Q: questionnaire, I: interview, R: medical records, PC: prospective cohort, NCC: nested case control, CS: Cross-sectional, CC: case control

Figure 28 Risk of bias in studies of solid food introduction and Coeliac Disease

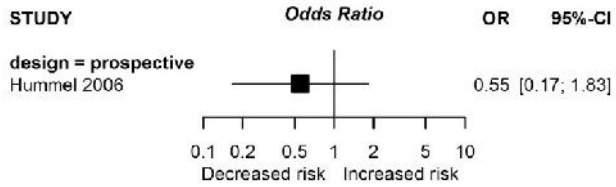


3.1.2 Solid food introduction and Coeliac Disease

3.1.2.1 SF ≥3-4 months vs. <3-4 months

There was a non-significant reduction in risk of coeliac disease associated with delaying solid food introduction until after 3-4 months (Figure 29, OR 0.55, 95% CI 0.17, 1.83).

Figure 29 SF ≥3-4 months vs. <3-4 months and risk of Coeliac Disease



3.2 Solid food introduction and inflammatory bowel disease

3.2.1 Overall characteristics of studies, risk of bias and summary of results

One study reported the association between timing of solid food introduction and risk of inflammatory bowel disease (Ulcerative colitis; Table 15). This was a case control study of unknown location reporting relevant data for 231 subjects. Data on solid food introduction was collected by questionnaire and medical diagnosis of IBD (including histology) was used as the outcome measure of interest. The authors reported that age of solid food introduction was not different in children with ulcerative colitis (no estimates provided).

Figure 30 demonstrates the results of risk of bias assessment using the NICE Methodological guideline for case control studies. The study was considered to have a low overall risk of bias, scoring well in all domains.

Main Findings

We found no evidence to support a relationship between timing of SF introduction and risk of inflammatory bowel disease. Only narrative data were reported on the lack of association between exposure and outcome, so meta-analysis was not undertaken.

Table 15 Characteristics of included studies evaluating solid food introduction and inflammatory bowel disease

Study	Design	N/ cases	Exposure	Outcome	Age (yrs)	Country	Population
Koletzko, 1991 [20]	CC	231/ 93	Q	DD including histology	15	Not Available	Source of cases unclear. Sibling controls

Q: questionnaire, I: interview, R: medical records, PC: prospective cohort, NCC: nested case control, CS: Cross-sectional, CC: case control

Figure 30 Risk of bias in studies of solid food introduction and inflammatory bowel disease



3.2.2 Data for solid food introduction and IBD which were not suitable for meta-analysis

The study by Koletzko et al found that age at solid food introduction did not affect risk of inflammatory bowel disease (Table 16), with a p-value >0.05.

Table 16 Studies reporting solid food introduction and IBD which were not suitable for meta-analysis

Study	Design	N/ n cases	Age at SF introduction (months)	Descriptive measure	Effect	P-value
Koletzko, 1991 [20]	CC	231/93	>0 vs 0 months	Adj.OR		NS

3.3 Solid food introduction and juvenile rheumatoid arthritis

3.3.1 Overall characteristics of studies, risk of bias and summary of results

One study reported data regarding timing of solid food introduction and risk of JRA (Table 17). This was an Australian case control study with relevant data regarding 655 subjects. Exposure data was collected via questionnaire and medical diagnosis of JRA was used as the outcome measure.

Risk of bias was assessed and reported in Figure 31 Risk of bias in studies of solid food introduction and Juvenile rheumatoid arthritis. The study had a high overall risk of bias, due to a high dropout rate and therefore high selection bias.

Main Findings

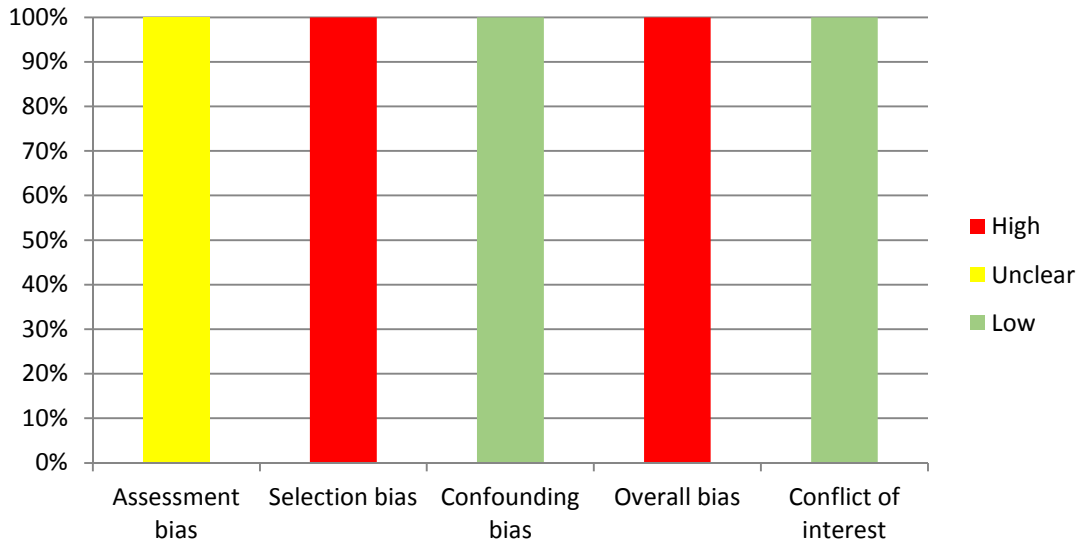
We found no evidence to support a relationship between timing of SF introduction and risk of JRA. Only narrative data were reported, which are shown below.

Table 17 Characteristics of included studies evaluating solid food introduction and juvenile rheumatoid arthritis

Study	Design	N/n cases	Exposure	Outcome	Age (yrs)	Country	Population characteristics
Ellis, 2012 [26]	CC	655/246	Q/I	DD	18	Australia	CLARITY. Cases from paediatric rheumatology clinic; controls from paediatric surgery unit born in the same area

Q: questionnaire, I: interview, R: medical records, PC: prospective cohort, NCC: nested case control, CS: Cross-sectional, CC: case control

Figure 31 Risk of bias in studies of solid food introduction and Juvenile rheumatoid arthritis



3.3.2 Data for solid food introduction and juvenile rheumatoid arthritis which were not suitable for meta-analysis

The study by Ellis et al showed no significant difference in mean age at solid food introduction between cases and controls (Figure 18).

Table 18 Studies reporting solid food introduction and juvenile rheumatoid arthritis which were not suitable for meta-analysis

Study	Design	N/n cases	Age (yrs)	Measure	TBF in No JRA	TBF in JRA	P
Ellis, 2012 [26]	CC	655/246	continuous	Mean (SD)	5.6 (2.2)	5.5 (3.8)	NS

3.4 Solid food introduction and Thyroid disease

3.4.1 Overall characteristics of studies, risk of bias and summary of results

The only study reporting data on solid food introduction timing and risk of thyroid disease is shown in Table 19. This was an American case control study with relevant data about 189 subjects. Outcome assessment included medical diagnosis and autoantibody testing, reporting data on Hashimoto and Grave's disease. Interviews were used to collect information on timing of solid food introduction.

The study was assessed as having a high overall risk of bias (Figure 32), due to lack of adjustment for confounders.

Main Findings

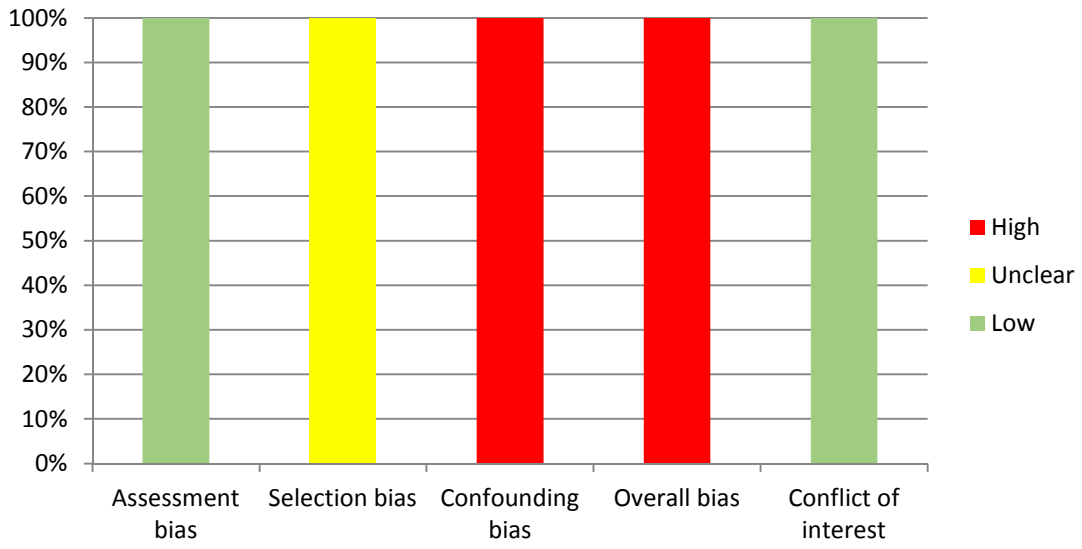
We found no evidence to support a relationship between timing of SF introduction and risk of thyroid disease. The paper reported only narrative data, which is shown below.

Table 19 Characteristics of included studies evaluating solid food introduction and Thyroid disease

Study	Design	N/n cases	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Fort, 1990 [25]	CC	189/59	I	DD including autoantibody testing - Hashimoto (52) and Graves (7)	15	USA	Cases being followed up in clinics with sibling or other controls

Q: questionnaire, I: interview, R: medical records, PC: prospective cohort, NCC: nested case control, CS: Cross-sectional, CC: case control

Figure 32 Risk of bias in studies of solid food introduction and Thyroid disease



3.4.2 Data for solid food introduction and thyroid disease which were not suitable for meta-analysis

Table 20 shows the results of the study by Ford et al, who found there was no significant difference in mean age at introduction of solid food between cases and controls.

Table 20 Data for solid food introduction and thyroid disease

Study	Design	N/n cases	Measure	TBF in no thyroid disease	TBF in thyroid disease	P-value
Fort, 1990 [25]	CC	189/59	Mean (SD)	3.3 (3)	3.7 (3.3)	NS

4 Conclusion

This report summarises the results of 30 studies investigating the association between total and exclusive breastfeeding duration, timing of solid food introduction and risk of autoimmune disease. The majority of studies were retrospective case-control studies. Overall, we found some evidence to support an association between longer duration of total and exclusive breastfeeding and reduced risk of coeliac disease. However, there were high levels of statistical heterogeneity in all relevant analyses, attributed to negative findings in 2 prospective studies but positive findings of an association in the retrospective studies. This is similar to the pattern seen with TIDM, where there are a greater number of studies and events included in meta-analyses.

The current recommendations from the Committee on Nutrition of the European Society for Paediatric Gastroenterology, Hepathology and Nutrition (ESPGHAN) suggest to avoid both early (< 4 months) and late (7 or more months) introduction of gluten. The American Academy of Pediatrics (AAP) recommends that complementary foods can be introduced between 4 and 6 months of age; gluten-containing foods should be introduced while the infant is receiving only breast milk and not infant formula or other bovine milk products. Both AAP and ESPGHAN recommend that gluten is introduced whilst the infant is being breastfed, but do not make specific recommendations about breastfeeding duration in relation to coeliac disease or other autoimmune diseases as an outcome. We did not identify other systematic reviews of these exposures and outcomes with which to compare our findings. Our data would suggest that there is currently no consistent evidence to support a relationship between breastfeeding duration and risk of coeliac disease.

Our data suggest no association between UC and TBF, but the data were extremely heterogeneous for Crohn's and TBF, such that it is not possible to exclude a significant association – part of this heterogeneity may relate to varied and unreliable methods of exposure assessment.

Analyses of JRA, thyroid disease, and timing of solid food introduction, were limited by small numbers of included subjects and studies, and cannot be taken as evidence for or against an association between the relevant exposure and outcome. For other

autoimmune diseases vitiligo and psoriasis, we found no eligible studies. Given the inconsistent signal seen with coeliac disease and TIDM, further study of the relationship between TBF, EBF and other autoimmune diseases such as Crohn's disease, JRA, thyroid disease, vitiligo and psoriasis seems warranted.

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Breastfeeding, Solid Food Introduction and Wheeze

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1 Total breastfeeding and wheeze

1.1 Overall characteristics of studies, risk of bias and summary of results

Table 1 describes the main characteristics of the studies that assessed total breastfeeding duration (TBF) in relation to wheeze risk. There were a total of 105 studies of which one was a cluster randomised controlled trial, 68 were prospective cohort studies (2 of which were parental studies to a cross-sectional (CS) and to a nested case-control study), 3 retrospective cohorts, 10 case-control, 2 nested case-control, and 19 cross-sectional studies. The majority of studies (n=57) are from Europe – others are from the Asia-Pacific region (n=18) and North America (n=17), 5 from South America, 3 from Africa, 1 from the Middle East (Iraq), and 1 has an unknown provenance. There are also 2 studies from the International Study of Allergies and Asthma in Childhood (ISAAC), which included multiple countries.

Overall, valid data on TBF duration in the first 2 years of life and wheeze risk were available from over 463,000 subjects. Information on wheeze was obtained solely from parental or self-reported in 25 studies, through Dr-diagnosis in 31 studies, and from the ISAAC questionnaire in 16 studies. A further 4 studies use spirometry alone. Another 27 studies used a combination of self /parental report, Doctor diagnosis, and/ or objective measures (e.g. bronchial hyper-responsiveness (BHR)). One study used an unclear method for defining wheeze.

With regards to time of outcome diagnosis, 34 studies explored the association between TBF duration and wheeze at age 0-4 years, 41 at age 5-14 years, and 14 at age 15 years or beyond. A further 15 studies investigated the association between TBF duration and wheeze at various time points between the ages of 1 and 22 years. To ascertain exposure to TBF, 64 studies used a questionnaire method, 13 used an interview, 3 used medical records, 2 used a diary, and 1 used a food frequency questionnaire (FFQ). A further 18 studies used a combination of 2 or more of these methods, whilst 3 studies had no information available on the method used.

Risk of bias was assessed using the NICE Methodological checklists for cohort and case-control studies. Figure 1 illustrates the distribution of bias across the five main

methodological areas of the studies. At least half of the studies were considered to have a low risk of assessment, selection and confounding bias, with over a third of studies had a low risk of overall bias. Over a third of the studies had a high risk of overall bias, mainly due to lack of controlling for potential confounders. Risk of conflict of interest was generally assessed as low.

Where data were available, five levels of comparison were used to assess the risk of wheeze according to TBF duration, namely 'ever vs. never', '≥1-2 months vs. <1-2 months', '≥3-4 months vs. <3-4 months', '≥5-7 months vs. <5-7 months', and '≥8-12 months vs. <8-12 months'.

Main findings

In the single intervention trial, there was no evidence of a relationship between breastfeeding promotion and risk of wheeze at age 1 year or 6.5 years. For observational studies, across in children aged 0-4 years, we found no consistent evidence for an association between TBF and wheeze or recurrent wheeze. There was weak evidence for an association in dose-response analysis of four studies for wheeze (Figures 4 to 6) and three studies for recurrent wheeze (Figures 28 to 30). In other analyses there was either extreme heterogeneity, or no consistent association between TBF duration and wheeze or recurrent wheeze. Heterogeneity could not always be explained, but in some cases was likely due to differences in adjustment for potential confounders. In some sensitivity analyses unadjusted data showed greater evidence of association than adjusted data.

In children aged 5-14 years old, we found limited evidence from observational studies for an association between TBF and wheeze or recurrent wheeze. Meta-analysis of data for ever vs. never breastfed showed reduced odds of wheeze, but with high heterogeneity and evidence of publication bias; inconclusive findings from dose/response analysis, and no association seen with other durations of TBF. Meta-analysis of data for ever vs. never breastfed showed reduced odds of recurrent wheeze, with moderate heterogeneity and evidence of publication bias; but supportive findings from dose-response analysis, and significant or borderline significant associations seen with other durations of TBF (3 to 4 months, 5 to 7 months, over 18 months). The evidence for an association between TBF and recurrent wheeze at age 5-14 was graded as VERY LOW (-1 publication bias).

In people aged 15 years or older, we found no consistent evidence for an association between TBF and risk of wheeze or recurrent wheeze. Data were sparse for analyses of wheeze. For analyses of recurrent wheeze, TBF 1 to 2 months or longer was associated with increased risk of recurrent wheeze in one prospective and one retrospective study (Figure 47); TBF 5 to 7 months or longer was associated with decreased risk of recurrent wheeze in one prospective study at low risk of bias (Figure 49); and analyses of TBF ever vs. never, or TBF 3 to 4 months or longer showed no significant association with recurrent wheeze.

We found no evidence for an association between TBF and atopic wheeze, or between TBF and wheeze when TBF was reported as a continuous measure (e.g. average number of months breastfed in those with and without a history of wheeze).

We found no evidence for an association between TBF and bronchial hyper-reactivity (BHR) in children aged 5 to 14 years, and no consistent evidence for an association between TBF and measures of lung function. Eight studies investigated the association between lung function outcomes and TBF in over 37,800 subjects aged 10 to 51 years old, summarised in Table 12. Outcomes reported included forced expiratory volume in 1 second (FEV_1), FEV_1 as percentage of predicted value (FEV_1%predicted), peak expiratory flow rate (PEFR), forced expiratory mid flow (FEF_{50}), FEV_1 decline, airflow obstruction ($FEV_1/FVC<0.80$), FEV_1/FVC as percentage of predicted value, and post-bronchodilator measures of FEV_1, FVC and FEV_1/FVC. One cross-sectional study reported a positive association between FEV_1% and TBF ever vs. never. A prospective cohort reported a positive association between TBF and FEF_{50}, whilst two prospective cohort studies reported a positive association between TBF and FEV_1. Two studies reported an association between TBF ever and FEV_1/FVC% and FVC. However a number of non-significant associations reported, and no measure of lung function was consistently associated with TBF across different studies.

A total of 36 studies with data on wheeze and TBF exposure were identified which did not report data in a way that could be included in meta-analyses (Table 11). There were 25 prospective cohorts, 1 retrospective cohort, 1 case-control, 1 a nested case-control, and 8 cross-sectional studies. Seven prospective cohort studies reported associations between TBF and reduced wheeze (n=1) or recurrent wheeze (n=6), and 2 cross-sectional studies reported associations between TBF and reduced recurrent wheeze. Twenty five studies showed no

evidence of an association between TBF and wheeze outcomes. Four studies reported borderline associations (P=0.05).

Overall, TBF analyses were marked by statistical heterogeneity, evidence of publication bias in 3 analyses (ever vs. never and wheeze at age 5-14; ever vs. never and recurrent wheeze at age 5-14; TBF for at least 3 to 4 months and recurrent wheeze at age 5-14) – suggesting that the relationship reported between TBF and wheeze/recurrent wheeze may be influenced by publication of studies showing a protective association, and non-publication of studies finding TBF is not associated with, or is associated with increased risk of wheeze/recurrent wheeze.

Conclusion

We found VERY LOW (-1 publication bias) evidence that longer TBF is associated with reduced risk of recurrent wheeze at age 5-14 years, and no consistent evidence for an association between TBF and other wheeze or lung function outcomes.

Table 1 Characteristics of included studies evaluating total breastfeeding and wheeze

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Kramer, 2001 (1); Kramer, 2007 (2)	8865/8181	Cluster RCT	Belarus	-	SPT-Aero	6.5	Breastfeeding promotion program based on the WHO/UNICEF baby friendly hospital initiative, versus standard local breastfeeding policies
Wright, 2002 (3)	PC	499	Q/I	Parent reported wheeze	0-1	USA	Part of a metropolitan Boston prospective birth cohort study of infants born between 1994-1996 with family history of asthma or recruited from a Boston hospital
Al-Kubaisy, 2005 (4)	CS	2262	Q	DD plus ISAAC	12	Iraq	Primary school urban and rural children
Hesselmar, 2010 (5)	PC	184	I	DD asthma (>=3 episodes of wheeze)	1.5	Sweden	ALLERGYFLORA study. Population based study of babies selected from antenatal clinics between 1998 and 2003 - mainly high risk of allergic disease
Elliott, 2008; Granell, 2012; Sherriff, 2001 (6-8)	PC	9100	Q	DD asthma PLUS current wheeze; Parent reported wheeze; BHR: (metacholine PC20)	3, 3.5, 7, 7.5	UK	ALSPAC study. Population based cohort of children born 1991-1992
Kull, 2002 (9)	PC	3790	Q	Self-reported wheeze; >=3 episodes of wheeze OR inhaled corticosteroids	2	Sweden	BAMSE study. Population based cohort of children born between 1994-1996

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Lewis, 1996 (BCS58) (10)	PC	9820	I	Parent reported current wheeze	16	UK	British Cohort Study: Infants born in England, Wales, and Scotland England, Scotland and Wales in 1958
Lewis, 1995; Lewis, 1996 (BCS70) (10, 11)	PC	12835	Q, I	Parent reported wheeze ever/ current wheeze	5, 16	UK	British Cohort Study: sample of all infants born in 1970 in Britain
Burr, 1989; Burr, 1993; Burr, 1993 (b) (12-14)	PC	483	D, Q	Parent reported wheeze; Wheeze ever, DD	1, 6.7, 7	UK	Infants with family history of allergic diseases in South Wales
Alper, 2006 (15)	CS	858	Q	Parent reported wheeze classified using Martinez criteria	7	Turkey	7 years old children randomly selected from seven primary schools in Bursa in 1999
Businco, 1987 (16)	PC	244	I	DD asthma (>=3 episodes of wheeze)	8	Italy	Infants of atopic parents recruited from hospital and born in 1985-1988
Camara, 2003 (17)	CC	91	Q	DD (wheezing that required therapy with inhaled β2-agonists as judged by the attending physician)	12	Brazil	Cases and control were children who sought ED care

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Midodzi, 2010 (18)	PC	8499	Q	DD	5	Canada	Canadian Early Childhood Development Cohort Study- part of NLSCY. Longitudinal surveys of children representative of the Canadian population
Taylor, 1983 (19)	PC	12608	I	Parent reported wheeze; DD	5	UK	CHES study. Population based cohort of children born in England, Scotland, and Wales in 1970
Mihrshahi, 2007 (20)	PC	516	I	DD PLUS current wheeze	5	Australia	CAPS study. Infants born in 1997-1999 with family history of asthma or wheezing
Simon, 2008 (21)	PC	372	R/I	Transient wheezing: wheezing in the last 12 months at ages of 1,2 and/or 4 years but not at age of 6 years	6	USA	CAS study. Middle class mother-infant pairs enrolled in a health maintenance organisation in 1987-89
Larsson, 2008 (22)	PC	4779	Q	DD	9	Sweden	DBH study. Preschool children aged 1–6 years surveyed in 2000 and 2005.
Devereux, 2006 (23)	PC	1704	FFQ	ISAAC	5	Scotland, UK	Population based birth cohort of infants born in 1998
Nwaru, 2013 (24)	PC	3675	D	DD plus ISAAC; DD plus ISAAC (+/- sIgE)	5	Finland	DIPP study. Infants at high risk (HLA) for TIDM born between 1996-2004 invited to the allergy study between 1998 and 2000
Wilson, 1998 (25)	PC	545	Q	Self-reported wheeze; DD	7	UK	Dundee infant feeding study. Population based cohort of infants born between 1983-1986

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Ehrlich, 1996 (26)	CS	620	Q/I	ISAAC	9	South Africa	Second year elementary school (7- 8 years) children. All black
Visser, 2010 (27)	CS	1115	Q	Parent reported wheeze ever; >=3 episodes of wheeze	1	Netherlands	EISL study. One-year old infants from urban and rural primary care health clinics born in 2004-2006
Munro, 2011 (28)	PC	700	Q	Parent reported wheeze	1	UK	EuroPrevall-UK. Population based birth cohort of infants born in 2008
Farooqi, 1998 (29)	PC	1453	R	DD (recurrent episodes of wheeze after the age of two years)	16	UK	Representative sample of general practice both in 1975-84
Friday, 2000 (30)	RC	94	NA	Physician assessed asthma	10?	no data	Unclear
Fredriksson, 2007 (31)	PC	1933	Q	ATS questionnaire: wheezing apart from colds or wheezing most days or nights during the past year; DD	15	Finland	Population-based study of children born between 1984 and 1989
Tanaka, 2009(32)	CS	1957	Q	ISAAC	3	Japan	Fukuoka Child Health Study. All 3-year old children who had the examination at public public health centers in Fukuoka city
van der Voort, 2012 (33)	PC	5368	Q	ISAAC	1, 4	Netherlands	Generation R study. Population-based multicultural birth cohort of infants born between 2002 and 2009

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Gruskay 1982 (34)	PC	328 FH+/ 580 FH-	NA/Q	Physician assessment (recurrent wheezing)	3, 5, 15	USA	Children born in 1961-1966 in a private pediatric practice
Guida, 2009 (35)	PC	3041	Q	Parent reported wheeze	1	France	Population based birth cohort of infants born in 2003
Gustafsson, 1999 (36)	PC	94	Q	>=3 episodes of physician diagnosed wheezing	8	Sweden	Children with atopic dermatitis attending allergic clinic or referred by child welfare clinics
Halken, 1991(37)	PC	276	Q	>=2 episodes of physician diagnosed wheeze	1.5	Denmark	Population based birth cohort of children born in 1985
Han, 2009 (38)	CS	21371	Q	ISAAC	15	Taiwan	Elementary and middle school children aged 6-15 years old in 2004
Puig, 2010 (39)	PC	368	Q	DD	6	Spain	Part of AMICS. Population based cohort of infants born in 1996-1998 in Barcelona
Soto-Ramirez, 2013 (40)	PC	2833	Q	Parent reported current wheeze	1	USA	Population based birth cohort selected from nationally distributed consumer opinion panel of 500 000 household between 2005-2007
Oddy, 2003 (41)	PC	243	Q	Parent reported wheeze ever	1	USA	Birth cohort of infants participating in the Infant Immune Study in Tucson, Arizona.

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Infante-Rivard, 1993(42)	CC	914	I	DD	3.5	Canada	Cases were 3- and 4-year-old children with a first-time diagnosis of asthma made by a paediatrician 1988-90. Age and area matched controls chosen from computerized family allowance files for the target region.
Alm, 2008; Goksor, 2009 (43, 44)	PC	4987	Q, Q/FFQ	Wheeze ever; >=3 episodes of wheeze in past year	1.4, 4.5	Sweden	Infants of Western Sweden. Population birth cohort of infants born in 2003
Morales, 2012 (45)	PC	467	Q/I	Parent reported wheeze	1	Spain	INMA project. Population based birth cohort of infants born 2004-2006
Nagel, 2009 (46)	CS	31579	Q	Parent reported current wheeze; Parent reported asthma (+/- SPT); Spirometry; BHR:hypertonic saline PC1	12	Worldwide	ISAAC Phase 2. Schoolchildren aged 8–12 years from 27 centres in 21 affluent and nonaffluent countries
Björkstén, 2011 (47)	CS	103716	Q	ISAAC	7	Worldwide	ISAAC Phase 3: Schoolchildren aged 6-7 years from different countries and geographic regions
Awasthi, 2004 (48)	CS	2471	Q	ISAAC	7	India	ISAAC Phase 3-India: Schoolchildren aged 6-7 and 13-14 years old from India
Karmaus, 2008 (49)	PC	1336	Q	ISAAC PLUS DD asthma	10	UK	Isle of Wight Prevention Study. Population based birth cohort of infants born in semi-rural areas between 1989 and 1990

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Juca, 2012 (50)	CC	590	Q	ISAAC	14	Brazil	Adolescents age 13-14 years old in Mato Grosso State, Brazil
Karino, 2008 (51)	CS	9615	Q	Self-reported asthma	18	Japan	University freshmen students aged 18–19 years enrolled from 2003 through 2005.
Karunasekera, 2001 (52)	CC	582	Q	Physician assessment	10	Sri Lanka	Hospital-based cases aged 1-10 years old with age matched controls from inpatient clinics
Kaufman, 1976 (53)	PC	94	NA	DD	2	USA	Birth cohort of infants from allergic mothers
Kemeny, 1991(54)	PC	180	NA	>=2 episodes of wheeze	1	UK	Population based birth cohort of infants born at Dulwich and King's College Hospitals in London
Klinnert, 2001(55)	PC	145	Q	DD	8	USA	Birth cohort of infants at increased risk for atopy born between 1985 and 1987
Snijders, 2007; Snijders, 2008 (56, 57)	PC	2505	Q	>=4 episodes of wheeze	2	Netherlands	KOALA study. Population based birth cohort of infants born between 2000-2002 (consisting of cohorts with conventional and alternative lifestyle)
Galbally, 2013 (58)	PC	4507	I	Parent reported wheezing >=4 nights per week	1	Australia	Longitudinal Study of Australian Children. Population based study of infants born between March 2003 and February 2004 and were enrolled in the Australian Medicare database

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Marini, 1996 (59)	PC	Unclear	Q	Physician assessment (>=3 episodes of wheeze)	3	Italy	Infants with family history of allergy whose mother were proposed to participate in an allergy prevention program
Martel, 2008 (60)	NCC	1578	Q	DD PLUS asthma medication	<10	Canada	Data originating from 3 interlinked administrative health databases on children health in the first 10 years of life
Burgess, 2006 (61)	PC	4964	Q	Parent reported asthma	14	Australia	Mater-University of Queensland Study of Pregnancy. Population based birth cohort of infants born 1981-1984
Mavale-Manuel, 2003 (62)	CC	199	Q/I	DD PLUS asthma medication	8	Mozambique	Children aged between 18 months and 8 years attending pediatrics clinic with history of asthma with age-match controls attending the clinic immediately after selection of the index case
McConnochie, 1986(63)	RC	223	R/I	ATS guideline: wheezing with and without colds or most days or nights; DD (ATS guideline)	8	USA	Historical cohort with subjects were drawn from the patient population of a five-paediatrician group practice in a suburb of Rochester, New York
Miskelly, 1988 (64)	PC	482	D	Parent reported wheeze	1	UK	Infants from antenatal clinics with family history of allergy randomised into a dietary intervention program
Miyake, 2003 (65)	CS	6845	Q	ISAAC	15	Japan	12-15 years old children from all public junior high schools in Suita, Japan.
Morgan, 2004 (66)	PC	1600	I	DD	1.5	U.K.	Infants from five prospective randomised dietary trials conducted in the UK 1993-1997. Two term infant trials; one LBW infant trial; two preterm infant trials.

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Mann, 1992 (67)	PC	2139	Q	Self-reported wheeze; Spirometry	36	UK	MRC National Survey of Health and Development. Birth cohort of infants to wives of non-manual and agricultural workers, and one in four of all single, legitimate infants to wives of manual workers in England, Wales, or Scotland
Muiño, 2008 (68)	PC	897	Q	Parent reported current wheeze; Persistent wheeze: parent reported wheeze at 1, 4 and 8-10 year assessments; Early transient wheeze: parent reported	12	Brazil	Population based cohort of infants born in 1993
Bergmann, 2000 (69)	PC	1314	Q/I	Physician assessment	6	Germany	MAS study. Atopic risk enriched cohort of infants born in 1990 in 5 German cities
Rust, 2001(70)	CS	6783	I	DD; DD asthma ever	<6	USA	NHANES III survey. Children ages 2 months to 5 years from noninstitutionalized U.S. population
Evenhouse, 2005 (71)	CS	16903	Q	Unclear	12-18	USA	National Longitudinal Study of Adolescent Health (Add Health). Nationally representative samples of adolescents from 80 school districts, since 1994
Dell, 2001; Midodzi, 2008 (72, 73)	PC; CS	2711	NA; Q	>=2 episodes of wheeze; Preschool wheeze: <5 years but not beyond 6 years; Parent reported wheeze; DD	2,9	Canada	National Longitudinal Survey of Children and Youth (NLSCY). First of longitudinal surveys of 12-24 months old children representative of the Canadian population
Milner, 2004 (74)	PC	8071	Q	DD	3	USA	National Maternal and Infant Health Survey and Longitudinal Follow Up. Representative US population born in 1988. Black, low socioeconomic status, and premature infants intentionally overrepresented

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Silvers, 2009; Silvers, 2011 (75, 76)	PC	987	Q	DD PLUS current wheeze; Parent reported wheeze	1, 5	New Zealand	New Zealand Asthma and Allergy Cohort Study. Population based birth cohort of infants born between 1997 and 2001
Ronmark, 1999 (77)	NCC	258	Q	DD plus ISAAC; Physician assessment (+/-sensitisation)	8	Sweden	Obstructive Lung Disease in Northern Sweden Study. 7-8 years old children enrolled in school in 1996 in northern Sweden (born 1988-1989) (77)
Oliveti, 1995 (78)	CC	262	Q	DD PLUS asthma medication	9	USA	Cases and age matched controls were identified using rosters of patients followed during the previous year. he majority of children from each group were insured by Medicaid (low income)
Miyake, 2008 (79)	PC	763	Q	ISAAC	2	Japan	OMCHS study. Population based birth cohort of infants born in 2002-2003
da Costa Lima, 2003; Menezes, (80, 81)	PC	4297	I, Q/I	ISAAC	18, 22	Brazil	Pelotas Birth Cohort. Population based birth cohort of infants born in 1982 in the city of Pelotas
Perez Tarazona, 2010 (82)	PC	620	Q	Parent reported wheeze	1	Spain	Population based birth cohort of infants born in 2007-2008 in Valencia
Caudri, 2013; Scholtens, 2009 (83, 84)	PC	3115	Q	Current wheeze; Parent reported wheeze; Parent reported wheeze ever (+/- sIgE); ISAAC; BHR: metacholine PC20	8	Netherlands	PIAMA: population-based born in 1996-1997 (normal risk of disease)

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Kerr, 1981(85)	PC	269	I	Parent reported wheeze	0.5	New Zealand	Birth cohort hospital based, born 1977-1978 (normal risk of disease)
Porro, 1993 (86)	CC	465	Q	Parent reported wheeze	<1.6	Italy	Hospital based study with matched controls (normal risk of disease)
Kurt, 2008(87)	CS	25843	Q	Current wheeze; Parent reported current wheeze	15	Turkey	Prevalence and Risk Factors of Allergies in Turkey (PARFAIT): population representative sample of children aged 9-15 years old (normal risk of disease0
Schonberger, 2005 (88)	PC	443	D/Q	ISAAC	2	Netherlands	PREVASC study: cohort born in 1997-2000 with family history of asthma (high risk of disease)
Hagendorens, 2005 (89)	PC	693	Q	Parent reported current wheeze	1	Belgium	PIPO study: recruited from university service, born 1997-2001 (normal risk of disease)
Alho, 1990 (90)	PC	2130	Q	DD Wheeze	2	Finland	Birth cohort, population representative sample born 1985-1986 (normal risk of disease)
Rhodes, 2001(91)	PC	63	Q	Current wheeze AND BHR	22	UK	Hospital based, born 1976-1977, family history of allergy (high risk of disease)
Rona, 2005 (92)	RC	1213	R	ECRHS questionnaire; ECRHS questionnaire AND SPT AND BHR; BHR: metacholine PC_{20}	27	Chile	Infants born in a hospital in 1974-1978 (normal risk of disease)

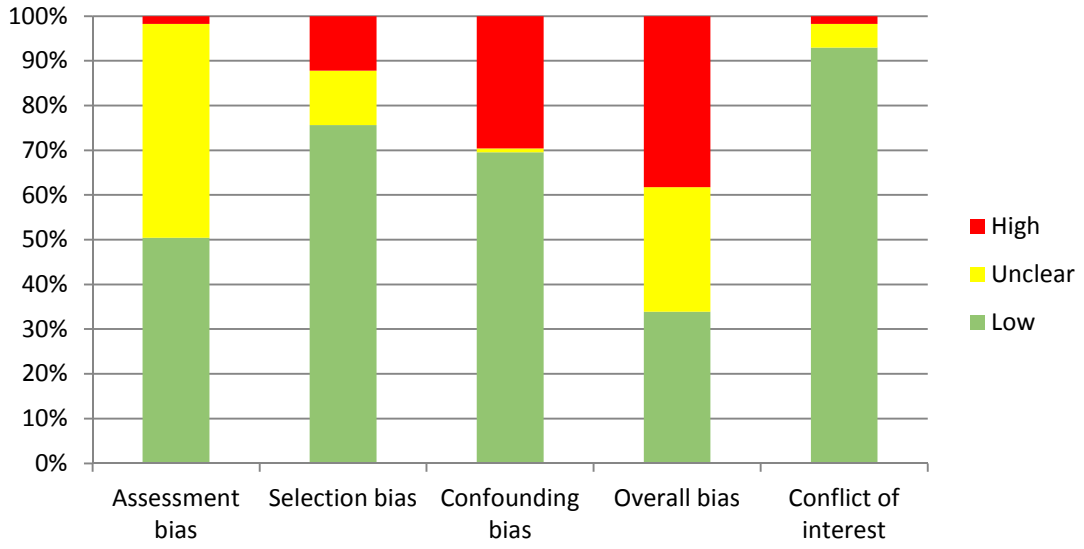
First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Rosas Vargas 2002 (93)	CC	148	Q	DD	3	Mexico	Hospital-based study, cases born in 2000 (normal risk of disease)
Rothenbacher, 2005(94)	PC	803	Q/I	DD	2	Germany	Recruited from university service, born in 2000-2001 (normal risk of disease)
Rusconi, 1999; Rusconi, 2005 (95, 96)	CS	16933	Q	Parent reported persistent wheezing: >=1 in first 2 years, and in past 12 months; Transient early wheeze: wheeze in first 2 years but not past 12 months; ISAAC	7	Italy	SIDRIA survey of a representative sample of children aged 6-7 years old
Saarinen, 1995 (97)	PC	150	R	Physician assessment	5, 17	Finland	Recruited from hospital and born in 1975 (normal risk of disease)
Selcuk, 1997 (98)	CS	5412	Q	Parent reported wheeze ever; Parent reported current asthma	12	Turkey	Children 7-12 ys of 18 primary schools (normal risk of disease)
Sunyer, 2006 (99)	PC	462	Q	DD	6.5	Spain	Population representative sample born in 1997-1998 (normal risk of disease)
Sunyer, 2001(100)	PC	596	Q	ISAAC	4	Tanzania	Cohort born in 1995-1996 in urban area (normal risk of disease)
Hide, 1981(101)	PC	843	D/Q	Wheeze ever; Parent reported wheeze	1	UK	The Isle of Wight Prevention study: born in 1977-1978 (normal risk of disease)

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Takemura, 2002 (102)	CS	23828	Q	ATS questionnaire: DD asthma PLUS >=2 episodes of wheeze	15	Japan	The Tokorozawa Childhood Asthma and Pollinosis Study: Representative sample of children in public elementary schools (normal risk of disease)
Tian, 2009 (103)	PC	472	I	Physician assessment	2	China	Infants from urban areas born in 2004-2006 (normal risk of disease)
Yamamoto, 2011(104)	PC	1344	Q	ISAAC	3	Japan	Tokyo Children's Health Illness and Development study (T-CHILD)
Wright, 1989; Wright, 1995 (105, 106)	PC	988	Q/I	DD; >=4 episodes of wheeze in past year	1, 6	USA	Tuscon Children's Respiratory Study: Healthy newborn infants recruited from local health maintenance organisation born in 1980-1984 (normal risk of disease)
Van Beijstervelft, 2008 (107)	PC	24018	Q	DD	5	The Netherlands	Netherlands Twin Register: born in 1987-2000 (normal risk of disease)
Wang, 2006 (108)	CS	8733	Q	ISAAC	10	China	Population representative sample of children in elementary schools and nurseries (normal risk of disease)
Oddy, 1999; Oddy, 2003; Oddy, 2004 (109-111)	PC, NCC	2456	D/I, Q, D/Q	DD; DD PLUS current wheeze; Parent reported current wheeze; DD asthma PLUS >=3 episodes of wheeze	1, 6, 8	Australia	Western Australia Pregnancy Cohort: Recruited from antenatal clinics born in 1989-1992 (normal risk of disease)

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Wickens, 2001 (112)	CC	474	I	ISAAC	6.5	New Zealand	Population-based study (normal risk of disease)
Zhu, 2012 (113)	CC	542	Q	DD	14	China	Population-based study (normal risk of disease)
Zutavern, 2004 (114)	PC	606	I	Parent reported current wheeze	2, 5.5	UK	Cohort recruited from general practices and born in 1993-1995 (normal risk of disease)
Ogbuanu, 2009 (115); Soto-Ramırez, 2012 (116)	PC	1033	NA, Q	Spirometry	18	UK	Isle of Wight Prevention Study. Population based birth cohort of infants born in semi-rural areas between 1989 and 1990
Dogaru, 2012 (117)	PC	1458	Q	Spirometry	12	UK	Population based sample of children of white and south Asian ethnic origin born between 1993 and 1997, part of the Leicestershire cohorts
Tennant, 2008 (118)	PC	392	Q	Spirometry	50	UK	Newcastle Thousand Families Study. Population based sample of subject born in 1947 who were either traced through the National Health Service Central Register or contacted the study team in response to media publicity in the mid 1990
Suwanpromma, 2012 (119)	CS	215	Q	Spirometry; BHR:hypertonic saline PC15	18	Thailand	Schoolchildren aged 6-18 years (normal risk of disease)

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Eneli, 2006 (120)	PC	536	Q	BHR:hypertonic saline PC15	10	Germany	The Child Health and Environment Cohort Study: community based in urban area, born 1994 (normal risk of disease)
Tennant, 2010 (121)	PC	122	Q	Spirometry	14, 51	UK	The Newcastle Thousand Families Study: born in 1947 (normal risk of disease)

Figure 1 Risk of bias in studies of total breastfeeding and wheeze



1.2 Total Breastfeeding and wheeze

The single intervention trial of a breastfeeding promotion intervention was rated as having a low risk of bias on all domains, and a low risk of conflict of interest. Kramer found no significant difference in odds of recurrent wheeze at age 1 year – cluster adjusted odds ratio 0.7 (95% CI 0.29, 1.70); or at age 6.5 years – cluster adjusted odds ratio 1.2 (95% CI 0.7, 1.9). There was also no significant difference in odds of wheeze ever OR 1.1 (0.6, 1.8) or wheeze in the past 12 months OR 1.0 (0.7, 1.6) at 6.5 years. All other evidence was derived from observational studies.

1.2.1 Age at outcome measurement 0-4

1.2.1.1 Ever vs. never

Figure 2 shows the outcomes of 14 eligible observational studies evaluating TBF ever vs never and risk of wheeze. The data were not pooled due to extreme heterogeneity across studies (I^2=83.3%). Thirteen studies were prospective cohorts and one was a cross-sectional study. All studies had low or unclear risk of bias in most domains. There was no evidence of publication bias and the reason for extreme statistical heterogeneity was not clear (Figure 3). Adjusted data showed no relationship, whereas unadjusted data showed reduced wheeze with TBF. There was a significant subgroup difference in the relationship between TBF ever and wheeze, between infants with a family history of wheeze or allergic disorder, and more representative populations, with a significant association and reduced heterogeneity in the high risk infants (Table 1).

In dose-response analysis there was some evidence that increasing duration of TBF is associated with a greater reduction in risk of wheeze, in this age group (Figure 4-Figure 6). This analysis was dominated by one study Elliott, which reported appropriately adjusted OR for different durations of TBF in relation to wheeze in the first 3 years. In the same cohort there was no relationship between TBF and wheeze at older ages.

Figure 2 Total breastfeeding ever vs. never and risk of wheeze in children aged 0-4 years

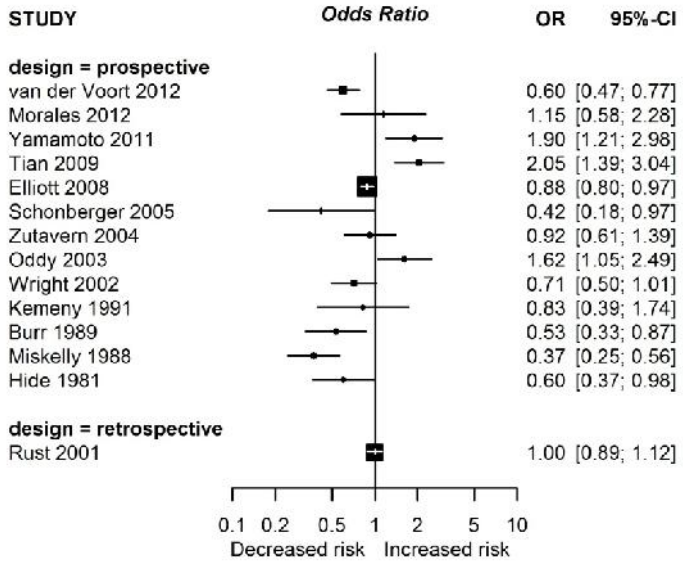
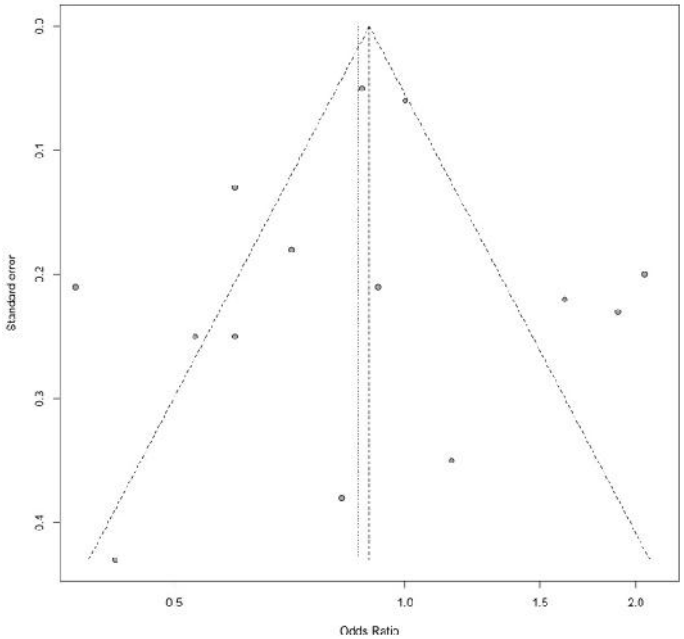


Figure 3 Risk of publication bias in studies investigating total breastfeeding ever vs. never and risk of wheeze in children aged 0-4 years



Egger's test p-value =0.736

Table 2 Subgroup and stratified analysis of TBF ever and risk of wheeze in children aged 0-4 years

	Number of studies	OR [95% CI]	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted used)	14	0.87 [0.71; 1.06]	83.3	
Adjusted	7	0.98 [0.72; 1.35]	76.8	Not tested
Unadjusted	12	0.79 [0.63; 0.99]	87.7	
Study Design – Prospective	13	0.85 [0.66; 1.10]	83.6	0.26
Study Design – Retrospective	1	1.00 [0.89; 1.12]	--	
Risk of disease – High	4	0.51 [0.37; 0.72]	48.7	< 0.001
Risk of disease – Normal	10	1.04 [0.85; 1.28]	81.7	
Risk of bias – Low	6	0.75 [0.54; 1.05]	74.8	0.25
Risk of bias – High/Unclear	8	0.96 [0.74; 1.25]	86.2	

Figure 4 Total breastfeeding (dose response) short vs. never and risk of wheeze in children aged 0-4 years

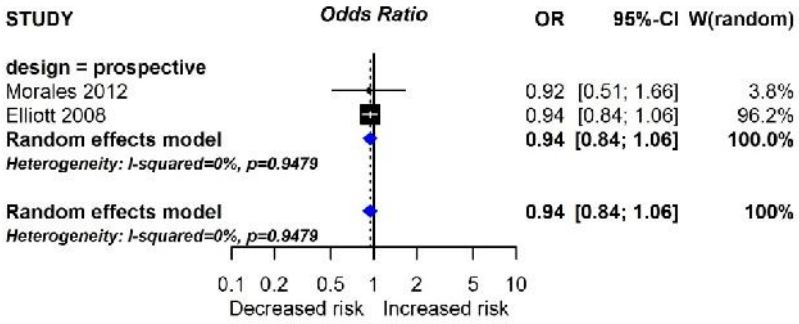


Figure 5 Total breastfeeding (dose response) medium vs. never and risk of wheeze in children aged 0-4 years

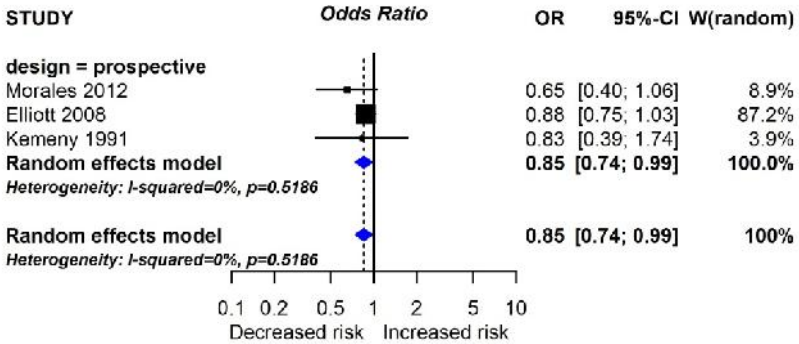
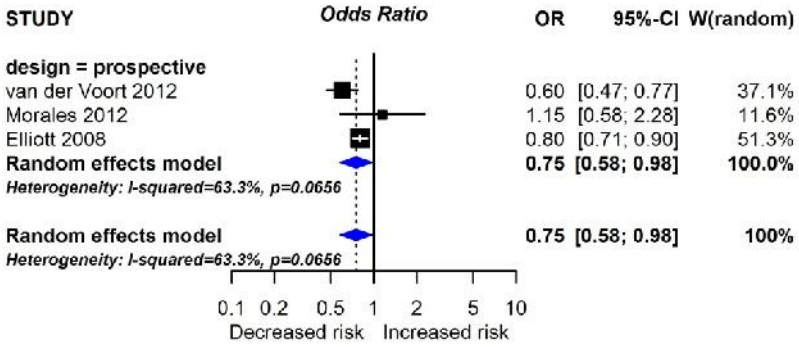


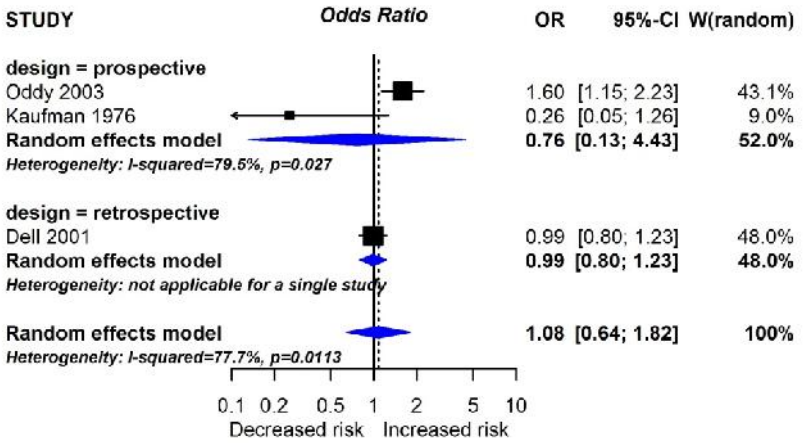
Figure 6 Total breastfeeding (dose response) long vs. never and risk of wheeze in children aged 0-4 years



1.2.1.2 1-2 Months

Figure 7 shows the pooled estimates of three studies which assessed risk of wheeze and TBF for ≥1-2 months vs. <1-2 months, suggesting no association, with very high heterogeneity between studies (I^2=77.7%). The study of Oddy and Dell provided adjusted odds ratios, whilst the study of Kaufman provided unadjusted estimates, and therefore carried a high risk of bias.

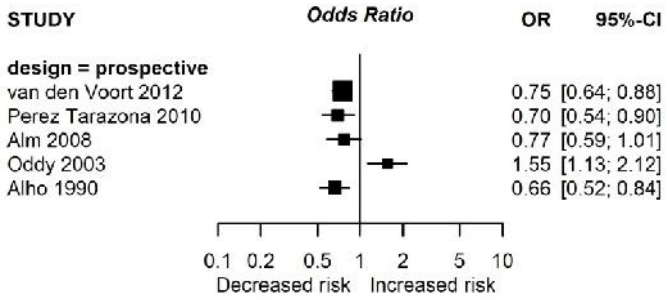
Figure 7 Total breastfeeding for ≥1-2 months vs. <1-2 months and risk of wheeze in children aged 0-4 years



1.2.1.3 3-4 Months

Five studies (all prospective cohorts) reported relevant data, which could not be combined in a meta-analysis due to extreme heterogeneity (I^2=81%; Figure 8). With the exception of the Oddy study, all the studies showed a tendency for a lower risk of wheeze if TBF lasted for at least 3-4 months when compared to less than this cut-off. The studies of Perez-Tarazona and Alho provided unadjusted estimates and therefore carried a high risk of bias. The other three studies had a low overall risk of bias and the source of heterogeneity is not clear.

Figure 8 Total breastfeeding for ≥3-4 months vs. <3-4 months and risk of wheeze in children aged 0-4 years



1.2.1.4 5-7 Months

Nine observational studies examined the association between TBF for ≥5-7 months vs. <5-7 months and risk of wheeze in children aged 0-4 years (Figure 9). There was no association between TBF and risk of wheeze in this analysis, but with high heterogeneity across studies (I^2=72.3%). Subgroup analyses (Table 3) show no important subgroup differences, and outcomes are similar in unadjusted and adjusted analyses. Heterogeneity remains high in all analyses, and we were unable to explain the heterogeneity in outcomes between studies.

Figure 9 Total breastfeeding for ≥5-7 months vs. <5-7 months and risk of wheeze in children aged 0-4 years

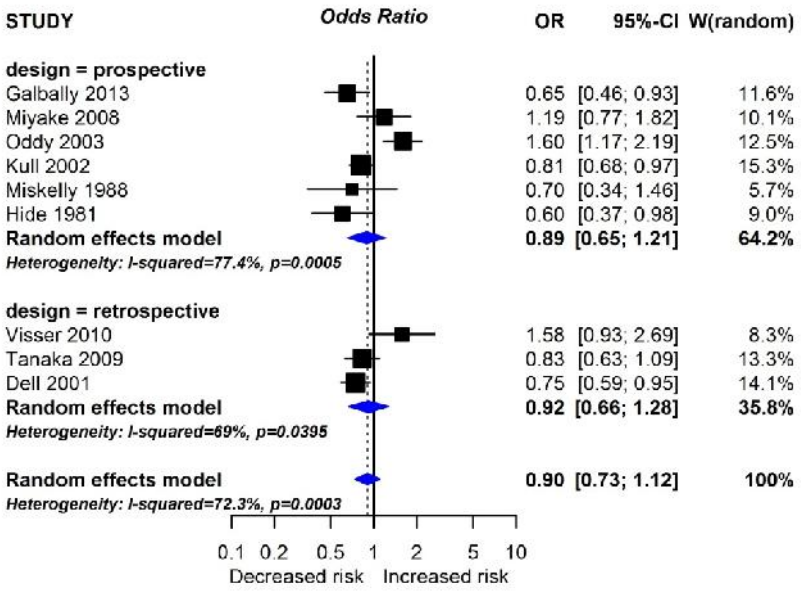


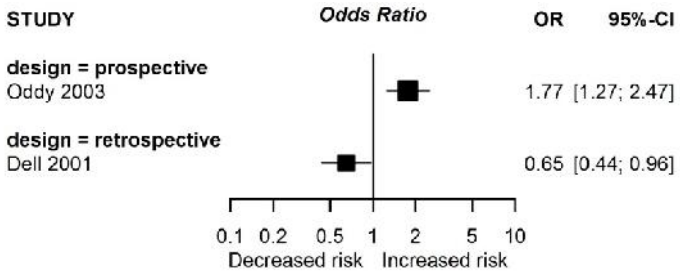
Table 3 Subgroup Analysis of risk of wheeze and total breastfeeding ≥5-7 months vs. <5-7 months in children aged 0-4 years

	Number of studies	OR [95% CI]	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted used)	9	0.91 [0.73; 1.12]	72.3	
Adjusted	7	0.96 [0.76; 1.22]	77.1	Not tested
Unadjusted	8	0.89 [0.63; 1.27]	89.3	
Study Design – Prospective	6	0.89 [0.65; 1.21]	77.4	0.89
Study Design – Retrospective	3	0.92 [0.66; 1.28]	69	
Risk of disease – High	1	0.71 [0.34; 1.46]	--	0.49
Risk of disease – Normal	8	0.92 [0.73; 1.15]	75.5	
Risk of bias – Low	3	0.94 [0.59; 1.51]	88.6	0.78
Risk of bias – High/Unclear	6	0.88 [0.69; 1.12]	54.3	

1.2.1.5 8-12 Months

Two prospective cohort studies had eligible data that could be pooled to calculate OR for wheeze in infants with TBF for ≥8-12 months vs. <8-12 months and are shown in Figure 10. Data could not be pooled due to extreme statistical heterogeneity (I^2=93.1%). The overall risk of bias in the Oddy study was assessed as low and that of Dell unclear.

Figure 10 Total breastfeeding for ≥8-12 months vs. <8-12 months and risk of wheeze in children aged 0-4 years

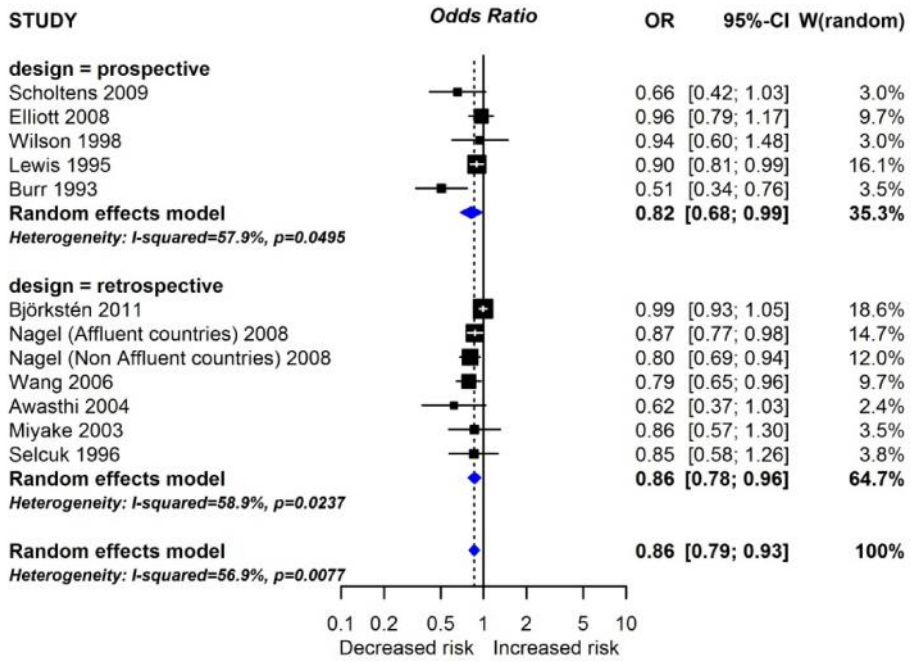


1.2.2 Age at outcome measurement 5-14

1.2.2.1 Ever vs. never

Figure 11 illustrates the pooled OR from 12 studies for risk of wheeze in children aged 5-14 years who ever initiated TBF vs. those who never did, suggesting an association between ever BF and reduced risk of wheeze. The statistical heterogeneity between studies was high (I^2=56.9%). Five studies were prospective cohorts, two of which had an overall low risk of bias, one had an unclear risk of bias due to unclear selection method, and two had unadjusted estimates (Wilson and Lewis), which carried a high risk of confounding. There were 7 case-control studies, five of which were considered to have a low or unclear overall risk of bias, whilst the studies of Nagel (affluent and non-affluent countries) and Miyake were considered to have a high risk of bias due to the selection of participants.

Figure 11 Total breastfeeding ever vs. never and risk of wheeze in children aged 5-14 year

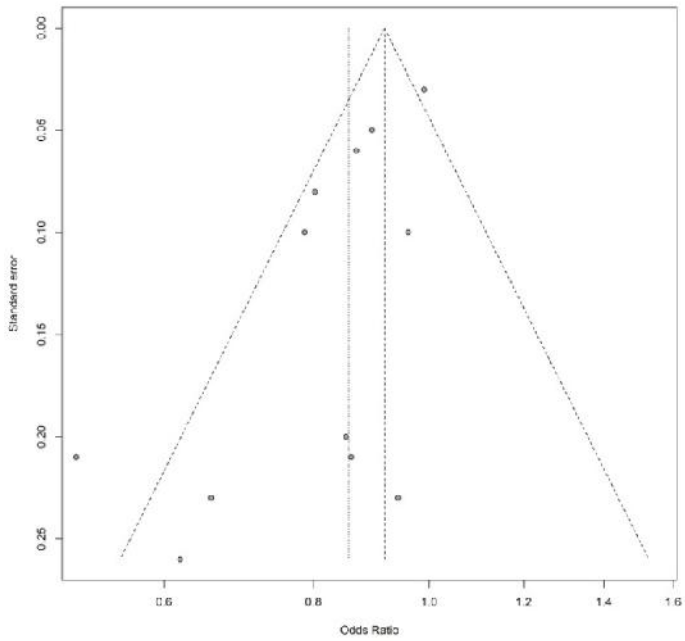


A Funnel plot to explore publication bias is shown in Figure 12. The plot is not symmetrical, and the Egger's test for asymmetry reaches statistical significance suggesting evidence of publication bias.

Subgroup and stratified analyses (Table 4) did not show clear subgroup differences, other than a difference for risk of disease based on one study (Burr 1993); and findings were similar in adjusted and unadjusted analyses.

Dose response analysis (Figure 13-Figure 15) did not show evidence of a dose response effect of increasing durations of TBF compared with never TBF on risk of wheeze.

Figure 12 Risk of publication bias in studies investigating breastfeeding ever vs. never and risk of wheeze in children aged 5-14 years



Egger's test p-value = 0.007

Table 4 Subgroup Analysis of risk of wheeze and total breastfeeding never vs. ever in children aged 5-14 years

	Number of studies	OR [95% CI]	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted value used)	12	0.86 [0.79; 0.93]	56.9	
Adjusted	10	0.88 [0.82; 0.95]	48.3	Not tested
Unadjusted	9	0.84 [0.77; 0.91]	33.9	
Study Design – Prospective	5	0.82 [0.69; 0.99]	57.9	0.65
Study Design – Retrospective	7	0.86 [0.78; 0.96]	58.9	
Risk of disease – High	1	0.51 [0.34; 0.77]	--	0.01
Risk of disease – Normal	11	0.88 [0.82; 0.95]	42.6	
Risk of bias – Low	4	0.76 [0.55; 1.05]	77.5	0.43
Risk of bias – High/Unclear	8	0.87 [0.82; 0.92]	0.0	

Figure 13 Total breastfeeding (dose response) short vs. never and risk of wheeze in children aged 5-14 years

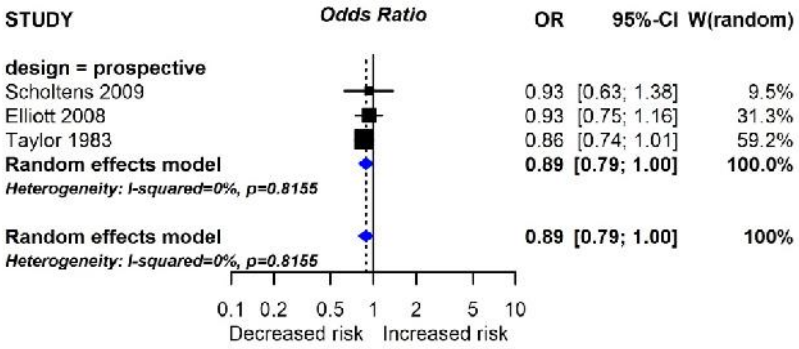


Figure 14 Total breastfeeding (dose response) medium vs. never and risk of wheeze in children aged 5-14years

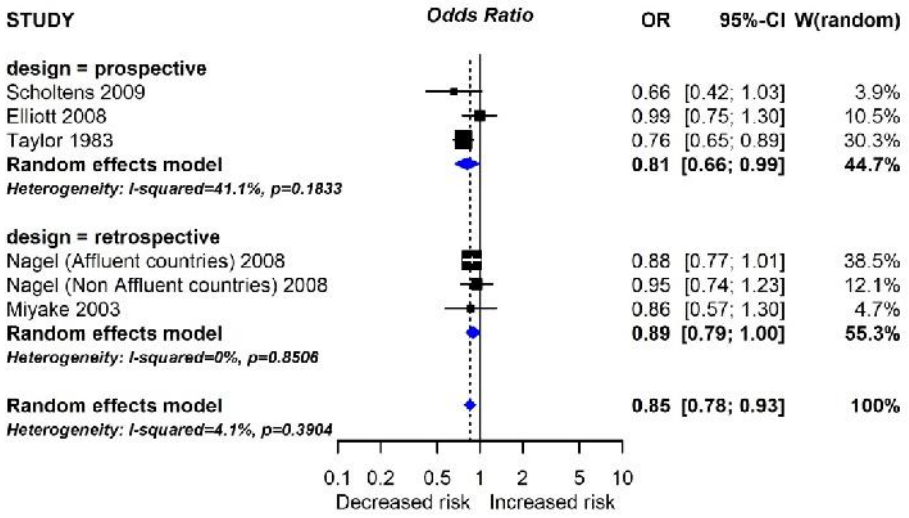
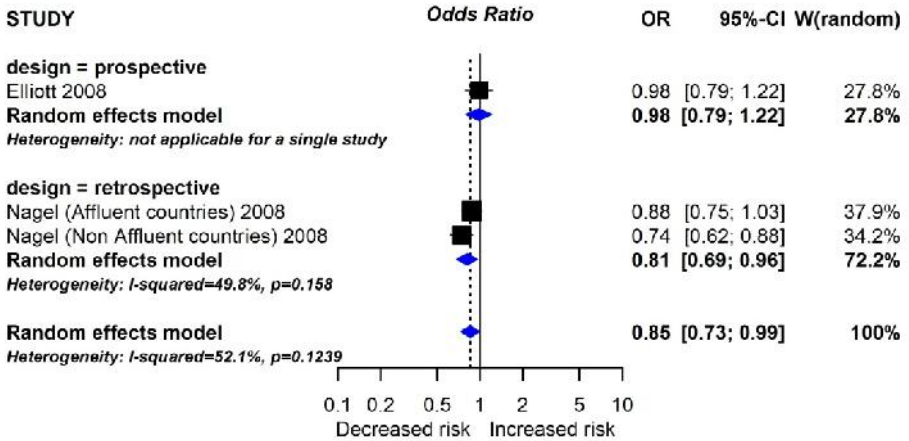


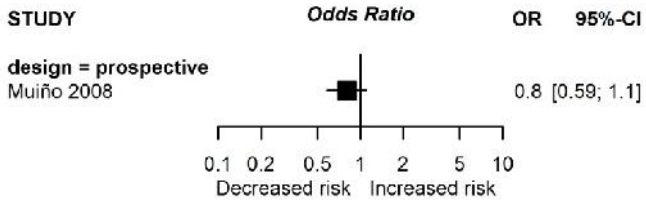
Figure 15 Total breastfeeding (dose response) long vs. never and risk of wheeze in children aged 5-14 years



1.2.2.2 1-2 Months

A cohort study of 897 infants born in Brazil showed no evidence of association between TBF for ≥1-2 months vs. <1-2 months in children aged 5-14 year (Figure 16). The study had an overall high risk of bias due to not controlling for relevant potential confounders.

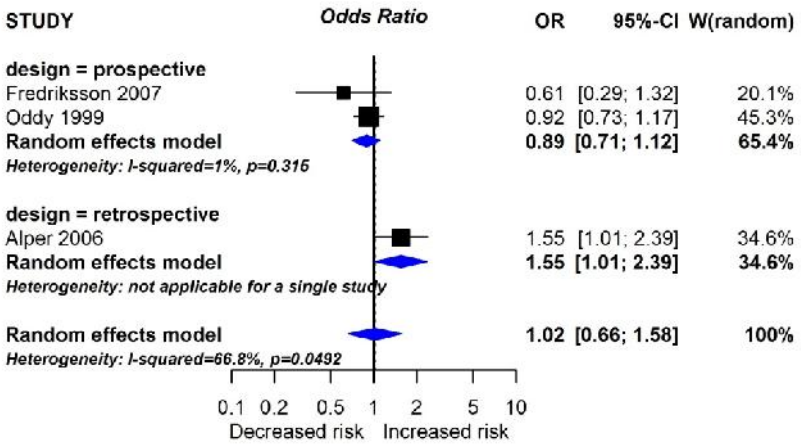
Figure 16 Total breastfeeding for ≥1-2 months vs. <1-2 months and risk of wheeze in children aged 5-14 years



1.2.2.3 3-4 Months

Two prospective cohort studies and one case-control study had eligible data to calculate a combined OR of wheeze in infants who had TBF for ≥3-4 months vs. <3-4 months at age 5-14 years, showing no clear evidence of an effect (Figure 17). There was high statistical heterogeneity between studies (I^2=66.8%). Two studies had an unclear risk of bias and the study of Oddy had a low risk of bias.

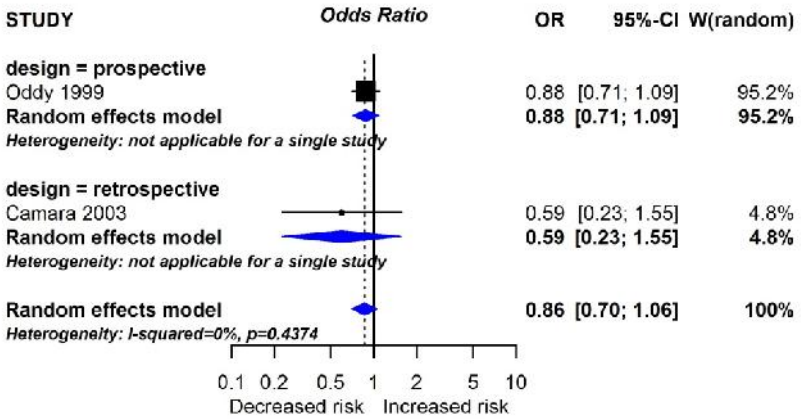
Figure 17 Total breastfeeding for ≥3-4 months vs. <3-4 months and risk of wheeze in children aged 5-14 years



1.2.2.4 5-7 Months

A case-control study and a prospective cohort had data eligible for meta-analysis, and their combined effect showed no evidence of association between TBF ≥5-7 months vs. <5-7 months and risk of wheeze in children aged 5-14 years (Figure 18). The study of Camara had a high risk of overall bias as it provided unadjusted data. There was no heterogeneity between studies (I^2=0.0%).

Figure 18 Total breastfeeding for ≥5-7 months vs. <5-7 months and risk of wheeze in children aged 5-14 years

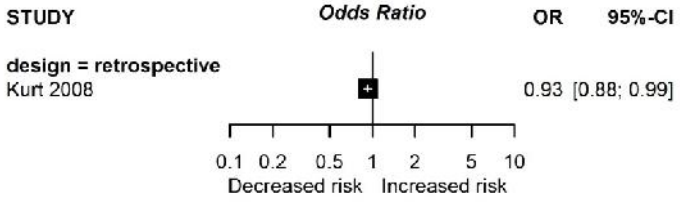


1.2.3 Age at outcome measurement 15+

1.2.3.1 Ever vs. never

One case-control study reported risk of wheeze at age 15 or beyond in infants who received any TBF compared to those who never did. The data are adjusted, the study had a low overall risk of bias, and they show a reduced risk of wheeze (Figure 19).

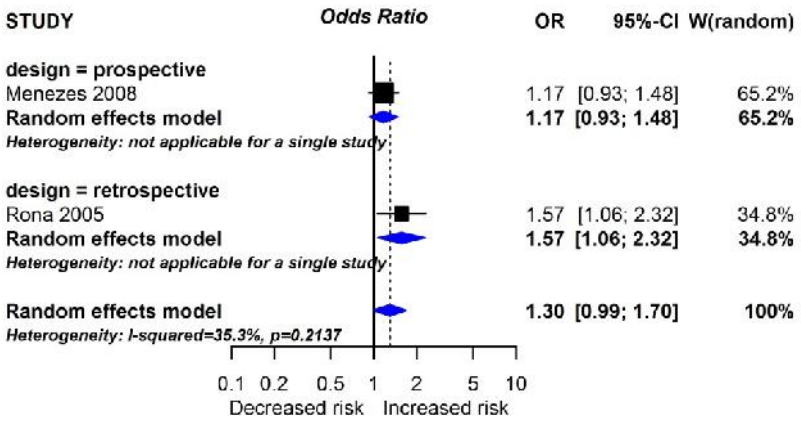
Figure 19 Total breastfeeding ever vs. never and risk of wheeze in children aged 15+ years



1.2.3.2 1-2 Months

Figure 20 illustrates the combined effect of two eligible studies, a retrospective and a prospective cohort, showing no clear evidence of an association with risk of wheeze in children at age 15 or beyond who received TBF for ≥1-2 months vs. <1-2 months. The studies had moderate statistical heterogeneity between them (I^2=35.3%) and had low or unclear overall risk of bias.

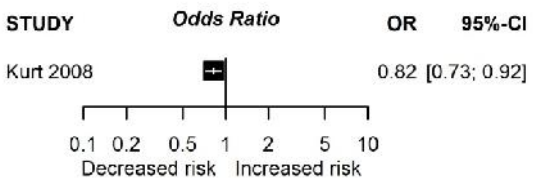
Figure 20 Total breastfeeding for ≥1-2 months vs. <1-2 months and risk of wheeze in children aged 15+ years



1.2.3.3 3-4 Months

One cross-sectional study reported the risk of wheeze at age 15 or beyond, in infants who had TBF for ≥3-4 months vs. <3-4 months, showing significantly reduced odds of wheeze with longer TBF (Figure 21). The study had a low overall risk of bias.

Figure 21 Total breastfeeding for ≥3-4 months vs. <3-4 months and risk of wheeze in children aged 15+ years



1.3 Total Breastfeeding and atopic wheeze

1.3.1 Age at outcome measurement 5-14

One study reported atopic wheeze at age 5-14 in relation to TBF. The findings are shown in Figure 22, and show no association. It was also possible to assess does response using this study, and there was no evidence of a dose-response relationship (Figure 23-Figure 24).

Figure 22 Total breastfeeding (dose response) ever vs. never and risk of atopic wheeze in children aged 5-14 years

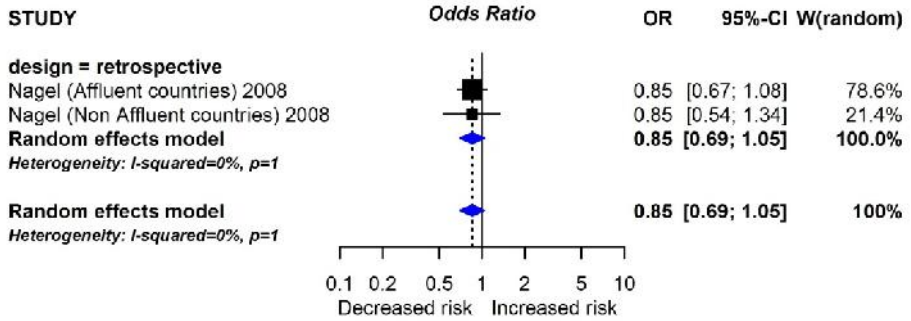


Figure 23 Total breastfeeding (dose response) medium vs. never and risk of atopic wheeze in children aged 5-14 years

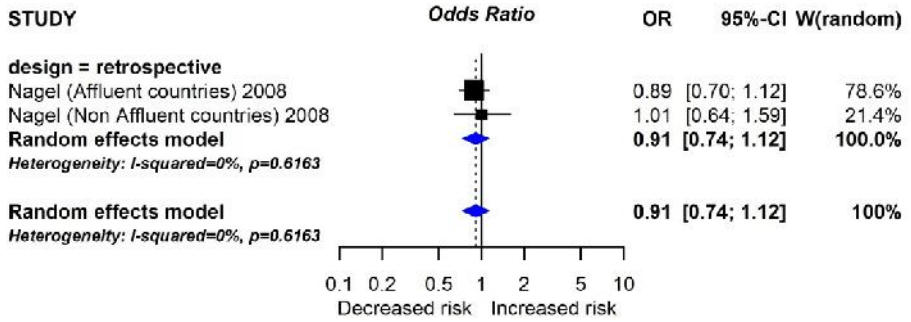
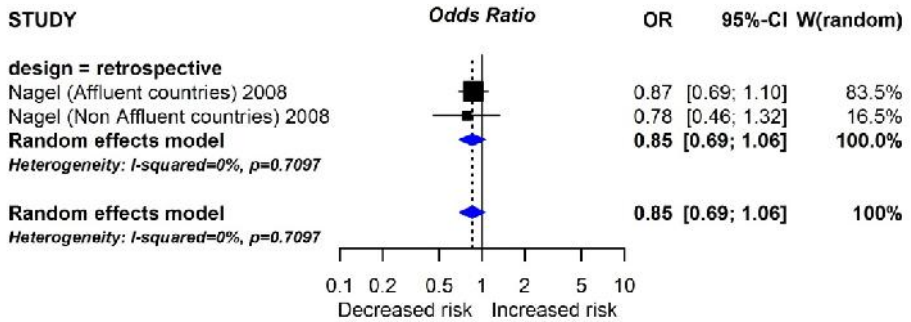


Figure 24 Total breastfeeding (dose response) long vs. never and risk of atopic wheeze in children aged 5-14 years

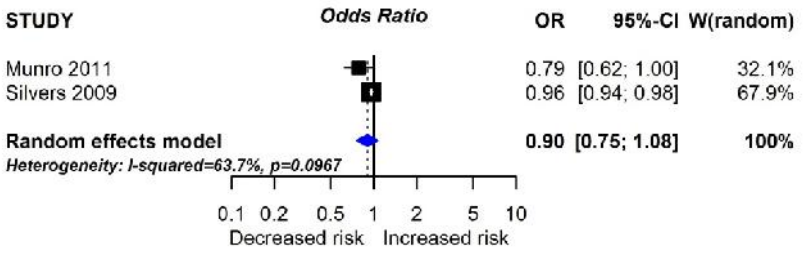


1.4 Total Breastfeeding per month and Wheeze

1.4.1 Age at outcome measurement 5-14

Two studies reported data for TBF exposure per month and risk of wheeze at age 5-14, and are shown in Figure 25. They show no significant association, with high statistical heterogeneity. Both studies are prospective cohort studies in a normal risk population, with the study of Silvers having a low risk of bias in all domains, whilst the study of Munro carried an unclear risk due to unclear selection bias, which may contribute to explain the high heterogeneity between studies.

Figure 25 Total breastfeeding per month and risk of wheeze in children aged 5-14 years



1.5 Total Breastfeeding and Recurrent Wheeze

1.5.1 Age at outcome measurement 0-4

1.5.1.1 Ever vs. never

Eleven observational studies had data that could be used to calculate combined OR of risk of recurrent wheeze in children 0-4 years old who were exposed to ever vs. never TBF, showing a negative association between this exposure and risk of wheeze. There were 9 prospective cohorts and 2 case-control studies. The study of Businco had a high overall risk of bias due to lack of adjustment for relevant potential confounders. The two case-control studies had unclear risk of bias, three prospective cohorts had unclear risk of bias, and 5 had a low risk of overall bias. These differences in overall risk might partly explain the very high heterogeneity observed between studies (I^2=80.7%). For this reason data were not pooled in meta-analysis

(Figure 26). There was no visual or statistical evidence of publication bias as illustrated in Figure 27. The subgroup analysis showed no difference between the various groups compared, with extreme heterogeneity in most analyses (Table 5). Dose response analysis (Figure 28-Figure 30) showed some evidence of a dose response, although only a small proportion of studies could be included in dose response analysis due to available data.

Figure 26 Total breastfeeding ever vs. never and risk of recurrent wheeze in children aged 0-4 years

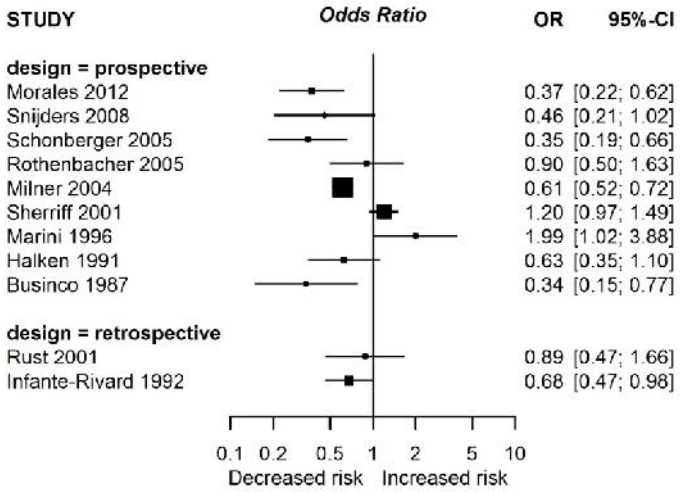
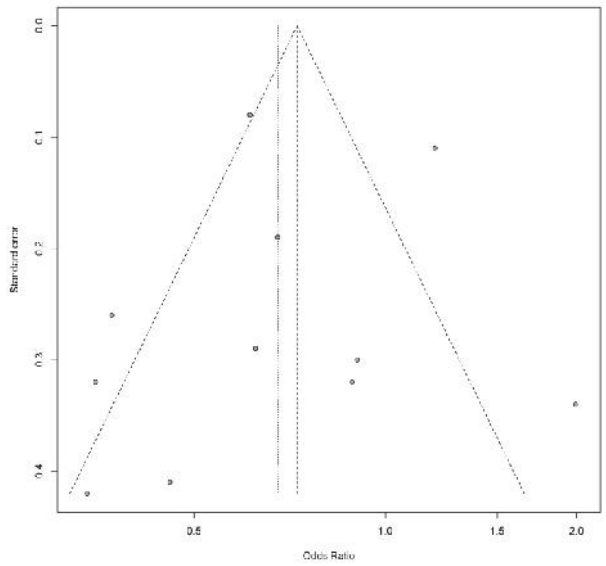


Figure 27 Risk of publication bias in studies investigating total breastfeeding ever vs. never and risk of recurrent wheeze in children aged 0-4 years



Egger's test p-value = 0.663

Table 5 Subgroup Analysis of risk of recurrent wheeze and total breastfeeding ever vs. never (or ever) months in children aged 0-4 years

	Number of studies	OR [95% CI]	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted value used)	11	0.68 [0.51; 0.91]	80.7	
Adjusted	7	0.78 [0.53; 1.15]	78.0	Not tested
Unadjusted	9	0.63 [0.50; 0.79]	77.1	
Study Design – Prospective	9	0.66 [0.46; 0.94]	84.4	0.68
Study Design – Retrospective	2	0.73 [0.53; 1.00]	0.0	
Risk of disease – High	3	0.62 [0.19; 2.03]	88.2	0.86
Risk of disease – Normal	8	0.69 [0.52; 0.94]	79.6	
Risk of bias – Low	5	0.68 [0.41; 1.12]	79.4	0.96
Risk of bias – High/Unclear	6	0.67 [0.47; 0.96]	73.9	

Figure 28 Total breastfeeding short vs. never term and risk of recurrent wheeze in children aged 0-4 years

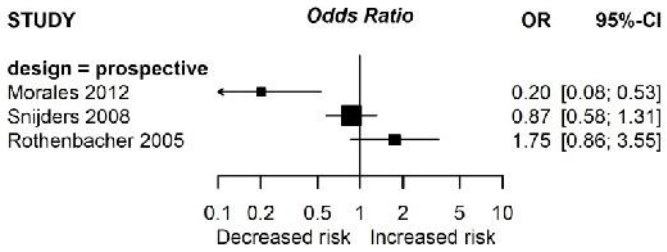


Figure 29 Total breastfeeding medium vs. never term and risk of recurrent wheeze in children aged 0-4 years

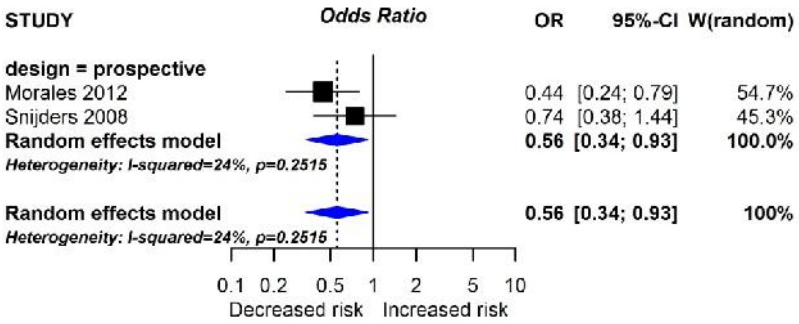
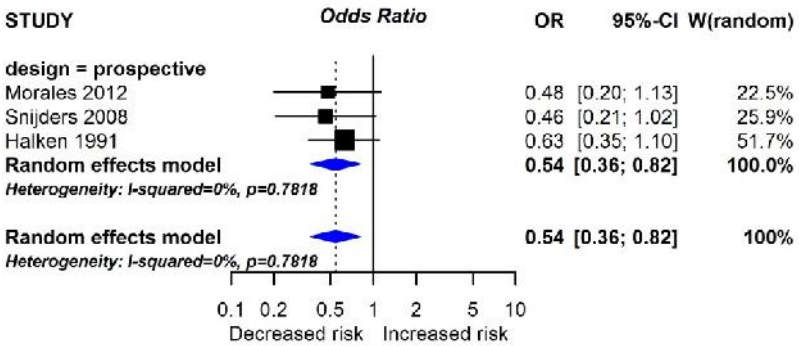


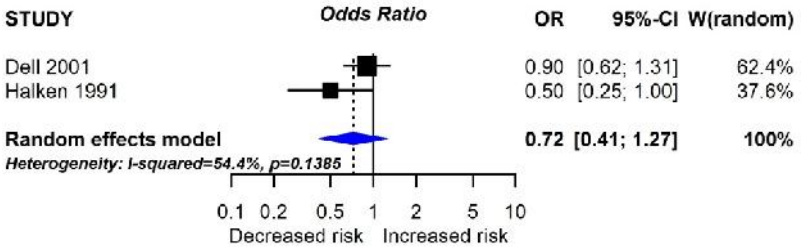
Figure 30Total breastfeeding long vs. never term and risk of recurrent wheeze in children aged 0-4 years



1.5.1.2 1-2 Months

Two prospective cohort studies had outcome data suitable for meta-analysis, showing no evidence of association between TBF for ≥1-2 months vs. <1-2 months and risk of recurrent wheeze in children aged 0-4 years. The study of Halken had an overall low risk of bias whilst the study of Dell had an unclear overall risk bias. There was evidence of high heterogeneity between the studies (I^2=54.4%)

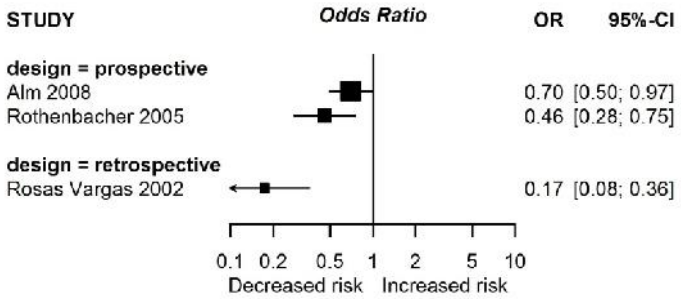
Figure 31 Total breastfeeding for ≥1-2 months vs. <1-2 months and risk of recurrent wheeze in children aged 0-4 years



1.5.1.3 3-4 Months

Three observational studies had data eligible for meta-analysis, however they could not be pooled due to extreme heterogeneity (Figure 32). The studies of Alm and Rothenbacher were prospective cohorts and one (Rosas-Vargas) was a case-control study. The latter had a high risk of overall bias due to lack of adjustment for potential confounders. The other two studies had a low overall risk of bias.

Figure 32 Total breastfeeding for ≥3-4 months vs. <3-4 months and risk of recurrent wheeze in children aged 0-4 years



1.5.1.4 5-7 Months

Three prospective cohort studies (Miyake, Kull, Gustaffson) and three case-control studies (Visser, Tanaka, Dell) reported data that could be pooled to calculate the OR for wheeze in children aged 0-4 years who were exposed to TBF for ≥5-7 months vs. <5-7 months. As shown in Figure 33, their combined effect suggests no difference in risk of wheeze (OR 0.79; 95% CI 0.61, 1.04), with moderate heterogeneity between studies (I^2=39.7%). In subgroup and stratified analyses (Table 6), there was evidence for a relationship between TBF ≥5-7 months and reduced risk of recurrent wheeze at age 0-4 in prospective studies, and studies reporting adjusted data and low risk of bias, but not in retrospective or unadjusted studies or studies at high/unclear risk of bias.

Figure 33 Total breastfeeding for ≥5-7 months vs. <5-7 months and risk of recurrent wheeze in children aged 0-4 years

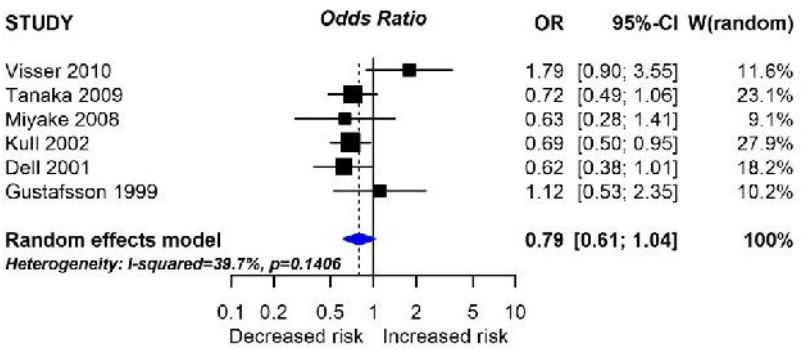


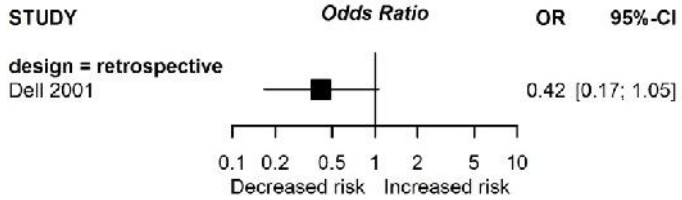
Table 6 Subgroup Analysis of risk of recurrent wheeze and total breastfeeding ≥5-7 months vs. <5-7 months in children aged 0-4 years

	Number of studies	OR [95% CI]	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted value used)	6	0.79 [0.61; 1.04]	39.7	
Adjusted	4	0.68 [0.55; 0.84]	0.0	Not tesed
Unadjusted	5	0.80 [0.56; 1.16]	60.6	
Study Design – Prospective	3	0.73 [0.56; 0.96]	0.0	0.56
Study Design – Retrospective	3	0.87 [0.51; 1.49]	69.7	
Risk of disease – High	-	-	-	-
Risk of disease – Normal	6	0.79 [0.61; 1.04]	39.7	
Risk of bias – Low	1	0.69 [0.51; 0.95]	--	0.39
Risk of bias – High/Unclear	5	0.85 [0.59; 1.23]	48.1	

1.5.1.5 8-12 Months

One case-control study reported risk of recurrent wheeze in children breastfeed ≥8-12 months vs. <8-12 months. The study had an overall unclear risk of bias and suggested no significant difference in OR of disease (Figure 34).

Figure 34 Total breastfeeding for ≥8-12 months vs. <8-12 months and risk of recurrent wheeze in children aged 0-4 years



Subgroup analyses to investigate differences in risk of recurrent wheeze and TBF ≥5-7 months vs. <5-7 months in children aged 0-4 years, showed no statistically significant differences (Table 7).

1.5.2 Age at outcome measurement 5-14

1.5.2.1 Risk of recurrent wheeze at age 5-14, in relation to TBF Ever vs. never

Twenty five observational studies reported the association between recurrent wheeze at age 5-14 and TBF ever vs. never. Most studies reported ORs below 1, with an overall effect size suggestive of a negative association between TBF and disease (OR 0.88; 95% CI 0.82, 0.94) and moderate heterogeneity across studies (I^2=36.5%) (Figure 35). Thirteen studies were prospective cohorts (9 of which had a low overall risk of bias, 3 had high risk, and 1 unclear), 1 retrospective cohort study (with a high overall risk of bias due to confounding not being accounted for in the analyses), 4 case-control studies (of which 3 had a high overall risk of bias and one had an unclear overall risk of bias), 1 nested case-control study (with high risk of bias due to selection bias), and six cross-sectional studies (of which 3 were considered to have a high overall risk of bias mainly due to selection or confounding bias, 2 had an unclear risk of bias and 1 study had a low risk of bias). A funnel plot was used to examine the likelihood of publication bias (Figure 36), which showed significant asymmetry, confirmed

by a statistically significant Egger's test P=0.01. Dose response analysis (Figure 37-Figure 39) suggests an association between increasing duration of TBF and greater protection against recurrent wheeze at age 5-14.

Figure 35 Total Breastfeeding ever vs. never and risk of recurrent wheeze in children aged 5-14 years

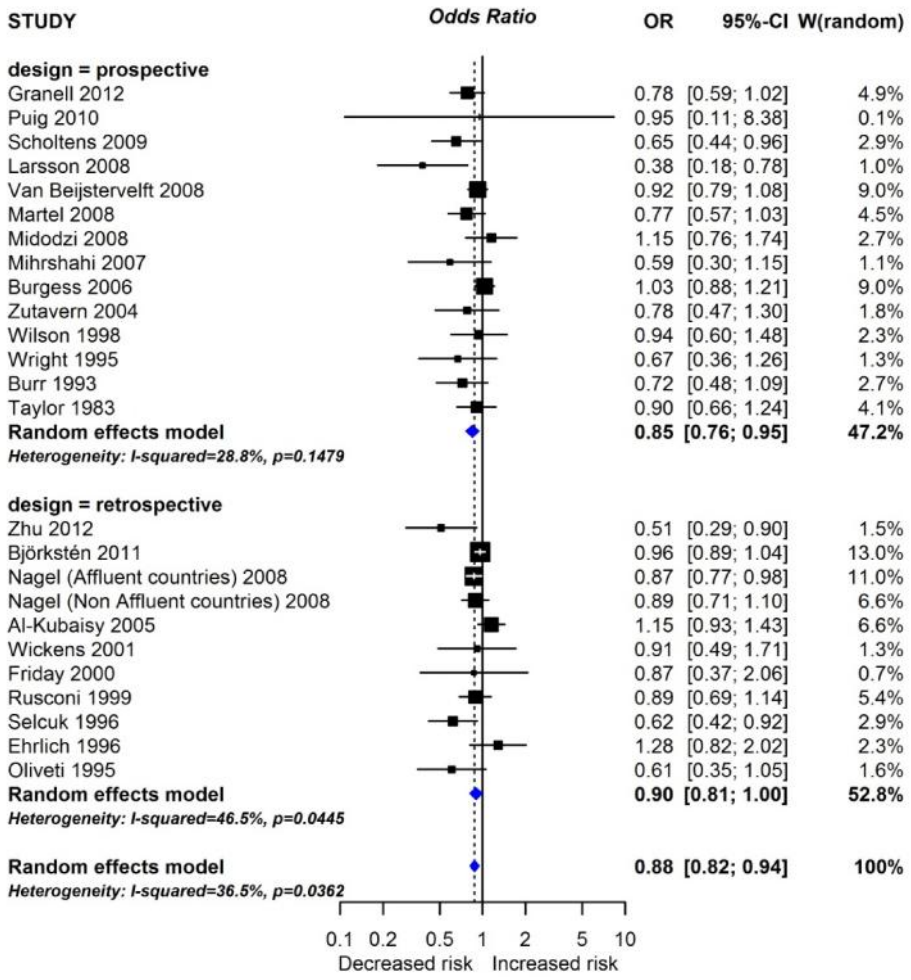
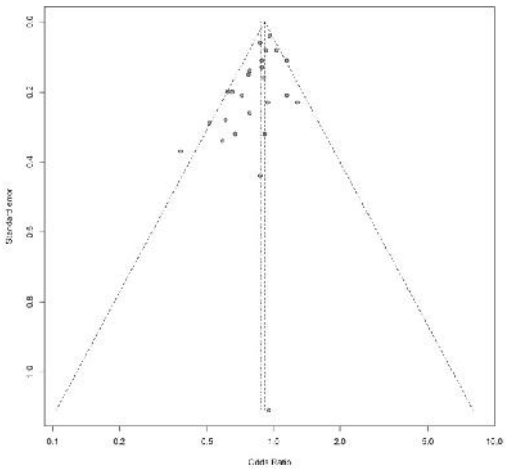


Figure 36 Risk of publication bias in studies investigating total breastfeeding ever vs. never and risk of recurrent wheeze in children aged 5-14 years



Egger's test p-value = 0.012

Table 7 Subgroup Analysis of risk of recurrent wheeze and total breastfeeding ever vs. never months in children aged 5-14 years

	Number of studies	OR [95% CI]	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted value used)	25	0.88 [0.82; 0.95]	36.5	
Adjusted	15	0.82 [0.74; 0.91]	44.9	Not tested
Unadjusted	22	0.83 [0.75; 0.91]	57.4	
Study Design – Prospective	14	0.85 [0.76; 0.95]	28.8	0.44
Study Design – Retrospective	11	0.90 [0.81; 1.00]	46.5	
Risk of disease – High	3	0.70 [0.51; 0.97]	0.0	0.18
Risk of disease – Normal	22	0.89 [0.82; 0.96]	39.7	
Risk of bias – Low	10	0.80 [0.68; 0.93]	55.9	0.16
Risk of bias – High/Unclear	15	0.90 [0.83; 0.98]	18.7	

Figure 37 Total breastfeeding (dose response) short vs. never term and risk of recurrent wheeze in children aged 5-14 years

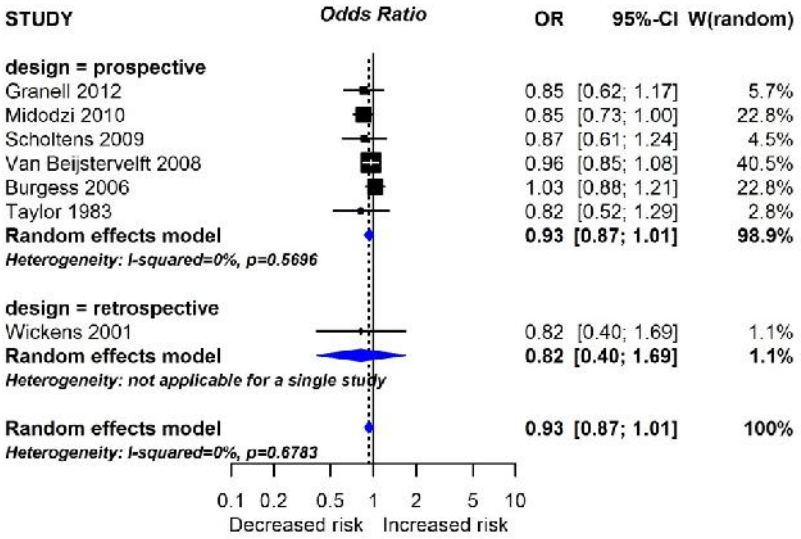


Figure 38 Total breastfeeding (dose response) medium vs. never term and risk of recurrent wheeze in children aged 5-14 years

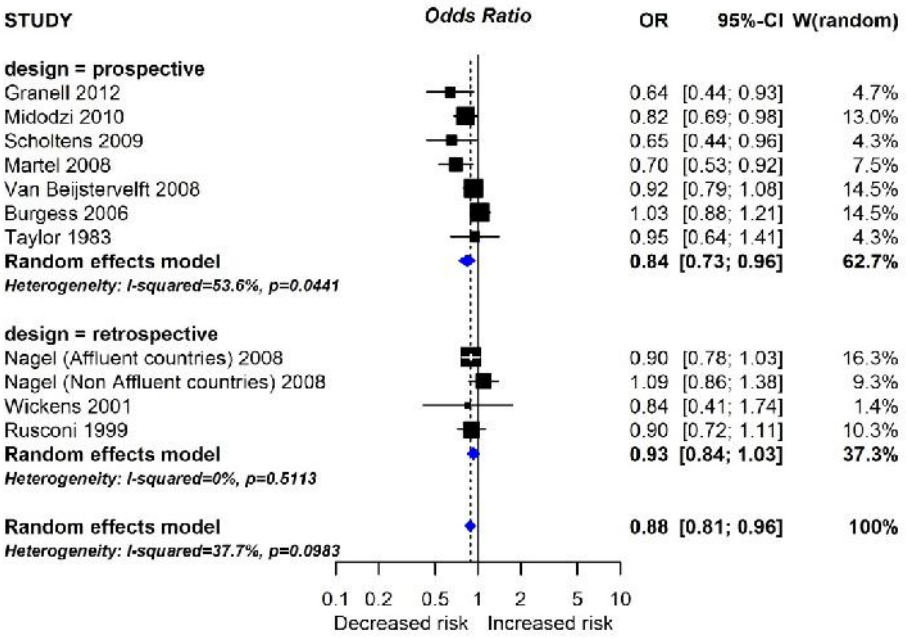
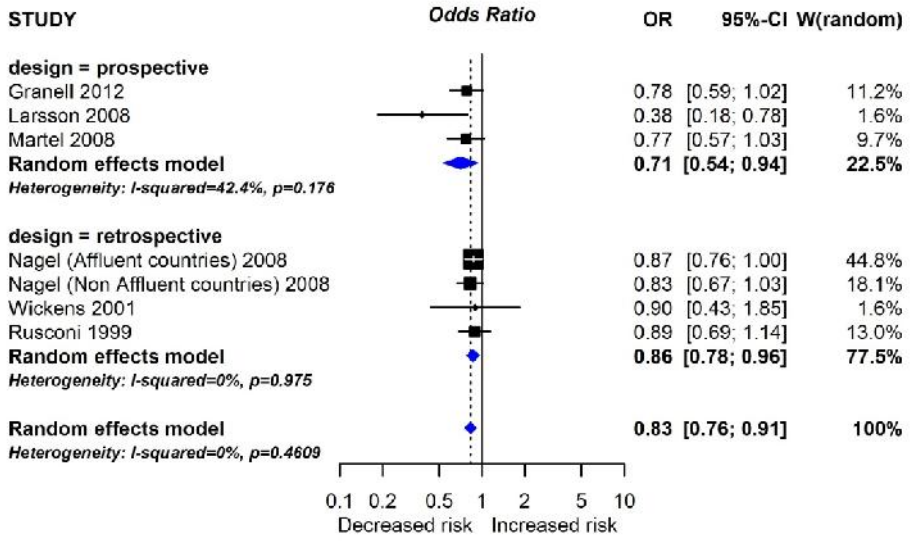


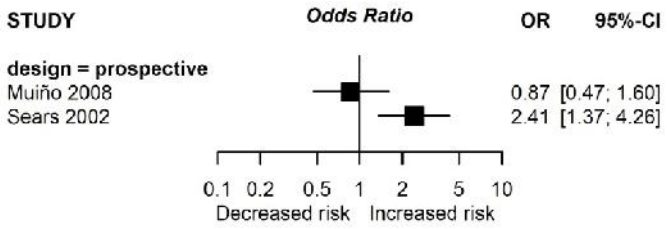
Figure 39 Total breastfeeding (dose response) long vs. never term and risk of recurrent wheeze in children aged 5-14 years



1.5.2.2 1-2 Months

Two observational studies reported risk of recurrent wheeze in infants with TBF for ≥1-2 months vs. <1-2 months, and could not be pooled due to extreme heterogeneity (I^2>80%). The study of Muino had an overall high risk of bias due to lack of adjustment for potential confounders, whilst the study of Sears reported adjusted data and had an unclear overall risk of bias (Figure 40).

Figure 40 Total breastfeeding for ≥1-2 months vs. <1-2 months and risk of recurrent wheeze in children aged 5-14 years



1.5.2.3 3-4 Months

Figure 41 shows the pooled OR from ten observational studies that reported risk of recurrent wheeze at age 5-14 in infants who had TBF for ≥3-4 months vs. <3-4 months, showing a statistically significant association with reduced risk of wheeze (OR 0.76; 95% CI 0.67, 0.87), and moderate heterogeneity across studies (I^2=33.7%). Six studies were prospective cohorts (4 of which had a low overall risk of bias, 1 had a high risk of bias due to lack of adjustment for potential confounders, and 1 had an unclear overall risk of bias), 2 were retrospective cohorts (1 with a high risk of bias due to lack of adjustment for confounders and 1 was considered to carry a low overall risk of bias), 1 nested case-control study (with unclear overall risk of bias) and one cross-sectional (with unclear overall risk of bias). Egger's test showed that there was statistical evidence of publication bias (P=0.01) (

Figure 42). Subgroup and stratified analyses (Table 8) did not show important group differences, and findings were similar in adjusted and unadjusted analyses.

Figure 41 Total breastfeeding for ≥3-4 months vs. <3-4 months and risk of recurrent wheeze in children aged 5-14 years

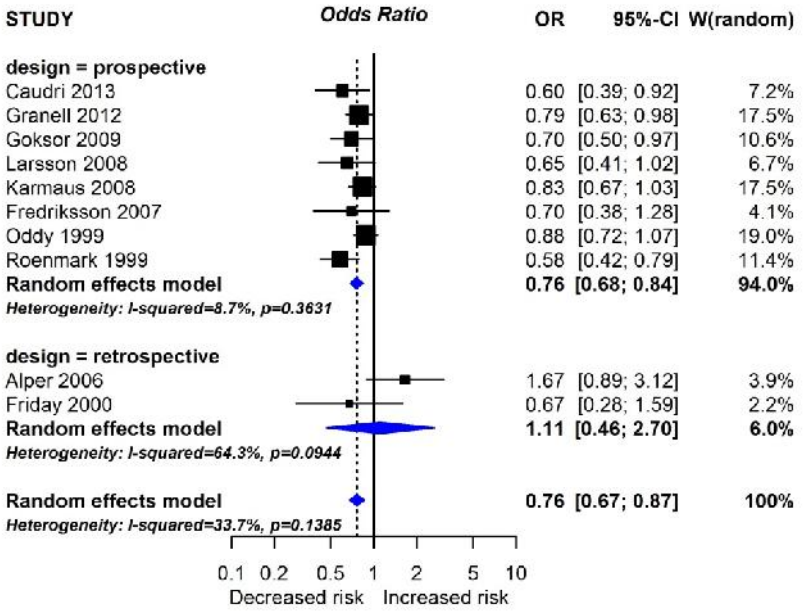
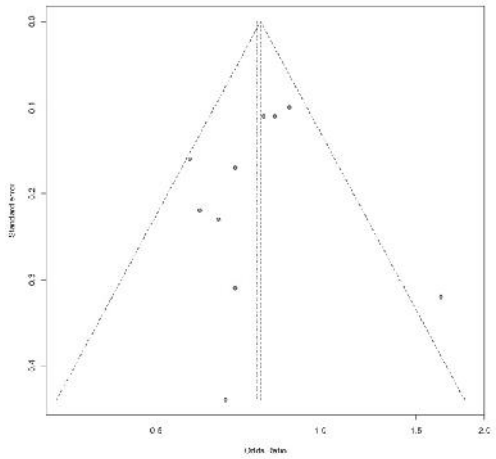


Figure 42 Risk of publication bias in studies investigating total breast feeding and recurrent wheeze ≥3-4 months vs. <3-4 months in children aged 5-14 years



Egger's test p-value = 0.012

Table 8 Subgroup Analysis of risk of recurrent wheeze and total breastfeeding ≥3-4 months vs. <3-4 months in children aged 5-14 years

	Number of studies	OR [95% CI]	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted value used)	10	0.76 [0.67; 0.87]	33.7	
Adjusted	5	0.74 [0.56; 0.96]	48.0	Not tested
Unadjusted	7	0.67 [0.58; 0.77]	0.0	
Study Design – Prospective	8	0.76 [0.68; 0.84]	8.7	0.40
Study Design – Retrospective	2	1.11 [0.46; 2.70]	64.3	
Risk of disease – High	1	0.67 [0.28; 1.59]	--	0.77
Risk of disease – Normal	9	0.76 [0.67; 0.88]	40.5	
Risk of bias – Low	5	0.80 [0.72; 0.90]	0.0	0.74
Risk of bias – High/Unclear	5	0.76 [0.55; 1.05]	54.6	

1.5.2.4 5-7 Months

Nine observational studies reported the risk of recurrent wheeze in infants who had TBF for ≥5-7 months vs. <5-7 months that was eligible to calculate the overall OR (Figure 43), showing a reduced overall risk of disease (OR 0.76; 95% CI 0.62, 0.92). There was no evidence of heterogeneity across studies (I^2=0.0%). Four studies were prospective cohorts (of which 1 had a high overall risk of bias mainly due to selection bias, 1 had unclear risk of bias, and 2 had a low overall risk of bias), 1 retrospective cohort (carrying a high risk of overall bias due to lack of adjustment for potential confounders), 2 case-control (one of which lacked adjustment for potential confounders, therefore it carries a high risk of bias, and the other had unclear risk of bias) and 2 cross-sectional studies (both of which did not include adjustment for potential confounders, therefore carrying a high overall risk of bias). Funnel plot showed some asymmetry, but Egger's test did not confirm any clear evidence of publication bias (Figure 44). Subgroup and stratified analyses (Table 9) did not show important group differences, and findings were similar in adjusted and unadjusted analyses.

Figure 43 Total breastfeeding for ≥5-7 months vs. <5-7 months and risk of recurrent wheeze in children aged 5-14 years

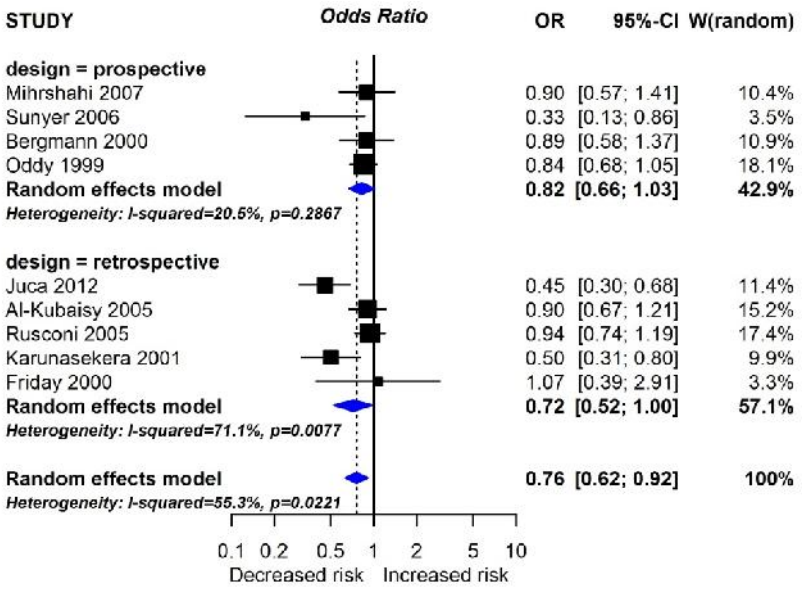
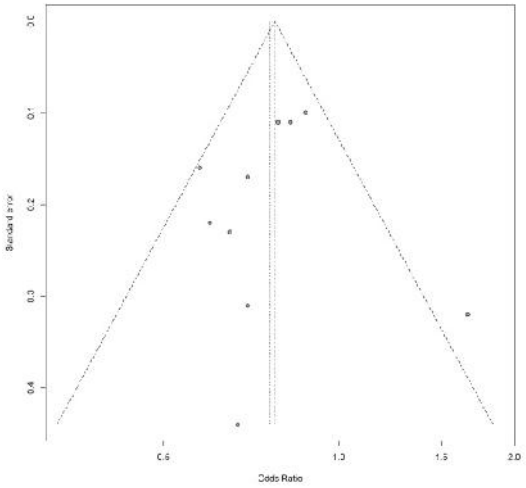


Figure 44 Risk of publication bias in studies investigating total breast feeding and recurrent wheeze ≥5-7 months vs. <5-7 months in children aged 5-14 years



Egger's test p-value = 0.637

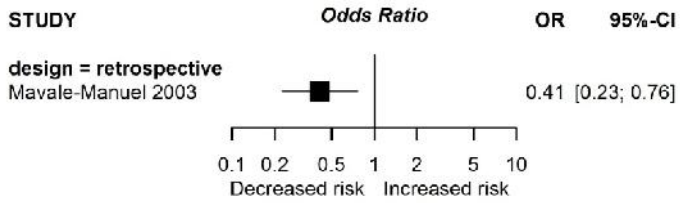
Table 9 Subgroup Analysis of risk of recurrent wheeze and total breastfeeding ≥5-7 months vs. <5-7 months in children aged 5-14 years

	Number of studies	OR [95% CI]	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted value used)	9	0.76 [0.62; 0.92]	55.3	
Adjusted	5	0.74 [0.56; 0.96]	48.0	Not tested
Unadjusted	6	0.72 [0.54; 0.97]	71.1	
Study Design – Prospective	4	0.82 [0.66; 1.03]	20.5	0.50
Study Design – Retrospective	5	0.72 [0.52; 1.00]	71.1	
Risk of disease – High	2	0.92 [0.61; 1.39]	0.0	0.32
Risk of disease – Normal	7	0.73 [0.58; 0.91]	65.3	
Risk of bias – Low	3	0.78 [0.55; 1.10]	45.6	0.87
Risk of bias – High/Unclear	6	0.75 [0.57; 0.98]	64.6	

1.5.2.5 18+ Months

One case-control study reported the risk of recurrent wheeze in children aged 5-14 years old if they were exposed to TBF for ≥18+ months vs. <18+ months, showing no indication of effect (Figure 45). The study did not adjust for potential confounders and therefore carried an overall high risk of bias.

Figure 45 Total breastfeeding for ≥18+ months vs. <18+ months and risk of recurrent wheeze in children aged 5-14 years



1.5.3 Age at outcome measurement 15+

1.5.3.1 Ever vs. never

Six observational studies reported risk of recurrent wheeze in children over 15 years old if they were exposed to any TBF, showing no indication of an effect (OR 0.99; 95% CI 0.89, 1.11) (Figure 46). Three studies were prospective cohorts, all of which had an overall high risk of bias due to selection bias or lack of adjustment for relevant potential confounders. The other three studies were of cross-sectional design, one of which had a high risk of overall bias (due to selection bias), and the other two had a low or unclear overall risk of bias. The presence of high risk of bias in these studies might partly explain the high heterogeneity observed across studies (I^2=73.2%). Subgroup and stratified analyses (Table 10) did not show important group differences, and findings were similar in adjusted and unadjusted analyses. There were insufficient data for meaningful dose response analysis for this comparison.

Figure 46 Total breastfeeding ever vs. never and risk of recurrent wheeze in children aged 15+ years

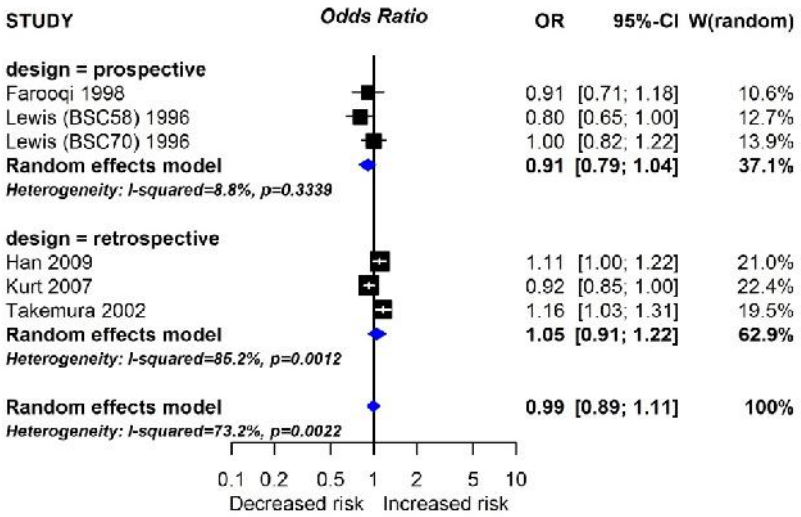


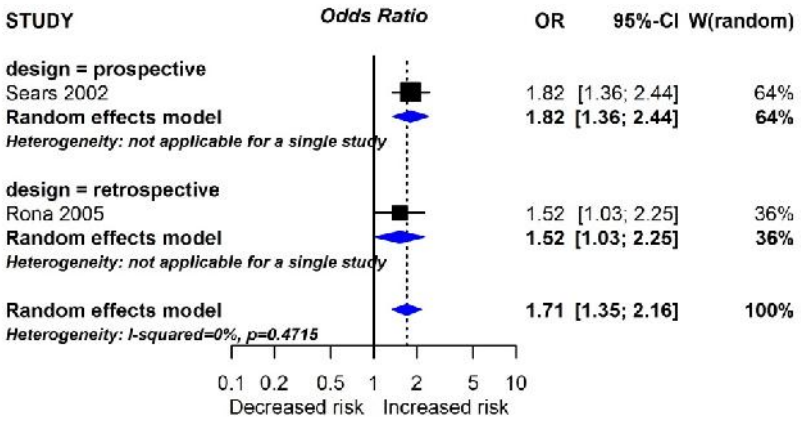
Table 10 Subgroup Analysis of risk of recurrent wheeze and total breastfeeding ever vs. never in children aged 15+ years

	Number of studies	OR [95% CI]	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted value used)	6	1.00 [0.89; 1.11]	73.2	
Adjusted	2	1.01 [0.85; 1.20]	87.3	Not tested
Unadjusted	5	1.01 [0.90; 1.14]	62.1	
Study Design – Prospective	3	0.91 [0.79; 1.04]	8.8	0.14
Study Design – Retrospective	3	1.05 [0.91; 1.22]	85.2	
Risk of disease – High	-	-	-	-
Risk of disease – Normal	6	1.00 [0.89; 1.11]	73.2	
Risk of bias – Low	1	0.92 [0.85; 1.00]	--	0.18
Risk of bias – High/Unclear	5	1.02 [0.90; 1.15]	63.8	
Clear definition of breastfeeding duration	4	0.92 [0.86; 0.99]	0.0	0.14
Unclear definition of breastfeeding duration	2	1.05 [0.91; 1.18]	68.6	

1.5.3.2 1-2 Months

Two retrospective cohort reported the risk of recurrent wheeze in infants exposed to TBF for ≥1-2 months vs. <1-2 months. In both studies, the data were adjusted, and the studies had an unclear overall risk of bias. Both studies showed an increased risk of recurrent wheeze in children aged 15 or more who received TBF for≥1-2 months vs. <1-2 months, and this was confirmed in their combined effect estimate (OR 1.71; 95% CI 1.35, 2.16). There was no heterogeneity between studies (Figure 47).

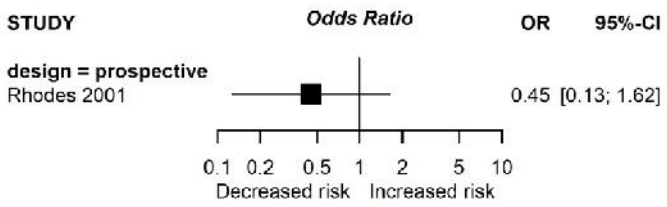
Figure 47 Total breastfeeding for ≥1-2 months vs. <1-2 months and risk of recurrent wheeze in children aged 15+ years



1.5.3.3 3-4 Months

One prospective cohort study reported OR for recurrent wheeze in infants breastfed for ≥3-4 months vs. <3-4 months, and is shown in Figure 48. The data are unadjusted and had a high risk of selection bias, and therefore carry a high overall risk of bias, and show no significant difference in OR for recurrent wheeze in relation to breastfeeding status.

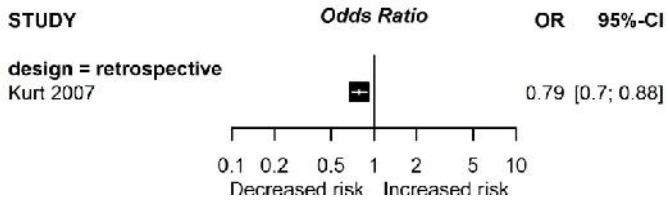
Figure 48 Total breastfeeding for ≥3-4 months vs. <3-4 months and risk of recurrent wheeze in children aged 15+ years



1.5.3.4 5-7 Months

One cross-sectional study reported OR for recurrent wheeze in infants breastfed for ≥5-7 months vs. <5-7 months, and is shown in Figure 49. The data are adjusted, and carry a low overall risk of bias, and show a statistically significant difference in the OR for recurrent wheeze in relation to breastfeeding status (OR 0.79; 95% CI 0.70, 0.88).

Figure 49 Total breastfeeding for ≥5-7 months vs. <5-7 months and risk of recurrent wheeze in children aged 15+ years



1.5.3.5 Total breastfeeding and bronchial hyper-responsiveness (BHR)

1.5.3.6 Age at outcome 5-14 years

1.5.3.7 Ever vs. never

Five observational studies reported ORs that could be pooled to assess the overall risk of BHR in children aged 5-14 years old if they were exposed to ever vs. never TBF. There was no suggestion of an association with BHR in the exposed group (Figure 50). Three studies were prospective cohorts and carry low or unclear overall risk of bias, and there were two cross-sectional studies with selection bias, and therefore carried an overall high risk of bias. Dose response analysis shows no evidence that prolonged TBF is associated with altered BHR (Figure 51-Figure 54).

Figure 50 Total Breastfeeding any duration vs. never and risk of bronchial hyper-responsiveness in children aged 5-14 years

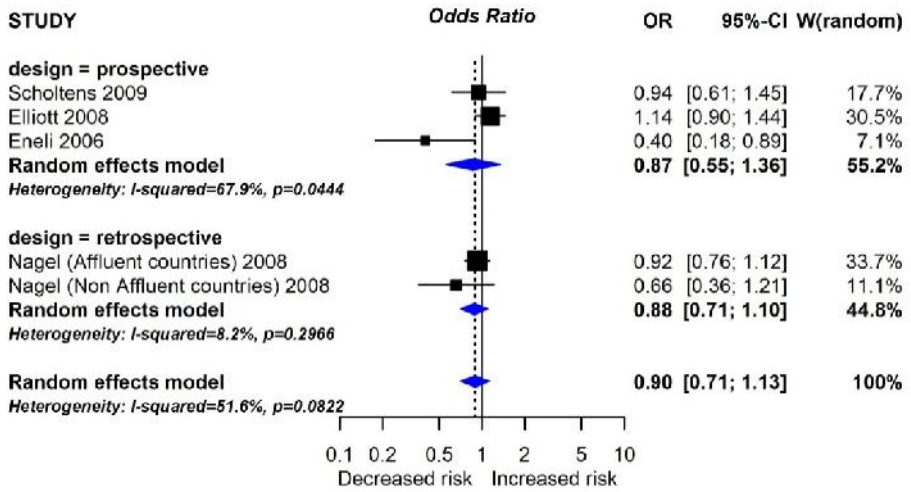


Figure 51 Total breastfeeding (dose response) never vs. ever and risk of bronchial hyper-responsiveness in children aged 5-14 years

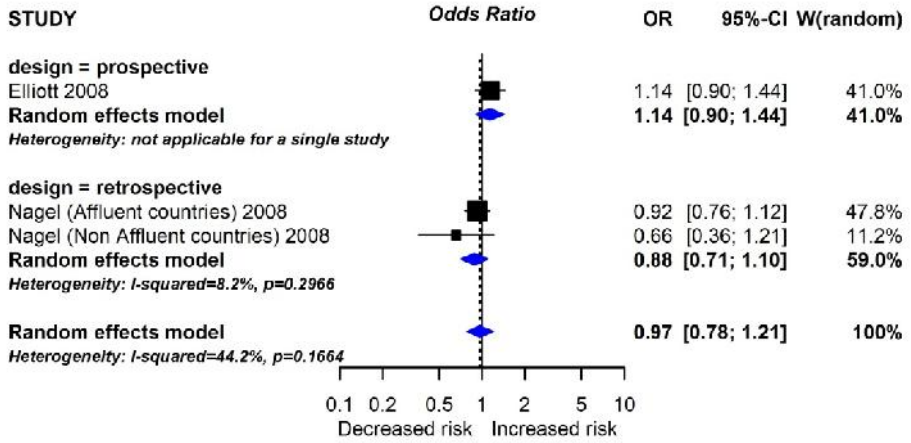


Figure 52 Total breastfeeding (dose response) short vs. never and risk of bronchial hyper-responsiveness in children aged 5-14 years

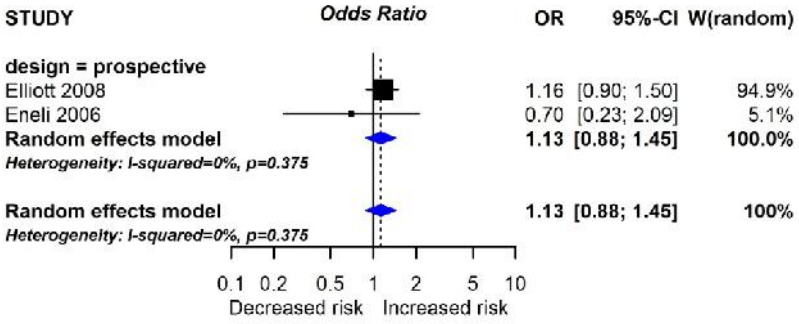


Figure 53 Total breastfeeding (dose response) medium vs. never and risk of bronchial hyper-responsiveness in children aged 5-14 years

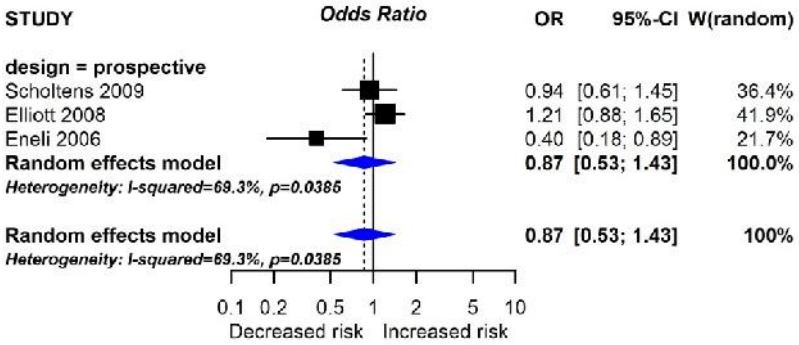
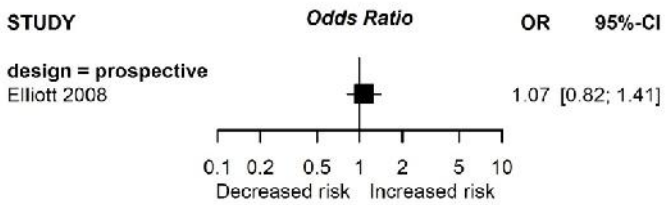


Figure 54 Total breastfeeding (dose response) long vs. never and risk of bronchial hyper-responsiveness in children aged 5-14 years

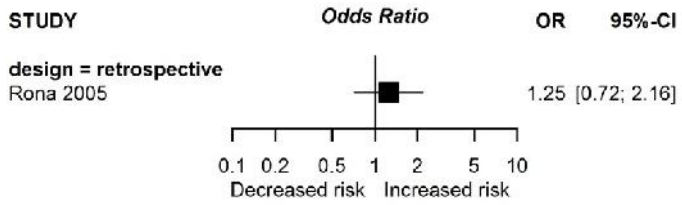


1.5.3.1 Age at outcome 15+ years

1.5.3.2 1-2 months

One retrospective cohort study reported risk of BHR in young adults according to their exposure to ≥1-2 months vs. <1-2 months of TBF (Figure 55). They show no suggestion of an association, and the study had unclear overall risk of bias.

Figure 55 Total Breastfeeding ≥1-2 months vs. <1-2 months and risk of bronchial hyper-responsiveness in children aged 15+ years

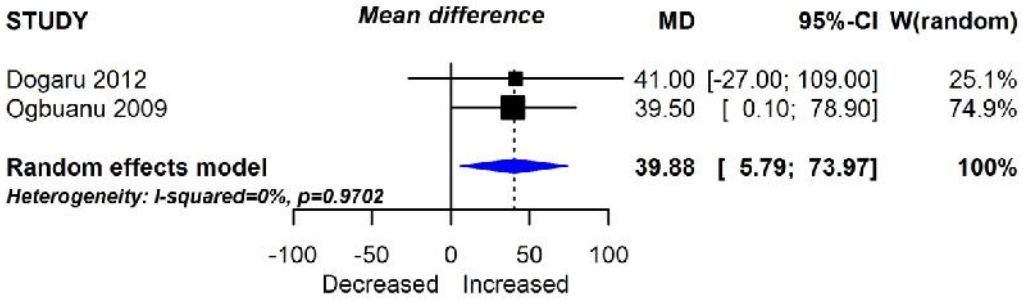


1.6 Data for TBF duration and lung function in children aged 5-14 years

1.6.1 Outcome: FEV1(ml)

Two prospective cohorts had results based on analysis with linear regression and adjusted mean differences: (1) Ogbuanu comparing breastfeeding never (reference) versus ≥ 4 months at 10 years of age; (2) Dogaru breastfeeding never (reference) versus ≥ 6 months at 12.2 years of age.

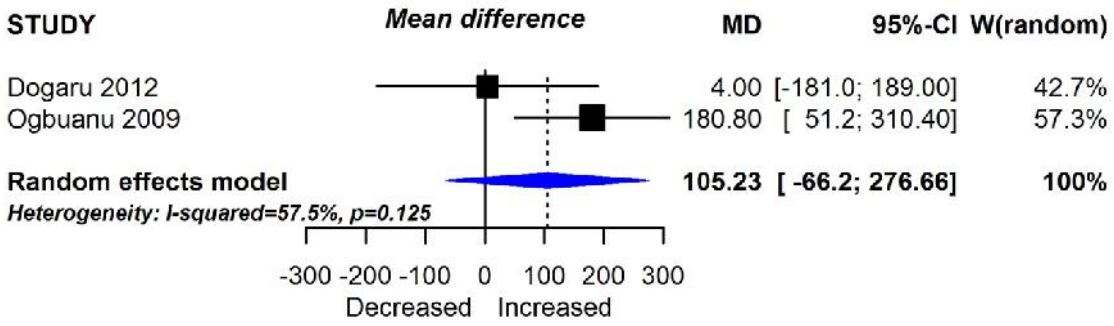
Figure 56 Total breastfeeding and FEV1 (ml) in children aged 5-14 years



1.6.2 Outcome: PEF (ml/sec)

Two prospective cohorts had results with adjusted mean differences based on linear regression: (1) Ogbuanu comparing breastfeeding never (reference) versus ≥ 4 months at 10 years of age; (2) Dogaru breastfeeding never (reference) versus ≥ 6 months at 12.2 years of age.

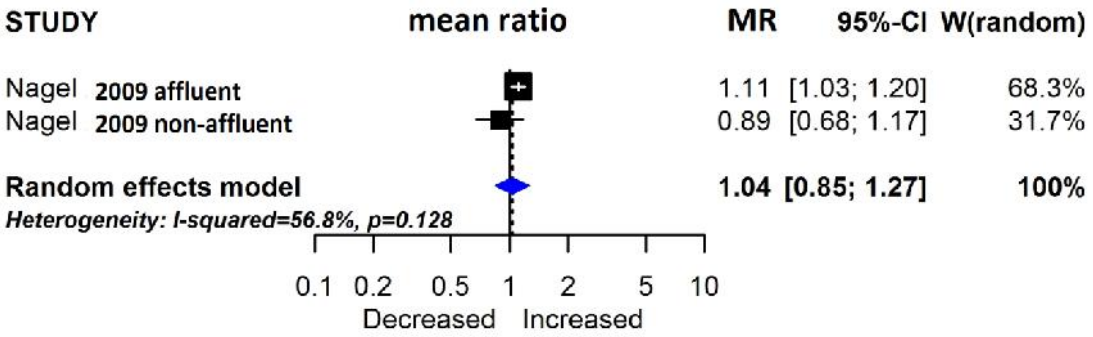
Figure 57 Total breastfeeding and PEF (ml/sec) in children aged 5-14 years



1.6.3 Outcome: FEV1% predicted

One large multicentre cross-sectional study, Nagel presented 2 adjusted estimates of mean ratio (MR) comparing breastfeeding never (reference) versus < 6 months, separately for affluent and non-affluent countries, based on ISAAC methodology, in children aged 8-12 years of age.

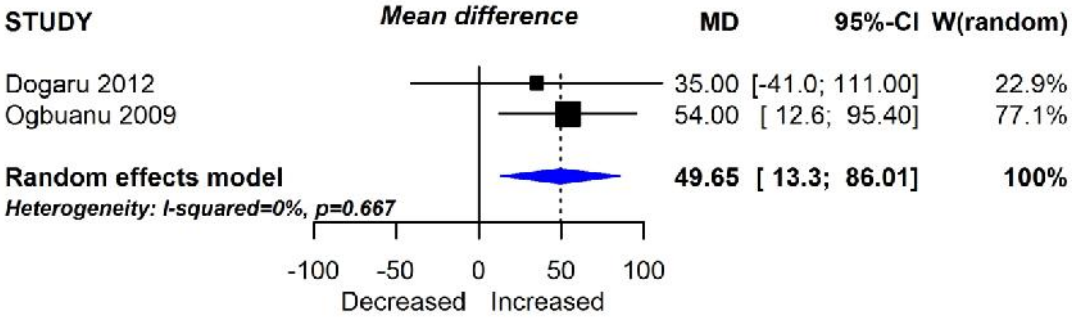
Figure 58 Total breastfeeding and FEV1% predicted in children aged 5-14 years



1.6.4 Outcome: FVC (ml)

Two prospective cohorts had results with adjusted mean differences based on linear regression: (1) Ogbuanu comparing breastfeeding never (reference) versus ≥ 4 months at 10 years of age; (2) Dogaru breastfeeding never (reference) versus ≥ 6 months at 12.2 years of age.

Figure 59 Total breastfeeding and FVC (ml) in children aged 5-14 years



1.6.5 Data for TBF duration and wheeze, BHR or lung function not included in meta-analysis

A total of 36 studies with data on wheeze and TBF exposure, not eligible for meta-analyses were identified (Table 11). Wheeze was measured between age 1 year and 36 years. There were 25 prospective cohorts, 1 retrospective cohort, 1 case-control, 1 a nested case-control, and 8 cross-sectional studies. 7 prospective cohort studies showed a negative association between wheeze (n=1) or recurrent wheeze (n=6) and TBF, whilst 2 cross-sectional studies showed a negative association between recurrent wheeze and TBF. Twenty one studies showed no evidence of an association between wheeze outcomes and TBF. Four studies showed a borderline association (P=0.05) and 2 studies had no data available to estimate size effect.

Data on the association between lung function outcomes and TBF from seven studies that could not be meta-analysed are summarised in Table 12. When P value was not reported in the paper, it was calculated (Altman, D. G. and J. M. Bland (2011). "How to obtain the P value from a confidence interval." BMJ **343**: d2304). Two studies were cross-sectional and five were prospective cohorts. Outcomes studied included forced expiratory volume in 1 second (FEV_1), forced expiratory mid flow (FEF_{50}), airflow obstruction ($FEV_1/FVC<0.80$), FEV_1/FVC as percentage of predicted value, FVC and BHR. Overall of 7 studies, 3 found a positive and statistically significant association between longer duration of TBF and at least one measure of lung function; however findings were not consistent between studies, and between meta-analyses and studies not included in meta-analysis.

Table 11 Studies investigating the association between total breastfeeding and wheeze which were not eligible for meta-analysis

First Author and year of publication	Design	Outcome	Age	N/n	TBF duration (continuous or categorical in months)	Measure of association	Effect	P-value
Munro, 2011 (28)	PC	wheeze	1	700	continuous per week	OR (95%CI) average	0.94 (0.97, 1.00)	<0.05
Soto-Ramirez, 2013 (40)	PC	wheeze	1	2833	continuous	Adjusted RR average	1.26 (1.08, 1.47)	<0.05
Kerr, 1981 (85)	PC	wheeze	0.5	269	0+	average		NS
Hagendorens, 2005 (89)	PC	wheeze	1	693	0+			NS
Sunyer, 2001 (100)	PC	wheeze	4	596	0+			NS
Porro, 1993 (86)	CC	wheeze	<1.6	465/266	>1			NS
Wright, 1989 (105)	PC	wheeze	1	949	>1			NS

First Author and year of publication	Design	Outcome	Age	N/n	TBF duration (continuous or categorical in months)	Measure of association	Effect	P-value
Morgan, 2004 (66)	PC	wheeze, recurrent wheeze	1.5	?	>3			NS
Devereux, 2006 (23)	PC	wheeze	5	1704	0+	Adjusted OR		NS
McConnochie, 1986 (63)	RC	wheeze	8	223/29	0+	Adjusted OR	2.1	0.05
Mann, 1992 (67)	PC	wheeze	36	2139	0+			NS
da Costa Lima, 2003 (81)	PC	Recurrent wheeze	18	2247	0+, 3+, 6+, 9+, 12+	Adjusted PR (95%CI)	Increased recurrent wheeze with longer TBF	NS for 0+, 3+, 6+; P<0.05 for 9+, 12+
Burr, 1993 (13)	PC	wheeze-atopic	7	453	continuous			NS
Silvers, 2009 (76)	PC	recurrent wheeze	1, 5	987	continuous	Adjusted OR (95%CI)	0.93 (0.89-0.97)	<0.05
Silvers, 2012 (75)	PC	recurrent wheeze	5	984	continuous	Adjusted OR (95%CI) average	0.99 (0.96-1.0)	NS

First Author and year of publication	Design	Outcome	Age	N/n	TBF duration (continuous or categorical in months)	Measure of association	Effect	P-value
Hesselmar 2010 (5)	PC	recurrent wheeze	1.5	184	continuous	Median (IQR)		-
Oddy, 2004 (110)	NCC	recurrent wheeze	8	335/166	continuous	Adjusted OR average		NS
Klinnert, 2001 (55)	PC	recurrent wheeze	8	unclear	continuous	average		NS
Awasthi, 2004 (48)	CS	recurrent wheeze	7	2471	0+	Adjusted OR		NS
McConnochie, 1986 (63)	RC	recurrent wheeze	8	223/15	0+	RR	2.6	0.05
Midodzi, 2010 (18)	PC	recurrent wheeze	5	8499/888	0+	Adjusted HR (95%CI)	0.8 (0.7-0.97)	<0.05
Saarinen, 1995 (97)	PC	recurrent wheeze	5, 17	unclear	>1	OR	<1	<0.05
Nwaru, 2013 (24)	PC	recurrent wheeze	5	3142	>5	Adjusted HR (95%CI)	1.9 (1.2-3.0)	<0.05

First Author and year of publication	Design	Outcome	Age	N/n	TBF duration (continuous or categorical in months)	Measure of association	Effect	P-value
Nwaru, 2013 (24)	PC	atopic wheeze	5	3675	>5, >9	Adjusted HR		NS
Evenhouse, 2005 (71)	CS	recurrent wheeze	12-18	16903	0+, continuous	Adjusted OR		NS
Karino, 2008 (51)	CS	recurrent wheeze	18	9615	0+, >1, >3, >6			NS

Table 12 Studies investigating the association between total breastfeeding and lung function which were not eligible for meta-analysis

First Author and year of publication	Outcome	Exposure variable	Comparison (reference)	Age at outcome	Statistics and results		
					Analysis	Result 95% C.I.	P value
Soto-Ramırez 2012 (114)	FEV1(ml)	continuous	ml/week	10-18	linear mixed model, adjusted	1.21 (0.07; 2.35)	0.03
Tennant 2008 (116)	FEV1(ml)	categorical	<4mo (ref.) vs ≥ 4mo	50	linear regression, adjusted	-148 (-269; -027)[2]	0.02
Tennant 2010 (119)	FEV1(ml)	categorical	<1mo (ref.) vs ≥1mo	14	linear regression, adjusted	115 (13; 218)	0.03
Ogbuanu 2009 (113)	FEV1/FVC%	categorical	0 (ref) vs ≥4mo	10	linear regression, adjusted	-0.4 (-1.44; 0.64)	0.45
Soto-Ramırez 2012 (114)	FEV1/FVC%	continuous	% increase per week	10-18	linear mixed model, adjusted	-0.001 (-0.02; 0.02)	0.92
Dogaru 2012 (115)	FEF50 (L/s)	categorical	0 (ref) vs ≤3mo	12.2	linear regression, adjusted	0.04 (0.06; 0.14)	**0.05***
Dogaru 2012 (115)	FEF50 (L/s)	categorical	0 (ref) vs 4-6mo	12.2	linear regression, adjusted	0.13 (0.01; 0.26)	**0.05**
Dogaru 2012 (115)	FEF50 (L/s)	categorical	0 (ref) vs >6mo	12.2	linear regression, adjusted	0.12 (0.01; 0.22)	**0.03**
Suwanpromma 2012 (117)	FEV1/FCV<0.8	categorical	<3mo (ref) vs ≥3mo	6-18	Odds ratio, model, adjusted	**0.87 (0.59; 2.24)**	**<0.05**
Soto-Ramırez 2012 (114)	FVC (ml)	continuous	mL/week	10-18	linear mixed model, adjusted	1.48 (0.30; 2.66)	0.01
Guilbert 2007 (176)	FVC (ml)	categorical	<1mo (ref) vs >4mo	11-16	random-effects model, adjusted	103 (24.6; 181.4)[8]	**0.01**
Rona 2005 (90)	Bronchial hyper-responsiveness	categorical	≥1-2mo vs <1-2mo	≥15	polytomous logistic regression, adjusted	1.25 (0.72-2.16)	**0.43**

*Note that there may be a data entry error in this paper, since the mean is not within the 95% confidence interval. It is possible that the correct finding is 0.04 (-0.06, 0.14) which is not statistically significant.

1.6.6 Conclusion on association between TBF duration and lung function and bronchial hyper-responsiveness

The majority of the studies (¼70%) reported at least one result indicating improvement in lung function, and the majority of these study estimates (around 70%) were statistically significant. However, findings were not consistent between studies or across closely related measures of lung function. Therefore we assessed the body of evidence as being inconclusive.

2 Exclusive breastfeeding and wheeze

2.1 Overall characteristics of studies, risk of bias and summary of results

Table 13 describes the main characteristics of the studies that assessed exclusive breastfeeding duration (EBF) in relation to wheeze risk. 2 systematic reviews reported combined risk of exposure to EBF and risk of wheeze. A total of 62 observational studies reported the association between EBF and wheeze. Of the observational studies, 42 were prospective cohort studies, 5 case-control studies, 3 nested case-control studies and 12 cross-sectional studies. The majority of studies (n=27) are from Europe – others are from the Asia-Pacific region (n=14) and North America (n=8), 7 from South America, 2 from South Asia and 2 from the Middle East. There are also 2 studies, which included multiple countries.

Overall, valid data on EBF duration in the first 2 years of life and wheeze risk were available from over 220,000 subjects. Information on wheeze was obtained solely from parental or self-reported in 13 studies, through Dr-diagnosis in 12 studies, and from the ISAAC questionnaire in 14 studies. One other study used spirometry alone. Another 18 studies used a combination of self /parental report, Doctor diagnosis, and/ or objective measures (e.g. bronchial hyper-responsiveness (BHR)). One study used the Canadian Asthma Consensus Guidelines. Three studies used an unclear method for defining wheeze.

With regards to time of outcome diagnosis, 25 studies explored the association between EBF duration and wheeze at age 0-4 years, 18 at age 5-14 years, and 2 at age 15 years or beyond. A further 15 studies investigated the association between EBF duration and wheeze at various time points between the ages of 1 and 22 years. Two studies examined children at a range of ages (8-18, 6-15). To ascertain exposure to EBF, 31 studies used a questionnaire method, 14 used an interview and 1 used a diary. A further 11 studies used a combination of 2 or more of these methods, whilst 5 studies had no information available on the method used.

Risk of bias in the intervention trials was low in the study of Kramer, and unclear due to unclear selection bias in the study of Kajosaari. Risk of bias in observational studies was assessed using the NICE Methodological checklists for cohort and case-control studies. Figure 56 illustrates the distribution of bias across the five main methodological areas of the

observational studies. Nearly 40% of studies were considered to have an overall high risk of bias, mainly due to lack of controlling for potential confounders and selection bias issues. Risk of conflict of interest was generally assessed as low.

Where data were available, five levels of comparison were used to assess the risk of wheeze according to TBF duration, namely 'ever vs. never', '≥0-2 months vs. <0-2 months', '≥3-4 months vs. <3-4 months', '≥5-7 months vs. <5-7 months', and '≥8-12 months vs. <8-12 months'.

Main findings

In children aged 0-4 years we found no consistent evidence for an association between EBF duration and risk of wheeze or recurrent wheeze. EBF ≥0-2 months was associated with reduced wheeze at age 0-4, but not recurrent wheeze. There was high heterogeneity in the analysis of wheeze, and subgroup analysis found a significant association in studies at low risk of bias, with no heterogeneity. EBF ≥3-4 months was not associated with wheeze or recurrent wheeze at age 0-4, but there was significant statistical heterogeneity in both analyses. EBF ≥5 months was associated with reduced wheeze in one prospective study, but not in one retrospective study, and there was no association with recurrent wheeze.

In children aged 5-14 we found no consistent evidence for an association between EBF duration and risk of wheeze or recurrent wheeze. EBF ≥0-2 months was associated with reduced wheeze in meta-analysis of two prospective studies, but not in two retrospective studies; and there was no association with recurrent wheeze. EBF ≥3-4 months was not associated with wheeze or recurrent wheeze, and there was extreme statistical heterogeneity and publication bias in the analysis of recurrent wheeze. EBF ≥5 months was associated with reduced wheeze in one prospective study and one retrospective study, but with borderline statistical significance; and there was extreme heterogeneity in the analysis of EBF ≥5 months and recurrent wheeze.

In people aged 15 years and over we found no evidence for an association between EBF and wheeze or recurrent wheeze.

When EBF was analysed as a 'per month' exposure, a significantly lower risk of wheeze was observed in children aged 0-4 years old, albeit with high statistical heterogeneity; and there

was significantly lower risk of recurrent wheeze at both 0-4 years and 5-14 years, with low heterogeneity.

We found no consistent evidence for a relationship between EBF and atopic wheeze, with one study reporting reduced atopic wheeze at age 0-4 with EBF ≥0-2 months, but no relationship with EBF ≥3-4 months; no evidence for a relationship between EBF ≥0-2 months and atopic wheeze at age 5-14 years; and one study reporting reduced risk of atopic wheeze at age 5-14 years with EBF ≥3-4 months.

Two studies reported decreased FEV1/FVC% associated with EBF ≥1 month, and meta-analysis was statistically significant with no heterogeneity. Other studies which could not be included in meta-analysis showed no consistent evidence for an association between EBF and measures of lung function.

Overall 18 studies reported data which could not be included in meta-analysis - 16 prospective cohort studies and 2 cross-sectional studies. These studies reported no consistent evidence for an association between EBF and wheeze.

Conclusion

We found no consistent evidence for an association between EBF and risk of wheeze, recurrent wheeze, atopic wheeze, BHR or measures of lung function.

Table 13 Characteristics of included studies evaluating exclusive breastfeeding and wheeze

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Brew, 2011 (122)	SR/PC/ CC/C-S	417,880	Q	'Current wheezing illness', defined in various ways, but usually including wheezing in last 12 months	5-18		31 studies included in the SR (180 – 168,330) participants and EBF for 3-4 months vs. less than 3-4 months
Kramer, 2012 (123)	SR /PC nested in RCTs	3,993 with wheeze data	Q	Self-reported symptoms, objective markers	5-7		Lactating mothers and their healthy, term, singleton infants exclusively or predominantly breast fed for at least 3 months
Kajosaari, 1991[1]	PC	135	-	DD asthma	1, 5	Finland	Solid food introduction at 6 months versus 3 months, in exclusively breastfed infants
de Vries, 2010 (124)	PC	4860	Q	Parent reported wheeze	0.5	Netherlands	ABCD study. Population based study of babies born between 2003 and 2004
Garcia-Marcos, 2010 (125)	CS	28687	Q	ISAAC ; >= 3 episodes of wheeze in the first 2 years	1	Spain, Netherlands and Latin America	EISL study. One-year old infants from urban and rural primary care health clinics born in 2004-2006
Hesselmar, 2010 (5)	PC	184	I	DD asthma : >=3 episodes of wheeze	1.5	Sweden	ALLERGYFLORA study. Population based study of babies selected from antenatal clinics between 1998 and 2003 - mainly high risk of allergic disease
Elliott, 2008 (6)	PC	8191	Q	Current wheeze; Wheeze ever; BHR: metacholine PC20	3, 7.5	UK	ALSPAC study. Population based cohort of children born 1991-1992.

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Kull, 2002; Kull, 2004; Kull, 2010 (9, 126, 127)	PC	3825	Q	>=4 episodes of wheeze OR inhaled corticosteroids (+/- sIgE); >=3 episodes of wheeze OR inhaled corticosteroids (+/- sIgE); Self reported wheeze; >=3 episodes of wheeze OR inhaled corticosteroids; >=3 episodes of wheeze PLUS inhaled glucocorticoids or cough/wheeze at excitement/stress; Spirometry	2, 4, 8	Sweden	BAMSE study. Population based cohort of children born between 1994-1996
Besednjak-Kocijancic, 2010 (128)	PC	408	NA	Unclear	1, 5	Slovenia	Infants with a positive history of parental allergy
Bacopoulou, 2009 (129)	PC	6643	Q	DD	7	Greece	Population based sample of neonates born in 1983
Cano Garcinuno, 2003 (130)	CS? Or PC	234	Q	DD	3	Spain	Children born in 1998-2002 attending primary health center
Salam, 2003 (131)	NCC	691	I	DD PLUS current wheeze; DD	8-18	USA	Cases and controls selected within the CHS study, a population based study of children recruited from public school classrooms from grades 4, 7, and 10 in 12 communities in southern California.

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Mihrshahi, 2007 (20)	PC	516	I	DD PLUS current wheeze	5	Australia	CAPS study. Infants born in 1997-1999 with family history of asthma or wheezing
Simon, 2008 (21)	PC	372	R/I	Transient wheezing: wheezing in the last 12 months at ages of 1,2 and/or 4 years but not at age of 6 years. vs never wheeze	6	USA	CAS study. Middle class mother-infant pairs enrolled in a health maintenance organisation in 1987-89
Fergusson, 1983; Horwood, 1995 (132, 133)	PC	1110	R/I	DD asthma (>=2 episodes of wheeze)	4, 6	New Zealand	Christchurch Child Development Study. Population based cohort of infants born in 1977 in the Christchurch urban region
Giwercman, 2010 (134)	PC	313	I	Parent reported wheeze	2	Denmark	COPSAC study. Infants of mothers with a history of doctor-diagnosed asthma, recruited from August 1998 to December 2001.
Linneberg, 2006 (135)	PC	34793	Q/I	Parent reported wheeze	1.5	Denmark	DNBC. Population based birth cohort of children born between 1997-2002
Erkkola, 2012; Nwaru, 2013 (24, 136)	PC	3675	D	DD plus ISAAC (+/-) sIgE	5	Finland	DIPP study. Infants at high risk (HLA) for TIDM born between 1996-2004 invited to the allergy study between 1998 and 2000
Wilson, 1998 (25)	PC	545	Q	Self-reported wheeze; DD	7	UK	Dundee infant feeding study. Population based cohort of infants born between 1983-1986

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Mandhane, 2007; Sears, 2002 (137) (138)	PC	1037	R/I	DD PLUS current wheeze; Current wheeze PLUS airway hyperresponsiveness; Spirometry; BHR: metacholine PC20	9, 26	New Zealand	Dunedin Multidisciplinary Health and Development Research Study. Population based cohort of infants born between 1972-1973
Hetzner, 2009 (139)	PC	7900	I	DD	2	USA	Early Child Longitudinal Study Birth Cohort. Nationally representative sample of children born in the United States during 2001
Castro-Rodriguez, 2010 (140)	CS	1409	Q	ISAAC	1.4	Spain	EISL study. One-year old infants from urban and rural primary care health clinics born in 2004-2006
Chong Neto, 2007 (141)	CS	3003	Q	Parent reported wheeze ever	1	Brazil	EISL study. One-year old infants from urban and rural primary care health clinics born in 2004-2006
Munro, 2011 (28)	PC	700	Q	Parent reported wheeze	1, 2	UK	EuroPrevall-UK. Population based birth cohort of infants born in 2008
Tanaka, 2009 (32)	CS	1957	Q	ISAAC	3	Japan	Fukuoka Child Health Study. All 3-year old children who had the examination at public public health centers in Fukuoka city
van der Voort, 2012 (33)	PC	5368	Q	ISAAC	1, 4	Netherlands	Generation R study. Population-based multicultural birth cohort of infants born between 2002 and 2009

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Ehlayel, 2008 (142)	CS	1278	Q	ISAAC; Parent reported recurrent wheezing/asthma	5	Qatar	Children 0-5 years old attending primary healthcare centers for routine immunisation
Huang, 2013 (143)	PC	684	Q	ISAAC	2	China	Mother-infant pairs registered in Putuo District, Changzheng Town Community Health Service Center Child Health Clinic within the period from January to December, 2008
Nagel, 2009 (46)	CS	31579	Q	Parent reported current wheeze/asthma; Parent reported current wheeze (+/-SPT)	12	International - Affluent countries (China, Germany, Greece, Iceland, Italy, Netherlands, New Zealand, Norway, Spain); International - Nonaffluent countries (Albania, Brazil, China, Ecuador, Georgia, Ghana, India, Latvia, West Bank, Turkey)	ISAAC Phase 2. Schoolchildren aged 8–12 years from 27 centres in 21 affluent and nonaffluent countries
Arshad, 1992; Kurukulaaratchy, 2004;	PC	1167	D/Q	DD asthma (>=3 episodes of wheeze); Parent reported wheeze; >=2 episodes of wheeze between age <4 and 10	1, 10	UK	Isle of Wight Prevention Study. Population based birth cohort of infants born in semi-rural areas between 1989 and 1990

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Kurukulaaratchy, 2006 (144-146)				years			
Juca (147)	CC	590	Q	ISAAC	14	Brazil	
Kemeny, 1991 (54)	PC	180	NA	>=2 episodes of wheeze	1	UK	Population based birth cohort of infants born at Dulwich and King's College Hospitals in London
Liu, 2012 (148)	CS	8733	Q	ISAAC; ATS guideline	8	China	Sample of children from kindergarden and elementary schools in Shenyang
Mai, 2007 (149)	NCC	723	Q	Canadian Asthma Consensus Guidelines: symptoms plus variable airway obstruction	10	Canada	Cases and controls selected from records of the Manitoba Health Services Insurance Plan and all were born 1995
Majeed, 2008 (150)	CC	398	Q/I	>=3 episodes of wheeze in past year	3	Pakistan	Cases are 1-12 years old children with wheeze/asthma admitted to paediatrics wards. Controls are age matched children and adolescents attending immediately after selection of the index case
Marini, 1996 (59)	PC	Unclear	Q	>=3 episodes of wheeze	1	Italy	Infants with family history of allergy whose mother were proposed to participate in an allergy prevention program

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Midwinter, 1987 (151)	PC	453	NA	DD asthma	5	UK	Children born to parents with a family history of atopy in 1979-1981
Miyake, 2003 (65)	CS	6845	Q	ISAAC	15	Japan	12-15 years old children from all public junior high schools in Suita, Japan.
Silvers, 2009; Silvers, 2012 (75, 76)	PC	987	Q	DD PLUS current wheeze; Parent reported wheeze	1, 5	New Zealand	New Zealand Asthma and Allergy Cohort Study. Population based birth cohort of infants born between 1997 and 2001
Nielsen, 2013 (152)	PC	5429	Q	Unclear	0.5	Denmark	Population based birth cohort of infants born in 1995
Miyake, 2008 (79)	PC	763	Q	ISAAC	2	Japan	OMCHS study. Population based birth cohort of infants born in 2002-2003
da Costa Lima, 2003(81)	PC	2247	I	ISAAC	18	Brazil	Pelotas Birth Cohort. Population based birth cohort of infants born in 1982 in the city of Pelotas
Pesonen, 2006 (153)	PC	164	I	DD OR >=2 episodes of wheezing	5, 20	Finland	Population based birth cohort of infants born in 1981
van Merode, 2007 (154)	PC	222	Q	ISAAC	1	Holland	PREVASC study: cohort born in 2005 with family history of asthma (high risk of disease)

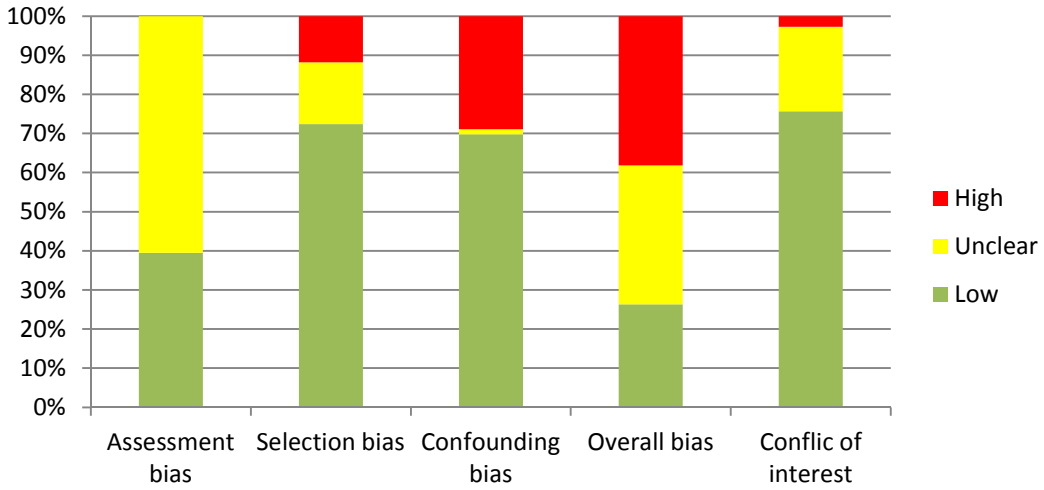
First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Prietsch, 2006 (155)	CS	685	Q	Unclear	13	Brazil	Population representative sample of infants aged 12-15 months (normal risk of disease)
Kramer, 2003; 2009; 2009 (b) (156-158)	PC	2951	I	ISAAC	1, 6.5	Belarus	PROBIT study: recruited in hospitals, born 1996-1997 (normal risk of disease)
Ratageri, 2000 (159)	CC	180	NA	DD asthma using International Paediatric Consensus Group criteria	9	India	Hospital-based study (normal risk of disease)
Rothenbacher, 2005 (94)	PC	803	Q/I	DD	2	Germany	Recruited from university service, born in 2000-2001 (normal risk of disease)
Rullo, 2007; Rullo, 2009; Rullo, 2009 (b); Rullo, 2010 (160-163)	PC	101	Q/I	>=3 episodes of wheeze in past year; Persistent wheeze: ever wheezing treated with inhaled corticosteroids and beta-2 agonists in the past year	1.5, 2.5, 4, 5	Brazil	Recruited from hospital (high risk of asthma)
Rylander, 1993 (164)	CC	550	I	Physician assessment	4	Sweden	Cases from a health service and control from population (normal risk of disease)

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Siltanen,2003 (165)	PC	285	Q	DD PLUS current wheeze; >=3 episodes of wheezing;	4	Finland	Infants recruited from maternal hospital born in 1994-1995 (normal risk of disease)
Salem, 2002 (166)	CS	424	Q	Wheeze ever	5	Iraq	Population representative sample of children aged 0.16-2 years old (normal risk of disease)
Silva, 2005 (167)	PC	73	Q	Physician assessment (>=3 episodes of wheeze)	4	Brazil	Recruited from health services in urban area, born in 1998 (high risk of disease)
Strassburger, 2010 (168)	PC	343	I	ISAAC	3.5	Brazil	Recruited from hospital, born 2001-2002 (normal risk of disease)
Mai, 2008 (169)	NCC	723	Q	Physician assessment	10	Canada	Study of Asthma, Genes and the Environment (SAGE) project: population-based study with children born in 1995 (normal risk of disease)
Matheson, 2007 (170)	PC	5729	Q	Self-reported current asthma	7, 32	Tasmania	Tasmanian ASTHMA Study: population based born in 1961 (high risk/low risk of disease)
Takemura, 2001 (102)	CS	23828	Q	>=2 episodes of wheeze PLUS DD asthma	6-15	Japan	The Tokorozawa Childhood Asthma and Pollinosis Study: Representative sample of children in public elementary schools (normal risk of disease)

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Wright, 2001 (171)	PC	1043	Q/I	DD PLUS wheeze >=2 times between 6 and 13 years	13	USA	Tuscon Children's Respiratory Study: Recruited from local health maintenance organisation born in 1980-1984 (normal risk of disease)
Van Asperen, 1983 (172)	PC	79	I	Parent reported wheeze	1	Australia	Cohort recruited from medical service, born in 1980-1981 with family history of atopy (high risk of disease)
Watson,2013 (173)	PC	369	Q/I	ISAAC	1.5	New Zealand	Recruited from Polynesian women, non-random sample (high risk of disease)
Oddy, 1999; Oddy, 2002; Oddy, 2003; Oddy, 2004 (109, 111, 174, 175)	PC	2456	D/I	DD PLUS wheeze in the past 12 months; Parent reported current wheeze; DD asthma PLUS >=3 episodes of wheeze	1, 6	Australia	Western Australia Pregnancy Cohort: Recruited from antenatal clinics born in 1989-1992 (high risk/low risk of disease)
Whu, 2007 (176)	CC	261	I	DD PLUS asthma medication	4	USA	Hospital-based study cases born in 2000 (normal risk of disease)
Zutavern 2004 (114)	PC	606	I	Parent reported current wheeze	2, 5.5	UK	Cohort recruited from general practices and born in 1993-1995 (normal risk of disease)

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Poysa, 1992 (177)	PC	68	NA	BHR: metacholine PC20	10	Finland	High risk of disease, born 1979-1980
Guilbert, 2007 (178)	PC	679	I	Spirometry	13	USA	Tuscon Children's Respiratory Study: A population-based cohort of healthy infants born in 1980-1984 (normal risk of disease)

Figure 60 Risk of bias in studies of exclusive breastfeeding and wheeze



2.2 Exclusive Breastfeeding and Wheeze

2.2.1 Systematic reviews

Two systematic reviews investigated overall association between exclusive breastfeeding and wheeze. Brew and colleague found no evidence that EBF for more than 3-4 months vs. less was associated with wheeze (OR 0.96 [0.86, 1.06]) (I^2=54.2%). Kramer reported no association between EBF for 6 or more months' vs 3-4 months and having at least 2 episodes of wheezing in the first 12 months RR 0.79 (0.49, 1.28; I^2=0%). No intervention trials were identified, other than the cluster RCT of Kramer which is included in the 'TBF' section of this report.

2.2.2 Age at outcome measurement 0-4

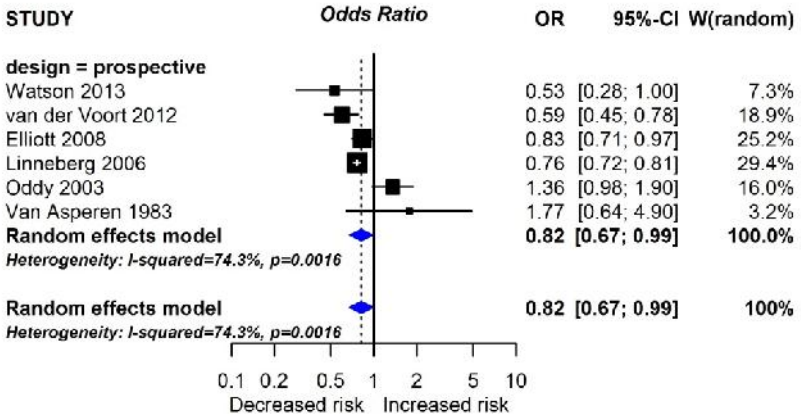
2.2.2.1 0-2 months

Six prospective cohort studies reported data on risk of wheeze that could be pooled to estimate the effect of exposure to EBF for ≥0-2 months vs. <0-2 months in children aged 0-4 years, suggesting a protective effect of EBF on wheeze in the exposed group (OR 0.82; 95% CI 0.67, 0.99) (Subgroup analyses for EBF for ≥0-2 months vs. <0-2 months and risk of wheeze showed a statistically significant difference between studies at low risk of overall bias and high/unknown risk (P=0.01) (Table 14).

Figure 61). There was very high heterogeneity between studies (I^2=74.3%). Two of the studies had a low overall risk of bias, whilst three had an unclear overall risk, and the study of Van Asperen lacked controlling for potential confounders, so carries an overall high risk of bias.

Subgroup analyses for EBF for ≥0-2 months vs. <0-2 months and risk of wheeze showed a statistically significant difference between studies at low risk of overall bias and high/unknown risk (P=0.01) (Table 14).

Figure 61 Exclusive breast feeding ≥0-2 months vs. <0-2 months and risk of wheeze in children aged 0-4 years



2.2.2.2 3-4 months

Nine observational studies reported data on risk of wheeze that could be pooled to estimate the effect of exposure to EBF for ≥3-4 months vs. <3-4 months in children aged 0-4 years, suggesting no evidence of an effect of EBF on wheeze in the exposed group (

Figure 62). There was very high heterogeneity between studies (I^2=73.2%). Six studies were prospective cohorts (of which 2 had an overall high risk of bias due to not accounting for potential confounders), two were cross sectional (both carry a high risk of overall bias due to selection bias), and one is a case-control study (which did not account for confounding and therefore carries an overall high risk of bias). A Funnel plot was used to investigate publication bias, showing a slight asymmetry but no statistical evidence of such a bias (Figure 63).

Prolonged exposure to EBF for ≥3-4 months vs. <3-4 months showed no difference in the subgroup analyses (Table 15).

Figure 62 Exclusive breast feeding ≥3-4 months vs. <3-4 months and risk of wheeze in children aged 0-4 years

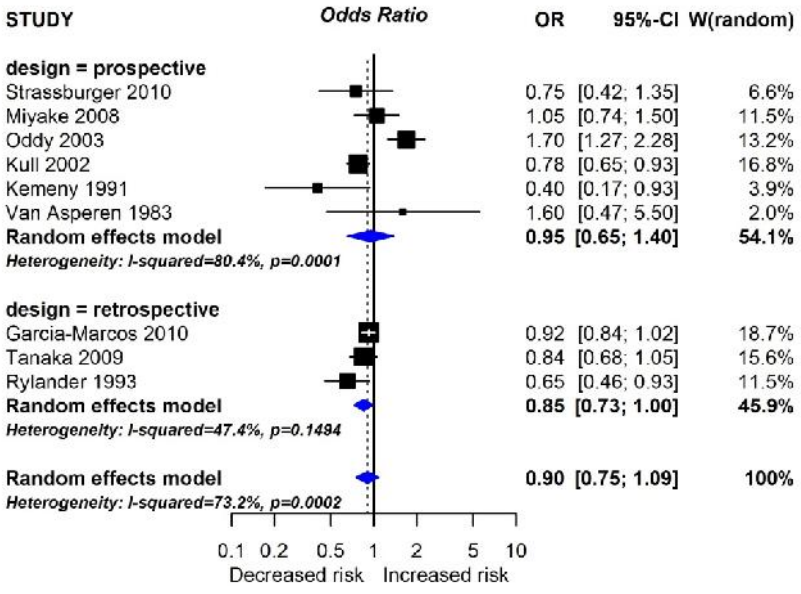
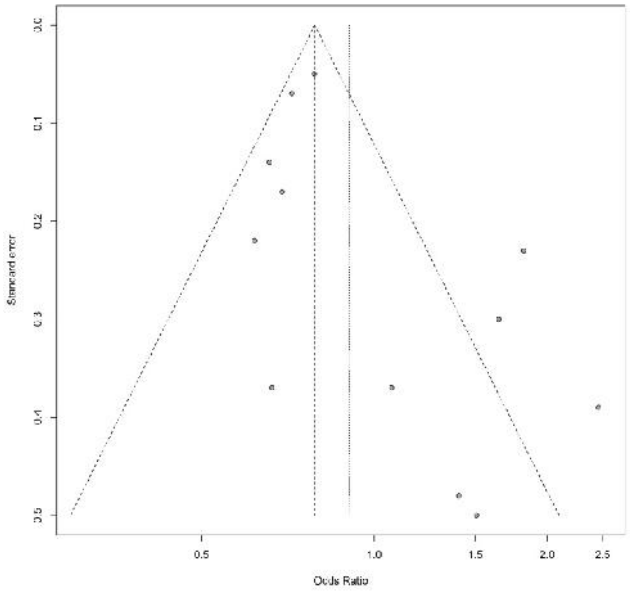


Figure 63 Risk of publication bias in studies of exclusive breast feeding ≥3-4 months vs. <3-4 months and risk of wheeze in children aged 0-4 years



Egger's test p-value = 0.141

2.2.2.3 5+ months

Two observational studies, a prospective cohort and a cross-sectional study reported data on risk of wheeze that could be pooled to estimate the effect of exposure to EBF for ≥5 months vs. <5 months in children aged 0-4 years (Figure 64). There was extremely high heterogeneity between the two studies (I^2=86.6%), possibly explained by the overall high risk of bias of the retrospective Salem study (mainly due to lack of adjustment for potential confounders) and the unclear overall risk of bias in the prospective Oddy study.

Figure 64 Exclusive breast feeding ≥5 months vs. <5 months and risk of wheeze in children aged 0-4 years

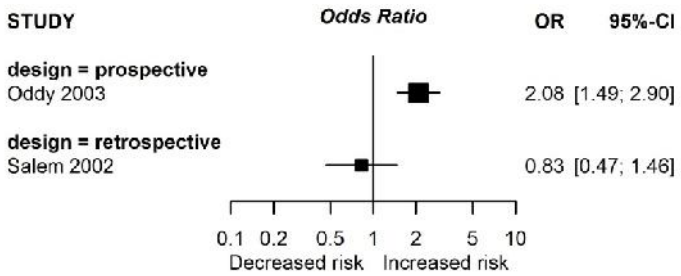


Table 14 Subgroup Analyses of risk of wheeze and exclusive breastfeeding ≥0-2 months vs. <0-2 months in children aged 0-4 years

	Number of studies	OR [95% CI]	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted value used)	6	0.82 [0.67; 0.99]	74.3	
Adjusted	4	0.85 [0.69; 1.05]	77.4	Not tested
Unadjusted	5	0.88 [0.52; 1.48]	93.6	
Study Design – Prospective	6	0.82 [0.67; 0.99]	74.3	--
Study Design – Retrospective	--	--	--	
Risk of disease – High	2	0.91 [0.28; 2.91]	74.1	0.87
Risk of disease – Normal	4	0.82 [0.67; 1.00]	80.7	
Risk of bias – Low	2	0.58 [0.45; 0.75]	0.0	0.01
Risk of bias – High/Unclear	4	0.92 [0.74; 1.16]	79.0	
Clear definition of breastfeeding duration	4	0.73 [0.54; 0.99]	62.8	0.34
Unclear definition of breastfeeding duration	2	1.00 [0.57; 1.76]	91.1	

Table 15 Subgroup Analyses of risk of wheeze and exclusive breastfeeding ≥3-4 months vs. <3-4 months in children aged 0-4 years

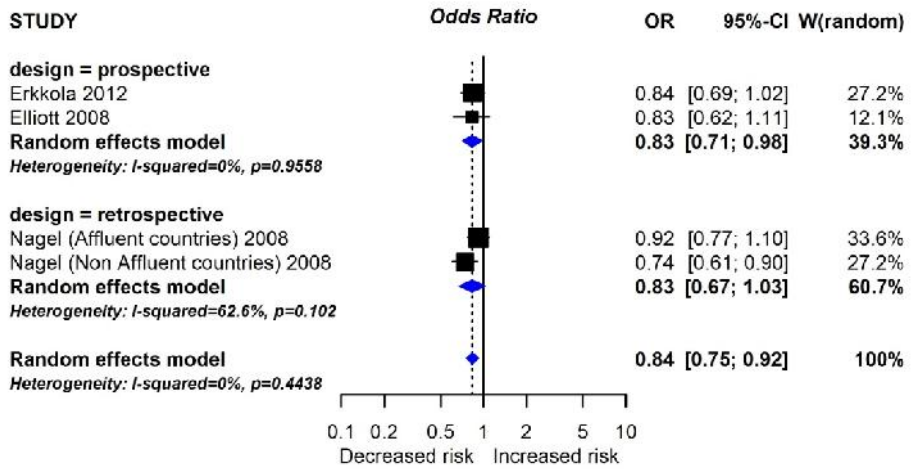
	Number of studies	OR [95% CI]	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted value used)	9	0.90 [0.75; 1.09]	73.2	0.28
Adjusted	6	0.97 [0.80; 1.17]	77.1	
Unadjusted	8	0.89 [0.65; 1.2157]	84.5	
Study Design – Prospective	9	0.95 [0.65; 1.40]	80.4	0.60
Study Design – Retrospective	3	0.85 [0.73; 1.00]	47.4	
Risk of disease – High	1	1.6000 [0.4654; 5.5002]		0.36
Risk of disease – Normal	8	0.8917 [0.7380; 1.0773]	75.9	
Risk of bias – Low	4	0.8468 [0.7022; 1.0213]	12.5	0.74
Risk of bias – High/Unclear	5	0.8980 [0.6724; 1.1993]	83.8	

2.2.3 Age at outcome measurement 5-14

2.2.3.1 0-2 months

Four observational studies reported data that could be pooled to estimate risk of wheeze with duration of EBF ≥0-2 months vs. <0-2 months, suggesting a reduced risk of disease (OR 0.84; 95% CI 0.75, 0.92; [Figure 65]). The analysis showed no statistical heterogeneity between studies (I^2=0.0%). Two studies were prospective cohorts, the study of Erkkola had an overall high risk of bias, mainly due to lack of adjustment for potential confounders, and the study of Elliot had an unclear risk of bias. The other two studies were of cross-sectional design and used the ISAAC questionnaire. Both had an overall high risk of bias, due to selection bias.

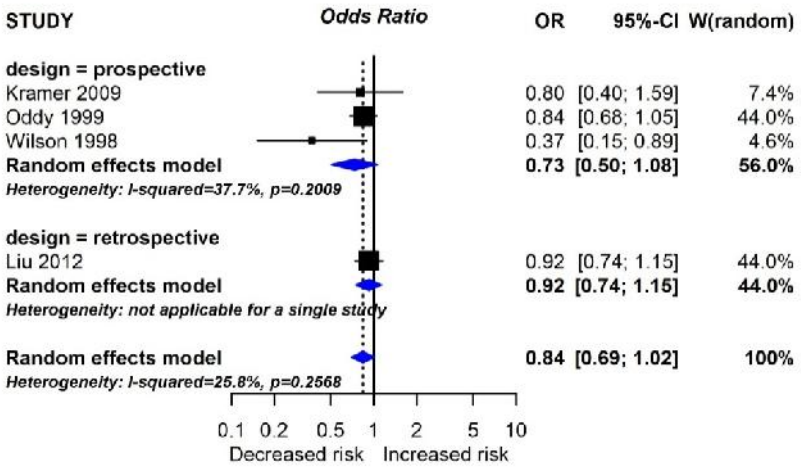
Figure 65 Exclusive breast feeding ≥0-2 months vs. <0-2 months and risk of wheeze in children aged 5-14 years



2.2.3.2 3-4 months

Four observational studies reported data that could be pooled to estimate risk of wheeze with exposure to EBF ≥3-4 months vs. <3-4 months. Although all studies showed an OR below 1.0, there was no evidence of an association in the meta-analysis (Figure 66). Three of the studies were prospective cohorts (one of which had a high risk of bias due to confounding), and one was cross-sectional (with high risk of overall bias due to confounding).

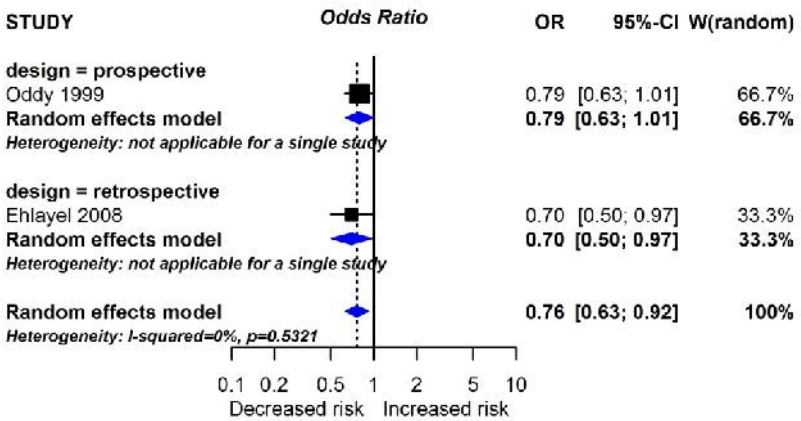
Figure 66 Exclusive breast feeding ≥3-4 months vs. <3-4 months and risk of wheeze in children aged 5-14 years



2.2.3.3 5+ months

Data were available from one cross-sectional study and one prospective study to examine the pooled effect of EBF for ≥5 months vs. <5 months and risk of wheeze in children aged 5-14 years old, showing a reduced risk of disease in the exposed group (OR 0.76; 95% CI 0.63, 0.92). The studies had no heterogeneity (I^2=0.0%) (Figure 67).

Figure 67 Exclusive breast feeding ≥5 months vs. <5 months and risk of wheeze in children aged5-14 years

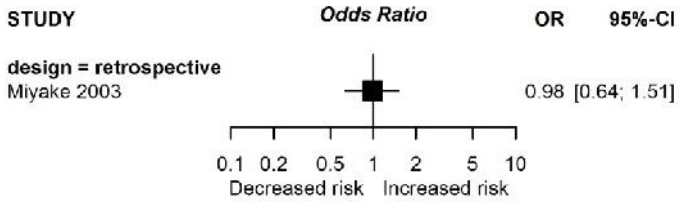


2.2.4 Age at outcome measurement 15+

2.2.4.1 0-2 months

One cross-sectional study reported risk of wheeze in children aged over 15 years old who were exposed to EBF for ≥0-2 months vs. <0-2 months (Figure 68). The study had high risk of bias due to lack of adjustment for potential confounders, and showed no association between exposure and disease.

Figure 68 Exclusive breast feeding ≥0-2 months vs. <0-2 months and risk of wheeze in children aged 15+ years

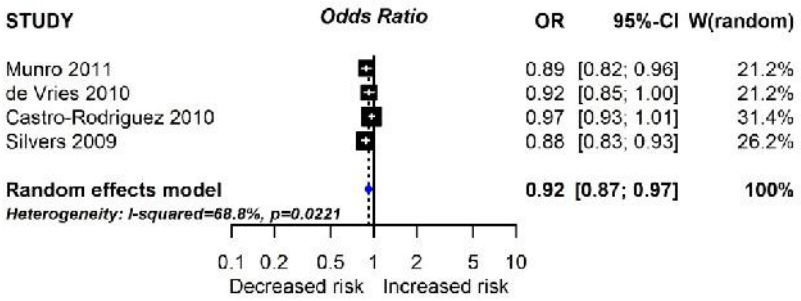


2.3 Exclusive Breastfeeding per month and Wheeze

2.3.1 Age at outcome measurement 0-4

Four observational studies reported associations between EBF per month and risk of wheeze in children aged 0-4 (Figure 69). The overall combined effect suggests a lower risk of disease in the exposed group (OR 0.92; 95% CI 0.87, 0.97). The analysis showed high statistical heterogeneity across studies (I^2=68.8%).

Figure 69 Exclusive breastfeeding per month and risk of wheeze in children aged 0-4 years



2.4 Exclusive Breastfeeding and Recurrent Wheeze

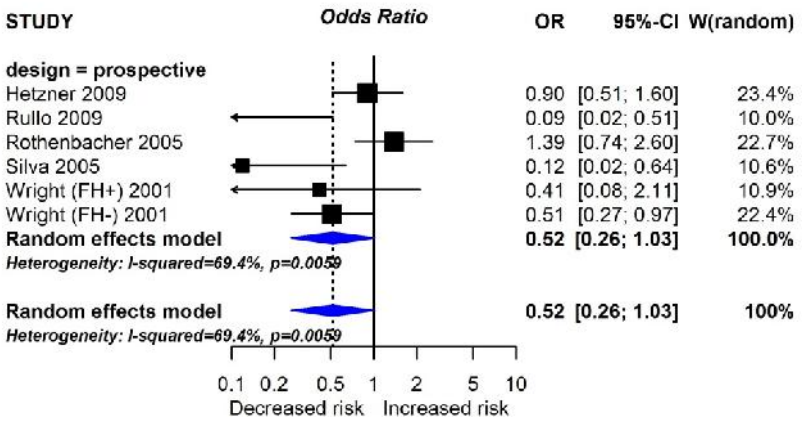
2.4.1 Age at outcome measurement 0-4

2.4.1.1 0-2 months

Five observational studies (six analyses) reported risk of recurrent wheeze with exposure to EBF for ≥0-2 months vs. <0-2 months in children aged 0-4 years old (Figure 70). There was no clear evidence of a significant effect and there was very high heterogeneity between studies (I^2=69.4%).

Subgroup analyses of risk of recurrent wheeze and exclusive breastfeeding ≥0-2 months vs. <0-2 months in children aged 0-4 years, showed statistically significant differences between children at high and low risk of disease (P<0.01) and between risk of bias (P=0.01) (Table 16). Studies at low risk of bias found no association between EBF and recurrent wheeze, with no statistical heterogeneity.

Figure 70 Exclusive breast feeding ≥0-2 months vs. <0-2 months and risk of recurrent wheeze in children aged 0-4 years



2.4.1.2 3-4 months

Thirteen observational studies reported data eligible to calculate combined OR of wheeze in children aged 0-4 comparing EBF ≥3-4 months vs. <3-4 months. There was no evidence of an overall effect (Figure 71) and the heterogeneity was very high (I^2=68.7%), which might have been partly influenced by the different outcome measurements used across studies. Nine

studies were prospective cohorts (six of which had high risk of overall bias, mainly due to confounding or selection bias), 2 were cross-sectional studies (both of which had a high risk of overall bias) and one was a case-control study (which also had a high risk of overall bias, due to lack of adjustment for potential confounders). There was no evidence of publication bias (

Figure 72).

Subgroup analyses of risk of recurrent wheeze and exclusive breastfeeding ≥3-4 months vs. <3-4 months in children aged 0-4 years showed no statistically significant differences between groups (Table 17).

Figure 71 Exclusive breast feeding ≥3-4 months vs. <3-4 months and risk of recurrent wheeze in children aged 0-4 years

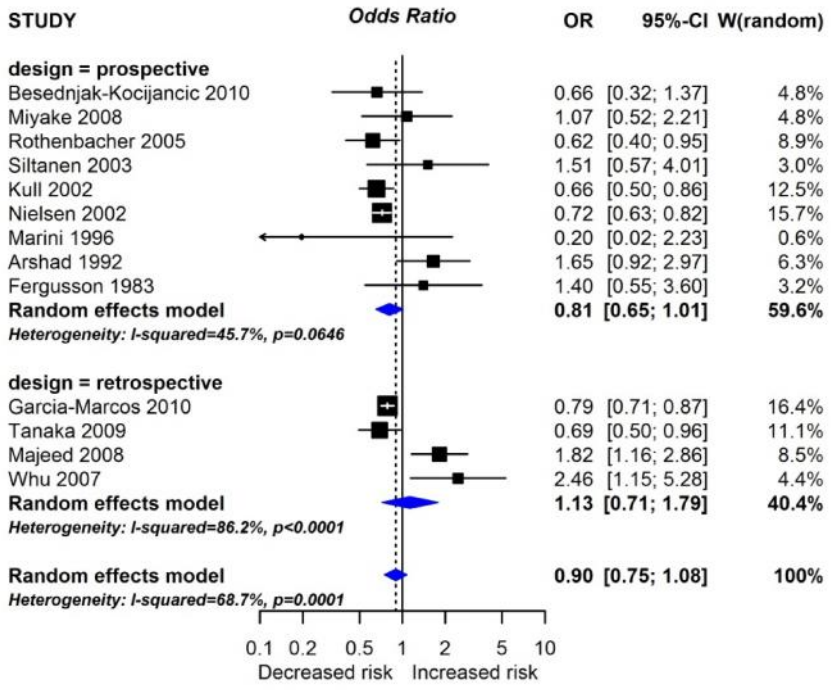
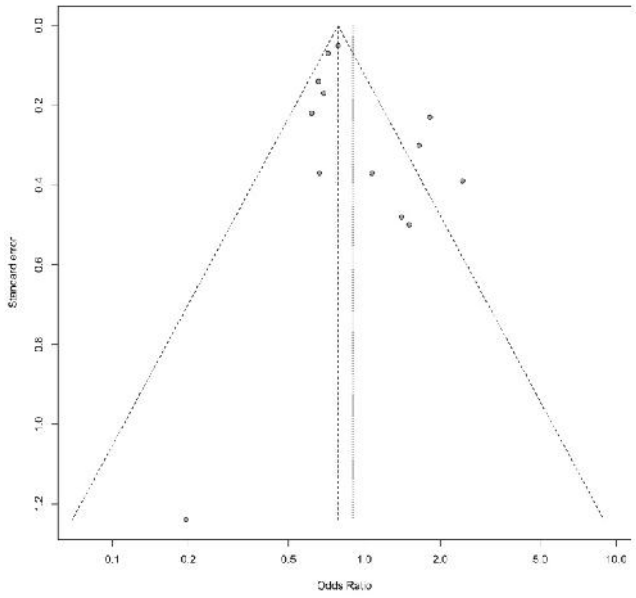


Figure 72 Risk of publication bias in studies of exclusive breast feeding ≥3-4 months vs. <3-4 months and risk of wheeze in children aged 0-4 years



Egger's test p-value = 0.159

2.4.1.3 5+ months

Three observational studies reported data on risk recurrent wheeze with EBF ≥5 months vs. <5 months in children aged 0-4 years old. There was no evidence of an effect in the combined analysis (Figure 73), and the studies had high heterogeneity across studies (I^2=61.7%).

Figure 73 Exclusive breast feeding ≥5 months vs. <5 months and risk of recurrent wheeze in children aged 0-4 years

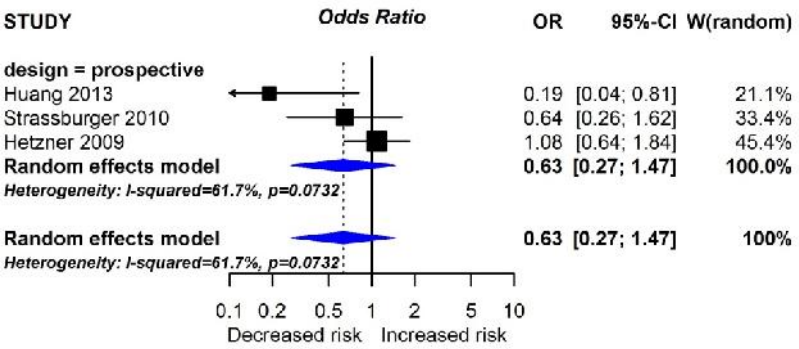


Table 16 Subgroup Analyses of risk of recurrent wheeze and exclusive breastfeeding ≥0-2 months vs. <0-2 months in children aged 0-4 years

	Number of studies	OR [95% CI]	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted value used)	6	0.52 [0.26; 1.03]	69.4	
Adjusted	3	0.25 [0.05; 1.37]	80.3	Not tested
Unadjusted	5	0.43 [0.18; 1.00]	73.7	
Risk of disease – High	3	0.17 [0.07; 0.45]	0.0	<0.01
Risk of disease – Normal	3	0.87 [0.50 1.50]	58.8	
Risk of bias – Low	2	1.10 [0.72; 1.67]	0.0	0.01
Risk of bias – High/Unclear	4	0.28 [0.12; 0.66]	42.3	

Table 17 Subgroup Analyses of risk of recurrent wheeze and exclusive breastfeeding ≥3-4 months vs. <3-4 months in children aged 0-4 years

	Number of studies	OR [95% CI]	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted value used)	13	0.90 [0.75; 1.08]	68.7	
Adjusted	9	0.79 [0.69; 0.92]	63.0	Not tested
Unadjusted	12	0.85 [0.67; 1.08]	69.2	
Study Design – Prospective	9	0.81 [0.65; 1.01]	45.7	0.20
Study Design – Retrospective	4	1.13 [0.71; 1.79]	86.2	
Risk of disease – High	2	0.60 [0.30; 1.20]	0.0	0.24
Risk of disease – Normal	11	0.92 [0.76; 1.12]	72.9	
Risk of bias – Low	3	0.83 [0.50; 1.37]	76.5	0.65
Risk of bias – High/Unclear	10	0.94 [0.76; 1.17]	69.4	

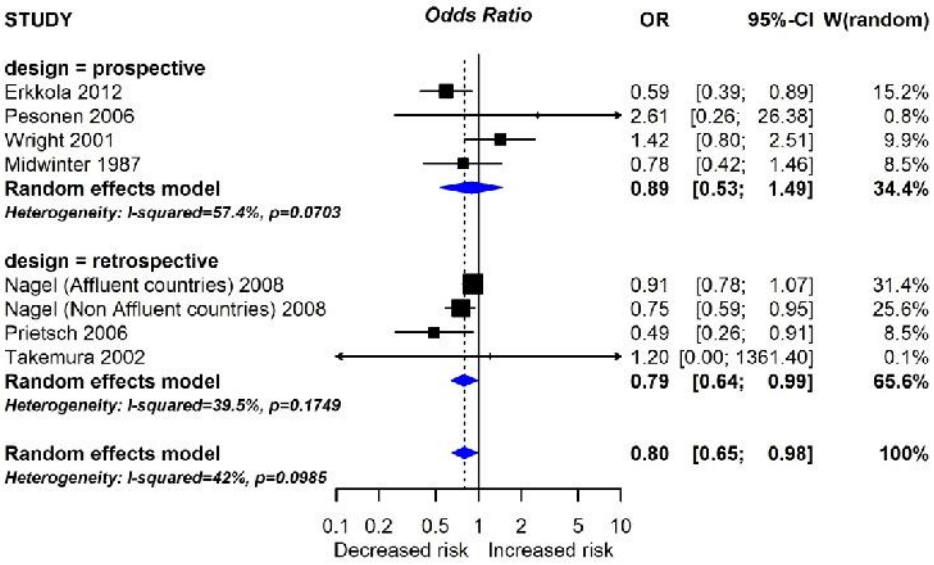
2.4.2 Age at outcome measurement 5-14

2.4.2.1 0-2 months

Eight observational studies reported data that could be pooled to assess the overall risk of recurrent wheeze in children aged 5-14 if with EBF ≥0-2 months vs. <0-2 months, and showed no evidence of an association with disease, but high heterogeneity between prospective studies was observed (I^2=57.4%) (Figure 74).

Subgroup analyses of risk of recurrent wheeze and EBF for ≥0-2 months vs. <0-2 months (Table 18) in children aged 5-14 years, showed no evidence of statistically significant differences between groups.

Figure 74 Exclusive breast feeding ≥0-2 months vs. <0-2 months and risk of recurrent wheeze in children aged 5-14 years



2.4.2.2 3-4 months

Fifteen observational studies reported data eligible to calculated pooled effect of EBF ≥3-4 months vs. <3-4 months on recurrent wheeze in children aged 5-14 years. Data could not be pooled due to extreme statistical heterogeneity (Figure 75). Ten of them were prospective cohorts, two were nested case-control studies, 1 was a case-control study and 2 were cross-sectional studies. Most studies had low or unclear risk of bias, with the exceptions of three studies in which confounding was not accounted for and therefore they carry an overall high risk of bias. A funnel plot was used to explore publication bias (Figure 75). There was asymmetry across studies indicating risk of publication bias, which was confirmed by the Egger's test (P=0.01).

Subgroup analyses of risk of recurrent wheeze and EBF for ≥3-4 months vs. <3-4 months (Table 19) showed no evidence of statistically significant differences between groups.

Figure 75 Exclusive breast feeding ≥3-4 months vs. <3-4 months and risk of recurrent wheeze in children aged 5-14 years

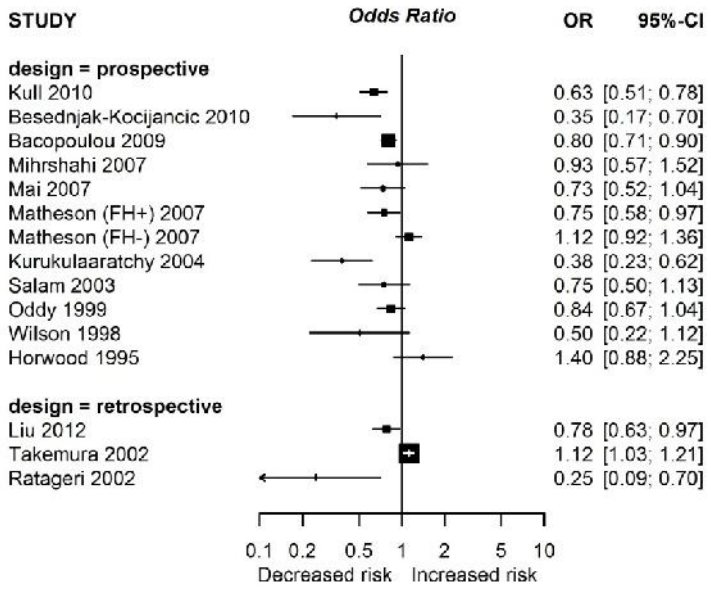
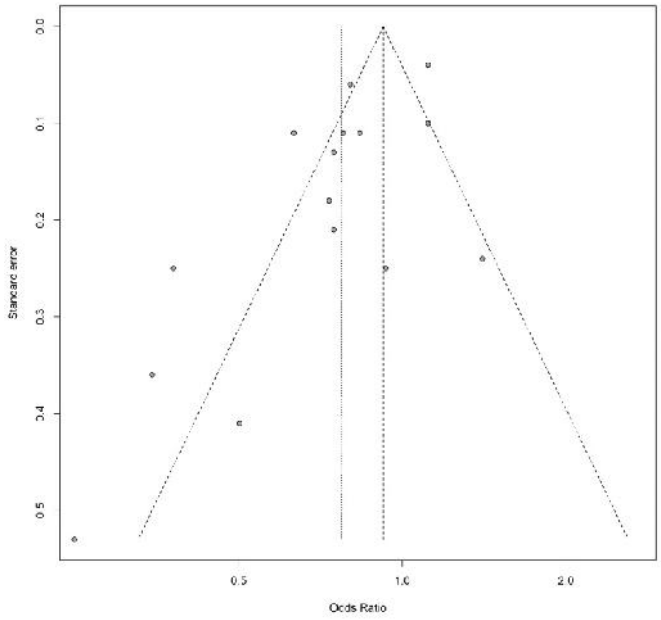


Figure 76 Risk of publication bias of studies investigating exclusive breast feeding ≥3-4 months vs. <3-4 months and risk of recurrent wheeze in children aged 5-14 years



Egger's test p-value = 0.01

2.4.2.3 5+ months

Four observational studies reported data that was eligible to calculate pooled estimates of risk of recurrent wheeze in children aged 5-14 years old and exposure to EBF for 5 or more months, showing no evidence of an association (Figure 77) and an extremely high heterogeneity between studies (I^2=86.9%).

Figure 77 Exclusive breastfeeding ≥5 months vs. <5 months and risk of recurrent wheeze in children aged 5-14 years

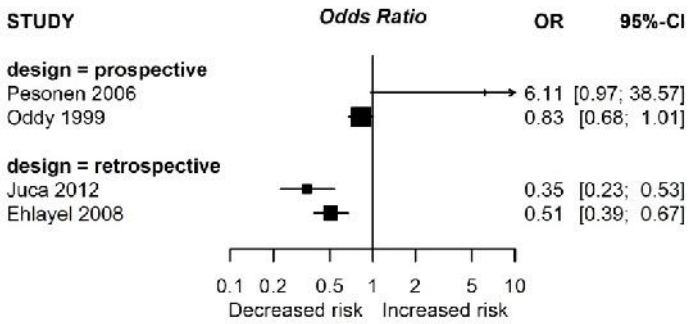


Table 18 Subgroup Analyses of risk of recurrent wheeze and exclusive breastfeeding ≥0-2 months vs. <0-2 months in children aged 5-14 years

	Number of studies	OR [95% CI]	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted value used)	9	0.91 [0.69; 1.19]	67.9	
Adjusted	5	0.93 [0.64; 1.35]	77.2	Not tested
Unadjusted	9	0.96 [0.75; 1.23]	81.9	
Study Design – Prospective	5	1.16 [0.63; 2.16]	78.1	0.26
Study Design – Retrospective	4	0.79 [0.64; 0.99]	39.5	
Risk of disease – High	1	0.78 [0.42; 1.46]	--	0.63
Risk of disease – Normal	8	0.93 [0.68; 1.25]	71.8	
Risk of bias – Low	1	2.61 [0.26; 26.38]	--	0.37
Risk of bias – High/Unclear	8	0.89 [0.68; 1.18]	70.9	

Table 19 Subgroup Analyses of risk of recurrent wheeze and exclusive breastfeeding ≥3-4 months vs. <3-4 months in children aged 5-14 years

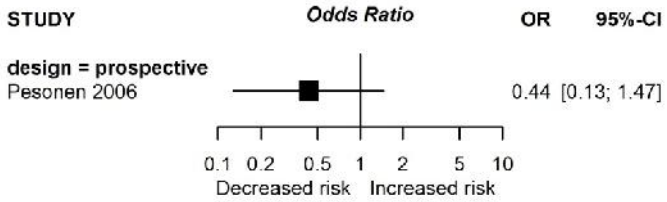
	Number of studies	OR [95% CI]	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted value used)	15	0.77 [0.66; 0.91]	83.2	
Adjusted	9	0.79 [0.69; 0.92]	63.0	Not tested
Unadjusted	11	0.77 [0.63; 0.95]	83.5	
Study Design – Prospective	12	0.76 [0.65; 0.90]	71.0	0.83
Study Design – Retrospective	3	0.80 [0.53; 1.22]	88.2	
Risk of disease – High	3	0.68 [0.44; 1.04]	62.1	0.51
Risk of disease – Normal	12	0.79 [0.66; 0.94]	85.0	
Risk of bias – Low	5	0.76 [0.55; 1.05]	78.3	0.87
Risk of bias – High/Unclear	10	0.79 [0.65; 0.95]	83.1	

2.4.3 Age at outcome measurement 15+

2.4.3.1 0-2 months

One prospective cohort study reported data for risk of recurrent wheeze in children aged 15+ and feeding ≥0-2 months vs. <0-2 months, showing no evidence of an association (Figure 78).

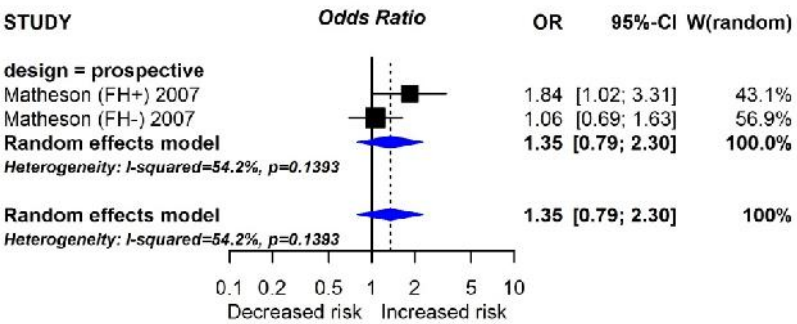
Figure 78 Exclusive breast feeding ≥0-2 months vs. <0-2 months and risk of recurrent wheeze in children aged 15+ years



2.4.3.2 3-4 months

The prospective cohort study of Matheson reported ORs that were eligible to calculate pooled ORs or recurrent wheeze, showing no evidence of an association with the disease in the exposed group. The study had an overall low risk of bias (Figure 79).

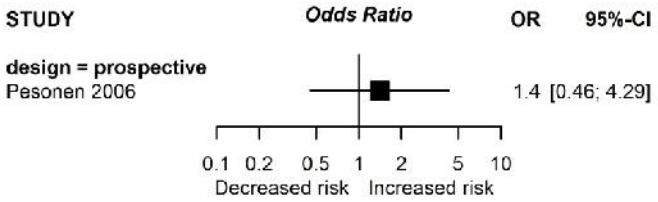
Figure 79 Exclusive breast feeding ≥3-4 months vs. <3-4 months and risk of recurrent wheeze in children aged 15+ years



2.4.3.3 5+ months

The study of Pesonen had reported data on risk of recurrent wheeze in children aged 15+ who were exposed to EBF for ≥5 months vs. <5 months, showing no indication of an effect (Figure 80).

Figure 80 Exclusive breast feeding ≥5 months vs. <5 months and risk of recurrent wheeze in children aged15+ years



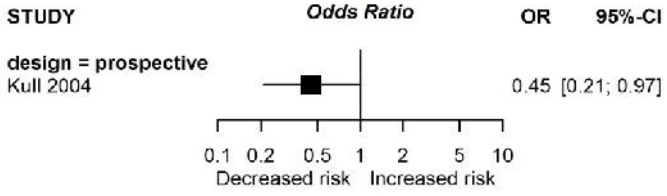
2.5 Exclusive Breastfeeding and Atopic Wheeze

2.5.1 Age at outcome measurement 0-4

2.5.1.1 0-2 months

The prospective cohort study of Kull (Figure 81) showed a lower risk of atopic wheeze in children aged 0-4 who were exposed to EBF for feeding ≥0-2 months vs. <0-2 months (OR 0.45; 95% CI 0.21, 0.97). The study carried a low risk of bias across all the domains studied.

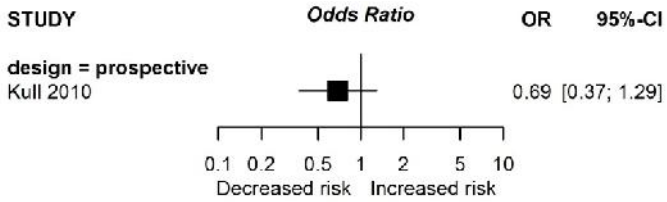
Figure 81 Exclusive breast feeding ≥0-2 months vs. <0-2 months and risk of atopic wheeze in children aged 0-4 years



2.5.1.2 3-4 months

The prospective cohort study of Kull (Figure 82) showed no evidence of a protective effect of prolonged EBF for ≥3-4 months vs. <3-4 months on atopic wheeze in children aged 0-4. The study carried a low risk of bias across all the domains studied.

Figure 82 Exclusive breast feeding ≥3-4 months vs. <3-4 months and risk of atopic wheeze in children aged 0-4 years

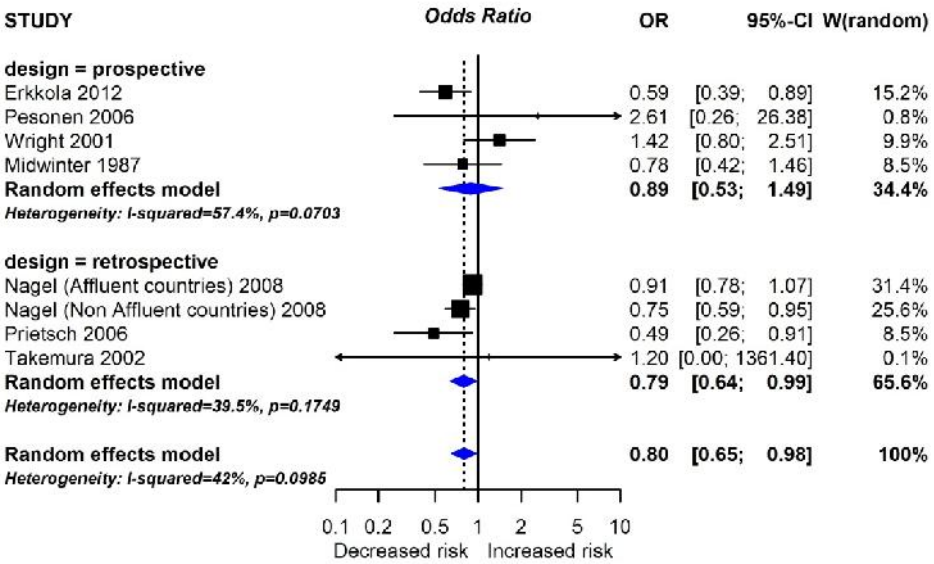


2.5.2 Age at outcome measurement 5-14

2.5.2.1 0-2 months

The cross-sectional study of Nagel investigated the risk of atopic wheeze at age 5-14 if EBF was ≥0-2 months vs. <0-2 months and reported no association with disease (Figure 83)

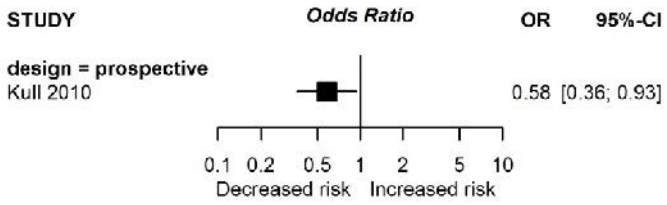
Figure 83 Exclusive breast feeding ≥0-2 months vs. <0-2 months and risk of atopic wheeze in children aged 5-14 years



2.5.2.2 3-4 months

The prospective cohort study of Kull (Figure 84) showed a reduced risk of atopic wheeze in children aged 5-14 years who were EBF for ≥3-4 months vs. <3-4 months (OR 0.58; 95% CO 0.36, 0.93). The study carried a low risk of bias across all the domains studied.

Figure 84 Exclusive breast feeding ≥3-4 months vs. <3-4 months and risk of atopic wheeze in children aged 5-14 years

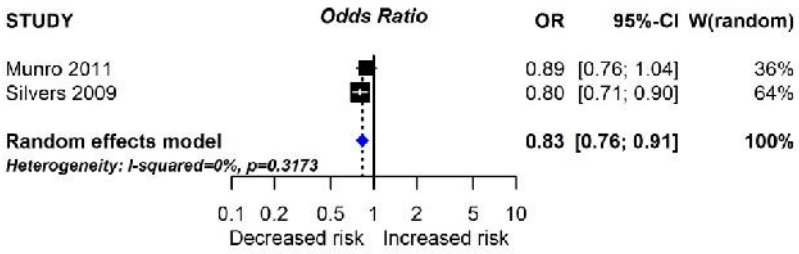


2.6 Exclusive Breastfeeding per month and recurrent wheeze

2.6.1 Age at outcome measurement 0-4

Two prospective cohort studies reported data eligible to calculate pooled effect estimates of risk of recurrent wheeze and exposure to EBF per month (Figure 85), suggesting a protective effect against disease in the exposed children between 0-4 years (OR 0.83; 0.76, 0.91). There was no evidence of heterogeneity between the two studies (I^2=0.0%). The study of Silvers had a low overall risk of bias, and the study of Munro had an unclear overall risk of bias.

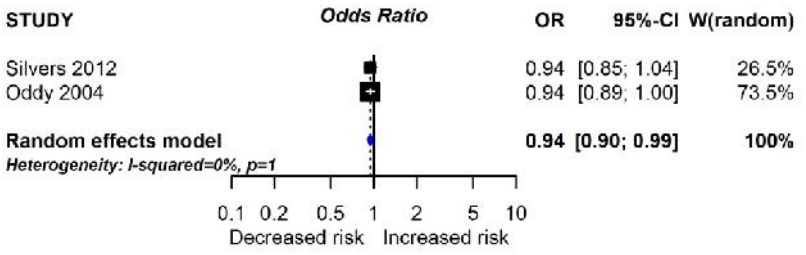
Figure 85 Exclusive breastfeeding per month and risk of recurrent wheeze in children aged 0-4 years



2.6.2 Age at outcome measurement 5-14

Two prospective cohort studies reported data eligible to calculate pooled effect estimates of risk of recurrent wheeze and exposure to EBF per month (Figure 86), suggesting a protective effect against disease in the exposed children between 5-14 years (OR 0.94; 0.90, 0.99). There was no evidence of heterogeneity between the two studies (I^2=0.0%). The study of Silvers had a low overall risk of bias, and the study of Oddy had an unclear overall risk of bias.

Figure 86 Exclusive breastfeeding per month and risk of recurrent wheeze in children aged 5-14 years



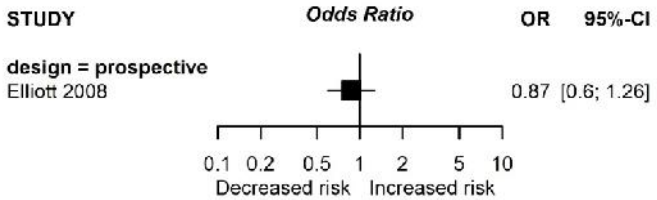
2.6.2.1 Exclusive breastfeeding and BHR

2.6.2.2 Age at outcome 5-14 years

2.6.2.3 0-2 Months

The prospective study of Elliot reported risk of BHR in children aged 5-14 who were exposed to EBF for ≥0-2 months vs. <0-2 months, showing no evidence of an association (Figure 87). The study had an unclear overall risk of bias, due to unclear risk of selection bias.

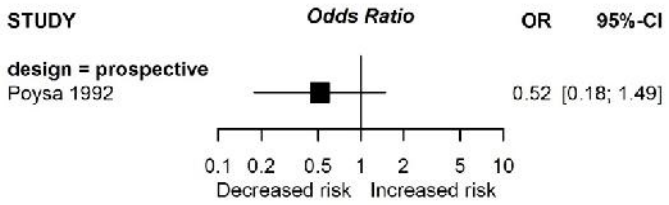
Figure 87 Exclusive breastfeeding ≥0-2 months vs. <0-2 months and risk of bronchial hyper-responsiveness in children aged 5-14 years



2.6.2.4 3-4 Months

The prospective study of Poysa reported risk of BHR in children aged 5-14 who were exposed to EBF for ≥3-4 months vs. <3-4 months, showing no evidence of an association (Figure 88). The study had a high overall risk of bias, due to risk of selection and confounding biases.

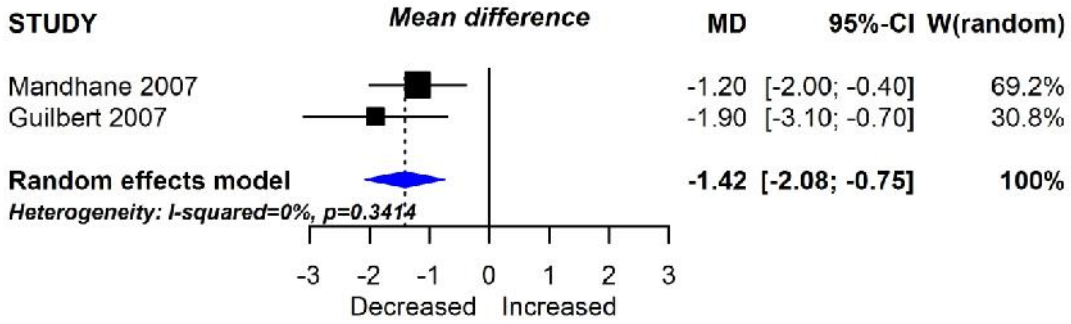
Figure 88 Exclusive breastfeeding ≥3-4 months vs. <3-4 months and risk of bronchial hyper-responsiveness in children aged 5-14 years



2.7 Data for EBF duration and lung function (FEV1/FVC%)

Two prospective cohorts had results with mean differences: (1) Mandhane, 2007, comparing breastfeeding < 1 month (reference) versus ≥ 1 months at 9 years of age, with unadjusted estimate; (2) Guilbert, 2007, breastfeeding < 1 month (reference) versus > 4 months between 11-16 years of age, with adjusted estimate.

Figure 89 Exclusive breastfeeding and FEV1/FVC% in children aged 5-14 years



2.8 Data for EBF duration and Wheeze, BHR or lung function that were not suitable for meta-analysis

Table 20 summarises the studies on wheeze, BHR or lung function for which data could not be meta-analysed. Meta-analysis was not possible due to the way the data were reported. In total there were 18 reports, of which 16 were prospective cohort studies and 2 cross-sectional studies.

From 9 studies reporting wheeze, and 10 reporting recurrent wheeze, just 2 reported a statistically significant association between increased EBF and reduced wheeze and 2 studies reported a significant association between increased EBF and increased wheeze.

There were 2 studies for BHR, both reporting no significant association between EBF and BHR. There were 14 measures reported from 3 prospective studies of lung function, in individuals aged 8-26 years old. Of these 14 measures, 2 were significantly associated with increased EBF, 2 with reduced EBF and 10 were not associated with EBF.

Table 20 Studies investigating the association between exclusive breastfeeding and wheeze which were not eligible for meta-analysis

First Author and year of publication	Design	Outcome	Age	N/n	EBF duration (continuous or categorical in months)	Measure of association	Effect	P-value
Giwercman, 2010 (134)	PC	wheeze	2	313	0+	Adjusted HR (95%CI)	0.67 (0.48-0.96)	<0.05
Zutavern 2004 (114)	PC	wheeze, recurrent wheeze	2, 5.5	606	>2	Adjusted OR		NS
Cano Garcinuno (130) (2003)	CS	wheeze	3	234	>3	Adjusted HR (95%CI)	0.83 (0.42-1.64)	0.60
Chong Neto, 2007 (141)	CS	wheeze	1	3003/1364	>4, >6	Adjusted PR		NS
Kramer, 2003 (156)	PC	wheeze	1	3483/8	>6	Adjusted OR (95%CI)	1.49 (0.66-3.36)	0.34
da Costa Lima, 2003 (81)	PC	wheeze	18	2247	0+	Adjusted PR (95%CI)	1.22 (1-1.5)	0.054
Kurukulaaratchy, 2006 (145)	PC	wheeze-atopic	10	unclear	>3	Adjusted OR (95%CI)	0.09 (0.01-0.93)	0.04

First Author and year of publication	Design	Outcome	Age	N/n	EBF duration (continuous or categorical in months)	Measure of association	Effect	P-value
Kurukulaaratchy, 2006 (145)	PC	wheeze-non atopic	10	492/178	>3	Adjusted OR		NS
Rullo, 2007 (163)	PC	recurrent wheeze	1.5, 5	101	>6	Adjusted OR		NS
Hesselmar 2010 (5)	PC	recurrent wheeze	1.5	184	continuous			NS
Nwaru, 2013 (24)	PC	recurrent wheeze	5	3675	0+, >3	Adjusted HR		NS
Mandhane, 2007 (138)	PC	recurrent wheeze	9	714/76	>1	Adjusted OR	1.22	0.04
Pesonen, 2006 (153)	PC	recurrent wheeze	5	160/1	>2	Prevalence	3.5% Vs 0%	-
Kramer, 2009 (157)	PC	recurrent wheeze	6.5	2951/44	>6	Adjusted OR (95%CI)	1.2 (0.6-2.4)	0.62

Table 21 Studies investigating the association between exclusive breastfeeding and BHR or lung function which were not eligible for meta-analysis

First Author and year of publication	Design	Outcome	Age	N/n	EBF duration (continuous or categorical in months)	Measure of association	Effect	P-value
Elliot 2008 (4)	PC	Bronchial hyper-responsiveness	5-14	3295	≥0-2mo vs <0-2mo	logistic regression, adjusted	0.87 (0.60-1.26)	0.46
Poysa 1992 (175)	PC	Bronchial hyper-responsiveness	5-14	119	≥3-4mo vs <3-4mo	Compared proportions, unadjusted	0.52 (0.18-1.49)	0.12
Kull, 2010 (127)	PC	FEV1(ml)	8	1838	>4	Adjusted Mean difference (95%CI)	17.4 (-5.7, 40.5)	NS
		PEF(L)	8	2168	>4	Adjusted Mean difference (95%CI)	4.5 (0.68, 8.29)	0.02
Mandhane, 2007 (138)	PC	FEV1/FVC%	26	714	>1	Mean difference (95%CI), unadjusted	-0.1 (-0.93; 0.73)	0.83
			9	714	>1	Mean difference (95%CI), unadjusted	-1.2 (-2.00; -0.40)	0.004
Guilbert, 2007 (178)	PC	FEF25–75(ml/s)	13	679	2-4 vs >1	Adjusted Mean difference (95%CI)	-2.9 (-132.3-126.5)	0.9

First Author and year of publication	Design	Outcome	Age	N/n	EBF duration (continuous or categorical in months)	Measure of association	Effect	P-value
Guilbert, 2007 (176)	PC	FEF25–75(ml/s)	13	679	>4 vs <1	Adjusted Mean difference (95%CI)	-124 (-267-19)	0.009
Guilbert, 2007 (176)	PC	FEF25–75/ FVC%	13	679	2-4 vs >1	Adjusted Mean difference (95%CI)	-2.7 (-6.8-1.5)	0.02
Guilbert, 2007 (176)	PC	FEF25–75/ FVC%	13	679	>4 vs <1	Adjusted Mean difference (95%CI)	-7.6 (-12.1;-3.1)	0.001
Guilbert, 2007 (176)	PC	FEV1(ml)	13	679	2-4 vs >1	Adjusted Mean difference (95%CI)	27 (-33.8-87.8)	0.1
Guilbert, 2007 (176)	PC	FEV1(ml)	13	679	>4 vs <1	Adjusted Mean difference (95%CI)	20 (-38 .8-78.8)	0.5
Guilbert, 2007 (176)	PC	FEV1/FVC%	13	679	2-4 vs >1	Adjusted Mean difference (95%CI)	-0.7 (-1.9, -0.5)	0.2
Guilbert, 2007 (176)	PC	FEV1/FVC%	13	679	>4 vs <1	Adjusted Mean difference (95%CI)	-1.9 (-3.1; -0.7)	0.004
Guilbert, 2007 (176)	PC	FVC(ml)	13	679	2-4 vs >1	Adjusted Mean difference (95%CI)	43 (-84.4, 170.4)	0.2

First Author and year of publication	Design	Outcome	Age	N/n	EBF duration (continuous or categorical in months)	Measure of association	Effect	P-value
Guilbert, 2007 (176)	PC	FVC(ml)	13	679	>4 vs <1	Adjusted Mean difference (95%CI)	103 (24.6, 181.4)	0.01
Elliot 2008 (4)	PC	Bronchial hyper-responsiveness	5-14	3295	≥0-2mo vs <0-2mo	logistic regression, adjusted	0.87 (0.60-1.26)	0.46
Poysa 1992 (175)	PC	Bronchial hyper-responsiveness	5-14	119	≥3-4mo vs <3-4mo	Compared proportions, unadjusted	0.52 (0.18-1.49)	0.12

3 Solid Food Introduction and Wheeze

3.1 Overall characteristics of studies, risk of bias and summary of results

Table 21 describes the main characteristics of the studies that assessed solid food introduction (SFI) in relation to wheeze risk. A total of 15 observational studies, and no intervention studies, reported the association between SFI and wheeze. Of these, 13 were prospective cohort studies and 2 were case-control studies. The majority of studies (n=9) are from Europe – others are from the Asia-Pacific region (n=4), North America (n=1), 1 from South Asia.

Overall, valid data on SFI duration in the first 2 years of life and wheeze risk were available from over 14,000 subjects. Information on wheeze was obtained solely from parental or self-reported in 3 studies and through Dr-diagnosis in 7 studies. Another 4 studies used a combination of self /parental report, Doctor diagnosis, and/ or objective measures (e.g. bronchial hyper-responsiveness (BHR)). One study used an unclear method for defining wheeze.

With regards to time of outcome diagnosis, 8 studies explored the association between SFI duration and wheeze at age 0-4 years and 4 at age 5-14 years. No studies investigated outcomes at age 15 years or beyond. A further three studies investigated the association between SFI duration and wheeze at various time points between the ages of 1 and 10 years. To ascertain exposure to SFI, 4 studies used a questionnaire method, 6 used an interview and 1 used a food frequency questionnaire (FFQ). A further 4 studies used a combination of 2 or more of these methods.

Risk of bias was assessed using the NICE Methodological checklists for cohort and case-control studies. Figure 84 illustrates the distribution of bias across the five main methodological areas of the studies. Over 40% of the studies had a high risk of overall bias, mainly due to confounding bias. The majority of the studies were considered to have a low risk of conflict of interest bias. Overall, there was no suggestion of an effect of SFI on wheeze. None of the meta-analyses that could be carried out showed an effect of SFI on wheeze. There were additionally three studies that could not be meta-analysed and showed no association with wheeze.

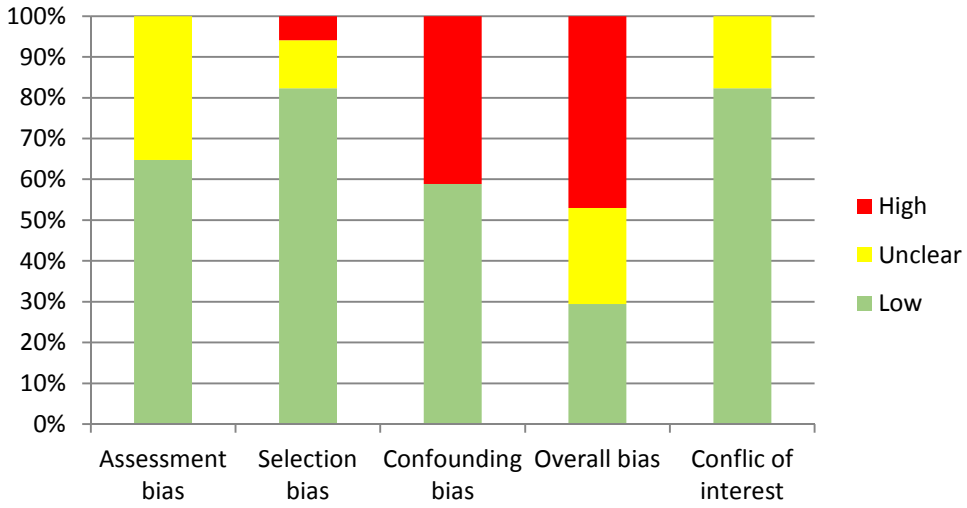
Table 22 Characteristics of included studies evaluating solid food introduction and wheeze

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Hesselmar, 2010 (5)	PC	184	I	DD asthma (>=3 episodes of wheeze)	1.5	Sweden	ALLERGYFLORA study. Population based study of babies selected from antenatal clinics between 1998 and 2003 - mainly high risk of allergic disease
Mihrshahi, 2007 (20)	PC	516	I	DD PLUS current wheeze	5	Australia	CAPS study. Infants born in 1997-1999 with family history of asthma or wheezing
Fergusson, 1983(132)	PC	1110	R/I	DD asthma (>=2 episodes of wheeze)	4	New Zealand	Christchurch Child Development Study. Population based cohort of infants born in 1977 in the Christchurch urban region
Larsson, 2008 (22)	PC	4779	Q	DD	9	Sweden	DBH study. Preschool children aged 1–6 years surveyed in 2000 and 2005.
Forsyth, 1993; Wilson, 1998 (25, 179)	PC	545	Q, D/I	Self-reported wheeze; DD; Physician assessment	2, 7.3	UK	Dundee infant feeding study. Population based cohort of infants born between 1983-1986
Karunasekera, 2001 (52)	CC	600	Q	Physician assessment	10	Sri Lanka	Hospital-based cases aged 1-10 years old with age matched controls from inpatient clinics
Snijders, 2008 (56)	PC	1894	Q	>=4 episodes of wheeze	2.0	Netherlands	KOALA study. Population based birth cohort of infants born between 2000-2002 (consisting of cohorts with conventional and alternative lifestyle)

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Zutavern, 2008 (180)	PC	2073	FFQ	Parent reported current wheeze OR asthma medication; DD	6	Germany	LISA study. Population based birth cohort of infants born between November 1997 and January 1999 at selected maternity hospitals in 4 German cities
Majeed, 2008 (150)	CC	398	Q/I	DD asthma AND >=2 episodes of wheeze	3	Pakistan	Cases are 1-12 years old children with wheeze/asthma admitted to paediatrics wards. Controls are age matched children and adolescents attending immediately after selection of the index case
Marini, 1996 (59)	PC	Unclear	Q	Physician assessment (>=3 episodes of wheeze)	3	Italy	Infants with family history of allergy whose mother were proposed to participate in an allergy prevention program
Morgan, 2004 (66)	PC	144	I	DD	1.5	U.K.	Infants from five prospective randomised dietary trials conducted in the UK between 1993 and 1997. Two trials involved term appropriate for gestational age (AGA) infants, one trial involved term small for gestational age (SGA) infants (birth weight 10th centile for gestational age and sex), and two trials involved preterm infants (37 weeks gestation, birth weight 2000g).
Hide, 1981; Kurukulaaratchy, 2004 (101, 146)	PC	843	D/Q, Q	Parent reported wheeze; >=2 episodes of wheeze between age <4 and 10 years; Late onset wheeze: onset >4 years of age and still wheezed at 10 years	1, 10	UK	The Isle of Wight Prevention study: born in 1977-1978 (normal risk of disease)
Van Asperen, 1983 (172)	PC	79	I	Parent reported wheeze	1.3	Australia	Cohort recruited from medical service, born in 1980-1981 with family history of atopy (high risk of disease)

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Joseph, 2012 (181)	PC	594	I	Unclear	3	USA	WHEALS STUDY: Recruited from hospital prenatal care and born in 2005 (normal risk of disease)
Zutavern 2004 (114)	PC	606	I	Parent reported current wheeze	2, 5.5	UK	Cohort recruited from general practices and born in 1993-1995 (normal risk of disease)

Figure 90 Risk of bias in studies of solid food introduction and wheeze



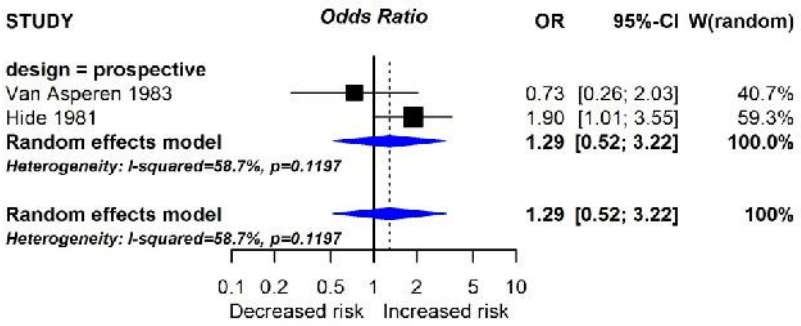
3.2 Solid Food Introduction and Wheeze

3.2.1 Age at outcome measurement 0-4

3.2.1.1 3-4 months

Two prospective cohort studies reported data that could be pooled to estimate the combined effect of SFI on wheeze at age 0-4 years, showing no suggestion of a protective effect (Figure 91). The study of Hide had a low overall risk of bias, whilst the study of Van Asperen had a high overall risk of bias (due to confounding bias), which might contribute to explain the high heterogeneity observed between studies (I^2=58.7%)

Figure 91 Solid Food Introduction ≥3-4 months vs. <3-4 months and risk of wheeze in children aged 0-4 years

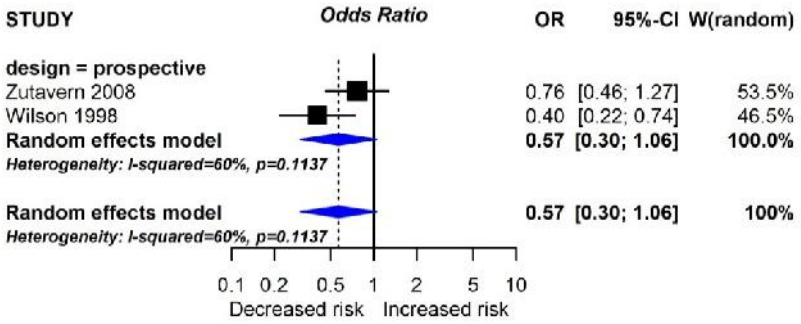


3.2.2 Age at outcome measurement 5-14

3.2.2.1 3-4 months

Two prospective cohort studies reported data that could be pooled to estimate the combined effect of SFI at ≥3-4 months vs. <3-4 months, on wheeze at age 5-14 years, showing no suggestion of a protective effect (Figure 92). The study of Zutavern had a low overall risk of bias, whilst the study of Wilson carried a had a high overall risk of bias (due to confounding bias), which might contribute to explain the high heterogeneity observed between studies (I^2=60.0%)

Figure 92 Solid Food Introduction ≥3-4 months vs. <3-4 months and risk of wheeze in children aged 5-14 years



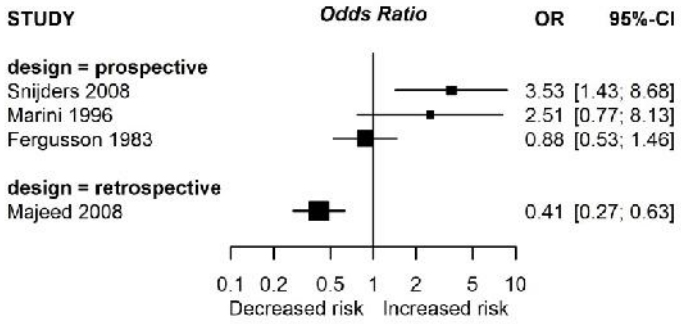
3.3 Solid Food Introduction and Recurrent Wheeze

3.3.1 Age at outcome measurement 0-4

3.3.1.1 3-4 months

Three prospective cohort studies and one case-control study reported data that could be pooled to estimate overall risk of recurrent wheeze at age 0-4 years comparing SFI at ≥3-4 months vs. <3-4 months. There was no evidence of an effect (Figure 93). Two studies (Majeed and Ferguson) had a high risk of overall bias (due to confounding bias), one had a low risk and one was unclear. These variations might explain the high heterogeneity observed between studies (I^2=87.3%)

Figure 93 Solid Food Introduction ≥3-4 months vs. <3-4 months and risk of recurrent wheeze in children aged 0-4 years

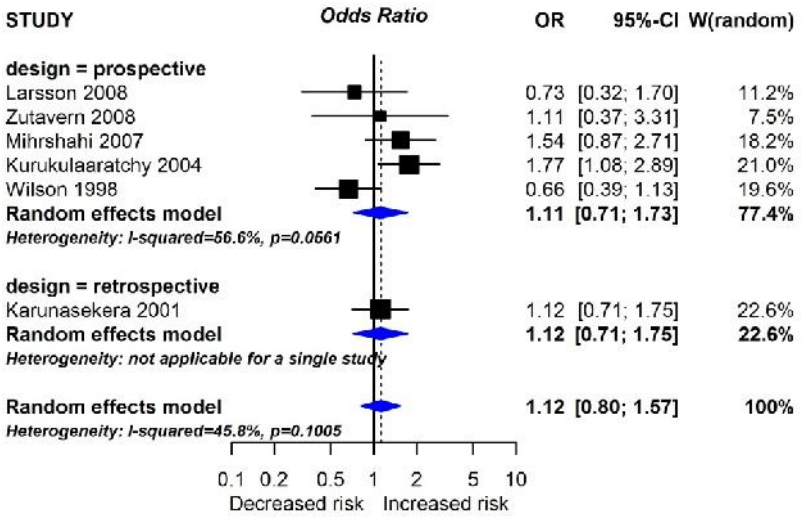


3.3.2 Age at outcome measurement 5-14

3.3.2.1 3-4 months

Five prospective cohort studies and one case-control study reported data that could be pooled to estimate overall risk of recurrent wheeze at age 5-14 years comparing SFI at ≥3-4 months vs. <3-4 months. There was no evidence of an effect (Figure 94). With the exception of the study of Wilson (which had a high risk of overall bias due to confounding bias), all prospective cohorts had a low risk of overall bias. The study of Karunasekera (case-control) had an unclear overall risk of bias. There was moderate heterogeneity observed between studies (I^2=45.8%)

Figure 94 Solid Food Introduction ≥3-4 months vs. <3-4 months and risk of recurrent wheeze in children aged 5-14 years



Subgroup analyses of risk of wheeze and solid food introduction ≥3-4 months vs. <3-4 months in children aged 5-14 years showed no indication of statistically significant differences between the various groups examined (Table 23). There were additionally three studies that could not be meta-analysed and showed no association with wheeze (Table 24).

Table 23 Subgroup Analyses of risk of wheeze and solid food introduction ≥3-4 months vs. <3-4 months in children aged 5-14 years

	Number of studies	OR [95% CI]	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted value used)	6	1.12 [0.80; 1.57]	45.8	
Adjusted	2	1.43 [0.87; 2.38]	0.0	Not tested
Unadjusted	5	1.11 [0.77; 1.60]	54.7	
Study Design – Prospective	5	1.11 [0.72; 1.73]	56.6	0.99
Study Design – Retrospective	1	1.12 [0.71; 1.75]	--	
Risk of disease – High	1	1.54 [0.87; 2.71]	--	0.27
Risk of disease – Normal	5	1.04 [0.71; 1.54]	49.8	
Risk of bias – Low	3	1.20 [0.77; 1.86]	3.0	0.82
Risk of bias – High/Unclear	3	1.10 [0.67; 1.88]	71.8	
Clear definition of breastfeeding duration	5	1.11 [0.72; 1.73]	56.6	0.99
Unclear definition of breastfeeding duration	1	1.12 [0.71; 1.75]	--	

Table 24 Studies investigating the association between solid food introduction and wheeze which were not eligible for meta-analysis

First Author and year of publication	Design	Outcome	Age	N/n	Age at SF introduction (continuous or categorical in months)	Average age at SF introduction	SF introduction Unaffected		SF introduction in Affected		P-value
Hesselmar 2010 (5)	PC	recurrent wheeze	1.5	184	continuous	Median (IQR)	4	4	4.2	4	NS
Joseph 2012 (181)	PC	wheeze	3	594	>4						NS
Forsyth, 1993 (179)	PC	wheeze	2	455	>2						NS

4 Conclusion

This systematic review on breastfeeding and solid food introduction did not find strong evidence of a relationship between these exposures and the outcomes of wheeze, recurrent wheeze, atopic wheeze, BHR or lung function. There were asymmetrical Funnel plots with evidence of publication bias in several meta-analyses of observational studies for TBF and EBF and wheezing, with small negative studies potentially missing. For this reason the only consistent finding, that TBF is associated with reduced risk of recurrent wheeze at age 5-14 years, was downgraded to VERY LOW certainty evidence, due to risk of publication bias. These findings highlight the importance of rigorous assessment of bias, including publication bias in the synthesis of existing scientific literature in this area, since previous reviews have not identified publication bias as an issue with this body of literature. The single intervention trial in this area found reduced risk of recurrent wheezing at age 1 year in infants born in centres randomised to a breastfeeding promotion intervention, but the outcome was not statistically significant OR 0.70 (0.29, 1.70). In the same trial there was no evidence for a difference in recurrent wheeze ('asthma ever') at age 6.5 years OR 1.2 (0.7, 1.9). Thus the intervention trial neither excludes nor supports an effect on wheezing.

Overall, the data for TBF and other outcomes, and for EBF and SF timing and all outcomes, showed significant heterogeneity in findings and rarely excluded the possibility of biological relationships. Thus we cannot confidently exclude the possibility that breastfeeding and solid introduction are related to risk of wheeze; however the currently available data do not support a relationship, aside from the VERY LOW certainty evidence that longer TBF is associated with reduced risk of recurrent wheeze at age 5-14 years.

We did not identify recent systematic reviews that met our requirements for inclusion in the review (i.e. R-AMSTAR score ≥32). There are however 3 recent important systematic reviews in this area which are relevant to discuss. The study of Dick (182) did not undertake meta-analysis, and no firm conclusions were made regarding the relationship between breastfeeding duration and risk of asthma at age ≤ 9 years. The systematic review of Waidyatillake (183) assessed the relationship between breastfeeding duration and lung function. Consistent with our approach and findings, Waidyatillake et al did not undertake meta-analysis, but identified the same studies as we did, and found evidence that increased

duration of TBF and EBF is associated with increased measures of lung function – especially FVC but also FEV1. We found evidence for a positive relationship between breastfeeding duration and lung function on at least one measure reported, for 5 of 7 studies reporting TBF, and 2 of 3 studies reporting EBF, with strongest evidence for FVC but also positive findings for measures of airway obstruction. However, findings were not consistent, and for two studies of EBF we found significant associations between longer duration and poorer lung function. We additionally studied bronchial hyper-responsiveness (BHR) where we were able to undertake limited meta-analysis and found no evidence of a relationship between TBF or EBF duration and BHR. The third relevant systematic review is the study of Dogaru, whose authors reported a strong association between increased breastfeeding duration and reduced risk of asthma, especially at age 0-2 years (184). Their approach of combining all durations of breastfeeding and creating a single pooled estimate for 'more' versus 'less' could be criticised on the basis that the reference group in some studies has significant overlap with the exposure group in other studies within the same meta-analysis. This may also lead to an exaggeration of any biases inherent in the included dataset. Our new finding of probable publication bias in this area, which has not been reported before, weakens the evidence base that prolonged breastfeeding duration reduces wheeze or asthma risk.

In summary we have found VERY LOW evidence that longer total duration of breastfeeding may be associated with reduced risk of recurrent wheeze at age 5-14 years. We have not found evidence for associations between duration of breastfeeding, or timing of solid food introduction, and other wheeze or lung function outcomes. The finding of probable publication bias means that these findings need to be interpreted with caution. We have identified a need for further investigation in this area – especially the study of mechanisms through which human milk feeding might promote lung growth in the developing infant, since we did not find evidence for an association between these exposures and allergic sensitisation; so if the association found here is real, then other mechanisms must be explored (183). A number of hypotheses have been proposed through which breastfeeding might promote lung growth – including reduced respiratory tract infections, reduced weight gain, altered respiratory dynamics during breastfeeding, increased exposure to breast milk derived growth factors, and as a secondary consequence of reduced asthma prevalence. Further work is needed to establish whether breastfeeding influences lung function in the developing infant, and whether the association seen here with recurrent wheezing from age 5-14 years can be confirmed.

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DIETARY INTAKE OF SOURCES OF FATTY ACIDS IN INFANTS AND MOTHERS, AND RISK OF ALLERGIC AND AUTOIMMUNE DISEASES

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1. Executive summary of findings on infant and maternal intake of sources of fatty acids and risk of allergic or autoimmune outcomes

1.1. Context of this report

This report is one of a series of systematic review reports included in Review C Part II, which focusses on evidence on dietary exposures during pregnancy, lactation and or infancy for reducing risk of allergic or autoimmune outcomes.. This report focuses on infant and maternal intake of dietary sources fats. It includes dietary fats derived from vegetable or animal sources, as well as specific foods rich in fat. Dietary supplementation with specific fatty acids is also included. As fish are a known source of essential omega 3 fatty acids, these are included in this report. Lean fish is also included as although its content of omega 3 fatty acids is much lower than that found in oily fish, they contain modest amounts of this macro-nutrient. Whenever possible, this report specifies the type of dietary source of fat studied, although in some cases this remained unspecified (e.g. 'fish').

1.2. Studies identified

A total of 26 studies investigated intake of fats and risk of allergic or autoimmune diseases. Thirty four studies investigated the association between infant or maternal intake of dietary sources of fats, and risk of allergic diseases. Amongst these, there were 20 were prospective cohort studies (PC), 1 nested case-control (NCC), 1 retrospective cohort (RC), 3 case-control (CC) and 1 cross-sectional study.

1.3. Outcomes evaluated

Outcomes studied included atopic dermatitis (AD) (n=13), food allergy (FA) (n=3), wheeze (n=13), lung function (LF) (n=1), allergic sensitisation (AS) (n=6), type 1 diabetes mellitus (T1DM) (n=3) and juvenile idiopathic arthritis (JIA) (n=1).

1.4. Dietary exposures studied

Studies showed a high degree of variation in the types of dietary fats studied. When studies had data not eligible for meta-analysis, these were summarised in a descriptive table. This included the reported effect sizes for each relevant dietary exposure included in the study and their effect size (if available). The main nutrient exposures included fat intake (in general), as well as specific macro-nutrients omega 3, omega 6, poly-unsaturated fatty acids (PUFAs),

saturated fatty acids, mono-unsaturated fatty acids (MUFA), α-linolenic acid, linoleic acid, docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA). Foods rich in fat included those of animal origin e.g. butter, as well those derived from vegetables e.g. margarine and oils. Several studies also included fish (any, unspecified, oily, lean, or both).

1.5. Dietary assessment

Table 3 summarises the types dietary instruments used to ascertain intake of fats. Most of the studies (n=32) used a form of questionnaire (specific dietary questionnaire), or as part of a general questionnaire). Other forms of dietary assessment included interviews and hospital records.

1.6. Presentation of results

We created a summary Table of Study Characteristics with key study features, presented separately for allergic (Table 1) and autoimmune outcomes (Table 2). There are seven main sections in this report that summarise the main findings for each of the following outcomes: atopic dermatitis (AD), food allergy (FA), lung function (LF), wheeze, rhino-conjunctivitis (RC), allergic sensitisation (AS), type I diabetes mellitus (T1DM), and juvenile idiopathic arthritis (JIA). We examined each of the studies for their eligibility to be meta-analysed. If two or more studies had data that could be combined, a meta-analysis was included in the corresponding section. If the heterogeneity across studies ≥ 80% then the overall effect of the studies is not included but that of each individual study is presented. As most of the studies included in this report had data that could not be combined in a meta-analysis, a table of main characteristics and main findings is provided at the end of each section. The tables provide specific details on the dietary intakes compared for each nutritional exposure as these varied between, and sometimes within study.

1.7. Risk of bias assessment

The risk of bias in included cohort and case control studies was assessed using a modified version of the National Institute for Clinical Excellence (NICE) methodological checklist for cohort and case-control studies, respectively (1). Key domains were:

- Selection Bias (low if cases and controls were selected from similar populations, if the participation rate was ≥80%, or <80% but investigators explored and adjusted for characteristic differences between participants and non-participants);
- Assessment Bias (low if validated and reliable tools were used to assess exposure and/or outcome), and;
- Confounding Bias (low if most likely confounders are identified and taken into account in study design and analysis).

Observational studies were considered at low overall risk of bias where the risk of bias was judged to be low for all 3 key domains for selection, assessment and confounding bias. For assessment of Confounding Bias, factors that we expected to be adjusted for within studies of allergic outcomes were: siblings (parity or birth order or family size); gender; age at outcome assessment; disease risk based on family history; maternal or household smoking (asthma/wheeze outcomes); maternal age; maternal education or socioeconomic status; mode of delivery. For studies on autoimmune outcomes we expected matching and/or adjusting for gender, age, address, socioeconomic status, smoking and disease risk. We also assessed possible Conflict of Interest, this being judged as low where there was no evidence of industry involvement in study design, analysis, interpretation or publication, and no evidence that study authors received remuneration from relevant industry partners for other activities. Given the nature of the studies included in this report (observational studies on reported dietary intake of foods or food groups), the risk of conflict of interest was judged as low in all cases. Therefore, conflict of interest bias is not systematically shown through this report. A Risk of Bias Figure is presented in each outcome section, reported for all studies contributing data, whether included in meta-analysis or reported narratively.

1.8. Key findings

i. **Overall risk of bias was low or unclear for the majority of the outcomes assessed.**

The overall bias was considered to be low in the majority of the studies on atopic dermatitis, food allergy, wheeze, allergic sensitisation, and for autoimmune diseases. In several studies it

was unclear whether adjustment for potential confounders had been made, which was the main factor influencing the 'unclear' assessment of this domain.

ii. Large variations in the dietary exposures studied and their comparison levels limited the possibility of meta-analyses

Although most studies used a questionnaire to ascertain dietary intake of the infant or the mother, there were large variations in the types of nutritional exposures assessed and the levels of intake compared. This means that opportunities for meta-analysis were very limited in this report. We present most data in narrative tables, and have detailed the effect estimates for each relevant exposure and indicated the levels of comparisons used for each effect estimate.

iii. There is no consistent evidence that maternal or infant fat intake influences risk of allergic outcomes or autoimmune diseases

We found inconsistent evidence regarding infant intake of fish and risk of AD and RC, and no evidence that other measures of infant fat intake, or maternal fat intake are associated with allergic outcomes or autoimmune diseases.

Overall we found no evidence of associations with infant or maternal intake of fats, fatty acids or fish, and risk of allergic or autoimmune diseases.

Table 1 Characteristics of included studies evaluating infant or maternal fat intake and allergic outcomes

Study	Design	N	Country	Type of dietary fat measured	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Willers, 2007 (2)	PC	1212	UK	Maternal fat intake from different sources	Q	AD (ISAAC), Lung function (Spirometry), AS-any by SPT, Wheeze (DD), Recurrent wheeze (DD asthma)	5	**Aberdeen birth cohort**: Population based birth cohort with pregnant women recruited 1997-99 while attending a hospital antenatal clinic at ~12weeks gestation
Kull, 2006; (3) Magnusson, 2013 (4)	PC	3230	Sweden	Infant fish intake	Q	AD (DD), AR (DD) AS-any by sIgE, Recurrent wheeze (≥ 3 episodes in past year)	4, 12	**BAMSE**: Prospective birth cohort of newborns in a predefined area of Stockholm, Sweden between 1994 and 1997

Study	Design	N	Country	Type of dietary fat measured	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Nwaru, 2012; (5) Nwaru, 2011; (6); Nwaru 2010 (7); Niinisto, 2012; (8) Lumia, 2011; (9) Erkkola, 2012; (10)	PC	3730	Finland	Maternal fish and margarine intake; infant fish intake	Q	AD (ISAAC), Wheeze (ISAAC), Recurrent wheeze (DD), AS (sIgE)	5, 0.5, <10	**DIPP**: Prospective birth cohort of children at high risk of TIDM (HLA genotype conferred susceptibility) born between 1997 and 2004 in Oulu and Tampere University Hospital Finland
Leermakers, 2013; (11) De Jong, 2012 (12)	PC	7210	The Netherlands	Maternal fish intake	Q	AD (ISAAC), Wheeze (ISAAC)	4	**GENERATION R**: Population based birth cohort , with pregnant women recruited < 25 weeks gestation in Rotterdam, The Netherlands
Hoppu, 2000 (13)	PC	114	Finland	Maternal fat intake	R	AS-any by SPT	1	Birth cohort of infants of breastfeeding mothers (for at least 3 months) with a positive family history of atopic disease

Study	Design	N	Country	Type of dietary fat measured	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Alm, 2009; (14) Goksor, 2011; (15) Alm, 2012;(16)	PC	4941	Sweden	Infant fish intake; infant fat intake	Q	Parent reported AD; DD Food Allergy	1, 4.5	**Infants of Western Sweden**: Population based birth cohort of infants born in the region in 2003
Jedrychowski, 2008 (17); 2011 (18)	PC	469	USA and Poland	Maternal fish intake	Q	AD - physician assessment; wheeze (parent reported)	1, 2	Prospective birth cohort of infants from non-smoking healthy mothers who gave birth at 29 - 43 weeks of gestation between 2001 and 2004
Laitinen, 2005 (19)	PC	95	Finland	Infant fat intake	D	AD (physician assessment), FA-cow's milk	0.5, 1	Children with a family history of AD (mother, father and/or older sibling with AD, AR or asthma), who participated in a prospective allergy prevention study (probiotic intervention trial)
Fitzsimon, 2007 (20)	PC	631	Ireland	Maternal fat intake	Q	Recurrent wheeze (physician assessment of asthma)	3	**LIFE-WAYS**: cohort of children born in 2002 whose mother had completed FFQ during pregnancy were followed up from birth through general practice records

Study	Design	N	Country	Type of dietary fat measured	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Sausenthaler, 2007 (21)	PC	2540	Germany	Maternal fat intake; maternal fish intake	Q	AD (DD; Parent reported), AS – any, food, aeroallergen by sIgE	2	**LISA**: Population based cohort study of newborns recruited between 1997 and1999 from 4 German cities: Munich, Leipzig, Wesel, and Bad Honnef.
Romieu, 2007; (22) Chatzi, 2008 (23)	PC	468	Spain	Maternal fish intake	I/Q, Q	Recurrent wheeze (parent reported), atopic wheeze (parent reported wheeze plus positive SPT), AS-aeroallergen by sIgE/SPT	4, 6, 6.5	**Menorca birth cohort**: Population based birth cohort with women recruited from antenatal care at all general practices in Menorca between 1997-1998

Study	Design	N	Country	Type of dietary fat measured	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Miyake, 2009 (24) Miyake, 2010 (25)	PC	771	Japan	Maternal fat intake, Maternal fish intake	Q	AD (DD, ISAAC), Wheeze (ISAAC)	0.33, 2	**OMCHS**: Population birth cohort with pregnant women between the 5-39th week of pregnancy recruited from a university hospital and three obstetric hospitals in municipality of Osaka between 2001 and 2003
Oien, 2010 (26)	PC	3067	Norway	Maternal fish/ fish oil intake	Q	AD (ISAAC), recurrent wheeze (DD asthma)		**PACT**: A controlled primary intervention study on allergic diseases conducted in the central part of Norway in the city of Trondheim. Inclusion in the control cohort began in September 2000, and the interventional programme started in a separate cohort in July 2002

Study	Design	N	Country	Type of dietary fat measured	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Roduit, 2012 (27)	PC	1041	Austria, Finland, France, Germany, and Switzerland	Infant fat source introduction	D	AD (DD)	1, 4	**PASTURE**: Population based birth cohort with women recruited in third trimester of pregnancy from rural areas in 5 European countries (Austria, Finland, France, Germany, and Switzerland) and divided into 2 groups: those who lived or worked on family run farms and those not living on a farm from the same area
Willers, 2008 (28)	PC	2811	The Netherlands	Maternal fish intake	Q	Wheeze (ISAAC), recurrent wheeze (DD asthma)	8	**PIAMA**: Population based birth cohort of children born in 1996/97 after prenatal recruitment through prenatal clinics in the northern, middle and south western part of the Netherlands. The children were allocated to an intervention study or to a natural history study depending on their family risk for allergy

Study	Design	N	Country	Type of dietary fat measured	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Narita, 2011 (29)	PC	1344	Japan	Maternal fish intake	Q	AD (ISAAC), wheeze (ISAAC)	3	**T-CHILD**: Population based birth cohort of Japanese mother-infant pairs with women recruited ~ second trimester in Tokyo
Wang, 2007 (30)	PC	1760	Taiwan	Maternal seafood intake/ fish oil supplementation	Q	AD (DD)	0.5	**Pilot study of Taiwan National Birth Cohort Study**: All postpartum women and new-borns from 29 towns were recruited with the multistage stratified systematic sampling design to obtain the representative samples from the national birth registration data in 2003
Oliver, 2010; (31) Grimshaw, 2012 (32)	NCC	123 (41 cases)	UK	Infant fat intake, maternal fish oil supplement	D, Q	FA-any (DBPCFC)	1, 2	**EuroPrevall** (UK birth cohort): cases were infants with food allergy, each matched to two controls.
Calvani, 2006 (FH+),Calvani , 2006 (FH-); (33)	RC	988	Italy	Maternal fat intake	Q	AS-aero-allergy, food, cow's milk, egg by SPT	5	**APAL**: RC study of children attending outpatients allergy clinic in Rome between 2001-2002

Study	Design	N	Country	Type of dietary fat measured	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Salam, 2005 (34)	CC	691 (279 cases)	USA	Maternal fish intake	I	Recurrent wheeze (DD asthma)	9-16	Children's Health Study: cases and controls selected from school-children who participated in a population-based study: USA
Castro-Rodriguez, 2010 (35)	CS	1409 (594 cases)	Spain	Maternal fat intake	Q	Wheeze (ISAAC)	1.4	**EISL**: Spanish population attending primary healthcare clinics, cases with wheeze in first year of life and controls without: Spain

PC Prospective cohort study; RC retrospective cohort study; Q questionnaire; AD atopic dermatitis; DBPCFC double blind placebo control food challenge; ISAAC International Study of Allergy and Asthma in Children; AS allergic sensitisation; SPT skin prick test, sIgE specific IgE; DD Doctor diagnosis (community); Physician assessment is assessment by study physician; AR allergic rhinitis, FA food allergy; CS cross-sectional study; NCC nested case-control study; FH+ having a family history of disease; FH- no family history of disease

Table 2 Characteristics of included studies evaluating infant or maternal fat intake and autoimmune outcomes

Study	Design	N	Country	Type of dietary fat measured	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Fronczak, 2003; (36) Lamb 2008 (37)	PC	642 (27 cases)	America, Australia	Maternal fat intake	Q	TIDM (serology)	4	**DAISY**: Prospective birth cohort of children at increased risk for T1DM (relative with T1DM via registries and hospital records) recruired from 1993 to 2004 in Denver, Colorado US were screened for human leukocyte antigen (HLA) genotype associated with celiac disease and TIDM
Brekke, 2010 (38)	PC	4005 (191 cases)	Sweden	Maternal fish intake	Q	TIDM (serology)	5	**ABIS**: Population based birth cohort of children born in Southeast Sweden between 1997 and 1999
Nwaru, 2012; (5) Nwaru, 2011; (6) Niinisto, 2012; (8) Lumia, 2011; (9) Erkkola, 2012; (10) Virtanen, 2011 (39)	PC	3730	Finland	Maternal fish and margarine intake; infant fish intake	Q	TIDM (serology)	5, 0.5, <10	**DIPP**: Prospective birth cohort of children at high risk of TIDM (HLA genotype conferred susceptibility) born between 1997 and 2004 in Oulu and Tampere University Hospital Finland

Study	Design	N	Country	Type of dietary fat measured	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Stene, 2000; (40)	CC	1131 (84 cases)	Norway	Maternal fish oil supplement	Q	TIDM (medical diagnosis)	<15	Cases were T1DM patients in Vest-Agder & on the National Childhood Diabetes Register 1982-98 and controls were selected randomly from the population register for the same area and period
Stene, 2003 (41), Stene, 2008 (42)	CC	2213 (545 cases)	Norway	Infant oil supplement, maternal fish oil supplement	Q	TIDM (medical diagnosis)	8.8, 10	**Norwegian Childhood Diabetes Study** Group: cases were all children on the diabetes registry diagnosed 1997-2000 and controls were matched from the national population registry.
Ellis, 2012 (43)	CC	655 (246 cases)	Australia	Maternal fish oil supplement	Q	JIA (ILAR criteria)	0-18	**CLARITY**: cases were recruited during a clinic visit to Royal Children's Hospital, with diagnosed JIA using ILAR criteria: controls were patients in for elective surgery, also at the Royal Children's Hospital Day Surgery Unit

PC Prospective cohort study; Q questionnaire; CC case-control study; SPT skin prick test, sIgE specific IgE; DD Doctor diagnosis (community); Physician assessment is assessment by study physician; AR allergic rhinitis, FA food allergy, T1DM Type 1 diabetes mellitus, RC retrospective cohort, JIA juvenile idiopathic arthritis; ILAR International League of Associations for Rheumatology

Table 3 Dietary instrument used to ascertain infant or maternal intake of dietary sources of fats

First author, year	Dietary assessment used
Alm, 2011	Specific question on fish intake in first year of life, as part of main questionnaire on risk factors for respiratory diseases
Brekke, 2010	22-item FFQ
Calvani, 2006	Standardised self-administered questionnaire
Castro-Rodriguez, 2010	Environmental questionnaire which included type of oil used for cooking or in dressing salads
Chatzi, 2008	Spanish version of the validated EPIC-Norfolk FFQ
Ellis, 2012	General questionnaire with dietary questions
Erkkola, 2012	Retrospective diary records of foods eaten during the month preceding delivery (8th month of pregnancy)
Fitzimon, 2007	'Hospital records'
Fronczak, 2003	Willett FFQ regarding third trimester diet of mother, administered at 2-3 months post-delivery
Goksor, 2011	Questions based on the ISAAC questionnaire for Sweden
Grimshaw, 2012	Questionnaire data from the general EuroPrevall questionnaire (fish oil use during pregnancy)
Hoppu, 2010	Four-consecutive-day food record with household measures
Jedrychowski, 2008	Interviews with a validated FFQ
Kull, 2006	Questionnaire about frequency of fish intake by the infant and age (months) of fish introduction
Lamb, 2008	Willet FFQ
Laitinen, 2005	Four day food diaries completed by parents or personnel at day-care
Leermakers, 2013	Modified version of a semi-quantitative FFQ
Lumia, 2011	Validated, self-administered, semi-quantitative 181-item FFQ

First author, year	Dietary assessment used
Magnusson, 2013	General parental questionnaire which included questions on other risk factors
Miyake, 2009	Self-administered DHQ that assessed dietary habits during the preceding month (150 foods)
Narita, 2011	Dietary history questionnaire
Niinisto, 2012	FFQ
Nwaru, 2010, 2011, and 2012	181-item FFQ
Oien, 2009	Questionnaire administered to the mother 1 year after delivery
Oliver, 2010	Food diaries with qualitative and quantitative data completed and returned every 4 weeks in the first year of life
Roduit, 2012	Dietary intake reported by parents in monthly diaries between the 3rd and 12th month of life
Romieu, 2007	Interviewer-administered FFQ at 3 months after delivery
Salem, 2005	Telephone interviews with mothers/guardians
Sausenthaler, 2007	Semi-quantitative FFQ capturing intake in the last 4 weeks of pregnancy
Stene, 2000 and 2003	Parental questionnaire, which included questions on fat intake and duration of exclusive breastfeeding
Wang, 2007	Questions on dietary intake included in environmental questionnaire
Willers, 2007	Semi-quantitative FFQ (Version 5.4 of the Scottish Collaborative Group FFQ) mailed at 32 weeks gestation (150 items divided into 20 food groups

EPIC= The European Prospective Investigation into Cancer Study

FFQ= Food frequency questionnaire

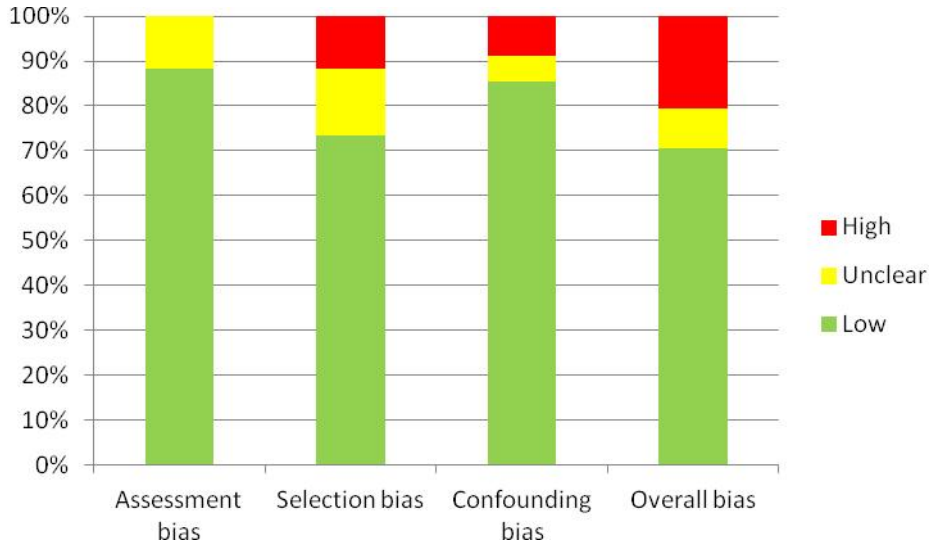
ISAAC=International Study of Allergy and Asthma in Children

DHQ= Dietary history questionnaire

2. Infant or maternal dietary intake of fats and risk of atopic dermatitis

Sixteen studies including over 26,000 children investigated the association between infant or maternal intake of fats and risk of AD. The quality assessment of studies on AD and intake of various types of fats is summarised in Figure 1. Overall, 70% of the studies were considered to be of low risk of bias. The assessment and confounding biases were judged to be low in over 80% of the studies. This was largely driven by the methodological quality of the prospective cohort studies that examined the association between this outcome and the exposure of interest.

Figure 1 Risk of Bias in studies of fat intake and atopic dermatitis



Figures 2 to 5 illustrate the combined effect sizes of cohort studies that had comparable estimates of maternal intake of fats and risk of AD in the offspring. The studies of **Miyake (2009)** and **Sausenthaler (2007)** showed no evidence of an association between maternal intake of butter during pregnancy and risk of this outcome in their children (Figure 2). Both studies had a similar effect size, and there was very low heterogeneity. This was likely to be a reflection of the similar methods used in both studies to ascertain dietary intake, and the time of outcome assessment (2 years old).

Figure 2 Maternal butter intake (highest vs. lowest) and risk of AD in children at age 0-4 years old

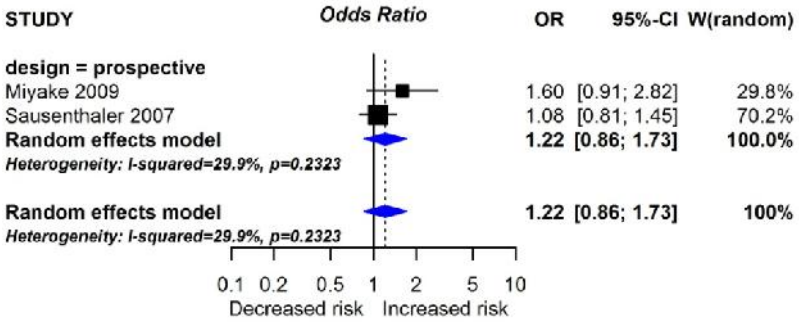
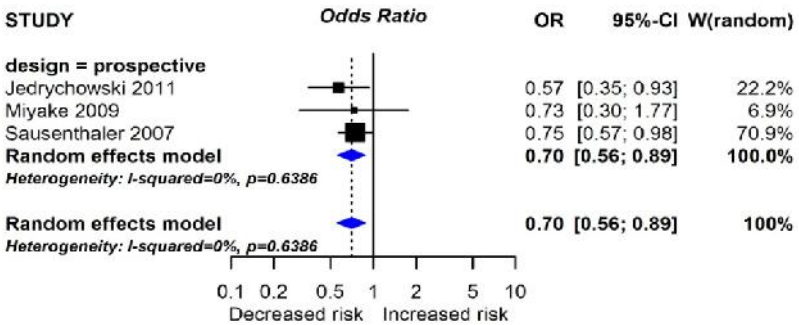


Figure 3 shows the combined effect estimates of association between maternal intake of marine sources of fat (omega 3, seafood or fish) and risk of AD. The prospective cohort studies of **Jedrychowski (2011)**, and **Sausenthaler (2007)** showed a statistically significant negative association, whilst **Miyake**'s findings **(2009)** were in the same direction but did not reach statistical significance. The overall effect of these three studies showed a 30% lower risk of AD (95% CI 0.56, 0.89) in the child of mothers who ate the highest vs lowest consumption categories of omega 3 fatty acids during pregnancy. There was no evidence of heterogeneity (I^2=0%) across studies.

Figure 3 Maternal intake of marine sources of fatty acids intake (highest vs. lowest) and risk of atopic dermatitis (eczema) in children at age 0-4 years old



Three prospective cohort studies (**Leermakers (2013)**, **Oien (2009)** and **Wang (2007))** had comparable data on maternal fish intake and risk of AD in the offspring (often vs rare) (Figure 4). There was no evidence of an association with AD in any of the studies or in the

combined effect size. There was no heterogeneity across studies (I^2=0%). Similarly, the studies of **Oien (2009)** and **Wang (2007)** showed no evidence of association between maternal supplementation with fish oils during pregnancy and risk of AD in the offspring (Figure 5).

Figure 4 Maternal intake of marine sources of fatty acids intake (often vs. rare) and risk of atopic dermatitis (eczema) in children at age 0-4 years old (odds ratio)

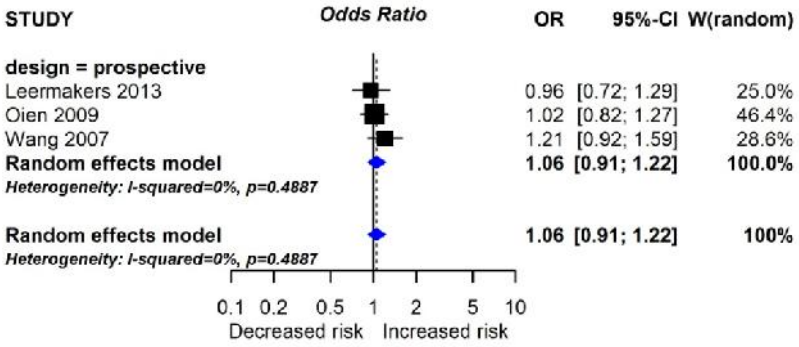


Figure 5 Maternal fish oil supplementation (often vs. rare) and risk of atopic dermatitis (eczema) in children at age 0-4 years old (odds ratio)

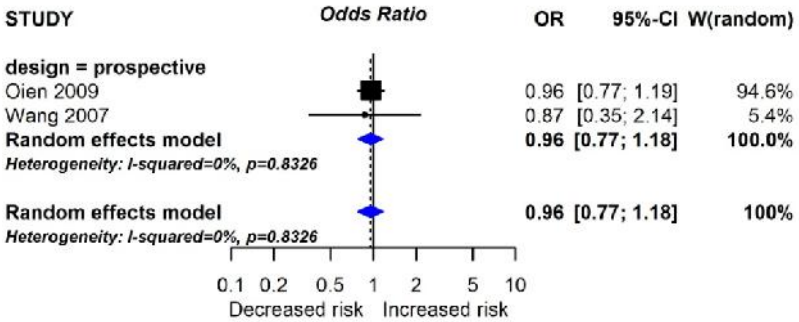
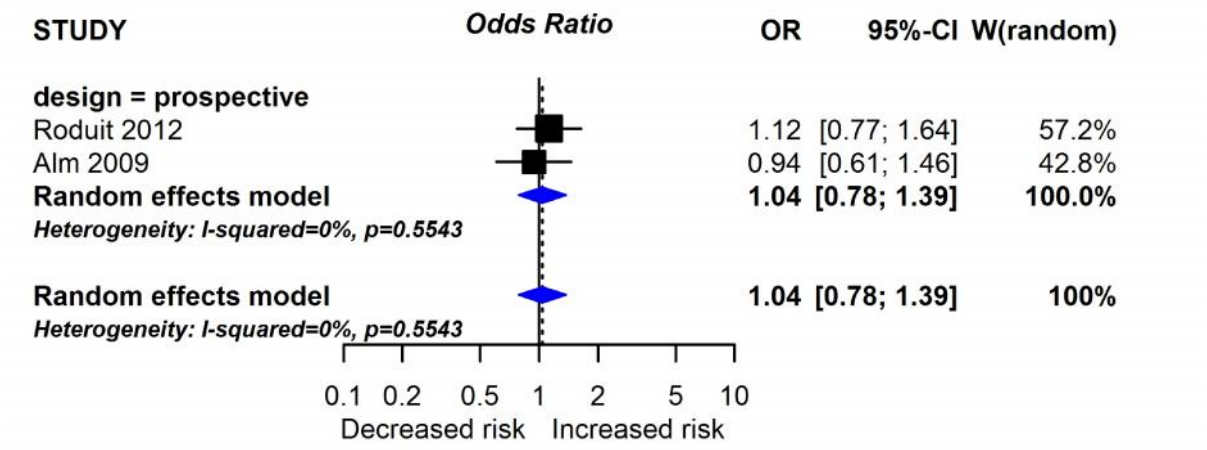


Figure 6 shows the association between introduction of fats in the infant's diet and risk of AD at age 0-4. The prospective studies of **Roduit (2012)** and **Alm (2009)** reported no evidence of

association between introduction of any type of fat spread for bread (Alm) or butter (Roduit) after month 8 of life compared to earlier, and AD.

Figure 6 Introduction of fats in the infant's diet (> 8 months vs earlier) and risk of AD at age 0-4 years old



2.1. Studies that investigated the association between infant or maternal intake of fats and risk of AD which were not eligible for meta-analysis

Table 4 summarises the findings of observational studies investigating intake of fats and risk of AD in childhood. Six studies investigated infant intake, whereas eight had data on maternal intake during pregnancy or lactation. The BAMSE prospective cohort study of **Kull (2006)** investigated risk of AD at age 4 in Swedish children according to their fish intake during the first year of life. The study showed a negative association between fish intake and risk of AD at age 4 in the entire sample of children studied (OR 0.69; 95% CI 0.57-0.84), and this association remained statistically significant when children with early onset eczema were excluded from analysis to account for potential reverse causation. The same cohort study followed up these children to age 12 years old (**Magnussonn, 2013**) and found that a higher intake of fish at age 1 was associated with a lower risk of AD when age 12. . The prospective study of **Alm (2009)** reported no association between level of fish intake in infancy and AD, although they did find an association between timing of fish introduction in infancy and AD (discussed in review B report). The rest of the studies on infant intake, showed no evidence

that other dietary sources of fats (e.g. margarine, lean fish, and cod liver oil) were associated with AD in children, regardless of the disease risk level studied.

The study of **Oien (2009)** showed that a higher intake of oily fish (any) in pregnancy women was negatively associated with risk of AD at age 2 (OR 0.65; 95% CI 0.45-0.94) and the association was strongest for oily fish. However this was not a consistent finding across studies.

Amongst the studies examining maternal intake of dietary sources and risk of AD in the offspring, there was little evidence of a consistent effect. The study of **Sausenthaler (2007)** showed that intake during the final 4 weeks of pregnancy of margarine and butter, but not deep frying vegetable fat, was associated with higher risk of AD at age 2 years in their offspring. However, these findings were not confirmed in two other studies who found no evidence of an association between intake of butter (**Nwaru 2012**) or margarine (**Willers 2007**) and risk of AD.

Conclusion

We found no evidence that fatty acid or fat intake during pregnancy, lactation or infancy is associated with risk of AD in offspring.

Table 4 Studies investigating the association between fat intake and atopic dermatitis which were not eligible for meta-analysis

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p<0.05)
					INFANT INTAKE		
Alm, 2009 (14)	PC	AD	1	4941	Fish intake in the first year of life (a few times a year vs ≥3 times per week)	OR	**1.32 (0.86-2.02)**
				2536/358	**Fish intake in the child's diet at 12 months of age** (≥2-3 times per month vs ≤ once month) Children who have eczema at age 1 excluded	OR	**0.76 (0.60-0.98)**
Kull, 2006 (3)	PC	AD	4	2896/551	All children	OR	**0.69 (0.57-0.84)**
Magnusson, 2013 (4)	PC	AD	12	2456	Fish intake in first year of life (≥2-3 times per month vs ≤ once a month)	OR	**0.61 (0.53-0.70)**
Laitinen, 2005 (19)					**Fat intake during the first year of life:**		
			0.5	60	Grams of fat intake/ mega joule per day energy intake	OR	1.06 (0.99-1.14)
			0.5	60	Percentage of energy intake as fat	OR	NS
	PC	AD	1	95	Grams of fat intake/ mega joule per day energy intake	OR	NS
					Food introduced in the first year of life vs none in the first year:	OR	

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p<0.05)
Roduit, 2012 (27)	PC	AD	4	1041	Margarine (high risk infants)		1.35 (0.75-2.45)
					Butter (high risk infants)	OR	0.92 (0.53-1.59)
					Margarine (low risk infants)	OR	1.61 (0.62-4.21)
Roduit, 2012 (25)	PC	AD	4	1041	**Food introduced in the first year of life vs none in the first year:** Butter (low risk infants)	OR	1.15 (0.55-2.42)
					Margarine (any risk infants)	OR	1.45 (0.86-2.44)
					Butter (any risk infants)	OR	1.00 (0.65-1.55)
			4	912	Margarine introduced into diet>12 months vs 3 to 12 months	OR	1.45 (0.86-2.44)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p<0.05)
			4	912	Butter introduced into diet>12 months vs 3 to 12 months	OR	1.00 (0.65-1.55)
			1	912	Margarine introduced into diet>12 months vs 3 to 12 months (single point measurement)	OR	1.32 (0.88-1.97)
			1	912	Butter introduced into diet >12 months vs 3-12 months (single point measurement)	OR	1.28 (0.86-1.91)
					MATERNAL INTAKE		
Leermakers, 2013 (11)	PC	AD	4	2796	**Maternal intake in first trimester of pregnancy (intake indicated below vs no intake):** Total fish 140-209g/week		0.96 (0.72-1.28)
					Total fish 1-69g/week		1.03 (0.85-1.25)
					Total fish 70-139g/week		1.06 (0.88-1.27)
					Lean fish 35-69 g/week		1.04 (0.89-1.22)
					Lean fish >70 g/week		0.99 (0.79-1.24)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p<0.05)
					Lean fish 1-34g/week		1.06 (0.88-1.27)
					Fatty fish 1-34g/week		1.17 (0.99-1.38)
					Fatty fish 35-69 g/week		1.17 (0.99-1.38)
					Fatty fish >70 g/week		1.06 (0.88-1.27)
					Shellfish 1-13 g/week		**1.18 (1.02-1.37)**
					Shellfish >14 g/week		1.02 (0.86-1.21)
Miyake (Saito), 2010 (25)	PC	AD	0.33	771	**Maternal intake during pregnancy (in the previous month) (highest vs lowest quartile):**		
					Saturated fat	OR	0.95 (0.43-2.09)
					Cholesterol	OR	0.96 (0.43-2.12)
					Arachidonic acid	OR	0.81 (0.37-1.79)
					Linoleic acid	OR	1.04 (0.43-2.49)
					n6 fatty acids	OR	1.14 (0.46-2.81)
					MUFA	OR	1.48 (0.59-3.73)
					Total fat	OR	1.38 (0.57-3.33)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p<0.05)
					Fish	OR	1.15 (0.50-2.62)
					α-linolenic acid	OR	0.76 (0.31-1.87)
					Omega 3/omega 6 fatty acids	OR	1.17 (0.52-2.62)
					DHA	OR	1.43 (0.67-3.07)
					Omega 3 fatty acids	OR	1.45 (0.64-3.31)
					EPA	OR	1.84 (0.82-4.15)
Miyake, 2009 (24)	PC	AD	2	763	**Maternal intake during pregnancy (in the previous month) (lowest vs highest quartile):** Cholesterol	OR	0.71 (0.40-1.27)
					Arachidonic acid	OR	0.69 (0.37-1.27)
					MUFA	OR	1.32 (0.70-2.49)
					Linoleic acid	OR	**2.11 (1.05-4.26)**
					Omega 6 fatty acids	OR	**2.25 (1.12-4.54)**
					Total fat	OR	1.49 (0.78-2.83)
					α-linolenic acid	OR	1.79 (0.92-3.50)
					DHA	OR	0.86 (0.32-2.28)
					EPA	OR	0.98 (0.38-2.50)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p<0.05)
					Omega 3/omega 6 fatty acids	OR	1.32 (0.64-2.71)
					Omega 3 fatty acids	OR	1.74 (0.81-3.73)
					Maternal consumption of fish during pregnancy: (Lowest vs highest quartile):		NS
					Fish		
Narita, 2011 (29)	PC	AD	3	1344	Omega 3/omega 6 fatty acids		NS
					Maternal intake during the 8th month of pregnancy (second/third tertile of intake vs lowest):		
					Consumption of margarines (no vs. yes)	OR	0.92 (0.78-1.09)
					Butter and butter spreads	OR	1.06 (0.85-1.32)
Nwaru, 2012 (5)	PC	AD	5	2441	Saturated fatty acid	OR	1.01 (0.81-1.25)
					MUFA	OR	1.11 (0.90-1.37)
					γ-linoleic fatty acids	OR	1.10 (0.89-1.35)
					Conjugated linoleic fatty acids	OR	1.08 (0.87-1.33)
					Omega 6 fatty acids	OR	1.03 (0.83-1.28)
					Linoleic fatty acid	OR	1.02 (0.83-1.26)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p<0.05)
					Arachidonic acid	OR	0.98 (0.79-1.21)
					Oils	OR	1.10 (0.88-1.36)
					'Industrial fats' (unclear term)	OR	1.06 (0.85-1.32)
					Trans-fatty acid	OR	1.19 (0.96-1.47)
					Total fatty acid	OR	1.19 (0.96-1.47)
					α-linoleic fatty acids	OR	0.95 (0.77-1.18)
					PUFA	OR	1.06 (0.85-1.32)
					Maternal intake during the 8th month of pregnancy(second/third tertile of intake vs lowest): Omega 3 fatty acids from plants	OR	1.03 (0.84-1.26)
					Omega 3 fatty acids	OR	0.97 (0.79-1.20)
					EPA	OR	0.93 (0.75-1.16)
					Omega 3 fatty acids from fish	OR	0.86 (0.70-1.06)
Nwaru, 2012 (5)	PC	AD	5	2441	DHA	OR	0.85 (0.68-1.05)
					Maternal intake of the following sources of fish up to the first year of life		
Oien, 2010 (25)	PC	AD	2	3055	Any fish (≥4 times/week vs never or < 1x/week)	OR	**0.65 (0.45-0.94)**

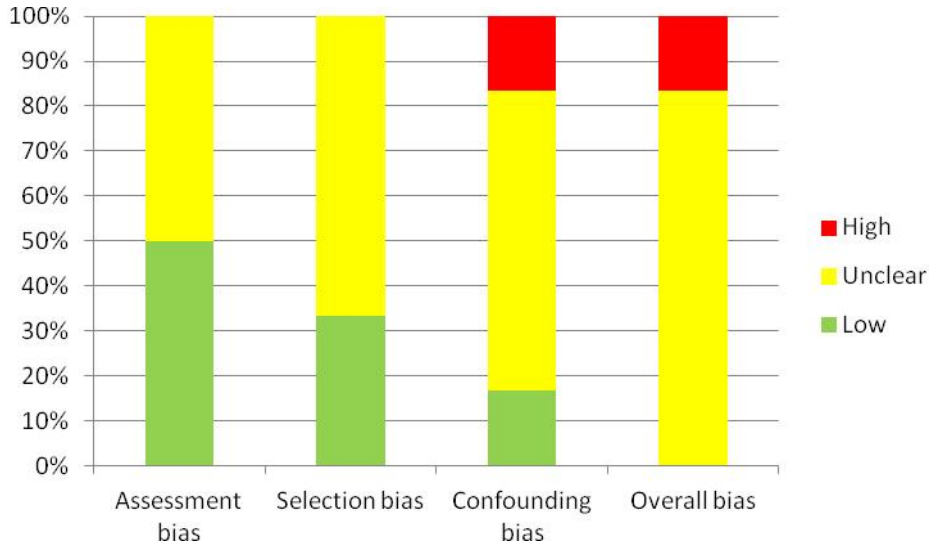
First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p<0.05)
Oien, 2010 (26)	PC	AD	2	3055	Cod liver oil (≥4 times/week vs never)	OR	0.89 (0.59-1.34)
				3055	Cod liver oil (≤3 times/week vs never)	OR	1.11 (0.68-1.81)
				3050	Lean fish e.g. cod and coalfish (≥1 per week vs never or < once per week)	OR	0.67 (0.42-1.08)
				3050	Oily fish e.g. redfish, halibut, salmon, trout herring and mackerel (≥ 1 per week vs never or < once per week)	OR	**0.21 (0.05-0.86)**
Sausenthaler, 2007 (21)	PC	AD	2	2427	**Maternal consumption during the last 4 weeks of pregnancy (high vs low tertile):** Margarine	OR	**1.49 (1.09-2.04)**
				2465	Deep frying vegetable fat	OR	1.10 (0.86-1.41)
				2492	Butter	OR	**1.48 (1.15-1.91)**
					Maternal diet during pregnancy: Fish intake ≥1/week vs never	OR	**0.57 (0.35-0.92)**
					Fat from dairy products (low vs high)		NS

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p<0.05)
Willers, 2007 (2)	PC	AD	5	1212	Margarine/low fat spread vs Butter spread		NS

3. Infant or maternal dietary intake of fats and risk of food allergy

Five studies which included over 5,500 children investigated the association between infant or maternal intake of fats and risk of FA. The quality assessment of observational studies examining the association between infant or maternal intake of fats and risk of food allergy is illustrated in Figure 7. Most of the studies were judged to have low or unclear risk of bias across the three domains investigated.

Figure 7 Risk of Bias in studies of fat intake and food allergy



3.1. Studies that investigated the association between infant or maternal intake of fats and risk of food allergy which were not eligible for meta-analysis

Table 5 summarises the findings of three observational studies on infant intake, and two on maternal intake of fats and risk of FA in the offspring, none of which showed evidence of an association between dietary fats and this outcome.

Conclusion

We found no evidence to suggest that infant or maternal intake of dietary fats influences the risk of FA in children.

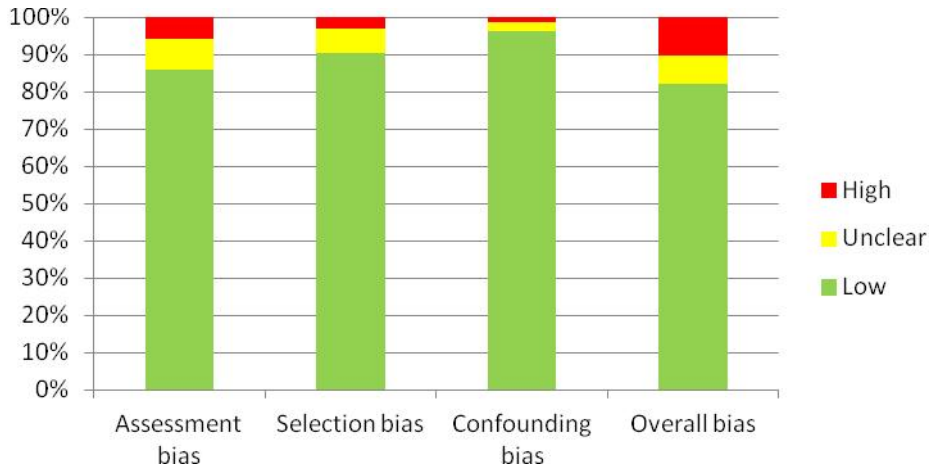
Table 5 Studies investigating the association between intake of dietary sources of fat and food allergy which were not eligible for meta-analysis

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p<0.05)
					INFANT INTAKE		
Goksor, 2011 (15)	PC	FA any food	4.5	4496	Frequency of fish consumption, assessed at 12 months age (unclear level of comparison)	Unclear	NS
Laitinen, 2005 (19)	PC	FA any food	1	95	Infant fat intake (% of energy intake [MJ/day])	Mean	(28% vs 33% in healthy vs allergic) NS
Oliver, 2010 (32)	NCC	FA any food	1	93/31	Dietary fat intake during the first year of life (unclear level of comparison)	OR	NS
					MATERNAL INTAKE		
Nwaru, 2010 (5)	PC	FA any food	5	931	Maternal n-3 PUFA intake at 8th month of pregnancy lowest tertile vs highest 2 tertiles	OR	0.73 (0.33-1.61)
Grimshaw, 2012 (31)	NCC	FA any food	2	123/41	Fish oils supplement during pregnancy (no vs yes)	OR	NS
					Fish oils supplement during lactation (no vs yes)	OR	NS

4. Infant or maternal dietary intake of fats and risk of wheeze

Fifteen studies which included over 27,000 children examined the association between infant or maternal intake of fats and risk of wheeze. The overall risk of bias was low for the majority of studies. The assessment of outcome and exposure were clearly described, and almost all studies reported adjusted data (Figure 8).

Figure 8 Risk of Bias in studies of fat intake and wheeze



Two birth cohorts from Japan (**Miyake 2009**; healthy, non-smoking mothers) and Poland (**Jedrychowski 2008**, population-based) had comparable data on maternal intake of marine sources of fat and risk of wheeze in the offspring (Figure 9). The study of Miyake compared highest vs lowest quartile of intake of seafood, whilst the study of Jedrychowski compared the effect of maternal intake of 150g of fish per week vs less than this cut-off. The combined effect estimates showed a small but statistically significantly lower risk of wheeze in children at age 2 from mothers whose fish intake was in the highest level of comparison (OR 0.97; 95% CI 0.95, 0.99). There was no heterogeneity between studies.

Another two prospective studies (**Chatzi 2008**, and **Willers 2008**) and one retrospective study (**Salam, 2005**) had comparable data to on maternal intake of fish and risk of childhood wheeze (Figure 10). The study of Chatzi compared a maternal reported intake of fish of at least 2.5 times per week vs < 2.5 times per week; in the study of Willers the authors

compared daily or regular intake of fish during pregnancy vs rare consumption or never. The study of Salam compared at least monthly intake of fish during pregnancy vs never or rare. There was no evidence of an association between this outcome and the dietary exposures. There was a high level of heterogeneity (I^2=65.8%), driven mostly by the heterogeneity observed between the two prospective studies.

Figure 9 Maternal intake of fish or seafood (highest vs lowest) and risk of wheeze in children at age 0-4 years old

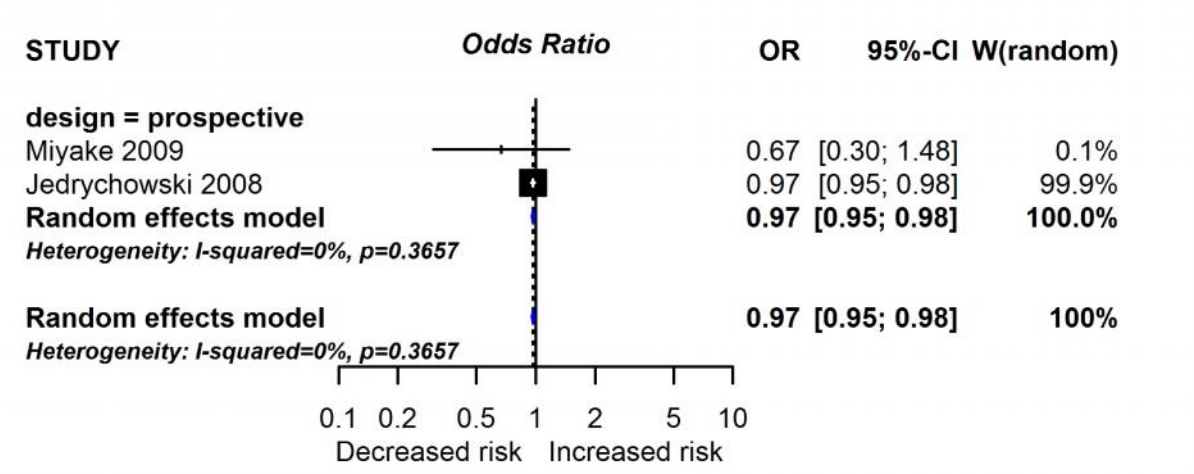
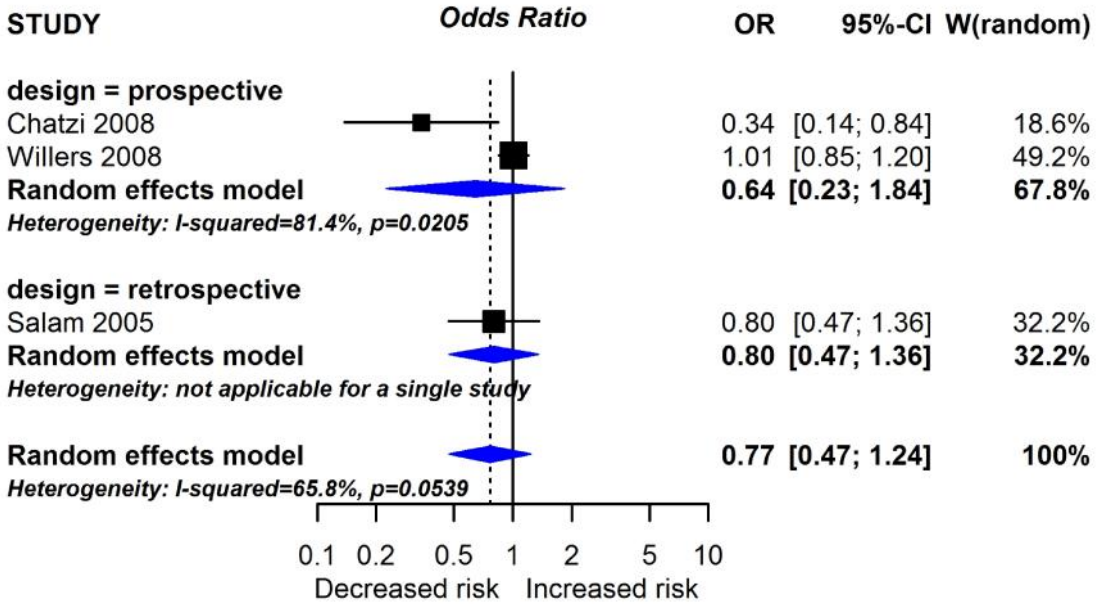
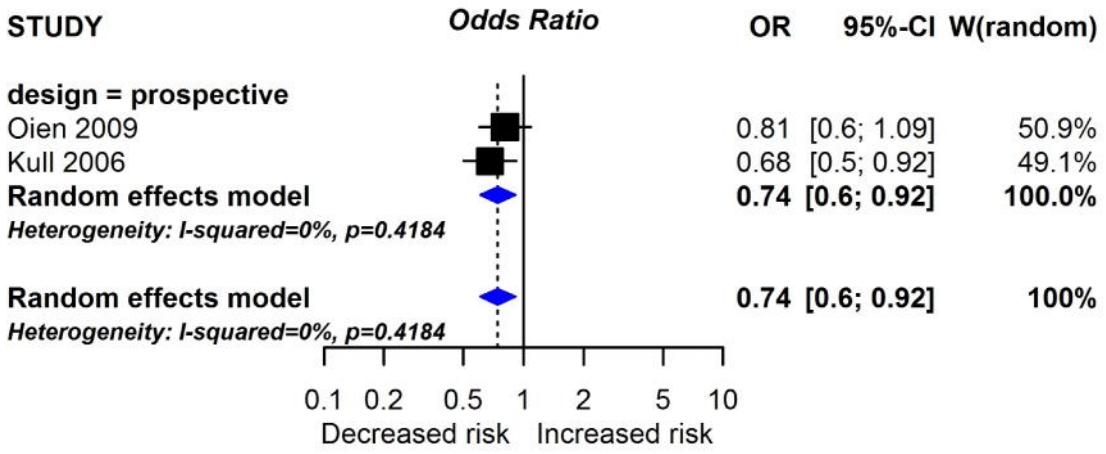


Figure 10 Maternal intake of fish (often vs rare-never) and risk of recurrent wheeze in children at age 5-14 years old



Two studies (**Oien 2009**, and **Kull 2006**) investigated infant intake of any type of fish in the first year of life and risk of recurrent wheeze. The study of Oien compared intake once a week vs never, and the study of Kull compared an intake of 2-3 times per month vs ≤ once per month. The pooled effect estimate showed an overall negative association between higher intake of fish and risk of recurrent wheeze at age 0-4 years old (OR 0.74; 95% CI 0.60, 0.92) (Figure 11), with no heterogeneity between studies (I^2=0%). Data from Kull which excluded infants with early onset eczema, in order to account for possible reverse causation, did not show an association between fish intake and recurrent wheeze (Table 6).

Figure 11 Infant intake of fish (often vs rare) and risk of recurrent wheeze at age 0-4 years old



4.1. Studies that investigated the association between wheeze and infant or maternal intake of fats which were not eligible for meta-analysis

Three prospective cohort studies investigated the association between infant intake of fish-related foods and risk of wheeze. The study of **Kull (2006)** and **Oien (2006)** measured the outcome at age 4 and 2 years old, respectively, whilst the study of **Magnusson (2013)**, measured the outcome at age 12. There was no evidence of an association between intake of specific types of fish or fatty acids in the first year of life and risk of wheeze later in childhood in these 3 studies (Table 6).

With regards to maternal intake, the studies of **Leermakers (2013)**, **Lumia (2011)**, and **Narita (2011)** found no association between maternal intake of fish observed in older

children (5-14 years old) when the outcome was studied in children aged 4, 5, and 3 years old, respectively. **Miyake (2009)** reported a lower risk of wheeze in children at age 2 whose mothers had a higher intake of α-linolenic acid and DHA. The study of **Nwaru (2012)** however, did not confirm an association between these nutrients and risk of wheeze in childhood.

Conclusion

We found no consistent evidence to suggest that a high infant or maternal intake of fish, seafood or specific fatty acids is associated with risk of wheeze or recurrent wheeze in children aged 0-4 or 5-14 years old. We also found no consistent evidence that dietary sources of fats other than those found in fish influence the risk of wheeze in childhood.

Table 6 Studies investigating the association between fat intake and wheeze which were not eligible for meta-analysis

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p<0.05)
					INFANT INTAKE		
Kull, 2006 (3)	PC	Rec wheeze	4	3926	**Infant's fish intake in first 12 months of life ≥2-3 times/month vs ≤1/month):** Children with eczema in first year excluded	OR	0.76 (0.52-1.11)
Magnusson, 2013 (4)	PC	Rec wheeze	12	2456	**Fish intake in 1st year of life:** ≥ 2-3 time/month vs ≤ once per month	OR	**0.71 (0.58-0.87)**
					Infant intake of cod liver oil up to 1 year of age:		
				3067	≤3 times per week vs never	OR	0.84 (0.55-1.29)
				3067	≥4 times per week vs never	OR	0.90 (0.64-1.26)
Oien, 2010 (26)	PC	Rec wheeze	2	2220	**Lean fish** ≥1 times per week vs never or < once per week	OR	0.76 (0.51-1.13)
			2	1681	**Oily fish (redfish, halibut, salmon, trout herring and mackerel)** ≥1 times per week vs never or < once per week	OR	1.06 (0.58-1.93)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p<0.05)
					MATERNAL INTAKE		
Castro-Rodriguez, 2010 (35)	RC	Wheeze	1.4	1409	Maternal intake of olive oil for salads (yes vs no)	OR	**0.57 (0.41-0.80)**
Erkkola, 2012 (10)	PC	Rec wheeze	5	2441	**Maternal intake during pregnancy (comparison levels in quarters, with mid-half (median) values as reference i.e. 149g to 315g) :**		
					Dietary sources of fat: 31-57.3 vs <31	OR	0.92 (0.71-1.18)
					Dietary sources of fat: 31-57.3 vs 57.3-264.8	OR	0.86 (0.66-1.12)
					Fish: 10.9-33.27 vs <10.9	OR	0.94 (0.74-1.20)
					Fish: 10.9-33.3 vs 33.3-254.8	OR	0.99 (0.78-1.25)
					Fish: 10.9-33.27 vs <10.9	HR	1.15 (0.70-1.89)
					Fish: 10.9-33.27 vs 33.28-254.8	HR	1.09 (0.67-1.78)
					Dietary sources of fat: 31-57.3 vs <31	HR	0.75 (0.46-1.21)
Fitzsimon, 2007 (20)	PC	Rec wheeze	3	631	**Added or spreadable fats considered included butter, margarine and other spreads, salad dressings and mayonnaise:**		
					Q1 vs Q3	OR	0.62 (0.24-1.60)
					Q1 vs Q2	OR	1.90 (0.98-3.70)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p<0.05)
Leermakers, 2013 (11)	PC	Wheeze	4	2796	**Maternal intake during 1st trimester of pregnancy (each of the following categories vs no fish):**		
					Total fish 140-209g/week	OR	0.86 (0.70-1.06)
					Total fish 70-139g/week	OR	0.91 (0.77-1.08)
					Total fish 1-69g/week	OR	0.92 (0.78-1.09)
					Lean fish 35-69 g/week	OR	0.86 (0.73-1.02)
					Lean fish 1-34g/week	OR	1.02 (0.87-1.19)
					Fatty fish 35-69 g/week	OR	0.91 (0.77-1.08)
					Fatty fish 1-34g/week	OR	1.02 (0.87-1.19)
					Shellfish 1-13 g/week	OR	1.20 (1.03-1.40)
					Lean fish >70 g/week	OR	0.99 (0.80-1.23)
					Fatty fish >70 g/week	OR	0.94 (0.77-1.15)
					Shellfish >14 g/week	OR	1.06 (0.92-1.22)
Lumia, 2011 (9)	PC	Rec wheeze	5	2679	**Dietary intakes during pregnancy (highest quartile vs mid-half of intake):**		
					MUFA	HR	0.71 (0.46-1.10)
					Omega 6	HR	0.75 (0.47-1.20)
					Oils	HR	1.26 (0.82-1.94)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p<0.05)
					Dietary intakes during pregnancy (highest quartile vs mid-half of intake):		
					Fish	HR	1.06 (0.68-1.65)
Lumia, 2011 (9)	PC	Rec wheeze	5	2679	PUFA	HR	0.84 (0.53-1.32)
					Maternal intake pregnancy (highest vs lowest quartile):		
					Cholesterol	OR	0.85 (0.49-1.47)
					Arachidonic acid	OR	0.77 (0.43-1.37)
					Linoleic acid	OR	0.79 (0.42-1.50)
Miyake, 2009 (24)	PC	Wheeze	2	763	MUFA	OR	0.79 (0.43-1.45)
					Omega 6	OR	0.80 (0.42-1.54)
					Total fat	OR	0.80 (0.45-1.43)
					α-linolenic acid	OR	**0.52 (0.28-0.97)**
					DHA	OR	**0.37 (0.15-0.91)**
					Omega 3	OR	0.53 (0.26-1.08)
					EPA	OR	0.76 (0.32-1.80)
					Omega 3/Omega 6 fatty acids	OR	0.81 (0.42-1.55)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p<0.05)
					Maternal consumption of fish during pregnancy (highest vs lowest quartile [specific amounts not reported]):		
Narita, 2011 (29)	PC	Wheeze	3	1344	Fish, omega 3		NS
					Maternal intake at 8th month of pregnancy (Second/ third quartile of intake vs lowest)		
					Saturated fatty	HR	1.01 (0.79-1.30)
					Butter and butter spreads	HR	0.92 (0.71-1.19)
					Arachidonic acid	HR	1.05 (0.81-1.36)
					Linoleic fatty acid	HR	0.99 (0.77-1.27)
Nwaru, 2012 (5)	PC	Wheeze	5	2441	Omega 6 fatty acids	HR	0.99 (0.77-1.27)
					Conjugated linoleic fatty acids	HR	0.84 (0.66-1.07)
					γ-linoleic fatty acids	HR	0.83 (0.65-1.06)
					Oils	HR	1.14 (0.88-1.47)
					α-linoleic fatty acids	HR	1.15 (0.90-1.47)
					PUFA	HR	1.06 (0.83-1.37)
					Omega 3 fatty acids from plant sources	HR	1.06 (0.84-1.35)
					Omega 3 fatty acids	HR	1.02 (0.80-1.30)
					EPA	HR	0.99 (0.83-1.19)
					DHA	HR	0.94 (0.74-1.21)
					Omega 3 fatty acids from fish	HR	0.93 (0.72-1.18)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p<0.05)
Oien, 2009 (26)	PC	Rec wheeze	2	3018	**Maternal intake of cod liver oil during pregnancy** ≤ 3 times per week vs never	OR	0.97 (0.63-1.50)
					Maternal consumption during pregnancy Oily fish (less then monthly (0.25 times per week vs never)	OR	1.01 (0.54-1.89)
					'Fish stick' [source of trans-fats] (less then monthly (0.25 times per week) vs never)	OR	1.15 (0.66-2.01)
Salam, 2005 (34)	CC	Rec wheeze	9-16	691/279	'Fish stick' (at least monthly i.e. 0.25 times per week vs never)	OR	**2.04 (1.19-3.51)**
Willers, 2007 (2)	PC	Wheeze Rec wheeze	5	1212	**Maternal diet during pregnancy:** Margarine (low fat spread vs butter spread) Fat from dairy (low vs high)	OR	NS

5. Infant or maternal dietary intake of fats and lung function

The prospective study of **Willers (2007)** investigated the association between maternal intake of various dietary sources of fat and lung function (assessed using spirometry) in a subsample of 510 children aged 5 years old from the Aberdeen prospective cohort (Table 7). The study was considered to have a low risk of bias across all domains. The authors reported no association between any of the dietary exposures and risk of wheeze (effect estimates not shown).

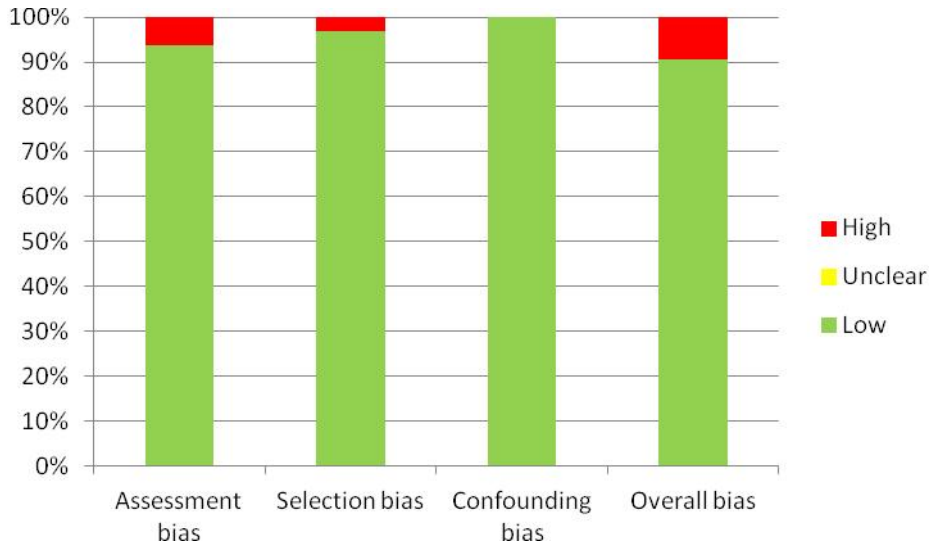
Table 7 Studies investigating the association between fat intake and lung function which were not eligible for meta-analysis

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p<0.05)
Willers, 2007 (2)	PC	LF	5	510	**Maternal diet during pregnancy:** Margarine/low fat spread vs Butter spread		NS
					Fat from dairy products (low vs high)		NS
					Fish (low vs high)		NS
					Fatty fish (low vs high)		NS

6. Infant or maternal dietary intake of fats and risk of allergic rhino-conjunctivitis

Six studies including over 10,000 children investigated the association between infant or maternal intake of fats and risk of RC. All the studies had a low risk of confounding bias, and over 80% had a low risk of selection bias. Nearly half of the studies were considered to have an overall high risk of bias due selection or assessment methods (Figure 12).

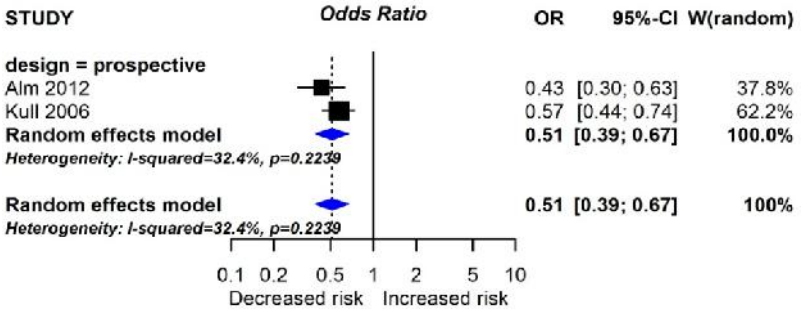
Figure 12 Risk of Bias in studies of fat intake and Rhino-conjunctivitis



The prospective cohort studies of **Alm (2012)** and **Kull (2006)**, both on Swedish children, had data eligible for meta-analysis on infant fish intake and risk of RC at age 4 years old (Figure 13). Both studies reported a reduced risk of disease in children who ate fish at least once a month (**Alm, 2012**) or 2-3 times per month (**Kull, 2006**) compared with children who ate fish less frequently. The overall effect size showed a 49% reduced risk of having RC if infants consumed fish more regularly in the first year of life. There was moderate statistical heterogeneity (I^2=32.4%). In the study of Alm, fish consumption was not statistically significantly associated with RC risk in the multivariate model – data shown in Figure 13 are for univariate analysis. In the study of Kull the relationship persisted in multivariate analysis excluding infants with early onset disease to account for potential reverse causation. Adjusted OR for rhinitis at age 1-12 in infants with regular (≥2-3 times per month) versus irregular (≤1

time per month) fish intake at age 1 were 0.74 (95% CI 0.60, 0.93) for prevalent rhinitis and 0.78 (95% CI 0.63, 0.95) for incident rhinitis.

Figure 13 Infant fish intake (often vs. rare) and risk of and rhino-conjunctivitis in children 0 to 4 years old (odds ratio)



6.1. Studies that investigated the association between infant or maternal intake of dietary sources of fat and risk of RC which could not be included in the meta-analyses

Table 8 summarises the main findings of studies that investigated infant or maternal intake of dietary sources of fats which were not eligible for meta-analysis. The prospective cohort study of **Kull (2006)** and **Magnusson (2013**) showed that a more frequent intake of fish during the first year of life was associated with a reduced risk of RC later in childhood. A further three studies investigated maternal intake of various types of fats in pregnancy in relation to RC but none of the exposures studied showed evidence of an association with RC later in childhood.

Conclusion

We found no consistent evidence for an association between fat intake in infants or lactating/pregnant women and risk of RC in the offspring.

Table 8 Studies investigating the association between fat intake and rhino-conjunctivitis which were not eligible for meta-analysis

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p<0.05)
					INFANT INTAKE		
					Fish intake in the child's first 12 months of life (≥2-3 time/month vs ≤ once per month)		
					Atopic children without sensitisation	OR	0.55 (0.30-1.01)
					High risk infants	OR	**0.62 (0.41-0.94)**
					Normal risk infants	OR	**0.56 (0.33-0.95)**
Kull, 2006 (3)	PC	RC	4	3230	Non-atopic infants without sensitisation	OR	**0.58 (0.35-0.96)**
Magnusson, 2013 (4)	PC	RC	12	2456	Fish intake in first year of life (≥2-3 time/month vs ≤ once per month)	OR	**0.68 (0.59-0.79)**

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p<0.05)
					MATERNAL INTAKE		
Erkkola, 2012 (10)	PC	RC	5	2441	**Maternal intake during pregnancy:**		
					Dietary fat (31-57.3 vs <31 g/d)	HR	0.88 (0.63-1.22)
					Dietary fat (31-57.3 vs 57.3-264.8 g/d)	HR	1.14 (0.80-1.62)
					Fish (10.9-33.27 vs <10.9 g/d)	HR	1.03 (0.75-1.41)
					Fish (10.9-33.27 vs 33.28-254.8 g/d)	HR	0.92 (0.66-1.28)
Nwaru, 2012 (5)	PC	RC	5	2441	**Maternal intake during the 8th month of pregnancy** (Second/third quartile of intake vs lowest quartile of intake)		
					Saturated fatty acid	HR	0.94 (0.77-1.16)
					Butter and butter spreads	HR	0.93 (0.70-1.24)
					Omega 6 fatty acids	HR	1.18 (0.90-1.54)
					Arachidonic acid	HR	1.16 (0.88-1.54)
					Linoleic acid	HR	1.16 (0.91-1.49)

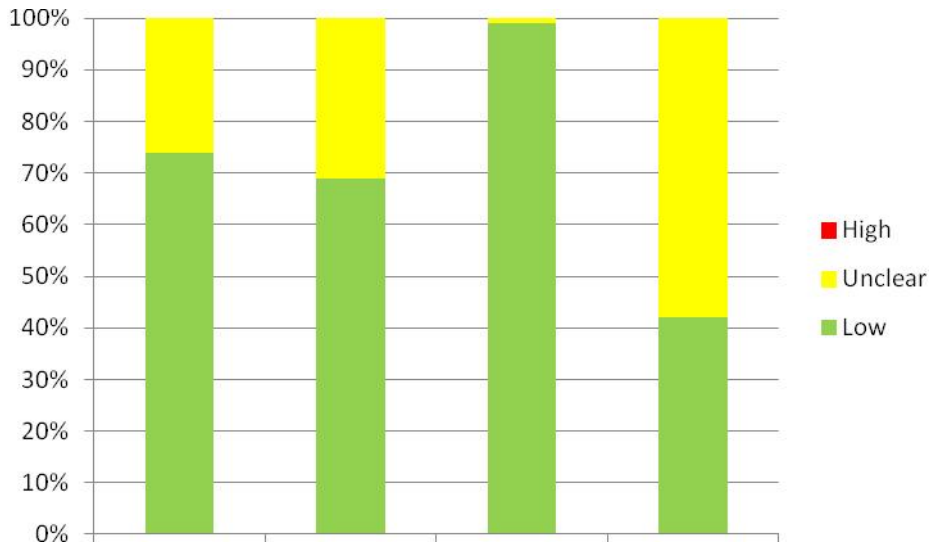
First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p<0.05)
					Maternal intake during the 8th month of pregnancy (Second/third quartile of intake vs lowest quartile of intake):		
					MUFA	HR	1.12 (0.85-1.48)
					Conjugated linoleic acids	HR	1.02 (0.79-1.32)
					γ-linoleic acid	HR	0.93 (0.72-1.21)
					'Industrial fats'	HR	1.32 (1.00-1.73)
Nwaru, 2012 (5)	PC	RC	5	2441	Oils	HR	1.16 (0.89-1.51)
					Total fatty acid	HR	1.09 (0.83-1.42)
					Trans-fatty acid	HR	1.05 (0.80-1.39)
					α-linoleic acids	HR	0.99 (0.78-1.26)
					PUFA	HR	1.22 (0.93-1.59)
					Omega 3 fatty acids	HR	1.12 (0.87-1.45)
					DHA	HR	1.06 (0.82-1.38)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p<0.05)
					Maternal intake during the 8th month of pregnancy (Second/third quartile of intake vs lowest quartile of intake):		
					Omega 3 fatty acids from plants	HR	1.03 (0.80-1.33)
Nwaru, 2012 (5)	PC	RC	5	2441	EPA	HR	1.01 (0.78-1.32)
					Omega 3 fatty acids from fish	HR	1.01 (0.78-1.31)
					Margarine (no vs yes)	HR	0.89 (0.71-1.11)
					Maternal intake during pregnancy		
					Butter spread vs margarine	OR	NS
Willers, 2007 (2)	PC	RC	5	1212	Oily fish (≥1/week vs never)	OR	0.28 (0.07-1.19)

7. Infant or maternal dietary intake of fats and risk of allergic sensitisation

Nine studies including over 10,000 children investigated the association between infant or maternal intake of fats and risk of RC. Over 70% of the studies were considered to have a low risk of assessment bias, and all but one study were considered to have a low risk of confounding bias. Some studies had an unclear method of assessment or selection bias, which resulted in over half of the studies having an overall risk of bias judged to be unclear (Figure 14).

Figure 14 Risk of bias in studies of fat intake and risk of allergic sensitisation at any age



Two prospective cohort studies (**Nwaru, 2010**; and **Sausenthaler, 2007**) had comparable data to estimate the combined effect size of maternal intake of omega 6 fatty acids, and butter, respectively, and risk of allergic sensitisation to aero-allergens in children (Figure 15). Neither study showed evidence of an association. The overall effect confirmed the lack of association. There was no heterogeneity between studies (I^2=0%). The studies of **Nwaru** and **Sausenthaler** also had comparable data to examine the association between frequent maternal intake of omega 3 fatty acids (**Nwaru, 2010**) and fish (**Sausenthaler, 2007**) compared with rare, and risk of sensitisation to aero-allergens in children (Figure 16). The combined effect estimate showed no evidence of an association. There was no heterogeneity between studies (I^2=0%). When the highest intakes (highest quartiles) were compared to the lowest in these two studies, the lack of association between fish or omega 3 fatty acids and risk of AS was confirmed (I^2=0%) (Figure 17).

Figure 15 Maternal fat intake (highest vs. lowest) and risk of allergic sensitisation to aeroallergens in children at any age

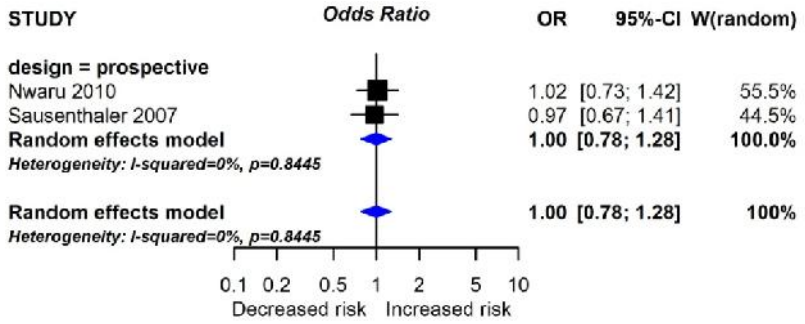


Figure 16 Maternal fish or omega 3 fatty acid intake (often vs. rare) and risk of allergic sensitisation to aeroallergens in children at any age

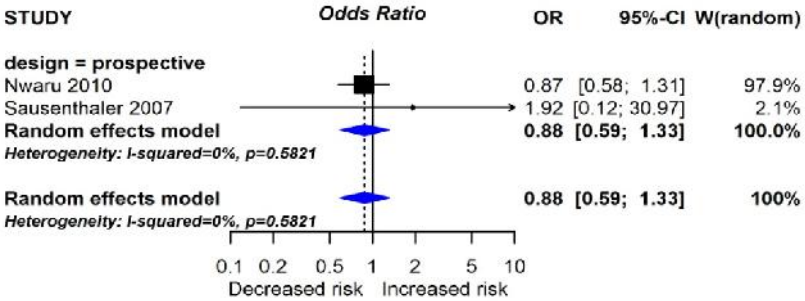
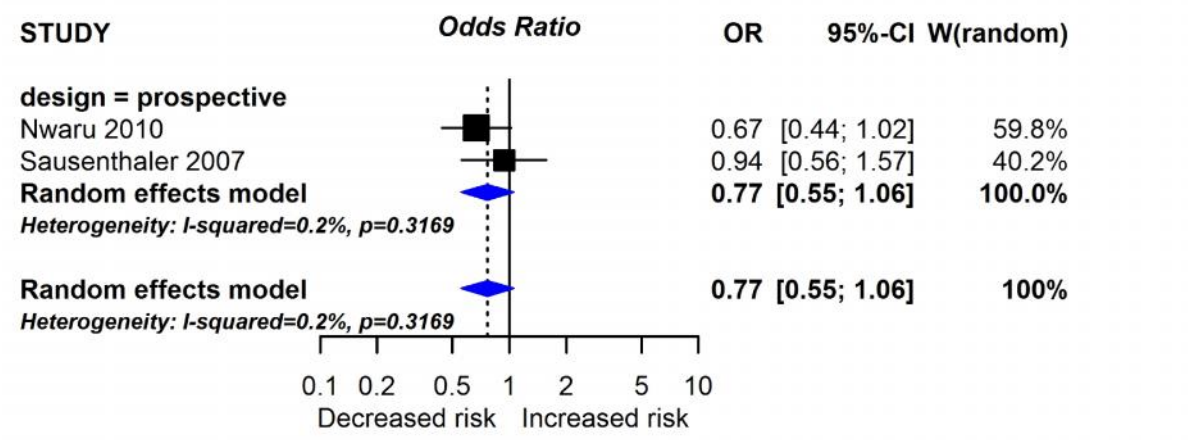
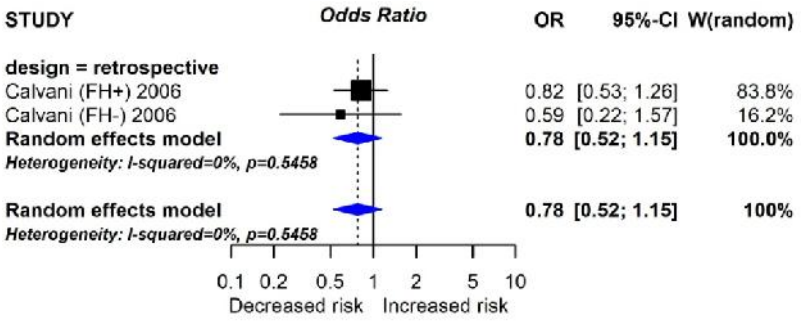


Figure 17 Maternal fish or omega-3 intake (highest vs. lowest) and risk of specific sensitisation to aeroallergen in children at any age



We identified two prospective cohort studies (**Nwaru, 2010; and Sausenthaler, 2007**) and one retrospective cohort study (**Calvani, 2006**) which had data that could be combined to estimate the overall effect of maternal fat intake and risk sensitisation to food allergens in the child. In the study of **Calvani (2006)**, the authors separately examined the risk of food allergy in the child according to whether the mother was allergic or not. There was no evidence of an association between maternal intake of fish and risk of this outcome in children at age 5 years old (Figure 18).

Figure 18 Maternal fish intake (often vs. rare) and risk of sensitisation to food allergens in children at any age



Similarly, there was no evidence of an association between maternal intake of omega 3 fatty acids (**Nwaru, 2010**) or fish (**Sausenthaler, 2007**) and risk of sensitisation to food allergens in the offspring (Figure 19). The level of heterogeneity was very high (I^2=75%). Both studies were birth cohorts, and they used a similar diagnostic tool (IgE concentrations assayed using CAP and considering a response as positive if>0.35kU/l). However, there were some differences in the participants; the Finnish infants in the study of **Nwaru** were all at high risk of type 1 diabetes, whilst the **Sausenthaler** study was a population-based cohort study of German children, and it specifically excluded any children with existing chronic diseases. The time at outcome measurement was also different (2 and 5 years old, in the Nwaru and Sausenthaler studies, respectively). Maternal intake of varying frequencies of fat or fish intake in these two studies in relation to food sensitisation showed no evidence of an association (Figures 20 and 21).

Figure 19 Maternal fish omega-3 intake (highest vs. lowest) and risk of sensitisation to food allergens in children (odds ratio)

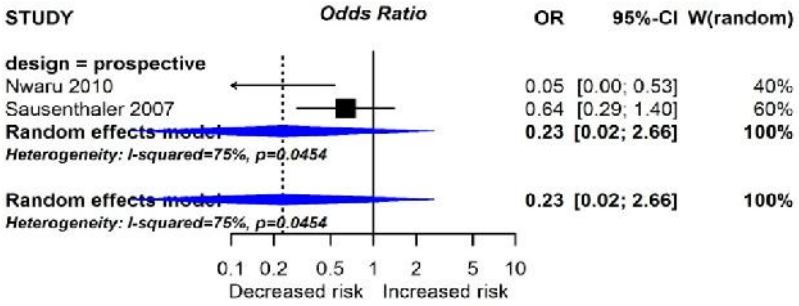


Figure 20 Maternal fat intake (highest vs lowest) and risk of allergenic sensitisation to any food in children (odds ratio)

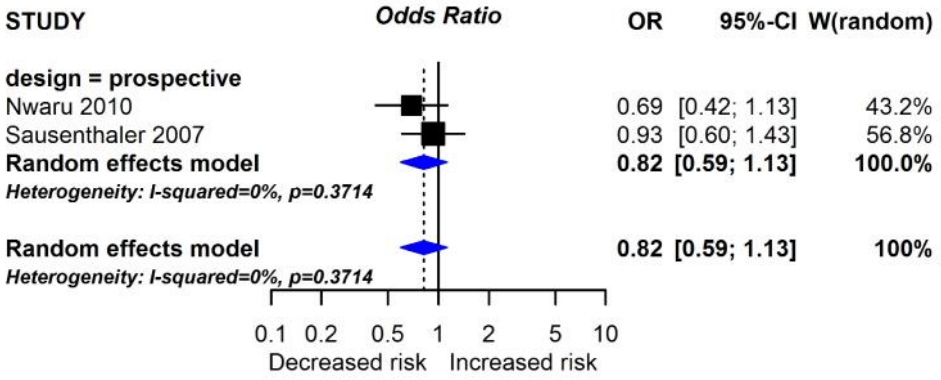
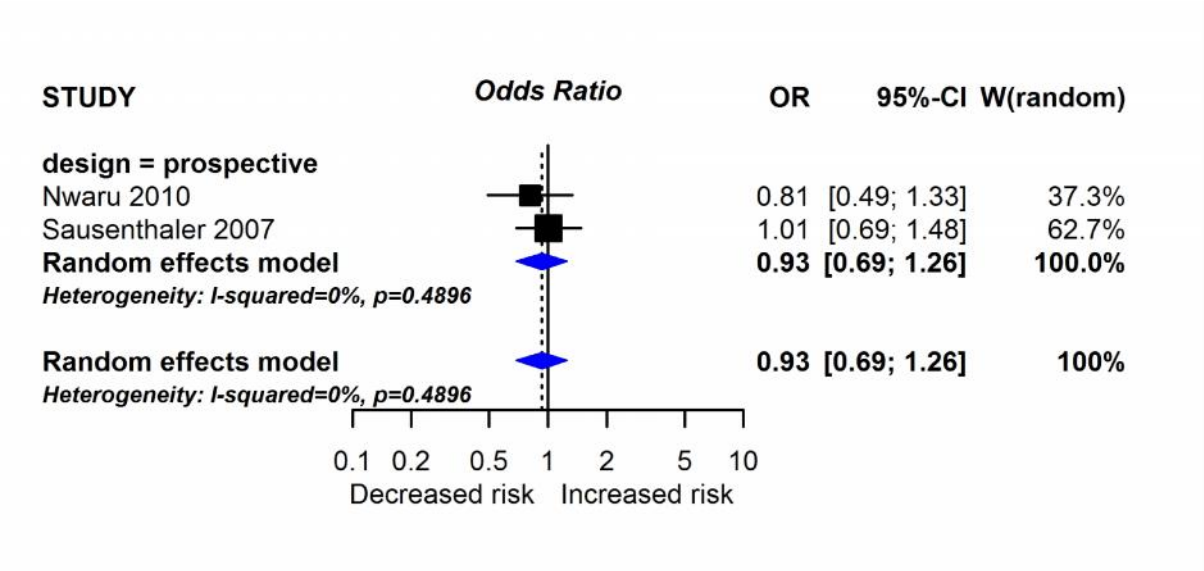


Figure 21 Maternal fish or omega 3 intake (highest vs lowest) and risk of allergenic sensitisation to any food in children (odds ratio)



7.1. Studies that investigated the association between infant or maternal intake of fats and risk of allergic sensitisation which could not be included in the meta-analyses

We identified one study that investigated infant intake of fish in the first year of life and risk of having specific IgE (sIgE) to any allergens (**Kull, 2006**). The authors reported that in normal/low risk infants there was an association between frequent intake of fish and reduced sensitisation to any allergen (AS-Any) at age 4 (OR 0.52; 95% CI 0.36-0.76) (Table 9).

With regards to maternal intake (Table 9), nine studies investigated the association of dietary sources of fat or fish-related products with sensitisation to various allergens. Overall, there were few studies that found a statistically significant association. The study of **Calvani (2006)** reported that in children of mothers who were not allergic, fish intake was associated with reduced AS-CM or AS-Egg at age 5 years. However, **Nwaru (2010)** found no evidence of an association between a higher intake of fish (or related foods) and risk of sIgE to egg in children at the same age. **Nwaru (2010**) reported that a higher intake of omega 6 fatty acids in late pregnancy was associated with reduced risk of being sensitised to aero-allergens (OR 0.60; 95% CI 0.39, 0.93). Several other studies showed no association between omega 6, omega 3 or any other type of PUFAs and allergic sensitisation.

Conclusion

We found no evidence that maternal or infant intake of fish, fat or fatty acids is associated with risk of allergic sensitisation.

Table 9 Studies investigating the association between fat intake and allergic sensitization which were not eligible for meta-analysis

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p<0.05)
					INFANT INTAKE		
					Infant intake of fish in the first 12 months of life (≥2-3 times per month vs ≤ once per month):		
					High risk infants	OR	1.14 (0.76-1.72)
Kull, 2006 (3)	PC	sIgE any	4	3230	Low risk infants	OR	**0.52 (0.36-0.76)**
					MATERNAL INTAKE		
					Maternal intake during pregnancy (in children with family history of allergies [FH+]):		
		SPT aero			Margarine (≥ 2-3 times/week vs ≤1 month)	OR	0.81 (0.60-1.10)
		SPT aero			Margarine (once a week vs ≤1 month)	OR	0.39 (0.10-1.48)
		SPT any food			Margarine (once a week vs ≤1 month)	OR	0.26 (0.03-2.54)
Calvani, 2006 (FH+) (33)	RC	SPT any food	5	988	Butter (once a week vs ≤1 month)	OR	0.49 (0.17-1.43)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p<0.05)
					Maternal intake during pregnancy (once a week vs ≤1 month) (in children with no family history of allergies [FH-]) :		
		SPT cow's milk			Fish	OR	**0.15 (0.04-0.59)**
		SPT egg			Fish	OR	**0.26 (0.09-0.76)**
		SPT any food			Butter	OR	0.91 (0.37-2.25)
		SPT aero			Margarine	OR	1.28 (0.53-3.07)
		SPT any food			Margarine	OR	1.63 (0.39-6.87)
		SPT aero			Butter	OR	**1.73 (1.00-2.99)**
Calvani, 2006 (FH-) (33)	RC	SPT aero	5	988	Margarine (≥ 2-3 times/week vs ≤1 month)	OR	0.92 (0.66-1.28)
					Maternal intake during pregnancy:		
					Butter (once a week vs ≤1 month; allergic mother)	OR	**0.27 (0.10-0.73)**
					Fish (≥ 2-3 times/week vs ≤1 month; allergic mother)	OR	0.74 (0.23-2.37)
					Fish (once a week vs ≤1 month; allergic mother)	OR	0.89 (0.30-2.60)
Calvani, 2006 (33)	RC	SPT aero	5	988	Fish (≥ 2-3 times/week vs ≤1 month; non-allergic mother)	OR	0.55 (0.28-1.08)
					Fish (once a week vs ≤1 month; non allergic mother)	OR	0.70 (0.38-1.30)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p<0.05)
					Maternal intake during pregnancy:		
					Fish (≥ 2-3 times/week vs ≤1 month; allergic mother)	OR	1.13 (0.31-4.10)
					Fish (once a week vs ≤1 month; allergic mother)	OR	1.15 (0.38-3.47)
					Fish (once a week vs ≤1 month; non-allergic mother)	OR	**0.22 (0.09-0.55)**
					Fish (≥ 2-3 times/week vs ≤1 month; non-allergic mother)	OR	**0.23 (0.08-0.69)**
Calvani, 2006 (33)	RC	SPT any food	5	988	Fish (once a week vs ≤1 month; all)	OR	**0.34 (0.15-0.75)**
Chatzi, 2008 (23)	PC	SPT aero	6.5	468	**Maternal intake of fish during pregnancy** (>2.5 times per week vs ≤ 2.5 per week)	%	NS
Hoppu, 2000 (13)	PC	SPT any food	1	114	**Maternal intake of saturated fats during breastfeeding** (mean % energy from saturated fat)	OR	1.15 (0.98-1.35)
					Maternal intake at 8th month of pregnancy		0.83 (0.35-1.99)
		sIgE aero	5	931	Saturated fat (mean daily intake in grams)	OR	
Nwaru, 2010 (7)	PC	sIgE aero	5	931	Margarine (mean daily intake in grams)	OR	0.96 (0.79-1.17)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p<0.05)
					Maternal intake at 8th month of pregnancy:		
					Omega 6 (2nd and 3rd quartile vs 1st)	OR	**0.60 (0.39-0.93)**
					Oils (mean daily intake in grams)	OR	0.97 (0.63-1.49)
					Fat (mean daily intake in grams)	OR	1.12 (0.32-3.93)
					Fish (mean daily intake in grams)	OR	1.02 (0.93-1.12)
					Omega 3 4th quartile vs 2nd and 3rd)	OR	0.68 (0.44-1.05)
					PUFA (1st quartile vs 2nd and 3rd)	OR	0.63 (0.41-0.97)
Nwaru, 2010 (7)	PC	sIgE aero	5	931	PUFA (4th quartile vs 2nd and 3rd)	OR	0.33 (0.06-1.82)
					Saturated fats (mean daily intake in grams)	OR	0.91 (0.34-2.43)
					Omega 6 (2nd and 3rd quartile vs 1st)	OR	0.78 (0.49-1.25)
					Fat (mean daily intake in grams)	OR	0.68 (0.17-2.76)
					Oils (mean daily intake in grams)	OR	0.83 (0.51-1.36)
		sIgE any food	5	931	PUFA (2nd and 3rd quartile vs 1st)	OR	1.03 (0.65-1.62)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p<0.05)
					Maternal intake at 8th month of pregnancy:		
					Margarine (mean daily intake in grams)	OR	0.95 (0.75-1.20)
Nwaru, 2010 (7)	PC	SPT any food	5	931	Fish (mean daily intake in grams)	OR	0.99 (0.90-1.09)
					Omega 3 (4th quartile vs 2nd and 3rd)	OR	0.80 (0.49-1.31)
					Maternal intake during breastfeeding (g/day increase in total intake during 2nd month lactation):		
					Saturated fatty acid	OR	1.14 (0.62-2.08)
					Margarine and low fat spread	OR	0.96 (0.70-1.31)
					Omega 6	OR	0.92 (0.60-1.41)
Nwaru, 2011 (6)	PC	sIgE cow's milk	5	652	Oil consumption	OR	1.15 (0.86-1.54)
					Fish and fish product	OR	0.80 (0.57-1.12)
					Total PUFA	OR	0.96 (0.62-1.49)
					Omega 3	OR	1.09 (0.71-1.68)
					Omega 3 from vegetables	OR	1.21 (0.81-1.81)

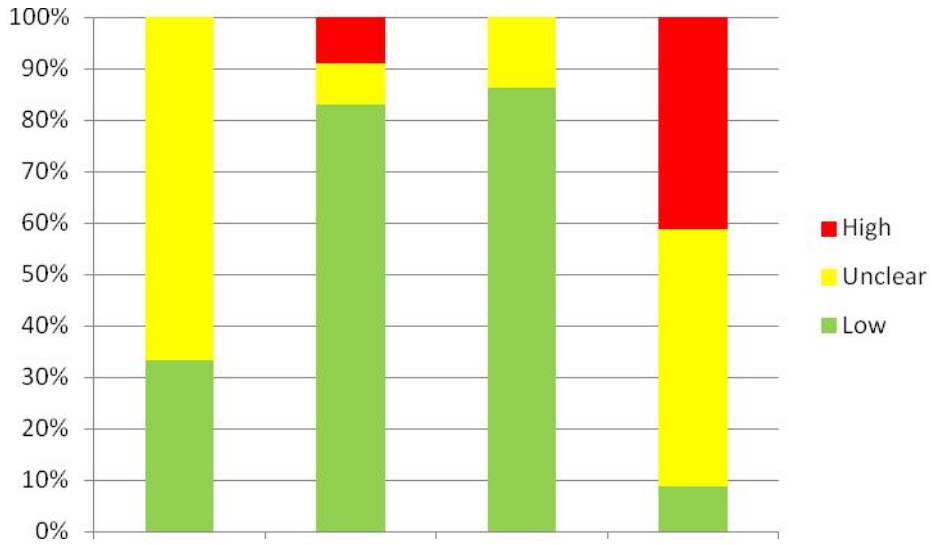
First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p<0.05)
					Maternal intake during breastfeeding (g/day increase in total intake during 2nd month lactation):		
					Saturated fatty acid	OR	1.71 (0.89-3.27)
					Margarine and low fat spread	OR	0.80 (0.51-1.26)
					Omega 6	OR	0.88 (0.51-1.53)
Nwaru, 2011 (6)	PC	sIgE egg	5	652	Oils	OR	0.92 (0.62-1.36)
					Fish and fish products	OR	0.97 (0.69-1.37)
					Omega 3	OR	0.76 (0.47-1.24)
					PUFA	OR	0.84 (0.47-1.49)
					Omega 3 from fish	OR	0.84 (0.53-1.33)
			4	333	Maternal fish consumption during all pregnancy	OR	0.93 (0.59-1.47)
Romieu, 2007 (22)	PC	allergic sensitization	6	399	Maternal fish consumption during all pregnancy	OR	0.74 (0.50-1.09)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p<0.05)
					Maternal consumption during the last 4 weeks of pregnancy (highest vs lowest tertile) (variation in N refers to individuals with data in the multi-variate analysis)		
			2	2068	Margarine	OR	0.93 (0.50-1.73)
		sIgE aero	2	2117	Vegetable oils	OR	0.89 (0.52-1.51)
			2	2091	Deep frying vegetable fat	OR	1.61 (1.02-2.54)
Sausenthaler, 2007 (21)	PC		2	2069	Margarine	OR	0.85 (0.57-1.27)
			2	2118	Vegetable oils	OR	0.88 (0.62-1.25)
			2	2092	Deep frying vegetable fat	OR	1.25 (0.92-1.70)
			2	2076	Margarine	OR	0.80 (0.50-1.27)
			2	2125	Vegetable oils	OR	0.91 (0.62-1.34)
		sIgE any food	2	2099	Deep frying vegetable oil	OR	1.12 (0.79-1.58)
					Maternal diet during pregnancy:		
					Margarine/low fat spread vs Butter spread		NS
					Fat from dairy (low vs high)		NS
Willers, 2007 (2)	PC	SPT any	5	1212	Fish		NS
					Oily fish		NS

8. Infant or maternal dietary intake of fats and risk of type 1 diabetes mellitus

Six studies including over 9,000 children examined the association between infant or maternal intake of fats and risk of T1DM. The majority of the studies had a low or unclear bias in most domains (Figure 22).

Figure 22 Risk of bias in studies of fat intake and risk of allergic sensitisation at any age



8.1. Studies that investigated the association between infant or maternal intake of dietary fats and risk of T1DM which were not eligible for meta-analysis

We identified one study (**Stene, 2003**) reporting the association between dietary intake of cod liver oil supplement in the first year of life and risk of T1DM later in childhood (Table 10). The authors reported that a more frequent intake of cod liver oil supplement in the first year was associated with a lower risk of disease in children. With regards to maternal intake (Table 10), five prospective cohort studies investigated the association between intake of various types of fats or oils and risk of T1DM in the offspring. In the study of **Niinisto (2012)** the authors reported that maternal consumption of vegetable oils during lactation was associated with a higher risk of T1DM later in childhood, whilst **Virtanen (2011, [2])** reported that maternal intake of butter was associated with a lower risk of disease of T1DM in children at age 8 years old. Two other studies reported no association between maternal

intake of various types of fatty acids (**Fronczak 2003**) or fish (**Lamb 2008**) and risk of T1DM.

Conclusion

We found VERY LOW evidence from one case-control study suggesting that intake of cod liver oil in the first year of life (after month 7) is associated with reduced T1DM later in childhood. Maternal intake of vegetable oils during lactation was associated with an increased risk of T1DM, and intake of butter during pregnancy was associated with a reduced risk of T1DM. Overall, we found no conclusive evidence that maternal intake of fats influences the risk of T1DM in childhood.

Table 10 Studies investigating the association between fat intake and type 1 diabetes mellitus which were not eligible for meta-analysis

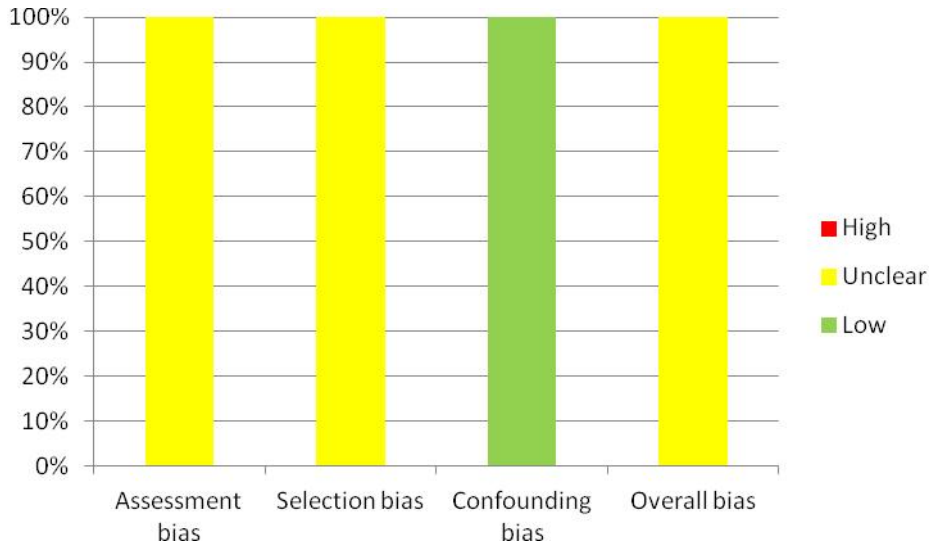
First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect
					INFANT INTAKE		
Stene, 2003 (41)	CC	TIDM	8.8	2213/545	**Infant intake of cod liver oil supplement in 1st year of life:**		
					Starting at age 7-12 months (Yes vs no)	OR	**0.55 (0.32-0.96)**
					Starting at age 0-6 months	OR	0.80 (0.60-1.06)
					1-4 times per week vs No	OR	0.81 (0.55-1.19)
					≥5 times per week vs No	OR	**0.74 (0.55-0.99)**
					MATERNAL INTAKE		
Brekke, 2010 (38)	PC	DM			**Maternal intake in the 3rd trimester of pregnancy:**		
					Fish (open sea) (1-2 times per week vs <1 per week)	OR	0.76 (0.5-1.17)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect
Fronczak, 2003 (36)	PC	DM	4	222/16	**Maternal intake during pregnancy**: Linoleic acid (7.92-11.78g/day vs <7.92g/day)	HR	2.01 (0.55-7.37)
					Omega 6 (g/day, continuous)	HR	0.88 (0.50-1.56)
					Omega 3 (g/day, continuous)	HR	1.16 (0.75-1.80)
					Omega 3 (highest vs. lowest)	OR	0.64 (0.24-1.70)
					Omega 6 (highest vs. lowest)	OR	1.04 (0.26-4.19)
Lamb 2008 (37)	PC	TIDM	15	642/27	**Maternal intake in the last trimester of pregnancy** Fish (No. servings)	HR	0.90 (0.54-1.51)
Niinisto, 2012 (8)	PC	TIDM	9.7	2939/143	**Maternal intake of vegetable oils during lactation** (Yes vs no)	HR	**1.22 (1.03-1.44)**
Virtanen, 2011 (39)	PC	TIDM	<10	3730/165	Maternal intake of butter during pregnancy	Change in risk per 2-fold increase in energy-adjusted consumption	**0.83 (0.70-0.98)**

9. Infant or maternal dietary intake of fats and risk of juvenile idiopathic arthritis

We identified one study that investigated the association between maternal intake of fats and risk of JIA, which was considered to have an overall unclear bias due to unclear assessment and selection of participants (Figure 24).

Figure 23 Risk of Bias in studies of fat intake and juvenile idiopathic arthritis



The CLARITY - ChiLdhood Arthritis Risk factor Identification sTudY (**Ellis, 2012**) is a case-control study established in Australia with the aim of identifying genomic and environmental disease risk factors in children diagnosed with juvenile idiopathic arthritis (JIA). Cases (n=262) were children ≤18 years old with a diagnosis of JIA, who were matched to healthy children. As part of the early life risk factors investigated, the author reported that maternal fish oil supplementation during pregnancy was not related to the risk of having JIA later in childhood (Table 11).

Conclusion

We found no evidence to suggest that maternal intake of dietary sources of fat modulates the risk of JIA in childhood.

Table 11 Studies investigating the association between fat intake (dietary exposure) and Juvenile idiopathic arthritis (outcome) which were not eligible for meta-analysis

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect
Ellis, 2012 (43)	RC	JIA		262/458	Maternal fish oil supplement intake (often vs. rare) and risk of juvenile idiopathic arthritis in children	OR	0.7 (0.15-3.35)

General conclusions

In this report of observational studies on infant or maternal intake of dietary sources of fats and risk of allergic and selected autoimmune diseases, we found some evidence to suggest that intake of fish, particularly oily/fatty, in the first year of life reduces the risk of AD in early and late childhood. Consumption of other sources of dietary fats during infancy did not appear to be associated with risk of AD. We found inconsistent evidence suggesting that a more frequent intake of fish during the first year of life is associated with a reduced risk of RC later in childhood and that maternal fish or omega 3 intakes could reduce the risk of wheeze and AD early in childhood.

With regards to wheeze, we found evidence of a 3% reduction in risk in infants with a higher intake of fish, but this was not consistent. Our review also shows no evidence to suggest that infant or maternal intake of dietary fats influences the risk of food allergy or that is related to lung function in children.

We found very little evidence to suggesting that a higher intake of fish in normal/low risk infants is associated with a lower risk of allergic sensitisation. Maternal intake of omega 3 fatty acids does not appear to influece the risk of sensitisation in childhood. Maternal intake of other dietary sources of fats showed limited and contradictory evidence on the direction in which fat intake could modulate the risk of sensitisation.

With regards to autoimmune diseases, we found limited evidence suggesting that intake of cod liver oil in the first year of life (after month 7) might reduce the risk of T1DM later in childhood. Maternal intake of butter during pregnancy was associated with a reduced risk of disease. But this evidence was too limited to suggest that maternal intake of fats during pregnancy is involved in the modulation of risk of childhood T1DM. Similarly, we found no evidence to suggest that maternal intake of dietary sources of fat modulates the risk of JIA in childhood.

Overall, we found no consistent evidence to suggest that maternal or infant intake of fats might contribute to reduce the risk of allergic or autoimmune outcomes in early childhood.

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INFANT AND MATERNAL FRUIT AND VEGETABLE INTAKE, AND RISK OF ALLERGIC AND AUTOIMMUNE DISEASES

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1. Executive summary of findings on infant and maternal intake of fruits and vegetables and risk of allergic and autoimmune diseases

1.1. Context of this report

This report is one of a series of systematic review reports included in Review C Part II, which focusses on evidence on dietary exposures during pregnancy, lactation and or infancy for reducing risk of allergic or autoimmune outcomes. It describes the current evidence from observational studies on infant or maternal intake of fruits and vegetables and risk of allergic or autoimmune diseases. There was a high degree of variation in the type of dietary exposures studied, which limited the possibilities for meta-analyses. Within each outcome section, a narrative table is provided, which describes the main findings and effect sizes (when available) for each study.

1.2. Studies identified

A total of 35 observational studies reported the association between infant and/or maternal intake of fruit and vegetable and allergic (n=28) or autoimmune (n=7) diseases. Of these studies, 27 were prospective cohort studies, 6 case-controls, and 2 nested case control studies. The majority of studies (n=24) are from Europe – others are from North America (n=5), Asia Pacific (n=5), and Latin America (n=1).

1.3. Outcomes evaluated

Nineteen studies investigated the association between risk of atopic dermatitis (AD) and fruit or vegetable intake, nine studies investigated food allergy (FA), 1 study investigated lung function (LF), 19 studied wheeze, seven studied rhino-conjunctivitis (RC), 15 studied allergic sensitisation, nine studied type 1 diabetes mellitus (T1DM) and one investigated inflammatory bowel disease (IBD).

1.4. Dietary exposures studied

Dietary exposures for fruits and vegetables varied greatly across studies. In some studies, only a single question was used to ascertain habit of consumption, often as part of other risk factors investigated in the study. In others, there was a specific questionnaire used to

ascertain intake of several individual and/or grouped fruits and vegetables. Our approach to meta-analysis considered the classification of foods of the same family if possible (e.g. 'apples', 'any fruit'). If studies used only a generic question to ascertain fruit or vegetable intake (e.g. 'does your baby eat any fruit') this variable was included in the meta-analysis along with other studies where only a single fruit was assessed, provided that the outcomes were comparable.

1.5. Presentation of results

We created a summary Table of Study Characteristics with key study features, presented separately for allergic (Table 1) and autoimmune outcomes (Table 2). There are seven main sections in this report that summarise the main findings for each of the following outcomes: atopic dermatitis (AD), food allergy (FA), lung function (LF), wheeze, rhino-conjunctivitis (RC), allergic sensitisation (AS), type I diabetes mellitus (T1DM), and inflammatory bowel disease (IBD).We examined each of the studies for their eligibility to be meta-analysed. If two or more studies had data that could be combined, a meta-analysis was included in the corresponding section. If the heterogeneity across studies ≥ 80% then the overall effect of the studies is not included but that of each individual study is presented. As most of the studies included in this report had data that could not be combined in a meta-analysis, a table of main characteristics and main findings is provided at the end of each section. The tables provide specific details on the intakes compared for each dietary exposure as these varied between, and sometimes within study.

1.6. Risk of bias assessment

The risk of bias in included cohort and case control studies was assessed using a modified version of the National Institute for Clinical Excellence (NICE) methodological checklist for cohort and case-control studies, respectively (1). Key domains were:

- Selection Bias (low if cases and controls were selected from similar populations, if the participation rate was ≥80%, or <80% but investigators explored and adjusted for characteristic differences between participants and non-participants);
- Assessment Bias (low if validated and reliable tools were used to assess exposure and/or outcome), and;
- Confounding Bias (low if most likely confounders are identified and taken into account in study design and analysis).

Observational studies were considered at low overall risk of bias where the risk of bias was judged to be low for all 3 key domains for selection, assessment and confounding bias. For assessment of Confounding Bias, factors that we expected to be adjusted for within studies of allergic outcomes were: siblings (parity or birth order or family size); gender; age at outcome assessment; disease risk based on family history; maternal or household smoking (asthma/wheeze outcomes); maternal age; maternal education or socioeconomic status; mode of delivery. For studies on autoimmune outcomes we expected matching and/or adjusting for gender, age, address, socioeconomic status, smoking and disease risk. We also assessed possible Conflict of Interest, this being judged as low where there was no evidence of industry involvement in study design, analysis, interpretation or publication, and no evidence that study authors received remuneration from relevant industry partners for other activities. Given the nature of the studies included in this report (observational studies on reported dietary intake of foods or food groups), the conflict of interest was low in all cases. Therefore, we only included the first three domains, and the overall bias. These domains were assessed for all studies and included in the Risk of Bias Figure regardless of whether the studies were eligible for meta-analysis or for narrative. A Risk of Bias Figure is presented in each outcome section.

1.7. Key findings

i. Overall risk of bias was low or unclear for the majority of the outcomes assessed

The overall risk of bias was considered to be low in the majority of included studies. In several studies it was unclear whether adjustment for potential confounders had been made, leading to an 'unclear' risk of bias.

ii. Classification of dietary exposures and varying comparison levels of intake reduced the possibilities of meta-analyses

Very few studies had comparable information which could be meta-analysed. The main reason for this was the large variations in the ways of reporting associations between the relevant dietary exposures and risk of allergic or autoimmune diseases. In general, the few available meta-analyses showed low statistical heterogeneity.

iii. There was no evidence of an effect of fruits or vegetables on studied outcomes

Overall, we found no consistent evidence to suggest that intake of fruits and vegetables early in life influences risk of other allergic or autoimmune diseases.

Table 1 Characteristics of included studies evaluating fruit and vegetable supplementation and allergic outcomes

Study	Design	N/n	Country	Type of fruit and vegetable studied	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Martindale, 2005; (2) Willers, 2007(3)	PC	1300	UK, Netherlands	Fruits; citrus fruits; fruit juice; vegetables; green leafy vegetables; apples	Q	AD: Parent reported and/or UK Working Party Criteria; LF: Spirometry; RC and wheeze: Parent reported (ISAAC Q); SPT any; rec wheeze: DD asthma	2, 5	**Aberdeen birth cohort**: Population based birth cohort with pregnant women recruited 1997-99 while attending a hospital antenatal clinic at ~12weeks gestation
Hesselmar, 2010 (4)	PC	184	Sweden	Fruits	I/Q	AD: Physician assessment, and full-filling Williams' criteria; FA cm: Physician assessment plus Open Food Challenge; sIgE any	0.5; 1.5	**ALLERGYFLORA:** Birth cohort in Sweden enriched with children with family history of allergies

Study	Design	N/n	Country	Type of fruit and vegetable studied	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Lack, 2003 (5)	PC; NCC	11352	UK	Allergenic food avoidance (peanuts/nuts); allergenic food avoidance (soybean meat); peanut	Q	FA peanut: History of reaction to peanut (without food challenge), DBPCFC alone or plus DD	5.5, 6	**ALSPAC**: The study enrolled pregnant women living in the Avon Health Authority are, UK, expected to delivery between 1991-92. Cases and controls, who did and did not develop food allergy respectively, were not matched.
Binkley, 2011 (6)	CC	1413/1300	Canada	Allergenic food avoidance (peanut)	Q	FA peanut DD	5to14, <18	Cases & controls were anaphylaxis registry's previous survey respondents, all having had previous anaphylactic food allergy reactions, although only cases to peanuts: Canada.

Study	Design	N/n	Country	Type of fruit and vegetable studied	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Fergusson, 1990 (7)	PC	1067	New Zealand	Fruits; vegetables	R/D	AD Physician assessment	10	**CHRISTCHURCH CHILD DEVELOPMENT STUDY:** A cohort of children born in the Christchurch urban region New Zealand during mid1977
Maslova, 2012 (8)	PC	4501	Denmark	Peanut and pistachio; nuts (tree nuts)	Q	RC:DD plus medication records; wheeze: DD; Rec wheeze: parent reported >3 episodes of wheeze; Rec wheeze: DD asthma plus medication records	1.5, 7	**DNBC**: Population based birth cohort with pregnant women recruited between 1996 and 2002 at ~12weeks gestation in Denmark
DesRoches, 2010 (9)	CC	401/202	Canada	Allergenic food avoidance (nut); allergenic food avoidance (soya); allergenic food avoidance (peanut)	Q	FA peanut :History of a clinical reaction within 60 minutes of exposure to peanuts, combined with positive IgE and/or SPT to peanut	<1.5	Cases and controls were recruited from the Paediatric University Centre between 1998-2004: Canada

Study	Design	N/n	Country	Type of fruit and vegetable studied	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Maijaliisa, 2011; (10) Nwaru, 2010; (11) Nwaru, 2011; (12) Nwaru, 2013; (13) Erkkola, 2012; (14) Nwaru, 2010b; (15)	PC	5619/237	Finland	malaceous fruits; green leafy vegetables; berries; citrus fruits; fruit juice; fruits; vegetables and roots; nuts and pulses; potatoes; fruits and berries; root vegetables; fruits and vegetables; vegetables; cabbage; carrots	Q	AD, wheeze, rec wheeze, and RC: Parent reported (ISAAC Q); sIgE-aero; sIgE cm; sIgE to egg; sIgE to food; wheeze; rec wheeze (atopic): DD asthma plus positive sIgE; rec wheeze: DD asthma plus medication and/or current symptoms	0.5, 5, <10	**DIPP:** Prospective birth cohort of children at high risk of TIDM (HLA genotype conferred susceptibility) born between 1997 and 2004 in Oulu and Tampere University Hospital Finland
Fox, 2009 (16)	CC	293/133	UK	peanut	Q	FA to peanut: DD DBPCFC	<4	Cases and controls from specialist food allergy clinics, with cases sensitised to peanut and controls sensitised to egg but not peanut: UK.

Study	Design	N/n	Country	Type of fruit and vegetable studied	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Venter, 2009; (17) Dean, 2007 (18)	PC	937	UK	allergenic food avoidance (peanut)	Q	SPT peanut	2	**The Isle of Wight cohort:** Population based birth cohort recruited through antenatal clinics and included all babies born on the Isle of Wight UK between 2001 and 2002
Fitzsimon, 2007 (19)	PC	631	Ireland	fruits and vegetables	Q	Rec wheeze: Physician assessment asthma	3	**LIFE-WAYS**: cohort of children born in 2002 whose mother had completed FFQ during pregnancy were followed up from birth through general practice records

Study	Design	N/n	Country	Type of fruit and vegetable studied	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Zutavern, 2006; (20) Zutavern, 2008; (21) Sausenthaler, 2007 (22)	PC	2540	Germany	fruits; vegetables; apples; bananas; strawberries; citrus fruits; fruit juice; cabbage; salad; celery; sweet peppers; spinach; nuts; carrots; seeds; tomatoes	Q	AD:DD; Parent reported; sIgE to food; sIgE aero; sIgE any	2, 6	**LISA:** Population based cohort study of newborns recruited between 1997 and1999 from 4 German cities: Munich, Leipzig, Wesel, and Bad Honnef.
Marini, 1996 (23)	PC	68	Italy	citrus fruits	Q	AD: Physician assessment plus parent reported; RC: Physician assessment plus parent reported; Recurrent wheeze: Physician assessment > 3 episodes of wheeze	1, 3	Infants with family history of allergy born in maternity wards of 3 hospitals from 1989 whose mothers were refused to participate in an allergy prevention intervention program

Study	Design	N/n	Country	Type of fruit and vegetable studied	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Chatzi, 2008 (24)	PC	468	Spain	fruits; legumes; nuts; vegetables	Q	SPT-aero; Atopic wheeze: Parent reported wheeze plus positive SPT; rec wheeze: parent reported ≥1 episodes of wheeze	6.5	**Menorca birth cohort:** Population based birth cohort with women recruited from antenatal care at all general practices in Menorca between 1997-1998
Miskelly, 1988 (25)	PC	482	UK	fruits	D	AD: Physician assessment and parent reported; wheeze :Parent reported wheeze	1	Infant recruited through two antenatal clinics in South Wales born to mothers with positive allergy history in at least one member of family, whose mothers were asked to participate in allergy preventive program
Morgan, 2004 (26)	PC	257	UK	fruits; vegetables	I	AD: Physician assessment and parent reported	1	Healthy preterm births (<37 weeks gestational) from 3 hospitals in southeast England

Study	Design	N/n	Country	Type of fruit and vegetable studied	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Miyake, 2010 (27)	PC	763	Japan	fruits; apples; citus fruits; vegetables; green and yellow vegetables;veget ables other	Q	AD and wheeze: Parent reported (ISAAC Q)	2	**OMCHS:** Population birth cohort recruited during pregnancy from a university hospital and three obstetric hospitals in municipalities of Osaka 2001 - 2003
Oien, 2009 (28)	PC	3050	Norway	vegetables	Q	AD: Parent reported (ISAAC Q); rec wheeze: DD asthma	2	**PACT:** Trondheim, Norway. Inclusion in the control cohort began in September 2000, and the interventional programme started in a separate cohort in July 2002

Study	Design	N/n	Country	Type of fruit and vegetable studied	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Roduit, 2012 (29)	PC	1041	Austria, Finland, France, Germany, and Switzerland	fruits and vegetables	D	AD:DD	1, 4	**PASTURE:** Population based birth cohort recruited in third trimester of pregnancy from rural areas in 5 European countries from farming and non-farming families
Willers, 2008 (30)	PC	2828	The Netherlands	nuts; fruits; vegetables	Q	Total IgE; sIgE-aero; sIgE to food; wheeze: Parent reported (ISAAC Q) wheeze; Rec wheeze: DD asthma plus medication and/or current symptoms	8	**PIAMA:** Population based birth cohort recruited prenatally Netherlands. The children were allocated to an intervention study or to a natural history study depending on their family risk for allergy

Study	Design	N/n	Country	Type of fruit and vegetable studied	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Sariachvili, 2010 (31)	NCC	557/252	Belgium	fruits; fruit juice; vegetables	Q	AD: Parent reported (ISAAC Q)	4	**PIPO Cohort:** cases and controls with data regarding development of eczema and timing of introduction of solid foods were identified from this PC: Belgium.
Litonjua, 2006 (32)	PC	1290	USA		Q	AD:DD; wheeze: parent reported wheeze; rec wheeze: parent reported wheeze in at least one questionnaire (1,2,3 years old)	2	**Project Viva:** Population based birth cohort with pregnant women at <22 weeks of gestation recruited from 8 obstetric offices of a large multispecialty suburban/urban group practice in eastern Massachusetts US between 1999 and 2002

Study	Design	N/n	Country	Type of fruit and vegetable studied	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Dunlop, 2006 (33)	PC	1326	Slovakia	citrus fruits	Q	AD: Physician assessment	1	**Slovak birth cohort:** The 1st 250 pregnant women delivering at maternity hospitals in the selected study sites were recruited between 1997 and 1999,
Strassburger, 2010 (34)	PC	338	Brazil	salty pureed food; fruit juice	R	SPT aero; Wheeze: Parent reported wheeze	3.5	Birth cohort study nested in a dietary intervention randomized field trial in the city of São Leopoldo, southern Brazil in 2002
Kemp, 2011 (35)	PC	310	Tasmania	allergenic food avoidance (peanut)	Q	sIgE to peanut	16	**THIS:** cohort of infants at high risk for sudden infant death syndrome born in 1988-1989 were identified in the northern region of Tasmania through school records

Study	Design	N/n	Country	Type of fruit and vegetable studied	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Andreasyan, 2007; (36)	PC	498	Australia	fruit syrup; fruit juice (orange)	Q	AD, wheeze and RC: Parent reported (ISAAC Q); SPT any	9	**CARHS:** Some of the participants in the THIS cohort of infants at high risk for sudden infant death syndrome born in 1988-1989 were identified in the northern region of Tasmania through school records
Sicherer, 2010 (37)	PC	503	USA	Peanut	Q	sIgE to peanut	1	**The Consortium of Food Allergy Research** enrolled infants at 3 to 15 months of age with likely egg or milk allergy but without previously known peanut allergy

Study	Design	N/n	Country	Type of fruit and vegetable studied	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Zutavern, 2004; (38)	PC	606	UK	vegetables; fruits	Q	AD:DD; SPT aero; wheeze: Parent reported wheeze; rec wheeze: Parent reported asthma	2, 5.5	Population based birth cohort of newly pregnant women who presented at one of three general practices in Ashford, Kent UK between 1993 and 1995

PC Prospective cohort study; RC retrospective cohort study; Q questionnaire; AD atopic dermatitis; DBPCFC double blind placebo control food challenge; ISAAC International Study of Allergy and Asthma in Children; AS allergic sensitisation; SPT skin prick test, sIgE specific IgE; DD Doctor diagnosis (community); Physician assessment is assessment by study physician; AR allergic rhinitis, FA food allergy; rec wheeze recurrent wheeze; CS cross-sectional study; NCC nested case-control study

Table 2 Characteristics of included studies evaluating fruit and vegetable supplementation and autoimmune outcomes

Study	Design	N/n	Country	Type of fruit and vegetable studied	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Brekke, 2010 (39)	PC	4005/ 191	Sweden	potatoes and root vegetables; vegetables	Q	TIDM: Islet autoimmunity (GADA and/or IA2A and/or IAA)	5	**ABIS:** Population based birth cohort of children born in Southeast Sweden between 1997 and 1999
Baron, 2005 (40)	CC	444/ 222	France	Vegetables	I	IBD-CR:DD; IBD-UC:DD	<17	Cases with Crohn's disease were identified from the **EPIMAD** registry with matched controls from the same area identified by random digit dialling: France; Cases with ulcerative colitis were identified from the EPIMAD registry with matched controls from the same area

Study	Design	N/n	Country	Type of fruit and vegetable studied	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Norris, 1996; (41) Frederikson, 2012; (42) Lamb 2008 (43)	NCC; PC	1698/ 49	USA; Australia	fruits; vegetables; potatoes; root vegetables	Q/I	TIDM: Islet autoimmunity (GADA and/or IA2A and/or IAA)	<7; 15; unclear	**DAISY:** Prospective birth cohort of children at increased risk of T1DM. Cases & their non-diabetic siblings, as controls, taken from diabetes care clinics & Colorado IDDM registry; recruited from 1993 to 2001
Visalli, 2003 (44)	CC	900/ 150	Italy	fruits; vegetables	Q	TIDM:DD WHO criteria	12	**EURODIAB Italy**: Cases with T1DM selected from within the EURODIAB ACE study, born 1977-89, with controls selected from school records for the same period
Savilahti, 2009 (45)	NCC	6209/ 45	Finland	vegetables	R/D	TIDM:DD	11.5	Cases and controls taken from the NHI database, Finland
Strotmeyer, 2004; (46)	CC	688/ 247	China	vegetables; fruits	Q	TIDM: DD WHO criteria	9.7	**DiaMond:** WHO Multinational Project; cases selected from T1DM incidence registries 1985-98 and matched controls from local population

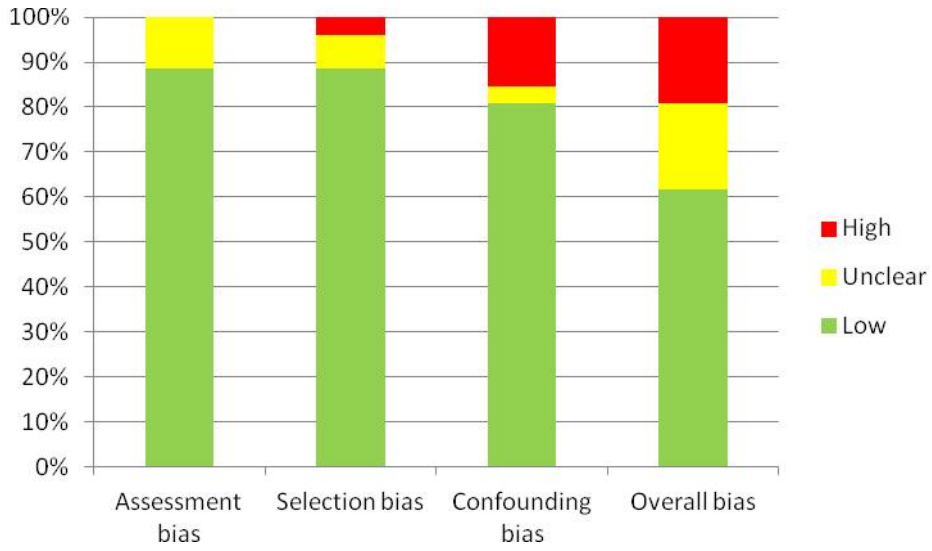
Study	Design	N/n	Country	Type of fruit and vegetable studied	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Virtanen, 2011; (47) Virtanen, 2006; (48)	PC	6069	Finland	Vegetables	Q	TIDM: DD WHO criteria	<10	A prospective birth cohort infants with HLA-conferred susceptibility to type 1 diabetes was recruited between 1996 and 2004

PC Prospective cohort study; Q questionnaire; CC case-control study; SPT skin prick test, sIgE specific IgE; DD Doctor diagnosis (community); Physician assessment is assessment by study physician; AR allergic rhinitis, FA food allergy, T1DM type 1 diabetes mellitus, RC retrospective cohort, JIA juvenile idiopathic arthritis; ILAR International League of Associations for Rheumatology; HLA human leukocyte antigen serotype

2. Infant or maternal dietary intake of fruit and vegetables and risk of atopic dermatitis (AD)

Nineteen studies investigated intake of fruits or vegetables during infancy or pregnancy in relation to AD. The majority showed a low risk of bias, which was reflected in the low risk of assessment and selection bias of the prospective cohort studies. A few studies had a high risk of bias due to the absence of adjustment for confounding (Figure 1).

Figure 1 Risk of bias in studies of fruit and vegetable intake and risk of atopic dermatitis



2.1. Infant Intake of fruit and vegetable and AD risk

Three prospective cohort studies with comparable data investigated fruit introduction between 0 and 4 months, and risk of AD at age 0-4 years old (

Figure 2). The study of **Sariachvilli (2010)** and **Zutavern (2006)** examined the association between fruit introduction and risk of AD, and the study of **Marini (2006)** studied citrus fruit introduction. **Andreasyan** (**2007)** investigated fruit or fruit syrup introduction and **Zutavern** (**2004**) investigated fruit introduction, and risk of AD at age 5-14 years (Figure 3). Neither meta-analysis showed evidence of association nor evidence of statistical heterogeneity (I^2=0%).

Figure 2 Introduction of fruit at age >4 months vs 0-4 months and risk of atopic dermatitis (odds ratio) in children aged 0-4 years old

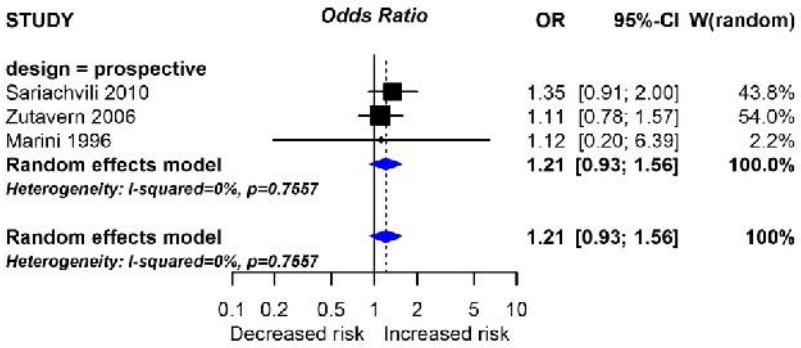
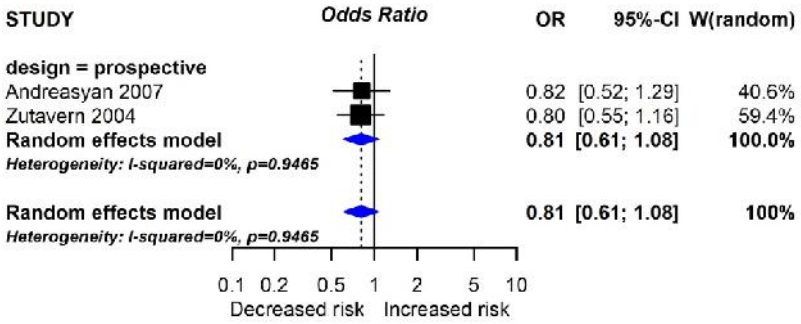


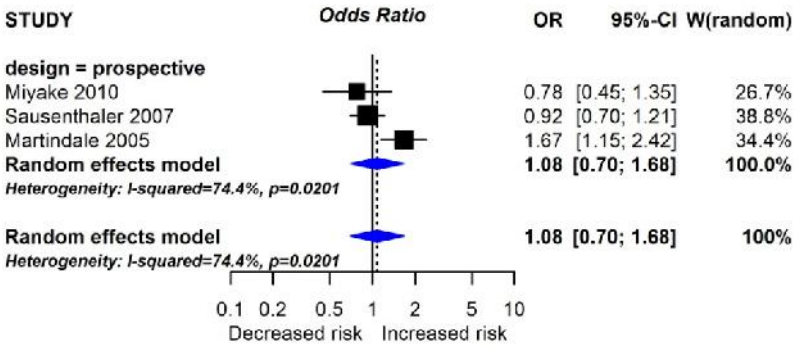
Figure 3 Introduction of fruit at age > 4 months vs 0-4 months and risk of atopic dermatitis (odds ratio) in children aged 5-14 years old



2.2. Maternal Intake of fruits and vegetables and risk of AD in childhood

Maternal dietary intake of fruits or vegetables and risk of AD in childhood was investigated in three prospective cohort studies with comparable data for meta-analysis. Intake of fruit during pregnancy was unrelated to AD in children at age 0-4 years (Figure 4). The studies of **Miyake** (**2010**; any fruits), **Martindale** (**2005**; any fruits) and **Sausenthaler** (**2007**; apples) had high heterogeneity. This may be explained by differences in the populations and dietary habits of the study populations, and/or the method of assessing fruit intake. The LISA study **(Sausenthaler)** was based on German children, whereas the Osaka cohort (OMCHS, **Miyake)** recruited Japanese children, and the Aberdeen cohort was based on a Scottish population (**Martindale**). Dietary intake of fruits was analysed using different, but comparable approaches.

Figure 4 Maternal fruit intake (highest vs. lowest) and risk of atopic dermatitis (odds ratio) in children aged 0-4 years old



2.3. Studies on infant or maternal intake of fruits and vegetables that were not suitable for meta-analysis

The main results from observational studies that could not be included in meta-analysis are shown in Table 3. All the studies were prospective cohorts, with the exception of **Sariachvili (2010)**, which was a nested case-control study. There was no evidence of an association between fruit and vegetable intake or introduction and AD. There was some evidence of an association in three studies on infant intake. The study of **Sariachvili (2010)** which reported a higher risk of AD in infants who were introduced to fruit juice after 4 months of age in their diet, compared to those who started drinking it earlier. The study of **Nwaru (2010)** reported that a higher intake of berries was statistically negatively associated with risk of AD. There was some evidence on maternal intake of green and yellow vegetables, and citrus fruit reducing risk of AD in one study (**Miyake 2010**) but this was not confirmed in other studies.

We found no consistent evidence to suggest that infant or maternal intake of fruits and vegetables might influence the risk of AD.

Table 3 Studies investigating the association between fruit and vegetable and atopic dermatitis which were not eligible for meta-analysis

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value<0.05)
					INFANT INTAKE		
Fergusson, 1990 (7)	PC	AD	10	1067	Fruit and vegetable introduction (>4 months vs. ≤ 4months)	HR	NS
Nwaru, 2013 (13)	PC	AD	0.5	3109	Fruits and berries >4 months vs. <3.5 and 3.5-4 months		NS
					Fruits and berries (continuous intake)	Reduced AD	**P=0.03**
					Root vegetables/ >4 months vs. <3.2 and 3.2-4 months		NS
Roduit, 2012 (13)	PC	AD	4	1041	**Fruit and vegetable intake in the first year of life** Intake before 6 months (high risk infants)	OR	1.92 (0.94-3.92)
					Intake before 6 months (low risk infants)	OR	1.69 (0.74-3.91)
				912	Fruits and vegetables introduced into diet >6 months vs. <6 months	OR	1.23 (0.80-1.91)
Andreasyan, 2007 (36)	PC	AD	9	495	Fruit juice (orange) consumption at >1 month vs. ≤ 1 month	RR	1.49 (0.42-5.35)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value<0.05)
Hesselmar, 2010 (4)	PC	AD	1.5	184	Fruits introduced to the diet (age in months compared as continuous variable)		NS
Zutavern, 2006 (20)	PC	Parental reported AD	2	2,540	Fruits at 5-6 months vs. 0-4 months	OR	1.02 (0.77-1.35)
					Fruits >6 months vs. 0-4 months	OR	1.03 (0.74-1.44)
					Vegetables at 5-6 months vs. 0-4 months	OR	1.02 (0.78-1.34)
					Vegetables>6 months vs. 0-4 months	OR	1.22 (0.88-1.69)
		DD AD	2	2,540	Fruits at 5-6 months vs. 0-4 months	OR	1.14 (0.85-1.53)
					Vegetables at 5-6 months vs. 0-4 months	OR	1.21 (0.90-1.62)
Zutavern, 2004(38)	PC	AD	5.5	642	Introduction of vegetables >4 months vs earlier	OR	0.83 (0.53-1.30)
Miskelly, 1988 (25)	PC (of RCT)	AD	1	482	Fruits/ early introduction (continuous comparison scale (months)		NS
Morgan, 2004 (26)	PC	AD	1	257	Introduction of fruits or vegetables (weeks)		NS
Oien, 2009 (28)	PC	AD	2	3050	Infant intake of vegetables during 1st year / ≤1x/week vs. 2 to 5 times	OR	0.91 (0.46-1.80)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value<0.05)
Sariachvili, 2010 (31)	NCC	AD	4	557/252	**Infant food introduction (**>4 months vs. ≤4 months) Fruit juice	OR	**1.56 (1.08-2.27)**
					Vegetables	OR	1.39 (0.93-2.06)
Dunlop, 2006 (33)	PC	AD	1	1326	Introduction of citrus fruit in months 8 and beyond	OR	0.90 (0.55-1.48)
					MATERNAL INTAKE		
Oien, 2009 (28)	PC	AD	2	3013	Vegetables/maternal intake of vegetables during pregnancy (2-5 times per week vs ≤once a week)	OR	0.76 (0.54-1.06)
Maijaliisa, 2011(10)	PC	AD	5	2441	**Maternal intake of malaceous fruits during 8th month pregnancy** (not low consumption vs. low consumption) Apple		NS
					Green leafy vegetables		NS
Willers, 2007 (3)	PC	AD	5	1212	**Maternal intake during pregnancy** (highest vs lowest tertile) Any fruits		NS
					Any vegetables		NS

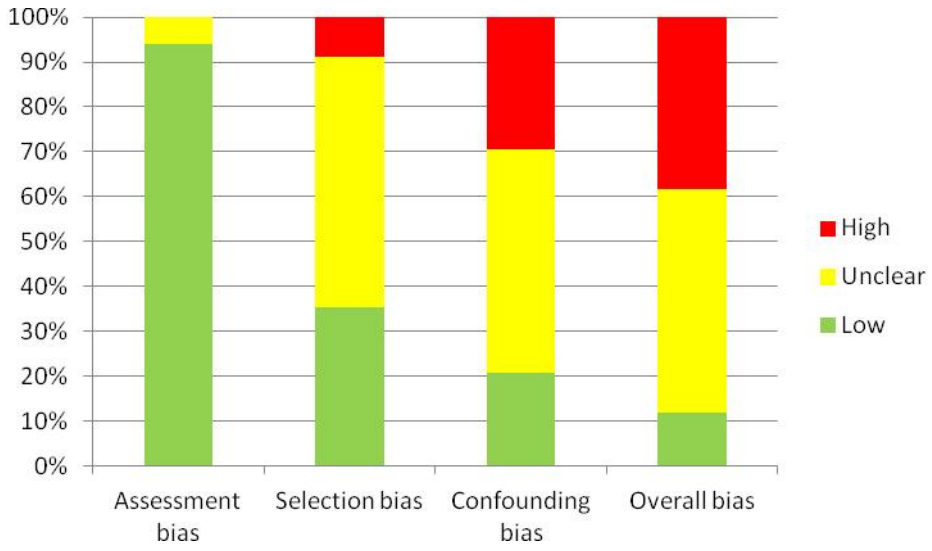
First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value<0.05)
Martindale, 2005 (2)	PC	AD	2	1300	**Maternal intake during pregnancy** (>1 portion per day vs ≤ 1 portion per day)		
					Fruit juice	OR	NS
					Any vegetables	OR	NS
Sausenthaler, 2007 (22)	PC	AD	2	2473	**Maternal consumption during the last 4 weeks of pregnancy** (highest vs lowest tertile)		
					Bananas	OR	1.03 (0.77-1.38)
					Strawberries	OR	1.02 (0.77-1.35)
					Citrus fruits	OR	1.03 (0.79-1.35)
					Fruit juice	OR	1.18 (0.90-1.54)
					Salad	OR	0.92 (0.69-1.22)
					Celery	OR	0.94 (0.67-1.31)
					Sweet pepper	OR	0.97 (0.74-1.27)
					Spinach	OR	1.26 (0.99-1.61)
					Raw carrots	OR	1.12 (0.86-1.46)
					Seeds	OR	1.24 (0.94-1.64)
					Tomato	OR	0.83 (0.63-1.10)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value<0.05)
Miyake, 2010 (27)	PC	AD	2	763	**Maternal intake during pregnancy** (highest vs lowest tertile)		
					Any vegetables	OR	0.85 (0.49-1.46)
					Green and yellow vegetables	OR	**0.41 (0.24-0.71)**
					Apple	OR	0.87 (0.50-1.52)
					Citrus fruits	OR	**0.53 (0.30-0.93)**
Litonjua, 2006 (32)	PC	AD	2	1290	**Maternal intake at 26-28 weeks of pregnancy**(highest quartile intake vs lowest)		
					Any fruit		NS
					Any vegetable		NS
Maijaliisa, 2011(10)	PC	AD	5	2441	**Maternal intake at 8th month of pregnancy** (not low consumption vs. low consumption)		
					Apple		NS
					Green/leafy vegetables		NS

3. Infant or maternal dietary intake of fruit and vegetable and risk of food allergy

Nine observational studies (5 prospective cohorts, and 4 case-control studies) investigated the association between intake of fruits and vegetables and risk of food allergy. Over one third of studies were assessed as at high risk of bias. This was mostly due to unadjusted or poorly reported adjusting leading to a risk of confounding bias. Assessment bias was considered to be of low risk for over 90% of the studies (Figure 5).

Figure 5 Risk of Bias in studies of fruit and vegetable intake and food allergy



3.1. Maternal Intake of fruit and vegetables and risk of childhood food allergy

Three prospective cohort studies with data eligible for meta-analysis investigated the association between maternal peanut avoidance and risk of peanut allergy in children at any age, between 0-4 years old, or later in childhood (5-14 years old). The pooled estimates of three prospective cohorts examining the association between maternal peanut avoidance during pregnancy and risk of peanut allergy in children showed no indication of association (Figure 6). The studies compared eating peanuts ever vs never (**Kemp 2011**), ≥2 times per week vs ≤ twice per week, (**Sicherer 2010**), and no vs yes (**Dean 2007**). There was no evidence of heterogeneity in these studies (I^2=0%). The retrospective studies of **DesRoches (2010)** and **Fox (2009)** showed no association between maternal peanut avoidance in pregnancy and risk of peanut allergy in children at age 0-4 years old (Figure 7). The study of **DesRoches (2010)** investigated peanut avoidance as a binary exposure (no vs yes) and the

study of **Fox** (**2009)** compared an intake of >15g per week vs none per week. There was very high heterogeneity in these studies (I^2=72.1%) probably due to the variability in the assessment of peanut consumption in these two studies.

Figure 6 Maternal peanut avoidance during pregnancy (often vs. rare) and risk of food allergy to peanut (odds ratio) in children (at any age)

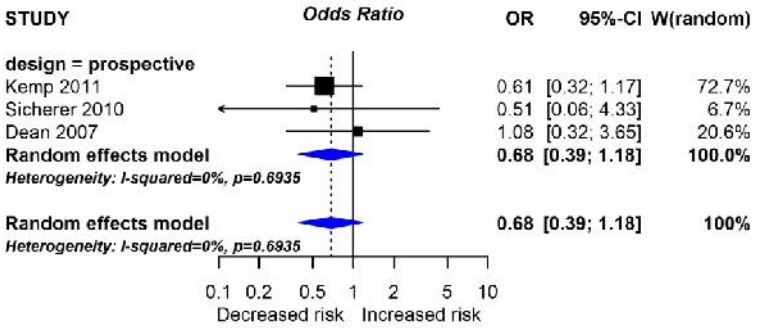
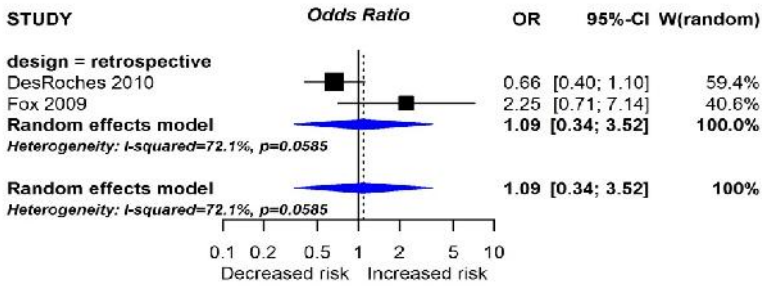


Figure 7 Maternal peanut avoidance during pregnancy (often vs. rare) and risk of food allergy to peanut (odds ratio) in children aged 0 to 4 years old



3.2. Studies on infant or maternal intake of fruits and vegetables that were not suitable for meta-analysis

Table 4 summarises the findings of six observational studies that investigated the association between fruits and vegetable intake and risk of food allergy. **Des Roches 2010** reported increased peanut allergy in infants of mothers who consumed peanut and soya during pregnancy or lactation. This association (for peanut) was not supported by a second study (**Fox 2009)**.

Overall we found no evidence for association between fruit and vegetable intake and food allergy.

Table 4 Studies investigating the association between fruit and vegetable and any food allergy which were not eligible for meta-analysis

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					INFANT INTAKE		
Hesselmar, 2010 (4)	PC	Any food allergy	1.5	184	Fruit introduction (in months)	OR	NS
		Food allergy to cow's milk	0.5	184	Fruit introduction (in months)	OR	NS
					MATERNAL INTAKE		
Lack, 2003 (5)	PC	Food allergy to peanut	5.5	11352	**Maternal avoidance during pregnancy:** Nuts (including peanuts) during pregnancy yes vs. no	OR	0.98 (0.53-1.81)
					Soybean meat avoidance (intake vs no intake)	OR	1.09 (0.39-3.03)
Sausenthaler, 2007 (22)	PC	Food allergy (any)	2	2473	Maternal fruit intake (highest vs. lowest)	OR	0.33 (0.10-1.07)
					Maternal vegetable intake (highest vs. lowest)	OR	0.81 (0.50-1.32)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
Binkley, 2011 (6)	CC	Food allergy to peanut	18	1413/1300	Peanut avoidance in pregnancy (reduced intake vs no intake)	OR	0.78 (0.43-1.40)
DesRoches, 2010 (9)	CC	Food allergy to peanut or soy	1.5	202/201	Maternal avoidance Peanut avoidance during pregnancy (no vs yes)	OR	**4.22 (1.57-11.30)**
				202/201	Soya avoidance during pregnancy (no vs yes)	OR	**1.88 (1.20-2.94)**
				202/201	Maternal avoidance Peanut avoidance during lactation (no vs yes)	OR	**2.28 (1.31-3.97)**
				202/201	Soya avoidance during lactation (no vs yes)	OR	**1.81 (1.08-3.03)**
Fox, 2009 (15)	CC	Food allergy to peanut	<4	293/133	**Maternal peanut intake during pregnancy/lactation:** Lactation (≥15g per week vs no intake)	OR	0.63 (0.15-2.70)
					Lactation (3.75-15 g/week vs no intake)	OR	0.70 (0.27-1.80)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
Fox, 2009 (16)	CC	Food allergy to peanut	<4	293/133	Lactation (0.1-3.75 g/week vs no intake)	OR	0.80 (0.34-1.90)
					Pregnancy (3.75-15 g/week vs no intake)	OR	1.00 (0.42-2.40)
					Pregnancy (0.1-3.75 g/week vs no intake)	OR	2.11 (0.93-4.80)
					Pregnancy (≥15g per week vs no intake)	OR	2.25 (0.70-7.10)

4. Infant or maternal dietary intake of fruit and vegetables and risk of poor lung function

4.1. Lung function

One prospective cohort study was identified, which investigated intake of various types of fruits and vegetables in relation to lung function. The study was considered to have a low overall risk of bias. There was no evidence of an association between maternal intake of specific fruits and vegetable groups during pregnancy and lung function measured in the offspring when 5 years old (Table 5).

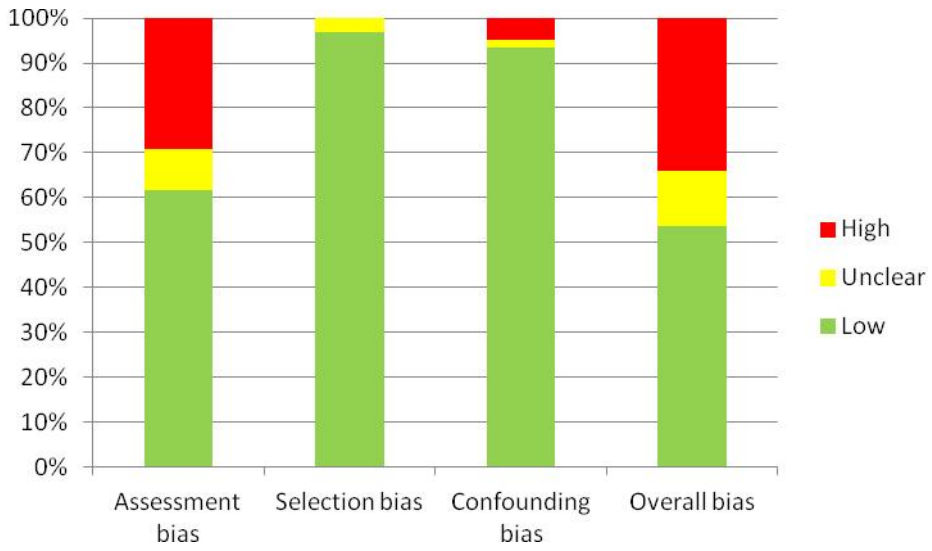
Table 5 Studies investigating the association between fruit and vegetable (dietary exposure) and lung function (outcome) which were not eligible for meta-analysis

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect
					MATERNAL INTAKE		
Willers, 2007 (3)	PC	LF	5	510	**Maternal intake during pregnancy (high vs low tertiles):** Fruits		NS
					Citrus fruits		NS
					Fruit juice		NS
					Vegetables		NS
					Green leafy vegetables		NS

5. Infant or maternal dietary intake of fruit and vegetables and risk of wheeze

Nineteen observational studies were identified which investigated the relation between infant or maternal intake of fruits and vegetables and risk of wheeze or recurrent wheeze. Over half of the studies were considered to be of low risk of overall bias, with most of them having a low risk of selection or confounding bias (Figure 8).

Figure 8 Risk of bias in studies of fruit and vegetables intake and wheeze



5.1. Infant intake of vegetables and fruits and risk of wheeze

Meta-analysis was possible for two prospective studies reporting the association between introduction of fresh fruit in the infant diet between 0-4 months of age and risk of wheeze (

Figure **9**). The study of Strassburger (2010) investigated 'introduction of fruit juice' and risk of wheeze at age 3.5 years, whereas the study of Zutavern (2004) investigated 'introduction of fruit' and risk of wheeze at age 2 years. The pooled effect estimates showed no evidence of a relationship between early fruit intake and this outcome, and there was no statistical heterogeneity between studies (I^2=0%). Similarly, there was no evidence of an association between introduction of fruit juice (Strassburger 2010) and introduction of citrus fruit (Marini 1996) and recurrent wheeze, as shown in Figure 10. There was moderate heterogeneity between these studies (I^2=40.6%).

Figure 9 Introduction of fruit in months 0 to 4 and risk of wheeze (odds ratio) in children aged 0 to 4 years old

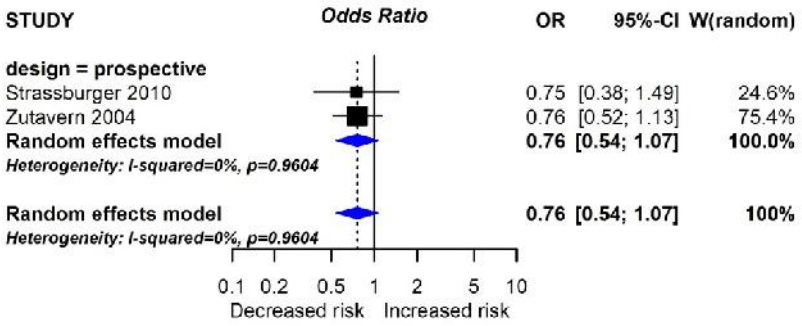
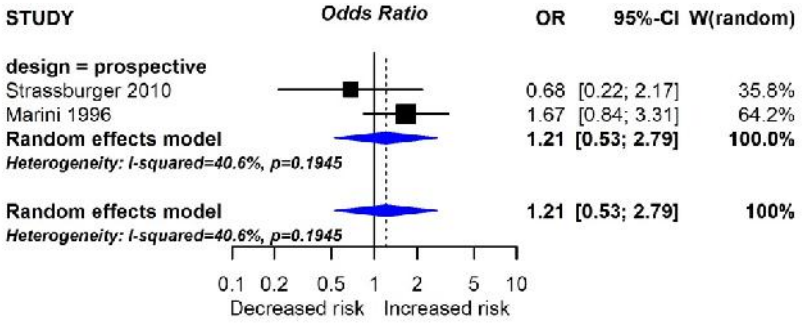


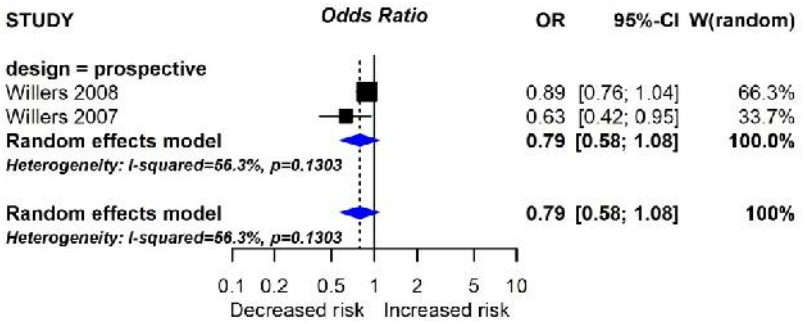
Figure 10 Introduction of fruit in month ≥4 and risk of recurrent wheeze (odds ratio) in children aged 0 to 4 years old



5.2. Maternal intake of fruits and vegetables and risk of wheeze

Figure 11 shows the pooled effect estimates of the two prospective studies of **Willers**, one from **2007** (apple intake) and one from **2008** (any fruit intake) and risk of wheeze at age 5 years and 8 years, respectively. The meta-analysis showed no evidence of association between this outcome and fruit intake.

Figure 11 Maternal fruit intake (often vs rare) and risk of wheeze (odds ratio) in children aged 5 to 14 years old



5.3. Studies on infant or maternal intake of fruits and vegetables that were not suitable for meta-analysis

Table 6 summarises the results of 15 studies with data on dietary intake of fruits or vegetables during pregnancy or infancy and its association with risk of wheeze or recurrent wheeze. These studies were considered not suitable for meta-analysis due to the large variations in the comparison levels used to describe dietary intake and its relation to disease. The age at time of outcome measurement ranged between 1 year and 9 years old.

There was some evidence of an association between higher intake of fruits or vegetables during pregnancy and reduced wheeze in children at age 5 years. The study of **Maijaliisa** (**2011**) showed that higher intakes of green/leafy vegetables and of malaceous fruits in the last month of pregnancy were negatively associated with disease risk. In the study of **Erkkola** (**2012)** and colleagues there was evidence suggesting that pregnant mothers with a higher intake of various types of fruits (including malaceous and berry juice), as well as of several groups of vegetables, was related to a lower risk of wheeze in the offspring at age 5. In The Danish prospective cohort study of **Maslova (2012)** the authors reported that a lower intake of peanuts (avoidance) during the second trimester of gestation was associated with a reduced risk of recurrent wheeze in the offspring, both at age 18 months and at 7 years old. There was no evidence from other studies that infant intake of fruits or vegetables to suggest an association between fruit or vegetable intake and risk of wheeze or recurrent wheeze, nor there was evidence that early introduction of these foods was related to the outcomes of interest.

Overall, we found no consistent evidence to suggest that intake of fruits or vegetables in infancy, pregnancy or lactation influences the risk of wheeze.

Table 6 Studies investigating the association between fruit and vegetable and wheeze which were not eligible for meta-analysis

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					INFANT INTAKE		
Strassburger, 2010 (34)	PC	**Infant introduction (≥4 months vs. <4 months)** Wheeze			Salty pureed food	OR	0.60 (0.25-1.39)
		Rec wheeze	3.5	338	Salty pureed food	OR	0.45 (0.12-1.61)
Andreasyan, 2007 (36)	PC	Wheeze	9	497	Infant fruit juice (orange) introduction >1 month vs. ≤ 1 month	RR	1.33 (0.49-3.66)
Miskelly, 1988 (25)	PC	Wheeze	1	482	Fruits intake (continuous months)	OR	NS
Hesselmar, 2010 (4)	PC	Rec wheeze	1.5	184	Fruits/age in months when introduced	OR	NS

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
Oien, 2009 (35)	PC	Rec wheeze	2	2220	Infant intake of vegetables during 1st year (2 to 5 times per week vs ≤1/week)	OR	NS
					Fruits and berries/ intake >4 months vs. <3.5 and 3.5-4 months	HR	NS
					Root vegetables//>4 months vs. <3.2 and 3.2-4 months	HR	NS
Nwaru, 2013 (13)	PC	Rec wheeze	0.5	3109	Fruits and berries// >4 months vs. <3.5 and 3.5-4 months	HR	NS
					Root vegetables/ >4 months vs. <3.2 and 3.2-4 months	HR	**0.65 (0.51-0.82)**
Maijaliisa, 2011 (10)	PC	Wheeze	5	2441	Malaceous fruit (not low vs. low consumption)	OR	**0.69 (0.54-0.88)**

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					MATERNAL INTAKE		
Erkkola, 2012 (14)	PC	Wheeze	5	2441	**Intake during pregnancy:** Fruits/ 326.2-793.9 g/d vs. <326.2 g/d	OR	1.19 (0.93-1.53)
					Intake during pregnancy: Malaceous fruits/17.1-97.5 g/d quarter vs. <17.7 g/d	OR	**0.74 (0.58-0.94)**
					Fruits and vegetables/ 49.5-138.7g/d vs. <49.5 g/d	OR	0.89 (0.70-1.14)
					Berries / 6.74-32.7 g/d vs. <6.74 g/d	OR	1.11 (0.87-1.42)
					Citrus fruits / 7.04-71.8 g/d vs. <7.04 g/d	OR	0.87 (0.69-1.10)
					Fruit and berry juices / 5.67-145.7 g/d vs. <5.67 g/d	OR	1.03 (0.81-1.31)
					Malaceous fruit / 17.1-97.5 g/d vs. 97.6-935 g/d	OR	1.14 (0.90-1.45)
					Berries 6.74-32.7 g/d vs. 32.7-611 g/d	OR	1.12 (0.88-1.42)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					Citrus fruit / 7.04-71.8 g/d vs. 71.8-778.8 g/d	OR	1.00 (0.79-1.27)
					Fruit and berry juice / 5.67-145.7 g/d vs. 145.7-1700 s g/d	OR	**1.27 (1.00-1.61)**
					Vegetables / 149.1-315.1 g/d vs. <149.1 g/d	OR	**0.76 (0.60-0.97)**
Erkkola, 2012 (14)		Wheeze	5	2441	Leafy vegetable / 9.6-36.1 g/d vs. <9.6 g/d	OR	**0.68 (0.53-0.86)**
					Root vegetables and potatoes/ 117.8-207.5 g/d vs. <117.8 g/d	OR	**0.78 (0.61-0.99)**
					Green leafy vegetables/ 9.6-36.1 g/d vs. 36.1-260.7 g/d	OR	1.05 (0.82-1.34)
					Root vegetables and potatoes/ 49.5-138.7 g/d vs. 207.5-788.5 g/d	OR	1.14 (0.88-1.47)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					Fruit and berry juices/ 5.67-145.7 g/d vs. 145.7-1700 g/d	HR	0.71 (0.45-1.13)
					Root vegetables and potatoes/ 117.8-207.5 g/d vs. <117.8 g/d	HR	0.93 (0.58-1.50)
					Green leafy vegetables/ 9.6-36.1 g/d vs. <9.6 g/d	HR	0.96 (0.59-1.56)
					Root vegetables and potatoes/49.5-138.7 g/d vs. 207.5-788.5 g/d	HR	1.52 (0.88-2.64)
					Berries/ 6.74-32.7 g/d vs. <6.74 g/d	HR	0.93 (0.53-1.61)
					Citrus fruits/ 7.04-71.8 g/d vs. <7.04 g/d	HR	0.77 (0.48-1.23)
					Fruit and berry juices/ 5.67-145.7 g/d vs. <5.67 g/d	HR	0.93 (0.57-1.49)
					Malaceous fruits/ 17.1-97.5 g/d vs. 97.6-935 g/d	HR	1.12 (0.68-1.85)
					Berries/6.74-32.7 g/d vs. 32.7-611 g/d	HR	1.56 (0.96-2.54)
Erkkola, 2012 (18)	PC	Rec wheeze	5	2441	Citrus fruits/ 7.04-71.8 g/d vs. 71.8-778.8 g/d	HR	0.77 (0.47-1.27)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					Maternal intake during pregnancy (high vs low tertiles)		
					Green leafy vegetables	OR	NS
					Citrus fruits	OR	NS
Willers, 2007 (3)	PC	Rec Wheeze	5	1212	Fruit juice	OR	NS
					Vegetables	OR	NS
					Green leafy vegetables	OR	NS
					Vegetables	OR	NS
Martindale, 2005 (2)	PC	Wheeze	2	1300	Fruit juice intake during pregnancy / >1 portion per day vs ≤1 portion per day	OR	NS

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					Maternal intake during pregnancy (highest vs lowest quartile)		
					Apple	OR	NS
Miyake, 2010 (27)	PC	Wheeze	2	763	Citrus fruits	OR	NS
Litonjua, 2006 (32)	PC	Wheeze	2	1290	Fruits/ maternal diet / lowest vs. highest quartiles	OR	NS
					Maternal intake of peanut 21-25th week of gestation		
				38223	≥once per week vs 0 times per week	OR	NS
				38279	2-3 times per month vs 0 times per week	OR	NS
				13313	. ≥ once per week vs 0 per week	OR	NS
				13415	≥ once per month vs 0 times per month	OR	NS
Maslova, 2012 (8)	PC	Wheeze	1.5	38223	≥once per week 0 times per week	OR	NS

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
Martindale, 2005 (2)	PC	Wheeze	2	1300	Vegetable maternal intake in pregnancy / ≤1 portion per day vs. >1 portion per day	OR	NS
Miyake, 2010 (27)	PC	Wheeze	2	763	Maternal intake during pregnancy (highest vs lowest quartiles) Green and yellow vegetables	OR	NS
Willers, 2008 (30)	PC	Wheeze	8	2806	**Maternal intake during pregnancy** Nuts (daily vs rarely)	OR	NS
					Nuts (regularly vs rarely)	OR	NS
Litonjua, 2006 (32)	PC	Wheeze	2	1290	**Maternal intake in the first trimester of gestation (highest vs lowest quartiles)** Vegetables	OR	NS
					Fruits	OR	NS
Oien, 2009 (28)	PC	Rec wheeze	2	2220	Vegetables/Maternal consumption during pregnancy / ≤ once/week vs. almost daily	OR	0.98 (0.86-1.04)

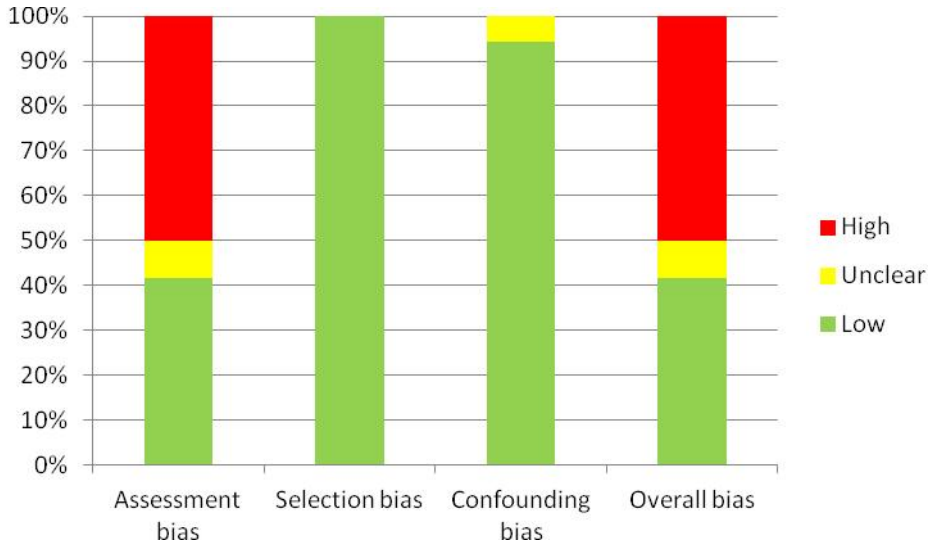
First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
Fitzsimon, 2007 (19)	PC	Rec wheeze	3	631	Grouped fruits and vegetables (highest vs. lowest quartiles)	OR	NS
Maijaliisa, 2011 (10)	PC	Rec wheeze	5	2441	**Maternal intake during pregnancy** Fruit / 326.2-793.9 g/d vs. <326.2 g/d	HR	NS
					Malaceous fruit 17.1-97.5 g/d vs. <17.7 g/d	OR	NS
					Green leafy vegetable/ Not low vs. low consumption	OR	NS
Erkkola, 2012 (14)	PC	Wheeze	5	2441	**Maternal intake during pregnancy** Vegetable / 149.1-315.1 g/d vs. <149.1 g/d	HR	NS
					Green leafy vegetables/ 9.6-36.1 g/d vs. 36.1-260.7 g/d	HR	NS

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
	PC	Rec wheeze	6.5	468	**Maternal intake during pregnancy:** Fruit >14 servings per week vs ≤14 servings per week	OR	NS
					Legumes >1 serving per week vs ≤1 servings per week	OR	NS
Chatzi, 2008 (24)		Wheeze	6.5	468	Nut >1 serving per week vs ≤1 serving per week	OR	NS
					Fruit intake >14 servings per week vs ≤14 servings per week	OR	NS
					Vegetable >8 servings per week vs ≤8 servings per week	OR	NS
					Legume >1 servings per week vs ≤1 servings per week.	OR	NS
					Nut >1 servings per week vs ≤1 serving per week	OR	NS

6. Infant or maternal dietary intake of fruit and vegetables and risk of allergic rhino-conjunctivitis (RC)

Seven prospective cohorts investigated the association between infant or maternal dietary intake of fruits and vegetables and risk of RC in childhood. None of the studies had comparable data eligible for a meta-analysis. All studies had low selection bias, and the majority had low risk of confounding bias. Due to the proportion of studies with high risk in assessment bias, half of them were considered to have an overall high risk of bias (Figure 12).

Figure 12 Risk of Bias in studies of fruit and vegetables intake and rhino-conjunctivitis



The summary results of the studies that assessed the association between infant or maternal dietary intake of fruits and vegetables is presented in Table 7. The studies of **Nwaru (2013)**, **Marini (2006)** and **Andreasyan (2007)** investigated the association between early exposure to fruits (0-4 months age) and risk of RC, showing no evidence of association. Four studies investigated the association between maternal intake of fruits or vegetables at various stages of pregnancy, with risk of RC. Only one study found a evidence of an association between maternal intake of vegetables and reduced RC in children at age 7 years (**Maslova 2012).** They also reported reduced RC in the offspring of mothers who consumed peanuts 2-3 times per month vs less frequently. There was no evidence from other studies to suggest an association between intake of fruits or vegetables and risk of RC. We found no consistent evidence to suggest that maternal or infant fruit or vegetable intake influences risk of RC in childhood.

Table 7 Studies investigating the association between fruit and vegetable and rhino-conjunctivitis which were not eligible for meta-analysis

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					INFANT INTAKE		
Nwaru, 2013 (13)	PC	RC	0.5	3109	Fruits and berries introduction / >4 months vs. <3.5 and 3.5-4 months old	HR	NS
					Root vegetables introduction / >4 months vs. <3.2 and 3.2-4 months old	HR	NS
Andreasyan, 2007 (36)	PC	RC	9	497	Fruit juice (orange) introduction / >1 vs. ≤1 month old	RR	3.45 (0.52-22.83)
					Introduction of fruit >1 vs. ≤1 month old	RR	0.84 (0.56-1.27)
Marini, 1996 (23)	PC	RC	<4		Introduction of fruit at age 0-4 months	OR	1.12 (0.83-1.50)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					MATERNAL INTAKE		
Erkkola 2012 (14)	PC	RC	5	2441	**Fruit and vegetable intake during pregnancy** Fruit and vegetable/ 49.5-138.7 g/d vs. <49.5 g/d	HR	1.15 (0.82-1.61)
					Malaceous fruit / 17.1-97.5 g/d vs. <17.7 g/d	HR	0.85 (0.62-1.16)
					Malaceous / 17.1-97.5 g/d vs. 97.6-935 g/d	HR	1.14 (0.83-1.57)
					Berries / 6.74-32.7 g/d vs. <6.74 g/d	HR	0.91 (0.66-1.26)
					Berries / 6.74-32.7 g/d vs. 32.7-611 g/d	HR	1.14 (0.83-1.57)
Erkkola 2012 (14)	PC	RC	5	2441	Citrus fruit / 7.04-71.8 g/d vs. <7.04 g/d	HR	0.88 (0.65-1.21)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					Citrus fruit / 7.04-71.8 g/d vs. 71.8-778.8 g/d	HR	1.03 (0.75-1.42)
					Fruit and berry juices / 5.67-145.7 g/d vs. <5.67 g/d	HR	1.04 (0.75-1.44)
					Fruit and berry juices / 5.67-145.7 g/d vs. 145.7-1700 g/d	HR	1.40 (1.03-1.90)
					Fruits/ 326.2-793.9 g/d vs. >793.9-3908 g/d	HR	0.95 (0.67-1.34)
					Vegetable intake / 149.1-315.1 g/d g/d vs. <149.1 g/d	HR	1.06 (0.75-1.51)
					Leafy vegetable / 9.6-36.1 quarter vs. <9.6 g/d	HR	1.15 (0.81-1.63)
					Leafy vegetable / 9.6-36.1 g/d vs. 36.1-260.7 g/d	HR	1.06 (0.78-1.44)
					Root vegetable and potato/ 117.8-207.5 g/d vs. <117.8 g/d	HR	0.88 (0.64-1.20)
Erkkola, 2012 (14)	PC	RC	5	2441	Root vegetable and potato / 117.8-207.5 g/d vs. 207.5-788.5 g/d	HR	0.97 (0.69-1.37)

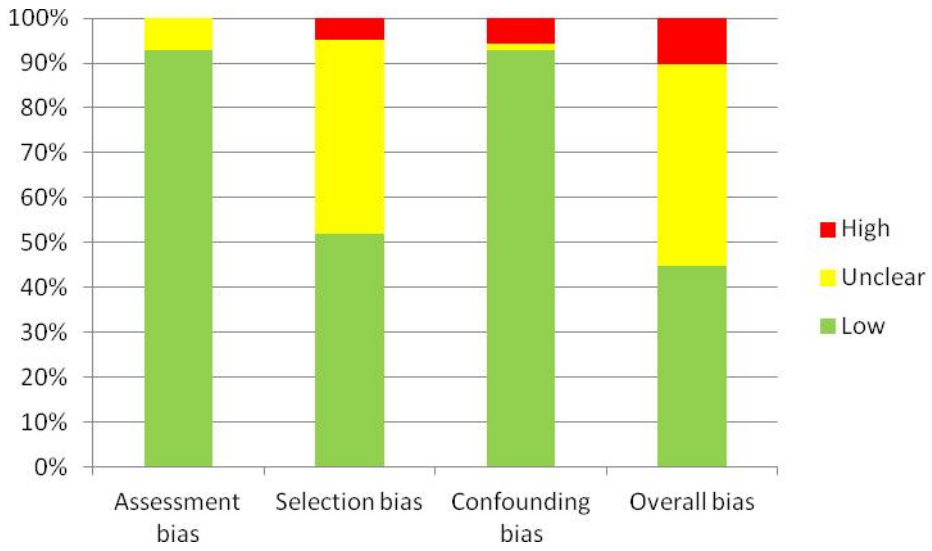
First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					Maternal intake during 8th month pregnancy / Not low consumption vs. low consumption		
					Malaceous fruit intake	OR	NS
Maijaliisa, 2011 (10)	PC	RC	5	2441	Green leafy vegetable	OR	NS
					Maternal intake of peanut during 21-25th week of gestation		
				13313	Peanut ≥1 per week vs 0 per week	OR	0.78 (0.56-1.08)
			7 1.5	44956	Peanut 2-3 times per month vs 0 per month	OR	**0.83 (0.72-0.96)**
				38223	Peanut ≥1 per week vs 0 per week	OR	0.92 (0.77-1.10)
			7				
				13415	Peanut once a month vs 0 per month	OR	0.95 (0.84-1.08)
Maslova, 2012 (8) (1.5 years)	PC	RC	1.5	38279	Peanut 2-3 times per month vs 0 per month	OR	0.99 (0.86-1.14)
Maslova, 2012 (12) (7 years)	PC	RC	7		Maternal vegetable intake (often vs. rare)	OR	**0.84 (0.75-0.95)**

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
Willers, 2007 (3)	PC	RC	5	1212	**Intake during pregnancy**(high vs lowest tertile)		
					Vegetable	OR	NS
					Green leafy vegetables	OR	NS
					Fruit	OR	NS
					Citrus fruit	OR	NS

7. Infant or maternal dietary intake of fruits and vegetables and risk of allergic sensitisation

Fifteen studies investigated the association between infant or maternal intake of fruits and vegetables and risk of allergic sensitisation (positive skin prick test [SPT] or sensitisation to a specific allergen [sIgE]). Overall, the studies were considered to have a low or unclear risk of bias. Most of the studies had a low risk of assessment and confounding bias, with nearly 40% of the studies having an unclear method of sample selection (Figure 13).

Figure 13 Risk of Bias in studies of fruits and vegetables intake and allergic sensitisation



Few prospective cohort studies had comparable data to estimate pooled size effects of fruit or vegetable intake on allergic sensitisation. Early introduction of vegetables or fruits was unrelated to the risk of having specific sensitisation to aero-allergens in children. The studies of **Nwaru (2010)** and **Zutavern (2004)** showed no evidence of an effect of introduction of cabbage or any vegetables, respectively, with the meta-analysis having no heterogeneity (Figure 14, I^2=0%). The studies of **Strassburger (2010)** and **Zutavern (2004)** showed no evidence of an association between early introduction of fruit juice or fruit, respectively, and specific sensitisation to aero-allergens (Figure 15). The meta-analysis had moderate heterogeneity (I^2=45.8%). Maternal intake of peanuts during pregnancy (**Kemp 2011**; **Dean 2007**) or during lactation (**Sicherer 2010**) was unrelated to risk of specific aero-allergen

sensitisation in childhood (Figure 16). Maternal intake of any fruit (**Nwaru 2010**) or of apple (**Sausenthaler 2007**) was not associated with risk of specific sensitisation in childhood (Figure 17).

Figure 14 Introduction of vegetables months 0 to4 and risk of specific sensitisation to aero-allergens in children (any age) (odds ratio)

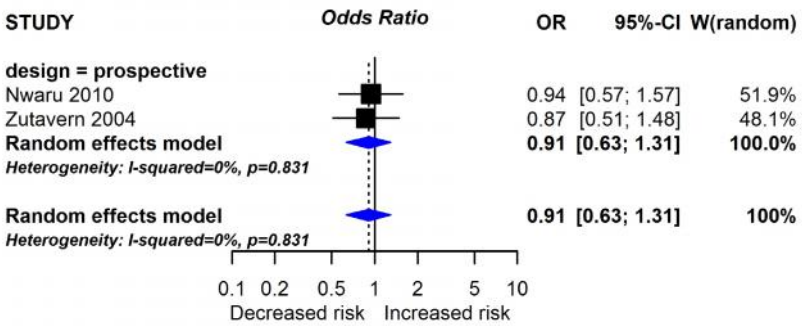


Figure 15 Introduction of fruit months 0 to4 and risk of specific sensitisation to aero-allergens in children (any age) (odds ratio)

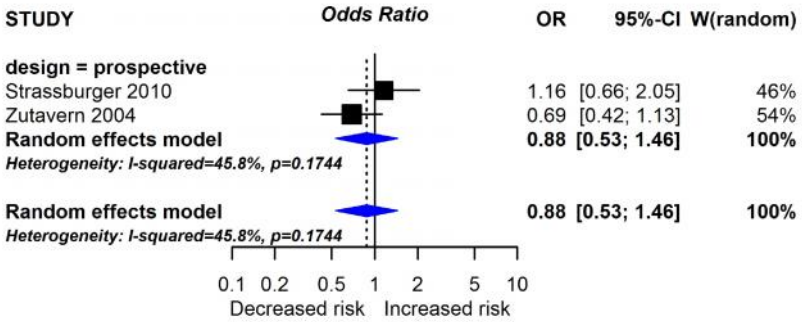


Figure 16 Maternal peanut intake during pregnancy or lactation (often vs. rare) and risk of specific sensitisation to peanut in children (any age) (odds ratio)

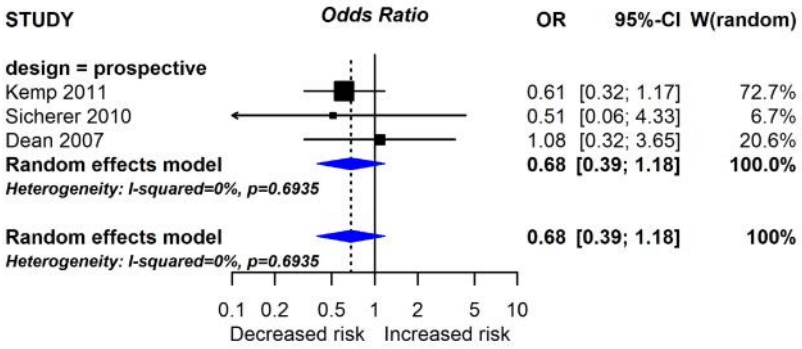
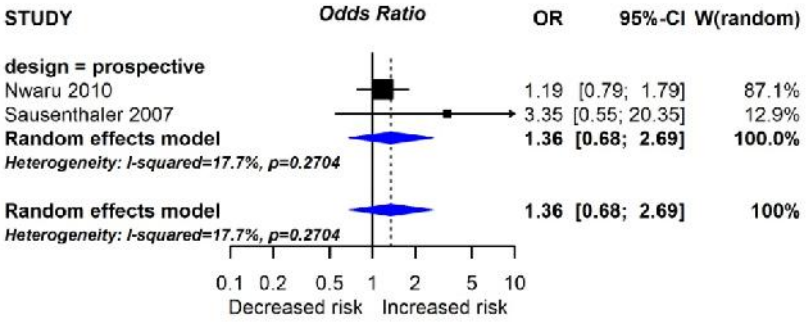


Figure 17 Maternal fruit intake (highest vs. lowest) and risk of specific sensitisation to aero-allergens in children (any age) (odds ratio)



7.1. Studies on infant or maternal intake of fruits and vegetables that were not suitable for meta-analysis

Findings from studies that had narrative or descriptive information on the association between infant or maternal intake of fruits and vegetables and risk of allergic sensitisation are summarised in Table 8. The studies of **Nwaru (2010)** and **Sausenthaler (2007)** reported increased maternal citrus fruit intake during pregnancy was associated with increased sensitisation to aero-allergens. The study of **Willers (2007)** found no association between citrus fruit intake in pregnancy and allergic sensitisation in offspring. The study of **Kemp (2011)** found that consuming peanuts during pregnancy was related to a lower risk of sensitisation to peanut in children at age 16 years old, but only in those with no parental history of asthma. The study of **Sicherer (2010)** reported that a reduced intake of peanuts during late stages of pregnancy was associated with a higher risk of sensitisation to this food in high risk infants aged 1 year. Other studies found no association between maternal peanut intake and AS-Peanut.

We found no consistent evidence to suggest that intake of fruits or vegetables in infancy or pregnancy influences the risk of allergic sensitisation later in life.

Table 8 Studies investigating the association between fruit and vegetable and allergic sensitization which were not eligible for meta-analysis

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					INFANT INTAKE		
Strassburger, 2010 (34)	PC	Aero	3.5	321	Time of introduction of salty pureed food [mostly vegetables] / ≥4 months vs. <4 months	OR	1.11 (0.65-1.89)
Nwaru, 2010 (15)	PC	sIgE-aero	5	994	**Introduction of vegetables:** Cabbage/. 4.1-5.2 months vs <4.1 months	OR	1.00 (0.64-1.57)
					Fruits and berries/ 3.46-4 months vs < 3.46 months	OR	1.09 (0.70-1.69)
					Fruits and berries/ >4 months vs < 3.46 months	OR	1.54 (0.97-2.45)
					Carrots/ 3. 5-4 months vs <3.5 months	OR	1.02 (0.66-1.57)
					Potatoes/ 3.1-4 months vs <3.1 months	OR	1.30 (0.87-1.95)
					Carrots/ >4 months vs <3.5 months	OR	1.37 (0.86-2.18)
					Potatoes/>4 months vs <3.1 months	OR	**1.93 (1.20-3.11)**

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
Hesselmar, 2010 (4)	PC	sIgE-any	1.5	169	Fruits/age in months when foods were introduced in months (continuous)	OR	NS
Nwaru, 2010 (15)	PC	sIgE cow's milk	5	994	**Introduction during first month vs later:** Cabbage, fruits and berries, Carrots, potatoes	OR	NS
Nwaru, 2010 (15)	PC	sIgE to egg	5	994	**Introduction to infant diet in the first month vs. 2nd and 3rd months** Cabbage, fruits and berries, carrots, potatoes	OR	NS
Nwaru, 2010 (15)	PC	sIgE to egg	5	994	**Introduction to infant diet in the first month vs. 2nd and 3rd months**		
					Cabbage/ 4.1-5.2 months vs <4.1 months	OR	1.00 (0.61-1.65)
					Fruits and berries / 3.5-4 months vs < 3.5 months	OR	1.30 (0.78-2.16)
					Fruits and berries/ >4 months vs < 3.5 months	OR	**1.70 (1.00-2.90)**
					Carrots/ 3.5-4 months vs <3.5 months	OR	1.15 (0.70-1.90)
					Potatoes/ 3.1-4 months vs <3.1 months	OR	1.50 (0.93-2.42)
					Carrots/ >4 months vs <3.5 months	OR	1.66 (0.97-2.83)
					Potatoes/>4 months vs <3.1 months	OR	**2.56 (1.49-4.39)**

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
Zutavern, 2008 (21)	PC	sIgE to food	6	2073	Fruits or vegetables introduced into infant's diet by 4 months vs. 4-6 months	OR	NS
Andreasyan, 2007 (36)	PC	SPT any	9	498	Fruit juice (orange)/Introduction at 1 month. / >1 month vs. ≤1 months	RR	1.16 (0.58-2.34)
					MATERNAL INTAKE		
Nwaru, 2010 (11)	PC	sIgE-aero	5	931	**Consumption by the mother during the 8th month of pregnancy: (continuous):**		
					Nuts and pulses	OR	1.10 (0.95-1.28)
					Root vegetables	OR	0.92 (0.63-1.35)
					Citrus fruit	OR	1.14 (1.04-1.25)
					Fruit juice/syrup	OR	0.98 (0.91-1.06)
		sIgE food	5	931	Apple	OR	0.97 (0.83-1.13)
					Berries	OR	1.07 (0.92-1.25)
					Citrus fruit	OR	1.00 (0.92-1.09)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
Nwaru, 2010 (11)	PC	sIgE food	5	931	**Consumption by the mother during the 8th month of pregnancy: (continuous):** Fruit juice/syrup	OR	0.99 (0.91-1.08)
					Nuts	OR	1.11 (0.93-1.33)
					Root vegetables	OR	0.73 (0.43-1.23)
Sausenthaler, 2007 (22)	PC	sIgE aero	2	2102	**Maternal consumption during the last 4 weeks of pregnancy /High intake vs low:** Bananas	OR	1.10 (0.63-1.93)
					Strawberries	OR	1.46 (0.86-2.47)
					Citrus fruits	OR	**1.72 (1.01-2.92)**
					Salad	OR	0.92 (0.52-1.62)
					Fruit juice	OR	0.78 (0.47-1.30)
					Spinach	OR	1.18 (0.73-1.91)
					Celery	OR	1.39 (0.75-2.58)
					Sweet pepper	OR	**2.16 (1.20-3.90)**
					Nuts	OR	0.84 (0.46-1.53)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					Maternal consumption during the last 4 weeks of pregnancy/ High maternal intake vs low		
					Carrots	OR	0.77 (0.46-1.28)
					Seeds	OR	0.75 (0.42-1.33)
					Tomatoes	OR	1.05 (0.62-1.77)
					Bananas	OR	1.08 (0.75-1.55)
					Strawberries	OR	1.06 (0.74-1.51)
					Citrus fruits	OR	**1.82 (1.29-2.56)**
					Fruit juice	OR	1.03 (0.73-1.46)
					Spinach	OR	0.97 (0.71-1.32)
					Salad	OR	1.09 (0.76-1.57)
Sausenthaler, 2007 (22)	PC	sIgE any	2	2103	Sweet pepper	OR	**1.45 (1.02-2.06)**

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					Maternal consumption during the last 4 weeks of pregnancy/ High maternal intake vs low		
					Celery	OR	**1.61 (1.08-2.41)**
					Nuts	OR	0.92 (0.63-1.34)
					Carrots	OR	0.85 (0.61-1.18)
					Seeds	OR	0.78 (0.53-1.14)
Sausenthaler, 2007 (21)	PC	sIgE any	2	2103	Tomatoes	OR	0.81 (0.57-1.16)
					Maternal intake during breastfeeding/ g/day increase in total intake during 2nd month lactation:		
					Berries	OR	1.12 (0.86-1.46)
					Nuts and pulses	OR	1.02 (0.77-1.36)
Nwaru, 2011 (12)	PC	sIgE to cow's milk	5	652	Potatoes	OR	0.77 (0.54-1.10)
		sIgE to egg	5	652	Butter/butter	OR	1.05 (0.74-1.50)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
Nwaru, 2010 (11)	PC	Allergic Sensitization	5	931	**Maternal intake during the 8th month of pregnancy (mean daily consumption [grams]):**		
					Malaceous fruits	OR	0.97 (0.83-1.13)
					Berries	OR	1.07 (0.92-1.25)
					Citrus fruits	OR	1.00 (0.92-1.09)
					Fruit juice	OR	0.99 (0.91-1.08)
					Nuts and pulses	OR	1.11 (0.93-1.33)
					Potatoes	OR	0.73 (0.43-1.23)
					Fruits	OR	0.97 (0.76-1.23)
					Vegetables and roots	OR	1.28 (0.82-1.99)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
Sausenthaler, 2007 (22)	PC	sIgE food	2	2110	**Maternal consumption during the last 4 weeks of pregnancy/ high vs low maternal intake:**		
					Spinach	OR	0.82 (0.57-1.17)
					Salad	OR	1.14 (0.76-1.72)
					Sweet pepper	OR	1.16 (0.80-1.69)
					Celery	OR	**1.85 (1.18-2.89)**
					Nuts	OR	1.10 (0.72-1.67)
					Carrots	OR	1.02 (0.70-1.49)
					Seeds	OR	0.72 (0.46-1.12)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
Sausenthaler, 2007 (22)	PC	sIgE to food	2	2110	**Maternal consumption during the last 4 weeks of pregnancy/ high vs low maternal intake:**		
					Tomatoes	OR	0.74 (0.49-1.11)
					Bananas	OR	1.14 (0.76-1.72)
					Strawberries	OR	0.90 (0.60-1.34)
					Citrus fruits	OR	**1.73 (1.18-2.53)**
					Fruit juice	OR	1.12 (0.76-1.65)
Kemp, 2011 (35)	PC	sIgE to peanut	16	310	**Maternal peanut avoidance /Intake in 3rd trimester vs./ never in a month:**		
					Ever eaten vs never (no family history of asthma)	OR	**0.18 (0.04-0.78)**
					Ever eaten vs never (parental history of asthma)	OR	NS

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
Sicherer, 2010 (37)	PC	sIgE to peanut	1	503	**Maternal intake during pregnancy:** Peanut/ ≥2 times per week vs <2 times per week	OR	**2.93 (1.76-4.88)**
Chatzi, 2008 (24)	PC	SPT-aero	6.5	468	**Maternal intake during pregnancy:** Fruits >14 servings per week vs ≤14 servings per week	OR	NS
					Legumes >1 servings per week vs ≤1 servings per week	OR	NS
					Nuts >1servings per week vs ≤1 servings per week	OR	NS
Willers, 2007 (3)	PC	SPT any	5	1212	**Maternal intake during pregnancy (high vs low intakes):** Fruit	OR	NS
					Citrus fruits	OR	NS
					Fruit juice	OR	NS
					Vegetables	OR	NS
					Green leafy vegetables	OR	NS

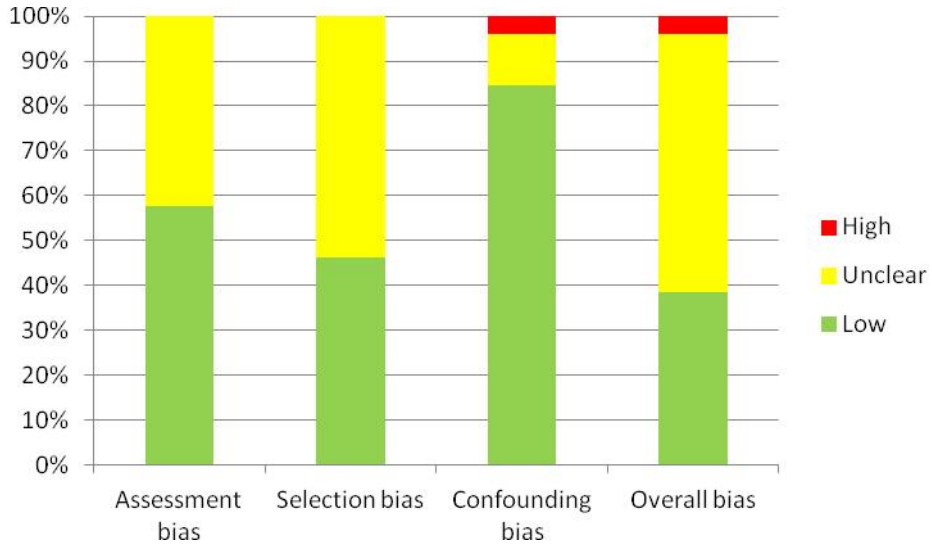
First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
Venter, 2009 (17)	PC	SPT to peanut	2	937	Peanut avoidance during pregnancy (yes/no [unclear])		NS
Willers, 2008 (30)	PC	Total-IgE sIgE to food sIge aero	8	1657	Nut consumption during pregnancy (frequency in the last month of reporting data)	OR	NS

8. Infant or maternal dietary intake of fruits and vegetables and risk of autoimmune diseases

8.1. Type 1 diabetes mellitus (TIDM)

Nine observational studies (7 prospective cohorts and 2 case-control studies) investigated the association between dietary intake of fruits or vegetables during infancy or pregnancy and risk of type I diabetes mellitus. Overall, studies were considered to be of low or unclear risk of bias, with one study having high risk of bias due to lack of control for confounding (Figure 18).

Figure 18 Risk of Bias in studies of fruit and vegetable intake and type I diabetes mellitus



Two prospective cohorts and a case-control study which examined the association between fruit introduction and risk of T1DM had comparable data suitable to be pooled in a meta-analysis. The pooled effect of the prospective studies showed a lower risk of TIDM in children who started eating fruits between 0-4 months of age compared with those who started later. This meta-analysis had no heterogeneity (I^2=0%). The effect size was attenuated and lost statistical significance when the three studies were pooled, and the heterogeneity increased slightly but remained low (I^2=25.8%) (Figure 19).

Figure 19 Infant fruit introduction in months 0 to 4 and risk of type I diabetes mellitus in children

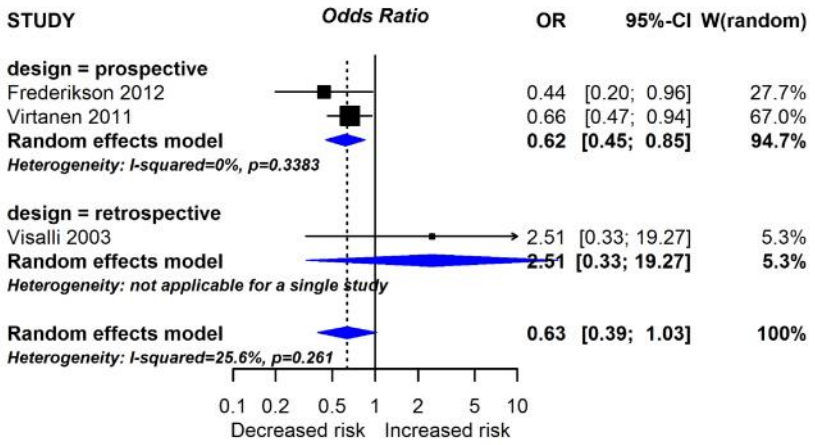


Table 9 summarises the findings of studies that could not be meta-analysed. The study of Virtanen found that early introduction of root vegetables (including potatoes), was associated with increased risk of T1DM later in childhood. These findings were not supported by other studies. The finding in the meta-analysis of 2 prospective studies that early fruit introduction is associated with reduced TIDM was also not supported by other studies which could not be included in the same meta-analysis.

Overall, we found no consistent evidence that infant or maternal intake of other fruits or vegetables influences the risk of T1DM.

Table 9 Studies investigating the association between fruit and vegetable and type 1 diabetes mellitus which were not eligible for meta-analysis

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					INFANT INTAKE		
Visalli, 2003 (44)	CC	TIDM	12	900/150	Vegetables/age at introduction / ≥3 months vs. <3 months	OR	1.32 (0.16-10.86)
					Fruit introduction first 12months		
					>7.0-12 months vs. 7-12 months	OR	NS
					>4–6 months vs. 4-6 months	OR	NS
					>1–3 months vs. 1-3months months	OR	NS
					Vegetable introduction first 12 months		
					5-7 months vs. <5-7 months	OR	**0.66 (0.45-0.98)**
Strotmeyer, 2004 (46)	CC	TIDM	9.7	688/247	>7.0-12 months vs. 7-12 months	OR	NS

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
Virtanen, 2006 (48)	PC	TIDM	<10	2435/54	Fruits and berries introduction / 0-3.5 months vs. 4+ months	HR	**0.50 (0.25-0.97)**
				2435/53	Root vegetable introduction / 0-3 months vs. 4+ months	HR	0.96 (0.53-1.75)
Virtanen, 2011 (47)	PC	TIDM	<10	5619/237	Fruits and berries introduction / 3.5-4 months vs. 4+ months	HR	0.75 (0.54-1.04)
					Root vegetables introduction / 3-4 months vs. 4+ months	HR	**1.79 (1.22-2.62)**
					Root vegetables introduction / 0-3 months vs. 4+ months	HR	**1.75 (1.11-2.75**)
Brekke, 2010 (39)	PC	TIDM	5	4005/191	Infant vegetable intake (often vs. rare)	OR	0.77 (0.41-1.44)
Savilahti, 2009 (45)	PC	T1DM			Infant vegetable introduction in months 0-4	OR	1.73 (0.84-3.58)
Norris, 1996 (41)	PC	TIDM			Fruit and vegetable introduction months 5-7 vs. <5-7 months	OR	0.73 (0.28-1.95)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					MATERNAL INTAKE		
Brekke, 2010 (39)	PC	TIDM	5	4005/191	Maternal intake of potatoes and root vegetables during pregnancy/ 3-5 times/week vs. 1-2 times/week	OR	0.75 (0.44-1.29)
Virtanen, 2011(47)	PC	TIDM	<10	3730/165	**Maternal intake during pregnancy / Change in risk per 2-fold increase in energy-adjusted consumption of the specific food:**		
					Potatoes and root vegetables	HR	1.20 (0.92-1.56)
					Fruit	HR	1.02 (0.88-1.18)
					Vegetables	HR	0.92 (0.74-1.14)
Lamb, 2008 (43)	PC	TIDM	15	642/27	**Food intake during last trimester of pregnancy (continuous; number servings per month):**		
					Fruits	HR	0.86 (0.52-1.42)
					Potatoes	HR	**0.49 (0.28-0.87)**
					Vegetables	HR	0.61 (0.34-1.09)
					Other root vegetables	HR	1.04 (0.72-1.51)

8.2. Infant or maternal dietary intake of fruit and vegetable and risk of inflammatory bowel disease (IBD)

One case-control study was identified, which investigated the risk of IBD according to the timing of vegetable introduction. The study of **Baron (2005)** included as cases, children aged <17 who were diagnosed with Crohn's disease and who were matched to healthy controls. The study was considered to have unclear overall bias as there was no clear description of the assessment of outcomes (Figure 20). There was difference in the risk of IBD according to the months of vegetable introduction (Table 10).

Figure 20 Risk of Bias in studies of fruit and vegetable intake and IBD

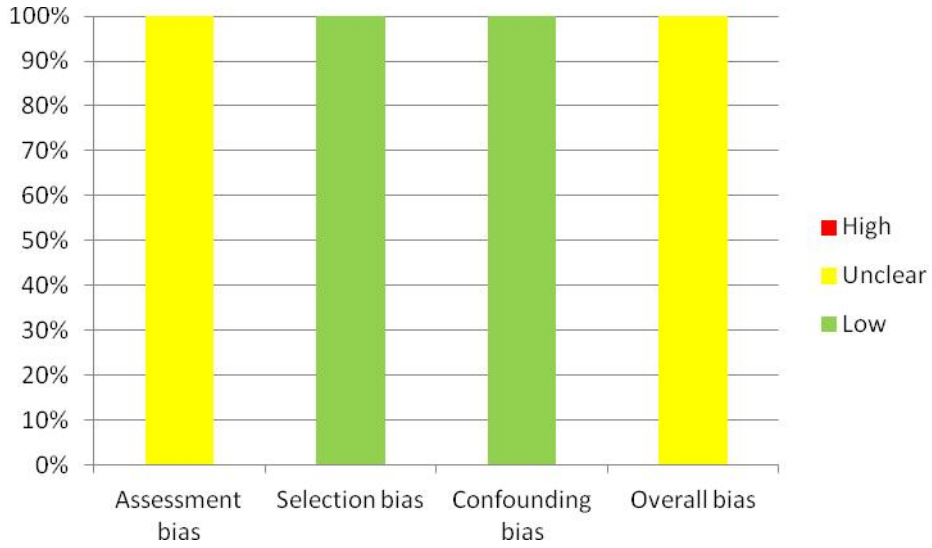


Table 10 Studies investigating the association between fruit and vegetable (dietary exposure) and IBD (outcome) which were not eligible for meta-analysis

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect
Baron, 2005 (40)	CC	IBD-CR	<17	444/222	Vegetables introduction in months (continuous)	OR	NS
		IBD-UC			Vegetable introduction in months (continuous)	OR	NS

Conclusions

Overall, this report on dietary intake of fruits and vegetables and risk of allergic and autoimmune diseases shows that although there are a significant number of well designed (low bias) observational studies, the evidence base for these foods is hindered by the lack of comparable data between studies. The few studies that could be meta-analysed contributed just a small part of the overall picture of no consistent evidence that fruit or vegetable intake or introduction during infancy, pregnancy or lactation are associated with allergic or autoimmune outcomes.

From the point of view of epidemiological research, these findings highlight the need to improve the homogenisation of epidemiological tools to assess dietary exposure in population-based studies.

Overall we found no evidence to suggest that infant or maternal intake of fruits or vegetables influences the risk of allergic or autoimmune diseases.

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MATERNAL ALLERGENIC FOOD AVOIDANCE AND RISK OF ALLERGIC OR AUTO-IMMUNE DISEASES IN OFFSPRING

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1. Maternal AFA and risk of allergic/ autoimmune outcomes – summary of interventions and findings

In this analysis we included studies of any type of allergenic food avoidance (AFA) in mothers – during any part of pregnancy, lactation or both periods of time. We did not include studies where maternal diet was modified during lactation for management of established allergic disease in the infant. We included studies of multifaceted interventions, if maternal AFA was part of the intervention – and where appropriate undertook subgroup analysis of single versus multifaceted interventions. We defined allergenic foods as cow's milk, soya, egg, peanut, tree nuts, wheat, fish, seafood, which are the 'major food allergens' as defined by the US Food Allergen Labelling and consumer Protection Act of 2004. We planned to undertake subgroup analyses for meta-analyses which included >5 studies, which was possible only for AD ≤4 years. We planned to assess publication bias using Funnel plots and Egger's test where there were ≥10 studies in a meta-analysis, although no such meta-analysis was undertaken.

In total we identified 1 high quality recent systematic review which included 5 trials (925 participants), and we identified 12 original trials (9 RCT with ~1500 participants, 3 CCT with ~330 participants) investigating the effect of maternal AFA on allergic or autoimmune outcomes.

Interventions used:

Two studies intervened in pregnancy only, 6 during lactation and 4 during both periods of time. Seven studies were single intervention (AFA), 5 were multifaceted (typically both maternal and infant dietary interventions, with environmental control measures to reduce allergen/ irritant exposure). The foods excluded were: milk alone (2), milk and egg (3), egg alone (1) or multiple other food groups (6), the latter usually including milk and egg as well.

Populations and outcomes assessed:

Seven studies were undertaken in Europe, 1 in Australia, 2 in Asia and 2 in North America. All study populations were at high allergic disease risk based on family history, but populations were not at increased risk of autoimmune outcomes. Outcomes assessed were wheeze/lung function (6), allergic rhinitis (AR; 6), eczema (AD; 11), food allergy (FA; 5), allergic sensitisation (AS; 10) and type 1 diabetes (TIDM; 2). Age at outcome assessment ranged between 3 months and 18 years.

Overall findings:

Overall risk of bias was high or unclear in all studies, mainly due to risk of selection bias, based on inadequate randomisation or treatment allocation procedures – seen most clearly in the 3 CCTs where the process used for treatment allocation was judged likely to lead to imbalanced treatment groups. Risk of assessment bias was also unclear in the majority of cases, and risk of conflict of interest was judged as low in most studies.

Data were sparse for all outcomes, especially TIDM, food allergy and allergic rhinitis. No studies evaluated participants at 'normal risk' of allergic outcomes.

Overall there is no evidence that maternal allergenic food avoidance reduces risk of allergic of autoimmune outcomes in the offspring.

Table 1 Characteristics of included studies evaluating maternal AFA and allergic outcomes

Study	Design	N Intervention/ Control	Country	Excluded food	Intervention	Disease risk	Age at outcome (years)	Outcomes reported
Kramer (1)	SR	5 trials (925)	-		Pregnant/lactating women	high		Eczema, Allergic sensitisation, Wheeze, Allergic rhinitis
Falth-Magnusson, 1987 (2) Falth-Magnusson 1992 (3) Ludvigsson, 2003 (4)	RCT	108/ 104	Sweden	Cow's milk and egg	**Pregnant women**. Cow's milk and egg exclusion from 28 weeks gestation to delivery.	high	1.5, 5	Allergic rhinitis (physician assessment), Asthma (≥3 episodes of wheeze), Eczema (Hanifin and Lobitz), Allergic sensitisation (SPT), Food allergy (history), Total IgE, TIDM (serology)
Hattevig, 1990 (5) Paronen, 2000(6) Hattevig, 1999 (7) Hattevig, 1989 (8) Sigurs, 1992 (9)	CCT	54/ 67	Sweden	Cow's milk, fish and egg	**Lactating women**. Cow's milk, egg and fish exclusion during first 3 months post-partum.	high	0.25, 1.5, 4, 10	Allergic sensitisation TIDM (serology), Eczema, Asthma, Wheeze, Recurrent wheeze Allergic rhinitis, Food allergy (history), Total IgE
Herrmann, 1996 (10)	CCT	50/ 50	Germany	Cow's milk and egg	**Pregnant/lactating women**. Cow's milk and egg exclusion from 28 weeks gestation through lactation, versus 1 litre cow's milk and 1 egg per day.	high	1	Eczema (DD), Allergic sensitisation (sIgE)

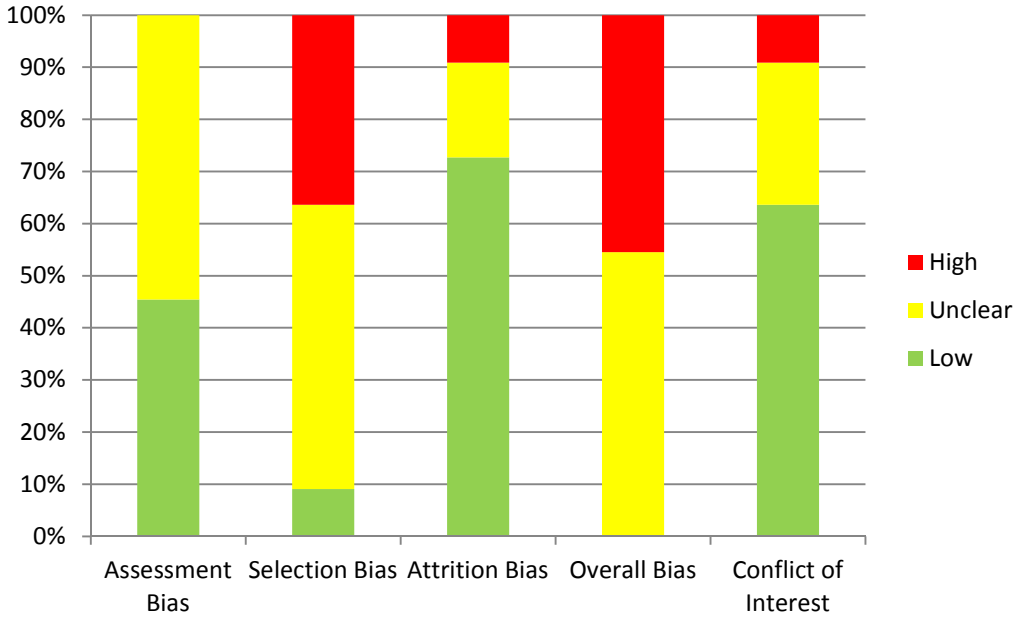
Study	Design	N Intervention/ Control	Country	Excluded food	Intervention	Disease risk	Age at outcome (years)	Outcomes reported
Jirapinyo, 2013 (11)	RCT	30/ 32	Thailand	Cow's milk	**Lactating women**. Cow's milk exclusion during lactation up to 4 months postpartum.	high	<0.5	Eczema (method unclear)
Kilburn, 1998 (12)	CCT	15/ 96	UK	'Allergenic foods'	**Lactating women**. Milk, egg, fish and nuts exclusion throughout lactation.	high	1.5	Eczema (Hanifin and Rajka), Allergic sensitisation (SPT)
Lovegrove, 1994 (13)	RCT	12/ 14	UK	Cow's milk	**Pregnant/lactating women**. CM exclusion during pregancy and lactation with hydrolysed milk if necessary. BF encouraged for 6 months and eHF if needed.	high	1	Eczema (DD)
Metcalfe, 2016{Metcalfe, 2016 #832}	RCT	40, 44, 36	Australia	Egg	**Lactating women.** First 6 weeks of lactation. Randomised to high-egg diet (>4 eggs per week), low-egg diet (1-3 eggs per week) and egg-free diet	high	0.33	Allergic sensitisation (sIgE-egg)
Shao, 2006 (14)	RCT	23/ 23	China	'Allergenic foods'	**Lactating women**. eBF encouraged for 4 months, allergenic food exclusion during	high	1.5	Eczema (Wolkerstorfer score), Allergic Sensitisation (SPT)

Study	Design	N Intervention/ Control	Country	Excluded food	Intervention	Disease risk	Age at outcome (years)	Outcomes reported
					lactation, delayed solid (4 months) and allergenic (6-12 months) food, pHF if necessary.			
Becker, 2004 (15); Chan-Yeung, 2000 (16); Chan-Yeung 2005 (17); Wong, 2013 (18)Protudjer, 2011(19); Carlsten 2013(20) **CAPPS Study**	RCT	281/ 268	Canada	Nuts, seafood	**Pregnant/lactating women**. BF encouraged for 4 months, allergenic food exclusion during pregnancy/lactation, delayed solid (6 months) and allergenic (12 months) food, whey pHF if necessary, environmental control.	high	1, 7, 15	Allergic Sensitisation (SPT), Allergic Rhinitis (DD), Wheeze (ISAAC and modified ECRHS), Eczema (DD), bronchial hyper-responsiveness (PC20 <7.8mg/ml), Lung function (FEV1)
Hide, 1994 (21) Hide, 1996(22) Arshad, 1992 (23) Arshad, 2003 (24) Arshad, 2007 (25) Scott, 2012 (26) **Isle of Wight Study**	RCT	71/ 68	UK	Cow's milk, egg, fish and nuts	**Lactating women.** Allergenic food exclusion during lactation, delayed allergenic (9-11 months) food, soya hydrolysate if necessary, environmental control.	high	1, 2,4,8,18	Recurrent wheeze (>=3 episodes), BHR (PC20<8mg/ml), Eczema (Physician assessment), Food allergy (Open food challenge ; Physician assessment),

Study	Design	N Intervention/ Control	Country	Excluded food	Intervention	Disease risk	Age at outcome (years)	Outcomes reported
								Allergic sensitisation (SPT, total IgE), Allergic rhinitis (physician assessment), Total IgE
Zeiger, 1992 (27) Zeiger 1989 (28), 1994 (29)	RCT	103/ 185 [seen at 4 months]	USA	Cow's milk, egg, peanut; and partial soya and wheat avoidance	**Pregnant/lactating women**. Allergenic food exclusion during pregnancy/lactation, delayed allergenic (1-3 years) food, casein eHF if necessary.	high	1, 4, 7	Eczema (Hanifin and Rajka Criteria), Allergic Rhinoconjunctivitis (DD), Food Allergy - Any (DD), Wheeze (≥2 physician diagnosed episodes), Allergic Sensitisation (SPT)
Lilja, 1989 (30)	RCT	84/ 87	Sweden	Cow's milk, egg	**Pregnant women.** Milk and Egg exclusion during third trimester, versus 1 litre milk and 1 egg per day.	High	1.5	Asthma (physician assessment), Allergic sensitisation (SPT), Allergic rhinitis (physician assessment), Eczema (physician assessment), Food allergy (history)

BF breastfeeding; eBF exclusive breastfeeding; pHF partially hydrolysed formula; eHF extensively hydrolysed formula; CM cow's milk; RCT randomised clinical trial, SPT skin prick test, BHR bronchial hyperresponsiveness, FE_{V1} forced expiratory volume in one second; Physician assessment refers to assessment by a study physician , DD refers to community diagnosis.

Figure 1 Risk of bias in studies of maternal AFA and allergic or auto-immune diseases



2. Maternal AFA and risk of AD

One systematic review and 11 original trials (8 RCT, 3 CCT; total 1700 participants) were included in this analysis. Table 2 summarises findings from the recent high quality systematic review of Kramer, which excluded multi-faceted studies and CCTs, but did not exclude studies where AFA was practiced in the context of infant allergic disease. Kramer identified 2 studies of AFA in pregnancy and 1 study of AFA in lactation. Meta-analysis did not show any evidence for a protective effect.

Figure 2 summarises the risk of bias for original studies of maternal AFA and AD. Overall risk of bias was high or unclear in all studies, mainly due to risk of selection bias, based on inadequate randomisation or treatment allocation procedures – seen most clearly in the 3 CCTs where the process used for treatment allocation was judged likely to lead to imbalanced treatment groups. Risk of assessment bias was also unclear in the majority of cases, and risk of conflict of interest was judged as low in most studies.

Meta-analysis of data from the original studies did not show a significant association between maternal AFA and AD risk – albeit with high heterogeneity in both the RCT (Figures 3 and 5) and CCT (Figure 4) analyses. A single small RCT (Arshad) found evidence that maternal AFA, as part of a multi-faceted intervention study, reduces risk of AD associated with positive SPT at the age of 8 (Figure 6). Other small single study analyses were not statistically significant (Figures 7 and 8). Subgroup analysis of RCT evidence for prevention of AD at age ≤4 years showed evidence for a subgroup difference according to timing of intervention – with AFA during lactation reducing AD risk, but AFA during pregnancy having no effect (Table 3). The effect of AFA during lactation on AD risk was not supported by the CCT evidence from 2 trials with a similar number of participants (Figure 4).

The CCT of Kilburn did not report data for meta-analysis, but did report a trend towards increased AD in the AFA group, which was not statistically significant. In the CCT of Hattevig AD was significantly reduced at age 4, but not at other ages (Figures 4 and 7). In the RCT of Arshad AD was significantly reduced at age 2, but not at other ages (Figures 3, 5 and 8).

Overall we found no consistent evidence that maternal AFA impacts on child AD risk.

Figure 2 Risk of bias in studies of maternal AFA and AD risk

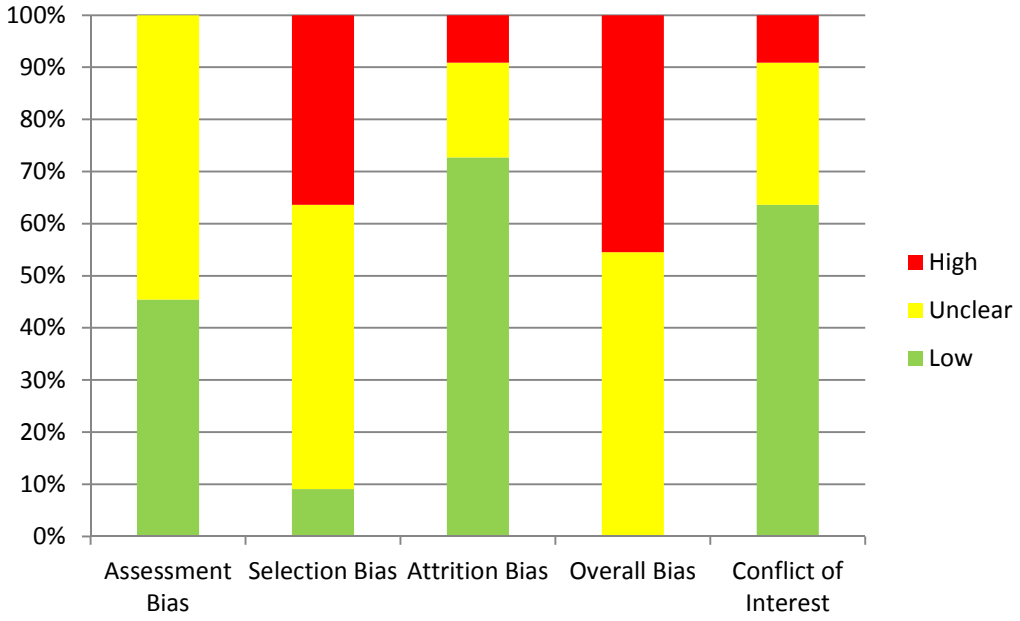


Table 2 Systematic review evidence for AFA and AD risk

Study	Outcome measure	Intervention timing	No. participants (studies)	Outcome (95% CI)	I^2
Kramer (1)	AD at ≤18 months	Pregnancy	334 (2)	RR 1.01 [0.57, 1.79]	48%
Kramer (1)	AD at ≤18 months	Lactation	26 [1]	RR 0.73 [0.32, 1.64]	-

Figure 3 Maternal AFA and risk of AD at age ≤ 4 yrs - RCT

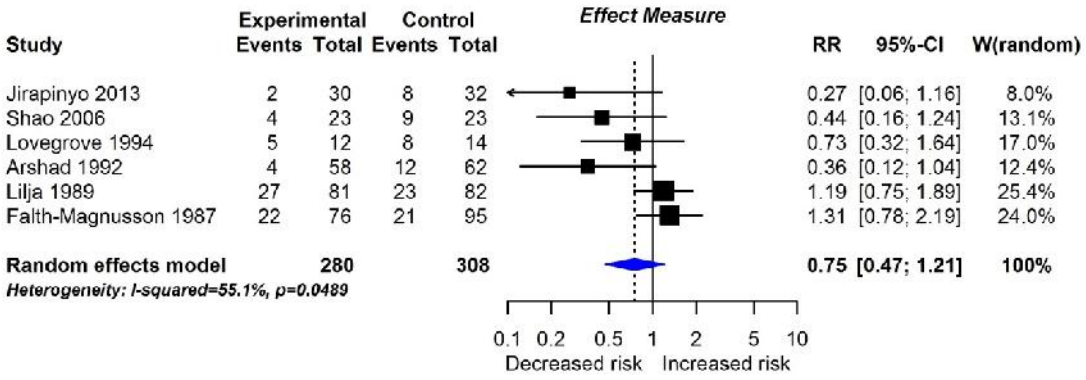


Table 3 Subgroup analysis of maternal AFA and AD risk at age ≤4 years

	Number of studies	RR [95% CI]	I^2 (%)	P-value for between groups difference
Intervention – pregnancy only	2	1.24 [0.88-1.75]	0	0.003
Intervention – lactation +/- pregnancy	4	0.48 [0.29-0.81]	0	
Intervention – multifaceted including AFA	3	0.53 [0.30-0.91]	0	0.09
Intervention – AFA alone	3	1.04 [0.60-1.80]	52	
Overall risk of bias – Low	-	-	-	-
Overall risk of bias – High/Unclear	4	0.75 [0.47-1.21]	55	
Conflict of interest bias – Low	2	0.66 [0.15-2.84]	73	0.94
Conflict of interest bias – High/Unclear	4	0.70 [0.38-1.31]	57	

Figure 4 Maternal AFA and risk of AD at age ≤ 4 yrs - CCT

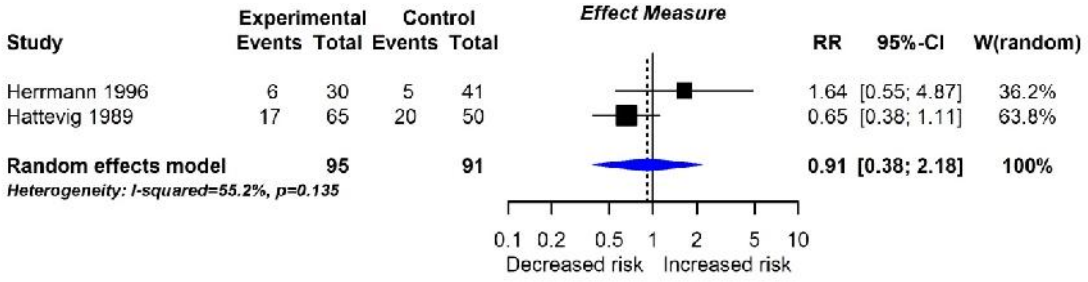


Figure 5 Maternal AFA and risk of AD at age 5-14 yrs - RCT

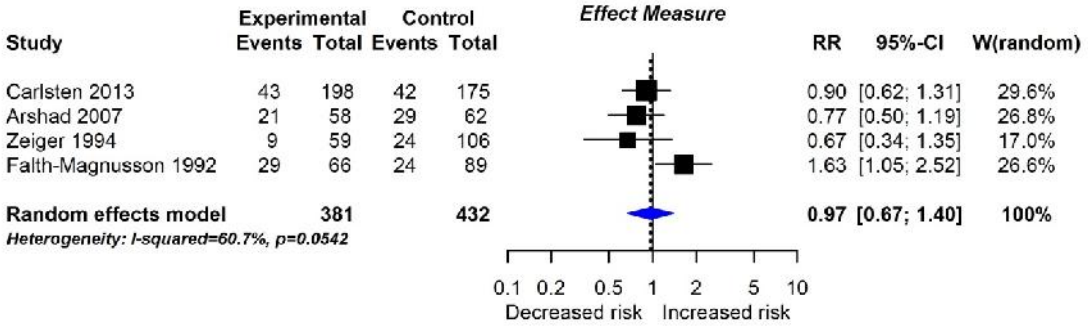


Figure 6 Maternal AFA and risk of 'atopic' AD at age 5-14 yrs - RCT

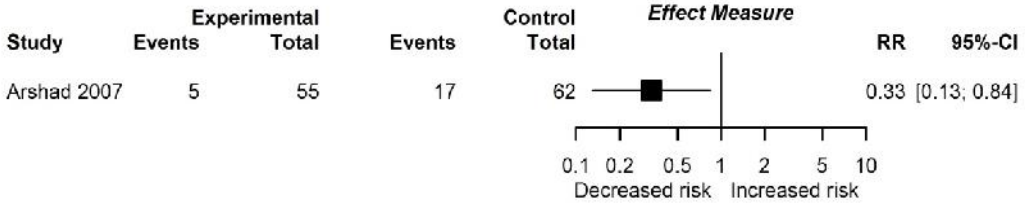


Figure 7 Maternal AFA and risk of AD at age 5-14 yrs - CCT

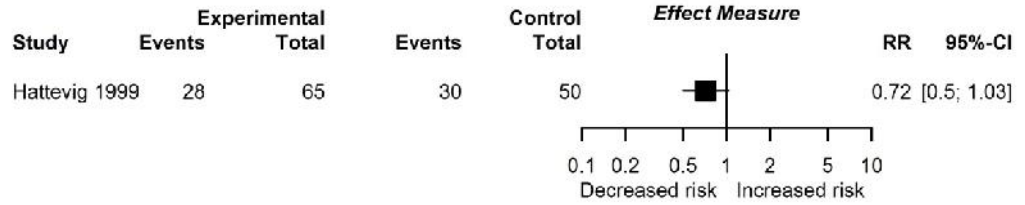
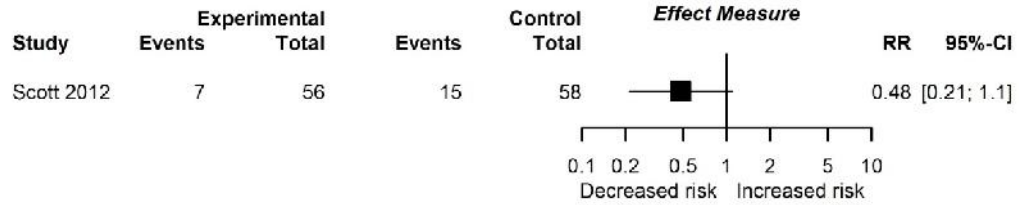


Figure 8 Maternal AFA and risk of AD at age ≥15 yrs - RCT



3. Maternal AFA and risk of allergic rhinitis +/- conjunctivitis

One systematic review and 6 original trials (1400 participants) were included in this analysis.

The recent high quality systematic review of Kramer identified 1 study (163 participants) of AFA in pregnancy from which a RR could not be estimated due to low event numbers.

Figure 9 summarises the risk of bias for original studies of maternal AFA and AR. Overall risk of bias was high or unclear in 4 of 5 studies, mainly due to risk of selection bias, based on inadequate randomisation or treatment allocation procedures. Risk of assessment bias was also unclear in the majority of cases, and risk of conflict of interest was judged as low in most studies.

Meta-analysis of data from the original studies showed a borderline significant association between maternal AFA and AR risk, with low heterogeneity in the RCT analysis (Figure 10) and just 1 study in the CCT analysis (Figure 11) analysis. The RCT analysis was dominated by a single multifaceted intervention trial (Chan-Yeung) which is described further in the multifaceted intervention report. The AFA-only trials (Lilja, Falth-Magnusson and Sigurs) included in these analyses did not show evidence of an impact on AR at age ≤4 years. Analysis at age 5-14 showed no evidence of an effect (Figure 12), although a single small RCT (Arshad; Figure 13) found reduced 'atopic' AR at aged 5-14. This was not seen in a similar sized CCT evaluating AR at the same age (Figure 14).

The multifaceted RCT of Zeiger also reported AR at age 4 in graphical form, where no significant difference was seen in this outcome between treatment groups. The CCT of Hattevig/Sigurs and the RCT of Arshad/Hide reported AR at other timepoints and/or using other methods in addition to those shown in meta-analysis – with broadly similar findings. We did not identify any studies reporting allergic conjunctivitis as an outcome.

Overall we found no consistent evidence that maternal AFA impacts on child AR risk.

Figure 9 Risk of bias in studies on maternal AFA and AR risk

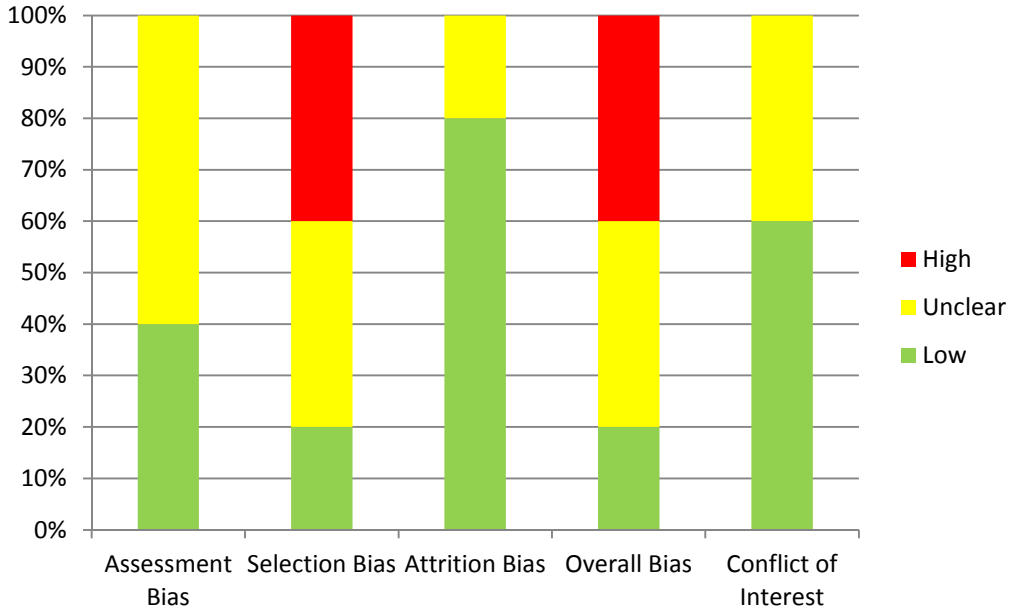


Figure 10 Maternal AFA and risk of AR at age ≤4 yrs - RCT

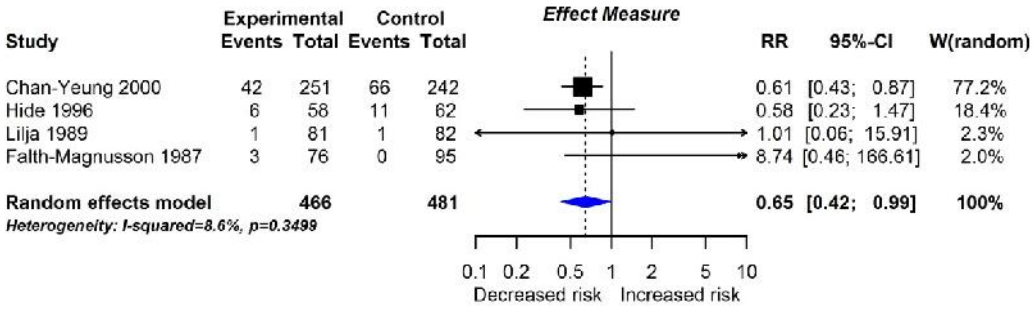


Figure 11 Maternal AFA and risk of AR at age ≤4 yrs - CCT

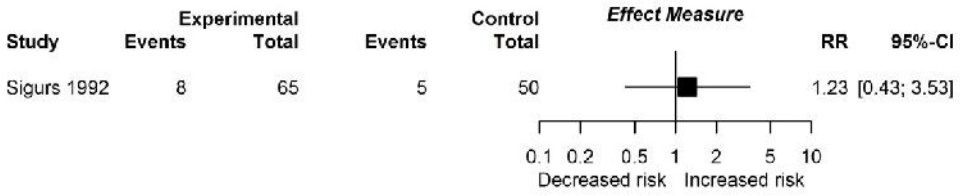


Figure 12 Maternal AFA and risk of AR at age 5-14 yrs - RCT

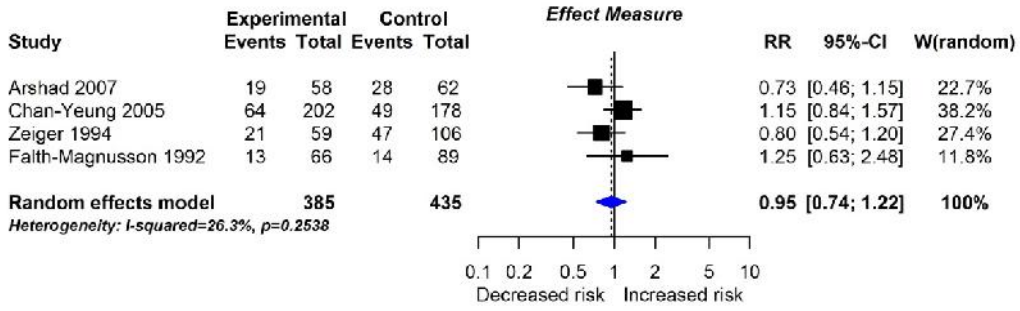


Figure 13 Maternal AFA and risk of 'atopic' AR at age 5-14 yrs - RCT

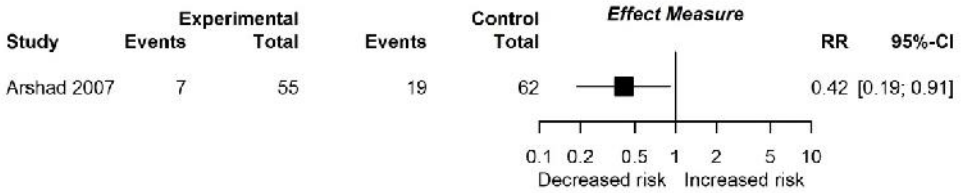


Figure 14 Maternal AFA and risk of AR at age 5-14 yrs - CCT



4. Maternal AFA and risk of food allergy

No systematic review and 5 original trials (800 participants) were included in this analysis.

Figure 15 summarises the risk of bias for original studies of maternal AFA and FA. Overall risk of bias was high or unclear in all 5 studies, mainly due to risk of selection bias, based on inadequate randomisation or treatment allocation procedures. Risk of conflict of interest was judged as low in most studies.

Meta-analysis of data from the original studies showed no significant association between maternal AFA and FA risk, with high heterogeneity in the RCT analysis (Figure 16) and just 1 study in the CCT analysis (Figure 17) analysis. The heterogeneity in the RCT analysis may be explained by combination of a multifaceted intervention trial (Arshad) with a AFA-only intervention trial (Falth-Magnusson). At age 5-14 there was also no significant effect, again with high heterogeneity which may be explained by combination of 2 multifaceted with 1 AFA-only study (Figure 18). Other analyses, including analysis of cow's milk and egg allergy were limited by small study and participant numbers and wide confidence intervals, but showed no evidence of an effect of maternal AFA on child food allergy (Figures 19 to 26).

The multifaceted RCT of Zeiger also reported FA at age 4 in graphical form, where no significant difference was seen in current FA, but a significant reduction in FA ever was seen in the intervention group ($P<0.01$). The multifaceted RCT of Arshad/Hide reported no significant difference in physician diagnosed food allergy at age 2.

Overall we found no consistent evidence that maternal AFA impacts on child FA risk.

Figure 15 Risk of bias of intervention studies of maternal AFA and FA risk

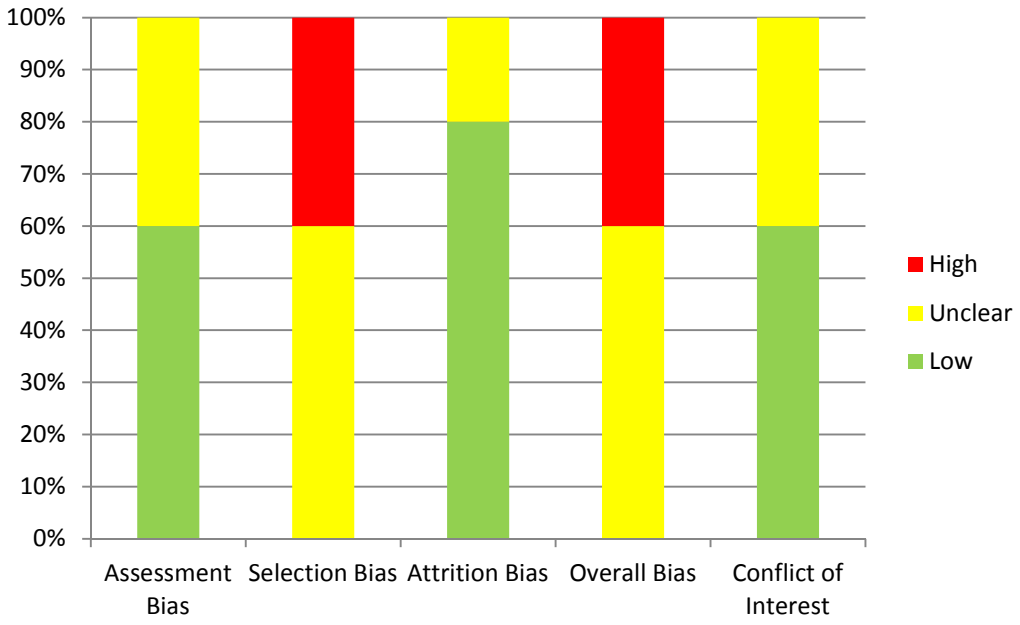


Figure 16 Maternal AFA and risk of food allergy (any) at age ≤ 4 yrs - RCT

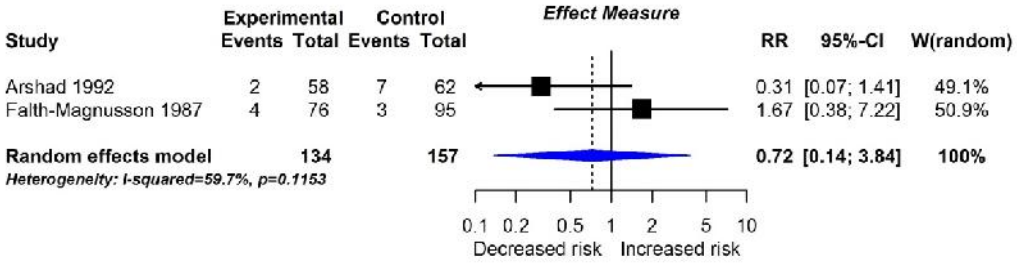


Figure 17 Maternal AFA and risk of food allergy (any) at age ≤ 4 yrs - CCT

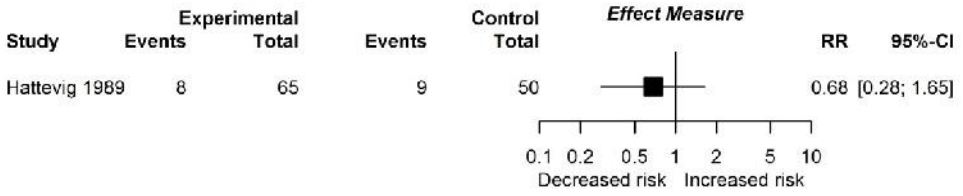


Figure 18 Maternal AFA and risk of food allergy (any) at age 5-14 yrs - RCT

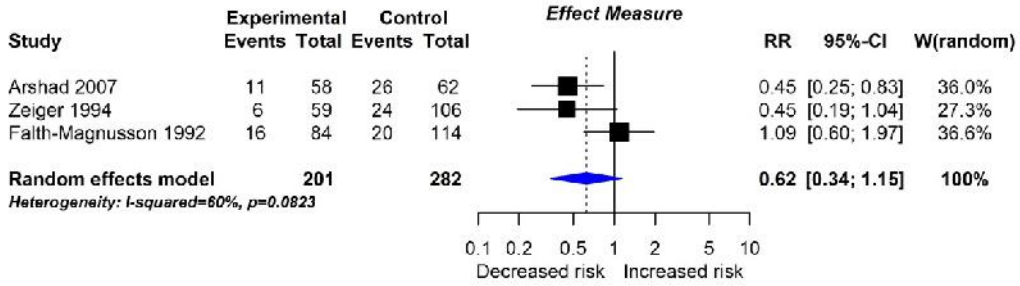


Figure 19 Maternal AFA and risk of food allergy (any) at age 5-14 yrs - CCT

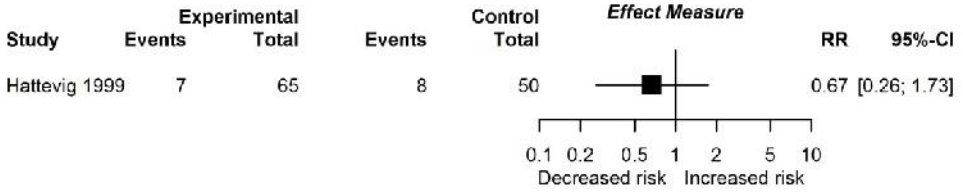


Figure 20 Maternal AFA and risk of CMA at age ≤ 4 yrs - RCT

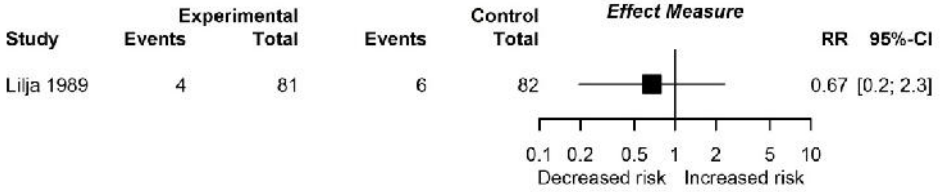


Figure 21 Maternal AFA and risk of CMA at age ≤ 4 yrs - CCT

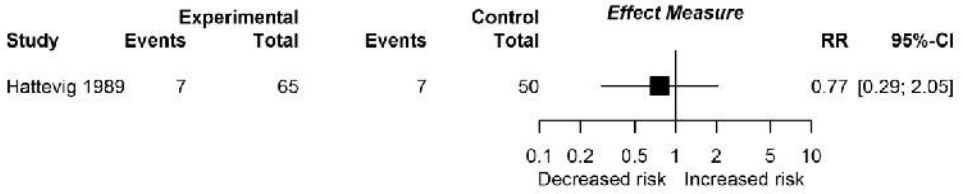


Figure 22 Maternal AFA and risk of CMA at age 5-14 yrs - CCT

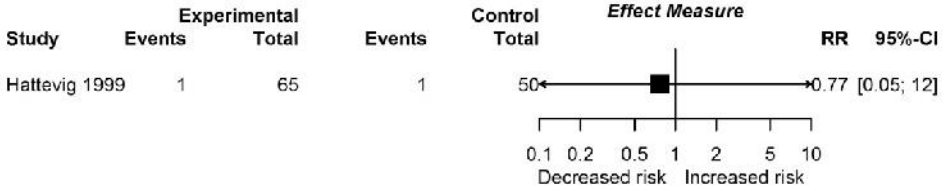


Figure 23 Maternal AFA and risk of Egg allergy at age ≤ 4 yrs - RCT

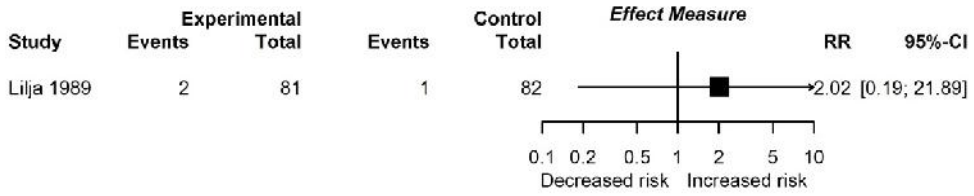


Figure 24 Maternal AFA and risk of Egg allergy at age ≤ 4 yrs - CCT

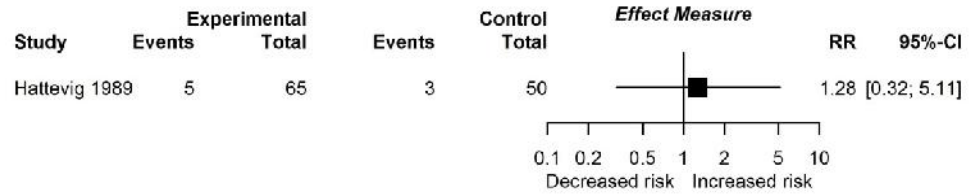


Figure 25 Maternal AFA and risk of Egg allergy at age 5-14 yrs - RCT

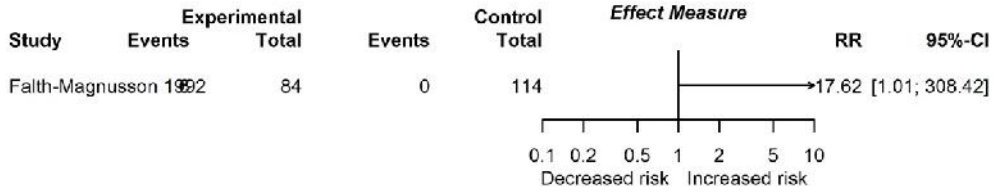
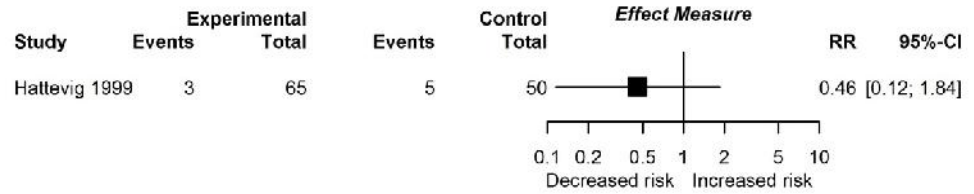


Figure 26 Maternal AFA and risk of Egg allergy at age 5-14 yrs - CCT



5 Maternal AFA and risk of allergic sensitisation

One systematic review and 10 original trials (1700 participants) were included in this analysis. The recent high quality systematic review of Kramer identified 2 studies (340 participants) of AFA in pregnancy and 1 study (497 participants) of AFA during lactation which examined allergic sensitisation. Data are summarised in Table 4 and do not show consistent evidence for an effect of maternal AFA on child AS to egg, milk or peanut.

Figure 27 summarises the risk of bias for original studies of maternal AFA and AS. Overall risk of bias was high or unclear in most studies, mainly due to risk of selection bias, based on inadequate randomisation or treatment allocation procedures. Risk of assessment bias and risk of conflict of interest were judged as low in most studies.

Meta-analysis of data from the original studies showed no evidence for an effect of maternal AFA on AS to any allergen (Figures 28 and 29). RCT but not CCT evidence supported a reduction in AS to aeroallergens with maternal AFA (Figures 30 and 31) however all RCTs included in this analysis were multifaceted intervention studies, which included measures to reduce aeroallergen exposure in mother and infant. There was some evidence that maternal AFA may reduce AS to 'any food' in the child, from RCT (Figure 32) but not CCT (Figure 33) studies. However, larger numbers of studies and participants could be included in analysis of specific AS to individual foods, since some studies reported AS to individual foods but not a summed 'any food' outcome. Here there was no evidence that maternal AFA influences AS to cow's milk (Figures 34 and 35), egg (Figures 36 and 37) or peanut (Figures 38 and 39).

Data that could not be included in meta-analysis

The studies of Falth-Magnusson, Hattevig and Arshad/Hide all reported total IgE, and found no difference between active and control groups although data could not be meta-analysed. The CCT of Kilburn reported SPT to aeroallergens at 1.5 years and stated there was a non-significant trend to increased sensitisation in the control group. The RCT of Lilja reported SPT to milk and egg components at 1.5 years and stated there was no significant difference between groups in any outcome. The RCT of Metcalfe reported specific IgE to egg at 4 months was detectable in 1 infant from the egg-free group, 1 infant from the high-egg group and two infants from the low-egg group. Denominators were not presented for these data, but they do not suggest a significant difference between groups. Several of the studies included in meta-analyses reported AS outcomes

at other times and/or using other methods, with similar findings to those presented in the analysis Figures.

Overall we found no consistent evidence that maternal AFA impacts on child AS risk.

Figure 27 Risk of bias of intervention studies of maternal AFA and AS

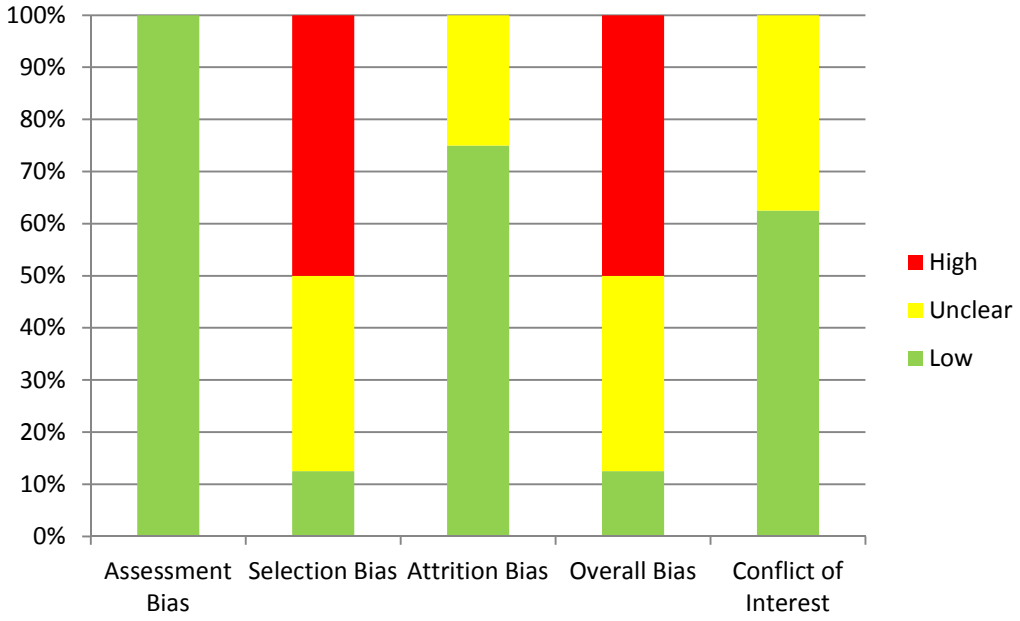


Table 4 Systematic review evidence for AFA and AS risk

Study	Outcome measure	Intervention/ outcome timing	No. participants (studies)	Outcome (95% CI)	I^2
Kramer		**Pregnancy**			
(1)	Egg SPT	6 months	340 (2)	RR 0.58 [0.32,1.05]	0%
		18 months	335 (2)	RR 0.95 [0.52,1.74]	0%
	Milk SPT	6 months	340 (2)	RR 1.15 [0.29, 4.51]	0%
		18 months	335 (2)	RR 0.86 [0.16, 4.59]	13%
Kramer		**Lactation**			
(1)	Egg SPT	1 year	497 (1)	RR 1.31 [0.88, 1.94]	-
		2 years	473 (1)	**RR 1.91 [1.03, 3.53]**	-
		7 years	354 (1)	RR 0.15 [0.02, 1.25]	-
	Milk SPT	1 year	497 (1)	RR 1.43 [0.68, 3.01]	-
		2 years	473 (1)	RR 4.30 [0.94, 19.67]	-
		7 years	354 (1)	RR 0.91 [0.13, 6.41]	-
	Peanut SPT	1 year	497 (1)	RR 1.41 [0.76, 2.60]	-
		2 years	473 (1)	RR 1.00 [0.56, 1.80]	-
		7 years	354 (1)	RR 1.60 [0.81, 3.15]	-

Figure 28 AFA and risk of allergic sensitisation (any) - RCT

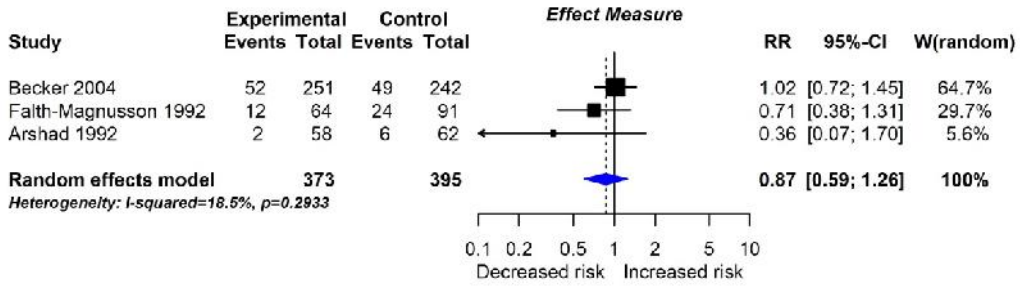


Figure 29 AFA and risk of allergic sensitisation (any) - CCT



Figure 30 AFA and risk of allergic sensitisation (aero) - RCT

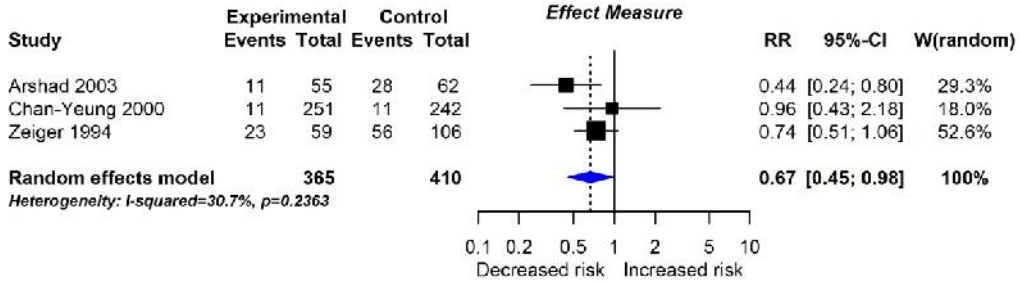


Figure 31 AFA and risk of allergic sensitisation (aero) - CCT

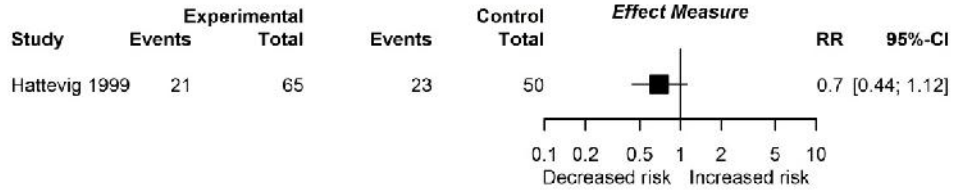


Figure 32 AFA and risk of allergic sensitisation (food) - RCT

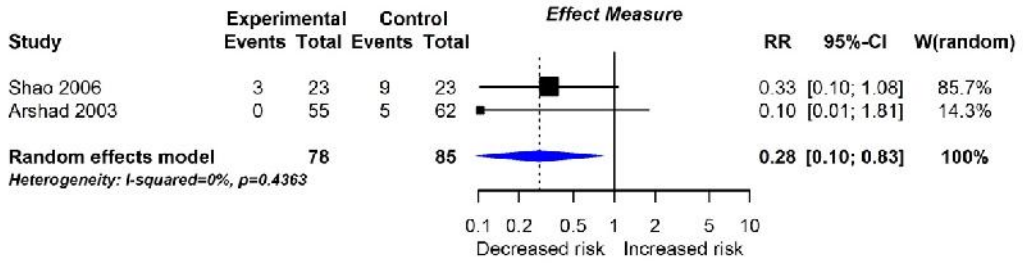


Figure 33 AFA and risk of allergic sensitisation (food) - CCT

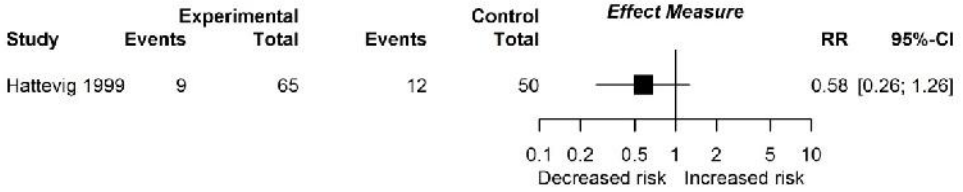


Figure 34 AFA and risk of allergic sensitisation (CM) - RCT

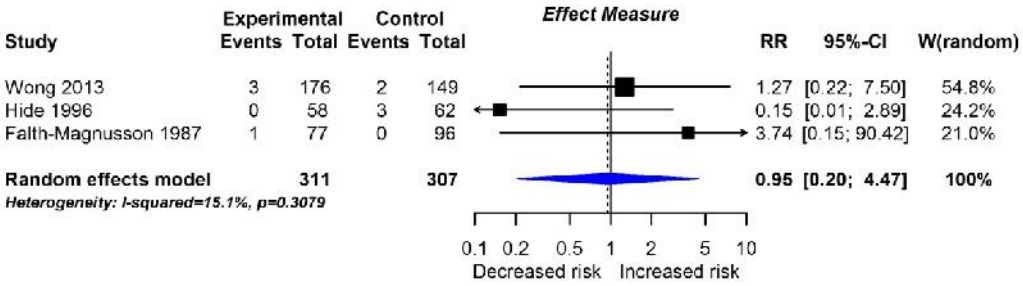


Figure 35 AFA and risk of allergic sensitisation (CM) - CCT

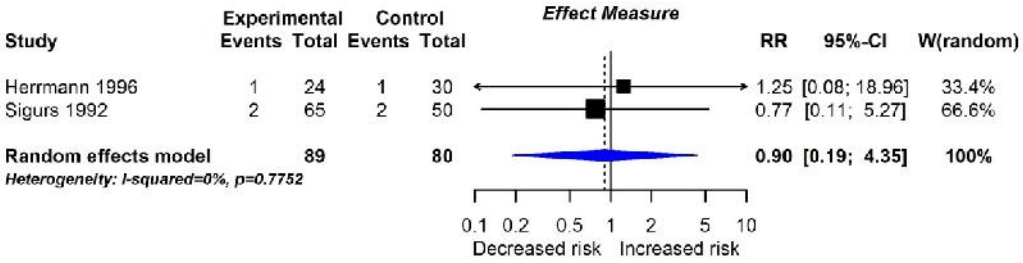


Figure 36 AFA and risk of allergic sensitisation (Egg) - RCT

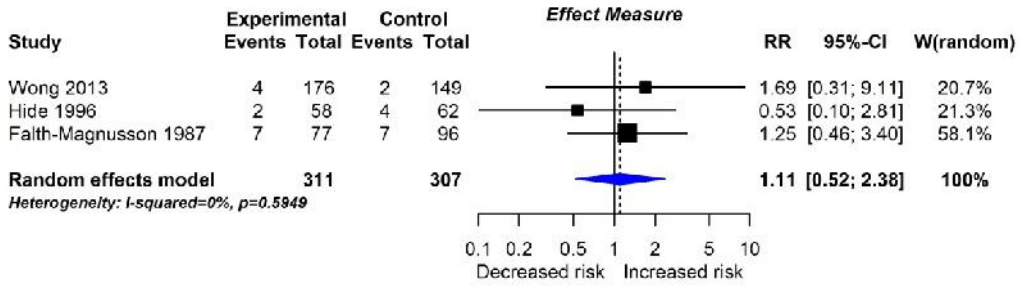


Figure 37 AFA and risk of allergic sensitisation (Egg) - CCT

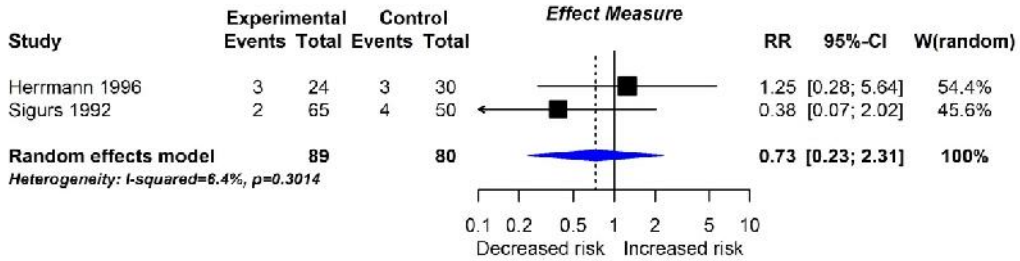


Figure 38 AFA and risk of allergic sensitisation (Peanut) - RCT

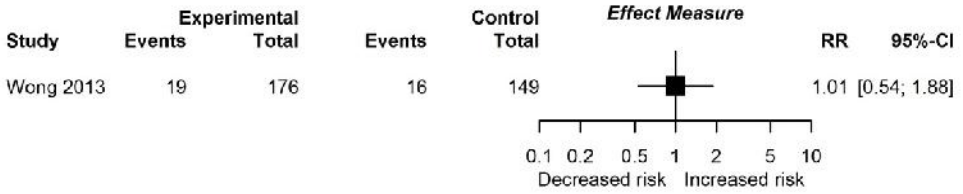
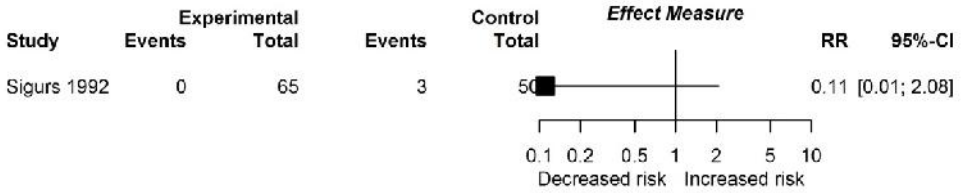


Figure 39 AFA and risk of allergic sensitisation (Peanut) - CCT



6. Maternal AFA and lung function, wheeze or asthma

One systematic review and 6 original trials (1400 participants) were included in this analysis. The recent high quality systematic review of Kramer identified 2 studies (334 participants) of AFA in pregnancy and wheeze. Data are summarised in Table 5 and do not show any evidence for an effect of maternal AFA on child wheeze, with no statistical heterogeneity.

Figure 40 summarises the risk of bias for original studies of maternal AFA and AS. Overall risk of bias was high or unclear in most studies, mainly due to risk of selection bias, based on inadequate randomisation or treatment allocation procedures. Risk of assessment bias and risk of conflict of interest were judged as low in most studies.

Meta-analysis of data from the original studies showed no evidence for an effect of maternal AFA on wheeze or recurrent wheeze at age ≤4 (Figures 41-43). Two multifaceted RCTs found significantly reduced risk of wheeze at age 5-14, with no statistical heterogeneity (Figure 44). However a larger number of participants and studies reported recurrent wheeze at this age, where no evidence for an effect of maternal AFA was seen albeit with high heterogeneity (Figures 45-46). The statistical heterogeneity seen in this analysis may be explained by the difference between the multifaceted intervention trials (RR generally <1) and the AFA-only trial (RR>1). A single RCT found no evidence of an effect on asthma at age 18 (Figure 47). Two multifaceted RCTs found no evidence for an effect on bronchial hyper-responsiveness (Figure 48), nor in one of them on FEV1 (Figure 49).

Data that could not be included in meta-analysis

Zeiger reported current wheeze and wheeze ever at aged 4 in graphical form, with similar proportions in each treatment group and no significant difference found. The studies of Becker, Hattevig, and Arshad/Hide also reported wheeze at other times and/or using other methods, with similar findings to those presented in the analysis Figures.

Overall we found no consistent evidence that maternal AFA impacts on child wheezing risk or lung function.

Figure 40 Risk of bias in studies of maternal AFA and lung function, wheeze/asthma



Table 5 Systematic review evidence for AFA and wheeze risk

Study	Outcome measure	Intervention timing	No. participants (studies)	Outcome (95% CI)	I^2
Kramer (1)	Wheeze at ≤18 months	Pregnancy	334 (2)	RR 2.22 [0.39, 12.67]	0%

Figure 41 Maternal AFA and risk of wheeze at ≤ 4 yrs - CCT

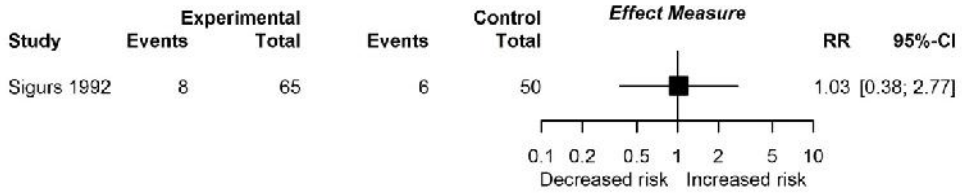


Figure 42 Maternal AFA and risk of recurrent wheeze at ≤ 4 yrs - RCT

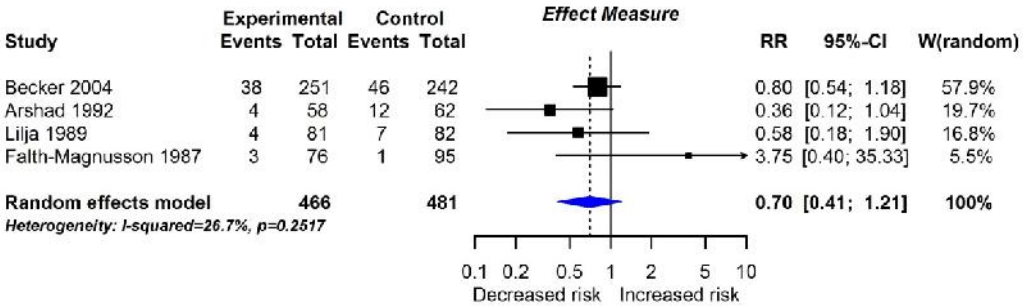


Figure 43 Maternal AFA and risk of recurrent wheeze at ≤ 4 yrs - CCT

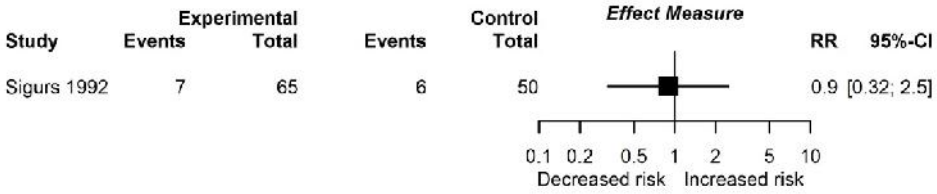


Figure 44 Maternal AFA and risk of wheeze at 5-14 yrs - RCT

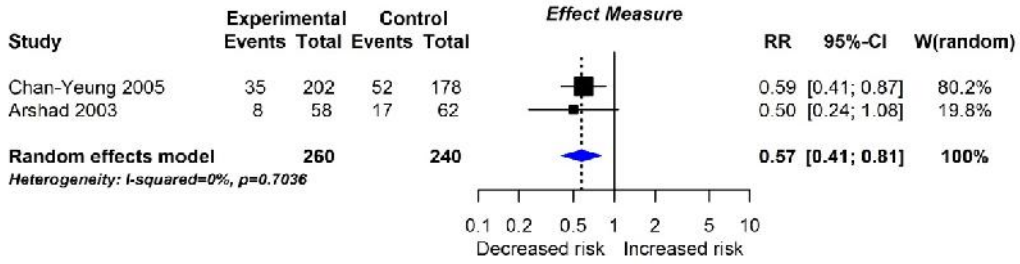


Figure 45 Maternal AFA and risk of recurrent wheeze at 5-14 yrs - RCT

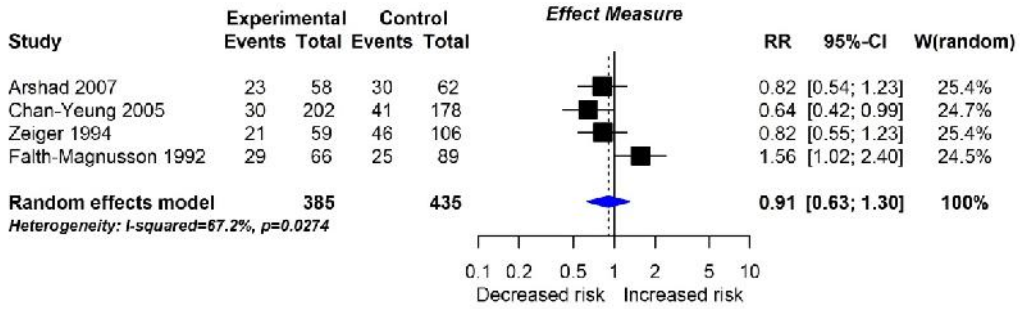


Figure 46 Maternal AFA and risk of recurrent wheeze at age 5-14 yrs – CCT

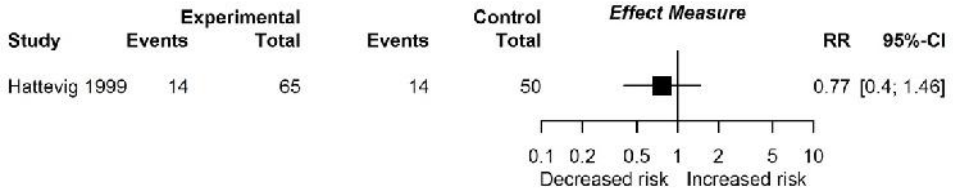


Figure 47 Maternal AFA and risk of recurrent wheeze at ≥15 yrs - RCT

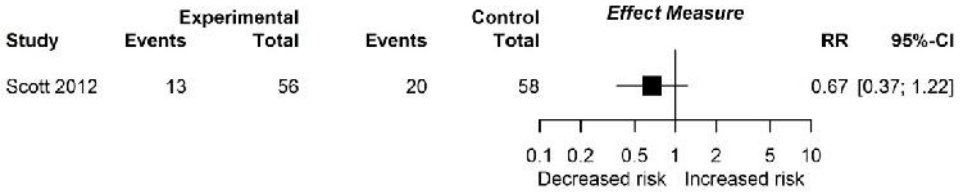


Figure 48 Maternal AFA and risk of BHR at 5-14 - RCT

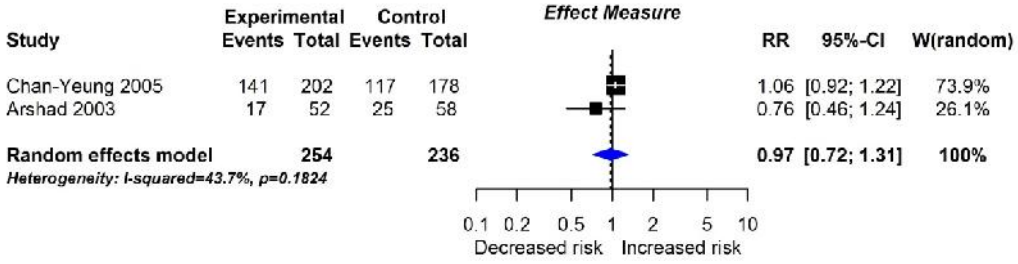
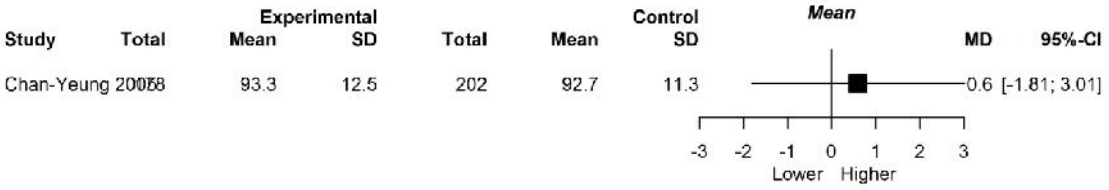


Figure 49 Multi-faceted interventions and FEV_1 as % predicted



7. Maternal AFA and risk of TIDM

No systematic review, and 2 original trials (340 participants) reported serological measures of TIDM – with mixed risk of bias (Figure 50). These data were not reported in a way that they could be used in meta-analysis. The CCT of Paronen assessed human IgG anti-insulin antibodies at 3 months, 1, 2 and 4 years. They reported a significantly raised level of insulin-IgG at age 2 in the AFA group, but this was not seen at age 3 months, 1 and 4 years, with no significant differences at these other timepoints. The RCT of Falth-Magnusson assessed multiple TIDM associated antibodies (IA2A, GADA and IAA) using a radioligand binding assay at 6 weeks, 6 months, 18 months and 5 years, and reported no significant difference between groups in autoantibody levels.

Overall we found no evidence that maternal AFA influences TIDM risk. We did not identify any intervention trials of AFA and other autoimmune diseases.

Figure 50 Risk of bias in studies on maternal AFA and TIDM



8. Conclusions

In this review we found no evidence to support a relationship between maternal AFA during pregnancy and/or lactation, and allergic or autoimmune outcomes in offspring. In general data were sparse for all outcomes reported, such that clinically meaningful effects cannot be confidently excluded. However the available data do not suggest a relationship. Data were absent for autoimmune diseases other than TIDM, and the included trials all carried high or unclear overall risk of bias, mainly related to randomisation and treatment allocation procedures. It is also worth noting that all included trials studied infants at high risk of allergic (but not autoimmune) outcomes due to family history of allergic disease.

In our overview of recent high quality systematic reviews, we identified a 2012 Cochrane review of maternal AFA and allergic outcomes (31). Kramer's review differed from ours in some important respects. Kramer excluded multi-faceted studies and CCTs, but did not exclude studies where AFA was practiced in the context of infant allergic disease. In our review we included multifaceted studies, but interpreted their findings cautiously if not supported by similar findings from AFA-only trials. We included CCTs and indeed observational studies (summarised in a separate report), but our focus was on primary prevention so we did not include studies of maternal AFA for established allergic disease in the infant. For these reasons Kramer identified fewer studies and participants than we did - 5 trials including 925 participants. However findings are similar, with quite sparse data, high or unclear risk of bias in most studies, but overall no evidence to support the hypothesis that maternal AFA can influence allergic outcomes in childhood. In the 2017 update of our systematic review, we did not identify any further high quality systematic reviews of maternal allergenic food avoidance intervention studies and allergic or autoimmune outcomes.

These data do not support any specific dietary recommendations for pregnant or lactating women with regard to allergenic food intake.

Some recent studies suggest that allergenic food exposure from environmental sources may be an important determinant of food allergy, so that total household consumption of allergenic foods may be more important than maternal consumption (32)(33). Other data suggest that there may be an important gene-environment interaction in the relationship between environmental allergenic food exposure and food allergy (34). Future work

might explore the association between whole household allergenic food exposure, environmental allergenic food protein levels, and infant allergic outcomes in the context of specific predisposing genotypes.

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MULTI-FACETED INTERVENTIONS IN PREGNANCY/ LACTATION/ INFANCY AND RISK OF ALLERGIC SENSITISATION OR ALLERGIC DISEASE

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1. Multi-faceted interventions and risk of allergic or auto-immune diseases – summary of interventions and findings

In this analysis we included studies of multi-faceted interventions, defined as an intervention which included more than one category of dietary intervention that was eligible for inclusion in the overall FSA systematic review project. Many such studies included non-dietary components to the intervention – environmental control measures designed to reduce exposure to airborne inhalants/ irritants. We undertook subgroup/stratified analyses for meta-analyses which included >5 studies, in this case only eczema (AD) at age ≤4 years. We planned to assess publication bias where there were ≥10 studies in a meta-analysis but no meta-analysis had sufficient studies included. In total we identified 9 RCT investigating the effect of multifaceted interventions during pregnancy/lactation/infancy on allergic outcomes.

Interventions used

Six of the 9 trials used an intervention which included promotion of prolonged breastfeeding, avoidance of at least some allergenic foods for the mother and/or infant, and delayed introduction of solid foods to the infant. Five of these trials also included environmental control measures, and 4 used an alternative formula when infant formula milk was introduced - soya in the study of **Matthew (1)**, pHF in the **Canadian asthma primary prevention study (CAPPS)** of Becker **(2-4)**, and the study of **Shao (5)**, and eHF in the **PREVASC study** of Schonberger **(6).** The **SPACE** study of Halmerbauer **(7, 8)**, and the study of **Poysa (9-11)** did not use special formula milk.

The other three studies used more limited interventions – delayed allergenic food exposure plus extensively hydrolysed formula in the studies of **Lovegrove (12)** and **Zeiger (13)**; plus soya hydrolysate formula and environmental control in the **Isle of Wight study** of Hide **(14, 15)**. Environmental control measures were aimed at reducing house dust mite allergen exposure, pet exposure and/or tobacco smoke exposure.

Populations and Outcomes assessed

Outcomes studied were allergic sensitisation, total IgE, food allergy, AD, allergic rhinitis, wheeze/asthma and lung function – forced expiratory volume in 1 second (FEV1), bronchial hyper-responsiveness (BHR). Overall approximately 2,200 infants were randomised, 1,100 to an intervention arm. All studies were in infants at high risk of allergic disease, six studies were carried out in Europe, one in Asia-Pacific and two in North America. The definitions of study

outcomes varied across studies but in general studies used accepted criteria for outcome assessment.

Overall findings

Overall the quality of evidence was mixed. There was an unclear risk of bias in most studies, largely due to insufficient details about the randomisation process (Selection bias; Figure 1), and this may be partly explained by many of the included studies having taken place prior to CONSORT (1996) clinical trial guidance and/or ICMJE (2005) clinical trial registration requirements were developed. Individual meta-analyses were usually limited by small numbers of studies and participants leading to imprecision in estimates of treatment effect. Overall we found no clear evidence that multifaceted interventions prevent AD, allergic sensitisation or food allergy, although analyses were limited by small study numbers and wide confidence intervals – such that further work will be needed in order to confidently exclude a beneficial effect. All studies were undertaken in populations at high risk of allergic disease, so conclusions only apply to this population.

We did find evidence for reduced allergic rhinitis at age ≤4 years based on meta-analysis of 2 studies (RR=0.61; 95% CI 0.44 to 0.84) with no statistical heterogeneity. However a further study which couldn't be included in this meta-analysis found no significant difference in allergic rhinitis. Both studies included house dust mite avoidance measures, delayed allergenic food introduction to the infant, and use of a hydrolysed formula if necessary as part of the intervention. The intervention in the study which found no significant difference, was limited to allergenic food exclusion in mother and infant. The allergic rhinitis meta-analysis was dominated by the CAPPS study, which also included avoidance of nursery/daycare until age 1, avoidance of environmental tobacco smoke exposure, and pet avoidance as part of the intervention. Given that environmental tobacco smoke is a major trigger of respiratory symptoms, it is unclear whether the dietary components of the intervention were relevant. We did not find any evidence that multifaceted interventions reduce allergic rhinitis at age 5-14, although in one small study atopic AR (here AR associated with allergic sensitisation measured by SPT) was reduced.

We found evidence that multifaceted interventions reduce the risk of wheeze (RR 0.57 95%CI 0.41, 0.81) or recurrent wheeze/asthma at age 5-14 (RR 0.77 95%CI 0.61, 0.97), with no

statistical heterogeneity. However no such effects were seen at age 0-4 years, and no effect on lung function.

Conclusion

These data suggest that in infants at high risk of allergic disease, multifaceted interventions which include environmental control measures, may reduce the risk of AR at age ≤ 4 years, and recurrent wheeze in school-age children and adolescents. Evidence is inconsistent, and effect estimates are imprecise due to sparse data, so further work is needed to confirm these findings.

Multifaceted interventions prevent AR at age ≤4.

GRADE of evidence: LOW (-1 indirectness of intervention; -1 imprecision due to sparse data, inconsistent with data at age 5 to 14).

Multifaceted interventions prevent wheeze/recurrent wheeze at age 5-14.

GRADE of evidence: LOW (-1 indirectness of intervention; -1 imprecision due to sparse data, inconsistent with data at age ≤4).

Table 1 Characteristics of included studies

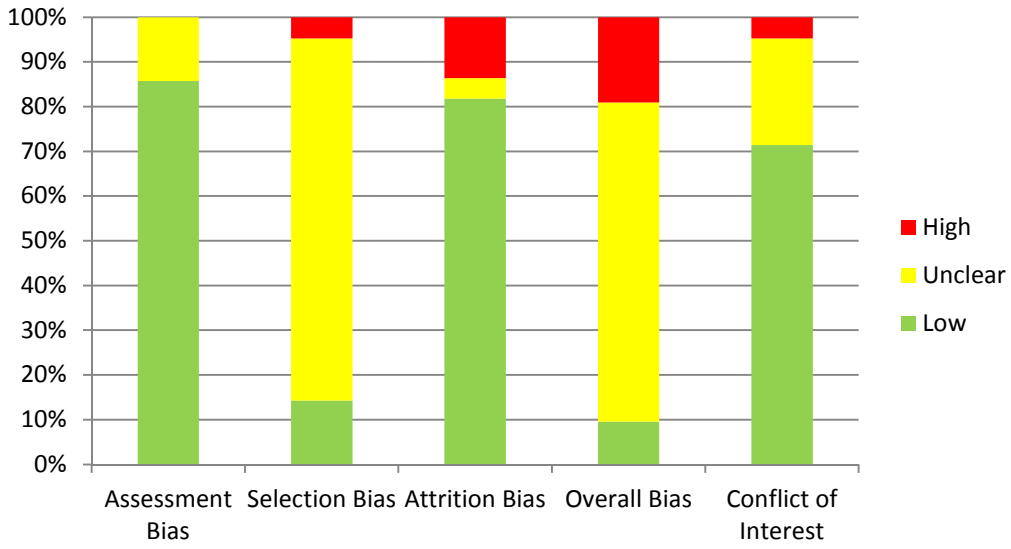
Study	Design	N Int/ Control	Country	Intervention	Disease risk	Age (yrs)	Outcomes reported
Becker, 2004 (2); Chan-Yeung, 2000 (16); Chan-Yeung 2005 (3); Wong, 2013 (17)Protudjer, 2011(18); Carlsten 2013(4) **CAPPS Study**	RCT	281/ 268	Canada	BF encouraged for 4 months, allergenic food exclusion during pregnancy/lactation, delayed solid (6 months) and allergenic (12 months) food, whey pHF if necessary, environmental control.	High	1, 7, 15	Allergic Sensitisation (SPT), Allergic Rhinitis (DD), Wheeze (ISAAC and modified ECRHS), AD (DD), bronchial hyper-responsiveness (PC20 <7.8mg/ml), Lung function (FEV1)
Lovegrove, 1994 (12)	RCT	12/ 14	UK	CM exclusion during pregancy and lactation with hydrolysed milk if necessary. BF encouraged for 6 months and eHF if needed.	High	1	AD (DD)
Matthew, 1977 (1)	RCT	27/ 35	UK	BF encouraged for 6 months, delayed solid food (3 months) and allergenic food (6 months), soy milk if necessary, environmental control.	High	1	AD (Physician assessment), Allergic sensitisation, Total IgE
Poysa, 1991 (9) Poysa 1989 (10) Kuikka 1985 (11)	RCT	Unclear - outcome reported in 35/ 33	Finland	eBF encouraged for 3 months, solid food and cow's milk formula after 3 months plus environmental control.	High	5, 10	Asthma (>=3 episodes of wheeze), Allergic rhinitis/ conjunctivitis (Physician assessment), Allergic sensitisation (SPT, total IgE), Food allergy (oral food challenge), AD (Hanifin and Rajka)

Study	Design	N Int/ Control	Country	Intervention	Disease risk	Age (yrs)	Outcomes reported
Shao, 2006 (5)	RCT	23/ 23	China	eBF encouraged for 4 months, allergenic food exclusion during lactation, delayed solid (4 months) and allergenic (6-12 months) food, pHF if necessary.	High	1.5	AD (Wolkerstorfer score), Allergic Sensitisation (SPT)
Zeiger, 1992 (13) Zeiger 1989 (19), 1994 (20)	RCT	103/ 185 [seen at 4 months]	USA	Allergenic food exclusion during pregnancy/lactation, delayed allergenic (1-3 years) food, casein eHF if necessary.	High	1, 4, 7	AD (Hanifin and Rajka Criteria), Allergic Rhinoconjunctivitis (DD), Food Allergy - Any (DD), Wheeze (≥2 physician diagnosed episodes), Allergic Sensitisation (SPT)
Hide, 1994 (14) Hide, 1996(21) Arshad, 1992 (15) Arshad, 2003 (22) Arshad, 2007 (23) Scott, 2012 (24) **Isle of Wight Study**	RCT	71/ 68	UK	Allergenic food exclusion during lactation, delayed allergenic (9-11 months) food, soya hydrolysate if necessary, environmental control.	High	1, 2,4,18	Recurrent wheeze (>=3 episodes), BHR (PC20<8mg/ml), AD (Physician assessment), Food allergy (Open food challenge ; Physician assessment), Allergic sensitisation (SPT, total IgE), Allergic rhinitis (physician assessment), Total IgE
Halmerbauer, 2002 Halmerbauer, 2003 (7, 8) **SPACE Study**	RCT	349/ 347	UK, Germany, Austria	eBF encouraged beyond 3 months, delayed solid (6 months) and allergenic (1-3 years) food, environmental control.	High	1	AD (DD), Allergic sensitisation (SPT, sIgE), Wheeze (Parent reported wheeze ever), Asthma (>=3 episodes of wheeze), Food allergy (DD)

Study	Design	N Int/ Control	Country	Intervention	Disease risk	Age (yrs)	Outcomes reported
Schonberger, 2005 (6) **PREVASC study**	RCT	212/ 208	Netherlands	BF encouraged to ≥6 months, delayed solid and allergenic (6 months) food, eHF if formula introduced, environmental control.	High	2	AD (ICHPPC), Wheeze (Dutch Guideline ‘‘Asthma in Children’’ and ISAAC), Allergic Sensitisation (sIgE)

BF breastfeeding; eBF exclusive breastfeeding; pHF partially hydrolysed formula; eHF extensively hydrolysed formula; CM cow’s milk; RCT randomised clinical trial, SPT skin prick test, BHR bronchial hyperresponsiveness, FE_{V1} forced expiratory volume in one second; Physician assessment refers to assessment by a study physician , DD refers to community diagnosis.

Figure 1 Risk of bias in trials of multi-faceted intervention studies



2. Multi-faceted interventions and risk of AD

All 9 trials (2200 participants) reported AD (AD) as an outcome. Age at time of outcome measurement ranged between 1 and 7 years. In 4 studies diagnosis was made by a doctor – in 3 cases at a scheduled study visit by a study physician; 2 studies used Hanifin & Rajka and others used either unclear or other methods of outcome assessment. The risk of bias was unclear in most studies, largely due to unclear selection bias (Figure 2).

Multi-faceted interventions did not significantly reduce AD risk at age ≤4, 5-14 or ≥15 years (Figures 3-5). In one small study (Isle of Wight) there was evidence for reduced atopic AD (i.e. AD associated with positive skin prick test) RR 0.3 95% CI 0.13, 0.84 (Figure 6). Subgroup analysis was undertaken for AD at ≤4 by risk of Conflict of Interest bias, and by inclusion of environmental control (house dust mite, tobacco smoke, pet exposure reduction methods) within the intervention. This showed no significant subgroup differences, as summarised below.

Environmental control 4 studies RR 0.72 (0.42, 1.22; I^2=69%); no environmental control 2 studies RR 0.60 (0.32, 1.14; I^2=0%) – test for subgroup difference P=0.68.

Low conflict of interest risk 1 study RR 0.86 (0.58, 1.29); unclear/high conflict of interest risk 5 studies RR 0.59 (0.32, 1.10; I^2=66%) – test for subgroup difference P=0.32.

Data that could not be included in meta-analysis

In the Isle of Wight Study 2-year outcomes were also reported, which could not be included in meta-analysis. Here there were increased odds for AD in control compared with intervention group – OR 9.5 95%CI 1.8, 50.1 (14). The study by Zeiger (13) reported AD in graphical form in 225 participants, so could not be included in meta-analysis. The graph suggests that ~20% in the control, and ~14% in the active group developed AD by 4 years, which the authors describe at not statistically significant.

Overall we found no evidence that multifaceted interventions reduce risk of AD, in high risk infants. However data were sparse and confidence intervals were wide, such that clinically significant beneficial effects cannot be confidently excluded.

Figure 2 Risk of bias in multi-faceted interventions and risk of AD

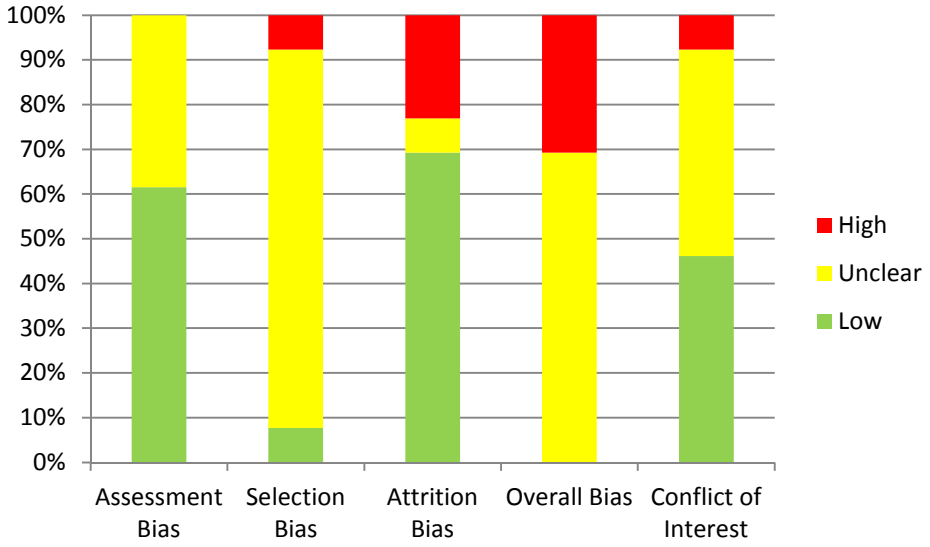


Figure 3 Multi-faceted interventions and risk of AD at age ≤ 4 years

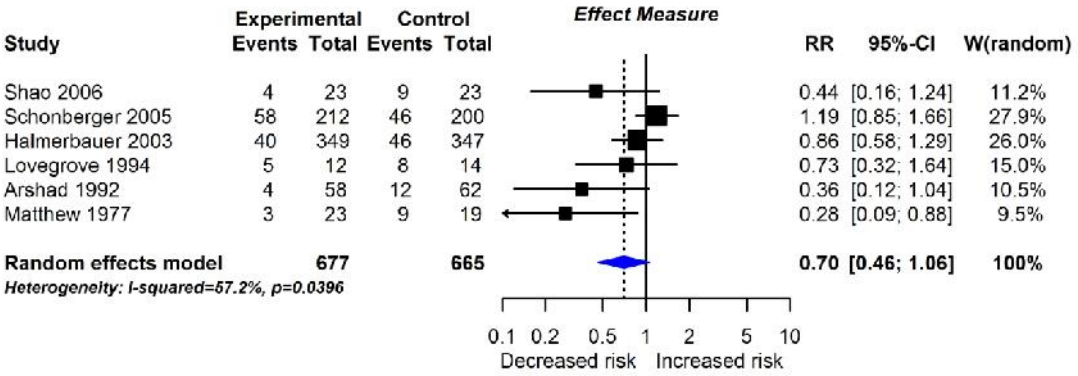


Figure 4 Multi-faceted interventions and risk of AD at age ≥ 5-14 years

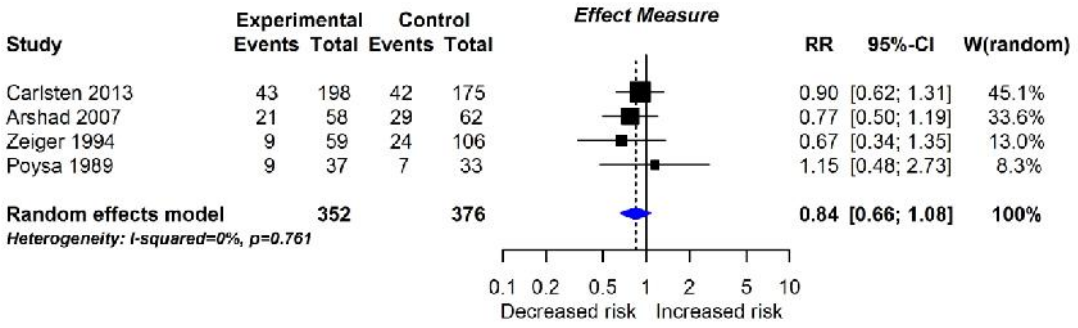


Figure 5 Multi-faceted interventions and risk of AD at age ≥ 15 years

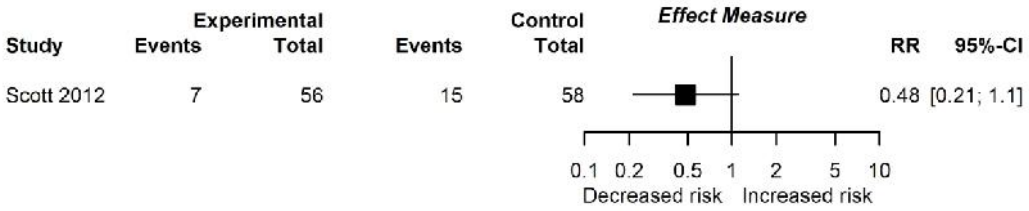
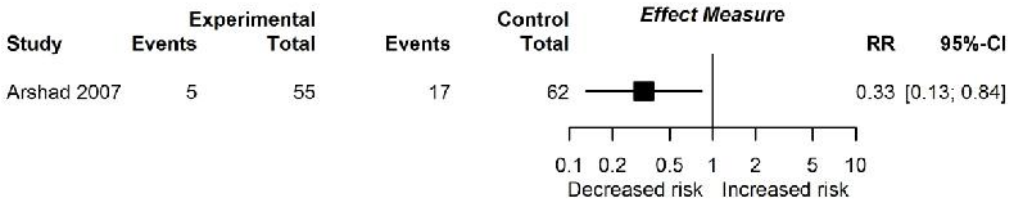


Figure 6 Multi-faceted interventions and risk of atopic AD at age 5-14 years



3. Multi-faceted interventions and risk of allergic rhinitis or conjunctivitis

Four trials (900 participants) reported allergic rhinitis (AR) and/or allergic conjunctivitis (AC) as an outcome. Age at time of outcome measurement ranged between 3 and 10 years. Diagnosis was made by a study physician in two studies, community doctor diagnosis in two studies. The risk of bias was unclear in most studies, largely due to unclear selection bias due to poorly reported methods of randomisation and treatment allocation (Figure 5).

At age ≤4 years two studies were suitable for meta-analysis which showed reduced risk of AR with multifaceted interventions (RR 0.61 95% CI 0.44, 0.84; 2 studies; 613 participants; Figure 6). There was no statistical heterogeneity. The study by Zeiger (13) reported AR in graphical form in a further 225 participants, so could not be included in meta-analysis. There was no significant difference between groups, with ~30% in both the intervention and the control groups developing AR by 4 years.

We found no evidence that multi-faceted interventions reduce AR or allergic conjunctivitis (AC) risk at age 5-14 years (Figure 7-8) but in one small study there was reduced atopic AR (i.e. AR associated with a positive SPT) in the intervention group at 8 years (Figure 9)

Overall we found LOW level evidence that multifaceted interventions reduce risk of AR at age ≤ 4 years (-1 indirect intervention; -1 imprecision). We found no evidence for an effect on AC, or on AR at age 5-14.

Figure 5 Risk of bias in multi-faceted interventions and risk of AR

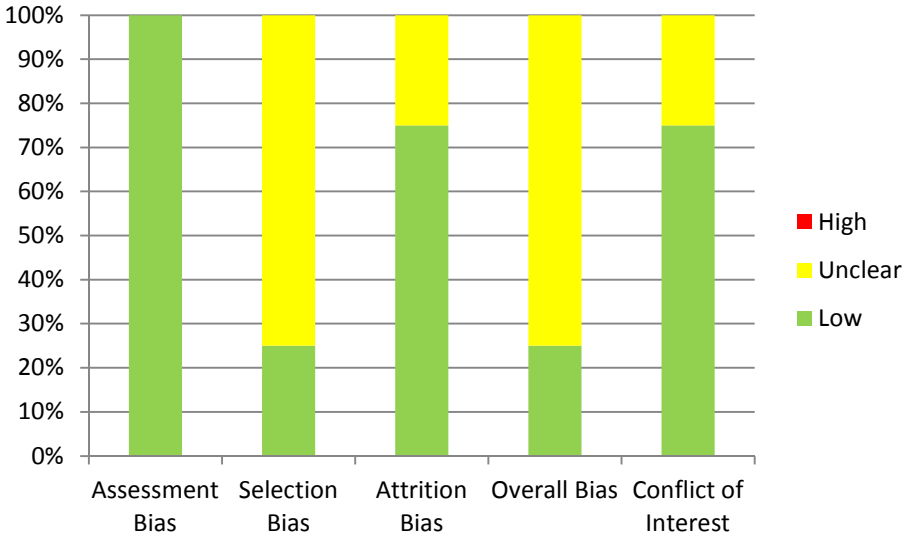


Figure 6 Multi-faceted interventions and risk of AR at age ≤ 4 years

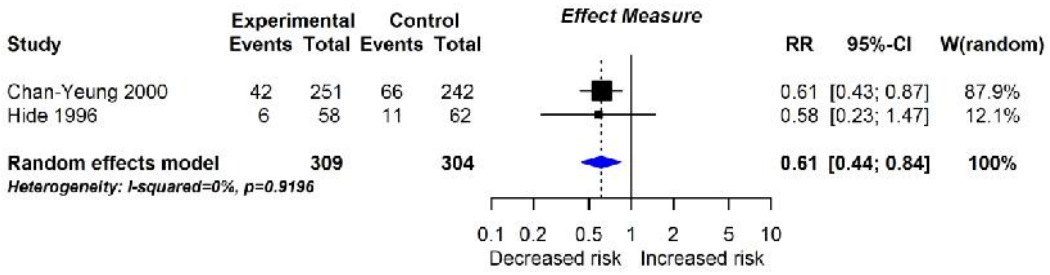


Figure 7 Multi-faceted interventions and risk of AR at age 5-14 years

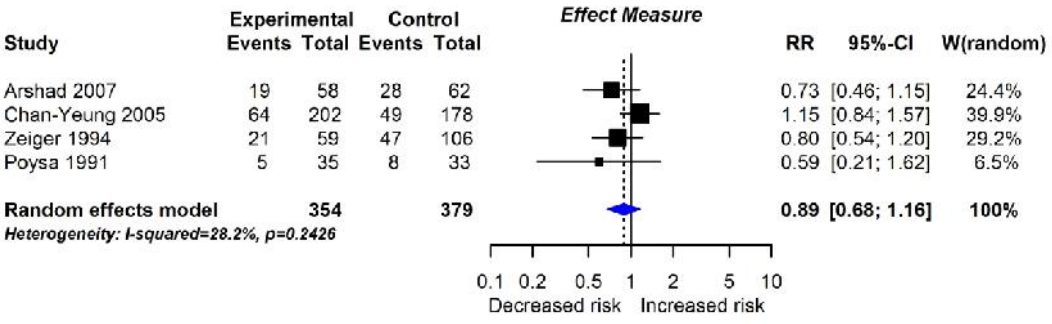


Figure 8 Multi-faceted interventions and risk of AC at age 5-14 years

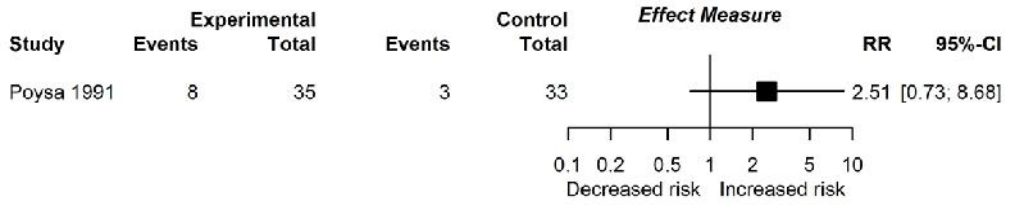
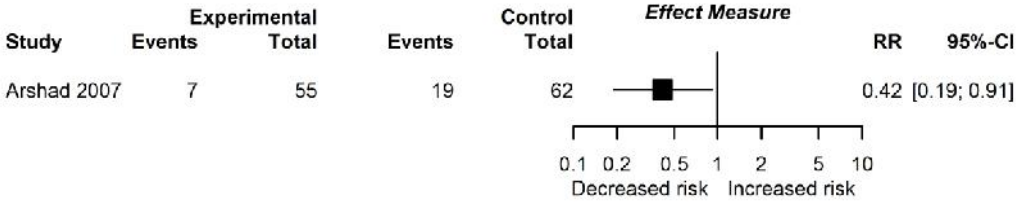


Figure 9 Multi -faceted interventions and risk of atopic AR at age 5-14 years



4. Multi-faceted interventions and risk of food allergy

Four trials (1000 participants) reported food allergy as an outcome. Age at time of outcome measurement ranged between 1 and 10 years. Diagnosis was made by doctor's diagnosis in two studies, oral food challenge in two studies. The risk of bias was unclear in most studies, largely due to unclear selection bias (Figure 10).

At age ≤4 years two studies were suitable for meta-analysis which showed no significant difference in food allergy risk, with high statistical heterogeneity (Figure 11). At age 5-14 three studies contributed to meta-analysis which again showed no significant difference in food allergy risk, with moderate statistical heterogeneity (Figure 12).

Data that could not be included in meta-analyses

The study of Arshad and Hide (Isle of Wight) found no significant difference in doctor diagnosed food allergy by age 2 – OR 1.25 (95% CI 0.27, 5.79). The study by Zeiger (13) reported food allergy in graphical form in a further 225 participants at age 4, which could not be included in meta-analysis. They found reduced food allergy to any food in the intervention group when using lifetime prevalence, but no significant difference when using 12-month prevalence at age 4.

Overall we found no evidence that multifaceted interventions reduce risk of food allergy. However data were sparse and confidence intervals were wide, such that clinically significant beneficial effects cannot be confidently excluded.

Figure 10 Risk of bias of multi-faceted interventions and risk of food allergy

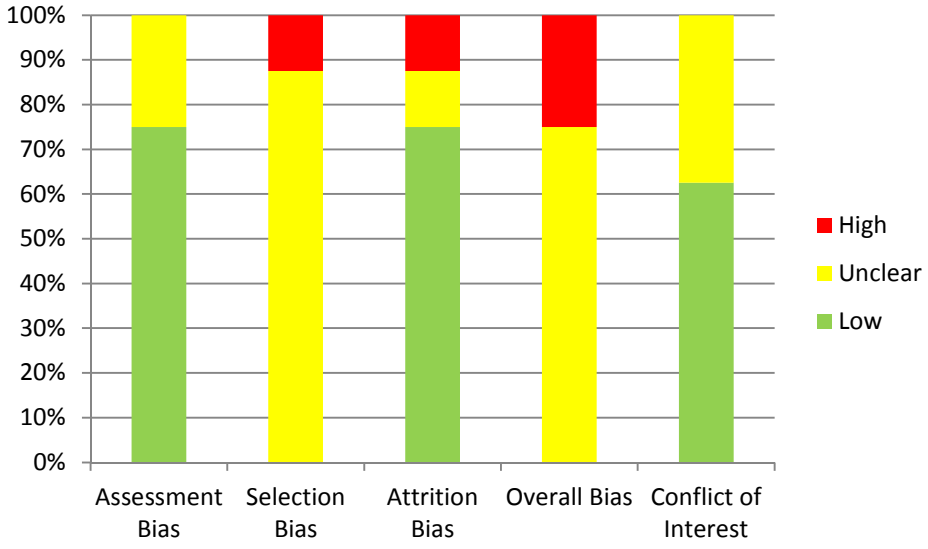


Figure 11 Multi-faceted interventions and risk of food and risk of food allergy at age ≤ 4 years

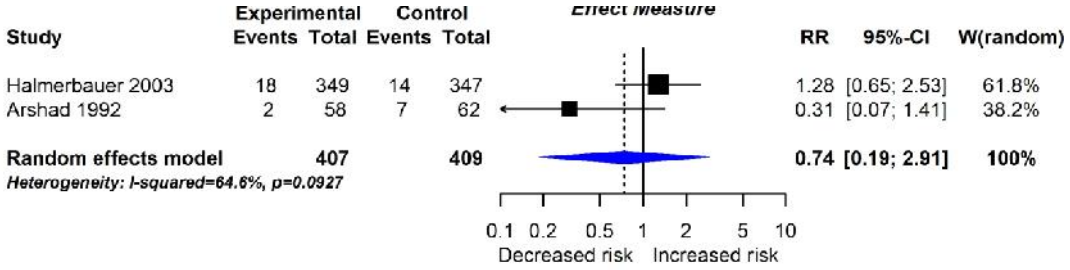
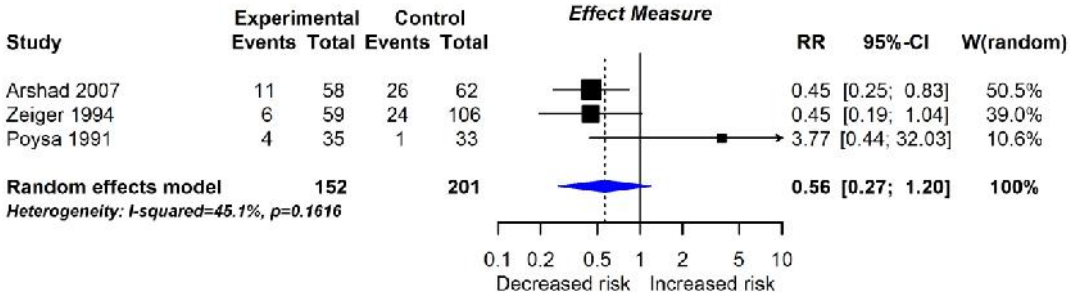


Figure 12 Multi-faceted interventions and risk of food allergy at age 5-14 years



5 Multi-faceted interventions and risk of allergic sensitisation

Eight trials (2100 participants) reported allergic sensitisation (AS) as an outcome. Age at time of outcome measurement ranged between 1 and 18 years. Diagnosis was made using SPT in seven studies, and sIgE in one study. Two studies reported total IgE. The risk of bias was unclear in most studies, largely due to unclear selection bias (Figure 13). For meta-analysis of specific allergic sensitisation SPT and sIgE were combined, and all age groups were combined – consistent with the approach taken in the other reports in this systematic review project.

We found no evidence for an effect of multi-faceted interventions on AS to any allergen (Figure 14), aeroallergens (Figure 15), and no consistent effect for food allergens (Figures 16-19). Zeiger separately reported no significant difference in AS to cow's milk, egg, peanut, any food or any aeroallergen at age 4, but no data were shown that could be included in meta-analysis. Chan-Yeung separately reported no significant difference in AS to any allergen at age 2 and age 7 in the same study as Wong 2013 (CAPPS). Scott separately reported no significant difference in AS to any food allergen, in a later follow up of the study of Arshad 2003 (Figure 16; RR 1.29 95% CI 0.54, 3.08).

There was evidence from one study that multifaceted interventions may be associated with significantly increased total IgE compared to the control group (Figure 20), however a separate study (Matthew 1977) found no such difference. Matthew found no significant difference in total IgE between intervention and control group at one year of age – mean IgE level 6.0 (sd 3.4; n=16) intervention, 7.6 (sd 4.4; n=11) control P=0.30.

Overall we found no evidence that multifaceted interventions reduce risk of AS.

Figure 13 Risk of bias of multi-faceted interventions and risk of allergic sensitisation

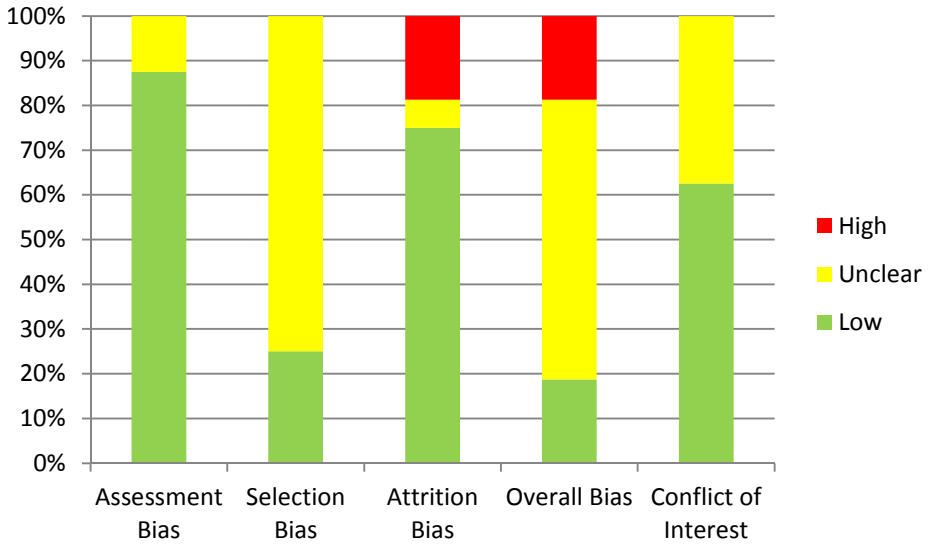


Figure 14 Multi-faceted interventions and risk of AS to any allergen

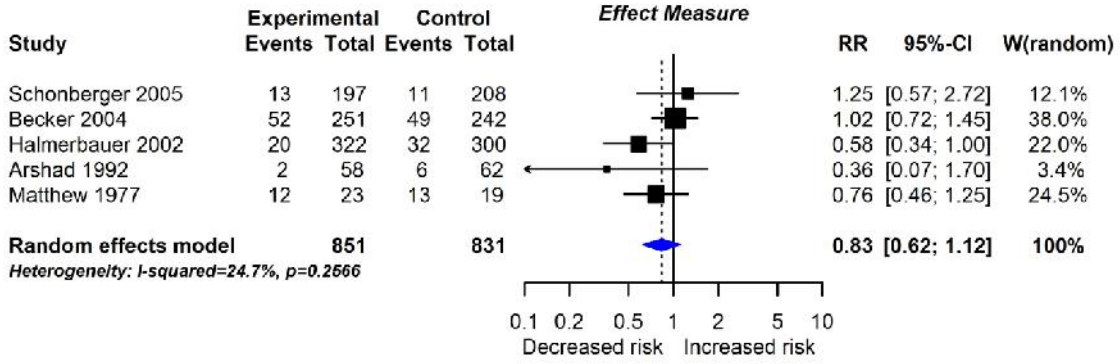


Figure 15 Multi-faceted interventions and risk of AS to aeroallergens

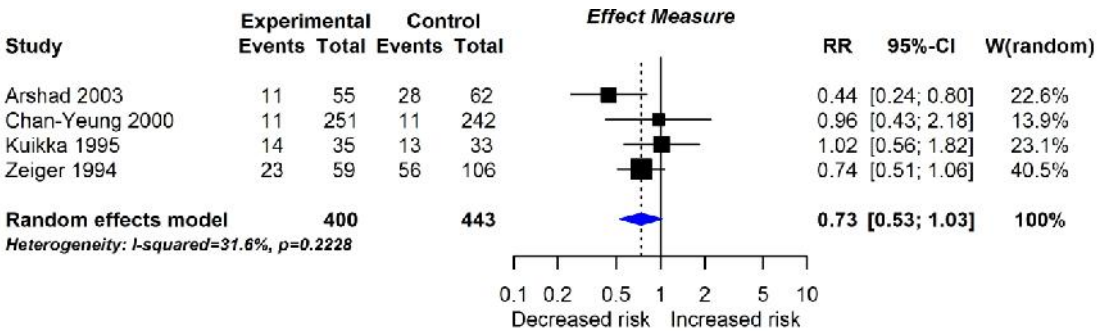


Figure 16 Multi-faceted interventions and risk of AS to any food

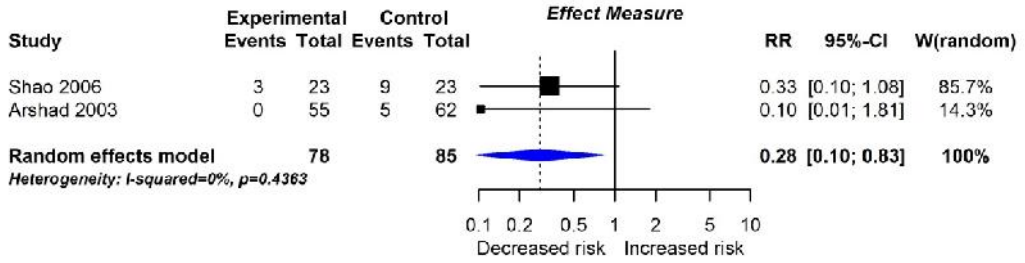


Figure 17 Multi-faceted interventions and risk of AS to cow's milk

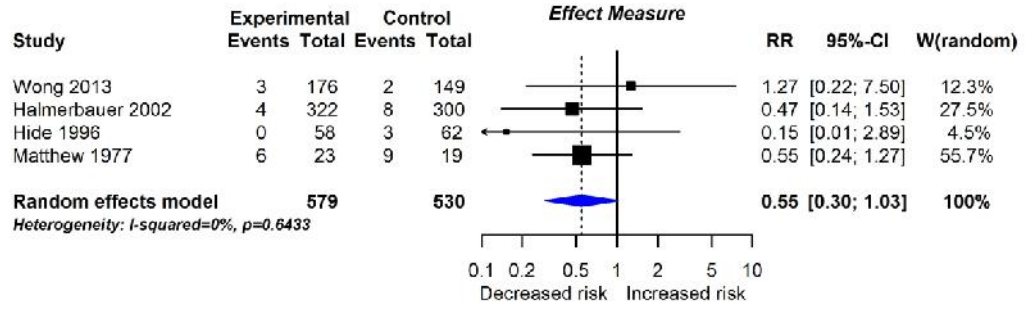


Figure 18 Multi-faceted interventions and risk of AS to egg

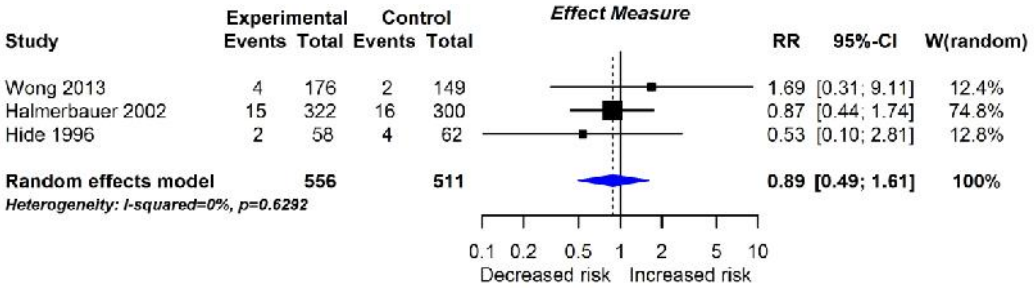


Figure 19 Multi-faceted interventions and risk of AS to peanut

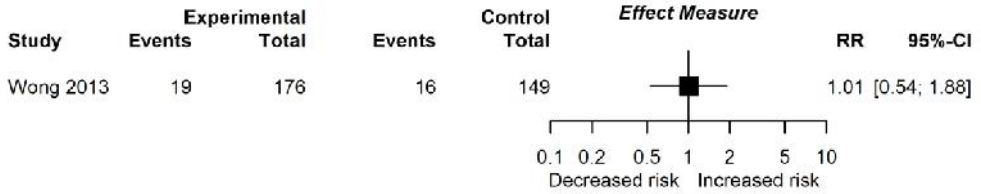
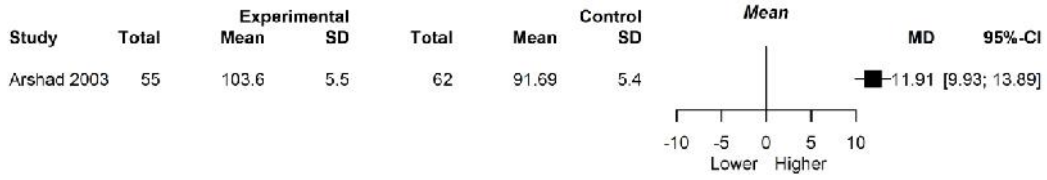


Figure 20 Multi-faceted interventions and Total IgE



6. Multi-faceted interventions and lung function, bronchial hyper-responsiveness and risk of wheeze

Six trials (1900 participants) reported wheeze as an outcome, and in two cases this included lung function or bronchial hyper-responsiveness. Age at time of outcome measurement ranged between 1 and 18 years. Studies mainly reported recurrent wheeze, using parent report. The risk of bias was unclear in most studies, largely due to unclear selection bias (Figure 21).

We found no evidence for an effect of multi-faceted interventions on lung function or bronchial hyper-responsiveness at the age of 5-14 years (Figures 22-23), and no evidence for an effect on wheeze or recurrent wheeze at age 0-4 (Figures 24-25).

We found evidence that multifaceted interventions reduce risk of wheeze (RR 0.57 95% CI 0.41, 0.81) or recurrent wheeze (RR 0.77 95% CI 0.61, 0.97) at age 5-14 (Figures 26-27), with no statistical heterogeneity. One of the four studies which contributed to this analysis also reported asthma at age 17 and found reduced asthma (OR 0.28 95% CI 0.09, 0.86) and reduced persistent asthma (OR 0.21 95% CI 0.05, 0.90) at this age. All these 4 studies included delayed introduction of allergenic foods into the infant diet as part of the intervention. Three of the studies also included maternal allergenic food exclusion during pregnancy/lactation, and three of the studies included environmental control measures such as house dust mite, pet and tobacco smoke avoidance.

Overall we found LOW level evidence (-1 indirectness of intervention; -1 imprecision) that multifaceted interventions reduce risk of wheeze/recurrent wheeze at age 5-14 years, in high risk children. We found no evidence for an effect on lung function, or on wheeze at age ≤ 4 years.

Figure 21 Risk of bias in multi-faceted studies and risk of wheeze or asthma

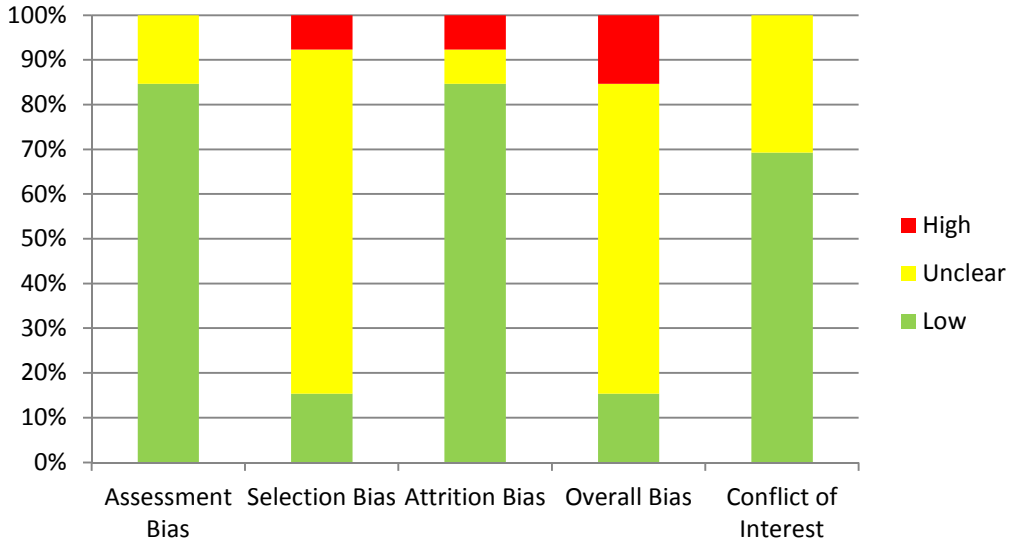


Figure 22 Multi-faceted interventions and FEV_1 as % predicted at age 5-14 years

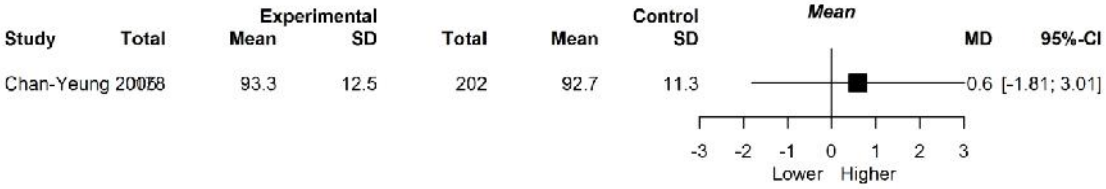


Figure 23 Multi-faceted interventions and risk of BHR at age 5-14 years

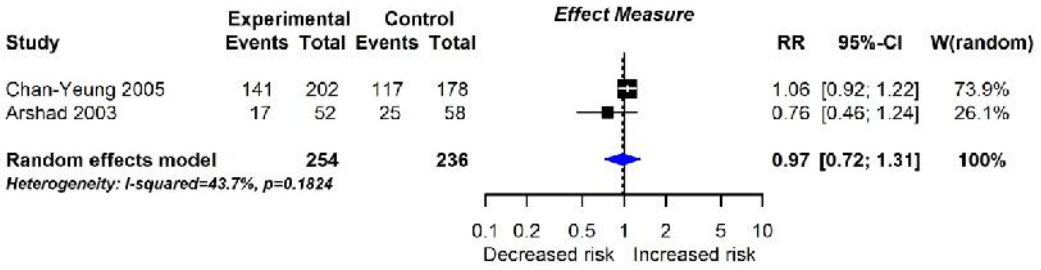


Figure 24 Multi-faceted interventions and risk of wheeze at age ≤ 4 years

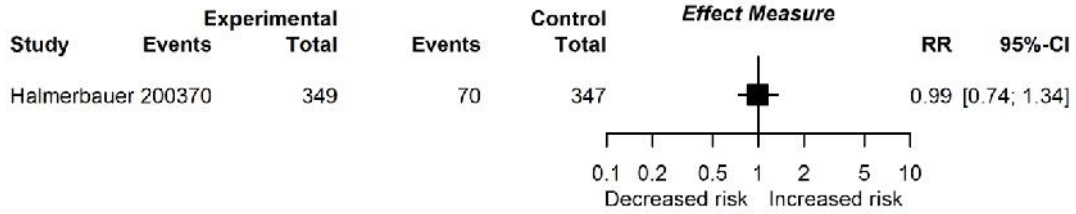


Figure 25 Multi-faceted interventions and risk of recurrent wheeze at ≤ 4 years

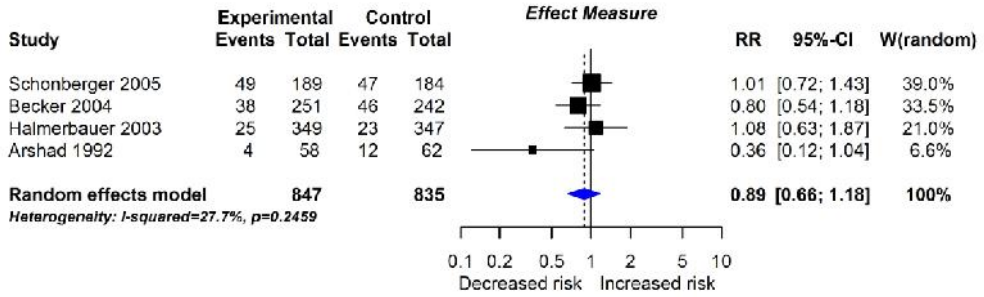


Figure 26 Multi-faceted interventions and risk of wheeze at age 5-14 years

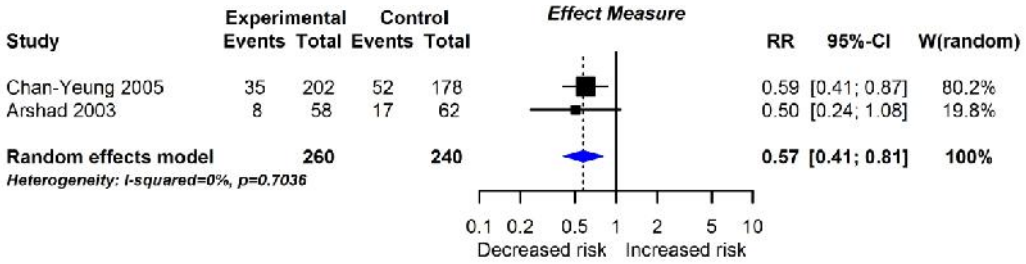
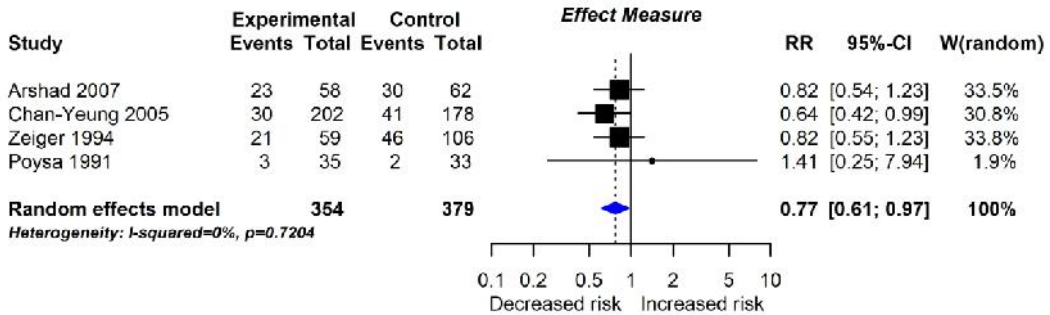


Figure 27 Multi-faceted interventions and risk of recurrent wheeze at age 5-14 years



General Conclusions

In this systematic review of multi-faceted interventions during pregnancy/lactation/infancy and risk of allergic outcomes, we found evidence that such interventions may reduce the risk of AR at age ≤ 4 years, and wheeze and recurrent wheeze at the age of 5-14 and 15+. We found no evidence for such effects at different ages, nor any effect on lung function. We found no evidence that multifaceted interventions influence other allergic outcomes, and we found no data for autoimmune outcomes. The findings are based on relatively small numbers of studies and participants, with unclear risk of bias due to uncertainty around methods of randomisation and treatment allocation. This is partly because some of the studies are relatively old and were therefore undertaken prior to guidance for reporting and registering of clinical trials in the form of CONSORT and ICMJE statements.

For AR at age ≤ 4 years there was some inconsistency (with the study of Zeiger finding no effect, but the 2 studies in meta-analysis finding an effect), and serious imprecision due to sparse data. The 2 studies included in meta-analysis used house dust mite avoidance measures, delayed allergenic food introduction to the infant, and use of a hydrolysed formula if necessary as part of the intervention. The Zeiger study, which found no significant difference, was limited to allergenic food exclusion in mother and infant. The CAPPS study, which dominated the positive meta-analysis, included avoidance of nursery/daycare until age 1, avoidance of environmental tobacco smoke exposure, and pet avoidance as part of the intervention. Given that environmental tobacco smoke is a major trigger of respiratory symptoms, it is unclear whether the dietary components of the intervention were relevant.

For analyses of wheeze/recurrent wheeze at age 5-14, there was no statistical heterogeneity, but there was imprecision due to sparse data. The included studies had diverse multifaceted interventions. However all studies that reported recurrent wheeze as an outcome measure included delayed introduction of allergenic foods into the infant diet as part of the intervention. Three of the studies also included maternal allergenic food

exclusion during pregnancy/lactation, and three of the studies included environmental control measures such as house dust mite, pet and tobacco smoke avoidance.

Systematic reviews of multi-faceted interventions for preventing allergic outcomes have not previously been undertaken, to our knowledge, and none was identified in our search for recent systematic reviews. However the systematic review of Dick 2014 (25) did assess a wide variety of environmental exposures in relation to childhood asthma. Dick found consistent evidence that tobacco smoke exposure, mould and air pollution are associated with increased risk for childhood asthma, and less consistent evidence that pet exposure is associated with increased asthma risk. Some of the house dust mite avoidance measures used in these multifaceted intervention studies may have also impacted on mould and/or pollutant exposure due to improved ventilation and cleaning of the indoor environment, so this should be considered as a possible mechanism of effect.

In our systematic review of breastfeeding and allergic/autoimmune outcomes (Review A) we found no consistent evidence for an association between increased exclusive breastfeeding duration and reduced risk of asthma, and Dick reported inconsistent evidence supporting the same association. Dick found evidence that exposure to house dust mite in isolation, is not associated with asthma risk. The multifaceted interventions also may have reduced wheeze/recurrent wheeze at age 5-14 and 15+ through the advice to increase breastfeeding / exclusive breastfeeding duration included in some intervention packages, but there is no direct evidence to support this possibility.

Overall these data suggest that multifaceted interventions, which include tobacco smoke avoidance, pet avoidance and increased duration of breastfeeding, and possibly allergenic food exclusion from the infant +/- maternal diet, improved home ventilation and cleaning, may reduce the risk of AR at age ≤ 4, and wheeze in older children and adolescents at high risk of allergic disease due to a family history.

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OTHER DIETARY EXPOSURES IN INFANTS AND MOTHERS, AND RISK OF ALLERGIC AND AUTOIMMUNE DISEASES

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1. Executive summary of studies and findings: Maternal and infant intake of other foods and risk of allergic and autoimmune diseases – Observational studies

1.1. Context of this report

This report is one of a series of systematic review reports included in Review C Part II, which focusses on evidence on dietary exposures during pregnancy, lactation and or infancy for reducing risk of allergic or autoimmune outcomes. This report focuses on dietary exposures that were considered inappropriate for inclusion in the themes of the other three reports, namely: 'Fruits and vegetables', 'Vitamins and Minerals', or 'Fats'. The report includes food introduction in the infant's diet if these foods are not considered as allergenic, in which case they will be added to the corresponding report in Review B (Introduction of allergenic food and risk of allergic or autoimmune diseases). This report also includes consumption of dairy products, and therefore observational studies that included dairy foods rich in probiotics are also included here. A separate report covers all intervention studies on pre- and probiotics.

1.2. Studies and outcomes identified

We identified a total of 47 observational studies that investigated the association between infant or maternal intake of other foods and allergic or autoimmune diseases. Of these, 27 studies were prospective cohorts (PC), 4 were nested case-controls (NCC), 12 were case-controls (CC), and 4 cross-sectional studies (CS).

1.3. Outcomes evaluated

22 studies included atopic dermatitis (AD) as outcome; 2 studied food allergy (FA); 2 lung function (LF); 21 wheeze; 7 rhino-conjunctivitis (RC); 10 allergic sensitisation (AS); 10 type 1 diabetes mellitus (T1DM); one studied juvenile idiopathic arthritis (JIA), and one studied inflammatory bowel disease (IBD). The characteristics of included studies that investigated allergic outcomes are summarised in Table 1, whilst those of studies that investigated autoimmune outcomes are presented in Table 2.

1.4. Dietary exposures studied

The majority of the studies included in this report examined the association between several foods and outcomes of interest. Dietary exposures that did not fit the characteristics of those included in the other three reports are included here. Alcoholic and non-alcoholic beverages such as alcohol, coffee, tea, and sterilised water were included in addition to individual foods, food groups, dietary patterns and dietary micro/macronutrients. Fats, fatty acids and specific foods rich in fatty acids are not included as they are covered in a separate report.

Table 3 summarises the types of approaches used by each study to ascertain dietary intake. The majority of the studies used some form of questionnaire, although it was not always possible to confirm if the questionnaires were a) designed for the specific study, and b) whether the questionnaire had been validated or piloted in any form.

1.5. Dietary assessment and comparators

Dietary assessment was performed via questionnaire in all the studies included in this report. Food intake was often analysed by deriving dietary patterns, though the definitions and methodological approaches to derive those patterns varied across studies. In some cases dietary patterns were derived using Principal Component Analysis (PCA), whereas in other studies the use of term ‘pattern’ only meant grouping certain foods according to their similarities e.g. Mediterranean foods. The intakes compared and their cut-offs varied greatly between studies, which made meta-analyses only rarely possible. We have illustrated the main comparison levels used in the studies in the tables within each section.

1.6. Presentation of findings

We created a summary Table of Study Characteristics with key study features separating them by allergic (Table 1) and autoimmune (Table 2) outcomes. There are seven main sections that summarise the findings for each outcome: atopic dermatitis (AD), food allergy (FA), lung function (LF), wheeze, rhino-conjunctivitis (RC), allergic sensitisation (AS), type I diabetes mellitus (T1DM), inflammatory bowel disease (IBD), and juvenile idiopathic arthritis (JIA). As most of the studies included in this report had data that could not be combined in a meta-analysis, a narrative table summarising study findings is provided at the end of each section.

1.7. Risk of bias assessment

The risk of bias in included cohort and case control studies was assessed using a modified version of the National Institute for Clinical Excellence (NICE) methodological checklist for cohort and case-control studies, respectively (1). Key domains were:

- Selection Bias (low if cases and controls were selected from similar populations, if the participation rate was ≥80%, or <80% but investigators explored and adjusted for differences between the characteristics of participants and non-participants);
- Assessment Bias (low if validated and reliable tools were used to assess exposure and outcome), and;
- Confounding Bias (low if most likely confounders are identified and taken into account in study design and analysis).

Observational studies were considered at low overall risk of bias where the risk of bias was judged to be low for all 3 key domains for selection, assessment and confounding bias. For assessment of Confounding Bias, factors that we expected to be adjusted for within studies of allergic outcomes were: siblings (parity or birth order or family size); gender; age at outcome assessment; disease risk based on family history; maternal or household smoking (asthma/wheeze outcomes); maternal age; maternal education or socioeconomic status; mode of delivery. For studies on autoimmune outcomes we expected matching and/or adjusting for gender, age, address, socioeconomic status, smoking and disease risk. We also assessed possible Conflict of Interest, this being judged as low where there was no evidence of industry involvement in study design, analysis, interpretation or publication, and no evidence that study authors received remuneration from relevant industry partners for other activities. Risk of conflict of interest bias was low in all studies presented in this report, so conflict of interest bias was not included in the risk of bias summary figures. A Risk of Bias Figure is presented in each outcome section, which summarises the risk of bias in all included studies reporting that outcome, whether presented in meta-analysis forest plots, in the narrative table or both.

1.8. Key findings

i. Overall risk of bias was low or unclear for the majority of the outcomes assessed.

The overall bias was considered to be low in the majority of the studies on atopic dermatitis, food allergy, wheeze, allergic sensitisation, and for autoimmune diseases. In several studies it was unclear whether adjustment for potential confounders had been made, which was the main factor influencing the 'unclear' assessment in this domain for some studies.

ii. There was limited opportunity to meta-analyse results

The large variations observed in the way data were reported made meta-analysis possible for only a few dietary exposures relevant to atopic dermatitis, rhino-conjunctivitis and Type I Diabetes Mellitus. Each section includes a table that summarises the main characteristics and findings of those studies that were not eligible for meta-analysis, and this represents the majority of the evidence in all sections of the report.

- **There was very little evidence suggesting that any of the foods included in this report were associated with allergic or autoimmune diseases.**

Allergic outcomes

- One prospective cohort study reported that maternal intake of yoghurt during pregnancy is associated with reduced rhino-conjunctivitis and reduced AD at age 3 years.
- One cross-sectional study reported that intake of farm milk during infancy is associated with reduced RC and reduced wheeze in childhood.
- One cross-sectional study reported that infant farm milk intake in the first year of life is associated with reduced AS-Aero as measured by specific IgE antibody testing.
- One study reported that a Mediterranean diet during pregnancy is associated with reduced AS-Aero at age 6.5, as measured by specific IgE blood testing

Autoimmune outcomes

- One case control study with a high risk of assessment bias, reported that consumption of nitrosamine-rich foods during pregnancy is associated with TIDM.

We found no evidence for associations between other maternal or infant dietary exposures and allergic or autoimmune outcomes.

1.9. Conclusions

Overall we found no consistent evidence for associations between maternal or infant diet and allergic or autoimmune outcomes in this report. Some single studies reported significant associations, but these require replication.

Table 1 Characteristics of included studies on allergic outcomes and infant or maternal intake of other foods

Study	Design	N/N cases	Country	Type of food or nutrient measured	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Willers, 2007 (2)	PC	1212	Netherlands	Whole grain products	Q	AD, RC, and wheeze: Parent reported (ISAAC Q); LF: Spirometry; SPT any; Rec wheeze: DD asthma	5	**Aberdeen birth cohort**: Population based birth cohort with pregnant women recruited 1997-99 while attending a hospital antenatal clinic at ~12weeks gestation
Shaheen, 2009 (3)	PC	9516	UK	Dietary Patterns: 'Traditional'; 'Health Conscious'; 'Processed'; 'Confectionery'; 'Vegetarian'; 'Processed'; 'Vegetarian'	Q	Rec wheeze: Parent reported persistent wheeze; DD asthma; AD: Parent reported; LF-BHR slope: Spirometry; LF-FEV_1: RC: Parent reported; SPT aero; Total IgE	0.5, 2.5, 3.5, 7, 7.5	**ASLPAC study**: Population based birth cohort study, of mother-child pair recruited in 1991-1992
Fergusson, 1990 (4)	PC	1067	New Zealand	Cereal, meat	R/D/ Q	AD: Physician assessment; AD: DD , duration of > 3years and use of regular medication	10	**CHRISTCHURCH CHILD DEVELOPMENT STUDY:** A cohort of children born in the Christchurch urban region New Zealand during 1977

Study	Design	N/N cases	Country	Type of food or nutrient measured	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Bisgaard, 2009 (5)	PC	354	Denmark	Alcohol	Q	AD: Physician assessment	3	**COPSAC study**: Healthy newborns of mothers with a history of doctor-diagnosed asthma recruited in Copenhagen, Denmark between 1998 and 2001
Linneberg, 2004; (6) Maslova, 2013 (7)	PC	60466	Denmark	alcohol; artificially-sweetened non-carbonated soft drinks	I, Q	AD: Parent reported + DD; RC: DD + Medication registry ; Rec wheeze: DD asthma	1.5, 7	**DNBC study**: Population based birth cohort recruited 1996-2002 at ~12weeks gestation in Denmark

Study	Design	N/N cases	Country	Type of food or nutrient measured	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Nwaru, 2010/11/13 (8-11) Virtanen, 2010 (12) Maijaliisa, 2011 (13) Niinisto, 2012 (14) Lumia, 2011 (15)Erkkola, 2012 (16) Uusitalo 2008 (17)	PC	5619/237	Finland	Various cereals, dairy products, meat, egg, alcohol, rice, tea, coffee, chocolate, sweets	Q	AD: DD, Parent reported ISAAC; RC: Parent reported (ISAAC); sIgE aero; sIgE cm; sIgE egg; sIgE food; Rec atopic wheeze: DD asthma + positive IgE; Rec wheeze: DD asthma; Wheeze; Rec wheeze: Parent reported (ISAAC Q) asthma	0.5, 5	**DIPP study**: Prospective birth cohort of children at high risk of TIDM (HLA genotype conferred susceptibility) born between 1997 and 2004 in Oulu and Tampere University Hospital Finland
Alm, 2009 (18)	PC	4941	Sweden	Dietary Pattern-Vegetarianism in the family, gluten, type of fat on bread, lactic acid (yoghurt ,fermented) vegetables, alcohol	Q	AD: Parent reported	1	**Infants of Western Sweden**: Population based birth cohort of infants born in the region in 2003

Study	Design	N/N cases	Country	Type of food or nutrient measured	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Laitinen, 2005 (19)	PC	60, 95	Finland	Dietary carbohydrates; dietary energy; dietary protein	D	AD: Physician assessment; FA cow's milk: Physician assessment	0.5, 1	Children with a family history of AD (mother, father and/or older sibling with AD, AR or asthma), who participated in a prospective allergy prevention study (probiotic intervention trial)
Zutavern, 2006; (20) Zutavern, 2008; (21) Sausenthaler, 2007 (22)	PC	2532	Germany	Cereal, milk, cheese, yoghurt	Q	AD: DD; Parent reported; sIgE food; sIgE aero; sIgE any	2, 6	**LISA study**: Population based cohort study of newborns recruited between 1997 and1999 from 4 German cities: Munich, Leipzig, Wesel, and Bad Honnef.
Marini, 1996 (23)	PC	68	Italy	Meat	Q	AD: Physician assessment + parent reported; RC: Physician assessment + parent reported; Rec wheeze: Physician assessment > 3 episodes of wheeze	1, 3	Infants with family history of allergy born in maternity wards of 3 hospitals from 1989 whose mothers were refused to participate in an allergy prevention intervention program

Study	Design	N/N cases	Country	Type of food or nutrient measured	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Chatzi, 2008 (24)	PC	468	Spain	Dietary Pattern-adherence to Mediterranean diet; cereal; dairy; meat; white meat	Q	Rec wheeze: parent reported ≥1 episodes of wheeze; Atopic wheeze: Parent reported wheeze + positive SPT; SPT aero	6.5	**Menorca birth cohort study**: Population based birth cohort with women recruited from antenatal care at all general practices in Menorca between 1997-1998
Miskelly, 1988 (25)	PC	482	UK	Meat; meat other than beef	D	AD: Physician assessment and parent reported; wheeze: parent reported	1	Infant recruited through two antenatal clinics in South Wales born to mothers with positive allergy history in at least one member of family, whose mothers were asked to participate in allergy preventive program

Study	Design	N/N cases	Country	Type of food or nutrient measured	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Morgan, 2004 (26)	PC	257	UK	Cereal; rice; rusks; desserts; meat; meat with vegetables	I	AD: Physician assessment and parent reported	1	Healthy preterm birth (<37 weeks gestational)were recruited from a cross section of socioeconomic groups in southeast England using the Royal Surrey County Hospital (Guildford), St Peter's Hospital (Chertsey), and Frimley Park Hospital (Frimley)
Bertelsen, 2013 (27)	PC	54740	Norway	Milk or yogurt products rich in probiotics	Q	AD: Parent reported; Rec wheeze: Parent reported asthma	0.5, 3	**MoBa study**: Population birth cohort with pregnant women recruited at ~17 weeks of pregnancy with children born between 2000 and 2005 in Denmark

Study	Design	N/N cases	Country	Type of food or nutrient measured	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Miyake, 2011; (28) Miyake, 2010a; (29) Miyake, 2010b (29) Miyake, 2009; (30) Satio, 2010 (31)	PC	771	Japan	Dietary patterns derived from Factor Analysis; dairy; cheese; milk; egg; meat; yoghurt	Q	AD and wheeze: Parent reported (ISAAC Q) wheeze; AD: DD	2, 0.33, 2	**OMCHS study**: Population birth cohort with pregnant women between the 5-39th week of pregnancy recruited from a university hospital and three obstetric hospitals in municipality of Osaka between 2001 and 2003

Study	Design	N/N cases	Country	Type of food or nutrient measured	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Roduit, 2012 (32)	PC	1041	Austria, Finland, France, Germany, and Switzerland	Cereal; bread; chocolate; cake; Farm milk' - either boiled or not boiled; meat	D	AD: DD	1, 4	**PASTURE study**: Population based birth cohort with women recruited in third trimester of pregnancy from rural areas in 5 European countries (Austria, Finland, France, Germany, and Switzerland) and were divided into 2 group: those who lived or worked on family run farms and those not living on a farm of the same area

Study	Design	N/N cases	Country	Type of food or nutrient measured	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Willers, 2008 (33)	PC	2818	The Netherlands	milk; egg	Q	Wheeze and rec wheeze: Parent reported (ISAAC Q) wheeze; Rec wheeze: DD asthma + medication and/or current symptoms	8	**PIAMA study**: Population based birth cohort of children born in 1996/97 after prenatal recruitment through prenatal clinics in the northern, middle and southwestern part of the Netherlands. The children were allocated to an intervention study or to a natural history study depending on their family risk for allergy
Lange, 2010 (34)	PC	1376	USA	Dietary Pattern derived from Principal Component Analysis - Alternate Healthy Eating Index for pregnancy (AHEI-P); Adherence to intake of Mediterranean foods	Q	DD asthma; rec wheeze: Parent reported wheeze in at least one questionnaire (1,2,3 years old), AD: DD	3	**Project Viva study**: Population based birth cohort with pregnant women at <22 weeks of gestation recruited from 8 obstetric offices of a large multispecialty suburban/urban group practice in eastern Massachusetts US between 1999 and 2002

Study	Design	N/N cases	Country	Type of food or nutrient measured	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Andreasyan, 2007 (35)	PC	498	Australia	Honey	Q	AD, RC and wheeze: Parent reported (ISAAC Q); SPT any	9	**CARHS study**: Some of the participants in an existing cohort ('THIS') of infants at high risk for sudden infant death syndrome born in 1988-1989 were identified in the northern region of Tasmania through school records
Narita, 2011; (36) Ohya, 2011 (37)	PC	1463	Japan	dietary energy	Q	AD, and wheeze: Parent reported (ISAAC Q)	3	**T-CHILD study**: Population based birth cohort of Japanese mother-infant pairs with women recruited ~ second trimester in Tokyo

Study	Design	N/N cases	Country	Type of food or nutrient measured	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Wang, 2007 (38)	PC	1760	Taiwan	Ginseng	Q	AD: DD	0.5	Pilot study of Taiwan National Birth Cohort Study: All postpartum women and newborns from these 29 towns were recruited with the multistage stratified systematic sampling design to obtain the representative samples from the national birth registration data in 2003
Harris, 2001; (39) Zutavern, 2004 (40)	PC	604, 622	UK	Rice; cereal; meat	Q	AD: DD; AD: Visible AD on examination; SPT aero; rec wheeze: Parent reported wheeze; rec wheeze: parent reported	2, 5.5	Population based birth cohort of newly pregnant women who presented at one of three general practices in Ashford, Kent UK between 1993 and 1995; Population based birth cohort of infants from all pregnant women presenting in three general practices in Ashford, Kent UK between 1993 and 1995

Study	Design	N/N cases	Country	Type of food or nutrient measured	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Dubakiene, 2012 (41)	PC	128	Lithuania	Maternal allergeni food avoidance [more than one foo group]: milk and egg	Q	SPT	1	The Lithuanian birth cohort "Alergemol" (n=1158) was established as a part of the multi-centric "EuroPrevall" birth cohort that recruited over 12000 newborns in 9 European countries. The "EuroPrevall" cohort was established in 2005–2009 using a standardised approach across 9 European countries
Oliver, 2010; (41)	NCC	117/39	UK	Dietary carbohydrates; Wheat; dietary energy; dietary protein	D	FA any: DD with DBPCFC	1	This case-control study was nested in the **EuroPrevall study** (UK birth cohort): cases were infants with food allergy, each matched to two controls.

Study	Design	N/N cases	Country	Type of food or nutrient measured	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Sariachvili, 2010 (42)	NCC	557/252	Belgium	Cereal, meat	Q	AD: Parent reported (ISAAC Q)	4	**PIPO Cohort study**: cases and controls with data regarding development of eczema and timing of introduction of solid foods were identified from this prospective cohort: Belgium.
Butiene, 2011(43)	NCC	43	Lithuania	Maternal allergenic food avoidance [more than one food group]: milk and egg	I	SPT/sIgE milk or egg	1	Children in Lithuanian birth cohort study, gestational age at least 34 weeks and APGAR score ≥7 at 5 min; 51.3% boys; <1year; sensitised to food allergens and their age-matched controls
Dai, 1993 (44)	CC	70	China	Maternal allergenic food avoidance [more than one food group]: any	Q	Rec wheeze (unclear)	0.5	Children from the community and they had to reside there the last year

Study	Design	N/N cases	Country	Type of food or nutrient measured	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Oliveti, 1995 (45)	CC	262/131	USA	Alcohol	R	Rec wheeze; DD asthma	4-9	Cases & controls were identified from rosters of patients followed up at the Rainbow Babies & Children's Hospital continuity care clinic, Ohio.
Lopez Campos, 2001 (46)	CC	75/58	Mexico	chocolate; mango	Q	Rec wheeze: DD asthma	6-10	Asthmatic patients were recruited from Allergy clinics and control patients from familial medicine clinics of Hospital de Especialidades, Mexico.
de Batlle, 2008 (47)	CS	1476/402	Mexico	Dietary pattern intake in pregnant mothers	Q	Wheeze: parent reported wheeze; Rec wheeze: parent reported asthma; RC: parent reported	6-7	Participants were recruited from a random sample of children in primary school in the Mexicali province, Mexico.

Study	Design	N/N cases	Country	Type of food or nutrient measured	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Dela Bianca, 2012 (48)	CS	467/467	Brazil	Processed food	Q	Rec wheeze: parent reported ≥1 episode of wheezing in the past year	1	Participants were infants aged from 12 to 15 months who attended 9 selected health centres for routine immunisations.
Riedler, 2001 (49)	CS	812/unclear	Austria, Germany, and Switzerland	Farm milk/environment	I	AD: DD; RC: parent reported; sIgE aero; Rec wheeze: DD asthma; asthma ≥1 episode of wheezing in the past year	9	**ALEX STUDY TEAM**: cases were children of farming families and controls of non-farming families from the study schools: Austria, Germany, & Switzerland
Castro-Rodriguez, 2010 (50) Binkley, 2011(51)	CS	1409/594	Spain	Mediterranean diet; industrial food	Q	Wheeze: Parent reported (ISAAC Q) wheeze	1.4	**EISL study**: Spanish population attending primary healthcare clinics, cases with wheeze in first year of life and controls without: Spain

PC Prospective cohort study; Q questionnaire; AD atopic dermatitis; ISAAC International Study of Allergy and Asthma in Children; AS allergic sensitisation; SPT skin prick test, sIgE specific IgE; DD Doctor diagnosis (community); Physician assessment is assessment by study physician; AR allergic rhinitis, FA food allergy; CS cross-sectional study

Table 2 Characteristics of included studies on autoimmune diseases and infant or maternal intake

Study	Design	N/N cases	Country	Type of dietary fat measured	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Wahlberg, 2006; (52) Brekke, 2010; (53)	PC	9414/44	Sweden	Coffee	Q	CD: DD + IgA-tTG +symptoms; TIDM: Islet autoimmunity (GADA and/or IA2A)	8.4, 2, 5	**ABIS study**: Population based birth cohort of children born in Southeast Sweden between 1997 and 1999
Wahlberg, 2006 (54)	PC	8715	Sweden	Maternal allergenic food avoidance [more than one food group]: all dairy	Q	TIDM: Islet autoimmunity (GADA and/or IA2A)	2.5	Born between Oct 1997 and Oct 1999 in South East Sweden. Representative of general Swedish population

Study	Design	N/N cases	Country	Type of dietary fat measured	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Nwaru, 2013; (8) Virtanen, 2011; (55) Nwaru, 2010; (9) Virtanen, 2011/10; (56) Virtanen, 2006; (57) Nwaru, 2011; (13) Niinisto, 2012; (14) Lumia, 2011; (15) Erkkola, 2012; (16) Uusitalo, 2008; (17) Nwaru, 2010 (10)	PC	561	Finland	Wheat , Rye, Oats, Barley, Other cereals (maize, rice, millet, and buckwheat); cereal; Other cereals (maize, rice, millet, and buckwheat); milk; milk and dairy; cheese; meat; egg; alcohol; rice; tea; coffee; chocolate; chocolate and sweets; dairy	Q	TIDM: Islet autoimmunity (ICA plus GADA and/or IA2A and/or IAA)	0.5, 5	**DIPP study**: Prospective birth cohort of children at high risk of TIDM (HLA genotype conferred susceptibility) born between 1997 and 2004 in Oulu and Tampere University

Study	Design	N/N cases	Country	Type of dietary fat measured	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Lamb, 2008 (58) Lamb, 2013; (59) Norris, 1996; (60)	PC, NCC	1698/49	USA, UK, Australia	rice; oats; wheat, rye, oats, cereal, meat	I, Q	CD: positive IgA-tTG on 2 consecutive visits or a positive small bowel biopsy after only a single tTG-positive visit. Secondary only those children who had a biopsy positive, as defined by Marsh score; TIDM: DD; TIDM: Islet autoimmunity (GADA and/or IA2A and/or IAA)	4; <5; <7; 9; <10; 15 ; unclear	**DAISY study:** Prospective birth cohort of children at increased risk for T1DM (relative with T1DM via registries and hospital records) recruited from 1993 to 2004 in Denver, Colorado US were screened for human leukocyte antigen (HLA) genotype associated with celiac disease and TIDM; DAISY: cases & their non-diabetic siblings, as controls, taken from Barbara Davies Centre Colorado, other diabetes care clinics & Colorado IDDM registry.

Study	Design	N/N cases	Country	Type of dietary fat measured	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Harsunen, 2012 (61)	NCC	33/33	Germany	Dietary energy intake	D	TIDM	<18	**BABYDIET study**: cases were study children who developed islet autoantibodies and T1DM during BABYDIET study follow-up and controls were children from the same original study cohort who did not: Germany.
Baron, 2005 (62)	CC	444/222	France	Flour, meat	I	IBD-CR: DD; IBD-UC: DD	<17	Cases with Crohn's disease were identified from the EPIMAD registry with matched controls from the same area identified by random digit dialling: France.
Virtanen, 1994 (63)	CC	1136/600	Finland	Coffee	Q	TIDM: DD	≤14	**Childhood Diabetes in Finland**: cases were newly diagnosed T1DM with matched controls selected from the general population

Study	Design	N/N cases	Country	Type of dietary fat measured	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Ellis, 2012 (64)	CC	655/246	Australia	Alcohol; coffee	Q	JIA: DD ILAR criteria	0-18	**CLARITY study**: cases were recruited during a clinic visit to Royal Children's Hospital, with diagnosed JIA using ILAR criteria: controls were patients in for elective surgery, also at the Royal Children's Hospital Day Surgery Unit: Australia
Visalli, 2003 (65)	CC	900/150	Italy	meat; tea; coffee	Q	TIDM: DD WHO criteria	12	**EURODIAB Italy study:** Cases with T1DM selected from within the EURODIAB ACE study, born 1977-89, with controls selected from school records for the same period

Study	Design	N/N cases	Country	Type of dietary fat measured	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Majeed, 2011 (66)	CC	395/96	Iraq	Coffee; tea	Q	TIDM: DD	1.5-17	Cases were T1DM patients admitted to hospitals or primary health centres in Basrah and controls were attendees to outpatients of the same institutions for non-diabetic complaints: Iraq
Rosenbauer, 2007/2008 2007 (67, 68)	CC	2631/760	Germany	coffee	Q	TIDM: DD	<5	German study of newly diagnosed T1DM cases selected from a hospital-based surveillance system ESPED and controls from local registration office records.
Sipetic, 2003 (69)	CC	315/105	Serbia	Alcohol; coca cola, nitrosamine-rich foods, coffee	Q	TIDM: maternal report	1-16	Cases and controls were children admitted to hospital due to allergic conditions 1994-97, Serbia

Study	Design	N/N cases	Country	Type of dietary fat measured	Exposure assessment	Outcomes	Age at outcome (years)	Population characteristics
Sipetic, 2005 (70)	CC	315/105	Serbia	Alcohol; coca cola; nitrosamines; tea; coffee	Q	TIDM: DD WHO criteria	≤16	Cases were children hospitalized with new diagnosis of T1DM in Belgrade, with controls selected from a population of children treated for skin disease as outpatients: Serbia
Strotmeyer, 2004 (71)	CC	690/247	China	steamed bread; rice; noodles; meat	Q	TIDM: DD WHO criteria	9.7	**DiaMond study**: WHO Multinational Project for Childhood Diabetes (cases selected from T1DM incidence registries 1985-98 and matched controls from locally resident populations (>95%).

PC Prospective cohort study; Q questionnaire; CC case-control study; SPT skin prick test, sIgE specific IgE; DD Doctor diagnosis (community); Physician assessment is assessment by study physician; AR allergic rhinitis, FA food allergy, T1DM Type 1 Diabetes Mellitus, RC retrospective cohort, JIA juvenile idiopathic arthritis; ILAR International League of Associations for Rheumatology

Table 3 Dietary instrument used to ascertain infant or maternal intake of other foods

First author, year	Dietary assessment used
Alm, 2009	Questions on maternal diet and timing of food introduction and allergic diseases. Food questions asked at 6 and 12 months
Andreasyan, 2007	Parental questionnaire including the ISAAC respiratory and dietary questions
Baron, 2005	Trained researchers interviewed child and mother
Bertelsen, 2013	FFQ
Binkley, 2011	Additional questions on diet added to anaphylaxis survey questionnaire
Bisgaard, 2009	Information collected during personal interviews at the clinical research unit during pregnancy by doctors with paediatric training
Brekke, 2010	22-item FFQ
Butiene, 2011	Self-administered parental questionnaire. Follow-up with telephone interview if there were missing data
Castro-Rodriguez, 2010	Environmental questionnaire which included food consumption of oil type used for cooking or dressing salads
Chatzi, 2008	Spanish version of the validated EPIC-Norfolk FFQ
De Batlle, 2008	Validated and adapted FFQ with 70 food items asking about the diet of the children in the last 12 months
Dubakiene, 2012	Data collected pre- and post-natal. Questionnaire with questions on food intake and nutritional supplement as well as other relevant risk factors and co-morbidities
Ellis, 2012	General questionnaire with dietary questions
Erkkola, 2012	Retrospective diary records of foods eaten during the month preceding delivery (8th month of pregnancy)
Fergusson, 1990	Child and maternal records kept at Plunket Community Nursery were reviewed to obtain estimates of the types of solid food that the child was given in first 4 months of life
Harris, 2001	Questionnaire - Trained nurses visited mothers and asked about breastfeeding and food introduction practices
Harsunen, 2012	3-day dietary records (after termination of breastfeeding)

First author, year	Dietary assessment used
	collected every 3 months
Lamb, 2008 and 2013	Willet FFQ (146 food items)
Laitinen, 2005	Four day food diaries completed by parents or personnel at day-care
Lange 2010	Self-administered 166-item semi-quantitative FFQ, answered twice, at 1st and 3rd trimester of pregnancy
Leermakers, 2013	Modified version of a semi-quantitative FFQ
Linneberg, 2004	Interview at 12 and 30 weeks of gestation, during which the mother answered a question on alcohol intake habits
Long, 1986	Unclear
Lopez-Campos, 2001	Questionnaire
Lumia, 2011	Validated, self-administered, semi-quantitative 181-item FFQ
Maslova, 2013	A validated 360-itemsemi-quantitative FFQ completed around gestation week 25 and covered intake during the previous four weeks
Maijaliisa 2011	Validated FFQ enquiring about maternal diet in 8th month pregnancy
Majeed, 2011	Specially designed study questionnaire for the study, which included questions on maternal habits, including maternal coffee/tea consumption habits
Marini, 1996	Parental questionnaire
Miyake, 2009, 2010, and 2011; and Saito 2010	Self-administered DHQ that assessed dietary habits during the preceding month (150 foods); dietary patterns derived with PCA
Miskelly, 1988	Feeding diaries were completed for the babies, dietary information being supplemented by notes made by the dietician
Morgan, 2004	FFQ administered by the study midwives to the mother on enrolment and at four monthly intervals to 12 months post-term
Narita, 2011	Dietary history questionnaire administered in the 3rd trimester of pregnancy
Niinisto, 2012	Validated FFQ capturing maternal diet during the 3rd month of lactation

First author, year	Dietary assessment used
Norris 1996	Infant diet questionnaire prior to auto-antibody knowledge. List of milks commonly given to infant in the first 15 months
Nwaru, 2010, 2011, and 2012	Validated 181-item FFQ
Nwaru 2013	Repeated age-specific dietary questionnaires at the ages of 3, 6, and 12 months and a follow-up "age at introduction of new foods-form"
Ohya 2011	Self-administered DHQ
Oliver, 2010	Food diaries with qualitative and quantitative data completed and returned every 4 weeks in the first year of life
Oliveti, 1995	Medical obstetric records had data on maternal alcohol intake as part of other variables registered during pregnancy
Riedler, 2001	Interview with parents to ascertain children's exposure to stables and farm and pet animals; duration of breastfeeding; timing of consumption
Roduit, 2012	Dietary intake reported by parents in monthly diaries between the 3rd and 12th month of life
Rosenbauer, 2007 and 2008	Self-administered parental questionnaire. Follow-up done with telephone interview if data missing
Sariachvili, 2010	When children were 1 year old, parents provided information on introduction of specific food item in weeks by answering the following question 'How old (in weeks) was your child when you gave him/her the following food items to eat or drink?'
Sausenthaler, 2007	Semi-quantitative FFQ capturing intake in the last 4 weeks of pregnancy
Shaheen, 2009	FFQ to assess maternal intake of 110 foods (43 groups) at 32 weeks of gestation; dietary patterns derived with PCA
Sipetic, 2003 and 2005	A main questionnaire was used, which covered a variety of parental and neonatal factors including diet
Strotmeyer, 2004	Retrospective questionnaire (yes/no), completed by primary caregiver for the age ranges of <1, 1–3, 4–6, and 7–12 months
Visalli, 2003	Parent-completed environmental questionnaire
Virtanen, 1994; 2006; 2010, and 2011; Uusitalo, 2008	A validated 181 food item FFQ

First author, year	Dietary assessment used
Wang, 2007	Questions on dietary intake included in environmental questionnaire
Wahlberg, 2006	Parental questionnaire at birth, 1 and 2.5 years
Willers, 2007	Semi-quantitative FFQ (Version 5.4 of the Scottish Collaborative Group FFQ) mailed at 32 weeks gestation (150 items divided into 20 food groups
Willers, 2008	The pregnancy questionnaire contained a question on frequency of consumption: 'How often did you consume vegetables, fresh fruit, fish, egg, milk, milk products, nuts, and nut products such as peanut butter during the last month?'
Zutavern, 2006 and 2008	A 48 food item questionnaire on timing of food introduction was asked to parents when babies were 6 months old
Zutavern, 2004	Information on dietary intake was obtained through a question included in the 1st year questionnaire: "When did you start feeding your son/ daughter the following foods?"(9 items)

EPIC= The European Prospective Investigation into Cancer Study

FFQ= Food frequency questionnaire

ISAAC=International Study of Allergy and Asthma in Children

PCA= Principal component analysis

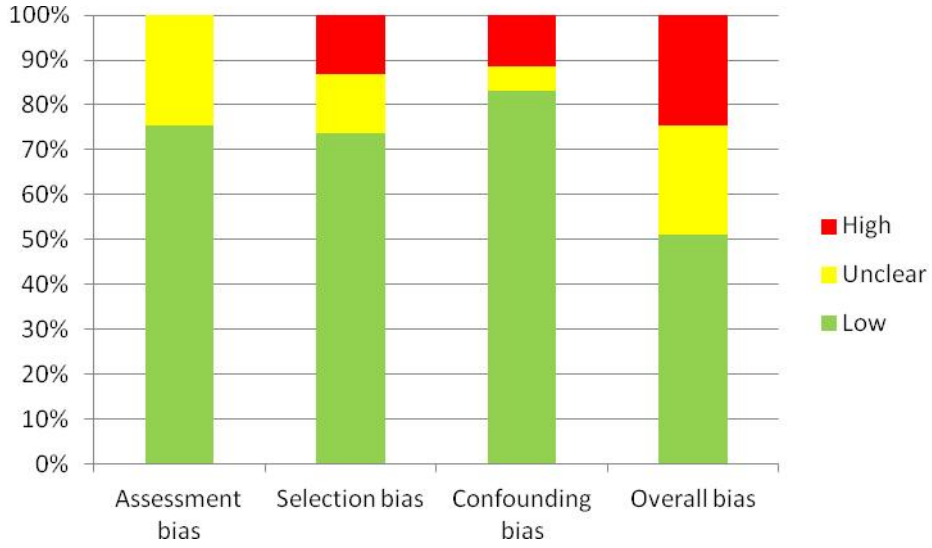
DHQ= Diet history questionnaire

2. Other foods and risk of atopic dermatitis

2.1. Overall risk of bias between other foods and atopic dermatitis

The overall risk of bias in the studies investigating the association between atopic dermatitis and various foods was considered to be low. Most studies had low risk of bias in all the domains evaluated. Just over 10% of studies had a high risk of confounding bias due to the lack of controlling for potential confounders (Figure 1).

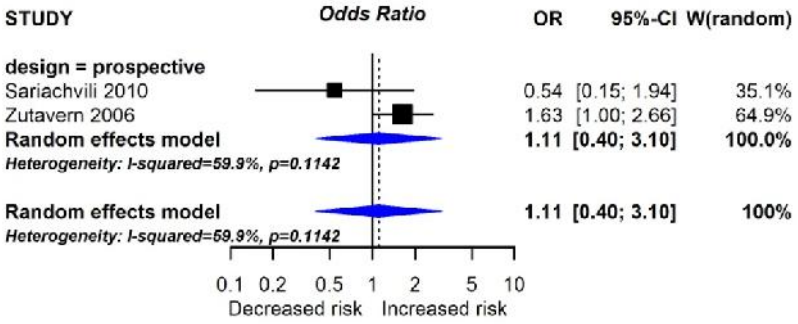
Figure 1 Risk of Bias in studies of other food intake and atopic dermatitis



2.2. Introduction of meat into infant's diet and risk of atopic dermatitis

The studies of **Sariachvili** (**2010**) and **Zutavern** (**2006**) had comparable data to examine the pooled effect estimate of timing of meat introduction and risk of atopic dermatitis in children aged 0-4 years old (Figure 2). The generic term 'meat' was used when assessing exposure. There was no evidence of an association between this outcome and meat introduction.. Differences in exposure assessment may account for the high statistical heterogeneity seen.

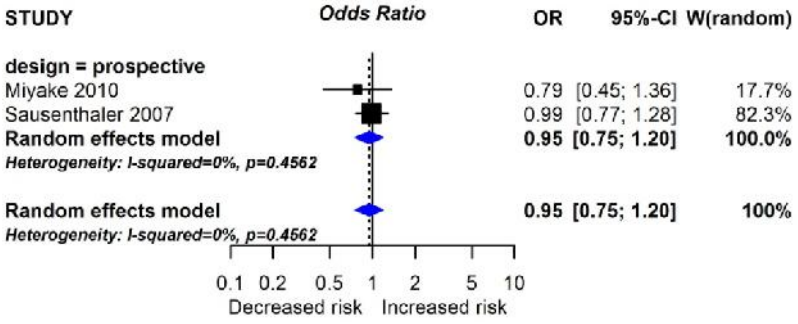
Figure 2 Introduction of meat in months 0 to 4 and risk of atopic dermatitis in children aged 0 to 4 years old



2.3. Dairy intake (maternal) and risk of atopic dermatitis

Figure 3 shows the pooled estimates from two prospective cohort studies (**Miyake 2010** and **Sausenthaler 2007**) that examined the association between maternal intake of yoghurt during pregnancy and risk of atopic dermatitis in children at age 0-4 years old. For both dietary exposures there was no evidence of an association with this outcome. There was no heterogeneity between studies (I^2=0.0%)

Figure 3 Maternal intake of yoghurt (highest vs. lowest) and risk of atopic dermatitis in children aged 0 to 4 years old



2.4. Studies not eligible for meta-analysis

Table 4 summarises the main characteristics and findings of the studies examining the association between various types of dietary exposures and risk of atopic dermatitis. The main dietary exposures studied included intake of confectionary products (e.g. chocolate, cakes, and desserts) (**Roduilt 2012; Morgan 2004; Maijaliisa 2011; Andreasyan 2007**). A

further three studies used different methods to characterise dietary patterns i.e. Healthy Index (**Lange 2010)** or Principal Component Analysis (**Shaheen 2009; Miyake 2011**). Infant exposure to farm milk (unclear subtypes but assumed to be unpasteurised) was included in the studies of **Roduit (2012)** and **Riedler (2001)**. Six studies investigated meat **(Roduilt 2012; Ferguson 1990; Zutavern 2006; Zutavern 2004; Miskelly 1998; Morgan 2004)**. Two studies investigated macro-nutrients or total energy intake **(Laitinen 2005, Ohya 2011),** and three studies investigated maternal intake of alcohol **(Linneberg 2004; Alm 2009; Bisgaard 2009).** One study investigated timing of introduction of rice in the infant **(Harris, 2001).** One study **(Bertelsen, 2013)** investigated maternal intake of probiotics and showed probiotic intake was associated with reduced AD in the offspring at age 6 months. Overall, there was no evidence to suggest that dietary intake of any of these (by the mother or the infant) could influence risk of AD.

Conclusion

The finding that intake of probiotic-rich milk products during pregnancy is associated with reduced AD requires replication. Overall we found no consistent evidence that other infant or maternal dietary exposures or dietary patterns are related to AD in the child.

Table 4 Studies investigating the association between other foods and atopic dermatitis which were not eligible for meta-analysis

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					INFANT INTAKE		
Laitinen, 2005 (19)	PC	AD			**Total infant daily energy intake (various measurements) (continuous):**		
				60	Total energy intake (mega joules)		NS
			0.5	60	% of energy intake as carbohydrate		NS
			1	95	Total energy intake (mega joules)		NS
			0.5	60	Energy intake (as kilo joule per day)		NS
			0.5	60	Energy intake (as kilo joule/ kg body weight)		NS
			1	95	Kilo joule per day energy intake		NS
			0.5	60	Protein intake (continuous)		NS
			0.5	60	% of energy intake as protein (continuous)		NS
			1	95	Protein intake (g) as mega joule per day energy intake (continuous)		NS

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
Roduit, 2012 (32)	PC	AD			**Intake in infancy (none vs introduction in the 1st year of life):**		
					Chocolate	OR	1.49 (0.85-2.61)
					Cake (None vs yes <8 Months)	OR	1.33 (0.66-2.68)
			4	483	Chocolate/ introduced into diet >12 months vs. 3 to 12 months	OR	1.37 (0.87-2.16)
			4	912	Cake/ introduced into diet >8 months vs. 3 to 8 months	OR	1.33 (0.83-2.15)
			1	912	Chocolate/ introduced into diet >12 months vs. 3 to 12 months	OR	**1.52 (1.02-2.25)**
			4	912	Cake/ introduced into diet >8 months vs. 3 to 8 months	OR	1.43 (0.98-2.08)
			1	912	Cake introduced into diet / >8 months vs. 3 to 8 months	OR	1.39 (0.93-2.06)
Morgan, 2004 (26)	PC	AD	1	257	Desserts/time of introduction (continuous)	OR	NS

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
Andreasyan, 2007 (35)	PC	AD	9	699	Introduction of confectionery in months 0 to 4 vs later	OR	2.27 (0.61-8.44)
					Meat/ no intake in the first 8 months vs. <8 months (high risk infants)	OR	1.23 (0.56-2.70)
				1,041	Meat/ no intake in the first 8 months vs. <8 months (low risk infants)	OR	0.99 (0.41-2.37)
Roduit, 2012 (32)	PC	AD	4	483	Meat/ introduced into diet >8 months vs. 3-8 months (onset after 1st year of life)	OR	1.15 (0.65-2.03)
			1	912	Meat/ introduced into diet >8 months vs. 3-8 months	OR	1.41 (0.93-2.14)
Fergusson, 1990 (4)	PC	AD	.33-10	1,067	Meat/introduced >4 months vs. ≤4 months	OR	NS
Nwaru, 2013 (8)	PC	AD	0-0.5	3,109	Meat introduction (median month of introduction in those with AD vs those with no AD)	OR	P-value <**0.001**
Nwaru, 2013 (8)	PC	AD	0-0.5	2,951	Meat introduction (median month in those with AD vs non AD) infants with parental history of allergy	OR	NS
					Meat/ 0-4 months vs. >6 months	OR	1.20 (0.79-1.83)
Zutavern, 2006 (20)	PC	AD	0-2	2,532	Meat/ 0-4 months vs. 5-6 months	OR	1.41 (0.88-2.25)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
Zutavern, 2004 (40)	PC	AD	5 ½	642	Introduction of meat in months 5 to 7 vs earlier	OR	1.08 (0.78-1.51)
Miskelly, 1988 (25)	PC	AD	1	482	Meat/early months introduction vs later (continuous)	OR	NS
					Meat other than beef/ early months introduction vs later (continuous)	OR	NS
Morgan, 2004 (26)	PC	AD	1	257	Meat/number of weeks from term meat introduced (continuous)	OR	NS
					Meat with vegetables/number of weeks from term meat with vegetables introduced (continuous)	OR	NS
Marini, 1996 (23)	PC	AD	3	80	Introduction of meat in months 5 to 7 vs earlier	OR	**0.18 (0.04-0.88)**
Alm, 2009 (18)	PC	AD	1	4941	Lactic acid (yoghurt, fermented vegetables, etc consumption first year / more than 3 times/ week vs. ≤3 times/per week	OR	1.14 (0.96-1.34)
					Consumption of dairy in infants (often vs. Rare)	HR	0.94 (0.67-1.31)
					Consumption of fermented food (rare vs. often)	**OR**	**2.86 (2.21-3.69)**

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
Roduit, 2012 (32)	PC	AD	4	1,041	'Farm milk' (either boiled or not boiled) none in 1st year life vs. farm milk in infant diet	OR	1.50 (0.78-2.89)
Riedler, 2001 (49)	CS	AD	9	812	Exposed to farm milk in the 1st year of life vs neither farm milk or stable exposure	OR	NS
					Infant intake of dairy foods (categorized at quartile points based on the distribution in 763 subject) / lowest vs. highest quartile		
			1.5-2	763	Cheese	OR	0.67 (0.38-1.16)
Miyake, 2010 (29)	PC	AD	1.5-2	763	Milk	OR	1.19 (0.69-2.06)
Harris, 2001 (39)	PC	AD	2	624	Introduction of rice in infant's diet >12 months vs earlier	OR	0.85 (0.17-1.18)
					MATERNAL INTAKE		
					Maternal alcohol intake in late (30 weeks of gestation) Beer/wine/spirits: No drinks per week/tiles vs. 0.5 drinks per week/tiles	HR	0.98 (0.82-1.17)
			0.1-1.5	10,218	No drinks per week vs. 2-3.5 drinks per week	HR	1.00 (0.83-1.21)
Linneberg, 2004 (6)	PC	AD	0.1-1.5	10,218	No drinks per week vs. 1-1.5 drinks per week	HR	1.08 (0.93-1.26)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					Maternal alcohol intake in late pregnancy (30 weeks of gestation) Beer/wine/spirits:		
					No drinks per week vs. ≥4 drinks per week	HR	1.06 (0.72-1.57)
					No drinks per week vs. 2-3.5 drinks per week	HR	1.09 (0.87-1.37)
Linneberg, 2004 (6)	PC	AD	0.1-1.5	11,357	No drinks per week vs. 1-1.5 drinks per week	HR	**1.32 (1.10-1.59)**
					Maternal alcohol intake in early pregnancy (12 weeks gestation) – Beer/wine/spirits:		
					No drinks per week vs. 1-1.5 drinks per week	HR	0.90 (0.80-1.01)
					No drinks per week vs. 0.5 drinks per week	HR	0.94 (0.83-1.06)
Linneberg, 2004 (6)	PC	AD	0.1-1.5	24,341	No drinks per week vs. 2-3.5 drinks per week	HR	1.02 (0.89-1.17)
					Dietary pattern-vegetarianism in family/ descriptive (Yes vs. No)	OR	NS
					Alcohol intake during pregnancy throughout lactation until 6 months of age (Yes vs. No)	OR	NS
Alm, 2009 (18)	PC	AD	1	4,941	Alcohol intake during lactation - 6 months of age (Yes vs. No)	OR	NS

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
Willers, 2007 (2)	PC	AD	5	1,212	Whole grain products/maternal diet during pregnancy. / low vs. High tiles	OR	NS
Maijaliisa, 2011 (13)	PC	AD	5	2,441	Chocolate/not low consumption vs. Low consumption	OR	NS
Lange, 2010 (34)	PC	AD	3	1,376	**Dietary pattern alternate healthy eating index for pregnancy (AHEI-P)/score comprised of 9 components contributing 10 possible points each:** Vegetables, fruit, ratio of white to red meat, fibre, trans fat, ratio of poly- to saturated fatty acids, folate, calcium, and iron from foods	OR	0.94 (0.82-1.08)
					Adherence to Mediterranean foods/ dairy, fish, fruit, legumes, nuts, fats, vegetables and whole grains (alcohol intake excluded) /	OR	1.00 (0.94-1.06)
					Maternal dietary pattern derived from principal component analysis (PCA) 'Prudent' pattern i.e. Fruits, tomatoes, cabbages, green leafy vegetables, poultry, and fish	OR	0.95 (0.83-1.09)
					'Processed' i.e. red meat, processed meat, refined grains, snacks, sweets, desserts, French fries, pizza	OR	1.06 (0.92-1.22)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					Maternal dietary patterns (effect estimates based on per-SD increase in dietary pattern score)		0.96 (0.88-1.05)
			7.5	7,693	'Processed'	OR	
			2.5	9,516	'Processed'	OR	0.97 (0.91-1.03)
Shaheen, 2009 (6)	PC	AD	7.5	7,693	'Traditional'	OR	0.99 (0.93-1.05)
					Maternal dietary patterns (effect estimates based on per-SD increase in dietary pattern score)		
				9,516	'Vegetarian'	OR	0.99 (0.94-1.04)
			2.5	9,516	'Traditional'	OR	1.00 (0.95-1.05)
			7.5	7,693	'Vegetarian'	OR	1.01 (0.94-1.08)
			2.5	9,516	'Confectionery'	OR	1.03 (0.98-1.08)
				7,693	'Confectionery'	OR	1.03 (0.96-1.11)
			7.5	7,693	'health conscious'	OR	1.04 (0.96-1.13)
Shaheen, 2009 (3)	PC	AD	2.5	9,516	'health conscious'	OR	**1.06 (1.00-1.12)**

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					Dietary pattern derived from factor analysis/maternal dietary habits based on intake of 150 foods in the last month / scores for each dietary pattern categorised in quartiles vs. Lowest quartile (1) scores for each dietary pattern categorised in quartiles		
			1.3 - 2	763	'Western'	OR	0.70 (0.41-1.20)
			1.3 - 2	763	'Health conscious'	OR	1.09 (0.64-1.85)
Miyake, 2011 (28)	PC	AD	1.3 - 2	763	'Japanese'	OR	1.11 (0.64-1.94)
Ohya, 2011 (37)	PC	AD	1.5	1,463	Dietary energy (continuous)	OR	NS
					Maternal intake during pregnancy / highest vs lowest quartile		
			3-4 months	771	Meat	OR	**2.59 (1.15-6.17)**
Saito, 2010 (31)	PC	AD	3-4 months	771	Dairy	OR	1.84 (0.82-4.27)

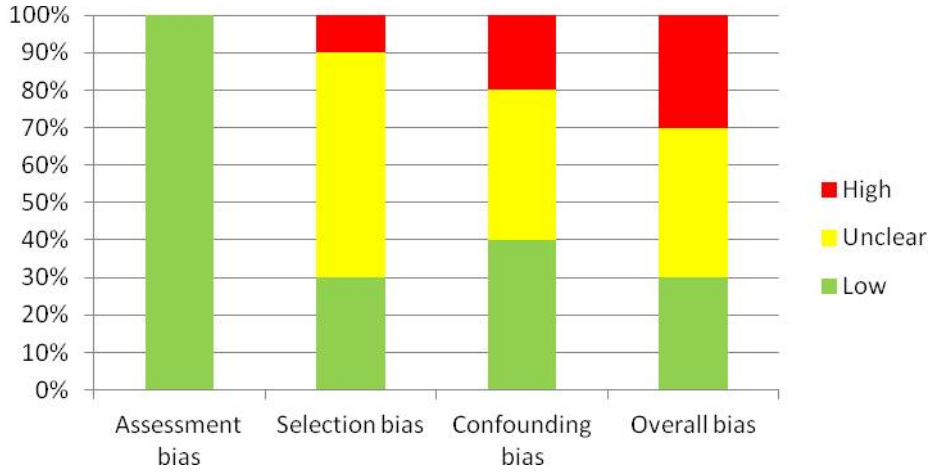
First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
Sausenthaler, 2007 (22)	PC	AD	2	2,473	**Maternal intake** of cheese during the last 4 months of pregnancy (≥4 times/week vs <2 times per week or never)	OR	0.87 (0.67-1.13)
Narita, 2011 (36)	PC	AD	3	1,344	**Maternal intake** of dairy during pregnancy (highest vs lowest quartile)	OR	NS
Bertelsen, 2013 (27)	PC	AD	0.5	40,614	Maternal intake of milk or yogurt rich in probiotics (yes vs no)	RR	**0.94 (0.89-0.99)**
Bisgaard, 2009 (5)	PC	AD	0-4		Maternal intake of alcohol (often vs. Rare)	OR	1.88 (0.94-3.75)
Wang, 2007 (38)	PC	AD	0-4		Maternal intake of tea (often vs. rare)	OR	0.59 (0.08-4.42)

3. Other foods and risk of food allergy

3.1. Overall risk of bias between other foods and food allergy

Three studies were identified in this part of the report. All studies were considered to have a low risk of assessment bias, whilst two of them had an unclear description of the selection of participants. Therefore the overall bias was considered to be low or unclear for the majority (Figure 4).

Figure 4 Risk of Bias in studies of other foods intake and food allergy



We found no data eligible for meta-analysis. Table 5 summarises the characteristics of studies with data that could not be meta-analysed. Two prospective cohort studies (**Laitinen 2005; Sausenthaler 2007**), one nested case-control study (**Oliver 2010**), investigated the association between infant intake of macro-nutrients (daily estimates) and food allergy, showing no evidence of an effect. The study of Sausenthaler also examined infant intake of dairy products and reported a statistically significant negative association with risk of food allergy. One case-control study (**Binkley, 2011**) investigated maternal avoidance of peanut intake in relation to food allergy to peanut in the offspring, but reported no association between outcome and exposure. We found no evidence of an association between risk of food allergy and dietary exposures relevant to this report.

Conclusion

We found no evidence that intake of proteins, carbohydrates or total energy is related to risk of food allergy. The finding of a single study reporting an association between dairy intake and reduced food allergy requires replication.

Table 5 Studies investigating the association between other foods and food allergy which were not eligible for meta-analysis

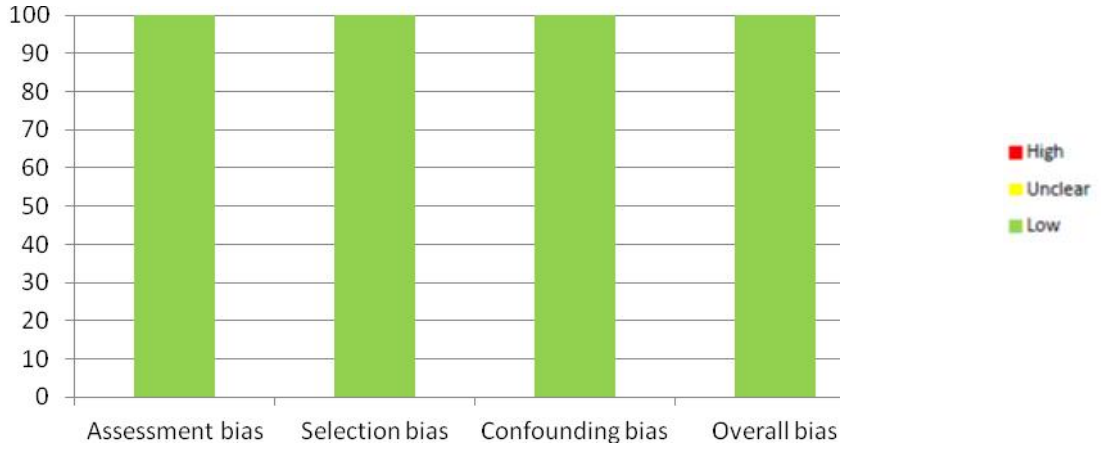
First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					Infant intake of Energy (continuous) - Total energy intake kJ/day		NS
Laitinen, 2005 (19)	PC	FA	1	95	Infant intake of Protein (continuous) - % of energy intake as Protein		NS
Sausenhaler, 2007 (22)	PC	FA	Any		Maternal intake of dairy (often vs. rare)	OR	**0.4 (0.22-0.72)**
			1	93	Dietary carbohydrate intake during the first year of life		NS
			1	93	Dietary energy intake during the first year of life		NS
Oliver, 2010 (41)	NCC	FA any	1	93	Dietary protein intake during the first year of life		NS

4. Other foods and lung function

4.1. Risk of Bias in studies of other food exposures and lung function

The prospective studies of **Shaheen (2009)** and **Willers (2007)** investigated the associations between relevant dietary exposures and measures of lung function. Both studies were considered to have a low overall risk of bias (Figure 5).

Figure 5 Risk of bias in studies of other foods intake and lung function



The study of **Shaheen (2009)** investigated the association between maternal dietary patterns and risk of bronchial hyper-responsiveness (BHR) in children from the ALSPAC cohort study at age 8-9 years old. The authors identified five types of patterns derived from PCA and there was no evidence that any of these patterns influenced the risk of BHR in the infant. There was also no association with Forced expiratory volume in 1 second (FEV_1). The authors reported weak evidence for a relationship between 'processed' foods type dietary pattern and reduced forced vital capacity (FVC). The study of **Willers (2007)** used a sample of children from the Aberdeen cohort study, a population-based birth cohort with pregnant women recruited from antenatal hospital clinics. They found no association between maternal cereal intake and measures of lung function in their children (Table 6).

Conclusion

Overall we found no consistent evidence to suggest that dietary patterns during pregnancy influence BHR or lung function in children.

Table 6 Studies investigating the association between other foods (dietary exposure) and lung function (outcome) which were not eligible for meta-analysis

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p>0.05)
					Maternal dietary patterns (per SD increase in score; GM ratio) 'Confectionery'		NS
					'Health Conscious'		NS
					'Processed'		NS
					'Traditional'		NS
Shaheen, 2009 (3)	PC	LF-BHR slope	8-9	4,113	'Vegetarian'		NS
					Maternal dietary pattern (Difference per SD of dietary pattern score) 'Health Conscious'		NS
		LF-FEV_1	8-9	6,192	'Confectionery'		NS

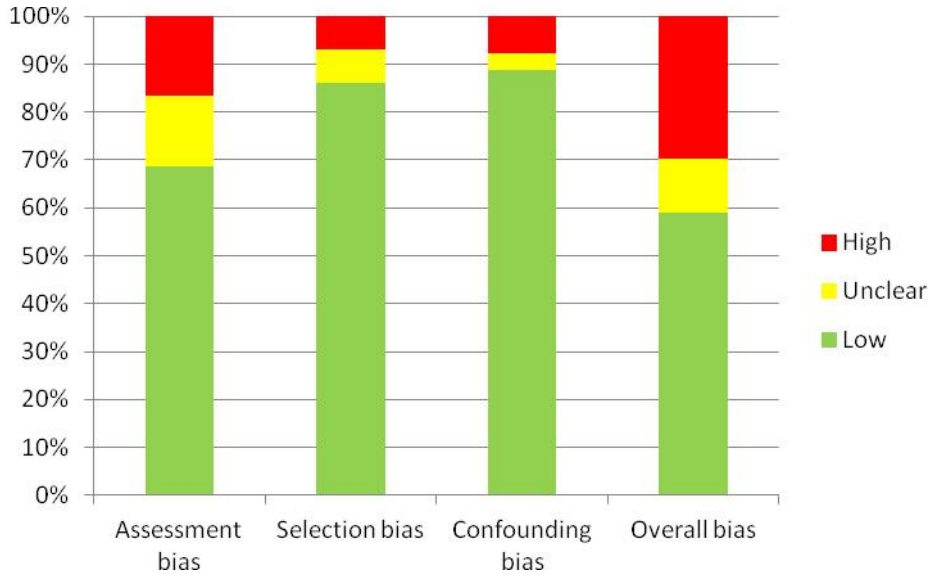
First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p>0.05)
					Maternal dietary pattern (Difference per SD of dietary pattern score)		
					'Processed'		NS
					'Traditional'		NS
Shaheen, 2009 (3)	PC	LF-FEV_1(SDS)	8-9y	6,192	'Vegetarian'		NS
					'Confectionery'		NS
					'Health conscious'		NS
					'Processed'		P-value= 0.02
					'Traditional'		NS
		LF-FVC (SDS)	8-9	6,285	'Vegetarian'		NS
Willers, 2007 (2)	PC	LF	5	510	Whole grain products/ Low vs. high quintile		NS

5. Other foods and risk of wheeze

5.1. Risk of bias in studies investigating the association between other foods and risk of wheeze

Twenty two studies investigated the relationship between maternal or infant intake of various foods and risk of wheeze. Most of the studies were considered to have a low risk of assessment, selection and confounding bias. Therefore the majority of the studies had an overall risk of bias judged as low. This was driven largely by population-based prospective cohorts. Approximately 15% of the studies were considered to have a high risk of assessment, and less than 10% were considered to have a high risk of bias due to lack of controlling for confounders (Figure 6).

Figure 6 Risk of Bias in studies of other foods intake and wheeze



5.2. Studies investigating the association between wheeze and other foods which were not eligible for meta-analysis

Despite of the number of studies investigating the association between infant or maternal intake and risk of wheeze in the offspring (Table 7), we did not identify any suitable studies that could have comparable data to pool estimates.

The main dietary exposures studied were maternal dietary patterns during pregnancy, maternal or infant intake of dairy products and intake of confectionary products. With regards to dietary patterns, these used different methodological approaches to define them. Some used a Healthy Index and adherence to Mediterranean diet (score) (**Lange 2010; de Batlle 2008; Castro-Rodriguez 2010; Chatzi 2008**), whilst the studies of **Shaheen (2009)** and **Miyake (2011)** derived dietary patterns from PCA using maternal reported intake of foods during pregnancy. The study of **Chatzi** reported a reduced risk of atopic wheeze (OR 0.55, 95% CI 0.31, 0.97) in children whose mothers had a high adherence to a Mediterranean diet compared with those with a lower score, but no association with other outcomes. The study of **Miyake (2011)** found that in Japanese women, a 'Western' dietary pattern was associated with a reduced risk of childhood wheeze (OR 0.59; 95% CI 0.36-0.98). The study of **Shaheen (2009)** identified five distinctive maternal dietary patterns, and found no evidence that any of these influenced the risk of childhood asthma at age 6 months, 3.5 years or 7 years old. Similarly, the study of **Lange (2010)** used three approaches to derive patterns of intake in pregnant mothers: a healthy eating index, adherence to Mediterranean diet, and PCA but none of these patterns showed evidence of an association between maternal intake of specific patterns and risk of childhood wheeze.

The study of **Andreasyan (2007)** showed that introduction of sterilised water in the first month was associated with a reduced risk of asthma at age 8 years (RR 0.64; 95% CI 0.45-0.88). This association remained after adjusting for several potential confounders including maternal and infant factors and style of bottle cleaning. However, the association was no longer statistically significant after adding low maternal educational level as potential confounder (RR 1.50; 95%CI 0.95–2.36).

Maternal intake of dairy products was investigated by several studies (**Bertelsen 2013; Erkkola 2012; Narita 2011; Willers 2007; Miyake 2010)** but there was no evidence of an association with wheeze. The study of **Riedler (2001)** examined infant intake in first year of life of farm milk (ie unpasteurised milk) with or without additional exposure to being in stables, and they found that infants who only consumed farm milk alone or that in addition to this intake they were in contact with stables, had a lower risk of wheeze or (for farm milk plus stables exposure only) recurrent wheeze. The study of **Bertelsen 2013** reported no association between maternal intake of milk or yogurt rich in probiotics during pregnancy and recurrent wheeze in offspring in the first 3 years.

With regards to maternal or infant intake of confectionary products, (e.g. sugary foods, chocolates, artificially sweetened products) the study of **Maijaliisa (2011)** found an association between infant intake of chocolate and reduced childhood wheeze (OR 0.74; 95% CI 0.59-0.72) but not recurrent wheeze. These findings were confirmed in the study of **Lopez-Campos (2001)** who reported a statistically significant association between infant intake of chocolate and wheeze. Maternal intake of chocolate was associated with reduced risk of wheeze in the study of **Erkkola (2012)** (OR 0.74; 95% CI 0.57-0.94). In the study of **Maslova (2013)** the authors found that pregnant mothers who had a higher intake of artificially-sweetened soft drinks were more likely to have a child with asthma. The study of **Long (1986)** reported that children who wheezed were more likely to have mothers who avoided peanuts ($p<0.05$)

Conclusion

One cross-sectional study that intake of farm milk in the first year of life is associated with a lower risk of wheeze, but this requires replication. Overall we found no consistent evidence of association between the dietary exposures included in this report, and wheezing or recurrent wheezing.

Table 7 Studies investigating the association between other foods and wheeze which were not eligible for meta-analysis

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					INFANT INTAKE		
					Introduction in 1st month yes/no		
					Sterilised water intake	OR	**0.64 (0.45-0.88)**
Andreasyan, 2007 (35)	PC	Wheeze	9	699	Honey	RR	1.12 (0.61-2.06)
		Wheeze			Chocolate (not low consumption vs. low consumption)	OR	**0.74 (0.59-0.92)**
Maijaliisa, 2011 (13)	PC	Rec wheeze	5	2,441	Chocolate (not low consumption vs. low consumption)		NS
Lopez Campos, 2001 (46)	CC	Rec wheeze	6-10	75	Chocolate during first year of life (yes/no)		**P-value<0.05**
					Rural exposure in 1st year of life (neither farm milk nor stable exposure as reference) **:**		
		Rec wheeze			Exposed to farm milk and stables	OR	**0.14 (0.04-0.48)**
		Wheeze			Exposed to farm milk and stables	OR	**0.17 (0.06-0.45)**
		Wheeze			Farm milk but not stables	OR	**0.43 (0.20-0.92)**
Riedler, 2001 (49)	C-S	Rec wheeze	9	812	Farm milk but not stables	OR	0.48 (0.21-1.10)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
Lopez Campos, 2001 (46)	CC	Rec wheeze	6-10	75	'Industrial milk' from birth to 1st year of life	OR	NS
					Infant intake (earlier vs. later months): Meat		NS
Miskelly, 1988 (25)	PC	Wheeze	0-1	482	Meat other than beef		NS
					MATERNAL INTAKE		
Lange, 2010 (34)	PC	DD asthma	3	1,376	**Alternate Healthy Eating Index for pregnancy (AHEI-P)/score comprised of 9 components contributing 10 possible points each:** Vegetables, fruit, ratio of white to red meat, fibre, trans fat, ratio of poly- to saturated fatty acids, folate, calcium, and iron from foods	OR	1.07 (0.88-1.30)
		Rec wheeze			**Alternate Healthy Eating Index for pregnancy (AHEI-P)** Vegetables, fruit, ratio of white to red meat, fibre, trans fat, ratio of poly- to saturated fatty acids, folate, calcium, and iron from foods	OR	1.07 (0.88-1.30)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					Adherence to intake of traditional Mediterranean foods		
		Rec wheeze			Dairy, fish, fruit, legumes, nuts, fats, vegetables and whole grains (alcohol intake excluded from score due to pregnant status of sample studied)	OR	0.98 (0.89-1.08)
Lange, 2010 (34)	PC		3	1,376	**Adherence to intake of traditional Mediterranean foods**		
		DD asthma			Dairy, fish, fruit, legumes, nuts, fats, vegetables and whole grains	OR	1.01 (0.94-1.09)
					Maternal dietary pattern derived from Principal Component Analysis (PCA):		
		Rec wheeze			Pattern comprised of red meat, processed meat, refined grains, snacks, sweets, desserts, French fries, pizza	OR	0.98 (0.81-1.19)
		Rec wheeze			'Prudent' pattern i.e. fruits, tomatoes, cabbages, green leafy vegetables, poultry, and fish	OR	1.02 (0.83-1.26)
		DD asthma			'Prudent' pattern i.e. fruits, tomatoes, cabbages, green leafy vegetables, poultry, and fish /	OR	1.08 (0.93-1.26)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
Lange, 2010 (34)	PC	DD asthma	3	1,376	Pattern comprised of red meat, processed meat, refined grains, snacks, sweets, desserts, French fries, pizza	OR	1.08 (0.93-1.26)
Castro-Rodriguez, 2010 (50)	C-S	Rec wheeze	1.4	1,409	Mediterranean diet during pregnancy-Mediterranean diet score (22 - point scale)	OR	0.96 (0.84-1.10)
Chatzi, 2008 (24)	PC	Atopic wheeze	6.5	468	Maternal adherence to Mediterranean diet (MD) during pregnancy / high MD quality/tiles vs. low MD quality/tiles (score=4-7 high MD quality vs ≤3, low MD quality)	OR	**0.55 (0.31-0.97)**
Miyake, 2011 (28)	PC	Wheeze	1.3 - 2	763	**Maternal intake during pregnancy/ Dietary patterns derived from PCA**/ Highest vs lowest quartiles of scores for each dietary pattern		
					'Western'	OR	**0.59 (0.36-0.98)**
					'Healthy'	OR	0.68 (0.40-1.15)
					'Japanese'	OR	1.41 (0.85-2.35)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					Maternal dietary patterns during pregnancy (estimates of risk per SD of dietary pattern score):		
					'Traditional'	OR	0.96 (0.85-1.08)
		Rec wheeze	0.5	8,886	'Health Conscious'	OR	1.00 (0.86-1.16)
					'Processed'	OR	1.00 (0.88-1.13)
					'Confectionery'	OR	1.02 (0.90-1.16)
Shaheen, 2009 (3)	PC				'Vegetarian'	OR	1.06 (0.97-1.16)
					Maternal dietary patterns during pregnancy (estimates of risk per SD of dietary pattern score):		
					'Health conscious'	OR	0.96 (0.88-1.05)
					'Vegetarian'	OR	0.97 (0.90-1.04)
					'Confectionery'	OR	0.98 (0.91-1.06)
					'Traditional'	OR	1.00 (0.93-1.07)
Shaheen, 2009 (3)	PC	Wheeze	3.5	8,886	'Processed'	OR	1.02 (0.95-1.10)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
				7,707	'Processed'	OR	0.92 (0.84-1.01)
				7,625	'Health Conscious'	OR	0.95 (0.87-1.04)
				7,625	'Traditional'	OR	0.96 (0.89-1.04)
				7,625	'Processed'	OR	0.98 (0.90-1.07)
				7,625	'Confectionery'	OR	1.00 (0.93-1.08)
Shaheen, 2009 (3)	PC	Asthma	7.5	7,707	'Health Conscious'	OR	1.00 (0.90-1.11)
				7,707	'Traditional'	OR	1.00 (0.93-1.08)
				7,707	'Confectionery'	OR	1.02 (0.93-1.12)
				7,625	'Vegetarian'	OR	1.02 (0.95-1.09)
				7,707	'Vegetarian'	OR	1.02 (0.95-1.10)
Narita, 2011 (36)	PC	Wheeze	3	1,344	Maternal consumption of dairy products during pregnancy (Lowest vs. highest quartile)		NS

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
Erkkola, 2012, (16)	PC	Wheeze	5	2,441	**Maternal intake of various foods during pregnancy** / in quarters (mid-half values as reference; cut-off values g/d):		
					Chocolate (7.14-26.7 vs. <7.14g/d)	OR	**0.74 (0.57-0.94)**
					Cereal (155.0-246.2 vs. <155.0 g/d)	OR	0.94 (0.72-1.23)
					Meat (119.2-197.7 vs. <119.2 g/d)	OR	1.06 (0.83-1.36)
					Fermented milk (100.0-309.6 vs. <100.0 g/d)	OR	0.92 (0.72-1.16)
					Cheese (30.3-85.8 vs. <30.3 g/d)	OR	1.16 (0.91-1.49)
					Milk (214.0-766.4 mL/d vs. <214.0 mL/d)	OR	1.04 (0.82-1.32)
					Probiotic (highest vs. lowest)	HR	1.38 (0.81-2.34)
					Probiotic (highest vs. lowest)	OR	0.81 (0.64-1.03)
					Dairy (highest vs. lowest)	OR	1.12 (0.88-1.41)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
Erkkola, 2012 (16)	PC	Rec wheeze	5	2,441	**Maternal intake of various foods during pregnancy / in quarters (mid-half values as reference; cut-off values g/d):**		
					Chocolate (7.14-26.7 vs. <7.14g/d)	HR	0.73 (0.45-1.18)
					Fermented milk (100.0-309.6 vs. <100.0 g/d)	HR	0.83 (0.52-1.32)
					Cereal (155.0-246.2 vs. <155.0 g/d)	HR	0.62 (0.35-1.08)
					Meat (119.2-197.7 vs. <119.2 g/d)	HR	0.80 (0.46-1.39)
					Cheese (30.3-85.8 vs. <30.3 g/d)	HR	1.61 (0.95-2.73)
					Milk (214.0-766.4 mL/d vs. <214.0 mL/d)	HR	0.98 (0.60-1.61)
					Confectionery/ sweet drinks (highest vs. lowest)	OR	1.00 (0.66-1.82)
Dai, 1993 (44)	CC	Rec wheeze	0.5	70	Maternal allergenic food avoidance (any) (no vs yes)		**P-value <0.001**
					Maternal intake during pregnancy (highest quartile vs mid-half intake) :		
					Meat (>156.4 vs. 88.49–156.44)	HR	1.06 (0.67-1.67)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
Lumia, 2011 (15)	PC	Rec wheeze	5	2,679	Milk and milk products (>1099.8 vs. 546.62–1099.8)	HR	0.73 (0.44-1.21)
					Maternal intake of artificially-sweetened carbonated soft drinks:		
			1.5-7		None vs. any servings (per week)	OR	0.98 (0.84-1.14)
			1.5-7		None vs. <1servings per week	OR	1.01 (0.86-1.19)
			1.5		None vs. any servings (weekly)	OR	1.06 (0.98-1.15)
			1.5		None vs. ≥ 1 servings per day	OR	1.10 (0.95-1.27)
Maslova, 2013 (7)	PC	Rec wheeze	1.5-7		**Maternal intake of artificially-sweetened carbonated soft drinks:** any (weekly) vs none	OR	1.13 (0.96-1.33)
			1.5		<1 serving per week vs none	OR	1.17 (1.08-1.27)
			1.5-7		<1 serving per week vs none	OR	1.20 (0.97-1.48)
			1.5		Any (weekly) vs none	OR	**1.21 (1.12-1.31)**
			1.5-7	60,466	≥ 1 serving per day vs none	OR	**1.30 (1.02-1.66)**

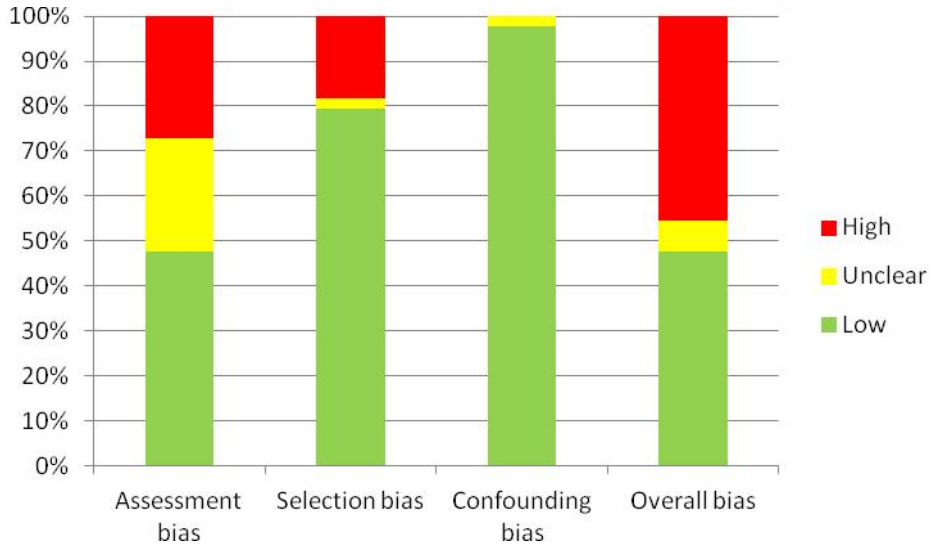
First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					Maternal intake (highest vs lowest quartile): Cheese	OR	0.51 (0.31-0.85)
			1.5-2		Milk	OR	**0.50 (0.29-0.87)**
					Yoghurt	OR	1.26 (0.74-2.16)
Miyake, 2010 (29)	PC	Wheeze	0-4	763	Dairy (highest vs. lowest)	OR	**0.45 (0.26-0.79)**
Bertelsen, 2013 (27)	PC	Rec wheeze	<3	54,740	**Maternal intake of milk-based products** containing probiotic lactobacilli during pregnancy / yes vs. no		NS
		Rec wheeze			Meat/ Introduction after 5.5 months vs. <5.1; or between 5.1-5.5 months vs less	HR	NS
Nwaru, 2013 (8)	PC	Rec atopic wheeze	0-0.5	3,109	Meat/ Introduction after 5.5 months vs. <5.1; or between 5.1-5.5 months vs less	HR	NS
Oliveti, 1995 (45)	PC	Rec wheeze	9	262	Maternal intake of alcohol (often vs. rare)	OR	2.28 (0.91-5.68)
		Wheeze			**Maternal intake pregnancy** Whole grain products		NS
					Whole grain products		NS
					Dairy (often vs. rare)	OR	0.88 (0.71-1.09)
Willers, 2008 (2)	PC	Rec wheeze	5	1,212	Egg (often vs. rare)	OR	0.96 (0.82-1.12)

6. Other foods and risk of rhino-conjunctivitis

6.1. Overall risk of bias between other foods and rhino-conjunctivitis

Eleven studies investigated the association between various foods and risk of rhino-conjunctivitis. Over 50% of these were judged to have a low or unclear overall risk of bias. The majority of the studies had a low risk of bias due to lack of confounding, whilst over 40% were considered to have a high risk of bias due to risk of selection or assessment bias (Figure 7).

Figure 7 Risk of Bias in studies of other foods intake and rhino-conjunctivitis



6.2. Studies not meta-analysed that examined risk of rhino-conjunctivitis and intake of various foods or nutrients

Across the nine studies that investigated the association between other foods and risk of rhino-conjunctivitis, there was little evidence for any associations. Two studies investigated dietary patterns. The study of **Shaheen (2009)** investigated maternal dietary patterns during pregnancy derived from PCA, whilst **de Batlle (2008)** derived a Mediterranean score adherence in children and examined their association with symptoms of rhino-conjunctivitis. Neither study found evidence of a relationship between dietary patterns and risk. The study of

Bertelsen (2013) reported that regular intake of probiotics during pregnancy was associated with lower risk of RC in children (OR 0.87; 95% CI 0.77-0.98). **Riedler (2001)** found that intake of farm milk (with or without spending time in the stables) in the first year was associated with a lower risk of RC ever and current RC at age 9 years old. Other dietary exposures studied included several single foods, for which no evidence of association was reported.

Conclusion

We found no evidence that specific dietary patterns consumed during pregnancy or childhood are related to risk of rhino-conjunctivitis. One prospective cohort study reported maternal intake of probiotics during pregnancy was associated with reduced rhino-conjunctivitis at age 3 years, but this requires replication. One cross-sectional study reported intake of farm milk during infancy is associated with reduced RC in childhood, but this also requires replication.

Table 8 Studies investigating the association between other foods and rhino-conjunctivitis which were not eligible for meta-analysis

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					INFANT INTAKE		
Andreasyan, 2007 (35)	PC	RC	9	711	**Introduction of non-milk fluids >1 month vs <1 month**		
					Fruit syrup	OR	3.45 (0.52-22.83)
					Sterilised water	OR	1.08 (0.77-1.51)
					Honey (by 1st month vs later)	OR	1.31 (0.65-2.64)
Marini, 1996 (23)	PC	RC	3	80	Introduction of meat in months 5 to 7 vs earlier	OR	1.43 (0.84-2.43)
Riedler, 2001 (49)	CS	RC	9	812	**Exposure to rural environment in the 1st year:**		
					Exposed to farm milk and stables	OR	**0.20 (0.08-0.50)**
					Exposed to farm milk but not stables vs neither	OR	**0.24 (0.10-0.56)**

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					MATERNAL INTAKE		
					Maternal dietary intake of various foods (median intake g/d as reference)		
					Chocolate (7.14-26.7 vs. <7.14)	HR	0.85 (0.61-1.17)
					Cereal (155.0-246.2 vs. <155.0)	HR	0.88 (0.62-1.24)
					Meat (119.2-197.7 vs. <119.2)	HR	1.18 (0.84-1.65)
Erkkola, 2012 (16)	PC	RC	5	2,441	Fermented milk products (100.0-309.6 vs. <100.0 mL)	HR	1.00 (0.72-1.38)
					Cheese (30.3-85.8 vs. <30.3)	HR	1.27 (0.89-1.79)
					Cheese (85.8-380.9 vs. 30.3-85.8)	HR	1.17 (0.86-1.60)
					Milk (214.0-766.4 vs. <214.0)	HR	1.09 (0.80-1.48)
Maijaliisa, 2011 (13)	PC	RC	5	2,441	Maternal intake of chocolate/ Not low consumption vs. low consumption	OR	NS
					Maternal intake of artificially-sweetened carbonated soft drinks during pregnancy		
			1.5-7		Weekly vs none	OR	1.15 (0.98-1.35)
			1.5		Weekly vs none	OR	0.86 (0.71-1.04)
			1.5		<1 serving per week vs none	OR	0.96 (0.76-1.21)
Maslova, 2013 (7)	PC	RC	1.5-7	60,466	<1 serving per week vs none	OR	0.97 (0.81-1.16)

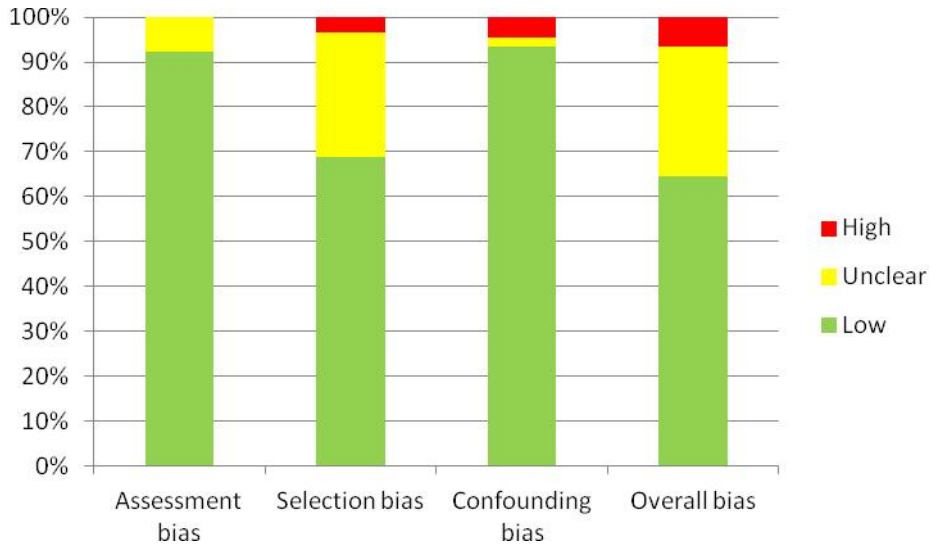
First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
Shaheen, 2009 (2)	PC	RC	7.5	7,674	**Maternal dietary intake (estimated as dietary patterns derived with PCA) -'risk estimates per SD of dietary pattern score)**		
					‘Traditional'	OR	1.04 (0.96-1.13)
					'Vegetarian'	OR	0.97 (0.89-1.06)
					'Health Conscious'	OR	1.00 (0.90-1.11)
					'Confectionery'	OR	1.01 (0.92-1.11)
					'Processed'	OR	1.04 (0.96-1.13)
Willers, 2007 (2)	PC	RC	5	1,212	Maternal intake of whole grain products		NS
Bertelsen, 2013 (27)	PC	RC	3	40,614	Maternal intake of probiotic (often vs. rare)	OR	**0.87 (0.77-0.98)**

7. Other foods and risk of allergic sensitization

7.1. Overall risk of bias between other foods and allergic sensitisation

We identified ten studies that investigated the association between other foods and risk of allergic sensitisation. Over 60% of the studies were judged to have a low risk of bias, whilst a third of the studies had an unclear risk of selection bias (Figure 8).

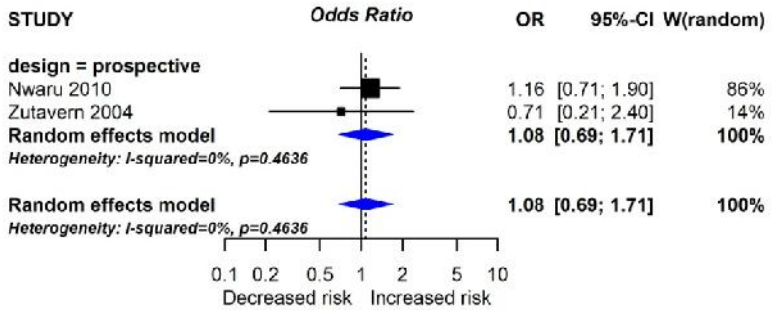
Figure 8 Risk of Bias in studies of other foods intake and allergic sensitisation



7.2. Introduction of meat and risk of aero-allergen sensitisation

The prospective cohort studies of **Nwaru (2010)** and **Zutavern (2004)** had comparable data to pool estimates of risk of rhino-conjunctivitis and meat introduction at months 5-7 (Figure 9). There was no evidence of an association with this exposure and outcome, with no statistical heterogeneity between studies (I^2=0%)

Figure 9 Introduction of meat in months 5 to 7 and risk of sensitisation to aero-allergens (odds ratio) in children



7.3. Studies that were not meta-analysed and that investigated the association between other foods and risk of allergic sensitisation

Amongst the studies identified (Table 9) the dietary exposures investigated included single foods (dairy, confectionary, meat, and cereal intake). Two studies included maternal food avoidance during pregnancy **(Butiene 2001; Dubakiene 2012**), and two studies (**Shaheen 2009; Chatzi 2008)** studied dietary patterns during pregnancy. The study of **Chatzi (2008)** found that children of mothers who had a higher adherence to a Mediterranean diet (MD) during pregnancy were less likely to be sensitised to aero-allergens at age 6.5 years old (OR 0.55; 95% CI 0.31–0.97). One further study investigated intake of farm milk in the first year (**Riedler 2001).** The studies of **Nwaru (2010)**, **Sausenthaler (2007)**, and **Chatzi (2008)** also investigated maternal intake of dairy products, but none of these found evidence of an association with outcomes of sensitisation in the offspring. While **Nwaru (2010)** found evidence from one analysis of meat introduction and AS-Egg that early meat introduction may decrease AS, other measures of AS and other comparisons related to timing or amount of infant meat intake from this study and others did not support an association.

Conclusion

We found no consistent evidence that any of these exposures are associated with risk of AS.

Table 9 Studies investigating the association between other foods and allergic sensitization which were not eligible for meta-analysis

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					INFANT INTAKE		
Andreasyan, 2007 (35)	PC	SPT to any	9	699	**Introduction of non-milk fluids** (After 1st month vs earlier) Fruit syrup	OR	1.16 (0.58-2.34)
					Sterilised water	OR	1.01 (0.81-1.27)
					Honey (By 1st month vs later)	OR	1.22 (0.80-1.86)
Zutavern, 2008 (21)	PC	sIgE food	6	2073	Infant meat introduction by 4 months vs. 4-6 months	OR	NS
Riedler, 2001 (49)	CS	sIgE aero	9	812	**Exposure to farm milk AND stable in the 1st year:** Exposed to farm milk and stables vs. Neither farm milk nor stable exposure	OR	**0.32 (0.17-0.62)**
		sIgE aero	9	812	Exposed to farm milk but not stables vs. Neither farm milk nor stable exposure	OR	**0.43 (0.24-0.77)**

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
Nwaru, 2010 (9)	PC				**Introduction to infant's diet:**		
		sIgE aero			Meat (5.1-5.5 months vs. <5.1 months)	OR	0.80 (0.48-1.33)
		sIgE cm			Meat (third tertile vs. second tertile)		NS
		sIgE egg			Meat (third tertile vs. first tertile)	Increased sensitisation	**P=0.029**
		sIgE food	5	994	Meat (5.1-5.5 months vs. <5.1 months)	OR	0.82 (0.45-1.48)
Chatzi, 2008 (24)	(C-S/ PC)				**Child's adherence to Mediterranean diet (MD) at age 6.5 years** (high MD quality vs. low MD quality ; where score≥7 high, 4-6 medium, and <4 low MD quality)		
		SPT aero	6.5	468	High MD score vs. low	OR	0.49 (0.18–1.32)
					Medium MD score vs. low	OR	0.58 (0.23–1.45)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					MATERNAL INTAKE		
Chatzi, 2008 (24)	PC	SPT aero	6.5	468	**Maternal dietary patterns during pregnancy:** Adherence to Mediterranean diet (MD) (high MD quality vs. low MD quality ; where score≥7 high, 4-6 medium, and <4 low MD quality) High MD score vs. low	OR	**0.55 (0.31–0.97)**
Shaheen, 2009 (3)	PC	SPT aero	7	6085	**Maternal intake as dietary patterns/ (odds per SD of dietary pattern score):** 'Processed'	OR	0.93 (0.86-1.01)
					'Health Conscious'	OR	0.95 (0.87-1.04)
					'Traditional'	OR	0.98 (0.91-1.05)
					'Vegetarian'	OR	1.02 (0.95-1.09)
					'Confectionery'	OR	**1.07 (1.00-1.15)**

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
Chatzi, 2008 (24)	PC	SPT aero	6.5	468	**Maternal intake during pregnancy (median servings per week):** Cereal (>11.5 vs. ≤ 11.5)	Prevalence (%)	NS
					Meat (≥3.25 vs. ≤3.25)		NS
					White meat (≥2.5 vs. ≤2.5)		NS
					Dairy (. >23 Median vs ≤23)		NS
Nwaru, 2010 (10)	PC				**Maternal intake at 8th month pregnancy** (continuous g/d):		
		sIgE aero	5	931	Cereal	OR	0.94 (0.53-1.66)
		sIgE food	5	931	Cereal	OR	1.26 (0.65-2.43)
		sIgE aero	5	931	Cheese	OR	1.05 (0.85-1.29)
		sIgE food	5	931	Cheese	OR	0.96 (0.77-1.19)
		sIgE aero	5	931	Milk	OR	0.91 (0.74-1.12)
		sIgE food	5	931	Milk	OR	0.95 (0.75-1.20)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					Maternal intake last 4 months of pregnancy (highest vs lowest tertile):		
		sIgE aero		2102	Cheese	OR	0.93 (0.57-1.53)
		sIgE any		2103	Cheese	OR	0.99 (0.72-1.36)
Sausenthaler, 2007 (22)	PC	sIgE food		2110	Cheese	OR	0.97 (0.68-1.39)
		sIgE any			Yoghurt	OR	0.81 (0.59-1.10)
		sIgE food			Yoghurt	OR	0.89 (0.62-1.27)
		sIgE aero	2	2110	Yoghurt	OR	0.69 (0.43-1.12)
					Maternal intake last 4 months of pregnancy (highest vs lowest tertile):		
		sIgE aero			Milk	OR	0.95 (0.58-1.57)
Sausenthaler, 2007 (22)	PC	sIgE any			Milk	OR	0.93 (0.67-1.28)
		sIgE food			Milk	OR	0.95 (0.66-1.37)
		sIgE any			Egg	OR	0.91 (0.56-1.28)
		sIgE food			Egg	OR	0.93 (0.63-1.38)
		sIgE aero	2	2110	Egg	OR	0.90 (0.53-1.53)

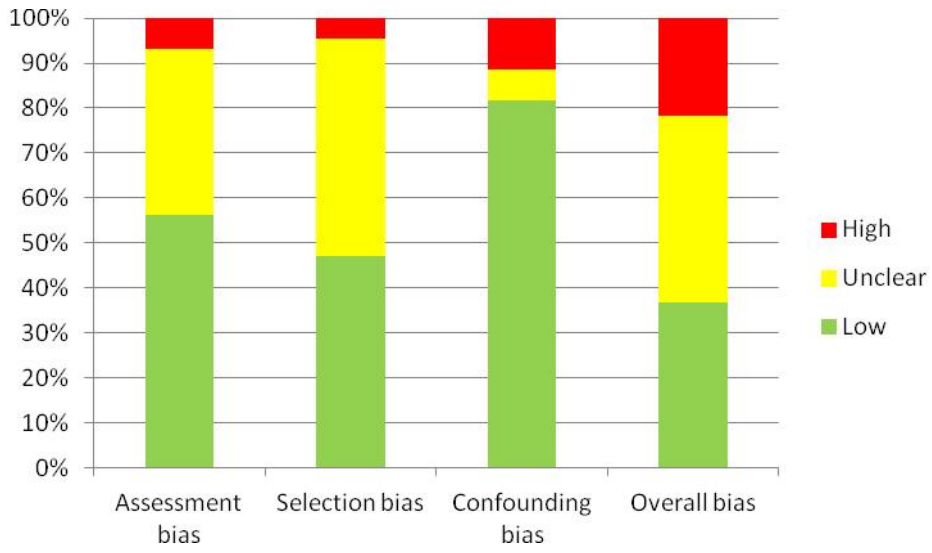
First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
Willers, 2007 (2)	PC	SPT any	5	1212	Maternal intake of whole grain products	OR	NS
Dubakiene, 2012 (72)	PC	SPT food	1	128	Maternal avoidance of milk and egg products during pregnancy and lactation	OR	NS
Butiene, 2011 (43)	NCC	SPT/sIgE milk or egg	1	43	Maternal allergenic food avoidance during pregnancy / milk and egg products	OR	NS

8. Other foods and risk of type 1 diabetes mellitus

8.1. Overall risk of bias between other foods and type 1 diabetes mellitus

We identified fifteen studies that investigated the association between other foods and risk of T1DM. The majority of these studies were considered to have a low or unclear overall risk of bias (Figure 10).

Figure 10 Risk of Bias in studies of other foods intake and type 1 diabetes mellitus



8.2. Studies not meta-analysed that explored the association between food intake and T1DM

The most commonly studied dietary exposure was coffee (six observational studies). Other foods included maternal intake of dairy products, eggs, meat, cereals (containing or not gluten), tea and alcohol intake (Table 10). For most of these exposures, there was no consistent evidence of association with T1DM in the offspring. The abstract publication of **Ninisto (2012)** reported an association between higher intake of fresh milk by mothers during lactation, and reduced T1DM in childhood (OR 0.49; 95% CI 0.28-0.87). However this was in the context of multiple dietary exposure assessments, and the association was only seen for serological diabetes in the first 3 years, in a study which also assessed clinical TIDM and outcomes up to 9 years. It is unclear from this abstract publication how robust this finding

was due to variations in the timing and nature of the outcome assessment. The study of **Sipetic (2003)** found increased maternal intake of tea, coffee, alcohol and coca-cola during pregnancy was associated with T1DM in children in univariate analysis, but this was not confirmed in multivariate analysis, nor in the separate study of **Virtanen (2011)**. There was evidence from one study **(Sipetic 2003)** that maternal intake of foods rich in nitrosamines was associated with increased T1DM in childhood, an association which persisted in adjusted analysis.

Conclusion

We found evidence from just one case control study with a high risk of assessment bias, that consumption of nitrosamine-rich foods during pregnancy is associated with TIDM. We found no evidence to suggest that other infant or maternal dietary exposures are associated with T1DM, and the finding for nitrosamine-rich foods requires replication.

Table 10 Studies investigating the association between other foods and type 1 diabetes mellitus which were not eligible for meta-analysis

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					INFANT INTAKE		
Brekke, 2010 (53)	PC	TIDM	5	4,005	Milk (1-2dL/day vs no milk)	OR	1.05 (0.71-1.58)
					Egg (1-2 times per week vs <1 per week)	OR	1.19 (0.82-1.72)
Norris, 1996 (60)	PC	TIDM	<7	171	Introduction of meat 5 to 7 months vs. earlier	OR	4.66 (0.92-23.73)
Visalli, 2003 (65)	PC	TIDM	12	900	Introduction of meat ≥3 months vs <3 months	OR	0.57 (0.06-5.49)
Harsunen, 2012 (61)	NCC	TIDM	<18	33/33	Infant intake of soluble fibre in the diet in the first year of life , adjusted for total energy intake	HR	0.68 (0.23-1.97)
Strotmeyer, 2004 (71)	CC	TIDM	9.7	688	**Introduction of meat to infant's diet**: >4–6 months vs. 4-6 months; or >7-12 vs 7-12	OR	NS

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					MATERNAL INTAKE		
Majeed, 2011(66)	PC	T1DM	17	395	Maternal consumption of tea during pregnancy (often vs no intake)	OR	**4.66 (1.36-16.05)**
					Maternal intake in the last trimester (No servings per month):		
					Gluten-containing foods	HR	0.89 (0.50-1.58)
					Non-gluten cereal grains	HR	0.98 (0.64-1.51)
					Meat	HR	0.91 (0.54-1.52)
Lamb 2008 (58)	PC	TIDM	15	642/27	Cow's milk products	HR	1.18 (0.74-1.87)
Niinisto, 2012 (14)	PC	TIDM	10	2939	Maternal diet during the 3rd month of lactation / High maternal consumption of fresh milk during lactation or intermediate intake vs. low maternal consumption of fresh milk during lactation	HR	**0.49 (0.28-0.87)**
					Maternal intake in pregnancy (yes vs. no):		
					Alcohol		NS
					Coca-Cola		NS
					Tea, Coffee		NS
Sipetic, 2005 (70)	CC	TIDM	16	315	Nitrosamine-rich foods		**4.33 (1.95–9.61)**

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
Visalli, 2003(65)	PC	T1DM	12	900	Tea intake during pregnancy (yes vs. no)	OR	0.66 (0.4-1.08)
Uusitalo, 2008 (17)	PC	TIDM	<10	3730/165	Maternal milk intake during pregnancy (change in risk per 2-fold increase in intake)	HR	1.03 (0.82-1.30)
Virtanen, 1994 (63)	CC	TIDM	9	1136	Maternal coffee intake during pregnancy (high intake vs low; cups per day)		NS
Virtanen, 2011 (55)	PC	TIDM	<10	3730/165	**Maternal intake of during pregnancy:** Coffee (highest vs. lowest)	OR	**0.59 (0.37-0.96)**
					Tea (highest vs. lowest)	OR	0.74 (0.45-1.21)
					Wheat (Continuous exposure)	HR	1.04 (0.79-1.37)
					Cereal	HR	1.09 (0.72-1.65)
Virtanen, 2011 (55)	PC	TIDM	<10	3730/165	Rice	HR	1.11 (0.93-1.32)
					Chocolate and sweets	HR	1.00 (0.89-1.12)
					Egg	HR	0.94 (0.74-1.20)
					Meat	HR	1.12 (0.87-1.44)
					Milk and dairy	HR	0.92 (0.72-1.17)
Wahlberg, 2006 (54)	PC	T1DM	2.5	8,715	Maternal food avoidance of milk	OR	NS

9. Other foods and risk of juvenile idiopathic arthritis (JIA)

9.1. Overall risk of bias between other foods and juvenile idiopathic arthritis

We identified one case-control study examining the association between maternal intake of alcohol and risk of JIA. The CLARITY - ChiLdhood Arthritis Risk factor Identification sTudY- is an Australian study aimed at identifying genomic and environmental disease risk factors for JIA. Within this study, the authors retrospectively examined alcohol intake in mothers during pregnancy and risk of JIA before age of 18 years old. The study was considered to have an unclear overall risk (Figure 15). The study found no evidence to suggest that maternal alcohol intake was a risk factor for JIA (Table 9).

Figure 11 Risk of Bias in studies of other foods intake and juvenile idiopathic arthritis

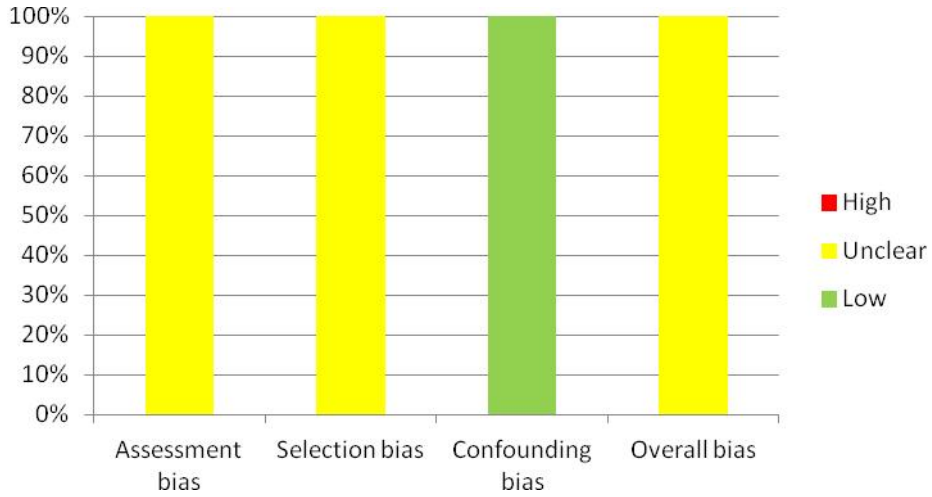


Table 11 Studies investigating the association between other foods and juvenile idiopathic arthritis which were not eligible for meta-analysis

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect
Ellis, 2012 (64)	RC	JIC	Any		Maternal intake of alcohol (often vs. rare)	OR	0.66 (0.36-1.21)

10. Other foods and risk of inflammatory bowel disease

10.1. Overall risk of bias in studies on other foods and inflammatory bowel disease

We identified a case-control study investigating the association between earlier introduction of meat and risk of IBD in children. The study had a low risk of selection and confounding bias, but had unclear assessment bias, which influenced the overall bias as being considered unclear (Figure 16). There was no evidence of an association between meat introduction and risk of disease (Table 10).

Figure 12 Risk of Bias in studies on other foods intake and inflammatory bowel disease

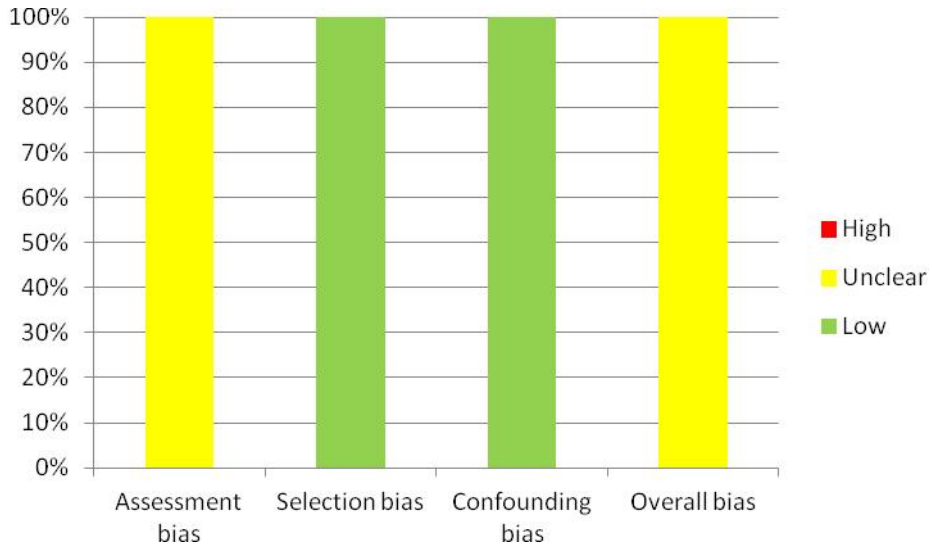


Table 12 Studies investigating the association between other food and irritable bowel disease which were not eligible for meta-analysis

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect
		IBD-CR	<17	444	Meat introduction months (continuous)	OR	NS
Baron, 2005 (62)	CC	IBD-UC	<17	444	Meat introduction months (continuous)	OR	NS

CONCLUSIONS

In this report, intake of several foods during pregnancy, or in the first year of life was investigated in relation to the risk of allergic and autoimmune diseases. Exposures were dietary pattern, maternal allergenic food avoidance, alcohol, tea or coffee intake, and maternal or infant meat, cereal, milk or egg intake. We found no consistent evidence to suggest that maternal dietary habits during pregnancy or lactation, or infant diet, influence the risk of any of the outcomes considered in this report. Our findings are consistent with those reported recently by Lv *at al* who found no evidence for a relationship between maternal dietary patterns and risk of allergic diseases in the offspring (73). The weak evidence generated from single case-control studies, studies at high risk of bias, and inconsistent datasets requires confirmation in replication studies before it can be accepted as evidence for relationships between other dietary exposures and allergic or autoimmune outcomes.

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PREBIOTIC SUPPLEMENTATION IN INFANTS AND RISK OF ALLERGIC SENSITISATION OR DISEASE

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1. Prebiotics and risk of allergic outcomes - summary of interventions and findings

Prebiotics are defined as selectively fermented ingredients (typically oligosaccharides), that allow specific changes in the composition and/or activity of the gastrointestinal microflora, and thereby confer a health benefit. Synbiotics are a combination of probiotic and prebiotic administered to the same individual. In this analysis we included studies of any oligosaccharide, given alone (=prebiotic) or in combination with a probiotic (=synbiotic) or other co-intervention. We planned to undertake subgroup/stratified analyses for meta-analyses which contained a total of >5 studies, and where appropriate to include probiotic/synbiotic intervention as a subgroup. We planned to assess publication bias using Funnel plots and Egger's test where there were ≥10 studies in a meta-analysis. In total we identified 10 trials with over 4000 participants investigating the effect of 9 different prebiotic interventions during infancy on allergic outcomes (Table 1). We identified 1 recent high-quality systematic review which included 4 of these studies, in our July 2013 search for existing systematic reviews. We did not identify any further systematic reviews in our updated search on 26th February 2017. Nine of the original trials studied supplementation of infant formula, and one studied direct supplementation of mothers and infants. Four trials studied variations of the same prebiotic (Immunofortis). Six trials investigated prebiotic, and 4 synbiotic.

Interventions used

The **Moro** study (1) used extensively hydrolysed cow's milk whey protein formula [Aptamil HA] supplemented with 8g/L galactooligosaccharides (GOS)/ fructooligosaccharides (FOS) per 100ml [a product called Immunofortis, Nutricia, Netherlands] for six months. The **MIPS-1** study (2) used cow's milk formula supplemented with Immunofortis plus specific acidic oligosaccharides (AOS) at 8g/L (6.8g/L neutral and 1.2g/L AOS). The study of **Van der Aa** (3) used an extensively hydrolyzed whey-based formula (Nutrilon Pepti ; Nutricia, Netherlands) with synbiotics for 12 weeks. The synbiotic contained Immunofortis at 8g/L, and *Bifidobacterium breve* M-6V (Morinaga Milk Co, Ltd., Tokyo, Japan) 1.3 x 10^9 colony forming units (cfu)/100 ml. The study of **Kukkonen** (4) used a probiotic during the last 2-4 weeks of pregnancy - *Lactobacillus rhamnosus* GG(ATCC 3103), 10^{10} cfu/day; *L rhamnosus* LC705 (DSM 7061), 10^{10} cfu/day; *Bifidobacterium breve* Bb99(DSM 13692), 4 x 10^8 cfu/day; and *Propionibacterium freudenreichii* ssp. shermanii JS(DSM 7076), 4 x 10^9 cfu/day (Valio, Helsinki, Finland). Infants then received the same probiotics with 20 drops of syrup containing

0.8 g GOS prebiotic daily for 6 months. The study of **Roze** (5) used infant formula containing a synbiotic - *Lactobacillus rhamnosus* LCS-742 and *Bifidobacterium longum* subsp infantis M63, and a 96% GOS/ 4% FOS prebiotic. The formula was also enriched with bovine α-lactalbumin, using whey protein concentrate, and was fed to infants for the first 6 months. The study of **Ziegler** (6) used infant formula containing prebiotics polydextrose (PDX) and GOS at 50:50 ratio 4g/L (n=74) or PDX, GOS and lactulose at 50:33:17 ratio 8g/L (n=76), from 14 days to 120 days age. The study of **Boyle** (11**)** used partially hydrolysed whey-based infant formula containing Immunofortis in infants up to 6 months age. The study of **Ivakhnenko (7)** used a standard infant formula supplemented with scGOS/lcFOS 9:1 at 8g/L for 2 months. The study of **Sierra** (8) used a standard formula supplemented with GOS 0.44g/dl initially and then 0.5g/dl when switched to follow on formula (6 months age) – infants received study formula until 1 year age. The study of Chien (9) used a standard infant formula, or a formula supplemented with either scGOS/lcFOS (0.8g/100ml) and B. breve M-16V (7.5x108CFU/100ml), or scGOS/lcFOS (0.8g/100ml) alone – from birth until age 4 months.

Populations and Outcomes assessed

The outcomes allergic sensitisation, eczema, wheeze, and allergic rhinitis were reported. No studies were identified reporting allergic conjunctivitis, food allergy or autoimmune outcomes. Overall 4000 infants were randomised. In four studies infants were at high risk of allergic outcomes, in seven studies the population studied was unrepresentative of the general population, due to early full formula feeding (6) or established eczema (one). Six studies were carried out in Europe, one in North America, two in Asia and one in Asia/Europe/Australasia. Definitions used to assess the same outcome varied across studies, but most studies used recognised assessment tools to define the outcomes of interest.

Overall findings

All studies had a high or unclear risk of conflict of interest due to direct or unclear industry involvement in the trial, in the form of possible study sponsorship, employment of study authors, and/or consulting fees paid to study authors. 20-50% of studies in each analysis had a high risk of attrition bias due to loss to follow up of over 30% of participants prior to outcome assessment. Assessment of publication bias was not undertaken due to small numbers of studies included in each meta-analysis.

Overall there was no evidence that prebiotics reduce risk of wheezing, allergic sensitisation, AD, food allergy or allergic rhinitis.

Table 1 Characteristics of included studies evaluating prebiotic supplementation and allergic outcomes

First Author & Publication Year	N Intervention/ Control	Study Design	Country	Population Studied	Disease risk	Intervention	Age (yrs)	Outcomes Reported
Osborn 2013 (10)	4 RCT (1428 participants)	SR	-	Infants in the first six months of life without clinical evidence of allergy.	All	Prebiotics added to human milk or infant formula, compared to control or a different prebiotic	All	Asthma/wheeze, , eczema, rhinitis (no data), food allergy (no data)
van Hoffen 2009 (11) Moro 2006 (1), Arslanoglu 2008 (12) Arslanoglu 2012 (13)	129/ 130	RCT	Italy	Formula introduced <2 weeks; full formula feeds <6 weeks (excluded post-randomisation, if BF continued beyond 6 weeks)	high	**Prebiotic** Immunofortis [GOS/FOS] until 6 months	0.5, 2, 5	Allergic sensitisation (sIgE to CM; total IgE), Eczema (Harrigan and Rabinowitz), Wheeze (≥3 episodes), Allergic rhinoconjunctivitis (doctor-diagnosed nasal and ocular symptoms not related to infection)
Boyle 2015 **(14)** Boyle 2016 (15) **PATCH Study**	432/431	RCT	Australia, Singapore, England and Ireland	Term infants with ≥one parent with allergic disease, and formula introduction <18 weeks.	high	**Prebiotic** Immunofortis [GOS/FOS] + AOS until 6 months. Co-intervention with partially hydrolysed formula	1	Eczema (Hanifin and Rajka)
Gruber 2010 (2) **Gruber, 2015** (16) **MIPS-1 Study**	414/ 416	RCT	Netherlands Austria Switzerland Italy Germany	Full formula feeds <8 weeks	low	**Prebiotic** Immunofortis [GOS/FOS] + AOS	1	Allergic sensitisation (sIgE to CM or egg; total IgE), Eczema (UK Working Party criteria)

First Author & Publication Year	N Intervention/ Control	Study Design	Country	Population Studied	Disease risk	Intervention	Age (yrs)	Outcomes Reported
Ivakhnenko 2013 (7)	80/ 80	RCT	Ukraine	Fully formula fed – no breastfeeding at all	normal	**Prebiotic** scGOS/lcFOS 9:1 at 8g/L until 2 months.	1.5	Eczema (Harrigan and Rabinowitz), Food allergy (unclear)
Sierra 2015 (8)	188/ 177	RCT	Spain	Infants aged <2 months, exclusively formula fed for ≥15 days	normal	**Prebiotic** Nutradefense. GOS 0.44-0.5g/dl formula until 1 year age	1	Eczema (physician assessment), Wheeze (physician assessment), Allergic sensitisation (SPT), Food allergy (unclear)
Ziegler 2007 (6)	150/ 76	RCT	USA	Full formula feeds <2 weeks	normal	**Prebiotic** GOS/Polydextrose +/- lactulose	0.3	Eczema (unclear)
Chien, 2016 (9)	Unclear – outcome reported in 45 (synbiotic), 39 (prebiotic), 45 (control)	RCT	Singapore	Mixed fed infants born by elective Caesarean. Intervention included in formula milk from birth until 4 months.	unclear	**Prebiotic & Synbiotic** scGOS/lcFOS (0.8g/100ml) and B. breve M-16V (7.5x108CFU/100ml), or scGOS/lcFOS (0.8g/100ml), or control formula	0.4	Eczema (unclear)
Van der Aa 2010 (3)	46/ 44	RCT	Netherlands	Infants who already had AD, with SCORAD >15	high	**Synbiotic** Immunofortis [GOS/FOS] + B. breve	1	Allergic sensitisation (Total IgE), Wheeze (≥3 episodes + interval symptoms)
Kuitunen 2009 (17) Kukkonen 2007 (4) Kukkonen 2011 (18)	610/ 613	RCT	Finland	Representative population	high	**Synbiotic** GOS + B. breve + L. rhamnosus. Cointervention with probiotic during pregnancy.	2, 5	Allergic sensitisation (+ve SPT or sIgE; total IgE), Eczema (Hanifin and Rajka), Wheeze (≥2 episodes + interval symptoms), Allergic rhinoconjunctivitis (symptoms + sensitisation)

First Author & Publication Year	N Intervention/ Control	Study Design	Country	Population Studied	Disease risk	Intervention	Age (yrs)	Outcomes Reported
Roze 2012 (5)	48/ 49	RCT	France	Full formula feeds until randomised (up to day 3)	normal	**Synbiotic** GOS/FOS + L.rhamnosus + B.infantis	0.5	Eczema (UK Working Party criteria)

2. Prebiotics and risk of allergic sensitisation

Five intervention studies examining the effect of prebiotic supplementation on allergic sensitisation were eligible for inclusion. In total over 3000 participants were randomised. Studies reported total IgE, and allergic sensitisation measured using specific IgE (sIgE) or skin prick testing (SPT). Four studies were carried out in high risk populations, and 4 studies were in very specific populations with either early formula feeding or established eczema. Risk of disease (outcome) was assessed between 6 months and 5 years age. Three of the studies were at high risk of attrition bias, and all studies were considered to have a high risk of conflict of interest (Figure 1). The outcomes are shown in Figures 2 to 6, and show no evidence for an effect on AS to any allergen, aeroallergen, food, or cow's milk or egg specifically.

Data that could not be included in meta-analyses

In the study of Kukkonen there was no significant reduction in odds of 'any allergic sensitisation' with synbiotics, using a combination of SPT and sIgE to common allergens in the first 2 years of life – OR 0.86 (95%CI 0.65 – 1.14; p=0.29) – SPT data shown in Figure 2 - and no effect on total IgE at this age – mean 25.7 ku/L synbiotic (95%CI 22.2 – 29.8), 27.2 control (23.1– 32.0) (4). At age 5 the same authors found no reduction in 'any allergic sensitisation' again using a combination of SPT and sIgE – OR 1.0 (95% CI 0.77 – 1.33; p=0.99). At age 5 they also examined SPT and sIgE to common allergens, SPT to foods separately and total IgE, and found no significant effect of synbiotics (17, 18). In the study of Moro there was reduced sIgE to cow's milk (median 0.75 versus 1.04 U/ml; p<0.05) and reduced total IgE (median 4 versus 10 kU/L; p<0.01) at 6 months in the prebiotic group (11), however, separate publications from the same study reported no significant difference in these outcomes at 6 months age (19, 20). In the MIPS-1 study there was no significant effect of prebiotics on total IgE at 1 year – mean 13 ku/L (95%CI 11 – 15.4) prebiotic, 11.9 (10.2 – 13.8) control (p=0.43) (21). In the study of Van der Aa there was a non-significant reduction in total IgE at 1 year in the synbiotic (median 20.4 range 2.9, 628.0) versus control group (median 47.7 range 3.7, 1529; p=0.13) (3). In the study of Boyle median total and specific IgE levels in a subgroup randomised before 4 weeks did not differ between groups. Total IgE 8.6 active, 9.0 control P=0.51; milk IgE 0.03 active 0.03 control P=0.46; egg IgE 0.0 active 0.01 control P=0.15

Overall we found no evidence that prebiotics reduce risk of allergic sensitisation.

Figure 1 Risk of bias in intervention studies of prebiotics and allergic sensitisation

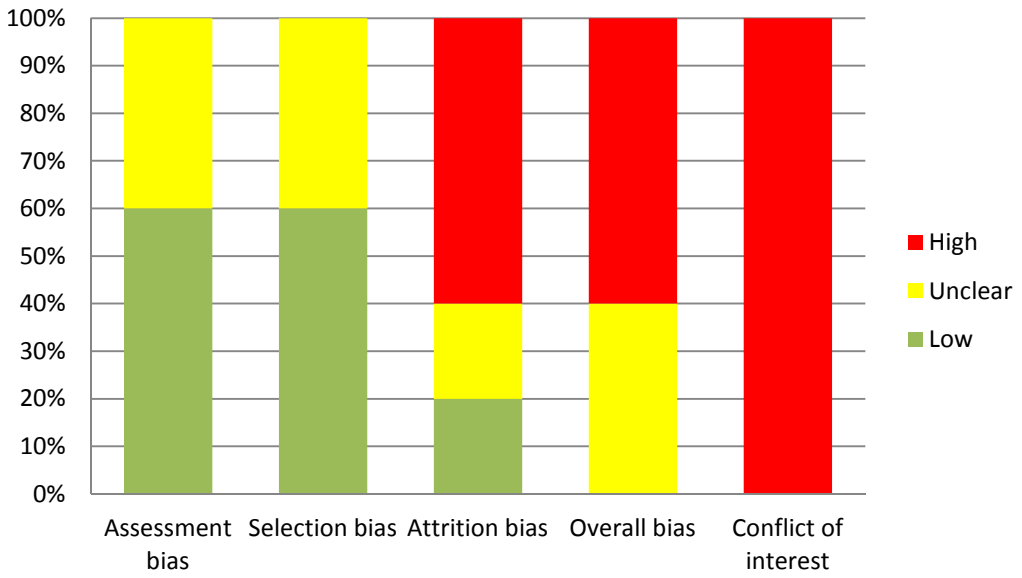


Figure 2 Prebiotics and allergic sensitisation to any allergen

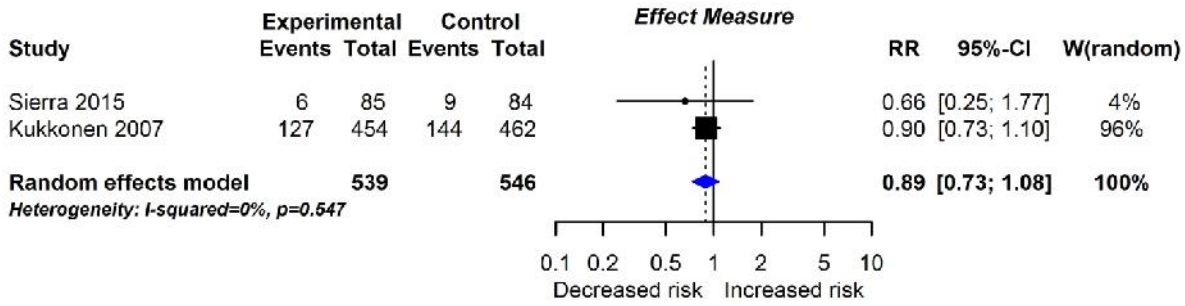


Figure 3 Prebiotics and allergic sensitisation to any aeroallergen

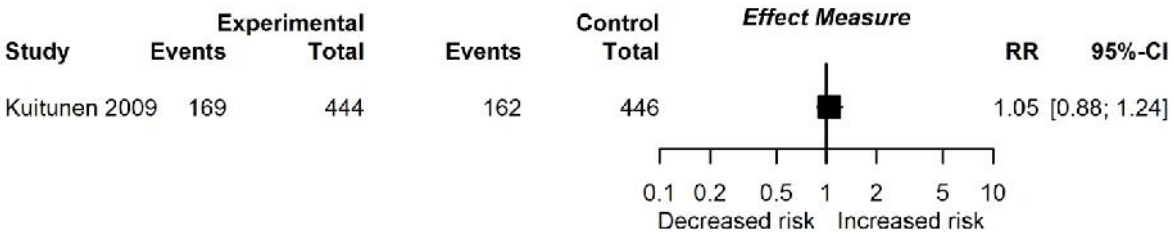


Figure 4 Prebiotics and allergic sensitisation to any food

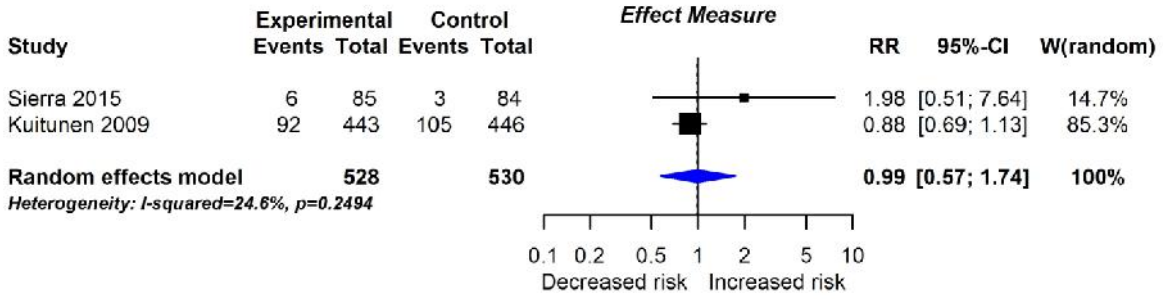


Figure 5 Prebiotics and allergic sensitisation to cow's milk

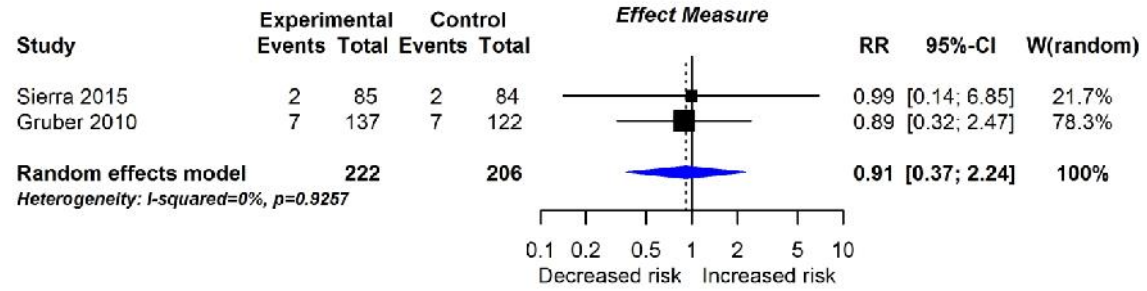
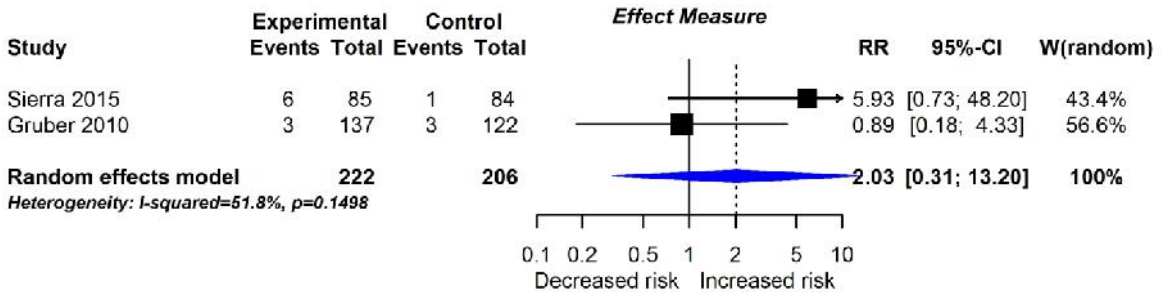


Figure 6 Prebiotics and allergic sensitisation to egg



3. Prebiotics and risk of food allergy

Three intervention studies investigated the effect of prebiotic supplementation on risk of food allergy. In total over 1300 participants were randomised to prebiotics or control treatment. The investigators studied infants at normal or low risk of disease. Food allergy (outcome) was assessed between 1 and 5 years of age. Studies' outcome assessment methods were either doctor diagnosis or not reported. All studies were considered to be at high or unclear risk of attrition bias, and either high or unclear risk of conflict of interest (Figure 7).

One study reported data that could be presented in a forest plot, and showed weak evidence of reduced food allergy and cow's milk allergy, of borderline statistical significance (Figures 8 and 9). In contrast in the study of Sierra no difference was reported in food allergy between prebiotic and control groups, but numerical data were only presented for a combined outcome of wheeze/ eczema/ food allergy, and not for food allergy as an outcome alone. In the study of Gruber no significant difference was reported between groups in food allergy – data were not presented in a form that could be included in meta-analysis.

Overall we found no evidence that prebiotics can prevent food allergy, but data were sparse and further work is needed to confirm whether or not prebiotics can prevent food allergy.

Figure 7 Risk of bias in intervention studies of prebiotics and food allergy

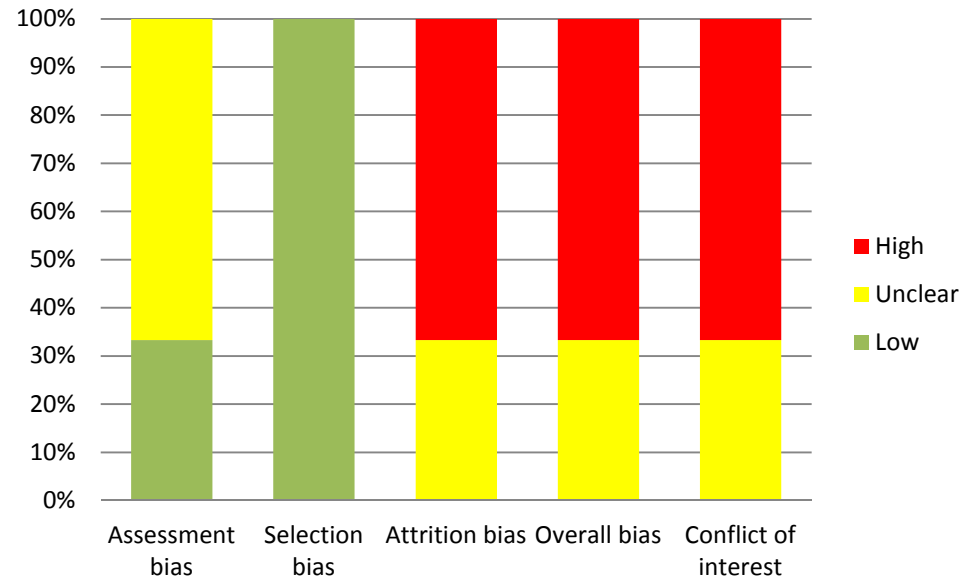


Figure 8 Prebiotics for preventing Food Allergy

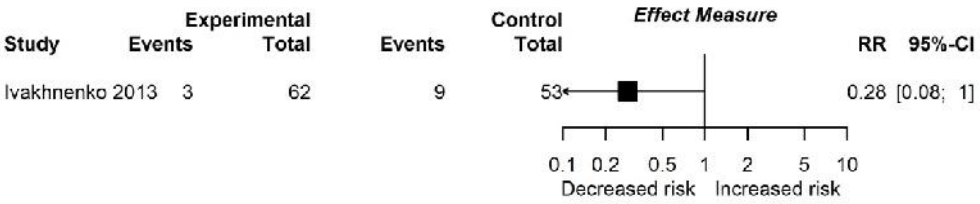
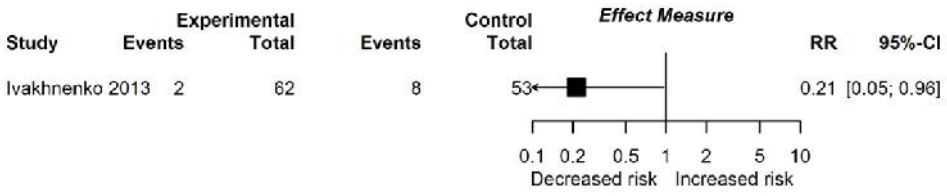


Figure 9 Prebiotics for preventing Cow's Milk Allergy



4. Prebiotics and risk of eczema

One systematic review and 9 original intervention studies investigated the effect of prebiotic supplementation on risk of eczema. The systematic review identified 4 studies, with overall significantly reduced AD with moderate statistical heterogeneity (Table 2). The benefit was seen most clearly in a single small study of high risk infants using a hydrolysed formula with vs without added prebiotic (Moro/Arslanoglu).

In total over 3800 participants were randomised in the original studies. Three studied infants at high risk of disease, four in infants at normal risk, one on infants with low disease risk and in one study disease risk was unclear. Risk of eczema (outcome) was assessed between 3 months and 5 years of age. Studies used one of four different outcome assessment methods. All studies were considered to be at high or unclear risk of conflict of interest, and one-third had a high risk of attrition bias (Figure 10).

Seven original studies were eligible for meta-analysis of eczema at age ≤4, and two at age >4. Meta-analysis showed evidence for a reduction in eczema risk in children at age ≤4 with borderline statistical significance, but not at age 5-14 (Figures 11 and 12). The heterogeneity in both meta-analyses was high. Subgroup analysis for eczema at age ≤4 showed no subgroup differences.

The study of Moro/Arslanoglu also reported eczema at the earlier time-point of 6 months, where this was significantly reduced in the prebiotic group - 10/102 (9.8%) prebiotic, 24/104 (23.1%) control (p=0.01) (1). The study of Kukkonen also reported atopic eczema (i.e. eczema plus positive SPT), where synbiotics reduced atopic eczema at 2 years – OR 0.66 (95%CI 0.46 – 0.95; p=0.02) but not at 5 years – OR 0.94 (0.70 – 1.28; p=0.71) (4, 17). In the study of Sierra no difference was reported in eczema between prebiotic and control groups, but data were only presented for a combined outcome of wheeze/ eczema/ food allergy, and not for eczema outcomes alone. In the study of Chien 3 participants in the synbiotic group, 9 in the prebiotic and 10 in the control group developed eczema by 3 months. The difference between synbiotic and other groups, adjusted for family history, was reported as statistically significant P<0.05. In the study of Gruber no significant difference was reported between groups in eczema at 5 years – data were not presented in a form that could be included in meta-analysis. In the study of Boyle data were also reported for cumulative incidence of eczema at 18 months, where there was no significant difference between groups RR 1.09

(0.89, 1.34); the authors also reported no difference between groups in time to first onset of eczema (P=0.81).

Evidence was downgraded to no evidence, due to concerns about study quality (-1, due to risk of bias and risk of conflict of interest in included studies); imprecision (-1, wide confidence intervals, borderline statistical significance); indirectness (-1, of study populations); and inconsistency (-1, high statistical heterogeneity) in analyses of prebiotics and AD.

So we conclude that there is no evidence that prebiotics prevent AD, but high quality studies at low risk of bias or conflict of interest are lacking.

Figure 10 Risk of bias in intervention studies of prebiotics and eczema



Table 2 Findings from the previous systematic review

Study	Outcome measure	No. participants (studies)	Outcome (95% CI)	I^2
Osborn (10)	AD at < 2 years*	1220 (4)	**RR 0.68 [0.48, 0.97]**	34%
	AD at < 2 years (high risk infants)	134 (1)	**RR 0.49 [0.24, 1.00]**	-
	AD at < 2 years (normal/low risk infants)	1086 (3)	RR 0.76 [0.51, 1.14]	42%
	AD at < 2 years (fed human milk)	92 (1)	RR 1.05 [0.41, 2.65]	-
	AD at < 2 years (fed mainly standard formula)	994 (2)	RR 0.71 [0.45, 1.11]	65%
	AD at < 2 years (fed mainly hydrolysed formula)	134 (1)	**RR 0.49 [0.24, 1.00]**	-

* the authors also analysed eczema according to type of prebiotic used, and found evidence that GOS/FOS (9:1) 6.8 grams/ and acidic OS 1.2grams/L reduced the incidence of eczema (1 trial, 830 participants, RR 0.58 95%CI 0.35, 0.97); GOS/FOS (9:1) 8grams/L was also associated with reduced eczema (1 trial, 134 participants, RR 0.49 95% CI 0.24, 1.00) whereas other prebiotics namely polydextrose and GOS 4g/L, polydextrose, GOS and lactulose 8grams/L and GOS/FOS and acidic OS (4:1) 1.5 grams/kg/day were not associated with a significant effect when analysed alone.

Figure 11 Prebiotics for preventing eczema at age ≤4 years

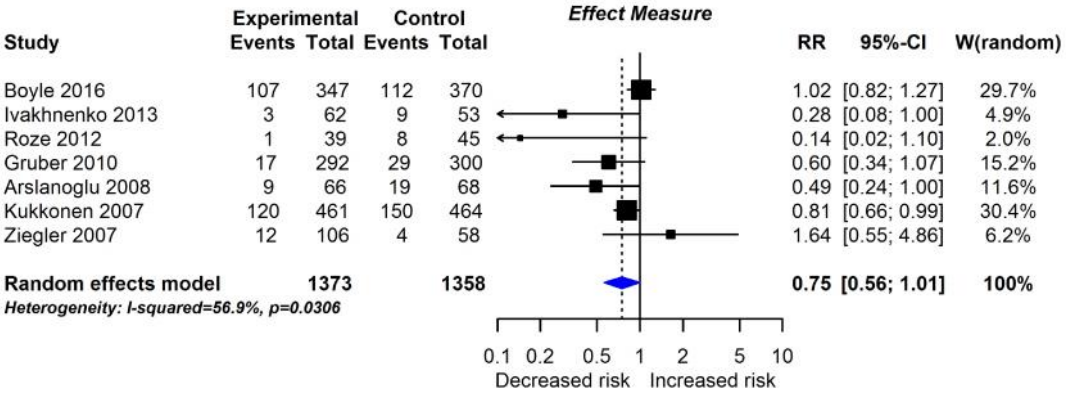
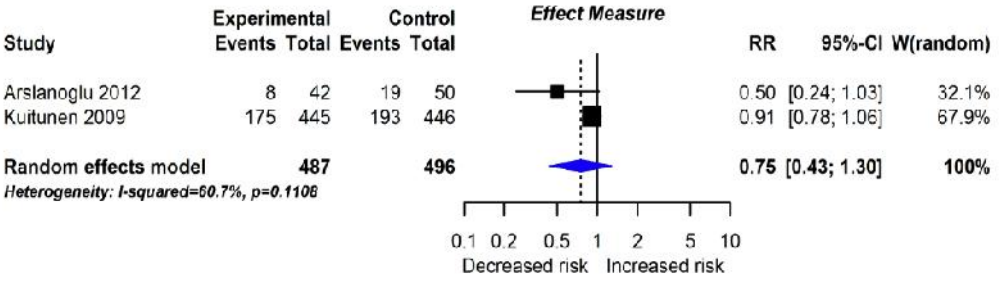


Figure 12 Prebiotics for preventing eczema at age 5-14 years



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Table 3 Subgroup analysis for prebiotics and risk of AD at age <4 years

	Number of studies	RR [95% CI]	I^2 (%)	P-value for between groups difference
Risk of disease – High	3	0.84 [0.64-1.10]	60	0.35
Risk of disease – Normal/Low	4	0.56 [0.24-1.26]	54	
Intervention – prebiotic	5	0.74 [0.44-1.22]	67	0.59
Intervention – synbiotic	2	0.46 [0.09-2.27]	64	
Overall risk of bias – Low	2	0.50 [0.08-3.24]	72	0.74
Overall risk of bias – High/Unclear	5	0.69 [0.48-0.98]	40	
Conflict of interest bias – Low	0	-	--	-
Conflict of interest bias – High/Unclear	7	0.75 [0.56-1.01]	57	

5. Prebiotics and risk of wheeze

One systematic review including 2 trials, and five original intervention trials investigated the effect of prebiotics on risk of wheezing or asthma. The systematic review found reduced wheezing in a subgroup analysis which included one study (Moro/Arslonagu) of high risk infants, but did not find an overall reduction in wheezing in the main analysis (Table 4).

In the original studies a combined total of over 2700 children were allocated to prebiotics or control treatment. All original studies were carried out in Europe, and in three studies children were at high risk of disease. Outcomes were assessed at 1 to 5 years, using different definitions of wheeze/asthma.

All studies had a high risk of conflict of interest, and 20% had a high risk of attrition bias (Figure 12). Three studies reported data eligible for meta-analysis, one in children below the age of 4, one over this age, and one at both age groups. In younger children (below 4 years old, Figure 13) there was evidence of a lower risk of recurrent wheeze if infants were fed with prebiotics (RR 0.39; 95% CI 0.20 – 0.77) in two studies with no statistical heterogeneity (I^2=0%). However this was not evident in older children (RR 0.90; 95% CI 0.66 – 1.23; figure 14) nor in data that could not be included in meta-analysis (discussed below). Both studies included in Figure 13 were in selected populations – one in infants who already had AD, one in infants fully formula fed prior to 6 weeks age. Both were at high risk of conflict of interest, and one at high overall risk of bias. This evidence was downgraded for study quality, inconsistency, imprecision and indirectness and is therefore not supportive of a relationship between prebiotic supplementation and reduced risk of recurrent wheezing.

Data that could not be included in meta-analyses

Analysis of a subgroup from the study of Kukkonen and colleagues found doctor diagnosis of asthma at age 5 in 4/64 (6.3%) children from the synbiotic group, and 4/67 (6.0%) control (p=1.0) (18), and no difference between groups in atopic asthma (ie asthma associated with positive SPT or sIgE) – OR 1.09 (95%CI 0.69 – 1.71; p=0.39). In the study of Van der Aa, there was a trend to reduced prevalence of ‘wheezing without colds’ (p=0.06) and significantly reduced ‘wheezing +/- noisy breathing’ (p<0.01) in the first year in synbiotic

treated infants (3). In the study of Sierra no difference was reported in wheeze between prebiotic and control groups, but data were only presented for a combined outcome of wheeze/ eczema/ food allergy, and not for wheeze outcomes alone – so data from this study could not be included in meta-analysis. In the study of Gruber no significant difference was reported between groups in doctor diagnosed asthma – data were not presented in a form that could be included in meta-analysis.

Overall we found no evidence that prebiotics reduce risk of wheezing or recurrent wheezing.

Figure 13 Risk of bias in intervention studies of prebiotics and wheeze

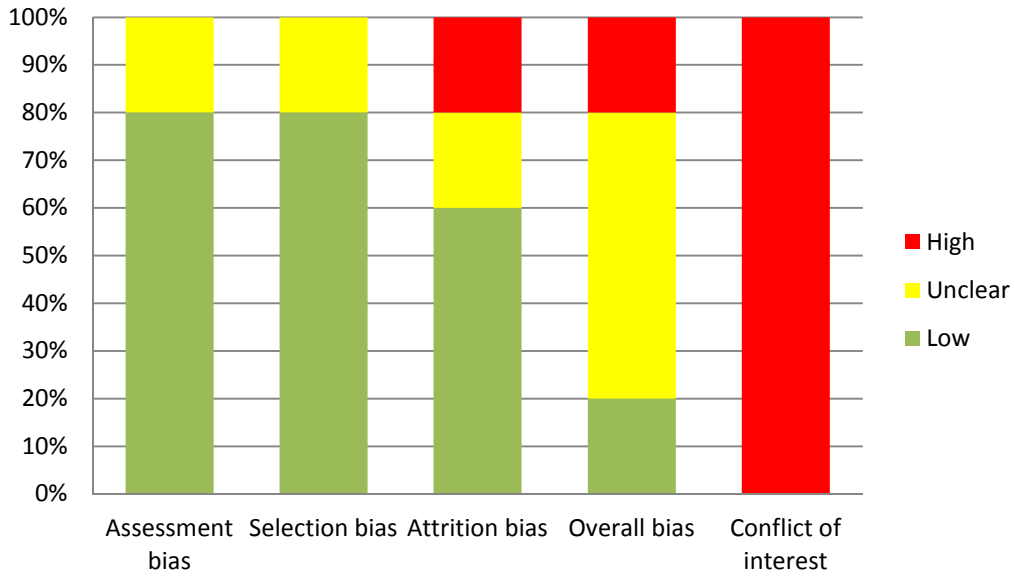


Table 4 Findings from the previous systematic review

Study	Outcome measure	No. participants (studies)	Outcome (95% CI)	I^2
Osborn (10)	Wheeze at < 2 years*	226 (2)	RR 0.70 (0.41, 1.19)	34%
	Wheeze at < 2 years (high risk infants)	134(1)	**RR 0.37 (0.14, 0.96)**	-
	Wheeze at < 2 years (normal/low risk infants)	92 (1)	RR 1.07 (0.56, 2.06)	42%
	Wheeze at < 2 years (fed human milk)	92 (1)	RR 1.07 (0.56, 2.06)	-
	Wheeze at < 2 years (fed mainly standard formula)	0 (0)	-	65%
	Wheeze at < 2 years (fed mainly hydrolysed formula)	134 (1)	**RR 0.37 (0.14, 0.96)**	-

* the authors also analysed wheeze according to specific prebiotic used, and found no evidence that any specific prebiotic is effective at reducing incidence of infant wheeze.

Figure 14 Prebiotics for preventing recurrent wheeze at age ≤ 4 years

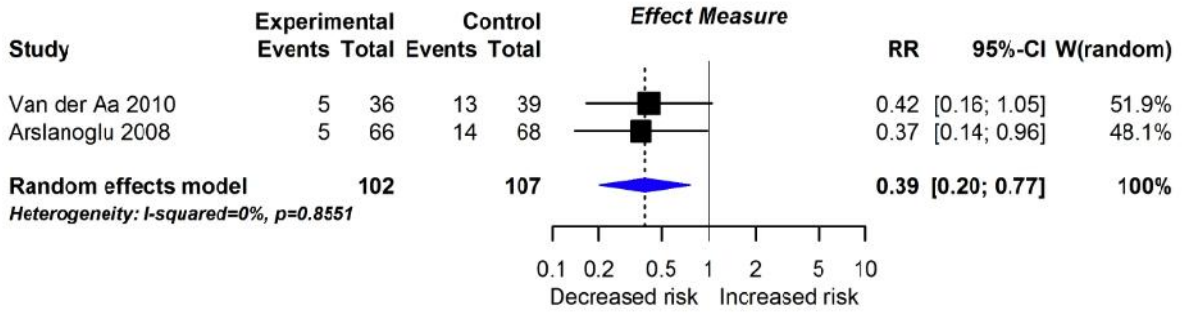
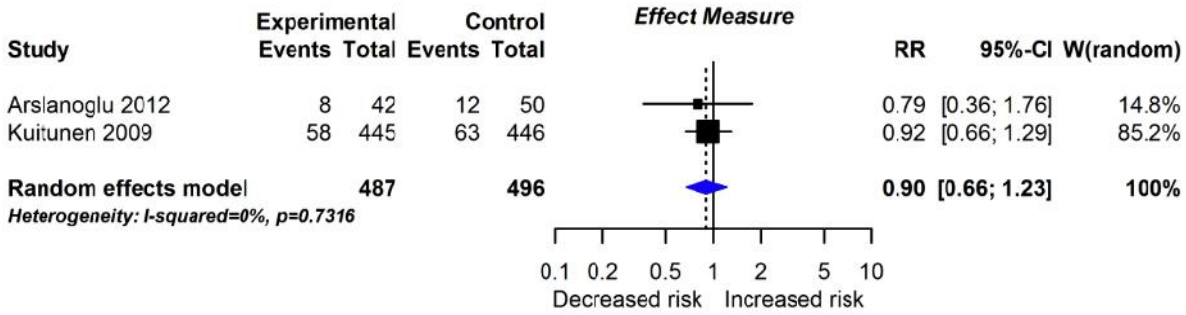


Figure 15 Prebiotics for preventing recurrent wheeze at age 5-14 years



6. Prebiotics and risk of allergic rhinitis

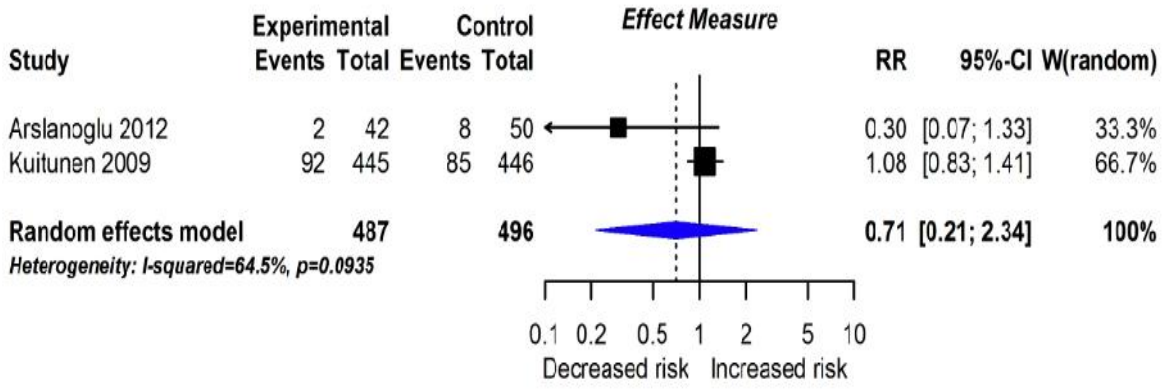
Three intervention trials assessed the effect of prebiotic supplementation on risk of allergic rhinitis. All were European studies, two in high risk populations and one in a low risk population. In total, over 1100 infants were allocated to prebiotics, and 1100 to a control treatment. The interventions lasted for 6 months, and the outcome was measured at age 5 years. The risk of conflict of interest was high in all studies, and one study had a high risk of attrition bias (Figure 15). The combined effect of prebiotic supplementation on risk of allergic rhinitis from two studies is shown in Figure 16. There was no evidence that prebiotics reduce the risk of allergic rhinitis (RR 0.71; 95% CI 0.2, 2.34), with high statistical heterogeneity. In the study of Gruber no significant difference was reported between groups in doctor diagnosed hayfever – data were not presented in a form that could be included in meta-analysis.

Overall we found no evidence that prebiotics influence risk of allergic rhinitis, in high risk infants.

Figure 16 Risk of bias in intervention studies of prebiotics and risk of allergic rhinitis



Figure 17 Prebiotics for preventing allergic rhinitis at age 5-14 years



Conclusions

In this systematic review of prebiotic supplementation for reducing risk of allergic outcomes, we found no evidence that prebiotics prevent wheeze, allergic sensitisation, allergic rhinitis or food allergy. Most studies identified had high risk of conflict of interest due to direct industry involvement in the trials, and a significant number of studies had high risk of attrition bias.

Our findings are similar to those of Osborn and colleagues (22), who conducted a Cochrane systematic review of prebiotics for preventing allergic outcomes which was included in our overview of recent systematic reviews in summer 2013. They included one trial in premature infants, which we excluded based on our study protocol which excludes populations which clearly represent <5% of the UK population, and they did not include some of the other publications identified in our systematic review. Osborn et al found that prebiotic supplementation reduced eczema risk in the first 2 years (RR 0.68; 95% CI 0.48 – 0.97) with moderate statistical heterogeneity (I^2 = 34%). In our analysis, which excluded one of the trials in Osborn's analysis, included two that were excluded by Osborn (Roze 2012; Kukkonen 2007) and included further trials published since Osborn's search, this effect was of borderline statistical significance at age 0-4 and not seen at all at age 5-14. Heterogeneity in our analysis was higher (I^2 = 57%), and all studies contributing to AD meta-analysis were considered to be at high risk of conflict of interest. We therefore judge that there is no evidence that prebiotics reduce AD risk.

Osborn also found a protective effect for wheeze in the first 2 years in infants at high risk of atopy based on one study (RR 0.37, 95% CI 0.14 – 0.96), but did not find a protective effect in all infants (2 studies; RR 0.70; 95%CI 0.41 – 1.19; I^2=70%). They concluded that further research is needed and the results should be interpreted with caution, due to the high risk of bias – citing attrition bias and possible publication bias – they identified several prebiotic trials where allergic outcomes may have been captured but had not yet been reported. We found a reduced risk of recurrent wheeze at aged 0-4 years in one analysis, based on two small studies (the same one as Osborn identified, and one extra). We did not however find an effect at age 5-14 years, and we downgraded this to no evidence due to inconsistency with other studies that could not be included in the meta-analysis, study quality, indirectness due

to the specific study populations, and imprecision. Our updated search on 26th February 2017 identified a further 2 systematic reviews of prebiotics or synbiotics for prevention of allergic outcomes. R-AMSTAR scoring identified no further high quality reviews. Dang 2013 (23) identified 18 trials of prebiotics, probiotics or synbiotics for preventing eczema (our review identified 29 such trials). They did not find any effect of prebiotics on AD risk or risk of allergic sensitisation, and did not assess later timepoints or other outcomes. De Moura 2013 (24) - included both treatment and prevention studies in the same analysis which may not be appropriate – and failed to identify several of the studies included in our review.

Taken together, the results of the current systematic review do not provide evidence to support the use of prebiotics for preventing allergic sensitisation or disease. The findings have largely arisen from industry-sponsored studies undertaken in populations of infants with very limited or no breastfeeding, and often with significant post-randomisation losses/exclusions. Given the very high levels of prebiotics naturally present in human breast milk, the role of prebiotics in infant nutrition is likely to be as an additive to formula milk in formula-fed infants, rather than as a supplement for all infants, but an allergy-prevention effect remains to be proven.

Conclusions:

Current evidence does not support an effect for prebiotics in reducing risk of wheeze, allergic sensitisation, AD, food allergy or allergic rhinitis.

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PROBIOTIC SUPPLEMENTATION IN PREGNANCY, LACTATION AND/OR INFANCY, AND RISK OF ALLERGIC SENSITISATION OR ALLERGIC DISEASE

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1. Probiotics and risk of allergic outcomes – summary of interventions and findings

Probiotics are traditionally defined as live microorganisms which, when administered in adequate amounts, confer a health benefit on the host. Synbiotics are defined as a combination of probiotic and prebiotic administered to the same individual. In this analysis we included studies of any microbial intervention, whether live or heat-killed, given either alone (=probiotic) or in combination with a prebiotic (=synbiotic). We included heat-killed microbes for two reasons. First observational studies exploring the hygiene hypothesis have found relationships between both live microbial exposures, and non-live microbial components, and allergic outcomes. Second there is a lack of good understanding of the mechanisms through which probiotics might prevent allergic outcomes, and while microbes may need to be live for some health indications of probiotics, it is unclear whether this is the case when they are used for the prevention of allergic outcomes. We planned to undertake subgroup/stratified analyses for meta-analyses which included >5 studies, and where relevant to include probiotic/synbiotic intervention as a subgroup. We planned to assess publication bias using Funnel plots and Egger's test where there were ≥10 studies in a meta-analysis. Due to the significant number of studies and participants included in intervention trials of reasonable quality, we did not analyse the very small number of observational studies which we identified reporting probiotic intake in relation to allergic outcomes, in keeping with the hierarchical approach outlined in the review protocols. In total we identified two high quality systematic reviews in our July 2013 literature search – data were extracted from these reviews, and included in relevant sections of this report. In our updated search on 26th February 2017, we identified three further high quality systematic reviews – the findings of these reviews are referred to in the Conclusions section of this report. In total we identified 28 original trials (27 RCT, 1 CCT) investigating the effect of 30 different probiotic interventions during infancy and/or pregnancy on allergic outcomes.

Interventions used

Characteristics of studies are shown in Table 1, and interventions used are summarised in Table 2. Below is a brief description of the intervention for each original study:

The **Abrahamsson** study (1) used 1 x 10^8 CFU/day freeze-dried *Lactobacillus reuteri* (strain American Type Culture Collection 55730; BioGaia AB, Stockholm, Sweden), suspended in

three-quarters refined coconut oil and one-quarter refined peanut oil containing cryo-protective components. This was given to pregnant mothers from week 36 until delivery, and then to the infants until 12 months of age. The **Allen** study (2) administered 2 strains of lactobacilli and 2 strains of bifidobacteria to pregnant mothers from week 36 and to their offspring until six months of age. The study by **Boyle** and colleagues (3) used 1.8 x 10^{10} colony forming units (cfu)/day of *L. rhamnosus* GG (LGG; American Type Culture Collection 53103; Dicofarm, Italy) each morning from 36 weeks gestation until delivery. The Cabana study used 10^{10} cfu/day of LGG to infants for the first 6 months (4). The Chien study used B. breve M-16V (7.5x10^{8}CFU/100ml) for the first 4 months to infants, within a formula milk, with added prebiotic (5). The **De Leon** study (6) used lactobacillus/bifidobacterium strains given daily for 4 months to infants or their breastfeeding mothers. The **Dotterud** study (7) used 250 mL probiotic low fat fermented milk, for 4 months, from 36 weeks prenatally to 3 months of age while breastfeeding (i.e. mother only). The probiotic milk, Biola (Tine BA, Oslo, Norway), contained LGG, *Bifidobacterium animalis* subsp. lactis Bb-12 (Bb-12) and *L. acidophilus* La-5 (La-5), equalling 5 x 10^{10} cfu of LGG and Bb-12, and 5 x 10^{9} of La-5 per day for its entire shelf life. The **Enomoto** study (8) used 5 x 10^{9} cfu *B. longum* BB536 (ATCC BAA-999) and 5 x 10^{9} cfu *B. breve* M-16V given to pregnant women from 36 weeks gestation then for 6 months to the infant. The **Huurre** study (9) used 1 x 10^{10} cfu/day each of LGG (ATCC 53103, Valio Ltd, Helsinki, Finland) and *B. lactis* Bb12 (Chr. Hansen, Horsholm, Denmark). The **Kalliomaki** study (10) used 2 x 10^{10} cfu of LGG (Valio Ltd; Helsinki, Finland) daily for 2–4 weeks before expected delivery and 6 months after birth (to mothers if breastfeeding, or to infants if not). The **Kim** study (11) used a mixture of *B. bifidum* BGN4 (1.6 x 10^{9} cfu), *B. lactis* AD011 (1.6 x 10^{9} cfu), and *L. acidophilus* AD031 (1.6 x 10^{9} cfu) (Bifido Inc., Hongchungun, Korea) daily from 8 weeks before expected delivery to 3 months after delivery to mother, and from 4 to 6 months to infant. The **Kopp** study (12) used 2 capsules containing 5 x 10^{9} cfu/day of LGG (American type culture collection 53103) by Infectopharm, Heppenheim, Germany. Mothers consumed this from 2-4 weeks before delivery until 6 months after birth. The **Kukkonen** study (13) used a probiotic during the last 2-4 weeks of pregnancy – LGG (ATCC 3103), 10^{10} cfu/day; *L.rhamnosus* LC705 (DSM 7061), 1010 cfu/day; *B. breve* Bb99(DSM 13692), 4 x 10^{8} cfu/day; and *Propionibacterium freudenreichii* ssp. shermanii JS(DSM 7076), 4 x 10^{9} cfu/day (Valio, Helsinki, Finland). Infants then received the same probiotics with 20 drops of syrup containing 0.8 g GOS prebiotic daily for 6 months. The **Lau** study used heat-killed

Escherichia coli Symbio DSM 17252 and *E faecalis* Symbio DSM 16440 4.5-13.5 x 10^7 cfu/day to the infant only, from 5 weeks age to 7 months age. The **Lodinová-Žádníková** study (14) gave 0.8 x 10^9 cfu *E. coli* 3 times per weeks to infants from <48 hours age to 4 weeks (Dyntec. Co. (Terezín, Czech Republic)). The Lundelin study used L. rhamnosus GG, B. lactis, L. paracasei ST11, B.longum BL999 for mothers and infants (15). In the study of **Morisset** and colleagues (16), participants were fed a fermented formula without live bacteria (FWLB), given from birth -or weaning- to 12 month of age. During breastfeeding, mothers ingested the same formula as their child. In the study of **Niers** (17), pregnant mothers during the last 6 weeks of pregnancy and their infants for 12 months, were fed 1 x 10^9 cfu each of *B. bifidum* W23, B. lactis W52 and *Lactococcus lactis* W58 (Ecologic Panda, Winclove Bio Industries B.V. In the **Ou** study (18), the authors used LGG (ATCC 53103; 1 x 10^{10} cfu/day; Valio Ltd.) beginning from 24 weeks gestation (second trimester) of pregnancy until delivery. After delivery, LGG was administered exclusively to breastfeeding mothers or to non-breastfeeding neonates, where it was mixed with water and given by spoon for 6 months. In the **Prescott** study (19), infants were fed 3 x 10^9 cfu/day *L. acidophilus* LAVRI-A1 in maltodextrin (Probiomics, Sydney, Australia) for six months. In the **Rautava 2006** study (20), authors used an infant formula (Enfamil, Mead Johnson Nutritionals, Evansville, IN) supplemented with 1 x 10^{10} cfu of both LGG and *B. lactis* Bb-12 (Chr. Hansen, Hoersholm, Denmark), given to infants daily until 12 months of age. The same group (**Rautava 2012**) investigated the effect of probiotics in a separate intervention (21), using *L. rhamnosus* LPR (CGMCC 1.3724) and *B. longum* BL999 (ATCC: BAA-999) [Nestle S.A.] at 1 x 10^9 cfu, each given daily as a sachet diluted in a glass of water. The study of **Roze** (22) used infant formula containing a synbiotic - *L. rhamnosus* LCS-742 and *B. longum* subsp infantis M63, and a 96% galactooligosaccharides (GOS)/ 4% fructooligosaccharides (FOS) prebiotic. The formula was also enriched with bovine a-lactalbumin, using whey protein concentrate, and was fed to infants for the first 6 months. The study of **Scalabrin** (23) used Nutramigen plus LGG at 10^8 cfu per gram of formula powder, given to infants for 1 year. In the study of **Soh** (24), the authors used a cow's milk-based infant formula supplemented with *B. longum* BL999 (BB536, Morinaga, Japan) 1 x 10^7 cfu/g and *L. rhamnosus* LPR (CGMCC 1.3724) 2 x 10^7 cfu/g, initiated within 12 hours of life for the first six months. The study of **Van der Aa** (25) used an extensively hydrolyzed whey-based formula (Nutrilon Pepti; Nutricia, Netherlands) with synbiotics for 12 weeks. The synbiotic contained Immunofortis at 8g/L, and *B. breve* M-6V (Morinaga Milk Co, Ltd., Tokyo, Japan) 1.3 x 10^9 cfu/100 ml. The study

of **West** (26) combined a daily intake of cereals with 1 x 10^8 cfu of strain LF19 per serving (Semper AB, Stockholm, Sweden) during weaning, from 4 to 13 months of age. The study of **Wickens** (27) used 6 x 10^9 cfu/day *L rhamnosus* HN001 or 9 x 10^9 cfu/day *B animalis* subsp lactis HN019, delivered in a freeze dried capsule (Fonterra Cooperative Group, Auckland, New Zealand). Capsule powder was given to the infant either undiluted or mixed with water, breast milk, or formula and given with a teaspoon. Mothers took the capsules from 35 weeks gestation until the end of the breastfeeding period or up to 6 months post-partum, whilst infants took it from 2-16 days of birth until 2 years of age.

Populations and Outcomes assessed

Outcomes studied were allergic sensitisation (total IgE, specific IgE and skin prick test (SPT)), food allergy, AD, allergic rhinitis, and wheeze/recurrent wheeze. Overall 6000 infants were randomly or non-randomly allocated to an intervention arm. Nineteen studies were in infants at high risk of allergic disease. 17 studies were carried out in Europe, 9 in Asia-Pacific and 2 in the USA. The definitions of diseases varied across studies but with few exceptions,studies used commonly accepted criteria for these definitions.

Overall findings

Overall the quality of evidence was moderate - there was a low or unclear risk of bias in most studies, although approximately a quarter of studies were considered to be at high risk of conflict of interest bias due to direct industry involvement. Overall we found MODERATE level evidence (-1 inconsistency) that probiotics can prevent atopic AD ie AD with associated positive skin prick test or specific IgE test (11 studies, 12 interventions; 3000 participants RR 0.78; 95% CI 0.65 to 0.92; I^2=0%). We found MODERATE level evidence (-1 inconsistency) that probiotics can prevent *all* AD (19 studies, 21 interventions; 4700 participants; RR 0.78; 95% CI 0.68 to 0.90; I^2=61%) in children ≤ 4 years old. The majority of the evidence in these positive meta-analyses came from studies of high risk infants i.e. those with a positive family history of allergic disease (10 of 12 interventions for atopic AD; 17 of 21 interventions for *all* AD).

We found LOW level evidence (-1 indirect outcome; -1 imprecision) that probiotics can prevent allergic sensitisation to cow's milk, but no evidence that probiotics or synbiotics prevent allergic sensitisation to other allergens or prevent clinical cow's milk allergy.

We found no evidence for persistence of the effect on atopic AD or *all* AD beyond age 4 years, and no evidence that probiotics prevent other allergic outcomes.

Table 1 Characteristics of included studies evaluating probiotic supplementation and allergic outcomes

Study	N Intervention / Control	Study Design	Country	Intervention & Population studied	Disease risk	Age at outcome (years)	Outcomes reported
Pelucchi (28)	14 RCT (1417 participants)	SR	-	Pregnant or lactating women or their infants; any probiotic(s) versus no probiotic	all	Up to age 12	AD, IgE-associated AD
Tang (29)	11 RCT (1007 participants)	SR	-	Pregnant or lactating women or their infants; probiotic versus no probiotic	high	All	AD, asthma, allergic sensitisation to any food
Abrahamsson 2007 (1) Abrahamsson 2013 (30)	117/ 115	RCT	Sweden	Probiotic Pregnant women (week 36) and infants (for 12 months)	high	2, 7	AD (Seymour), Wheeze (single, or ≥2 episodes), ARC (watery discharge ≥2 times with same allergen), Allergic sensitisation (SPT common allergens)
Allen 2012 (2) Allen 2014 (31)	220/ 234	RCT	UK	Probiotic Pregnant women (week 36) and infants (for 6 months)	high	2	AD (DD), Allergic sensitisation (SPT common allergens, CM, Egg), Wheeze (unclear), ARC (unclear), Food Allergy (parent report)
Boyle 2011 (3)	125/ 125	RCT	Australia	Probiotic Pregnant women (week 36)	high	1	AD (UK Working party criteria), Wheeze (wheeze + loose API), Allergic sensitisation (SPT common allergens)
Cabana, 2015 (4)	93/ 92	RCT	USA	Probiotic Infants (for 6 months)	high	2	Wheeze (unclear); AD (unclear)

Study	N Intervention / Control	Study Design	Country	Intervention & Population studied	Disease risk	Age at outcome (years)	Outcomes reported
Chien, 2016 (5)	Unclear – outcome reported in 45 (synbiotic), 39 (prebiotic), 45 (control)	RCT	Singapore	Prebiotic & Synbiotic scGOS/lcFOS (0.8g/100ml) and B. breve M-16V (7.5x108CFU/100ml), or scGOS/lcFOS (0.8g/100ml), or control formula from birth to 4 months, in mixed fed infants born by elective Caesarean	unclear	0.4	AD (unclear)
De Leon 2007 (6) Simon 2007 (32)	Total = 33	RCT	Philippines	Probiotic for 4 months to infants or to their breastfeeding mothers	high	0.5	AD (unclear) Allergic sensitisation (Total IgE)
Dotterud 2010 **(7)** **Simpson 2015** (33)	211/ 204	RCT	Norway	Probiotic Mothers only (36 weeks gestation to 3 months after birth)	normal	2	AD (UK Working party criteria), Wheeze (≥3 episodes + ICS), ARC (DD), Allergic sensitisation (SPT common allergens)
Enomoto 2014 (8)	130/36	CCT	Japan	Probiotic Pregnant women (week 36) and infants (for 6 months)	normal	1.5	AD (Hanifin and Rajka), Wheeze (physician assessment), ARC (physician assessment)
Huurre 2008 (9)	72/ 68	RCT	Finland	Probiotic Infants (for 6 months)	high	1	AD (Hanifin and Rajka), Allergic sensitisation (SPT common allergens)

Study	N Intervention / Control	Study Design	Country	Intervention & Population studied	Disease risk	Age at outcome (years)	Outcomes reported
Kalliomaki 2001 (34) Kalliomaki 2003 (10) Kalliomaki 2007 (35) Rautava 2002 (36)	77/ 82	RCT	Finland	Mothers and infants; from 2–4 weeks before expected delivery and 6 months of age	high	2	AD (relapsing itchy lesions with typical location), Wheeze (symptoms + ICS), ARC (symptoms with allergen exposure), Food Allergy (CMA by DBPCFC), Allergic sensitisation (Total IgE and SPT/sIgE to common allergens)
Kim 2010 (11)	57/ 55	RCT	Korea	Probiotic, pregnant women and infants from 4 to 6 months	high	1	AD (Hanifin and Rajka), Allergic sensitisation (Total IgE and sIgE to common allergens)
Kopp 2008 (12)	54/ 51	RCT	Germany	Probiotic Mothers (2-4 weeks before birth until 3 months post birth) and infants (months 4-6)	high	2	AD (UK Working party criteria), Wheeze (≥5 episodes), Allergic sensitisation (Total IgE and sIgE to common allergens)
Kukkonen 2007 (13) Kuitunen 2009 (37) Kukkonen 2011(38)	610/ 613	RCT	Finland	Synbiotic Pregnant women (2-4 weeks before delivery) and infants up to 6 months	high	2, 5	AD (UK Working party criteria), Wheeze (≥2 episodes + interval symptoms), ARC (symptoms + sensitisation), Allergic sensitisation (Total IgE and SPT/sIgE to common allergens)

Study	N Intervention / Control	Study Design	Country	Intervention & Population studied	Disease risk	Age at outcome (years)	Outcomes reported
Lau 2012 (39)	303/ 303	RCT	Germany	Probiotic Infant from 5 weeks up to 7 months age	high	2	AD (Hanifin and Rajka), Allergic sensitisation (Total IgE and sIgE)
Lodinová-Žádníková 2010 (40)	56/ 57	RCT	Czech Republic	Probiotic Infants - birth to age 4 weeks	high	1	AD (unclear), Food allergy (unclear), Wheeze (unclear) Allergic sensitisation (Total IgE and sIgE to common allergens)
Lundelin, 2016 (15) Luoto, 2014 (41)	31, 31, 32	RCT	Finland	Probiotic Pregnant women and infants	normal	1	Wheeze (ISAAC); ARC ISAAC); AD (ISAAC); FA (unclear)
Morisset 2008 (16)	59/ 56	RCT	France	Probiotic Infant – from birth or weaning, to age 1 year	high	1	Food allergy (CMA by physician assessment) Allergic sensitisation (sIgE to cow's milk)
Niers 2009 **(17)** **Gorissen, 2014 (42)**	78/ 78	RCT	Netherlands	Probiotic Pregnant women during the last 6 weeks of pregnancy and their infants until age 1 year	high	2	AD (modified ECRHS) Allergic sensitisation (Total IgE and SPT/sIgE to common allergens) AR (ISAAC) Wheeze (physician assessment), Food allergy (physician assessment), lung function (FEV1)

Study	N Intervention / Control	Study Design	Country	Intervention & Population studied	Disease risk	Age at outcome (years)	Outcomes reported
Ou 2012 (18)	95/ 96	RCT	Taiwan	Probiotic Pregnant women (third trimester) and then breastfeeding mothers, or directly to infants, until age 6 months	high	3	AD (ISAAC), Wheeze (ISAAC), ARC (ISAAC), Allergic sensitisation (sIgE to common allergens)
Taylor 2007 (43), Prescott 2008 (44) Jensen 2012 (termed Taylor 2012 in some meta-analyses) (45)	115/ 111	RCT	Australia	Probiotic, infants until 6 months	high	1, 2.5, 5	AD (DD), Food allergy (any food - physician assessment), Wheeze (DD), ARC (symptoms + sensitisation), Allergic sensitisation (SPT common allergens)
Rautava 2006 (20)	38/ 43	RCT	Finland	Probiotic Infant formula; infants until age 1 year	normal	1	AD (Hanifin and Rajka), Food allergy (CMA by DBPCFC) Allergic sensitisation (SPT food allergens)
Rautava 2012 (21)	82/ 78	RCT	Finland	Probiotic Infants fed daily until age 1 year	high	2	AD (Hanifin and Rajka), Allergic sensitisation (SPT common allergens)
Roze 2012 (22)	48/ 49	RCT	France	Synbiotic Infants (first 6 months)	normal	0.5	AD (UK Working party criteria)
Scalabrin 2009 (46) Scalabrin 2014 (47) Scalabrin 2017 (48)	95/ 95	RCT	USA	Probiotic Infants (first 12 months)	normal	0.4, 5	Allergic sensitisation (sIgE to common allergens), AD (unclear), Wheeze (unclear), ARC (unclear), Food Allergy (unclear)

Study	N Intervention / Control	Study Design	Country	Intervention & Population studied	Disease risk	Age at outcome (years)	Outcomes reported
Soh 2009 (49) Loo 2014 (50)	127/ 126	RCT	Singapore	Probiotic Cow's milk-based infant formula supplemented with Probiotic; infants up to 6 months of age	high	1	AD (Seymour), Allergic sensitisation (Total IgE and SPT/sIgE to common allergens) Food allergy (physician assessment), AR (physician assessment)
Van der Aa 2010 (51)	46/ 44	RCT	Netherlands	Synbiotic Whey-based formula combined with Synbiotic, for 3 months	high	1	Wheeze (≥3 episodes), Allergic sensitisation (Total IgE)
West 2009 (26) West 2013 (52)	89/ 90	RCT	Sweden	Probiotic To infant from 4 until 13 months	normal	1, 8-9	AD (itchy rash with typical distribution, or DD), Wheeze (DD), ARC (DD), Allergic sensitisation (Total IgE and sIgE to common allergens) Food allergy (physician assessment)
Wickens 2008 (27) Wickens 2012 (53) Wickens 2013 (54)	341/ 171	RCT	New Zealand	Probiotic To pregnant women (35 weeks gestation to end up of BF or 6 months post-partum) and infants from 2-16 days of birth to 2 years	high	2, 4, 6	AD (UK Working party criteria), Wheeze (ISAAC), ARC (ISAAC), Allergic sensitisation (SPT common allergens)

Seymour criteria and UK working party criteria are both modifications of the Hanifin and Rajka criteria. AR: Allergic Rhinitis. ARC: Allergic Rhinoconjunctivis. DD doctor's diagnosis; SPT skin prick test; sIgE specific IgE; RCT randomised controlled trial; CCT controlled clinical trial;

ISAAC International Study of Asthma and Allergies in Childhood; ICS inhaled corticosteroids; ECRHS European Community Respiratory Health Survey; API Asthma Predictive Index

Table 2 Probiotic(s) and daily dose used in intervention trials of probiotics/synbiotics for primary prevention of allergic outcomes

First Author & Publication Year	Intervention
Abrahamsson 2007 **(1)**	1 x 10^8 cfu/day freeze-dried L reuteri (strain American Type Culture Collection 55730)
Allen 2012 **(2)**	6.5 x 10^9 cfu/day L. salivarius CUL61, 1.25 x 10^9 cfu/day L. paracasei CUL08, 1.25 x 10^9 cfu/day B. animalis subsp. Lactis CUL34, 1.25 x 10^9 cfu/day B. bifidum CUL20
Boyle 2011 **(3)**	1.8 x 10^{10} cfu/day L. rhamnosus strain GG (ATCC 53103)
Dotterud 2010 **(7)**	250 mL probiotic milk with L. rhamnosus strain GG (ATCC 53103), B. animalis subsp. lactis Bb-12 and L. acidophilus La-5
Cabana, 2015 (4)	Lactobacillus GG from birth to 6 months to infants at 10^{10} cfu/day
Chien, 2016 (5)	Infant formula supplemented with scGOS/lcFOS (0.8g/100ml) and B. breve M-16V (7.5x108CFU/100ml), or formula with scGOS/lcFOS (0.8g/100ml), or control formula from birth until 4 months
Enomoto 2014 **(8)**	5 x 10^9 cfu B. longum BB536 (ATCC BAA-999) and 5 x 10^9 cfu B. breve M-16V
Huurre 2008 **(9)**	1 x 10^{10} cfu/day each of L. rhamnosus strain GG (ATCC 53103) and B. lactis Bb12
Kalliomaki 2001 **(10, 34-36)**	2 x 10^{10} cfu L. rhamnosus strain GG (ATCC 53103)
Kim 2010 **(11)**	B. bifidum BGN4 [1.6 x 10^9 cfu], B. lactis AD011 (1.6 x 10^9 cfu), and L. acidophilus AD031 (1.6 x 10^9 cfu)
Kopp 2008 **(12)**	2 capsules containing 5 x 10^9 cfu/day L. rhamnosus strain GG (ATCC 53103)

First Author & Publication Year	Intervention
Kuitunen 2009 **(37)**	5 x 10^9 cfu L. rhamnosus strain GG (ATCC 53103), 5 x 10^9 cfu L rhamnosus LC705 (DSM 7061), 2 x 10^8 cfu B. breve Bb99(DSM 13692), 2 x 10^9 cfu Propionibacterium freudenreichii ssp. shermanii JS(DSM 7076). Infants received 1 capsule with 20 drops of syrup containing 0.8 g GOS daily for 6 months.
Lau 2012 **(39)**	Heat-killed E coli Symbio DSM 17252 and E faecalis Symbio DSM 16440 4.5-13.5 x 10^7 cfu/day
Lodinová-Žádníková 2010 **(40)**	0.8 x 10^9 cfu E. coli 3 times weekly to infant, from <48 hours age to 4 weeks
Lundelin, 2016 (15) **Luoto, 2014 (41)**	L. rhamnosus GG, B. lactis, L. paracasei ST11, B.longum BL999 given to pregnant women and their infants
Morisset 2008 **(16)**	Fermented formula without live bacteria (FWLB)
Niers 2009 **(17)**	1 x 10^9 cfu each of B. bifidum W23, B. lactis W52 and Lc. lactis W58
Ou 2012 **(18)**	L. rhamnosus strain GG (ATCC 53103) 1 x 10^{10} cfu/day
Rautava 2006 **(20)**	Infant formula supplemented with 1 x 10^{10} cfu L. rhamnosus strain GG (ATCC 53103) and B. lactis Bb-12
Rautava 2012 **(21)**	L. rhamnosus LPR (CGMCC 1.3724) and B. longum BL999 (ATCC: BAA-999) at 1 x 10^9 cfu each daily
Roze 2012 **(22)**	Extensively hydrolysed casein based formula, plus L. rhamnosus strain GG (ATCC 53103) at 10e8 cfu per gram of formula powder
Scalabrin 2009 **(46)**	Extensively hydrolysed casein based formula, plus L. rhamnosus strain GG (ATCC 53103) at 10e8 cfu per gram of formula powder
Simon 2007 **(32)**	L./B. strains
Soh 2009 **(49)**	At least 60 mL (9.26 g) a day of cow's milk-based infant formula supplemented with [B. longum BL999 (BB536) 1 x 10^7 cfu/g and L. rhamnosus LPR (CGMCC 1.3724) 2 x 10^7 cfu/g
Prescott 2008 **(44)**	3 x 10^9 cfu/day L acidophilus LAVRI-A1

First Author & Publication Year	Intervention
Van der Aa 2010 **(51)**	Extensively hydrolyzed whey-based formula with synbiotics [B. breve M-6V (1.3 x 10^9 cfu/100 ml and 90% scGOS / 10% lcFOS (Immunofortis), 0.8 g/100 ml]
West 2009 **(26)**	1 x 10^8 cfu/serving L.paracasei LF19 per serving fed to infant from 4 to 13 months age
Wickens 2008 **(27)**	6 x 10^9 cfu/day L rhamnosus HN001 or 9 x 10^9 cfu/day B animalis subsp lactis HN019

2. Probiotics and allergic sensitisation

Twenty-four studies reported the effect of probiotics on allergic sensitisation in over 5000 participants. Studies reported skin prick test (SPT) or specific IgE to common allergens, SPT to food allergens, and total IgE. Children's age at time of outcome measurement ranged between 4 months and 7 years old – as in other parts of this project, allergic sensitisation data were combined for all ages, due to limited data available when age-groups were analysed separately. Assessment bias was low in 85% of studies, and over half had a low risk of selection or attrition bias. Approximately a quarter of studies were considered to have a high risk of conflict of interest (Figure 1).

Fourteen studies (16 interventions) reported AS to any allergen. There was no evidence that probiotics reduce the prevalence of AS to any one of a panel of common allergens (Figure 2), with low statistical heterogeneity. Subgroup analyses showed no evidence of different treatment efficacy according to features of the intervention, population or risk of bias (Table 4). We found no evidence of publication bias (Figure 3). Similarly analysis of AS to aeroallergen or any food (Figures 4 and 5) did not show any evidence of a treatment effect, and subgroup analyses showed no important subgroup differences (Tables 5 and 6). We found no evidence for publication bias in the analysis of 'sensitisation to any food' as an outcome (Figure 6).

Analysis of allergic sensitisation to specific foods showed some evidence that sensitisation to cow's milk may be reduced by probiotics (Figure 7) but not egg or peanut (Figures 8 and 9). Subgroup analyses for milk and egg allergy showed no evidence of different efficacy according to features of the intervention, population or risk of bias (Tables 7 and 8). It is worth noting that 7 of 8 studies included in meta-analysis of cow's milk sensitisation were considered to be at high/unclear overall risk of bias, and 5 of 8 at high/unclear risk of conflict of interest.

Four studies (~2000 participants) which reported geometric mean total IgE could not be pooled due to extreme statistical heterogeneity, but the studies tended to show reduced total IgE in the probiotic compared to control group (Figure 10). However ten further studies (also ~2000 participants) which couldn't be presented on a forest plot due to the nature of outcome

data reported, all showed no significant difference in total IgE between probiotic and control group (11, 12, 17, 18, 26, 32, 39, 46, 51, 54).

Four studies reported some data which could not be included in meta-analyses. Huurre and colleagues (9) found no effect of probiotic supplementation with L.rhamnosus on risk of positive SPT to any food at age 1 year (OR 0.92; 95% CI 0.45, 1.9; p=0.83). Rautava (2006) found no statistically significant differences in the percentage of children having a positive SPT to any food (p=0.84) (20). Scalabrin and colleagues (46) found no effect on sensitisation to cow's milk using sIgE (p=0.63). Finally Kalliomaki and colleagues (10) reported allergic sensitisation at 2 years (shown in Figure 2), but also reported no effect on AS-any at ages 4 and 7 (35). Gorrisen (42) reported outcomes from the trial of Niers (17) at 6 years, and found no difference between groups in total IgE, specific IgE or skin prick test response to common allergens. Simpson reported outcomes from the trial of Dotterud at 6 years, and found no difference between groups in specific IgE or skin prick test response to common allergens.

Overall we found LOW (-1 indirect outcome; -1 imprecision due to low event numbers and borderline statistical significance) evidence that probiotics reduce allergic sensitisation to cow's milk, but no evidence that probiotics or synbiotics reduce allergic sensitisation to other allergens.

Figure 1 Risk of bias in intervention studies of probiotics and allergic sensitisation

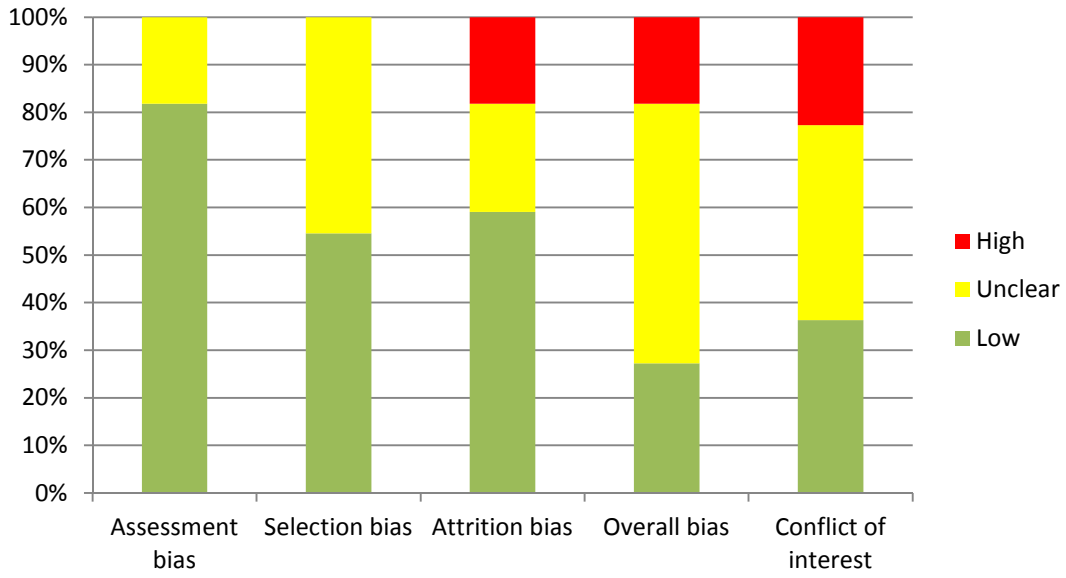


Table 3 Findings from a high quality systematic review identified in the 07/13 search

Study	Outcome measure	No. participants (studies)	Outcome (95% CI)	I^2
Tang (29)	AS-Food	1826 (7)	**RR 0.95 [0.80, 1.12]**	19

Figure 2 Probiotics and risk of AS to any allergen

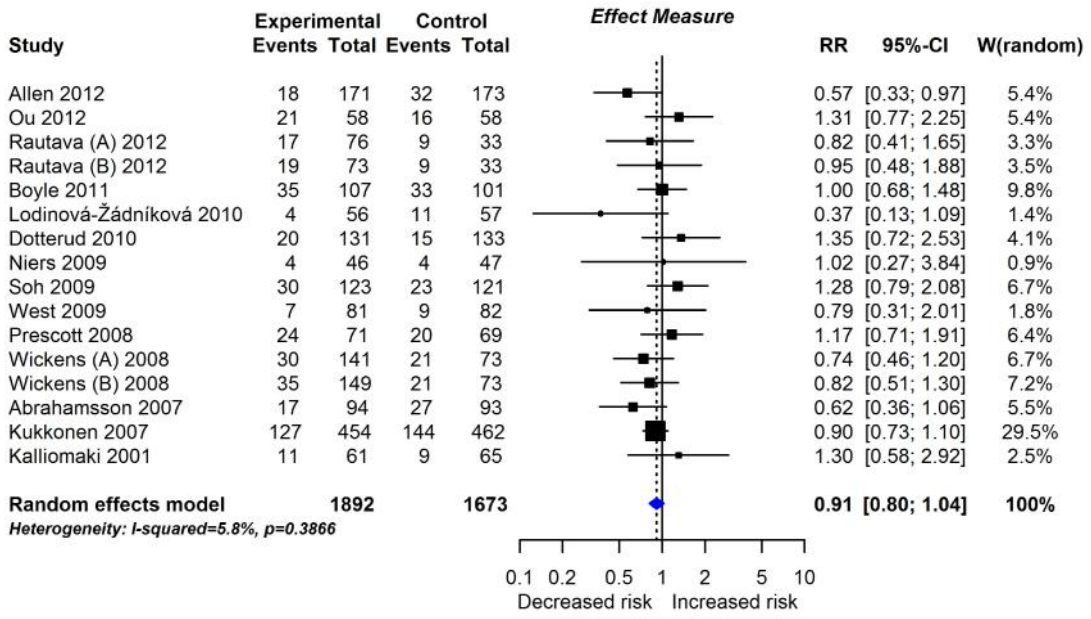
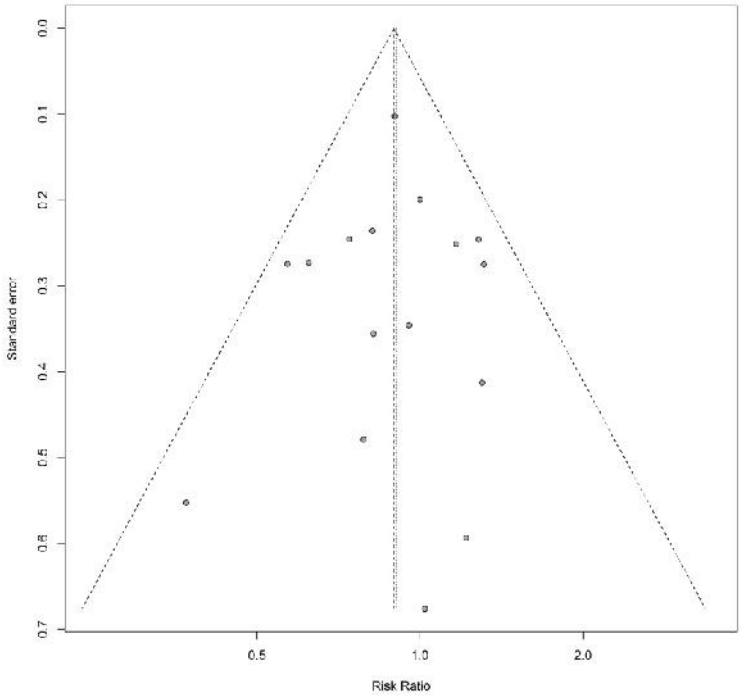


Table 4 Subgroup analyses of effect of probiotics on risk of allergic sensitisation to common allergen

	Number of studies	RR [95% CI]	I^2 (%)	P for between groups difference
Risk of disease – High	14	0.90 [0.76; 1.07]	16	0.92
Risk of disease – Normal	2	0.94 [0.45; 1.94]	0	
Method of assessment – sIgE	3	0.82 [0.39; 1.69]	56	0.80
Method of assessment – SPT	13	0.90 [0.79; 1.02]	0	
Type of Intervention – Probiotic	15	0.91 [0.77; 1.06]	4	0.95
Type of Intervention – Synbiotic	1	0.90 [0.73; 1.10]	--	
Type of Probiotic – L.rhamnosus	9	0.96 [0.83; 1.10]	0	0.15
Type of Probiotic – Other	7	0.77 [0.60; 0.99]	14	
Timing – Postnatal only	4	0.98 [0.64; 1.50]	38	0.62
Timing – Pre +/-Post-natal	12	0.88 [0.77; 1.00]	0	
*Postnatal Administration – Infant only	8	0.85 [0.67; 1.07]	33	0.65
*Postnatal Administration – Other	7	0.97 [0.78; 1.21]	0	
Overall risk of bias – High/Unclear	10	0.90 [0.73; 1.11]	29	0.96
Overall risk of bias – Low	6	0.90 [0.72; 1.11]	0	
Conflict of interest – High/Unclear risk	8	0.90 [0.71; 1.14]	35	0.93
Conflict of interest – Low risk	8	0.91[0.74; 1.11]	0	

*no postnatal administration in study of Boyle, 2011 – hence only 15 interventions included in this analysis

Figure 3 Risk of publication bias: probiotics and AS to any allergen



Egger's test p = 0.84

Figure 4 Probiotics and risk of AS to any aeroallergen

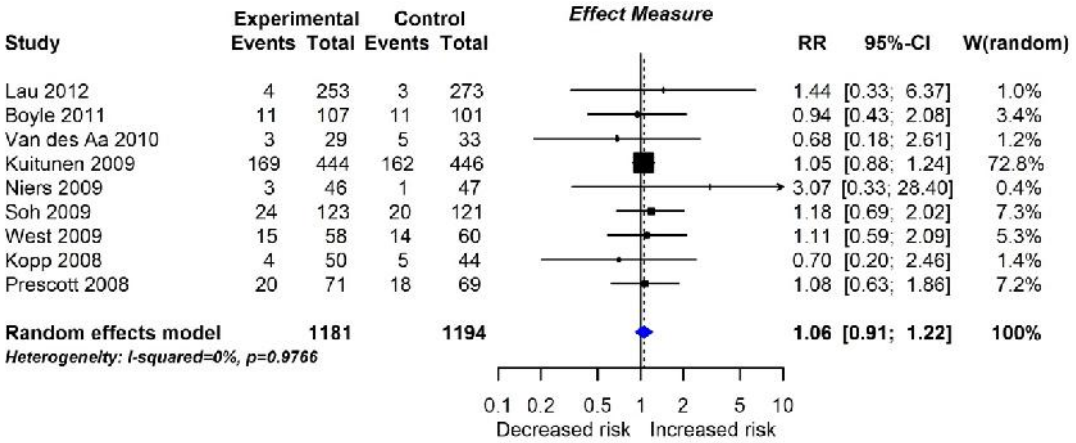


Figure 5 Probiotics and risk of AS to any food

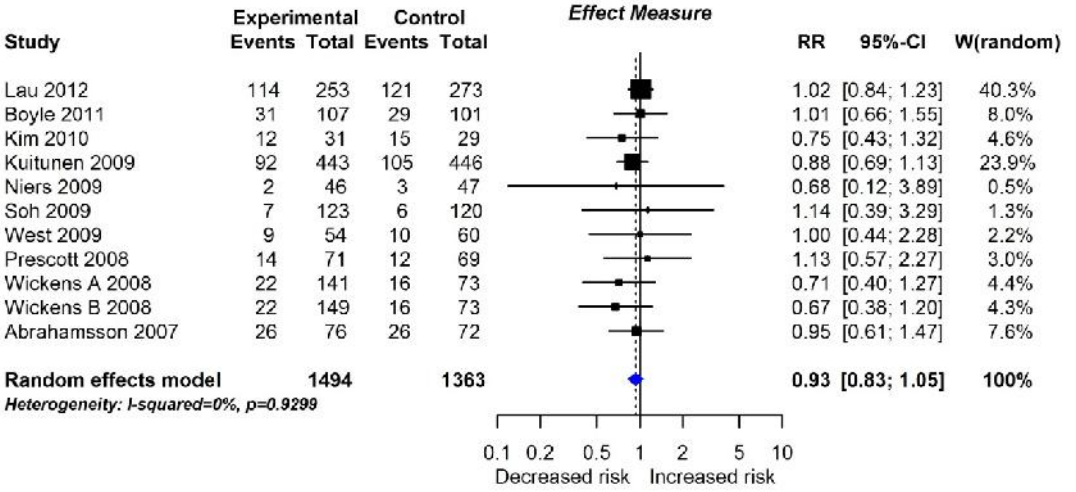


Table 5 Subgroup analyses of effect of probiotics on risk of allergic sensitisation to aeroallergen

	Number of studies	RR [95% CI]	I^2 (%)	P for between groups difference
Risk of disease – High	8	1.06 [0.91-1.22]	0	0.88
Risk of disease – Normal	1	1.11 [0.59-2.09]	-	
Method of assessment – sIgE	4	1.00 [0.61; 1.63]	0	0.70
Method of assessment – SPT	5	1.12 [0.80; 1.57]	0	
Type of Intervention – Probiotic	8	1.10 [0.83; 1.46]	0	0.50
Type of Intervention – Synbiotic	1	0.68 [0.18; 2.61]	--	
Type of Probiotic – L.rhamnosus	5	1.05 [0.90-1.23]	0	0.86
Type of Probiotic – Other	4	1.10 [0.69-1.75]	0	
Timing – Postnatal only	5	1.11 [0.81-1.51]	0	0.74
Timing – Pre +/-Post-natal	4	1.04 [0.88-1.23]	0	
*Postnatal Administration – Infant only	7	1.07 [0.92-1.24]	0	0.78
*Postnatal Administration – Other	1	0.70 [0.20-2.46]	-	
Overall risk of bias – High/Unclear	6	1.06 [0.91-1.24]	0	0.71
Overall risk of bias – Low	3	0.95 [0.51-1.74]	0	
Conflict of interest – High/Unclear risk	3	0.95 [0.51-1.74]	0	0.71
Conflict of interest – Low risk	6	1.06 [0.91-1.24]	0	

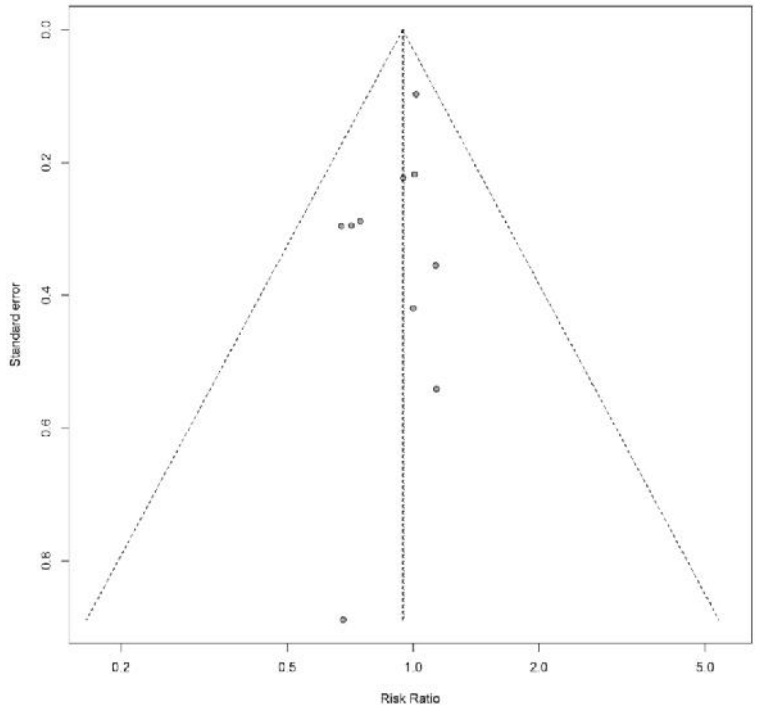
*no postnatal administration in study of Boyle, 2011 – hence only 8 interventions included in this analysis

Table 6 Subgroup analyses of effect of probiotics on risk of allergic sensitisation to any food

	Number of studies	RR [95% CI]	I^2 (%)	P for between groups difference
Risk of disease – High	10	0.93 [0.83-1.05]	0	0.87
Risk of disease – Normal	1	1.00 [0.44-2.27]	-	
Method of assessment – sIgE	4	0.98 [0.83; 1.15]	0	0.49
Method of assessment – SPT	7	0.88 [0.68; 1.14]	0	
Type of Intervention – Probiotic	11	0.95 [0.83; 1.09]	0	--
Type of Intervention – Synbiotic	0	--	--	
Type of Probiotic – L.rhamnosus	5	0.90 [0.74-1.09]	0	0.61
Type of Probiotic – Other	6	0.96 [0.82-1.12]	0	
Timing – Postnatal only	4	1.02 [0.86-1.22]	0	0.15
Timing – Pre +/-Post-natal	7	0.86 [0.73-1.01]	0	
*Postnatal Administration – Infant only	7	0.97 [0.85-1.11]	0	0.22
*Postnatal Administration – Other	3	0.71 [0.51-0.99]	-	
Overall risk of bias – High/Unclear	7	0.90 [0.75-1.09]	0	0.64
Overall risk of bias – Low	4	0.96 [0.82-1.12]	0	
Conflict of interest – High/Unclear risk	6	0.95 [0.83-1.09]	0	0.62
Conflict of interest – Low risk	5	0.88 [0.68-1.14]	0	

*no postnatal administration in study of Boyle, 2011 – hence only 10 interventions included in this analysis

Figure 6 Risk of publication bias: probiotics and AS to any food allergen



Egger's test p = 0.22

Figure 7 Probiotics and risk of AS to CM

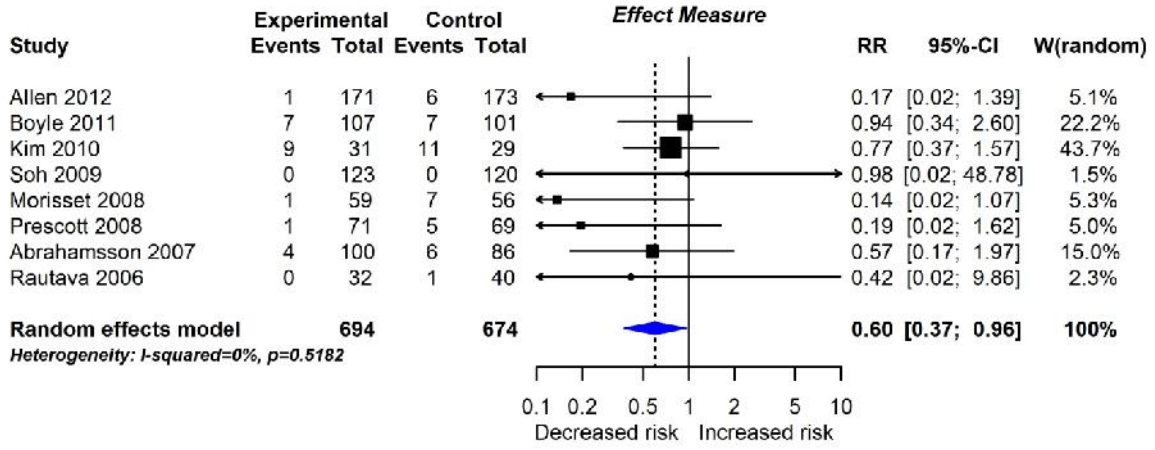


Figure 8 Probiotics and risk of AS to egg

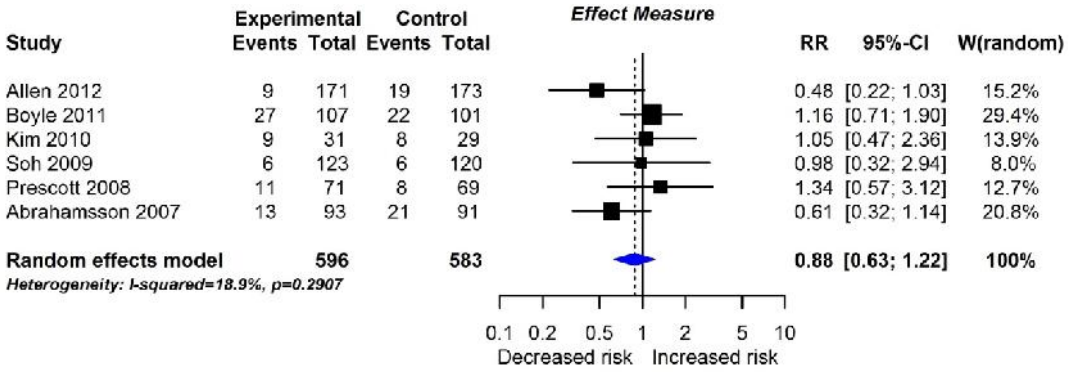


Figure 9 Probiotics and risk of AS to peanut

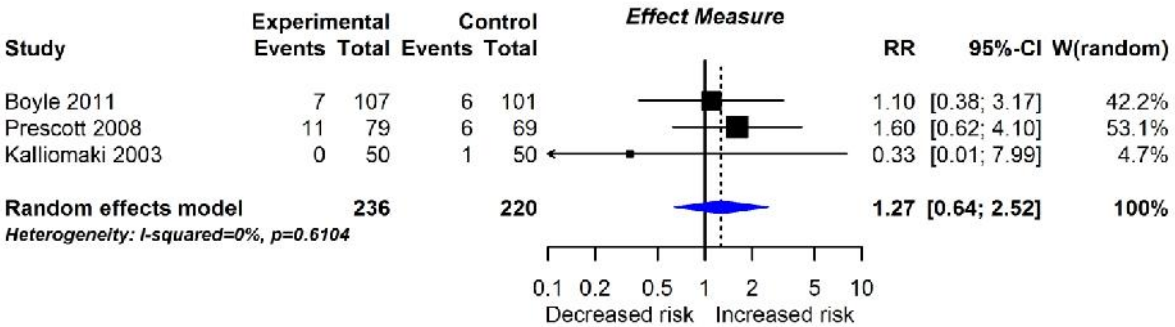


Table 7 Subgroup analyses of effect of probiotics on risk of allergic sensitisation to cow's milk

	Number of studies	RR [95% CI]	I^2 (%)	P for between groups difference
Risk of disease – High	7	0.60 [0.36; 0.98]	2	0.82
Risk of disease – Normal	1	0.42 [0.02; 9.86]	--	
Method of assessment – sIgE	2	0.41 [0.07; 2.33]	63	0.74
Method of assessment – SPT	6	0.57 [0.29; 1.10]	0	
Type of Intervention – Probiotic	8	0.60 [0.37; 0.96]	0	--
Type of Intervention – Synbiotic	0	--	--	
¶Type of Probiotic – L.rhamnosus	3	0.88 [0.35; 2.24]	0	0.26
¶Type of Probiotic – Other	4	0.56 [0.30; 1.04]	6	
Timing – Postnatal only	4	0.23 [0.06; 0.81]	0	0.11
Timing – Pre +/-Post-natal	4	0.70 [0.42; 1.17]	0	
*Postnatal Administration – Infant only	5	0.38 [0.16; 0.93]	0	0.40
*Postnatal Administration – Other	2	0.41 [0.07; 2.33]	63	
Overall risk of bias – High/Unclear	7	0.53 [0.31; 0.90]	0	0.32
Overall risk of bias – Low	1	0.94 [0.34; 2.56]	--	
Conflict of interest – High/Unclear risk	5	0.55 [0.29; 1.01]	6	0.69
Conflict of interest – Low risk	3	0.68 [0.28; 1.63]	0	

¶the study of Morisset, 2008 did not name the probiotic given, hence only 7 interventions included in this analysis

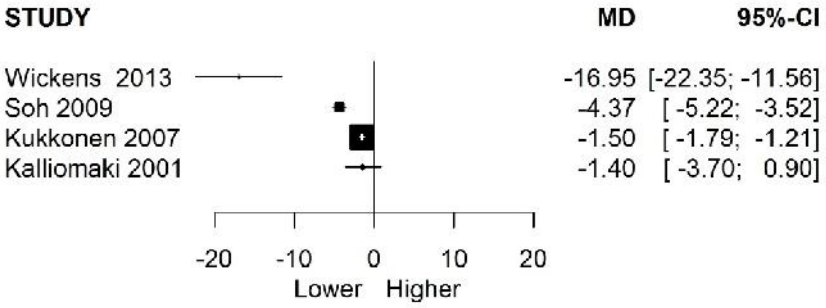
*no postnatal administration in study of Boyle, 2011 – hence only 7 interventions included in this analysis

Table 8 Subgroup analyses of effect of probiotics on risk of allergic sensitisation to egg

	Number of studies	RR [95% CI]	I^2 (%)	P for between groups difference
Risk of disease – High	6	0.88 [0.63; 1.22]	19	--
Risk of disease – Normal	0	--	--	
Method of assessment – sIgE	1	1.05 [0.47; 2.36]	0	0.65
Method of assessment – SPT	5	0.85 [0.57; 1.25]	32	
Type of Intervention – Probiotic	6	0.88 [0.63; 1.22]	19	--
Type of Intervention – Synbiotic	0	--	--	
Type of Probiotic – L.rhamnosus	2	1.13 [0.72; 1.77]	0	0.23
Type of Probiotic – Other	4	0.77 [0.49; 1.20]	29	
Timing – Postnatal only	2	1.19 [0.61; 2.33]	0	0.33
Timing – Pre +/-Post-natal	4	0.80 [0.52; 1.22]	41	
*Postnatal Administration – Infant only	4	0.73 [0.47; 1.14]	19	0.37
*Postnatal Administration – Other	1	1.05 [0.47; 2.36]	--	
Overall risk of bias – High/Unclear	5	0.78 [0.53; 1.13]	10	0.21
Overall risk of bias – Low	1	1.16 [0.71; 1.90]	--	
Conflict of interest – High/Unclear risk	4	0.67 [0.46; 0.99]	0	0.06
Conflict of interest – Low risk	2	1.21 [0.79; 1.85]	0	

*no postnatal administration in study of Boyle, 2011 – hence only 6 interventions included in this analysis

Figure 10 Probiotics and total IgE



3. Probiotics and risk of food allergy

Eleven intervention trials (1167 participants, 580 randomised to probiotics) assessed the effect of supplementation with probiotics on risk of developing food allergy. Interventions lasted 6-12 months postnatally. One study was carried out in Australia, one in the USA and 9 in Europe. Four studies had a normal disease risk, whilst the other 7 were carried out in high risk infants. Children's age at the time of outcome measurement ranged between 1 and 6 years. Three studies measured allergy to cow's milk, using either DBPCFC (Kalliomaki and Rautava), or physician assessment (Morisset). The other studies measured food allergy to any food, mainly using a physician's assessment, relying on a combination of a suggestive history and positive allergy test.

Risk of bias was generally unclear (Figure 11). There was a low risk of assessment and attrition bias in over 60% of studies. There was a high risk of conflict of interest in almost 30% of studies.

We found no evidence that probiotic supplementation reduces the risk of any food allergy at age ≤4 years or age 5 to 14 years (Figures 12 and 13), and no evidence that probiotics reduce the risk of having cow's milk allergy at age ≤4 years (Figure 14). Subgroup analysis showed no evidence that specific subgroups have different outcome with respect to any food allergy at age 5 to 14 years (Table 9).

The data from Prescott (19) at age 2.5 years old could not be combined with other studies in meta-analysis. They reported no effect of probiotics on odds of food allergy (OR 0.83; 95% CI 0.33 – 2.20). In an analysis including data from Luoto, together with other probiotic intervention studies, Lundelin (15) found no significant difference in food allergy between probiotic and placebo groups.

Overall we found no evidence that probiotics influence risk of food allergy.

Figure 11 Risk of bias in intervention studies of probiotics and food allergy



Figure 12 Probiotics and risk of any food allergy at age ≤ 4 years old

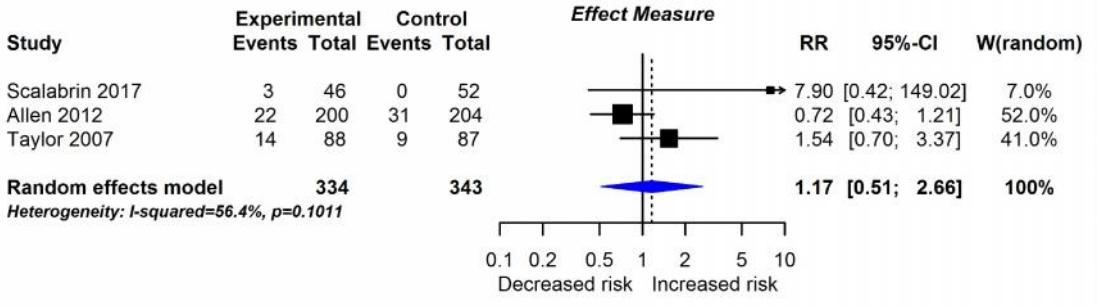


Figure 13 Probiotics and risk of any food allergy at age 5-4 years old

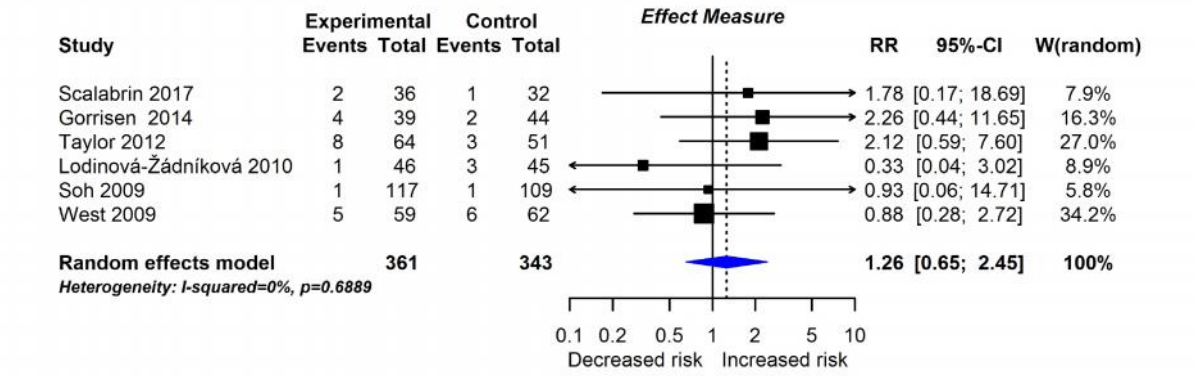
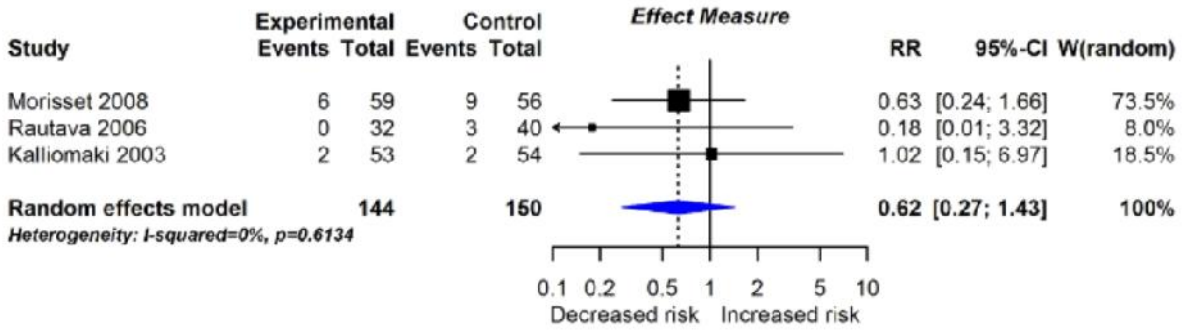


Table 9 Subgroup analyses of effect of probiotics on risk of any food allergy at age 5 to 14 years

	Number of studies	RR [95% CI]	I^2 (%)	P for between groups difference
Risk of disease – High	4	1.49 [0.63; 3.57]	0	0.56
Risk of disease – Normal	2	1.00 [0.36; 2.77]	0	
Type of Intervention – Probiotic	6	1.26 [0.65; 2.45]	0	--
Type of Intervention – Synbiotic	0	--	--	
Type of Probiotic – L.rhamnosus	3	0.99 [0.38; 2.58]	0	0.55
Type of Probiotic – Other	3	1.52 [0.55; 4.18]	14	
Timing – Postnatal only	5	1.13 [0.55; 2.32]	0	0.45
Timing – Pre +/-Post-natal	1	2.26 [0.44; 11.65]	--	
Postnatal Administration – Infant only	5	1.13 [0.55; 2.32]	0	0.45
Postnatal Administration – Other	1	2.26 [0.44; 11.65]	--	
Overall risk of bias – High/Unclear	6	1.26 [0.65; 2.45]	0	--
Overall risk of bias – Low	0	--	--	
Conflict of interest – High/Unclear risk	4	1.21 [0.42; 3.51]	0	0.93
Conflict of interest – Low risk	2	1.30 [0.55; 3.08]	4	

Figure 14 Probiotics and risk of CMA at age ≤ 4 years old



4. Probiotics and risk of AD

One systematic review (13 trials, 3000 participants) evaluated AD (28). They reported significantly reduced AD and atopic AD, with low statistical heterogeneity, and did not identify important subgroup differences.

Twenty-six original intervention trials (25 RCT; 1 CCT) evaluated over 6000 participants allocated to probiotic or control treatment with AD as an outcome. Sixteen studies were carried out in Europe, 2 in USA and 8 in Asia-Pacific. Seven studies were carried out in infants with normal risk of AD, 18 in infants at high risk of AD and in one study this was unclear. Age at time of outcome measurement ranged between 4 months and 7 years. Fourteen studies used Hanifin & Rajka or modifications of this method for outcome assessment, 5 used doctor diagnosis of AD and others used different assessment methods or (for 5 studies) method of outcome assessment was unclear. The overall risk of bias was low or unclear in over 80% of studies based on assessment, selection and attrition bias, however over 30% of studies had a high risk of conflict of interest due to direct industry involvement in the trial (Figure 15).

Probiotics reduced AD risk at age ≤4 years (Figure 16 – RCT) with high statistical heterogeneity (I^2=61%). In the CCT of Enomoto (8) there was significantly reduced AD risk at age 18 months in probiotic versus control group (Figure 17), despite a significant imbalance at randomisation with increased risk factors for allergic disease in the probiotic group. There was no evidence of publication bias in these two meta-analyses (Figure 18; Egger's test p=0.12). Subgroup analyses showed no clear evidence that one subgroup had different efficacy to another, however there was some evidence that postnatal administration to mother during lactation is more effective than infant supplementation alone during the postnatal period (p=0.016) – high statistical heterogeneity remained in this subgroup analysis. Probiotics also reduced risk of atopic AD at age ≤4 years (Figure 19), with no statistical heterogeneity (I^2=0%) and no evidence of publication bias (Figure 20). Subgroup analyses did not identify any important subgroup differences (Table 11).

We found no evidence that probiotics reduce AD or atopic AD risk at age 5-14 years (Figures 21 and 22) with moderate and no statistical heterogeneity respectively, and no evidence for

important subgroup differences in analysis of all AD (Table 12) or publication bias (Figure 23).

A further five studies were not eligible for meta-analysis. Huurre (9) reported reduced AD, but this was not statistically significant (9.7% probiotic, 17.6% control; p=0.13). De Leon (6, 32) found no difference at age 6 months (45% probiotic, 56% control). Scalabrin reported no difference in AD by age 5, but did not present numerical data. In an analysis including data from Luoto, together with other probiotic intervention studies, Lundelin found no significant difference in food allergy between probiotic and placebo groups. In the study of Chien 3 participants in the synbiotic group, 9 in the prebiotic and 10 in the control group developed eczema by 3 months. The difference between synbiotic and other groups, adjusted for family history, was reported as statistically significant P<0.05.

Overall we found MODERATE level evidence (-1 inconsistency between age ≤4 and age 5-14 findings) that probiotics can prevent atopic AD and MODERATE level evidence (-1 inconsistency between studies i.e. high statistical heterogeneity) that probiotics can prevent *all* AD in children ≤ 4 years old. The majority of the evidence in these positive meta-analyses came from studies of high risk infants i.e. those with a positive family history of allergic disease. So although in subgroup analyses we found no evidence that outcomes differed according to disease risk, our view is that these conclusions should only be seen as relevant for infants at high risk of AD.

Figure 15 Risk of bias in intervention studies of probiotics and AD

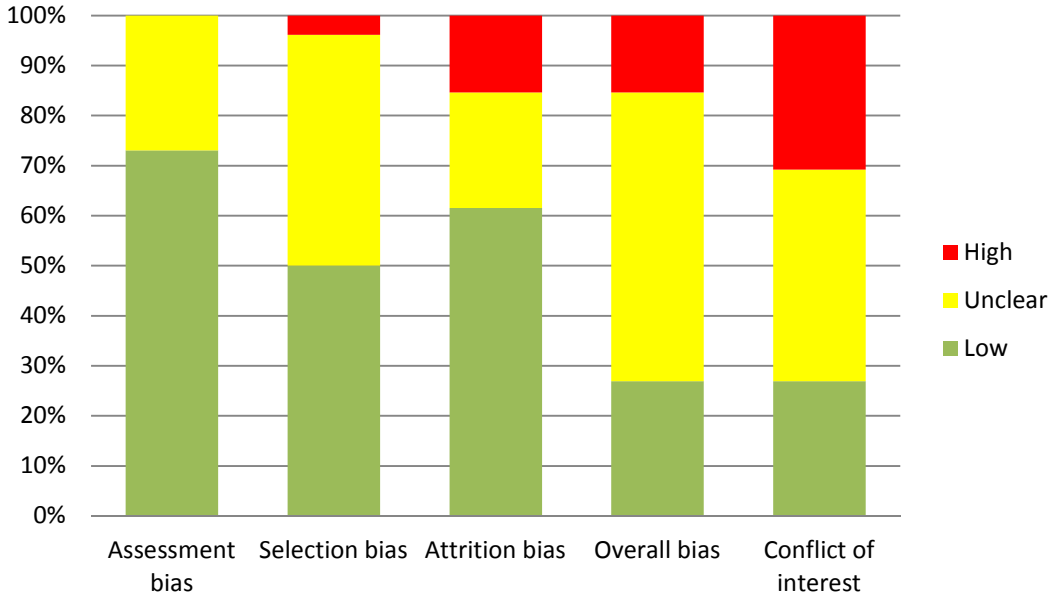


Table 10 Findings from the previous high quality systematic review found in 07/13 search

Study	Outcome measure	No. participants (studies)	Outcome (95% CI)	I^2
Pelucci (28)*	AD	3092 (13)	**RR 0.79 [0.71, 0.88]**	24
	IgE-associated AD	2711 (10)	**RR 0.80 [0.66, 0.96]**	32
	AD (high risk infants)	(12)	**RR 0.80 [0.70, 0.91]**	24
	AD (normal/low risk infants)	(2)	RR 0.35 [0.06, 2.01]	49
	AD (Hanifin and Rajka criteria)	(6)	RR 0.80 [0.61, 1.06]	49
	AD (UK working party criteria)	(5)	**RR 0.78 [0.67, 0.90]**	0
	AD (parent reported)	(2)	RR 0.70 [0.47, 1.04]	26
	AD at < 2 years	(6)	**RR 0.78 [0.65, 0.93]**	40
	AD at ≥ 2 years	(7)	**RR 0.79 [0.65, 0.95]**	1

* The authors also undertook meta-regression to examine the effect of pre/postnatal/combined treatment, treatment of mother/child/both, duration of treatment,

treatment dose, single versus multiple probiotic treatment, location of trial and apparent conflict of interest and found no significant effect for any of these factors.

Figure 16 Probiotics and risk of AD at age ≤ 4 years - RCT

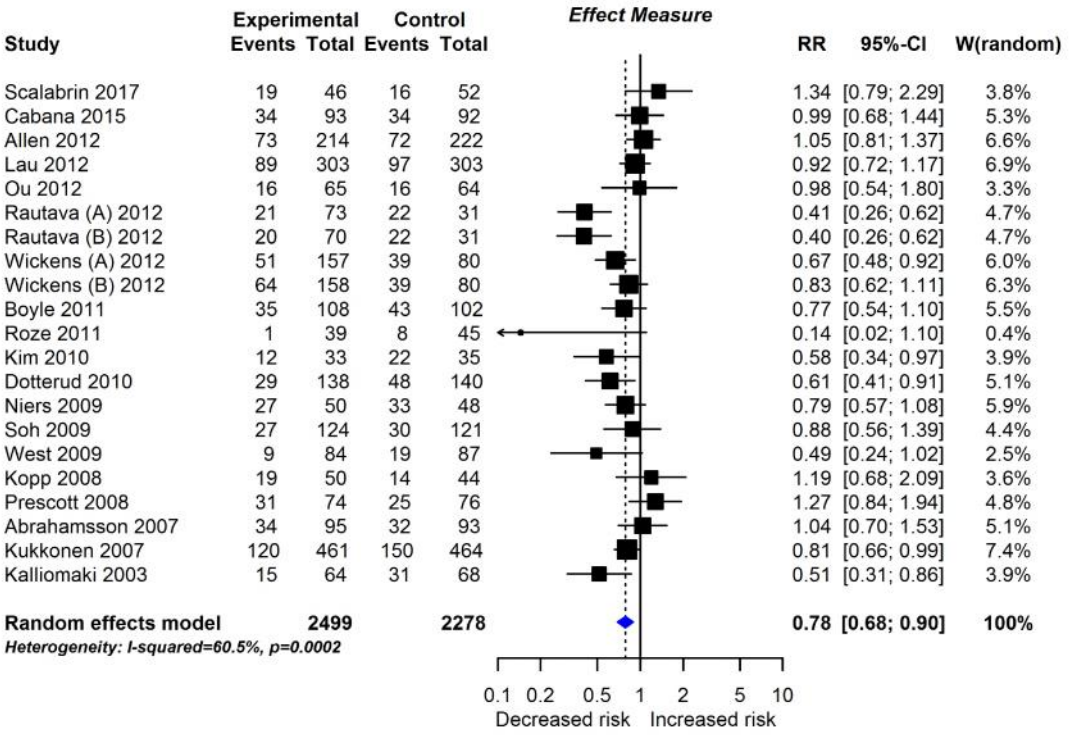


Figure 17 Probiotics and risk of AD at age ≤ 4 years - CCT

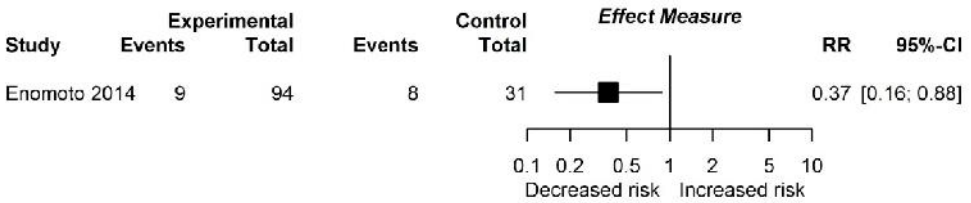
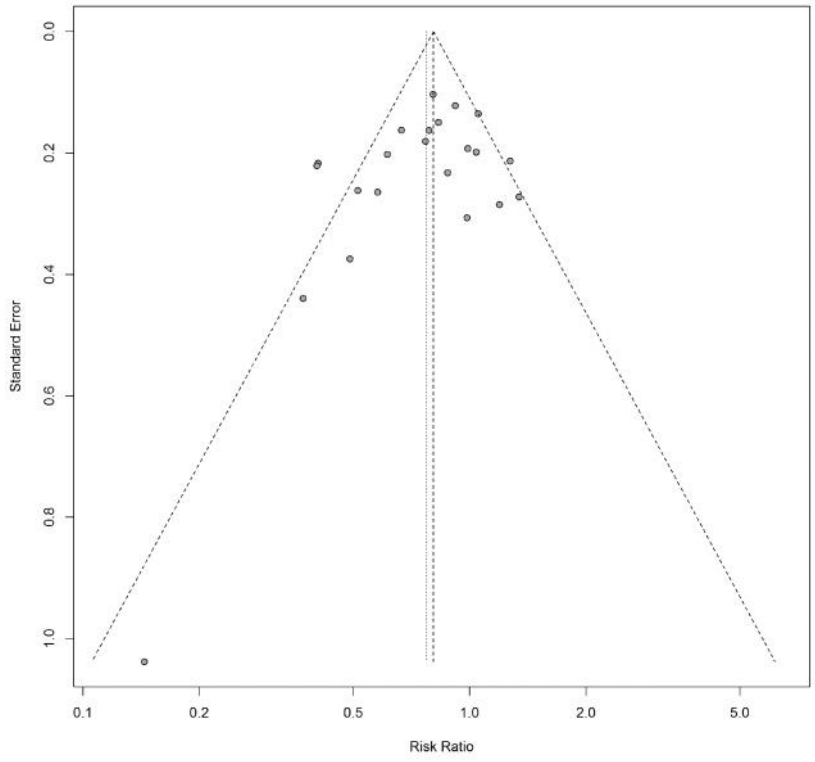


Table 10 Subgroup analyses of probiotics and risk of AD at age ≤ 4 years

Subgroups compared	Number of studies	RR [95% CI]	I^2 (%)	P for between groups difference
Type of Probiotic – L.rhamnosus	13	0.75 [0.62-0.89]	55	0.42
Type of Probiotic – Other	8	0.84 [0.68-1.03]	67	
Type of Intervention – Probiotic	19	0.79 [0.68; 0.91]	62	0.51
Type of Intervention – Synbiotic	2	0.46 [0.09; 2.27]	64	
Timing – Postnatal only	7	0.95 [0.76-1.20]	42	0.06
Timing – Pre +/-Post-natal	14	0.73 [0.62-0.86]	62	
*Postnatal Administration – Infant only	11	0.93 [0.81-1.06]	31	0.016
*Postnatal Administration – Other	9	0.64 [0.51-0.80]	59	
Risk of disease – High	17	0.80 [0.69-0.92]	61	0.58
Risk of disease – Normal	4	0.55 [0.38-0.80]	69	
Overall risk of bias – High/Unclear	12	0.88 [0.76-1.02]	43	0.06
Overall risk of bias – Low	9	0.67 [0.53-0.85]	69	
Conflict of interest – High/Unclear risk	14	0.86 [0.76-0.98]	37	0.10
Conflict of interest – Low risk	7	0.66 [0.49-0.88]	74	

*no postnatal administration in study of Boyle, 2011 – hence only 18 interventions included in this analysis

Figure 18 Risk of publication bias: probiotics and AD at age ≤4



Egger's test p = 0.12

Figure 19 Probiotics and risk of atopic AD at age ≤ 4 years

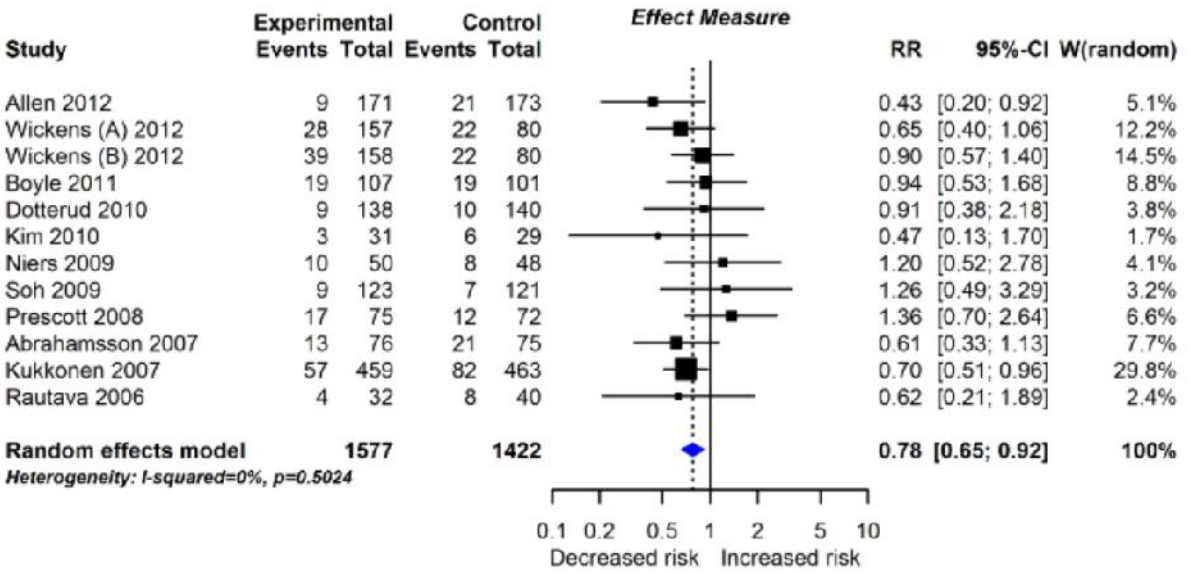
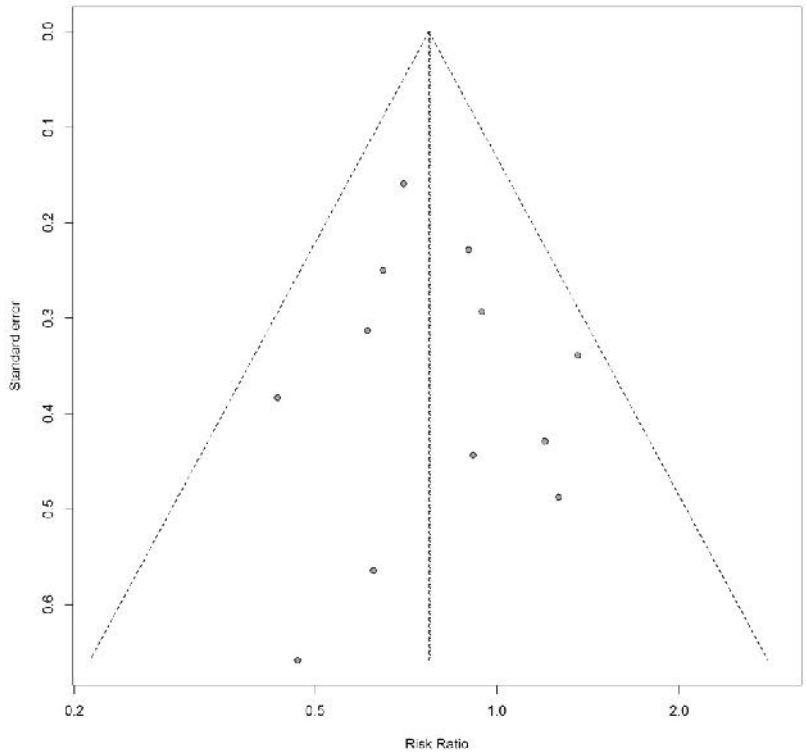


Figure 20 Risk of publication bias: probiotics and atopic AD at age ≤4



Egger's test p = 0.70

Table 11 Subgroup analyses of probiotics and risk of atopic AD at age ≤ 4 years

Subgroups compared	Number of studies	RR [95% CI]	I^2 (%)	P for between groups difference
Intervention – Probiotics	11	0.81 [0.66-0.99]	0	0.45
Intervention – Synbiotics	1	0.70 [0.51-0.96]	-	
Type of Probiotic – L.rhamnosus	6	0.75 [0.60-0.94]	0	0.38
Type of Probiotic – Other	6	0.80 [0.56-1.13]	34	
Timing – Postnatal only	3	1.15 [0.70-1.87]	0	0.10
Timing – Pre +/-Post-natal	9	0.73 [0.61-0.88]	0	
*Postnatal Administration – Infant only	7	0.78 [0.58-1.05]	27	0.93
*Postnatal Administration – Other	4	0.77 [0.57-1.04]	0	
Risk of disease – High	10	0.78 [0.64-0.95]	10	0.97
Risk of disease – Normal	2	0.79 [0.40-1.57]	0	
Overall risk of bias – Low	4	0.79 [0.60-1.05]	0	0.96
Overall risk of bias – High/Unclear	8	0.78 [0.60-1.01]	16	
Conflict of interest – High/Unclear risk	7	0.71 [0.57-0.90]	0	0.27
Conflict of interest – Low risk	5	0.87 [0.67-1.12]	0	

*no postnatal administration in the study of Boyle, 2011 – hence only 11 interventions included in this analysis

Figure 21 Probiotics and risk of AD at age 5-14 years

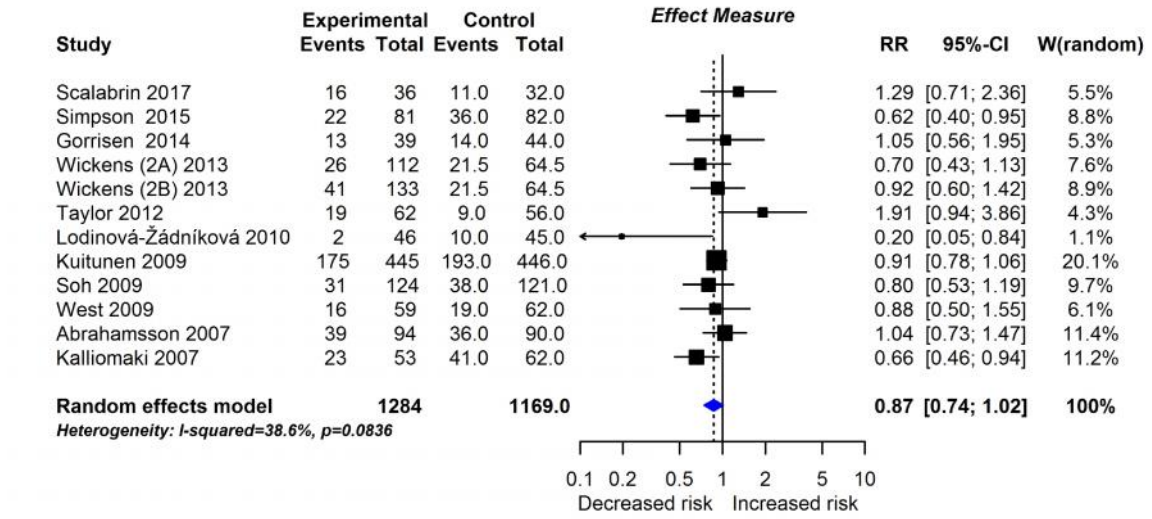


Figure 22 Probiotics and risk of atopic AD at age 5-14 years

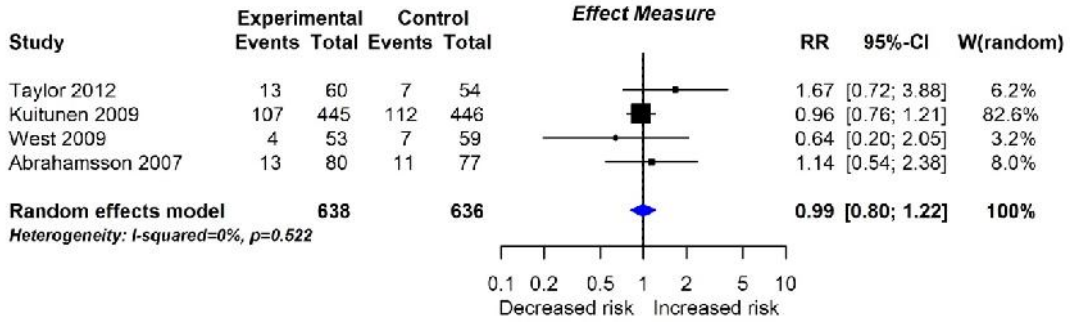
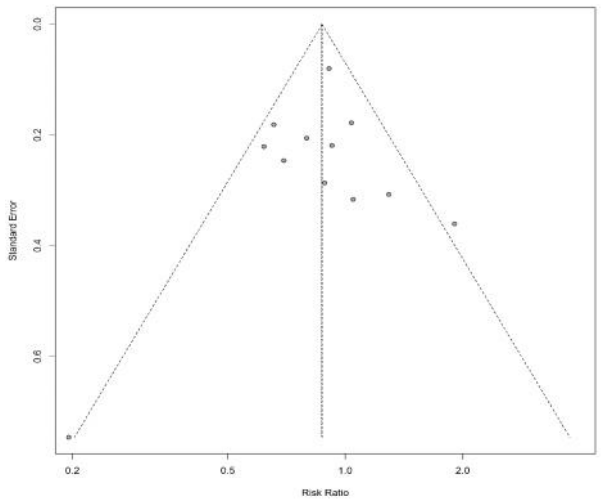


Figure 23 Risk of publication bias: probiotics and AD at age 5 to 14 years



Egger's test p = 0.73

Table 12 Subgroup analyses of probiotics and risk of AD at age 5-14 years

Subgroups compared	Number of studies	RR [95% CI]	I^2 (%)	P for between groups difference
Type of Probiotic – L.rhamnosus	7	0.82 [0.70-0.95]	19	0.28
Type of Probiotic – Other	5	1.02 [0.70-1.47]	51	
Type of Intervention – Probiotic	11	0.86 [0.70; 1.05]	43	0.67
Type of Intervention – Synbiotic	1	0.91 [0.78; 1.06]	-	
Timing – Postnatal only	5	0.96 [0.61-1.52]	60	0.58
Timing – Pre +/-Post-natal	7	0.84 [0.73-0.97]	18	
Postnatal Administration – Infant only	7	0.97 [0.77-1.21]	43	0.08
Postnatal Administration – Other	5	0.74 [0.61-0.90]	0	
Risk of disease – High	10	0.87 [0.74-1.03]	35	0.98
Risk of disease – Normal	2	0.87 [0.42-1.78]	74	
Overall risk of bias – High/Unclear	10	0.88 [0.73-1.06]	47	0.69
Overall risk of bias – Low	2	0.82 [0.59-1.12]	0	
Conflict of interest – High/Unclear risk	8	0.84 [0.69-1.01]	43	0.51
Conflict of interest – Low risk	4	0.96 [0.67-1.37]	45	

5. Probiotics and risk of allergic rhinitis or conjunctivitis

Fourteen intervention trials (13 RCT; 1 CCT – in total 15 interventions; 4450 participants) reported allergic rhinitis (AR) or allergic rhinoconjunctivitis (ARC) – here analysed together as 'allergic rhinitis'. No studies reported allergic conjunctivitis as an outcome. Eight studies were carried out in Europe, one in USA and five Asia-Pacific. Five studies were carried out in infants with normal risk of allergic disease, whilst the other nine were in children at high risk. Age at outcome assessment varied between 1 and 9 years. Two studies defined allergic rhinitis according to specific symptoms, 4 were based on previous Dr-diagnosis or physician assessment during the trial, 2 studies combined symptoms and having 1 or more positive SPTs, and four studies based the diagnosis on ISAAC questionnaires; two studies didn't report the method of outcome assessment. Risk of bias was similar to other analyses, with a low overall risk of bias in <10%, unclear in the majority, and high in over 35%. (Figure 24).

There was no evidence that probiotics reduce risk of AR at age ≤4 (Figure 25) with low statistical heterogeneity. There was also no evidence for an effect at age 5-14 (Figure 26) with no statistical heterogeneity, and no evidence of publication bias (Figure 27). Subgroup analyses did not identify a subgroup with different outcomes (Tables 13 and 14).

Enomoto (8) reported no cases of ARC in either active (n=94) or control (n=31) group at 18 months age. In an analysis including data from Luoto, together with other probiotic intervention studies, Lundelin found no significant difference in allergic rhinitis between probiotic and placebo groups.

Overall we found no evidence that probiotics influence risk of allergic rhinitis, and data were lacking for allergic conjunctivitis.

Figure 24 Risk of bias in intervention studies of probiotics and allergic rhinitis

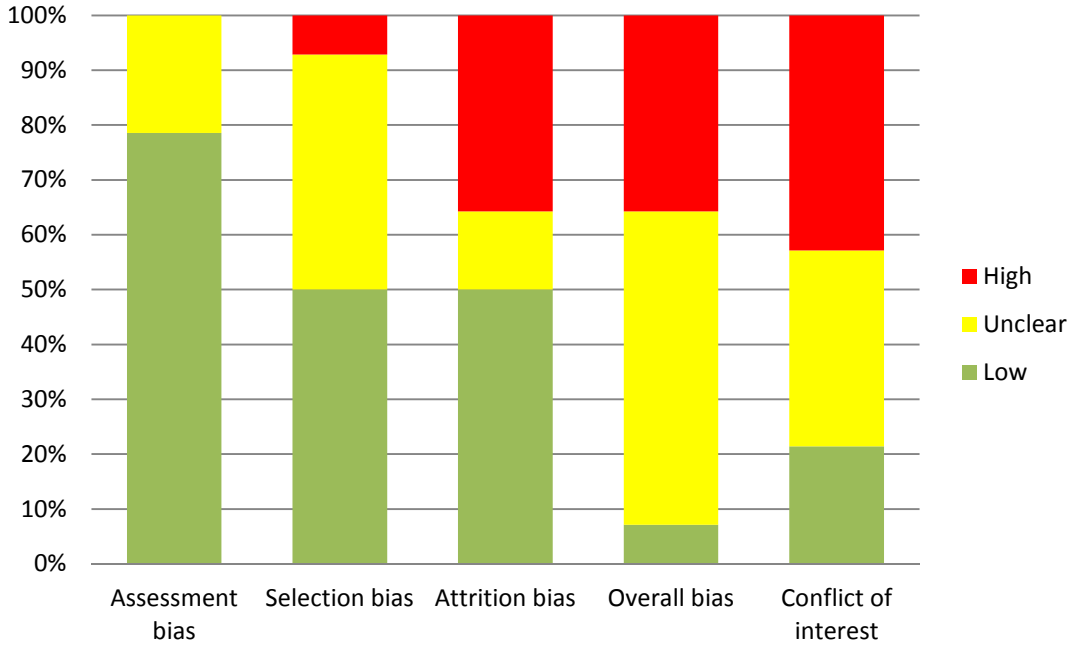


Figure 25 Probiotics and risk of allergic rhinitis at ≤ 4 years

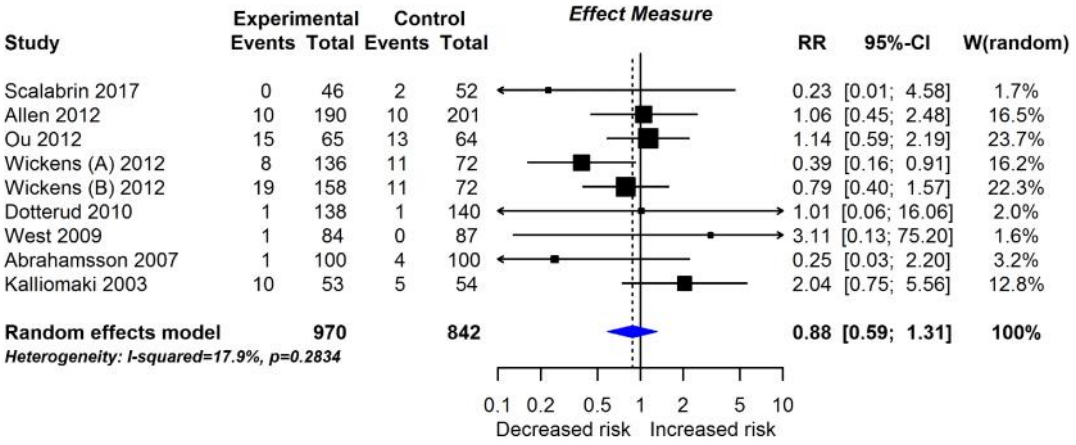


Figure 26 Probiotics and risk of allergic rhinitis at age 5-14 years

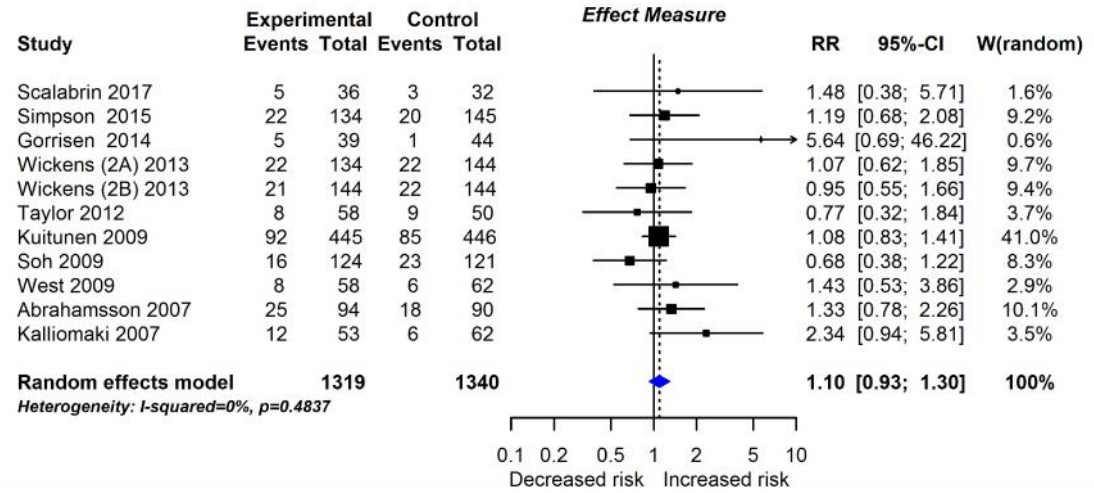
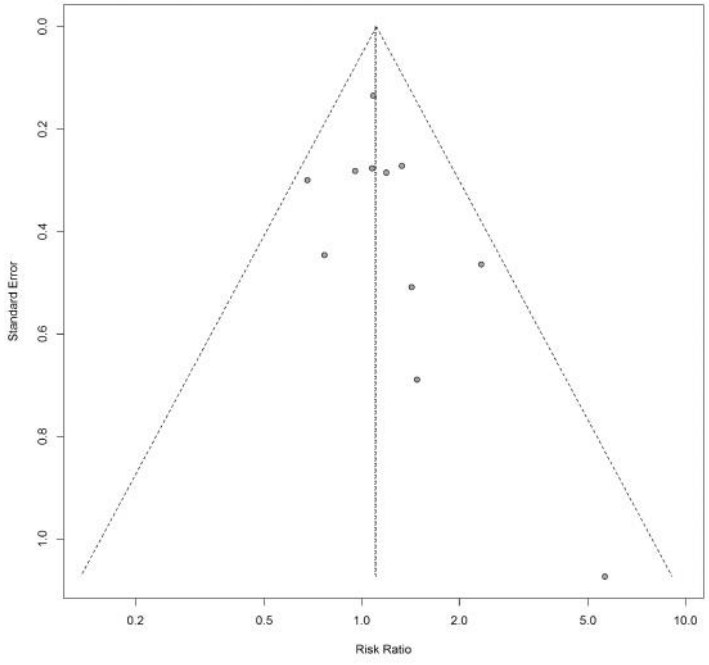


Figure 27 Risk of publication bias: probiotics and AR at age 5 to 14 years



Egger's test p = 0.22

Table 13 Subgroup analyses of probiotics and risk of allergic rhinitis at age ≤ 4 years

Subgroups compared	Number of studies	RR [95% CI]	I^2 (%)	P for between groups difference
Type of Intervention – Probiotic	9	0.81[0.59; 1.31]	18	--
Type of Intervention – Synbiotic	0	--		
Type of Probiotic – L.rhamnosus	6	0.86 [0.30-2.42]	47	0.94
Type of Probiotic – Other	3	0.82 [0.49-1.38]	0	
Timing – Postnatal only	2	0.79 [0.06-10.38]	27	0.99
Timing – Pre +/-Post-natal	6	0.80 [0.44-1.45]	47	
Postnatal Administration – Infant only	4	0.86 [0.41-1.82]	0	0.94
Postnatal Administration – Other	5	0.83 [0.39-1.74]	51	
Risk of disease – High	6	0.87 [0.55-1.40]	40	0.99
Risk of disease – Normal	3	0.86 [0.16-4.79]	0	
Overall risk of bias – Low	2	0.58 [0.29-1.16]	38	0.10
Overall risk of bias – High/Unclear	7	1.15 [0.74-1.78]	0	
Conflict of interest – High/Unclear risk	6	1.13 [0.73-1.76]	0	0.15
Conflict of interest – Low risk	3	0.62 [0.32-1.21]	23	

Table 14 Subgroup analyses of probiotics and risk of allergic rhinitis at age 5-14 years

Subgroups compared	Number of studies	RR [95% CI]	I^2 (%)	P for between groups difference
Type of Intervention – Probiotic	10	1.11 [0.89; 1.40]	12	0.88
Type of Intervention – Synbiotic	1	1.08 [0.83; 1.41]	--	
Type of Probiotic – L.rhamnosus	7	1.10 [0.90; 1.33]	0	0.94
Type of Probiotic – Other	4	1.12 [0.74; 1.68]	20	
Timing – Postnatal only	4	0.86 [0.56; 1.30]	0	0.19
Timing – Pre +/-Post-natal	7	1.16 [0.96; 1.39]	0	
Postnatal Administration – Infant only	6	1.06 [0.86; 1.30]	0	0.45
Postnatal Administration – Other	5	1.23 [0.87; 1.74]	20	
Risk of disease – High	8	1.08 [0.86; 1.36]	22	0.54
Risk of disease – Normal	3	1.27 [0.80; 2.00]	0	
Overall risk of bias – Low	2	1.01 [0.69; 1.49]	0	0.62
Overall risk of bias – High/Unclear	9	1.14 [0.91; 1.42]	13	
Conflict of interest – High/Unclear risk	7	1.17 [0.89; 1.54]	27	0.50
Conflict of interest – Low risk	4	1.01 [0.72; 1.41]	0	

6. Probiotics and risk of wheeze

One systematic review was identified in our July 2013 search. The study of Tang (29) included 5 trials and over 1500 participants, and concluded that probiotics do not reduce risk of wheezing prior to age 5 years (Table 15).

In our own systematic review we identified 18 intervention studies (17 RCT; 1 CCT; in total 19 interventions; 4950 participants) investigating the effect of probiotic supplementation on risk of wheeze. Five studies were from Asia-Pacific countries, two from USA, eleven from Europe. Age at time of outcome assessment ranged between 1 and 9 years old. In four studies the definition used for asthma was prior doctor diagnosis or study physician assessment, in 7 asthma was defined according to whether the child had had from 1 to 3 episodes of wheeze, accompanied sometimes by other symptoms; three studies used the ISAAC definition of wheeze, and in four studies the definition was unclear. Overall risk of bias was low in just over 20%, and unclear in over half of studies. Over one third of studies were considered to be at high risk of conflict of interest due to direct industry involvement in the trial (Figure 28).

We found no evidence that probiotics reduce risk of wheeze or recurrent wheeze at age ≤4 years (Figure 29 – RCT; Figure 31 – CCT; Figure 32– recurrent wheeze) or at 5-14 years (Figures 33 and 35), with low/moderate and no statistical heterogeneity respectively, and no evidence of publication bias for the analysis of wheeze at age ≤4 years or age 5-14 years (Figures 30 and 34).

Subgroup analyses (Table 16-19) demonstrated that the single synbiotic trial showed a positive effect, whereas the trials of probiotics without prebiotic showed no effect on wheeze at age ≤4 (test for subgroup difference p=0.02). The synbiotic trial also differed from other trials in the inclusion criteria of eczema and SCORAD >15 at enrolment. No other consistent subgroup differences were identified.

In an analysis including data from Luoto, together with other probiotic intervention studies, Lundelin found no significant difference in asthma between probiotic and placebo groups - OR 0.55 (0.24, 1.25) P=0.15.

Four studies reported measures of lung function. Abrahamsson reported no difference in forced expiratory volume in 1 second (FEV1) as % predicted at age 7 (Figure 36), and meta-analysis of 3 studies showed no difference in FEV1 reversibility after administration of bronchodilator (Figure 37). Abrahamsson and Wickens both reported FEV1 as % of forced vital capacity (FVC) – in Abrahamsson the median FEV1 as % of FVC was 87 (IQR 83.5, 95) in the intervention group, 88.5 (84.4, 96) in the control group. In the study of Wickens neither probiotic group showed a significant difference in FEV1 as % of FVC – mean difference compared with control group was -1.5% (95% CI -3.7, 0.8) for L. rhamnosus HN001, and -1.2 (-3.4, 0.9) for B. animalis HN019. Gorissen reported 'all spirometry measures were essentially equal in both groups', without presenting specific data.

Overall we found no evidence that probiotics influence risk of wheeze, recurrent wheeze or lung function.

Figure 28 Risk of bias in intervention studies of probiotics and wheeze

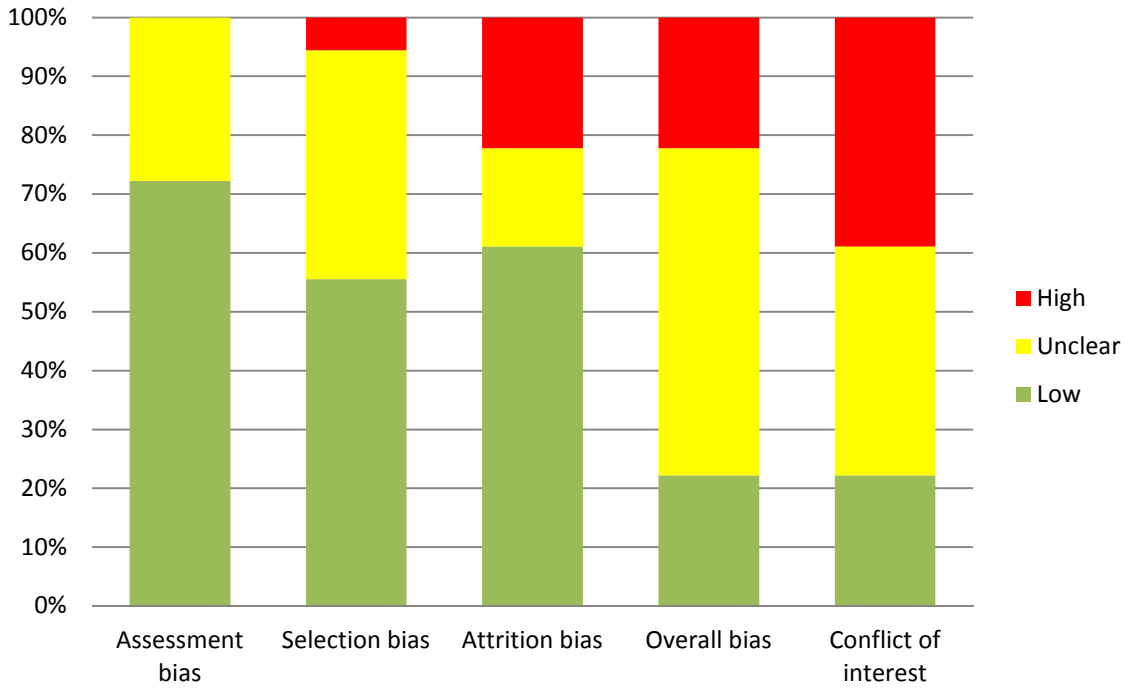


Table 15 Findings from the previous high quality systematic review found in 7/13 search

Study	Outcome measure	No. participants (studies)	Outcome (95% CI)	I^2
Tang (29)	Wheeze (under 5 years)	1536 (5)	**RR 0.93 [0.71, 1.21]**	0

Figure 29 Probiotics and risk of any wheeze at age ≤ 4 years – RCT

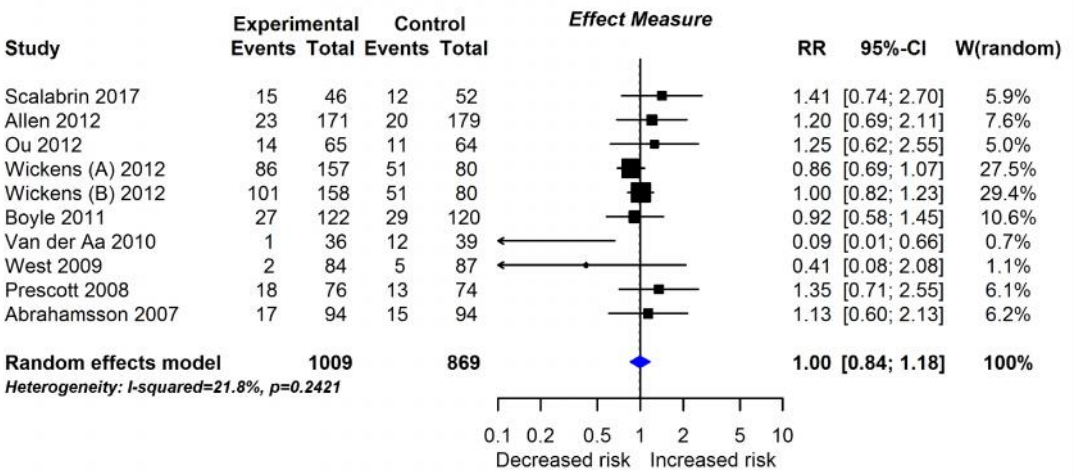
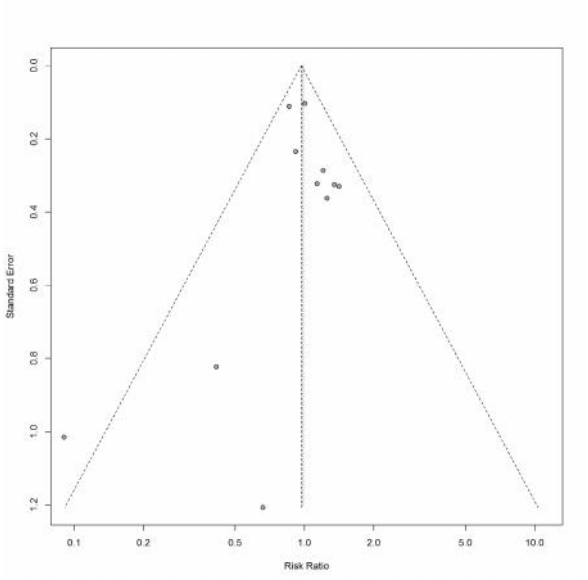


Figure 30 Risk of publication bias: probiotics and wheeze at age ≤ 4 years



Egger's test p = 0.73

Figure 31 Probiotics and risk of any wheeze at age ≤ 4 years - CCT

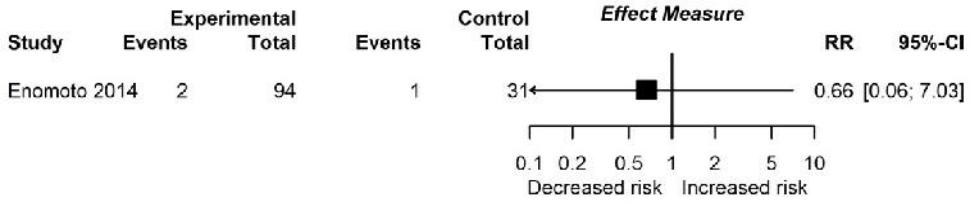


Figure 32 Probiotics and risk of recurrent wheeze at age ≤ 4 years

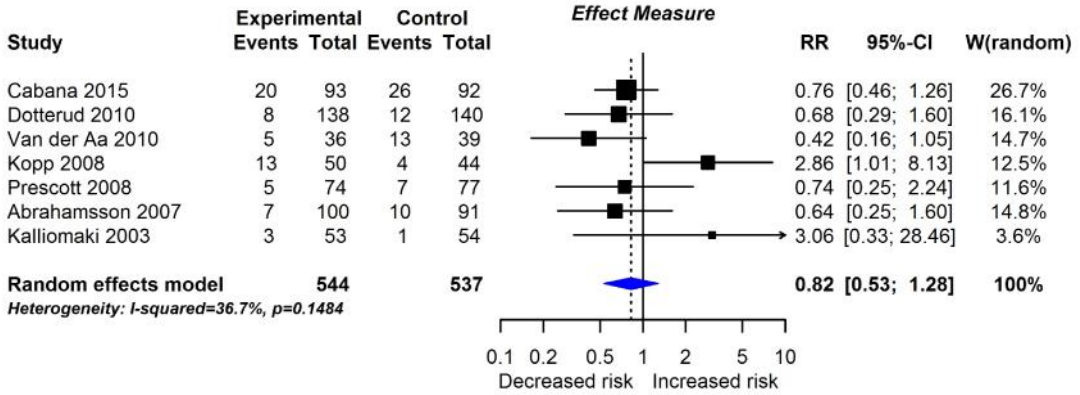


Table 16 Subgroup analyses of probiotics and risk of wheeze at age ≤ 4 years

Subgroups compared	Number of studies	RR [95% CI]	I^2 (%)	P for between groups difference
Intervention – Probiotics	9	0.98 [0.87; 1.12]	0	0.02
Intervention – Synbiotics	1	0.09 [0.01; 0.66]	-	
Type of Probiotic – L.rhamnosus	5	0.92 [0.76; 1.10]	0	0.47
Type of Probiotic – Other	5	1.05 [0.76; 1.46]	43	
Timing – Postnatal only	4	0.77 [0.31; 1.89]	68	0.62
Timing – Pre +/-Post-natal	6	0.96 [0.84; 1.10]	0	
*Postnatal Administration – Infant only	6	1.06 [0.68; 1.63]	45	0.88
*Postnatal Administration – Other	3	0.95 [0.82; 1.09]	0	
Risk of disease – High	8	0.98 [0.83; 1.17]	24	0.97
Risk of disease – Normal	2	0.96 [0.31; 2.98]	49	
Overall risk of bias – High/Unclear	6	1.22 [0.92; 1.61]	0	0.11
Overall risk of bias – Low	4	0.89 [0.69; 1.16]	56	
Conflict of interest – High/Unclear risk	5	1.11 [0.71; 1.72]	45	0.50
Conflict of interest – Low risk	5	0.94 [0.82; 1.08]	0	

*no postnatal administration in the study of Boyle, 2011 – hence only 7 interventions included in this analysis

Table 17 Subgroup analyses of probiotics and risk of recurrent wheeze at age ≤ 4 years

Subgroups compared	Number of studies	RR [95% CI]	I^2 (%)	P for between groups difference
Intervention – Probiotics	6	0.92 [0.58-1.46]	32	0.13
Intervention – Synbiotics	1	0.42 [0.17-1.05]	-	
Type of Probiotic – L.rhamnosus	4	1.14 [0.56-2.33]	56	0.13
Type of Probiotic – Other	3	0.57 [0.32-1.00]	0	
Timing – Postnatal only	3	0.67 [0.45-1.02]	0	0.25
Timing – Pre +/-Post-natal	4	1.16 [0.51-2.65]	54	
Postnatal Administration – Infant only	4	0.67 [0.46-0.97]	0	0.16
Postnatal Administration – Other	3	1.55 [0.50-4.76]	60	
Risk of disease – High	6	0.87 [0.51-1.49]	46	0.63
Risk of disease – Normal	1	0.68 [0.29-1.60]	0	
Overall risk of bias – Low	2	1.07 [0.16-7.13]	86	0.71
Overall risk of bias – High/Unclear	5	0.75 [0.52-1.08]	0	
Conflict of interest – High/Unclear	6	0.85 [0.51-1.42]	47	0.83
Conflict of interest – Low	1	0.74 [0.25-2.24]	-	

Figure 33 Probiotics and risk of any wheeze at age 5-14 years

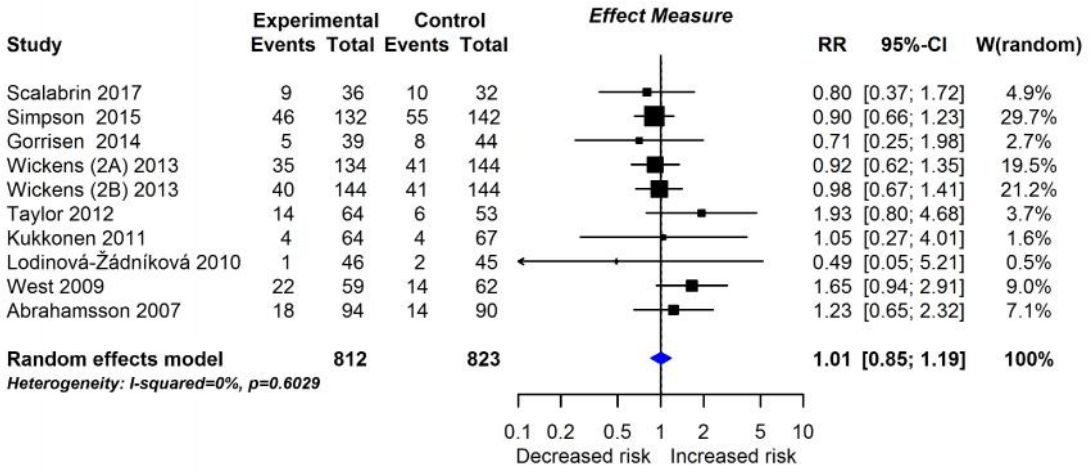
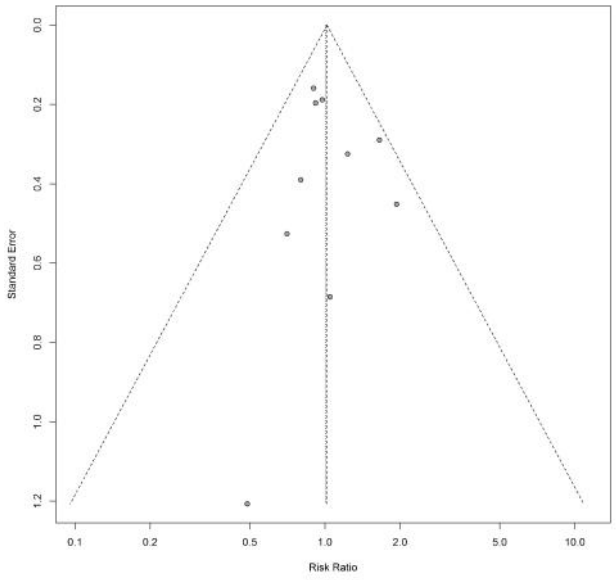


Figure 34 Risk of publication bias: probiotics and wheeze at age 5-14 years



Egger's test p = 0.68

Figure 35 Probiotics and risk of recurrent wheeze at age 5-14 years

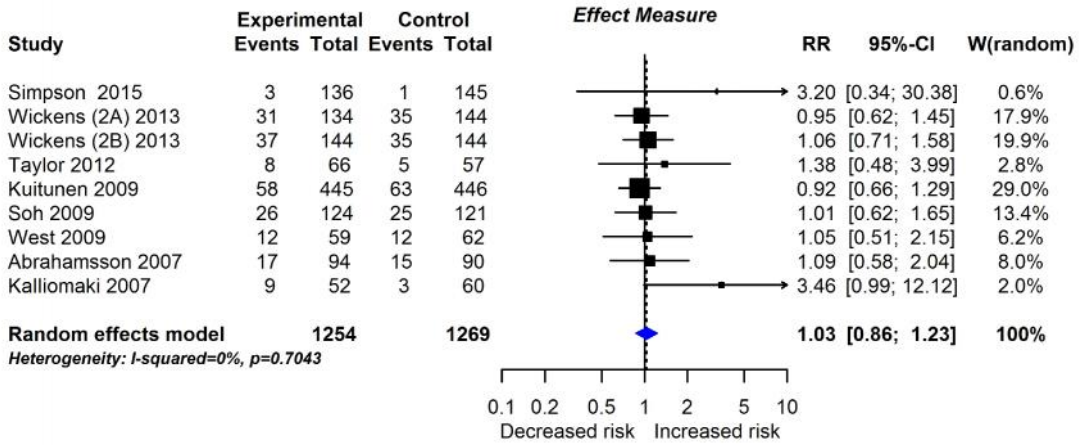


Table 18 Subgroup analyses of probiotics and risk of wheeze at age 5-14 years

Subgroups compared	Number of studies	RR [95% CI]	I^2 (%)	P for between groups difference
Intervention – Probiotics	9	1.01 [0.85-1.19]	0	0.95
Intervention – Synbiotics	1	1.05 [0.27-4.01]	-	
Type of Probiotic – L.rhamnosus	5	0.97 [0.79-1.21]	0	0.66
Type of Probiotic – Other	5	1.06 [0.80-1.41]	0	

Timing – Postnatal only	4	1.33 [0.84-2.11]	17	0.18
Timing – Pre +/-Post-natal	6	0.94 [0.78-1.14]	0	
Postnatal Administration – Infant only	6	1.30 [0.94-1.80]	0	0.08
Postnatal Administration – Other	4	0.92 [0.75-1.12]	0	
Risk of disease – High	8	1.08 [0.87-1.33]	0	0.28
Risk of disease – Normal	2	0.88 [0.66-1.18]	0	
Overall risk of bias – Low	2	0.95 [0.73-1.24]	0	0.56
Overall risk of bias – High/Unclear	8	1.05 [0.84-1.31]	0	
Conflict of interest – High/Unclear	6	0.92 [0.72-1.18]	0	0.29
Conflict of interest – Low	4	1.15 [0.84-1.57]	38	

Table 19 Subgroup analyses of probiotics and risk of recurrent wheeze at age 5-14 years

Subgroups compared	Number of studies	RR [95% CI]	I^2 (%)	P for between groups difference
Intervention – Probiotics	8	1.08 [0.87-1.34]	0	0.43
Intervention – Synbiotics	1	0.92 [0.66-1.29]	-	
Type of Probiotic – L.rhamnosus	6	1.01 [0.81-1.26]	2	0.70
Type of Probiotic – Other	3	1.09 [0.79-1.51]	0	
Timing – Postnatal only	3	1.07 [0.73-1.55]	0	0.87
Timing – Pre +/-Post-natal	6	1.03 [0.83-1.27]	4	
Postnatal Administration – Infant only	5	1.00 [0.79-1.26]	0	0.50
Postnatal Administration – Other	4	1.18 [0.78-1.78]	35	
Risk of disease – High	8	1.03 [0.86-1.23]	0	0.32
Risk of disease – Normal	1	3.20 [0.34-30.38]	-	
Overall risk of bias – Low	2	1.00 [0.75-1.35]	0	0.82
Overall risk of bias – High/Unclear	7	1.05 [0.84-1.32]	0	
Conflict of interest – High/Unclear	5	1.08 [0.79-1.47]	21	0.83
Conflict of interest – Low	4	1.03 [0.79-1.34]	0	

Figure 36 Probiotics and lung function at age 5-14 (FEV1<80% predicted)

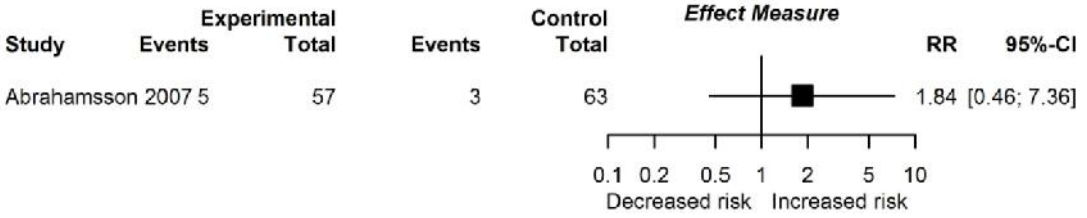
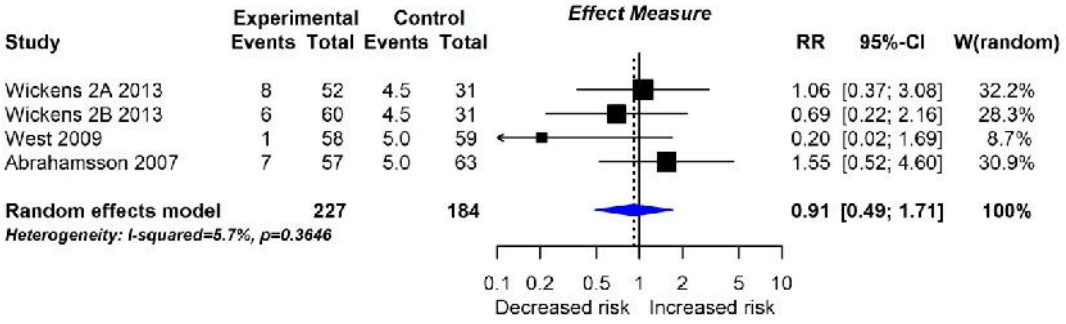


Figure 37 Probiotics and lung function at age 5-14 (FEV1 reversibility >12%)



Conclusions

In this systematic review of probiotic supplementation during pregnancy/lactation/infancy, (either as a probiotic alone or as part of a symbiotic) and risk of allergic outcomes, we found evidence that probiotics reduce the risk of AD or atopic AD, and allergic sensitisation to cow's milk. The positive findings for AD/atopic AD were not supported in analyses of longer term follow up data from a smaller number of trials at age 5-14. The positive finding for allergic sensitisation to cow's milk was not supported by data for allergic sensitisation to other allergens, nor by data for clinical cow's milk allergy. For the outcomes allergic rhinitis, food allergy and wheeze, there was no evidence that probiotics impact on disease risk. For allergic conjunctivitis and autoimmune disease, data were lacking.

In the analysis of AD, there was high statistical heterogeneity. Subgroup analysis identified that postnatal supplementation of mother during lactation may be important for a beneficial effect, and the data were predominantly from studies of infants at high risk of AD due to family history of allergic disease. In the analysis of atopic AD, there was no statistical heterogeneity. In the analysis of allergic sensitisation to cow's milk there was no statistical heterogeneity, but the number of events was low, and this led to high imprecision and borderline statistical significance.

In the systematic review of Pelucchi (28), which we included in our overview of systematic reviews in 2013, the authors also found reduced AD risk in children supplemented with probiotics (RR 0.79; 95%CI 0.71 – 0.88), with less statistical heterogeneity than we found (I^2=24%). For atopic AD they found RR 0.80 (95% CI 0.66 – 0.96), this time with more statistical heterogeneity than we found (I^2=31.5%). Also included in our overview Tang found no effect of probiotic supplementation on risk of allergic sensitisation to food in children (RR 0.95; 95% CI 0.80 – 1.12).

Our updated search on 26th February 2017 identified several new systematic reviews of probiotics or synbiotics for prevention of allergic outcomes. R-AMSTAR scoring identified 3 high quality reviews (Dick; Elazab; Azad) and a recent international guideline and systematic review (Fiocchi), which together found the following:

i. Fiocchi 2015 (55) in a World Allergy Organization systematic review and position paper have recommended the use of probiotics for preventing AD in high risk pregnancies/infants – for pregnant and lactating women, and directly to their infant. This is based on very low grade evidence.

ii. The review of Dick 2014 (56) covered a wide range of dietary influences on the development of childhood asthma. They cited the negative finding of Kukkonen 2011, but did not identify the other studies included in our systematic review.

iii. Elazab 2013 (57) found no evidence that probiotics prevent wheeze, but did find evidence for a protective effect on specific allergic sensitisation with borderline statistical significance. They also found evidence for reduced total IgE, but not in the context of primary prevention. The finding for specific sensitisation was statistically significant for studies which included a prenatal component to the intervention.. We did not find clear evidence for a subgroup difference in allergic sensitisation according to timing of probiotic intervention. Taken together our findings and the findings of Elazab suggest that a small effect (<20% risk reduction) of probiotics on risk of allergic sensitisation cannot be confidently excluded at this stage, and further research is warranted if a small reduction in incidence of allergic sensitisation is considered an important intervention goal.

iv. Azad and colleagues published a systematic review on probiotic supplementation and risk of wheeze, asthma or lower tract respiratory infections subsequent to our overview of systematic reviews and found no evidence of a protective effect of probiotics on this outcome (risk ratio 0.97; 95% CI 0.87 – 1.09; I^2=0%), nor on doctor diagnosed asthma (risk ratio 0.99; 95% CI 0.81 – 1.21; I^2=0%) (58). Azad 2013 found no evidence that probiotics prevent asthma (RR 0.99 95% CI 0.81, 1.21 I^2=0) or wheeze.

Two further systematic reviews had R-AMSTAR scores below 30, but were nevertheless reasonably comprehensive, and came to similar conclusions to ours. A systematic review by Mansfield identified 27 publications corresponding to 16 trials, and reported a protective effect of probiotic exposure for AD (RR 0.74; CI 0.67 – 0.82) (59). Dang 2013 (60) identified 18 trials of prebiotics, probiotics or synbiotics for preventing AD. We identified 31 trials (29 with AD as an outcome measure). Dang reported similar conclusions to us – probiotics/synbiotics reduce AD at age <2. They did not review later outcomes, and found no effect on allergic sensitisation.

Overall, our systematic review on probiotics and allergic outcomes provides evidence of a protective effect of these supplements against AD and atopic AD in high risk children ≤ 4 years old, but not beyond this age. Our data are consistent with other recent systematic reviews which did not include all the studies identified in our review.

Conclusion:

Probiotics/synbiotics reduce risk of AD in the first 4 years: grade of evidence MODERATE (-1 inconsistency i.e. statistical heterogeneity)

Probiotics/synbiotics reduce risk of atopic (IgE-associated) AD in the first 4 years: grade of evidence MODERATE (-1 inconsistency with age 5-14 outcome).

Probiotics may reduce risk of allergic sensitisation to cow's milk: grade of evidence LOW (-1 indirectness; -1 imprecision).

Further research is required in order to confirm whether probiotics reduce risk of allergic sensitisation.

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POLYUNSATURATED FATTY ACID SUPPLEMENTATION IN PREGNANCY/ LACTATION/ INFANCY, AND RISK OF ALLERGIC SENSITISATION OR ALLERGIC DISEASE

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1. PUFA supplementation and allergic outcomes – summary of interventions and findings

In this analysis we included studies of any type of polyunsaturated fatty acid (PUFA) supplementation, whether given as n-3, n-6 or combined interventions, as part of an infant formula, as a supplement, as part of a fish oil or dietary fish supplement during pregnancy, lactation and/or infancy. A formal definition of PUFA is given in the Glossary section of the summary document. We planned to undertake subgroup/stratified analyses for meta-analyses which included >5 studies, and where relevant to include specific fatty acid intervention as a subgroup. We planned to assess publication bias using Funnel plots and Egger's test where there were ≥10 studies in a meta-analysis. In total we identified 1 high quality recent systematic review in our July 2013 search, and no further high quality systematic reviews in our search update on 26th February 2017. We found 19 original trials investigating the effect of (predominantly) omega 3 fatty acids (n-3), omega 6 fatty acids (n-6), or both, during infancy and/or pregnancy on allergic outcomes. We did not identify any studies reporting autoimmune outcomes.

Interventions used:

The **Berman** study (1) used DHA (Ω -3) or EPA (Ω -3) rich fish oil supplementation prenatally, compared with soy oil. The **Bisgaard** study (2) used fish oil containing 2.4grams per day Ω -3 LCPUFA daily, or olive oil to pregnant women 24 weeks gestation until 1 week post-partum. The **Birch** study (3) used supplementation of infant formula with docosahexanoic acid (DHA; n-3) and arachidonic acid (AA; n-6) at concentrations of 0.32%-0.36%/0.64%-0.72% of total fatty acids, respectively. This was given to infants during their first year of life. The **Lucas** study (4) gave AA (0.30%) and DHA (0.32%) supplemented to formula. This was given to infants from birth to 6 months. The **van Gool** study (5) used Borage oil (containing 100 mg of gamma linoleic acid; GLA). This was given to infants, daily from 1-2 weeks of life to 6 months age. The **Harslof** study (6) used fish oil containing 1.2grams Ω-3 PUFA daily, or sunflower oil to infants from 9 to 18 months. The **Kitz study** (7) gave GLA at a dose of 100mg/day supplemented to mothers during lactation, or as infant formula (160mg/day) to the infants in their first 5 months of life. The **Linnamaa** study (8) used blackcurrant seed oil. This was given in a dose of 3g/day to pregnant women and to infants exclusively breastfeeding in a dose of 1ml/day until age 2 years. The **Mihrshahi** study (9) used fish oil (500mg, equivalent to 184mg n-3) daily from 6 months to 5 years, also given in infant formula if that was introduced before 6 months. The family of the participant infant was given canola oil (high in n-3 PUFA) for use in food. There

were follow-up times at 3 and 5 years of age(10, 11). The **Damsgaard** study (12) administered fish oil at a dose of 3.4mls/day (equivalent to 571mg eicosapentaenoic acid; EPA, and 381mg DHA) to infants from 9 to 12 months. The **Palmer** study (13) used fish oil capsules containing 800mg DHA, 100mg EPA daily. This was given to pregnant women from 21 weeks gestation to delivery. The **Dunstan** study (14) used 4g of fish oil 4g (containing 2.07g DHA, 1.02g EPA) to pregnant women, daily from 20 weeks gestation to delivery. The **D'Vaz** study (15) used fish oil (containing 280mg DHA and 110mg EPA). This was given to infants from birth to 6 months of age. The **Furuhjelm** study (16) used a daily dose of 1.6 g EPA, 1.1 g DHA, as fish oil. This was given to pregnant women from 25 weeks gestation through to the end of lactation. Outcomes were studied at age 1 (16) and 2 (17). The **Lauritzen** study (18) used 4.5 g fish oil daily (equivalent to 1.5 g/d of n-3) to lactating mothers from week 1-2 to 4 months of breastfeeding. The **Olsen** study (19) used 4g/day of fish oil (equivalent to 1.28g EPA, and 920mg DHA). This was given to pregnant women from 30 weeks of gestation to delivery. The **Dotterud** study (20) used oily fish twice a week and 5ml cod liver oil (1.2 g n-3) daily throughout pregnancy and to infants from 4–6 weeks. It then included a recommendation to give infants oily fish twice a week from the age of 6 months. The **Imhoff-Kunsch** study (21) used 400 mg DHA daily. This was given to pregnant women from 20 weeks of gestation to delivery. The **Noakes** study (22) used 2 portions (150g each) per week of farmed salmon (equivalent to 163mg EPA, 331mg DHA per day). This was given to pregnant women from 20 weeks of gestation to delivery.

Populations and Outcomes assessed:

Outcomes studied were allergic sensitisation (total IgE and skin prick test or specific IgE), food allergy, eczema, allergic rhinitis, wheeze, and lung function (forced expiratory volume in 1 second, FEV_1). Overall 14,479 infants were included. Eight studies were in infants at high risk of allergic diseases. Eleven studies were carried out in Europe, one in Latin America, three in the USA, and four in Australia. The definitions of diseases varied across studies.

Overall findings

Overall the quality of evidence was moderate - there was a low or unclear risk of bias in most studies. Just over 20% of studies were considered to have a high risk of overall bias. Overall we found some evidence that n-6 supplementation can prevent atopic dermatitis (RR 0.76; 95% CI 0.59 to 0.98) in children ≤ 4 years old, although this was considered unreliable because it was based on studies at high risk of bias or conflict of interest, and was dominated by one study (Linnamaa) which found no such effect at a later timepoint. We found evidence from one study

that n-3 fatty acid supplements during late pregnancy reduce asthma risk at age 16 compared to olive oil, but not compared to no oil supplement during late pregnancy. In one sensitivity analysis we found evidence that n-3 fatty acid supplementation during pregnancy may reduce risk of allergic rhinitis (AR) at age 5-14 years, however this effect was not seen at age ≤ 4 or ≥15 years, was not seen for the outcome atopic AR, and was not seen for infant supplementation.

We found MODERATE level evidence that n-3 fatty acids reduce the risk of allergic sensitisation to egg (RR 0.69; 95% CI 0.53 to 0.90), although one of the studies contributing to this analysis found no significant effect at later follow up, and no such effect was found for allergic sensitisation to other allergens or 'any allergen' or food allergy. This finding was derived from studies of fish oil supplementation during pregnancy +/- lactation, which were all undertaken in infants at high risk of allergic outcomes based on family history. Subgroup analysis found evidence that the effect was related to n-3 fatty acid supplementation initiated during pregnancy (RR 0.55 95% CI 0.40 to 0.76; test for subgroup difference P=0.03), and a similar finding was seen for n-3 fatty acid supplementation initiated during pregnancy, and allergic sensitisation to peanut (RR 0.62 95% CI 0.40 to 0.96). There was no evidence for any other protective effects on the rest of the outcomes studied, but data were sparse and inconclusive for n-3 supplementation and risk of food allergy, and for n-6 supplementation and all allergic outcomes. We did not find any studies reporting the effects of PUFA supplementation on autoimmune outcomes.

Overall we found MODERATE level evidence (-1 indirectness of outcome measure) that n-3 supplementation using fish oil during pregnancy +/- lactation, reduces allergic sensitisation to egg in high risk infants. No effect was seen for allergic sensitisation to other allergens, but the data for allergic sensitisation to peanut were consistent with those for allergic sensitisation to egg. We did not find evidence that fatty acid supplementation during pregnancy, lactation or infancy has an impact on risk of other allergic outcomes.

Table 1 Characteristics of included studies evaluating supplementation of long chain fatty acids and allergic outcomes

Study	Design	N Int/ Ctrl	Country	Fatty acid class	Intervention	Disease risk	Age	Outcomes reported
Klemens (23)	SR	5 RCT (949)	-	Ω-3	**Pregnant/lactating women**. Supplementation of pregnant or lactating women with n-3 PUFA, versus olive oil (3), placebo not described (1) or soya oil (1)	-	-	Wheeze, Eczema, Food allergy, Allergic sensitisation
Birch, 2010(3) Foiles, 2015 (24)	RCT	88/ 90	USA	Ω-3 and Ω-6	**Infants**. DHA (n-3) and Arachidonic acid (n-6) supplemented formula for first year as 0.32%-0.36%/0.64%-0.72% of total fatty acids, respectively.	normal	3	Wheeze (DD), Eczema (DD)
Lucas, 1999(4)	RCT	154/ 155	UK	Ω-3 and Ω-6	**Infants**. 0.3% arachidonic acid (n-6), 0.32% DHA (n-3) supplemented formula from birth to 6 months.	normal	0.75	Eczema (parent report), Wheeze/Asthma (parent report; DD)
van Gool, 2003(5)	RCT	61/ 60	The Netherlands	Ω-6	**Infants**. EFATOP trial. Borage oil (100 mg GLA) daily from 1-2 weeks to 6 months age, or sunflower oil.	high	1	Eczema (UKWP), Allergic sensitisation (sIgE), Total IgE
Kitz, 2006(7)	RCT	55/ 76	Germany	Ω-6	**Lactating women or their infants**. 100mg/day GLA supplementation of mothers during lactation, or infant formula (160mg/day) in first 5 months.	high	1	Eczema (Hanifin), Total IgE
Linnamaa, 2010(8)	RCT	151/ 162	Finland	Ω-6	**Pregnancy/lactating women**. 3g/day blackcurrant seed oil (essential fatty acid) during pregnancy and exclusive breastfeeding, 1ml/day to infant to age 2, or olive oil.	normal	1	Eczema (H&R), Allergic sensitisation (SPT), Total IgE

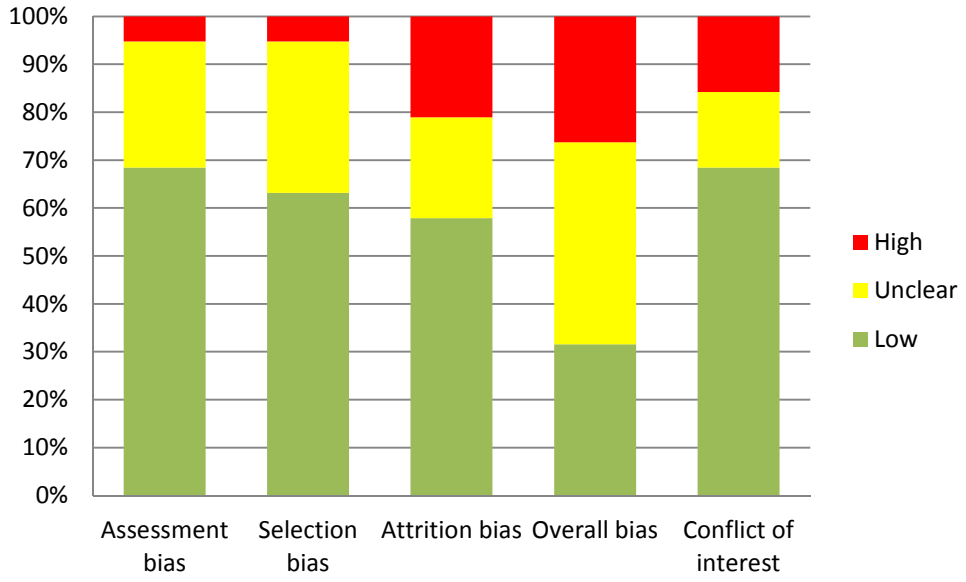
Study	Design	N Int/ Ctrl	Country	Fatty acid class	Intervention	Disease risk	Age	Outcomes reported
Mihrshahi, 2003(9) Peat, 2004(10) Marks, 2006(11)	RCT	312/ 304	Australia	Ω-3	**Infants**. CAPS trial. 500mg fish oil (=184mg n-3 PUFA) daily from 6 months, or in formula if introduced before then, plus canola oil (high in n-3 PUFA) for family, plus environmental control, until 5 years age.	high	1.5, 3, 5	Asthma (ISAAC/ parent report), FEV_1, Eczema (ISAAC-UKWP), Allergic Rhinitis (ISAAC), Allergic sensitisation (SPT), Total IgE
Damsgaard, 2007(12)	RCT	45/ 49	Denmark	Ω-3	**Infants**. Fish oil ~3.4mls/day (571mg EPA, 381mg DHA) from 9 to 12 months.	normal	1	Total IgE
Palmer, 2012 & 2013 (13, 25) Best, 2015 & 2016 (26, 27)	RCT	368/ 338	Australia	Ω-3	**Pregnant women**. DOMINO trial. Fish oil capsules with 800mg DHA, 100mg EPA daily from 21 weeks gestation to delivery, or vegetable oil.	high	1, 3	Eczema (Itchy rash on facial, flexural or extensor surface), Asthma (≥3 episodes of wheeze + SPT), Food allergy (parent report + SPT), Allergic rhinitis (history + SPT), Allergic sensitisation (SPT)
Dunstan, 2003(14)	RCT	52/ 46	Australia	Ω-3	**Pregnant women**. Fish oil 4g daily from 20 weeks gestation to delivery, containing 2.07g DHA, 1.02g EPA, from 20 week of gestation until delivery - or olive oil.	high	1	Food allergy (history), Asthma (≥2 episodes of wheeze), Eczema (DD), Allergic sensitisation (SPT)
D'Vaz, 2012(15)	RCT	218/ 202	Australia	Ω-3	**Infants**. Daily fish oil with 280mg DHA and 110mg EPA (changed to 250/60 part way through trial) from birth to 6 months, or 650mg olive oil.	high	1	Eczema (´typical skin lesions´), Allergic sensitisation (SPT), Food Allergy (parent report + SPT), Wheeze (unclear)

Study	Design	N Int/ Ctrl	Country	Fatty acid class	Intervention	Disease risk	Age	Outcomes reported
Furuhjelm, 2009(16) Furuhjelm, 2011(17)	RCT	70/ 75	Sweden	Ω-3	**Pregnant/lactating women**. Daily fish oil (1.6 g EPA, 1.1 g DHA) from 25 weeks gestation to end of lactation (or through 3.5 months of breastfeeding), or soy oil.	high	1, 2	Allergic sensitisation (SPT and sIgE), Food allergy (parent report), Allergic rhinitis (seasonal symptoms), Asthma (DD), Eczema (recurrent typical itchy rash)
Lauritzen, 2005(18)	RCT	62/ 60	Denmark	Ω-3	**Lactation**. 4.5 g fish oil daily (=~1.5 g/d of n-3 LCPUFA) from 1-2 week to 4 months, or olive oil.	normal	2.5	Wheeze (parent report), Food allergy (parent report), Eczema (DD),Total IgE
Olsen, 2008(19) Hansen, 2017 (28)	RCT	266/ 136	Denmark	Ω-3	**Pregnant women**. Fish oil 4g/day (=1.28g EPA, 920mg DHA) from 30 weeks gestation to delivery.	normal	16	Asthma (DD)
Dotterud, 2013(20)	CCT	2860/ 5743	Norway	Ω-3	**Pregnancy and infant**. PACT trial. Oily fish twice a week and 5ml cod liver oil (1.2 g n-3 PUFA) daily throughout pregnancy and to infant from 4–6 weeks with oily fish twice a week from 6 months.	normal	2	Wheeze/Asthma (parent report; DD), Eczema (Parent report)
Imhoff-Kunsch, 2011(21)	RCT	547/ 547	Mexico	Ω-3	**Pregnant women**. 400 mg DHA daily from ~20 weeks gestation to delivery, or corn/soy oil.	normal	0.5	Wheeze (parent report)
Noakes, 2012(22)	RCT	62/ 61	UK	Ω-3	**Pregnant women**. SiPS trial. 2 x 150g portions/week of farmed salmon (=~163mg EPA, 331mg DHA per day) from 20 weeks gestation to delivery.	high	0.5	Wheeze (study assessment), Eczema (Physician assessment), Allergic sensitisation (SPT)

Study	Design	N Int/ Ctrl	Country	Fatty acid class	Intervention	Disease risk	Age	Outcomes reported
Berman, 2015 (1)	RCT	Unclear – total 114	USA	**Fatty acids** Ω-3	DHA (Ω -3) or EPA (Ω -3) rich fish oil prenatal supplementation, or soy oil	Unclear	3	Wheeze (parent report); Eczema (parent report)
Bisgaard, 2016 (2)	RCT	365/371	Denmark	**Fatty acids** Ω-3	**COPSAC trial.** Fish oil (2.4g/d Ω -3 LCPUFA), or olive oil to pregnant women 24 weeks gestation until 1 week post-partum	Normal	5	Wheeze (physician assessment); Eczema (Hanifin and Rajka); AS (SPT, sIgE); ARC (DD); Lung function (FEV1)
Harslof, 2014 (6)	RCT	75/ 79	Denmark	**Fatty acids** Ω-3	Fish oil (1.2g/d Ω-3 PUFA), or sunflower oil to infants from 9 to 18 months	Normal	1.5	AS (total IgE)

SR systematic review; RCT randomised controlled trial; DHA docosahexanoic acid; EPA eicosapentaenoic acid; GLA gamma linolenic acid; LCPUFA long chain polyunsaturated fatty acid; SPT skin prick test; FEV_1 forced expiratory volume in one second; Physician assessment refers to assessment by a study physician , DD 'doctor diagnosis', which refers to community diagnosis; H&R Hanifin and Rajka criteria.

Figure 1 Risk of bias in intervention studies of PUFAs



2. PUFA supplementation and risk of atopic dermatitis

One systematic review (Table 2) and sixteen intervention trials (12,465 participants, at least 4,878 randomised to intervention) investigated the effect of n-3 or n-6 fatty acids on dermatitis. Ten studies were carried out in Europe and 5 in Australia. Seven studies were carried out in infants at high risk of atopic dermatitis (AD). One study used assessment of medical records by study nurse to define outcome, three studies used parental reported eczema, five studies used either the UK Working Party or Hanifin & Rajka criteria, one study used the ISAAC definition, three studies used typical skin lesions or rash (alone or combined with sIgE or SPT), and three studies used doctor diagnosed eczema. Children's ages at time of outcome measurement ranged between 6 months and 5 years of age. Assessment bias was low in two-thirds of studies, whilst 60% had a low risk of selection bias and 60% had low risk of attrition bias. Less than 20% of the studies were considered to have a high risk of conflict of interest due to direct industry funding of the trial or relevant industry connections of participating of authors (Figure 2).

The systematic review of 3 studies using n-3 fatty acid supplements during pregnancy/lactation found no evidence of an effect on AD. Twelve original studies reported data that could be included in meta-analysis. There was no evidence for an effect of n-3 fatty acids on AD risk in children ≤ 4 years (Figure 3; RR 1.08, 95% CI 0.82 to 1.42), at age 5-14 (Figure 4), or on atopic-AD (Figure 5; 3 studies; RR 0.69; 95% CI 0.42 – 1.14). The study of Palmer reported outcomes at 1 year (included in Figure 5) and at 3 years. At 3 years the authors used random imputation of missing outcome data, and found no significant difference in atopic AD in the supplemented group (RR 0.73 95% CI 0.51, 1.03). The study of Berman found increased eczema associated with n-3 fatty acid supplementation during pregnancy, but caused moderate heterogeneity in the meta-analysis (Figure 3). The reason why this small trial had different results to others was not clear, since the trial was reported in abstract form only. The CCT of Dotterud reported no difference in AD at age ≤ 4 – RR 0.95 (95%CI 0.83, 1.09).

There was evidence of a protective effect of n-6 fatty acids on AD in children age ≤ 4 years (Figure 6; 3 studies; RR 0.56; 95% CI 0.59 – 0.98) with no heterogeneity, based on 3 trials. Linnamaa found a significant reduction in AD at age 1 (shown in Figure 6) but no significant difference at age 2, and was at high risk of bias due to high attrition. The

study of van Gool was at high risk of conflict of interest; the study of Kitz, which showed no evidence of an effect, at unclear or low risk of bias on all domains including conflict of interest. Thus the GRADE of evidence for n-6 fatty acid supplementation and AD was downgraded (-2 study quality; -1 inconsistency; -1 sparse/imprecise data) to no evidence.

Figure 2 Risk of bias in intervention studies of PUFAs and AD

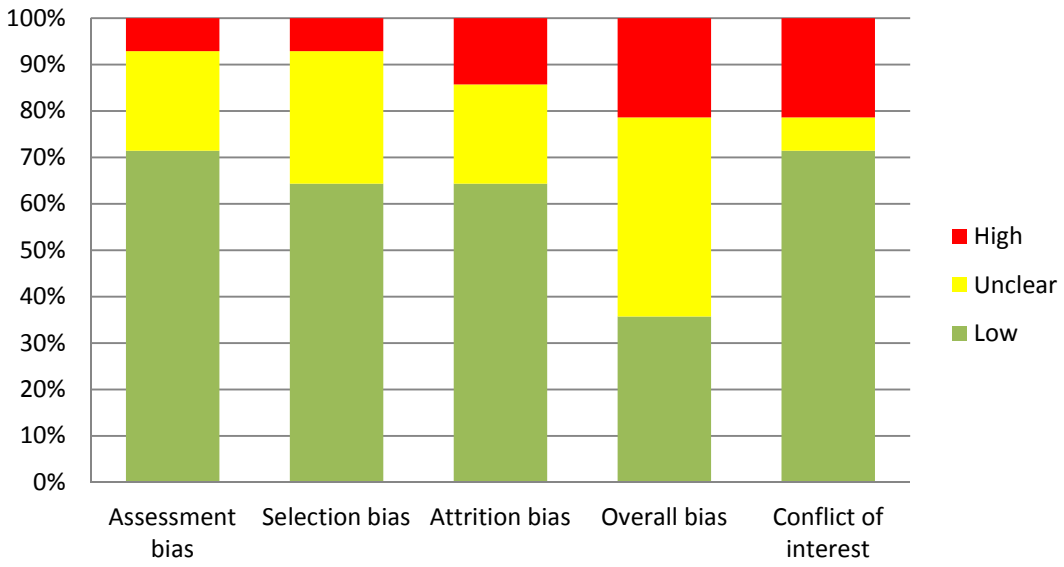


Table 2 Findings from the previous systematic review

Study	Outcome measure	No. participants (studies)	Outcome (95% CI)	I^2
Klemens (23)	Eczema	262 (3)	OR 0.92 [0.49, 1.75]	70%

Meta-analysis of 2 studies (482 participants) where supplementation was initiated during pregnancy rather than during lactation showed similar results to supplementation during pregnancy and/or lactation overall.

Figure 3 Omega 3 fatty acids and risk of AD at age ≤ 4

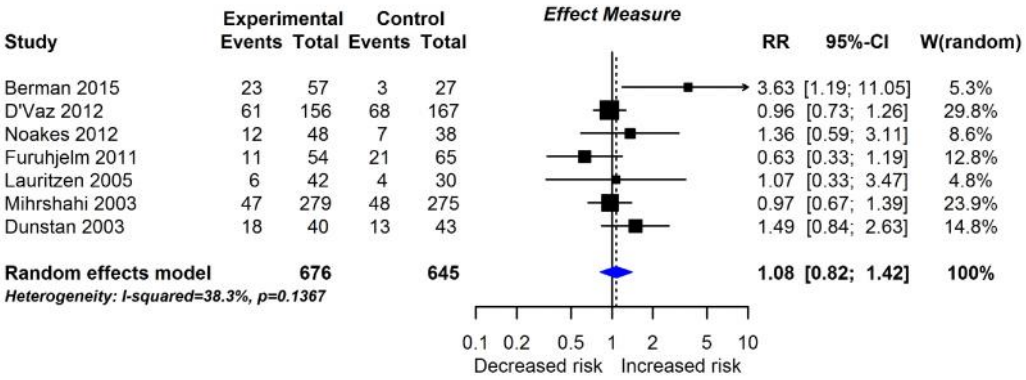


Table 3 Subgroup analysis of n-3 fatty acids and eczema risk in children aged 0-4 years

	Number of studies	RR [95% CI]	I^2 (%)	P-value for between groups difference
Intervention – prenatal +/- postnatal	5	1.28 [0.75-2.17]	53	0.43
Intervention – postnatal only	2	0.96 [0.77-1.19]	0	
Risk of disease – High	6	1.09 [0.81-1.47]	49	0.43
Risk of disease – Normal/Low	1	1.07 [0.33-3.47]	-	
Overall risk of bias – Low	3	0.98 [0.65-1.49]	49	0.83
Overall risk of bias – High/Unclear	4	1.31 [0.77-2.23]	49	
Conflict of interest bias – Low	5	1.03 [0.85-1.26]	0	0.68
Conflict of interest bias – High/Unclear	2	1.43 [0.25-8.29]	87	

Figure 4 Omega 3 fatty acids and risk of AD at age 5-14

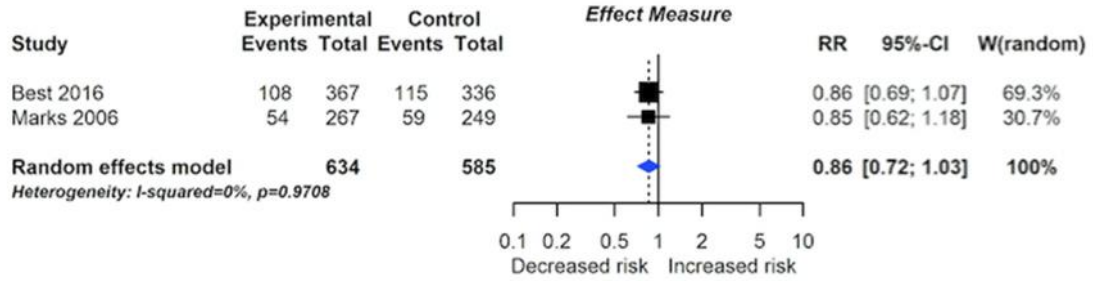


Figure 5 Omega 3 fatty acids and risk of 'atopic' AD at age ≤ 4

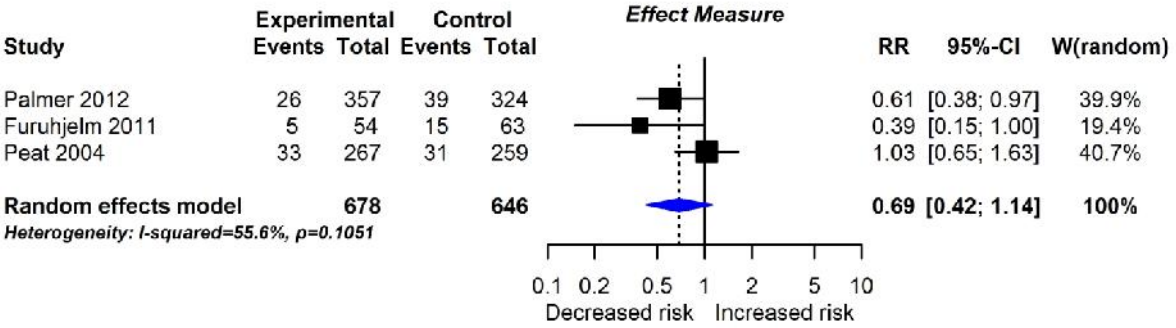
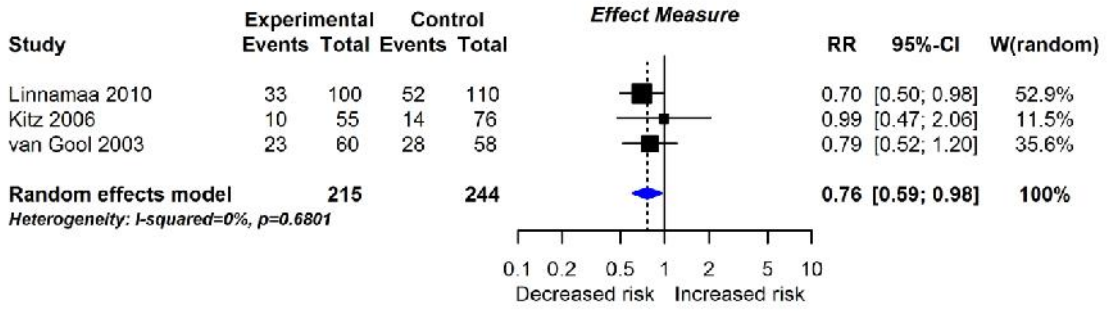


Figure 6 Omega 6 fatty acids and AD at age ≤ 4



PUFA supplementation and risk of atopic dermatitis – data that could not be included in meta-analyses

Two studies assessed an intervention which combined an n-3 (DHA) and an n-6 (Arachidonic acid) in the intervention. In both cases the intervention was as a supplementary formula milk introduced very early (<1 week) into the infant diet, and both studies were considered at high risk of conflict of interest due to direct industry involvement. The study of Birch, considered at high risk of bias due to 50% loss to follow up, found no difference in AD risk between active and control groups (RR 0.52, 95%CI 0.24, 1.12). Follow up of the same study by Foiles reported reduced 'skin allergic disease' in fatty acid versus control group (P=0.05), but the outcome definition included contact dermatitis and urticaria as well as eczema. The study of Lucas, considered at unclear overall risk of bias due to unclear assessment bias, also found no difference (OR 1.20, 95%CI 0.70, 2.10). The study of Bisgaard, considered at low overall risk of bias, due to low assessment, selection and attrition bias, furthermore found no difference (HR 1.10 95%CI 0.83, 1.44).

Overall we found no evidence that n-3 or n-6 supplementation reduces risk of AD. For n-3 supplementation the data make clinically meaningful effects unlikely. For n-6 supplementation the data are sparse and more work is needed to assess any possible role.

3. PUFA supplementation and risk of allergic rhinitis/rhinoconjunctivitis (AR)

Six intervention studies (2914 participants, 1469 randomised to the intervention arm) investigated the effect of n-3 fatty acids and risk of allergic rhino-conjunctivitis. One study was carried out in Australia, one in USA and two in Europe. Two studies recruited infants at high risk of atopic disease, and two a normal risk population. One study used the ISAAC definition of outcome, one used Hanifin and Rajka, one used doctor diagnosis and one used seasonal symptoms, combined with sIgE or SPT. The children's age at the time of outcome measure ranged between 2 and 5 years old. Four studies showed a low risk of bias, one had a high risk of attrition bias. One study had a high risk of conflict of interest (Figure 7). Forest plots showing data from five studies show no overall evidence for an effect on RC at age ≤ 4, age 5-14 or age ≥15 (Figures 8 to 11). High heterogeneity is seen in the analysis of AR at age 5-14 (Figure 9), and this is accounted for by the null findings of Marks, where infants were supplemented, and a reduction in AR in the studies of Best and Bisgaard (sensitivity analysis RR 0.75 95%CI 0.60, 0.93) where pregnant women were supplemented. Data from one study at high risk of bias and high risk of conflict of interest could not be included in a forest plot – Foiles reported that this outcome AR was recorded, but did not report outcome data for AR. They did report a composite outcome 'any allergic disease', which included AR and was reduced in the fatty acid supplemented group (P=0.04).

Overall we found no consistent evidence that n-3 supplementation reduces risk of allergic rhinitis. In one sensitivity analysis we found evidence that omega 3 fatty acid supplementation during pregnancy may reduce risk of AR at age 5-14 years, however this effect was not seen at age ≤ 4 or ≥15 years, was not seen for the outcome atopic AR, and was not seen for infant supplementation. We found no studies reporting data for allergic conjunctivitis.

Figure 7 Risk of bias in trials of PUFAs for preventing AR

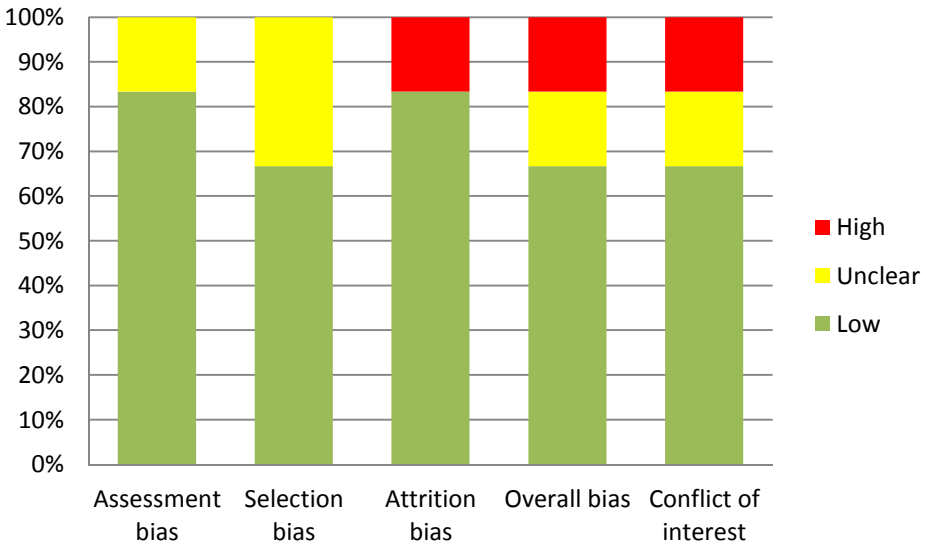


Figure 8 Omega 3 fatty acids and risk of AR at age ≤ 4

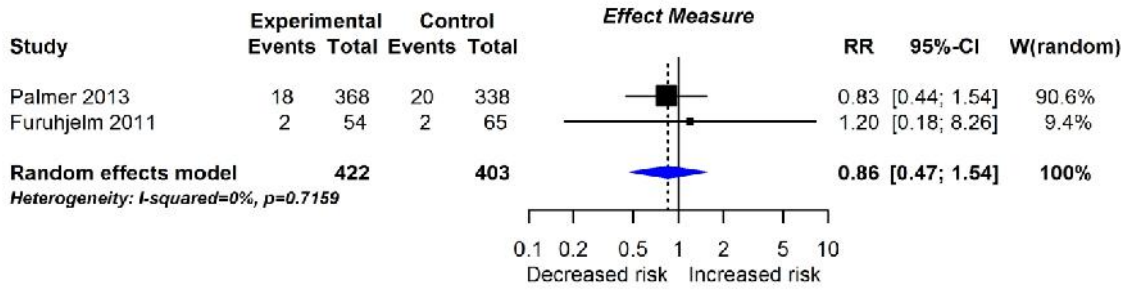


Figure 9 Omega 3 fatty acids and risk of AR at age 5-14

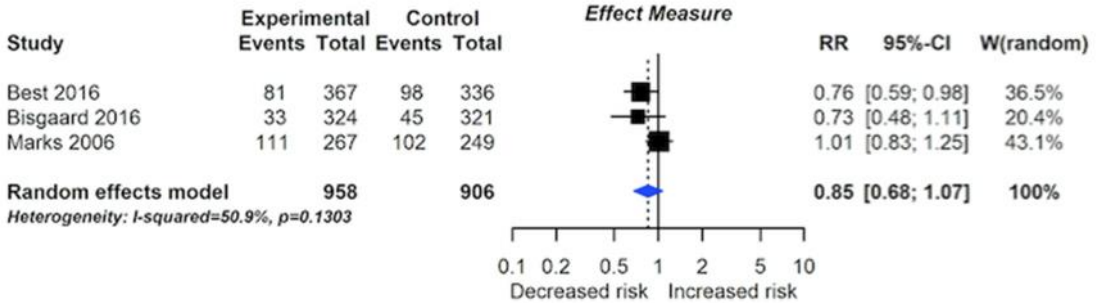


Figure 10 Omega 3 fatty acids and risk of AR at age ≥15

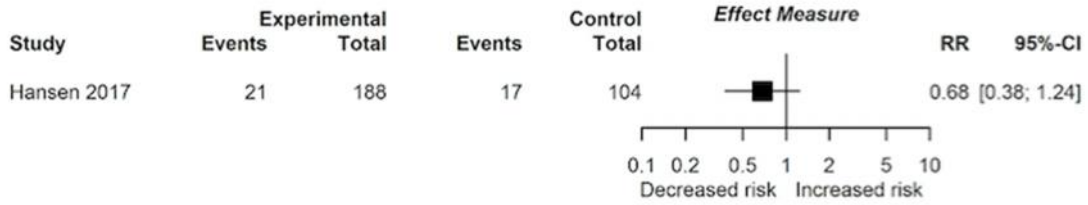
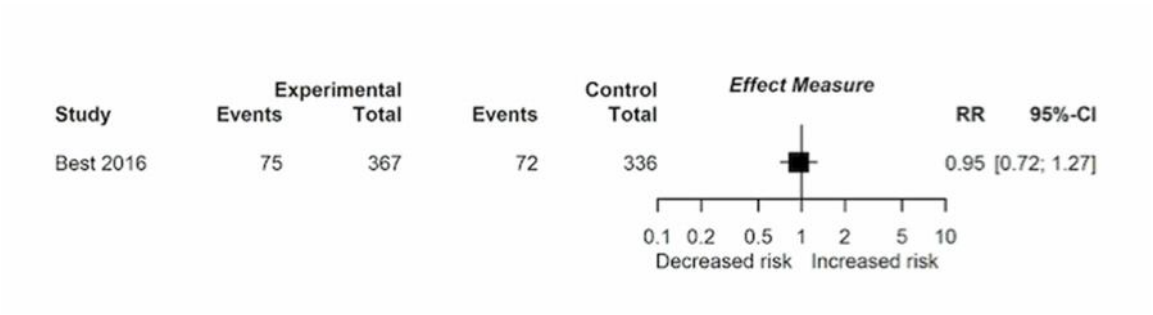


Figure 11 Omega 3 fatty acids and risk of atopic AR at age 5-14



4. PUFA supplementation and risk of food allergy

One systematic review and six intervention studies (1,669 participants, 858 randomised to the intervention arm) investigated the effect of n-3 fatty acid supplementation and risk of food allergy. Three studies were carried out in Australia, two in Europe and one in USA. All but one study was carried out in infants at high risk of food allergy. Two studies used parent reported food allergy as outcome definition, three used food allergy history plus SPT, one used doctor diagnosis. Children's age at time of outcome measurement ranged between 1 and 4 years old. Risk of bias was low in 50% (Figure 12). Risk of conflict of interest was low in most studies (Figure 12).

The systematic review of 3 studies using n-3 fatty acid supplementation during pregnancy and/or lactation found no evidence that this influenced risk of food allergy (Table 4).

Five of 6 studies were eligible for meta-analysis (Figure 13). There was no evidence that n-3 fatty acid supplementation alters food allergy risk (RR 0.76; 95% CI 0.52, 1.11), with no statistical heterogeneity between studies.

The study of Palmer reported outcomes at 1 year (included in Figure 13) and at 3 years. At 3 years the authors used random imputation of missing outcome data, and found no significant difference in food allergy in the supplemented group (RR 1.20 95% CI 0.60, 2.41). The study of Foiles was considered at a high risk of bias due to high attrition bias. The study recorded food allergy outcomes, but did not report results for food allergy separately, other than as part of 'any allergic disease', where there was reduced incidence in the PUFA supplemented group (P = 0.04).

Overall we found no evidence that n-3 supplementation reduces risk of food allergy, although data were sparse and further work is needed since significant effects cannot be confidently excluded based on the available data.

Figure 12 Risk of bias of intervention studies on PUFAs and risk of food allergy

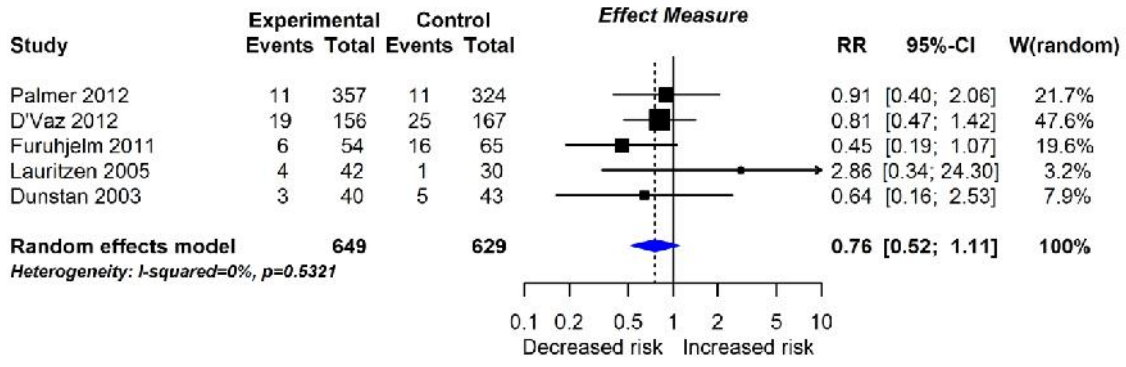


Table 4 Findings from the previous systematic review

Study	Outcome measure	No. participants (studies)	Outcome (95% CI)	I^2
Klemens (23)	Food allergy*	264 (3)	OR 0.46 [0.16, 1.38]	33%

*Meta-analysis of 2 studies (200 participants) where supplementation was initiated during pregnancy rather than during lactation showed OR 0.34, 95%CI 0.10, 1.15.

Figure 13 Omega 3 and risk of food allergy at age ≤ 4



5. PUFA supplementation and risk of allergic sensitisation

One systematic review (Table 5) and 14 intervention studies (4,131 participants, 2,162 randomised to the intervention arm) investigated the effect of fatty acids on allergic sensitisation (Table 6). Two original studies used n-6 fatty acids, and 12 used n-3 fatty acids. Ten studies were carried out in Europe and four in Australia. Eight studies were carried out in children at high risk of having allergic sensitisation. The age of the participants at time of outcome measurement ranged from 6 months to 24 years. The risk of bias was high in one third of studies, due to attrition bias (Figure 14).

The systematic review of 3 studies using n-3 fatty acid supplementation during pregnancy and/or lactation found evidence that this reduced the risk of egg sensitisation (Table 3).

Figures 15 to 22 show analyses of original studies assessing the effect of fatty acid supplementation on allergic sensitisation at any age. We did not find evidence of an effect of n-3 fatty acids on AS to any allergen or aeroallergen. There was however reduced AS to egg with n-3 supplementation (Figure 18; RR 0.71; 95% CI 0.56, 0.91), with low statistical heterogeneity. This was seen most clearly in the studies with a prenatal component to treatment (Table 5). Although the same effect was not seen for other foods individually when all studies were pooled, the same effect was seen for AS to peanut with *prenatal* n-3 supplementation (RR 0.62 95% CI 0.40, 0.96), with no heterogeneity. No effect was seen for n-6 fatty acids, or in the 2 studies reporting AS to any food. The study of Palmer reported reduced AS to egg at 1 year (included in Figure 18), but at 3 years there was no significant difference in egg sensitisation (RR 0.65; 95% CI 0.30, 1.41) or indeed any other allergic sensitisation, and at 6 years there was no difference in egg sensitisation (RR 1.12; 95%CI 0.35, 3.63) or any allergic sensitisation (Figure 15).

Eight studies assessed total IgE level as an outcome. In all studies there was no significant difference in total IgE between intervention and control groups. Marks reported the ratio of mean IgE at age 5 to be 0.86 (95% CI 0.64, 1.16). Damsgaard reported median total IgE 16µg/L (IQR 2, 475) in the supplemented group, 12 (2, 128) in the control group. Van Gool reported geometric mean total IgE 9.31 kU/L (sd 4.45) in

the intervention group, 6.87 (3.56 in the control group). Kitz reported no significant difference (data not shown). Linnamaa reported mean 20.5 (sd 37.2) intervention, 14.8 (17.5) control. Lauritzen reported similar average total IgE in intervention (8.9) and control (8.8) groups. Harslof reported that Total IgE did not differ between intervention and control groups (median fish oil 15.5 (IQR 3.3, 30.8); soya oil 7.5 (2.9, 29.7). Hansen also reported no difference in total IgE between groups (median 36 (IQR 15,84) fish oil; 38 (12,90) olive oil.

Overall we found MODERATE level evidence (-1 indirectness of outcome measure) that n-3 supplementation using fish oil during pregnancy +/- lactation, reduces allergic sensitisation to egg in high risk infants. No clear effect was seen for allergic sensitisation to other allergens, but the data for allergic sensitisation to peanut were consistent with those for allergic sensitisation to egg.

Figure 14 Risk of bias of intervention studies on PUFAs and risk of allergic sensitisation

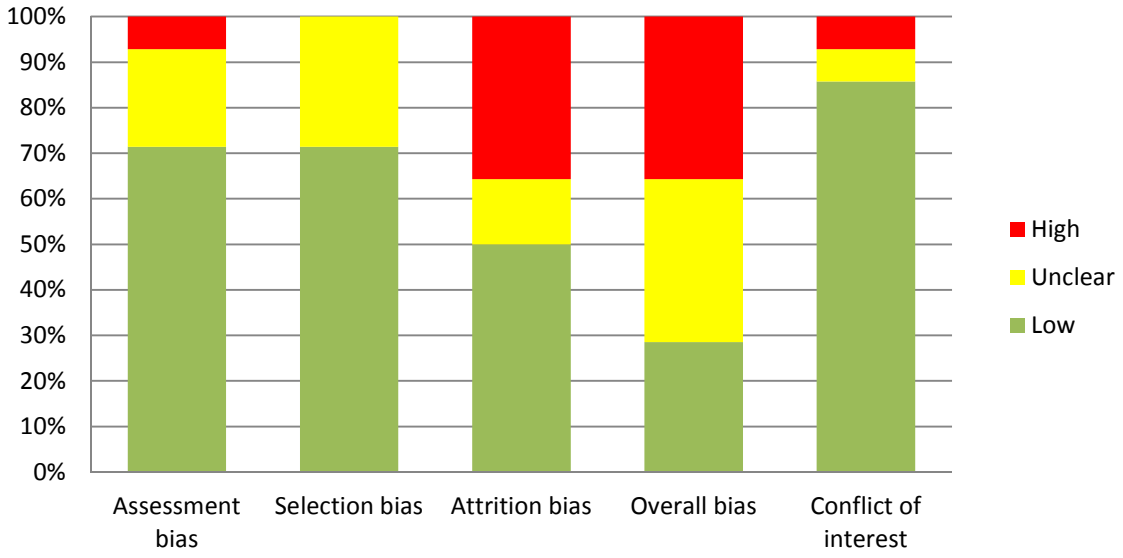
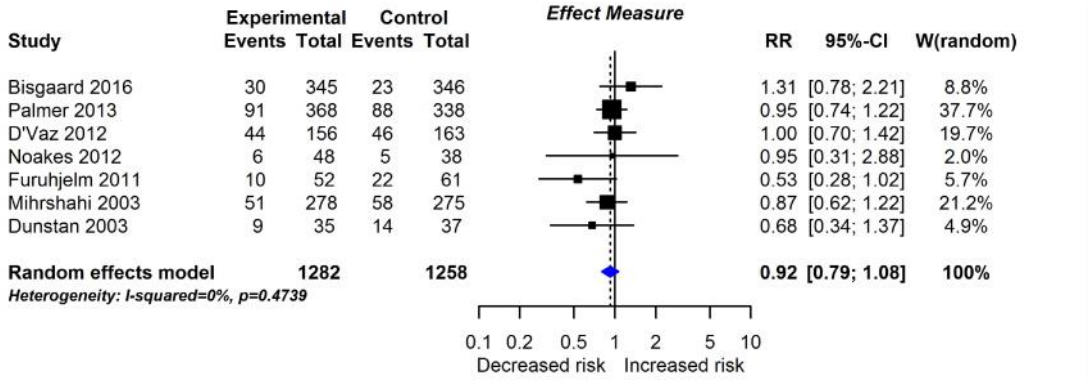


Table 5 Findings from the previous systematic review

Study	Outcome measure	No. participants (studies)	Outcome (95% CI)	I^2
Klemens (23)	SPT to egg at 1 yr	187 (2)	OR 0.33 [0.16, 0.70]	0%

Figure 15 Omega 3 fatty acids and risk of AS to any allergen



Data shown from Bisgaard are for SPT. The same study reported similar findings for sIgE – RR 1.65 (95% CI 0.95, 2.86).

Table 6 Subgroup analysis of n-3 fatty acids and allergic sensitisation to any allergen in children

	Number of studies	RR [95% CI]	I^2 (%)	P-value for between groups difference
Intervention – postnatal only	2	0.93 [0.73-1.19]	0	0.83
Intervention – prenatal +/- postnatal	5	0.89 [0.68-1.17]	24	
Risk of disease – High	6	0.85 [0.69-1.06]	0	0.15
Risk of disease – Normal/Low	1	1.34 [0.76-2.35]	--	
Overall risk of bias – Low	5	0.88 [0.71-1.11]	31	0.66
Overall risk of bias – High/Unclear	2	0.99 [0.63-1.56]	0	
Conflict of interest bias – Low	6	0.95 [0.81-1.12]	0	0.09
Conflict of interest bias – High/Unclear	1	0.53 [0.28-1.02]	--	

Figure 16 Omega 3 fatty acids and risk of AS to any aeroallergen

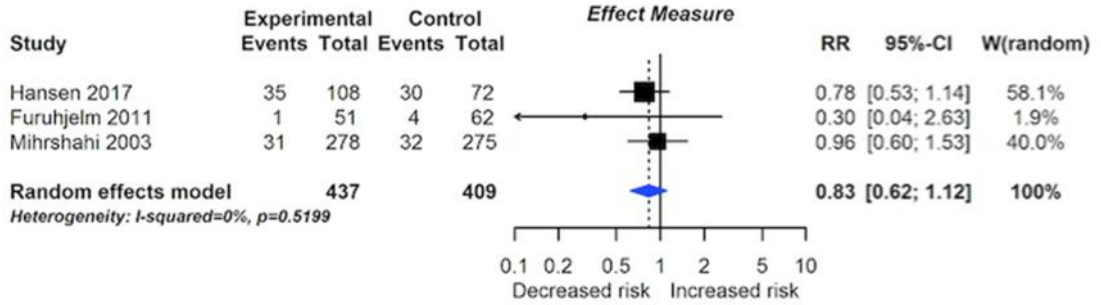


Figure 17 Omega 3 fatty acids and risk of AS to food

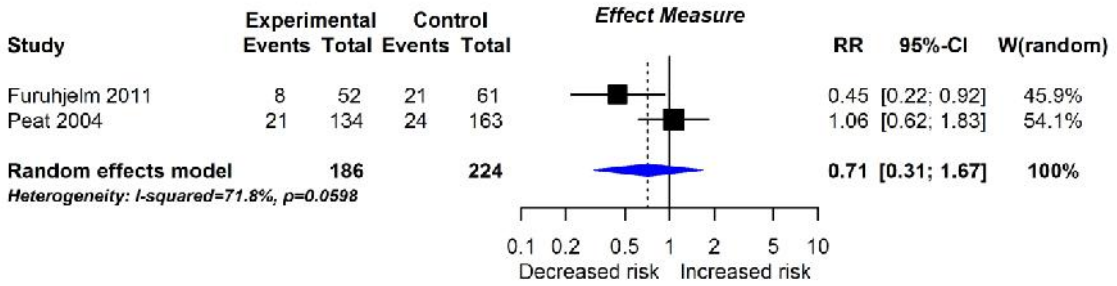


Figure 18 Omega 3 fatty acids and risk of AS to egg

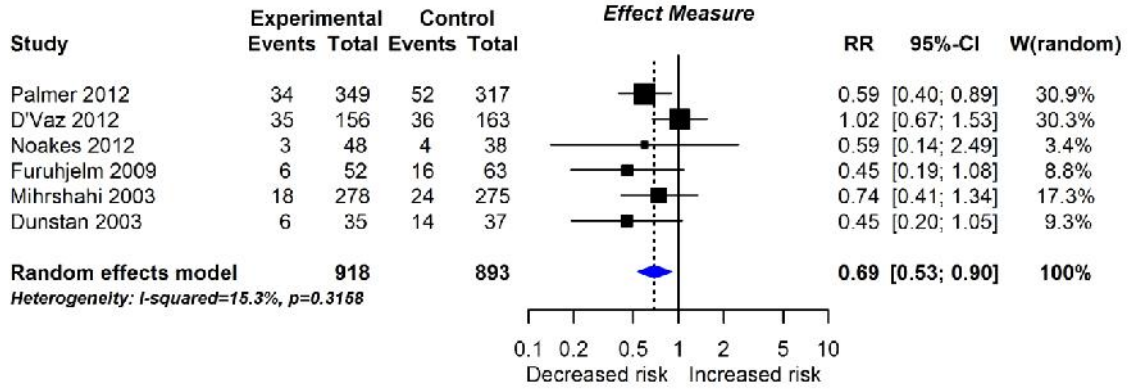


Table 7 Subgroup analysis of n-3 fatty acids and risk of AS to egg

	Number of studies	RR [95% CI]	I^2 (%)	P-value for between groups difference
Intervention – prenatal +/- postnatal	4	0.55 [0.40-0.76]	0	0.03
Intervention – postnatal only	2	0.92 [0.65-1.28]	0	
Risk of disease – High	6	0.69 [0.53-0.90]	15	-
Risk of disease – Normal/Low	0	-	-	
Overall risk of bias – Low	4	0.59 [0.44-0.79]	0	0.044
Overall risk of bias – High/Unclear	2	0.98 [0.66-1.45]	0	
Conflict of interest bias – Low	4	0.80 [0.58-1.12]	8.8	0.17
Conflict of interest bias – High/Unclear	2	0.57 [0.39-0.82]	0	

Figure 19 Omega 3 fatty acids and risk of AS to peanut

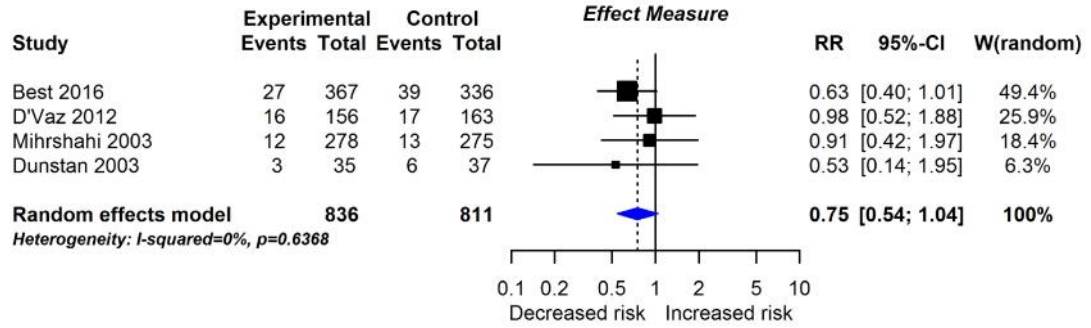


Figure 20 Omega 6 fatty acids and risk of AS to food

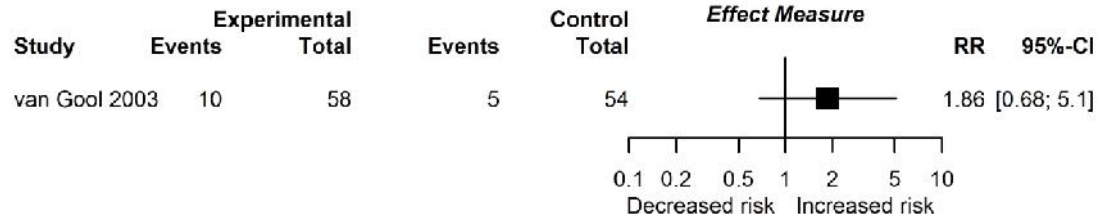


Figure 21 Omega 3 fatty acids and risk of AS to cow's milk

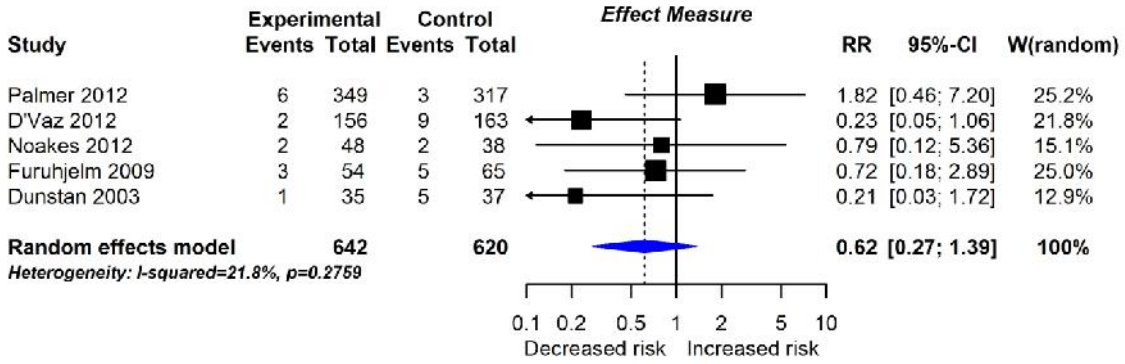
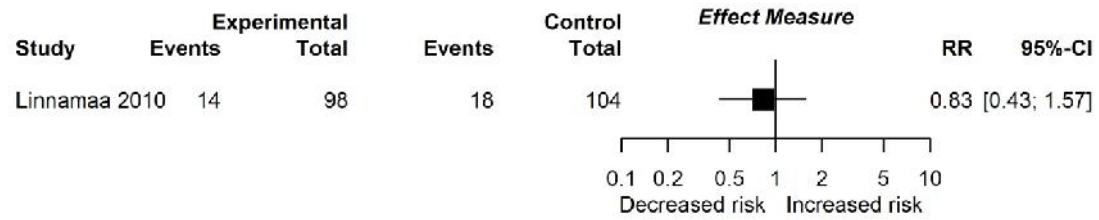


Figure 22 Omega 6 fatty acids and risk of AS to egg



6. PUFA supplementation and wheeze

One systematic review and thirteen intervention studies (13,666 participants, 5,771 randomised to the intervention arm) investigated the effect of fatty acids on wheeze +/- lung function (Table 8). Six studies were from Europe; four were from Australia, and four from the USA. Two studies used a combination of n-3 and n-6 fatty acids, and all other studies used n-3. Six studies were carried out in infants with high risk of disease. Age at time of outcome measurement ranged from 6 months to 24 years old. Nine studies used parental report of Dr diagnosed asthma or wheeze, one study used an unclear method to define the outcome, one study used current wheeze as definition, whilst another study used number of episodes of wheeze, and one study defined wheeze according to the ISAAC questionnaire. The risk of bias was low for just under half of studies (Figure 23). Slightly under 30% of studies had a high risk of bias, most commonly due to attrition bias, and 14% were considered to have a high risk of conflict of interest.

The systematic review of three trials of n-3 fatty acid supplementation during pregnancy/lactation, found no effect of this intervention on risk of wheeze.

Eight original studies were eligible to combine in a meta-analysis to examine the effect of n-3 fatty acids on risk of wheeze in children aged ≤ 4 years old (Figure 24) but there was no evidence of an effect (RR 0.95; 95% CI 0.79 – 1.14; I^2=13%). Subgroup analyses did not identify important subgroup differences. The CCT of Dotterud reported no difference in wheeze at age ≤ 4 – RR 0.94 (95%CI 0.85, 1.05). Smaller numbers of studies contributed to non-significant analyses of wheeze at age 5-14, atopic wheeze at age ≤ 4 years and age 5-14 years (Figures 25 to 27).

Four studies evaluated the effect of n-3 supplementation on recurrent wheeze in children aged ≤ 4 years old (Figure 28). There was no evidence of an effect in meta-analysis of 3 RCTs (RR 1.06; 95% CI 0.69 – 1.63; I^2=8%). In the CCT of Dotterud there was reduced recurrent wheeze at age ≤ 4 – RR 0.73 (95%CI 0.57, 0.94).It should be noted that the study of Dotterud included a smoking cessation programme as part of the intervention, which was successful, and this may have contributed to any positive effect on risk of wheeze/recurrent wheeze. Three studies evaluated the effect of n-3 supplementation on recurrent wheeze in children aged 5-14 years (Figure 29). There was no evidence of an

effect (RR 0.92; 95% CI 0.69 – 1.22; I^2=59.7%). The high statistical heterogeneity was caused by the study of Bisgaard, and could not be easily explained.

Marks reported both wheeze using ISAAC, and recurrent wheeze using ISAAC PLUS either DD wheeze or >12% FEV1 increase after bronchodilator at the age of 5 and found no effect (Figure 25 and 29).

Two studies assessed an intervention with combined omega 3 (DHA) and omega 6 (Arachidonic acid) supplements. In both cases the intervention was as a supplementary formula milk introduced very early (<1 week) into the infant diet, and both studies were considered at high risk of conflict of interest due to direct industry involvement. The study of Birch, considered at high risk of bias due to 50% loss to follow up, found reduced odds of recurrent wheeze by age 3 in those receiving n-6 supplements OR 0.31 (95%CI 0.11-0.97). The study of Lucas, considered at unclear overall risk of bias due to unclear assessment bias, found no significant difference for parent reported wheeze OR 1.10 (95%CI 0.60-1.80) or for doctor diagnosed asthma; OR 0.80 (95%CI 0.30- 2.50) at 9 months.

The study of Berman found no difference between intervention and control groups for childhood respiratory outcomes, including wheeze – no data were reported that could be included in meta-analysis.

Olsen reported significantly reduced recurrent wheeze at 16 years, when compared with olive oil, with small numbers of cases identified (RR 0.13, 95% CI 0.03, 0.60). However a third randomised group in this study, who received no oil supplementation at all, had similar outcomes to the fish oil group (0/ 129 cases of allergic asthma) suggesting that the outcomes in this study may have been due to an adverse effect of olive oil rather than a beneficial effect of fish oil. A later follow up of the same cohort by Hansen at 18 years of age found there was no significant difference for recurrent wheeze when comparing intervention and control groups (RR 0.79, 95% CI 0.55, 1.13).

This study also found that forced expiratory volume in one second (FEV_1) did not differ between groups at later follow up (mean 99.5 (SD 10.8) fish oil; 100.0 (10.0) olive oil). Bisgaard also found no difference between groups in FEV_1 in an assessment of 536 participants at age 5 years - mean difference 0 litres per minute 95% CI -0.02 to +0.03 P=0.70.

One other intervention study from Australia (616 participants, 312 randomised to the intervention arm) investigated the association between n-3 fatty acids and FEV_1 in infants at high risk of disease. Age at time of outcome measurement was 5 years old. The study had low risk of selection and assessment bias but this analysis had high risk of attrition bias. The authors reported mean $FEV_1$1.07 litres in active, 1.07 in control group - mean difference 0.0 litres (-0.03, 0.03). P=0.90.

Overall we found no consistent evidence that n-3 or n-6 fatty acid supplementation reduces risk of wheezing.

Figure 23 Risk of bias in intervention studies on PUFAs and risk of wheeze

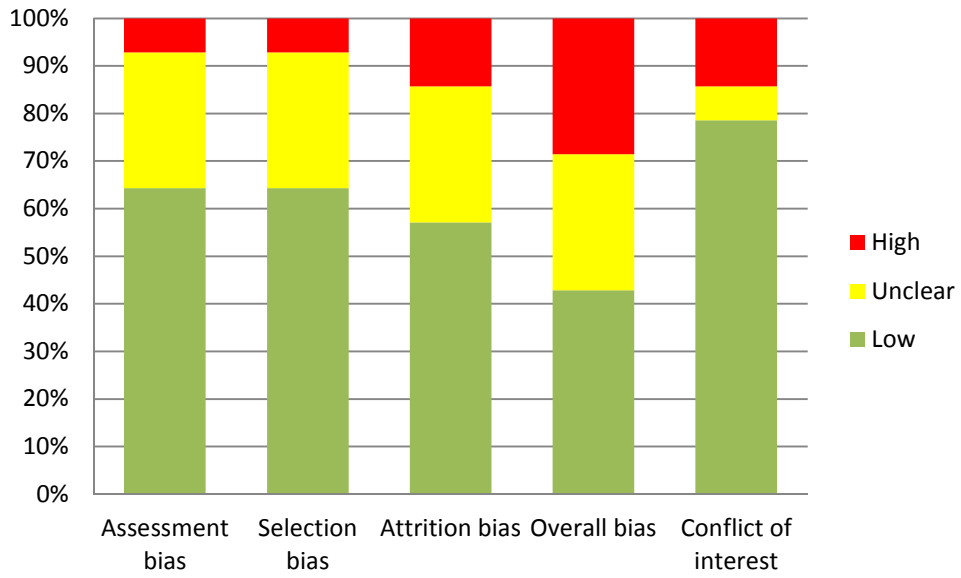


Table 8 Findings from the previous systematic review

Study	Outcome measure	No. participants (studies) contributing data	Outcome (95% CI)	I2
Klemens (23)	Wheezing	546 (3)	OR 0.58 [0.30, 1.13]	56%

*Meta-analysis of 2 studies (482 participants) where supplementation was initiated during pregnancy rather than during lactation showed reduced wheeze (OR 0.35, 95%CI 0.15, 0.79). However wheeze assessment was at 12 months and 16 years in these 2 studies, so meta-analysis may not be appropriate. The third study included above assessed wheeze at 30 months.

Figure 24 Omega 3 fatty acids and risk of wheeze at age ≤ 4

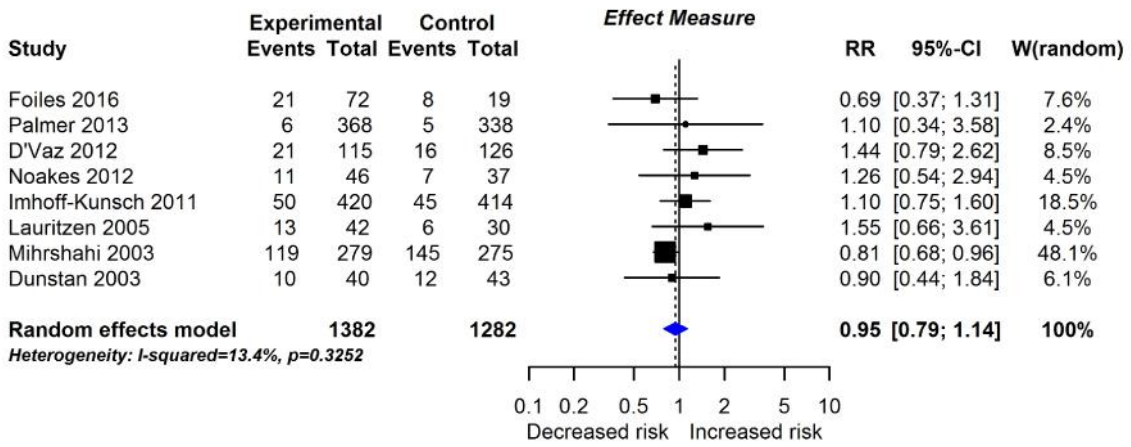


Table 9 Subgroup analysis of n-3 fatty acids and wheeze at age ≤ 4

	Number of studies	RR [95% CI]	I^2 (%)	P-value for between groups difference
Intervention – prenatal +/- postnatal	5	1.12 [0.84-1.49]	0	0.31
Intervention – postnatal only	3	0.89 [0.63-1.26]	46	
Risk of disease – High	5	0.91 [0.73-1.12]	9	0.57
Risk of disease – Normal/Low	3	1.03 [0.71-1.48]	20	
Overall risk of bias – Low	4	0.86 [0.74-1.00]	0	0.18
Overall risk of bias – High/Unclear	4	1.14 [0.78-1.69]	16	
Conflict of interest bias – Low	7	0.99 [0.80-1.21]	19	0.30
Conflict of interest bias – High/Unclear	1	0.69 [0.37-1.31]	-	

Figure 25 Omega 3 fatty acids and risk of wheeze at age 5-14

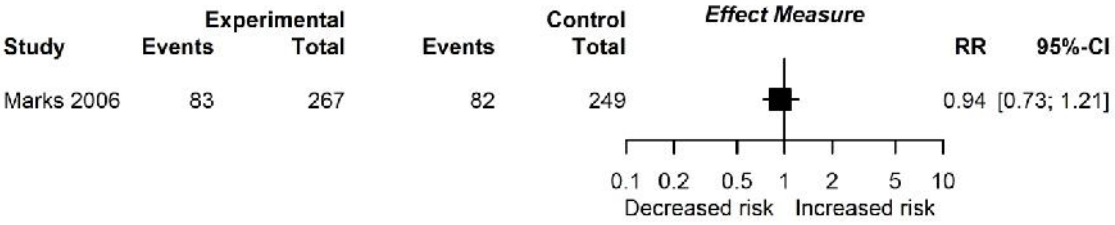


Figure 26 Omega 3 fatty acids and risk of atopic wheeze at age ≤ 4

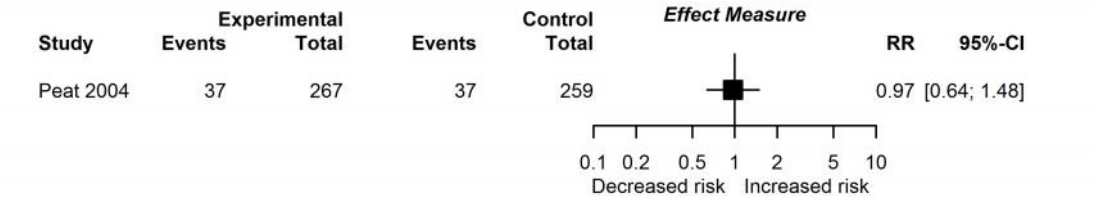


Figure 27 Omega 3 fatty acids and risk of atopic wheeze at age 5-14

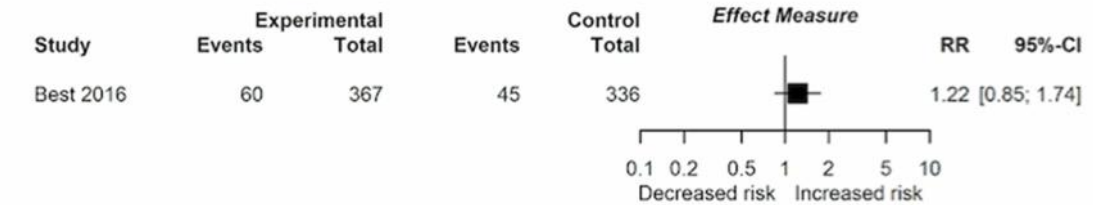


Figure 28 Omega 3 fatty acids and risk of recurrent wheeze at age ≤ 4

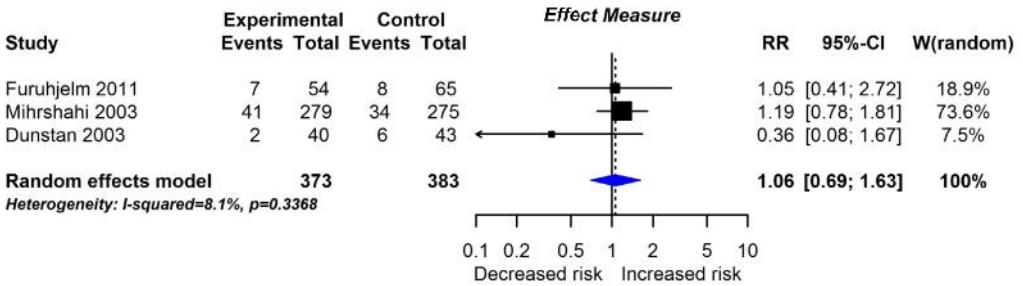
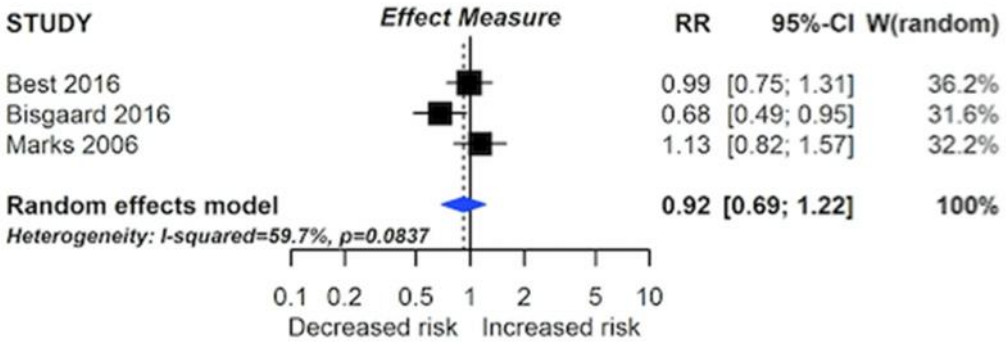


Figure 29 Omega 3 fatty acids and risk of recurrent wheeze at age 5-14


STUDY
Effect Measure
RR
95%-CI
W(random)
Best 2016
0.99 [0.75; 1.31] 36.2%
Bisgaard 2016
0.68 [0.49; 0.95] 31.6%
Marks 2006
1.13 [0.82; 1.57] 32.2%
Random effects model
0.92 [0.69; 1.22] 100%
Heterogeneity: I-squared=59.7%, p=0.0837
0.1 0.2 0.5 1 2 5 10
Decreased risk
Increased risk

General conclusions

A systematic review of this area by Sheikh and colleagues (29) published in 2009 found no evidence that fatty acid supplements reduce risk of allergic disease, but with wide confidence intervals suggesting that further trials were needed. They identified 6 relevant trials, which indicated the review was in need of updating.

A more recent systematic review from 2011 included 5 trials, restricted to omega 3 fatty acid supplementation during pregnancy/lactation, and has been incorporated in our report (23). The authors found evidence that n-3 fatty acid supplementation during pregnancy/lactation may reduce allergic sensitisation to egg, but not other allergic outcomes (wheeze, AD and food allergy).

There have been several subsequent systematic reviews, narrative reviews and overviews of this area by Best (30), Dick (31), Koletzko (32), Netting (33), Yang (34), Girdhar (35). These reports have all included small numbers of fatty acid supplementation trials, with limited or no new meta-analysis undertaken. The authors have generally reported positive findings in relation to allergic outcomes. One of these reviews (Dick) met our quality criteria of R-AMSTAR score over 32. This review identified one cohort study of fish consumption, and one of the intervention trials included in our review (Dunstan) which reported no association between fish oil supplementation during pregnancy and risk of wheezing.

The Cochrane review of Gunaratne differed from our systematic review in that they excluded the CCT of Dotterud 2013, and limited their review to maternal supplementation, with exclusion of infant supplementation studies which didn't also supplement mothers (36). Their findings and conclusions are overall similar to ours – that there is some evidence for a reduction in allergic sensitisation to egg for omega 3 supplementation during pregnancy/lactation. They stratified analyses by age at outcome, which led to some mixed positive and null findings for eczema and food allergy outcomes. But overall they concluded that omega 3 supplements during pregnancy or lactation showed little benefit in the reduction of allergic disease in childhood. Their positive finding in one age stratum for medically diagnosed eczema (but not for other age strata, nor for parent-reported eczema) has led to a national recommendation to use omega 3 fatty acid supplements for eczema prevention

https://www.allergy.org.au/images/pcc/ASCIA_Guidelines_infant_feeding_and_allergy_prevention.pdf .

In our more recent and comprehensive review we identified 19 trials, some of which were published subsequent to the reviews of Sheikh, Klemens and Gunaratne. We found evidence that maternal n-3 fatty acid supplementation may reduce allergic sensitisation to egg and peanut, the commonest food allergens in young children, but no evidence for other allergic sensitisation either to foods or aeroallergens or to 'any allergen'. We found no evidence of a reduction in food allergy, but this needs to be further explored because data were sparse with wide confidence intervals. One study of n-3 fatty acid supplementation during pregnancy found reduced asthma at age 16 when compared with olive oil supplementation during pregnancy, but no reduction when compared with no oil supplementation during pregnancy. Finally one analysis of n-6 supplementation during pregnancy/lactation, based mainly on studies at high risk of attrition bias or conflict of interest bias, found reduced eczema at ≤4 years. However, the study of Linnamaa which dominated this analysis found reduced eczema at age 1 (included in the meta-analysis), but no reduction at age 2.

Taken together these data do not provide conclusive evidence that fatty acid supplementation during pregnancy, lactation or infancy has an impact on childhood allergic disease risk. However further work is needed, especially for food allergy, given the positive findings for allergic sensitisation to food.

Overall we found MODERATE level evidence (-1 inconsistency; -1 indirectness of outcome measure) that n-3 supplementation using fish oil during pregnancy +/- lactation, reduces allergic sensitisation to egg in high risk infants. Data for peanut sensitisation were consistent with those for egg, but no effect was seen for allergic sensitisation to other allergens, nor for the outcomes AD, wheeze, food allergy or AR.

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MATERNAL AND INFANT INTAKE OF VITAMINS AND MINERALS, AND RISK OF ALLERGIC AND AUTOIMMUNE DISEASES – Observational and intervention studies

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1. Executive summary of studies and findings: Maternal and infant intake of vitamins and minerals and risk of allergic and autoimmune diseases – Observational and intervention studies

1.1. Context of this report

This report is one of a series of systematic review reports included in Review C Part II, which focusses on evidence on dietary exposures during pregnancy, lactation and or infancy for reducing risk of allergic or autoimmune outcomes. This report focuses on infant and maternal intake of vitamins and minerals. It includes all measures of vitamin and mineral intake, including those derived from food frequency questionnaires, records of direct vitamin supplementation, and for vitamin D for plasma/serum measurements of vitamin D level. Whenever possible, this report specifies the precise vitamin or mineral measured or used for supplementation, if such information is available from the original report.

1.2. Studies identified

We identified a total of 61 studies investigating the association between vitamins or minerals and allergic or autoimmune diseases. Of these, there were 11 RCT of vitamin supplementation in pregnant women (9) or infants (2), and 50 observational studies. Amongst these, 32 were prospective cohorts (PC), 4 were nested case-control studies (NCC), and 14 were case-control studies (CC).

1.3. Populations

Amongst the intervention studies, four were carried out in Europe, two in the US, two in Asia, one in Australasia and two in Africa. The majority of observational studies were carried out in European populations (n=30). The rest are from North America (n=8), Asia Pacific region (n=10), and the Middle East (n=2).

1.4. Dietary assessment and comparators used

The majority of the studies used a questionnaire to ascertain dietary intake of vitamins and minerals. Other studies used sera to analyse levels of vitamin D, 1 study used medical records or a combination of the above approaches. It was unclear if all studies using a dietary

questionnaire had validated or piloted the questionnaire, or if it was adapted to reflect the research question being addressed in the study.

1.5. Outcomes evaluated

Amongst the intervention studies, the outcomes investigated included wheeze (n=10), allergic sensitisation (n=6), atopic dermatitis (AD) (n=6), food allergy (n=2) and lung function (n=3). Amongst the observational studies, the outcomes studied included AD (n=18), food allergy (FA) (n=10), lung function (LF) (n=4), wheeze (n=28), rhino conjunctivitis (RC) (n=4), allergic sensitisation (AS) (n=12), type 1 diabetes mellitus (T1DM) (n=15), inflammatory bowel disease (IBD) (n=1), and juvenile idiopathic arthritis (JIA) (n=1).

1.6. Presentation of results

We created summary Tables of Study Characteristics with key study features (Table 1 allergic outcomes; Table 2 autoimmune outcomes). As most of the observational studies had data that could not be combined in a meta-analysis, a table of main characteristics and main findings for observational studies is also provided at the end of each section of this report.

1.7. Risk of bias assessment

Overall risk of bias for the intervention studies was high in 45% of studies, due to high attrition bias; no intervention study had a high risk of conflict of interest. The risk of bias in included cohort and case control studies was assessed using a modified version of the National Institute for Clinical Excellence (NICE) methodological checklist for cohort and case-control studies, respectively (1). Key domains were:

- Selection Bias (low if cases and controls were selected from similar populations, if the participation rate was ≥80%, or <80% but investigators explored and adjusted for characteristic differences between participants and non-participants);
- Assessment Bias (low if validated and reliable tools were used to assess exposure and/or outcome), and;
- Confounding Bias (low if most likely confounders are identified and taken into account in study design and analysis).

Observational studies were considered at low overall risk of bias where the risk of bias was judged to be low for all 3 key domains for selection, assessment and confounding bias. For assessment of Confounding Bias, factors that we expected to be adjusted for within studies of allergic outcomes were: siblings (parity or birth order or family size); gender; age at outcome assessment; disease risk based on family history; maternal or household smoking (asthma/wheeze outcomes); maternal age; maternal education or socioeconomic status; mode of delivery. For studies on autoimmune outcomes we expected matching and/or adjusting for gender, age, address, socioeconomic status, smoking and disease risk. We also assessed possible Conflict of Interest, this being judged as low where there was no evidence of industry involvement in study design, analysis, interpretation or publication, and no evidence that study authors received remuneration from relevant industry partners for other activities. Given the nature of the studies included in this report (observational studies on reported dietary intake of foods or food groups), the risk of conflict of interest was judged as low in all cases. Therefore, conflict of interest bias is not systematically shown through this report. A Risk of Bias Figure is presented in each outcome section, reported for all studies contributing data, whether included in meta-analysis or reported narratively.

1.8. Key findings

i. Overall risk of bias was low or unclear for the majority of the outcomes assessed.

The overall bias was considered to be low in the majority of the studies on atopic dermatitis, food allergy, wheeze, allergic sensitisation, and for autoimmune diseases. In some observational studies it was unclear whether adjustment for potential confounders had been done, which led to a judgement of 'unclear' overall risk of bias. In 5 of the 11 intervention trials identified in this review attrition bias was high; no intervention study had a high risk of assessment or selection bias, nor a high risk of conflict of interest.

ii. **The large variations in the methods of dietary assessment prevented us from combining the effect estimates reported in the majority of the studies**.

Despite the number of studies included in this report, meta-analysis of effect estimates was seldom possible due to the lack of comparability of dietary estimates for observational studies, and sparse data/mixed outcome assessments in the intervention trials. We summarised any evidence that could not be included in meta-analysis, in a narrative table for each study outcome.

iii. There was no consistent evidence to suggest that maternal or infant intake of specific vitamins or minerals might be protective against allergic outcomes or autoimmune diseases

The main dietary exposures studied were antioxidant vitamins A, C, E and their precursors; and vitamin D and folic acid.

Overall, we found no consistent evidence from observational or intervention studies to suggest that maternal or infant intake of vitamins or minerals influences the risk of AD, AR, FA, AS, TIDM or JIA.

From the intervention trials we found LOW (-1 indirectness of study population; -1 imprecision) evidence that vitamin supplementation during pregnancy increases lung function in offspring; but no evidence that vitamin supplementation during pregnancy reduces risk of wheezing in offspring.

Table 1 Characteristics of included studies evaluating vitamin and mineral supplementation or dietary intake and allergic diseases

Study	Design	No. participants (Intervention/Ctrl)	Country	Population characteristics	Intervention/ Exposure	Intervention/ Exposure details	Age at outcome (years)	Outcomes and Method of Assessment
INTERVENTION STUDIES								
Aage, 2015 (2)	RCT	2145/ 2200	Guinea-Bissau	Neonates at time of BCG vaccination. Population at high risk of vitamin A deficiency.	**Vitamin A**	Neonates supplemented with Vitamin A 50,000 IU plus 10IU vitamin E, or 10IU vitamin E alone at time of BCG vaccination.	**10**	AS (SPT); Wheeze (ISAAC); Eczema (ISAAC)
Chawes, 2016 (3)	RCT	315/308	Denmark	**COPSAC**. Pregnant women 24 weeks gestation to 1 week post-partum.	**Vitamin D**	Vitamin D3 (2400 IU/d) or placebo from 24 weeks gestation to 1 week post-partum. All women also took 400 IU/day of vitamin D3.	**3**	Wheeze (physician assessment); Eczema (Hanifin and Rajka); AS (SPT, sIgE)
Checkley, 2010 (4) **Checkley, 2011** (5)	cluster RCT	803, 885, 771	Nepal	**NIPPS 2 study.** Married women at high risk of vitamin A deficiency.	**Vitamin A or Beta Carotene**	Vitamin A (23,300 IU) or Beta Carotene (42mg) versus peanut oil placebo weekly from preconception through lactation	**11**	Wheeze (ISAAC, DD); LF (FEV_1; FVC; PEF)

Study	Design	No. participants (Intervention/Ctrl)	Country	Population characteristics	Intervention/ Exposure	Intervention/ Exposure details	Age at outcome (years)	Outcomes and Method of Assessment
Czeizel, 1994 (6); Dobo, 1998 (7)	RCT	2090/2032	Hungary	**Hungarian Optimal Family Planning Programme**. Women who wanted to become pregnant.	**Multivitamin**	Multivitamins from preconception to second missed period.	**1, 6**	Wheeze (physician assessment); Recurrent wheeze (physician assessment); Eczema (physician assessment); FA (unclear)
Devakumar, 2015 (8)	RCT	600/600	Nepal	Pregnant women in the second and third trimester. Population at risk of micronutrient deficiencies.	**Multivitamin**	Micronutrient daily supplement (800µg Vit A, 10mg Vit E, 5µg Vit D, 1.4mg Vit B1, 1.4mg Vit B2, 18mg Niacin, 1.9mg Vit B6, 2.6µg Vit B12, 400µg Folic acid, 70mg Vit C, 30mg Iron, 15mg Zinc, 2mg Copper, Selenium 65µg, Iodine 150µg) versus iron 60mg and folic acid 400µg, to pregnant women.	**8**	Lung function (FEV1, FVC); Wheeze (ISAAC); AR (ISAAC)
Grant, 2016 (9)	RCT	87, 86, 87	New Zealand	Pregnant women from 27 weeks gestation to birth and infants birth to 6 months	**Vitamin D**	Vitamin D daily from 27 weeks gestation to birth (pregnant women) and birth to 6 months (infants) at 1000 IU/ 400 IU, or 2000 IU/ 800 IU, versus placebo	**1.5**	Wheeze (DD); AS (SPT, sIgE)

Study	Design	No. participants (Intervention/Ctrl)	Country	Population characteristics	Intervention/ Exposure	Intervention/ Exposure details	Age at outcome (years)	Outcomes and Method of Assessment
Greenough, 2010 (10)	RCT	1199/1205	UK	**Vitamins in Pre-eclampsia trial.** Women with clinical risk factors for pre-eclampsia.	**Vitamin C + E**	Vitamin C (100mg) and Vitamin E (400IU) from 14-21 weeks to delivery.	**1**	Wheeze (parent-reported); Recurrent wheeze (parent-reported); Eczema (parent-reported)
Goldring, 2013 (11)	RCT	120/60	UK	Pregnant women from 27 weeks. Ethnically stratified as Asian, Middle Eastern, Black, White.	**Vitamin D**	Vitamin D 200,000 IU bolus at 27 weeks or 800IU daily from 27 weeks to delivery, versus no treatment	**3**	Wheeze (ISAAC); Recurrent wheeze (≥episodes); AR (ISAAC); AS (SPT); Eczema (ISAAC); FA (physician assessment); total IgE
Kiraly, 2013 (12)	RCT	227/235	Guinea-Bissau	Infants with no history of measles or vitamin A supplementation. Population at risk of vitamin A deficiency.	**Vitamin A**	Vitamin A 100,000-200,000 IU at 6-9 months age, versus no supplement,	**7**	AS (SPT)

Study	Design	No. participants (Intervention/Ctrl)	Country	Population characteristics	Intervention/ Exposure	Intervention/ Exposure details	Age at outcome (years)	Outcomes and Method of Assessment
Litonjua, 2016 (13)	RCT	Unclear – 881 total	USA	Pregnant women from 10-18 weeks gestation to delivery.	**Vitamin D**	Vitamin D (4000 IU/d) versus placebo from 10-18 weeks gestation to delivery. All women also received 400 IU/d vitamin D as part of a multivitamin supplement.	**3**	Wheeze (physician assessment); Eczema (DD); AS (total IgE, sIgE)
McEvoy, 2014(14)	RCT	89/90	USA	Women aged ≥15 years old who reported being current smokers (≥1 cigarette per day) randomised at 22 weeks of gestation.	**Vitamin C**	Vitamin C 500mg daily from ≤22 weeks gestation to delivery versus corn starch.	**1**	Wheeze (unclear); LF (spirometry)

Study	Design	No. participants (Case/Ctrl)	Country	Population characteristics	Exposure	Method of Exposure Assessment	Age (years)	Outcomes and Method of Assessment
OBSERVATIONAL STUDIES								
Martindale, 2005; (15) Devereux, 2006; (16) Devereux, 2007 (17)	PC	1704	UK	**Aberdeen birth cohort:** Population based birth cohort with pregnant women recruited 1997-99 while attending a hospital antenatal clinic at ~12weeks gestation	Maternal vitamin intake and mineral intake	Q	2,5	AD: Parent reported (ISAAC Q); UK Working Party Criteria; LF: Spirometry; RC: Parent reported (ISAAC Q); SPT any; wheeze: Parent reported (ISAAC Q) wheeze
Wills, 2013(18); Granell, 2008 (19)	PC	5368	UK	**ALSPAC:** Population based birth cohort study, of mother-child pair recruited in 1991-1992	Maternal plasma vitamin and vitamin supplement [any]	S, Q	7.5, 8, 8.7	AD: Parent reported; LF-BHR, -FEV_1(SDS): Spirometry; RC: Parent reported; SPT aero; Wheeze: Parent reported wheeze; Rec wheeze: DD asthma

Study	Design	No. participants (Case/Ctrl)	Country	Population characteristics	Exposure	Method of Exposure Assessment	Age (years)	Outcomes and Method of Assessment
Back, 2009 (20)	PC	123	Sweden	The first 206 babies born in 1998 recruited at University Hospital of Umea. All children were prescribed vitamin A&D supplements from 6 weeks to 24 months of age	Infant vitamin intake [any]	Q	6	AD: Parent reported (ISAAC Q); wheeze and rec wheeze: Parent reported (ISAAC Q)
Liu, 2011 (21)	PC	649	USA	**Boston Birth Cohort**: Mother-infant pairs recruited at birth at Boston Medical Centre	Vitamin D cord blood	S	2	sIgE cow's milk; sIgE egg; sIgE food; sIgE peanut
Maslova, 2013 (22)	PC	28758	Denmark	**DNBC**: Population based birth cohort with pregnant women recruited between 1996 and 2002 at ~12weeks gestation	Maternal vitamin intake	Q	1.5, 7	RC:DD; rec wheeze :DD asthma; rec wheeze: DD plus ≥1 episode of wheeze in the last year; rec wheeze :Admission registry - asthma

Study	Design	No. participants (Case/Ctrl)	Country	Population characteristics	Exposure	Method of Exposure Assessment	Age (years)	Outcomes and Method of Assessment
Erkkola, 2009; (23) Nwaru, 2010/11/11; (24) (25) (26) Marjamaki, 2010; (27) Uusitalo, 2008 (28)	PC; RC	3730	Finland	**DIPP:** Prospective birth cohort of children at high risk of TIDM (HLA genotype conferred susceptibility) born between 1997 and 2004 in Oulu and Tampere University Hospital	Maternal vitamin D	Q	5, <10	AD: Parent reported (ISAAC Q); sIgE aero; sIgE cow's milk; sIgE egg; sIgE food; Rec wheeze :DD asthma plus medication and/or current symptoms
Baiz, 2013(29)	PC	239	France	**EDEN:** Population based birth cohort with pregnant women recruited from prenatal clinics in Nancy and Poitiers, < 24th weeks of gestation in 2003	Vitamin D cord blood	S	1, 2, 3, 5	AD:DD; RC: Parent reported (ISAAC Q); rec wheeze :DD asthma plus medication and/or current symptoms
Gale, 2008 (30)	PC	440	UK	Population based birth cohort with pregnant women recruited on their first visit to midwives' antenatal booking clinic in 1991	Maternal plasma Vitamin D	S	0.75, 9	AD:UK Working Party Criteria; Visible AD on examination; Parent reported; Rec wheeze: Parent reported asthma

Study	Design	No. participants (Case/Ctrl)	Country	Population characteristics	Exposure	Method of Exposure Assessment	Age (years)	Outcomes and Method of Assessment
Whitrow, 2009 (31)	PC	490	Australia	**Generation 1**: Population based birth cohort of women and their children recruited in the first 16 weeks of pregnancy between 1998 and 2000 from 4 antenatal clinics in Adelaide	Maternal vitamin intake	Q	3.5, 5.5	Rec wheeze :DD asthma
de Jong, 2012 (32)	PC	8742	The Netherlands	**GENERATION R**: Population based birth cohort, with pregnant women recruited < 25 weeks gestation in Rotterdam	Maternal vitamin supplement [any]	Q	4	AD: Parent reported (ISAAC Q); wheeze: Parent reported (ISAAC Q) wheeze
Hoppu, 2000 (33)	PC	115	Finland	Birth cohort of infants of breastfeeding mothers (for at least 3 months) with a positive family history of atopic disease	Maternal vitamin intake	R	1	SPT any

Study	Design	No. participants (Case/Ctrl)	Country	Population characteristics	Exposure	Method of Exposure Assessment	Age (years)	Outcomes and Method of Assessment
Rothers, 2011 (34)	PC	208	US	**IIS:** prospective birth cohort study of healthy children born to pregnant women who planned to obtain care for their new-borns from collaborating paediatricians	Vitamin D cord blood	S	1, 2, 3, 5	RC:DD; sIgE aero: SPT aero: Total IgE; rec wheeze: DD asthma
Alm, 2009 (35)	PC	4941	Sweden	Infants of Western Sweden: Population based birth cohort of infants born in the region in 2003	Infant vitamin intake [any]	Q	1	AD: Parent reported
Morales, 2012 (36)	PC	1724	Spain	**INMA Project**: Population based birth cohort study with pregnant women attending their first routine specialized antenatal care visit in 4 study areas: Menorca (1997-98), Valencia (2003-05), Sabadell (2004-06), Gipuzkoa (2006-08)	Maternal plasma Vitamin D	S	1, 4, 5	Wheeze: parent reported wheeze; rec wheeze: DD asthma plus medication and/or current symptoms

Study	Design	No. participants (Case/Ctrl)	Country	Population characteristics	Exposure	Method of Exposure Assessment	Age (years)	Outcomes and Method of Assessment
Laitinen, 2005 (37)	PC	95	Finland	Children with a family history of AD (mother, father and/or older sibling with AD, AR or asthma), who participated in a prospective allergy prevention study (probiotic intervention trial)	Infant mineral intake and vitamin intake [any]	D	0.5, 1	AD: Physician assessment; FA cow's milk: Physician assessment
Mommers, 2009; (38) Magdelijn, 2011; (39) Cremers, 2011(40)	PC	2465	The Nether-lands	**KOALA**: Population based birth cohort with healthy pregnant women recruited in week 10 -14 of their pregnancy from an ongoing PC study on pregnancy-related pelvic girdle pain and through posters in organic food shops, anthroposophical, physician offices, and midwives.	Maternal plasma vitamin D and vitamin supplement [any]	S, Q	2, 5, 6.5 , 7	AD:UK Working Party Criteria; Parent reported (ISAAC Q); LF-FEV_1 (SDS):Spirometry; FEV_1%predictedy; FVC% predicted ; sIgE any: Total IgE: Wheeze: parent reported (ISAAC Q) wheeze; rec wheeze :DD asthma plus medication
Weisse, 2012 (41)	PC	272	Germany	**LINA**: Population based birth cohort with mother–child pairs recruited between 2006 and 2008 in Leipzig	Maternal plasma Vitamin D and Vitamin D cord blood	S	1, 2	AD:DD; Parent reported; FA any: DD; Total IgE; sIgE

Study	Design	No. participants (Case/Ctrl)	Country	Population characteristics	Exposure	Method of Exposure Assessment	Age (years)	Outcomes and Method of Assessment
Milner, 2004 (42)	PC	8073	USA	**NMIH:** survey of mothers who gave birth in 1988 with a follow-up survey (LF), conducted in 1991. Blacks, individuals with low socioeconomic status, and premature infants were intentionally overrepresented in the survey sample	Infant vitamin intake [any]	Q	3	FA any: DD; Rec wheeze: DD asthma
Carmargo, 2010 (43)	PC	823	New Zealand	**The New Zealand Asthma and Allergy Cohort study:** Population based birth cohort with pregnant women recruited at maternity care centres in Wellington and Christchurch 1997-2001	Vitamin D cord blood	S	1.25, 3, 5	Wheeze: Parent reported wheeze; rec wheeze :DD asthma plus medication and/or current symptoms

Study	Design	No. participants (Case/Ctrl)	Country	Population characteristics	Exposure	Method of Exposure Assessment	Age (years)	Outcomes and Method of Assessment
Hypponen, 2004; (44) Hypponen, 2001 (45)	PC	10366/81	Finland	**Northern Finland Birth Cohort:** Population based birth cohort with women recruited between the 24th and 28th week of gestation in Oulu and Lapland in 1995-1966	Infant vitamin intake [any]	Q	31, 2	SPT aero; rec wheeze: self-reported asthma plus medication and/or symptoms
Magnus, 2013 (46) Haberg, 2009 (47)	NCC, PC	32077	Norway	Cases with asthma & non asthmatic controls were recruited from the participants of the Norwegian Mother and Child Cohort Study.	Maternal plasma vitamin d and vitamin supplement [any]	S, R	1.5, 3	Rec wheeze :DD or asthma medication; wheeze: Parent reported
Miyake, 2010; (48) Miyake, 2010; (49) Miyake, 2011 (50)	PC	763	Japan	**OMCHS:** Population birth cohort with pregnant women between the 5-39th week of pregnancy recruited from a university hospital and three obstetric hospitals in municipalities of Osaka between 2001 and 2003	Maternal mineral and vitamin intake	Q	2	AD: Parent reported (ISAAC Q); wheeze: Parent reported (ISAAC Q)

Study	Design	No. participants (Case/Ctrl)	Country	Population characteristics	Exposure	Method of Exposure Assessment	Age (years)	Outcomes and Method of Assessment
Bekkers, 2012 (51)	PC	3786	The Nether-lands	**PIAMA:** Population based birth cohort of children born in 1996/97 recruited prenatally, Netherlands. The children were allocated to an intervention study or natural history study depending on their family risk for allergy	Maternal vitamin supplement [any] and Vitamin D cord blood	Q	2, 8	AD; LF-BHR: Spirometry; sIgE any: wheeze: Parent reported (ISAAC Q) wheeze; rec wheeze :DD asthma plus medication and/or current symptoms; rec wheeze :DD asthma plus ≥4 episodes of wheeze
Litonjua, 2006; (52) Carmargo, 2007 (53)	PC	1290	USA	**Project Viva:** Population based birth cohort with pregnant women at <22 weeks of gestation recruited from 8 obstetric offices of a large multispecialty suburban/urban group practice in eastern Massachusetts between 1999 and 2002	Maternal vitamin and mineral intake; infant vitamin and vitamin supplement [any]	Q	2, 3	AD:DD; wheeze: Parent reported wheeze; rec wheeze: Parent reported in at least one questionnaire (1,2,3 years old); rec wheeze: parent reported ≥2 episodes of wheeze plus medication and/or current symptoms

Study	Design	No. participants (Case/Ctrl)	Country	Population characteristics	Exposure	Method of Exposure Assessment	Age (years)	Outcomes and Method of Assessment
Pike, 2012 (54)	PC	739	UK	**SWS**: Population birth cohort with 20-34 year old women recruited pre-conception from general practitioners in Southampton between 1998 and 2002 and subsequently become pregnant	Maternal plasma vitamin d and vitamin intake	Q	1, 3, 6	LF-BHR slope, LF-FEV_1 and LF-FVC (SD):Spirometry; SPT any; wheeze: Parent reported (ISAAC Q) wheeze; rec wheeze: DD asthma
Narita, 2011; (55) Ohya, 2011 (56) Ohya, 2011 (56)	PC	1463	Japan	**T-CHILD:** Population based birth cohort of Japanese mother-infant pairs with women recruited ~ second trimester in Tokyo	Maternal vitamin and mineral intake	Q	0.6, 1.5, 3	AD: Parent reported (ISAAC Q); wheeze: Parent reported (ISAAC Q) wheeze; rec wheeze: DD asthma; wheeze: Parent reported (ISAAC Q)
West, 2012 (57)	PC	319	Australia	Mother-infant pairs from a pregnancy cohort, recruited in Perth, Western Australia from 2005 to 2008. Pregnant women with a family history of allergic diseases recruited to participate in a postnatal infant dietary intervention study	Maternal mineral and vitamin intake	Q	1	AD:DD; FA any: History of reaction to food plus positive SPT-food; SPT any; wheeze: DD

Study	Design	No. participants (Case/Ctrl)	Country	Population characteristics	Exposure	Method of Exposure Assessment	Age (years)	Outcomes and Method of Assessment
Wang, 2007 (58)	PC	1760	Taiwan	Pilot study of Taiwan National Birth Cohort Study: representative samples recruited postnatally using the national birth registration data in 2003	Maternal mineral supplement	Q	0.5	AD:DD
Jones, 2012 (59)	RC	231	Western Australia	Children with family history of atopy derived from a larger birth cohort in 2002-2009	Maternal vitamin supplement [any] and Vit D cord blood	Q, S	1	AD :DD or evidence of typical skin lesions ; FA any: History of reaction to food plus positive SPT-food; SPT any rec wheeze: unclear
Oliver, 2010; (60) Grimshaw, 2012 (61)	NCC	123/41	UK	**EuroPrevall** (UK birth cohort): cases were infants with food allergy, each matched to two controls	Infant mineral intake	D, Q	1, 2	FA any :DD with DBPCFC
Allen, 2013 (62)	NCC	2758/240	Australia	**HealthNUTS:** Cases & controls recruited from population-based sampling from governmental immunisation clinics in Melbourne	Infant plasma Vitamin D	S, Q	1	AD:DD; FA any, egg, peanut: :DD with OFCs

Study	Design	No. participants (Case/Ctrl)	Country	Population characteristics	Exposure	Method of Exposure Assessment	Age (years)	Outcomes and Method of Assessment
Binkley, 2011 (63)	CC	1413/1300	Canada	Cases & controls were anaphylaxis registry's previous survey respondents, all having had previous anaphylactic food allergy reactions, although only cases to peanuts	Maternal vitamin supplement [any]	Q	<18	FA peanut: DD
Mullins, 2012 (64)	CC	115/115	Australia	Cases were peanut allergic patients born in Australian Capital Territory and population matched-controls: Australia	Infant plasma vitamin D	S	6	FA peanut: History of acute systemic allergic reaction within 2 hours of known food exposure, combined with a SPT to the relevant food.

PC Prospective cohort study; Q questionnaire; AD atopic dermatitis; ISAAC International Study of Allergy and Asthma in Children; AS allergic sensitisation; SPT skin prick test, sIgE specific IgE; DD Doctor diagnosis (community); Physician assessment is assessment by study physician; AR allergic rhinitis, FA food allergy; LF lung function; FEV1 forced expiratory volume in 1 second; BHR bronchial hyper-responsiveness; PEF peak expiratory flow; CS cross-sectional study; DBPCFC double blind placebo-controlled food challenge; OFCs oral food challenges; SD standard deviation

Table 2 Characteristics of included studies evaluating vitamin and mineral supplementation and autoimmune diseases

Study	Design	No. participants	Country	Population characteristics	Intervention/ Exposure	Exposure assessment	Age (yrs)	Outcomes
Brekke, 2007 (65)	PC	8694	Sweden	**ABIS:** Population based birth cohort of children born in Southeast Sweden between 1997 and 1999	Infant vitamin intake [any] and maternal vitamin supplement [any]	Q	1, 2.5+17	TIDM: Islet autoimmunity
Fronczak, 2003 (66); Simpson, 2011(67)	PC	222, 222/16	USA	**DAISY**: Prospective birth cohort of children at increased risk for T1DM recruited 1993 to 2004 in Denver, Colorado	Maternal vitamin intake; infant plasma vitamin D	Q	4, 9	TIDM: Islet autoimmunity (GADA and/or IA2A and/or IAA)
Hypponen, 2004 (44) Hypponen, 2001 (45)	PC	10366/81	Finland	**Northern Finland Birth Cohort:** Population based birth cohort with women recruited between the 24th and 28th week of gestation in Oulu and Lapland in 1995-1966	Infant vitamin intake [any]	Q	31, 2	TIDM:DD
Sørensen, 2012 (68)	NCC	328/109	Norway	Cases and controls selected from a population birth cohort linked to Norwegian Childhood Diabetes Registry	Maternal plasma Vitamin D	S	<15	TIDM:DD

Study	Design	No. participants	Country	Population characteristics	Intervention/ Exposure	Exposure assessment	Age (yrs)	Outcomes
Miettinen, 2012 (69)	NCC	686/343	Finland	All selected from the Finnish Maternity Cohort, with cases identified from the Finnish Diabetes Register	Maternal plasma Vitamin D	S	3.4	TIDM:DD
Ahadi, 2011 (70)	CC	202/101	Iran	Cases were diagnoses of T1DM referred to Children's Medical Centre Hospital and matched controls	Infant vitamin intake [any]	Q	6.7	TIDM: DD
Ashraf, 2010 (71)	CC	195	USA	Cases and controls selected from electronic medical records	Infant mineral intake	Q	10	TIDM: DD
Ellis, 2012 (72)	CC	655/246	Australia	**CLARITY:** cases were recruited during a clinic visit to Royal Children's Hospital, with diagnosed JIA using ILAR criteria: controls were patients in for elective surgery, also at the Royal Children's Hospital Day Surgery Unit	Maternal iron, multivitamin, folate, calcium and vitamin d supplement	Q	18	JIA:DD ILAR criteria
Bener, 2009 (73)	CC	340/170	Qatar	Cases were insulin dependent or had a venous blood glucose >6.7mmol/L on 2 occasions with matched healthy controls selected from the community	Infant vitamin intake [any]	I/Q	<16	TIDM: DD

Study	Design	No. participants	Country	Population characteristics	Intervention/ Exposure	Exposure assessment	Age (yrs)	Outcomes
EURODIAB substudy 2 study group, 1999 (74)	CC	2934/746	Luxembourg, N. Ireland, Romania, Lithuania, Bulgaria and Australia	**EURODIAB**: cases were <15years at T1DM diagnosis and matched with population-based controls.	Infant vitamin intake [any]	I/Q	<15	TIDM:DD; TIDM :DD WHO criteria
Visalli, 2003 (75)	CC	900/150	Italy	**EURODIAB Italy**: Cases with T1DM selected from within the EURODIAB ACE study, born 1977-89, with controls selected from school records for the same period	Infant vitamin intake [any]	Q	12	TIDM :DD WHO criteria
EURODIAB substudy 2 study group, 1999 Europe (74)	CC	2934/746	Europe - multicentre	**EURODIAB:** cases were <15years at T1DM diagnosis and matched with population-based controls.	Infant vitamin intake [any]	I/Q	<15	TIDM:DD
Malcova, 2005 (76)	CC	2334/868	Czech Republic	Cases were identified from the Czech Childhood Diabetes Register, with unrelated aged-match controls selected from among the schoolmates of cases	Infant vitamin intake [any]	Q	7	TIDM:DD

Study	Design	No. participants	Country	Population characteristics	Intervention/ Exposure	Exposure assessment	Age (yrs)	Outcomes
Stene, 2003 (77)	CC	2213/545	Norway	**Norwegian Childhood Diabetes Study Group**: cases were all children on the diabetes registry diagnosed 1997-2000 and controls were matched from the national population registry	Infant vitamin intake [any] and maternal vitamin supplement [any]	Q	8.8	TIDM : DD WHO criteria
Stene, 2000 (78)	CC	1131/84	Norway	Cases were T1DM patients in Vest-Agder & on the National Childhood Diabetes Register 1982-98 and controls were selected randomly from the population register for the same age and period	Maternal vitamin supplement [any]	Q	<15	TIDM:DD
Svensson, 2005 (79)	CC	1152/475	Denmark	Cases identified from the Danish National Register of incident cases diagnosed 1996-99 and matched controls from the Danish Population Register	Infant vitamin intake [any]	Q	8.4	TIDM:DD
Tenconi, 2007 (80)	CC	429/131	Italy	Cases identified from T1DM population registry 1988-2000 and matched controls selected from hospitalised patients, not affected by metabolic disease or cancer	Maternal vitamin supplement [any]	Q	15.5	TIDM:DD

Study	Design	No. participants	Country	Population characteristics	Intervention/ Exposure	Exposure assessment	Age (yrs)	Outcomes
Gilat, 1987 (81)	CC	504/167	9 countries: USA, Canada, UK, Sweden, Denmark, Holland, France, Italy, Israel	**The International IBD Study Group**: cases were patients with proven Crohn's Disease in 14 centres across 9 countries with 2 controls per case, one with a different minor GI disease and the other with minor non-GI disease taken from hospitals or clinics.	Maternal vitamin supplement [any]	Q	<25	IBD-CR:DD; IBD-UC:DD

PC Prospective cohort study; Q questionnaire; NCC nested case-control study; CC case-control study; SPT skin prick test; sIgE specific IgE; DD Doctor diagnosis (community); Physician assessment is assessment by study physician; AR allergic rhinitis; FA food allergy; T1DM type 1 diabetes mellitus; RC retrospective cohort; JIA juvenile idiopathic arthritis; ILAR International League of Associations for Rheumatology; OBD inflammatory bowel disease; UC ulcerative colitis; CR Crohn's disease; GI gastro-intestinal

2. Infant or maternal dietary intake of vitamins and minerals and risk of atopic dermatitis (AD)

Nineteen observational studies and 6 intervention trials investigated the association between vitamin or mineral intake and risk of AD in childhood. The risk of bias in studies on vitamin and mineral intake during infancy or pregnancy in relation to atopic dermatitis is illustrated in Figure 1. This is low in most observational studies, but high in two intervention trials due to high loss to follow up (Figure 2).

Figure 1 Risk of Bias in observational studies of vitamin and mineral intake and AD

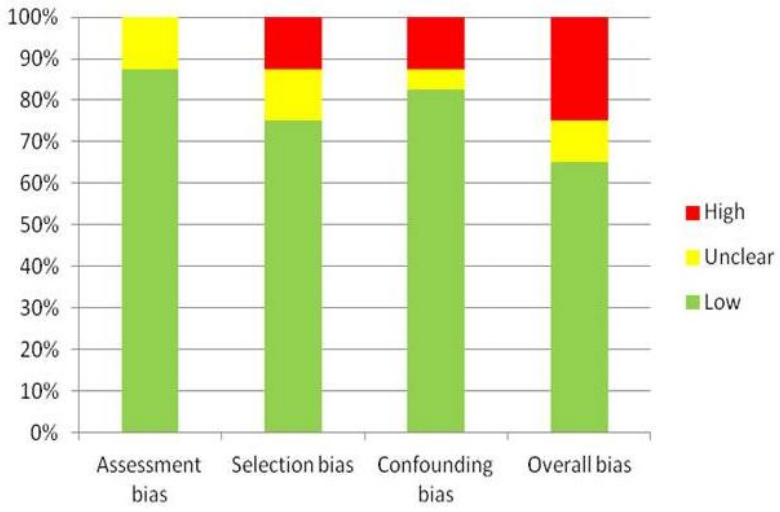
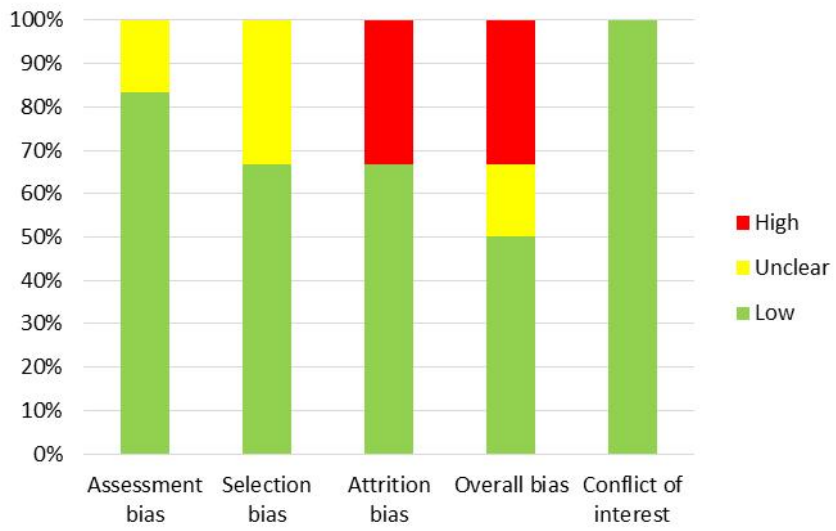


Figure 2 Risk of Bias in intervention trials of vitamin and mineral intake and AD



Studies which investigated AD as an outcome included vitamin intake/supplementation (A, D, C, E, folic acid), minerals copper and zinc, and selenium and magnesium.

2.1. Intervention studies eligible for meta-analysis

We identified five intervention studies using vitamin supplements during pregnancy: multi-vitamins (**Czeizel 1994**), vitamins C and E (**Greenough 2010**) or vitamin D (**Goldring 2013; Chawes 2016 and Litonjua 2016),** which had comparable data for meta-analysis (

Figure **3**). The study of Czeizel reported an increased risk of childhood AD in children of mothers who received the multi-vitamin supplement, in a population with a very low rate of eczema. The other four intervention studies showed no effect on AD, and the pooled estimate for the three studies of vitamin D supplementation showed no evidence of association. There was no heterogeneity between studies of vitamin D supplementation (I^2=0%). In the study of Czeizel, vitamins were given periconceptually rather than during the second/third trimesters of pregnancy, as in the other four intervention studies. **Dobo 1998** reported a substudy of 400 participants from Czeizel's trial, and found no significant difference in AD - RR 1.53 (0.91, 2.59) at age 2, and RR 1.05 (0.48, 2.31) at age 6 for the infants of supplemented women. Data from Czeizel's trial shown in Figure 3 are for AD at age 1 on the complete study dataset.

One intervention study supplemented infants with vitamins A and E at BCG vaccination (**Aage 2015**); no significant reduction in risk of AD in children at age 10 was observed (Figure 4).

Figure 3 Maternal vitamin interventions (by type) and risk of AD in children aged 0-4 years

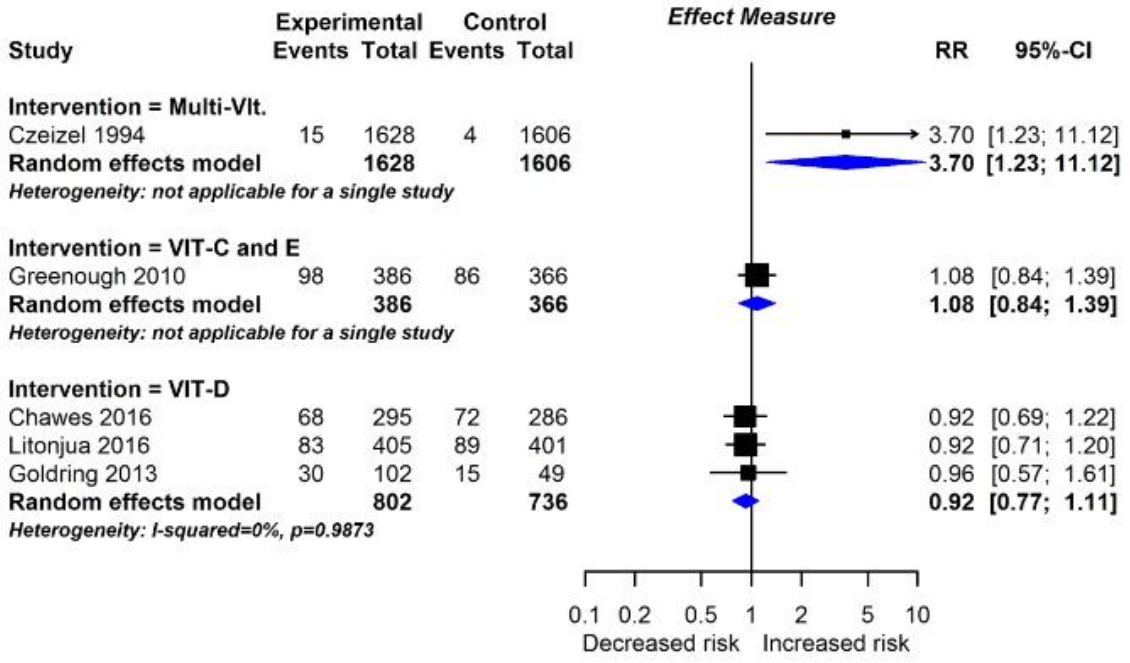
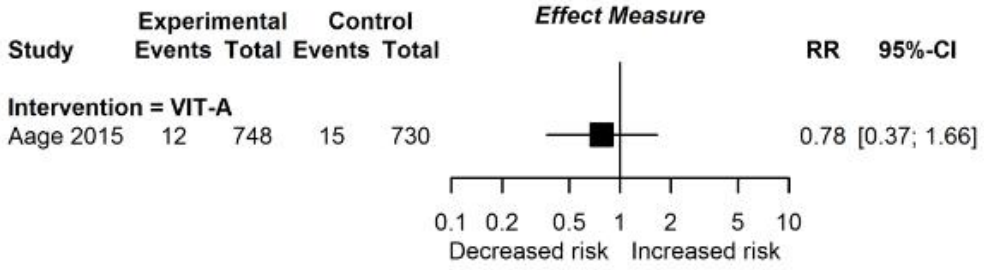


Figure 4 Maternal vitamin interventions (by type) and risk of AD in children aged 5-14 years



2.2. Observational studies eligible for meta-analysis

Thirteen studies contributed to one or more meta-analyses of observational study data. Two prospective cohort studies with data eligible for meta-analysis (**De Jong 2012; Magdeljins 2011**), showed no association between maternal folic acid supplementation during pregnancy and risk of AD at age 0-4 years. There was no heterogeneity in these studies (Figure 5;

I^2=0%). When the risk of AD was studied in children at any age in a *post hoc* analysis, the combined effect sizes of these two studies and that of **Bekkers (2012)** also showed no evidence of association with AD (Figure 6).

Figure 5 Maternal folic acid supplementation (often vs. rare) and AD at 0 – 4 years

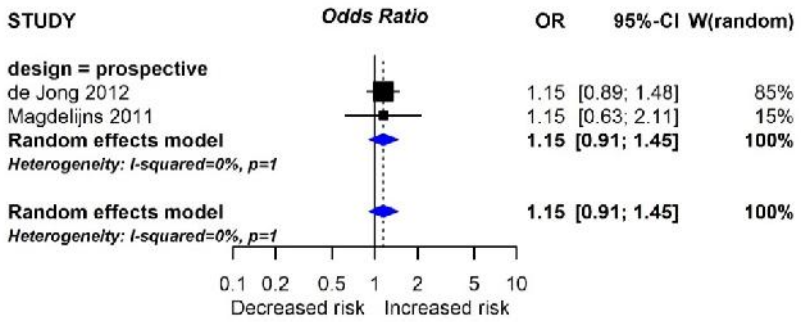
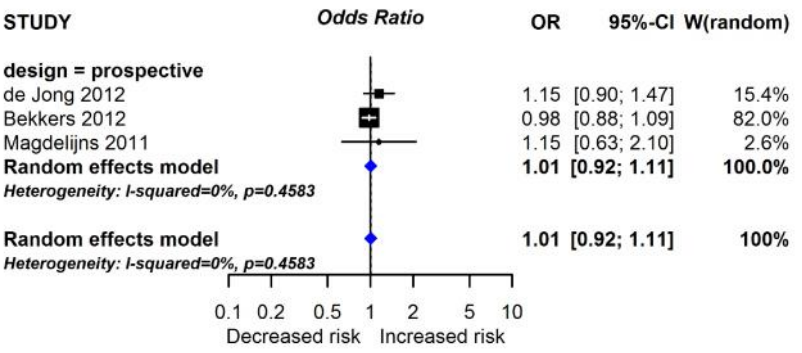


Figure 6 Maternal intake of folic acid supplement (often vs. rare) and AD at any age



Studies with comparable data on the association between maternal intake of calcium and zinc and risk of AD in children aged 0-4 years are shown in Figures 7 to 9. There was no evidence of association in either meta-analysis. The meta-analysis on calcium intake showed high heterogeneity between studies (I^2=59.4%; Figure 7). Although both studies were carried out in Japanese populations of normal risk infants, they used a different approach to obtain information on the exposure to dietary intake of sources of calcium, which might explain the heterogeneity observed. We did a post-hoc meta-analysis which enabled data from the study

of Devereux at age 5 years to be included within a meta-analysis alongside data for 0-4 years of age (Figure 9) which showed extreme statistical heterogeneity.

Figure 7 Maternal intake of calcium (highest vs. lowest) and AD at 0 – 4 years

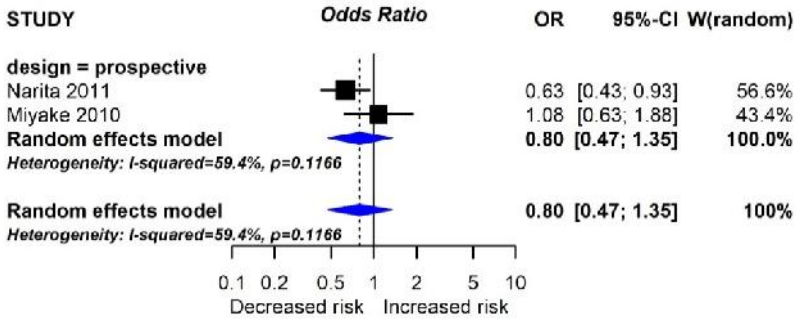


Figure 8 Maternal intake of zinc (highest vs lowest) and risk of AD in children aged 0-4 years

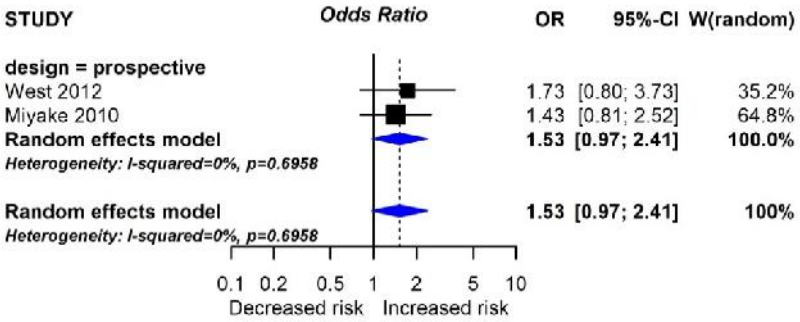
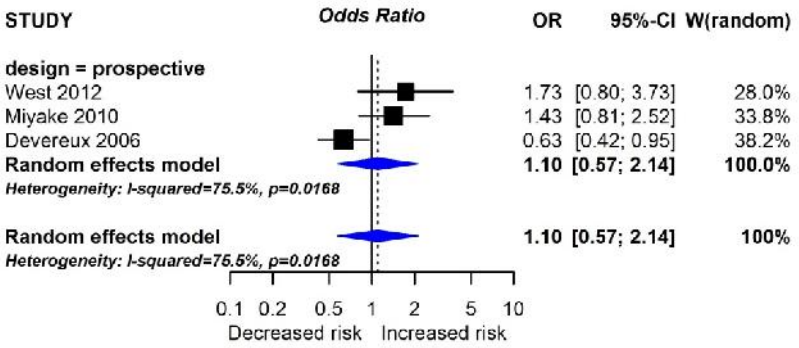


Figure 9 Maternal intake of zinc (highest vs lowest) and risk of AD in children aged 0-5 years



With regards to vitamin A, the studies of **West (2012)** and **Miyake (2010)** had comparable data which was meta-analysed (Figure 10). The combined effect size showed a 43% reduced risk of AD in children whose mothers had a higher intake of vitamin A. There was no heterogeneity between studies (I^2=0%). A large study which could not be included in this meta-analysis (**Nwaru 2011**) failed to confirm this association. Maternal intake of vitamin C on the other hand, was unrelated to risk of AD in children at age 0-4 years (Figure 11).

With regards to maternal intake of vitamin D, highest vs lowest intakes showed no evidence of association with AD risk at age 0-4 years (Figure 12) or at age 0-5 years (

Figure 13). A reduced risk of AD was observed in children of mothers who consumed vitamin D supplements often (monthly) vs those who rarely consumed them (OR 0.57; 95% CI 0.37, 0.88) (Figure 14), with no evidence of heterogeneity between studies (I^2=0%). Reports of other measures of vitamin D intake and status failed to confirm this association. Maternal plasma levels of vitamin D (Figure 15) or maternal intake of vitamin D were not related to AD risk at any age (Figure 16). Maternal intake of vitamin E was unrelated to risk of AD in children (Figure 17).

In infants plasma Vitamin D levels (Figure 18; Figure 19) were unrelated to risk of AD in childhood. Similarly, there was no evidence of association between infant intake of vitamin A and risk of AD (Figure 20). The studies of **Wills** (**2013**) and **Mommers** (**2009**) assessed the association between plasma levels of vitamin D in infants and risk of AD (Figure 18). There was no evidence of a relationship with this outcome. The studies showed high heterogeneity (I^2=66.6%). Both studies included populations from the UK with normal risk of disease, but they used different outcome definitions, which might partly explain the heterogeneity. The study of Wills used parental reported AD (subjective measure), whilst the study of Mommers also used this measure and clinical examination. Similarly, the meta-analysis on vitamin A intake showed no evidence of association between this exposure and risk of AD. There was very high heterogeneity between studies (I^2=72.2%), which could be partly explained by the different methods used to ascertain consumption of vitamin A.

Figure 10 Maternal intake of vitamin A (highest vs lowest) and risk of AD in children (at any age)

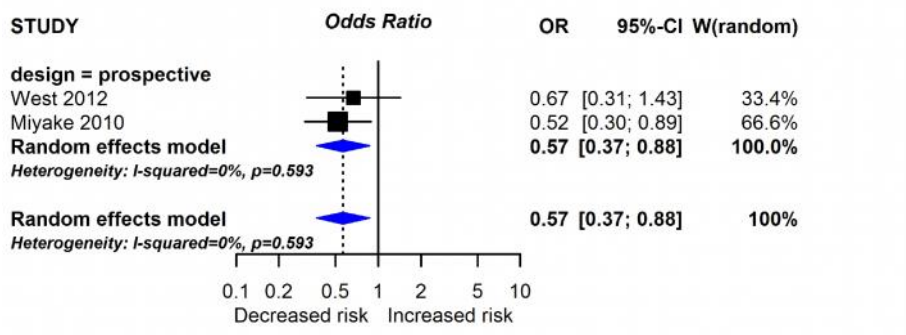


Figure 11 Maternal intake of vitamin C (highest vs lowest) and risk of AD in children aged 0-4 years

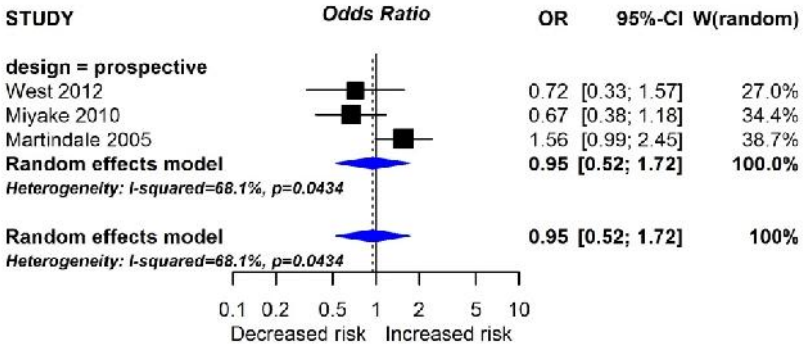


Figure 12 Maternal intake of vitamin D (highest vs lowest) and risk of AD in children aged 0-4 years

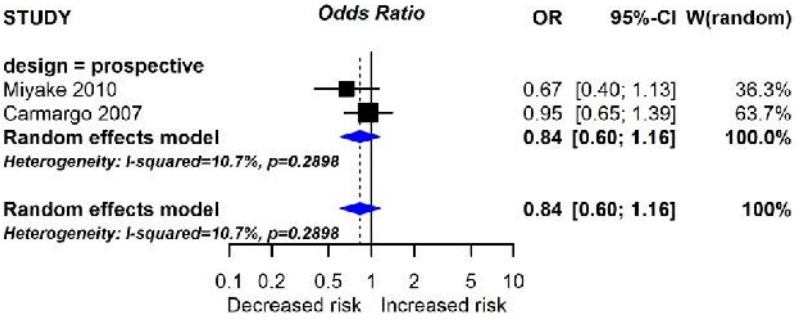


Figure 13 Maternal intake of vitamin D (highest vs lowest) and risk of AD in children aged 0-5 years

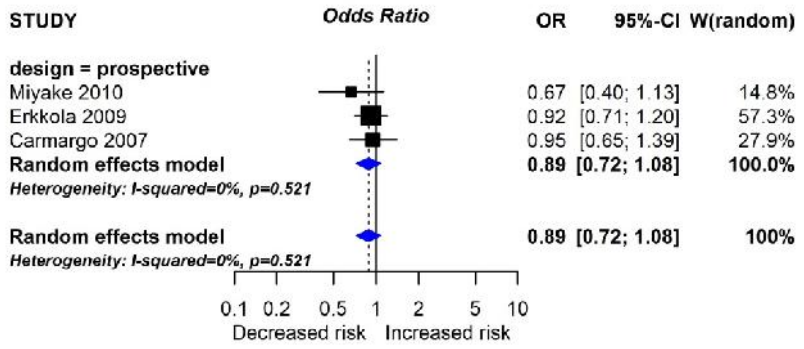


Figure 14 Maternal intake of vitamin D supplement (often vs rare) and risk of AD in children aged 0-4 years

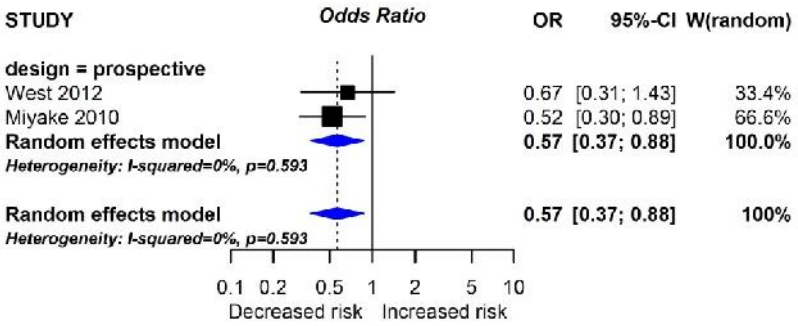


Figure 15 Maternal plasma levels of vitamin D (highest vs lowest) and risk of AD in children (at any age)

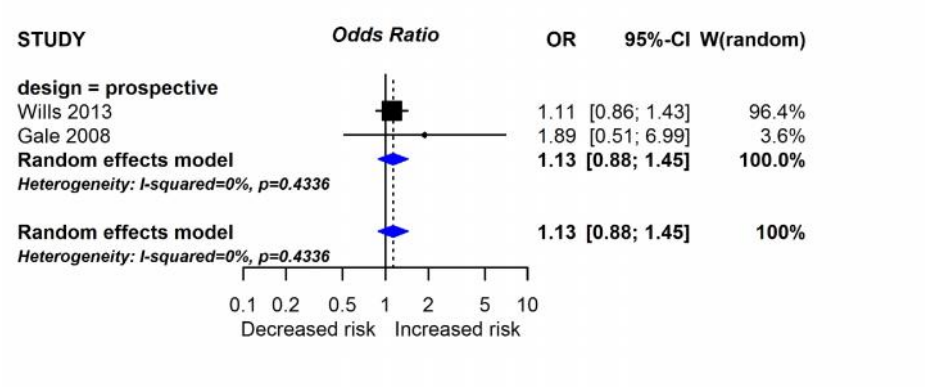


Figure 16 Maternal intake of vitamin D (highest vs lowest) and risk of AD in children (at any age)

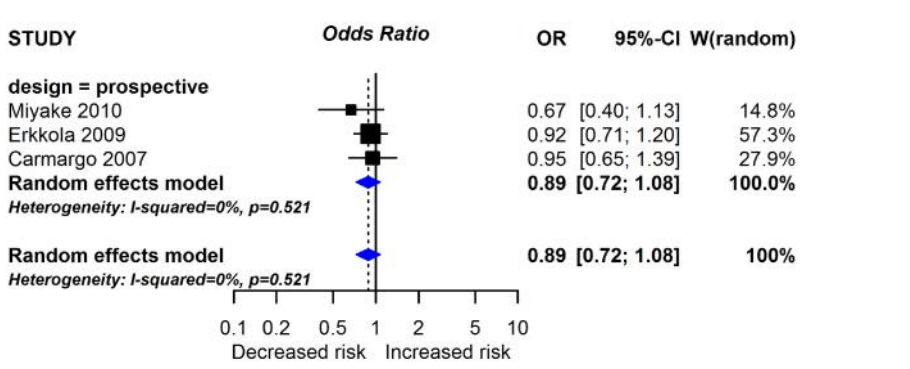


Figure 17 Maternal intake of vitamin E (highest vs lowest) and risk of AD in children aged 0-4 years

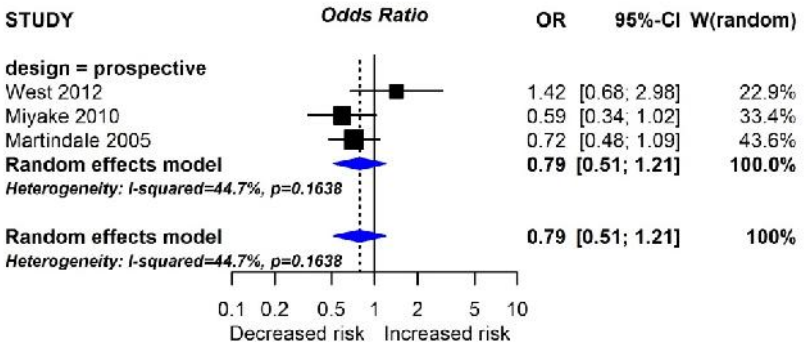


Figure 18 Infant plasma vitamin D (highest vs. lowest) and risk of AD in children aged 5– 14 years

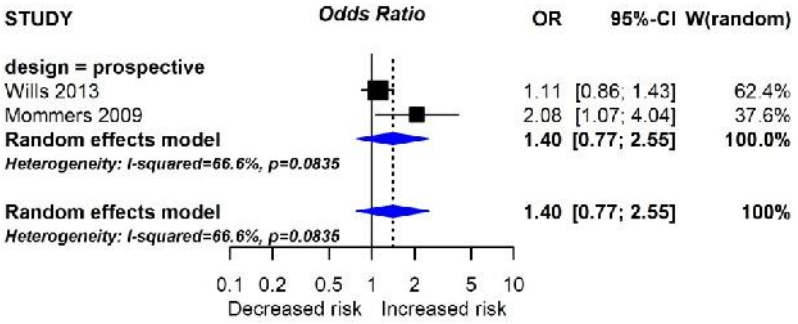


Figure 19 Infant plasma vitamin D (highest vs. lowest)and atopic dermatitis in children aged 0-4 years

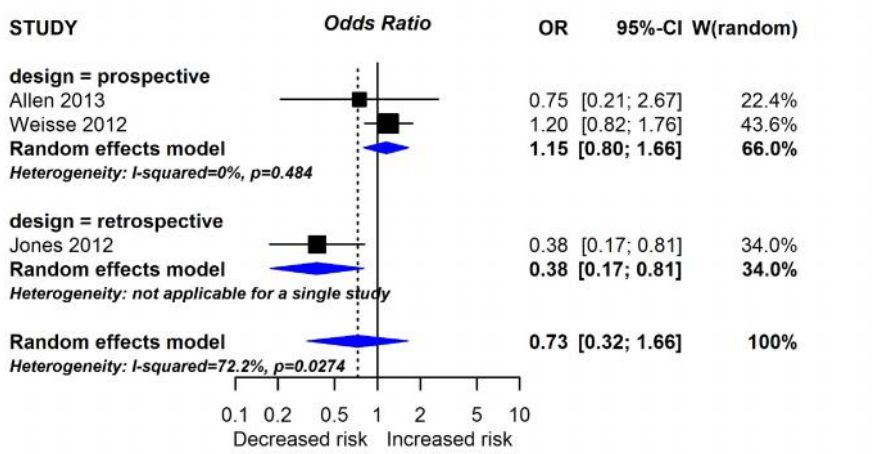
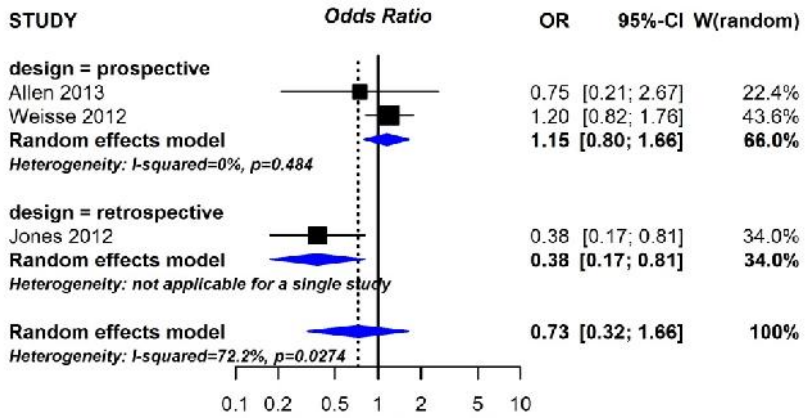


Figure 20 Infant vitamin A intake (highest vs lowest) and risk of AD in children aged 0-4 years



2.3. Studies on vitamin and mineral intake and risk of AD which were not eligible for meta-analysis

We identified 6 further studies that examined the association between AD and vitamins or minerals and had no data eligible for meta-analysis, and other relevant data from some of the studies included in meta-analysis (Table 3).

Two prospective cohort studies (**Baiz, 2013**; and **Jones, 2012**) investigated the association between vitamin D levels in cord blood and risk of AD. The study of Jones showed a negative association between cord levels of vitamin D and risk of AD in infants aged 1 year, whereas the study of **Baiz**, reported a negative association at age 2, 3 and 5 years. There was

no evidence of infant vitamin D intake having an association with AD as examined by the studies of **Back (2009)** and **Allen (2013**). Another six studies investigated various levels of maternal vitamin D intake and risk of AD. The studies of **Camargo** (**2007**) and **Erkkola** (**2009**) found no evidence of association at age 3 or 5, respectively. The study of **Miyake** (**2011)** found a lower risk of AD in children aged 2 whose mothers had an intake of vitamin D ≥172.4 μg/d. These authors also reported some, but not consistent, evidence of a negative association at age 18 months (**Miyake 2010**). Maternal serum levels of vitamin D were unrelated to risk of AD in infants at age 1 or 2 years (**Weisse, 2012**) or later in childhood at age 7.5 years (**Wills, 2013**).

The study of **Miyake** (**2010**) also reported a negative association between β-carotene and risk of AD in children at age 1.5 years. There was no other evidence of associations between vitamin intake (maternal or infant) and risk of AD. We found two studies (**Laitinen, 2005**; and **Nwaru, 2011**) reporting a negative association between AD and calcium and magnesium intake in children, respectively. The study of **Laitinen** showed a negative association at 6 months of age, whilst the study of **Nwaru** examined this association in children aged 5.

Overall, we found no consistent evidence for an association between vitamin or mineral intake during pregnancy, lactation or infancy and risk of AD.

Table 3 Observational studies investigating the association between vitamins and minerals and atopic dermatitis which were not eligible for meta-analysis

First Author and year of publication	Design	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
				INFANT INTAKE		
Alm, 2009 (35)	PC	1	4,941	Infant supplementation 1st year with vitamin D/ yes vs. no	OR	NS
Back, 2009 (20)	PC	6	123	Infant vitamin D intake (estimated >13.1mcg/kg versus ≤13.1mcg/kg)	OR	**3.63 (1.49-8.87)**
		1		Vitamin D Cord Blood/ ng/Ml (continuous)	OR	0.84 (0.71-1.00)
		2		Vitamin D Cord Blood/ ng/Ml (continuous)	OR	**0.82 (0.71-0.95)**
		3		Vitamin D Cord Blood/ ng/Ml (continuous)	OR	**0.82 (0.69-0.97)**
Baiz, 2014 (29)	PC	5	239	Vitamin D Cord Blood/ ng/Ml (continuous)	OR	**0.75 (0.64-0.88)**
			108	Infant energy-adjusted calcium intake (mg/MJ/day)	OR	**0.96 (0.94-0.99)**
Laitinen, 2005 (37)	PC	4	88	Zinc, Iron, calcium, vitamins A, C, D, E	OR	NS

First Author and year of publication	Design	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
				MATERNAL INTAKE		
Bekkers, 2012 (51)	PC	1-8 years	3,786	Supplementation during pregnancy (no vs yes) Folic acid, vitamins complex B, multivitamins	OR	NS
Carmargo, 2007 (53)	PC	3	1,194	Maternal vitamin D intake in 1st and 2nd trimesters (Harvard nutrient composition database and mean FFQ score) / Quartile 2 (513, 446-562 IU) vs Quartile 1 (356, 60-445 IU) IU	OR	0.88 (0.61-1.27)
				/ Quartile 3 (603, 563-658) IU vs Quartile 1 (356, 60-445 IU) IU	OR	0.94 (0.64-1.37)
Devereux, 2006 (16)	PC	5	1,704	Maternal and children's dietary and supplement intakes summated / highest (Q5) quintile vs lowest (Q1) Zinc, copper , iron, magnesium, B-carotene, and vitamin C	OR	NS

First Author and year of publication	Design	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
				Daily vitamin D intake during pregnancy (8th month)/ 4th quartile (>0.54) vs 2nd & 3rd quartiles [µg/MJ] (0.31-0.54)	OR	0.92 (0.71-1.20)
Erkkola, 2009 (23)	PC	5	1,669	Daily vitamin D intake during pregnancy (8th month)/ 2nd & 3rd quartiles [µg/MJ] (0.31-0.54) vs. 1st quartile (<0.31)	OR	1.07 (0.82-1.39)
				Serum maternal vitamin D during late pregnancy (28-42 weeks, nmol/L):		
		9	178	Q3 (50-75) vs. Q1 (<30)	OR	0.47 (0.08-2.68)
		9	178	Q4 (>75) vs. Q1 (<30)	OR	1.89 (0.51-6.99)
Gale, 2008 (30)	PC	9	178	Q2 (30-50) vs. Q1 (<30)	OR	0.71 (0.15-3.39)
		0.75	440	Q2 (30-50) vs. Q1 (<30)	OR	1.11 (0.43-2.84)
		0.75	440	Q3 (50-75) vs. Q1 (<30)	OR	1.75 (0.73-4.17)
Gale, 2008 (30)	PC	0.75	440	Q4 (<75) vs. Q1 (<30)	OR	1.62 (0.67-3.89)

First Author and year of publication	Design	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
Jones, 2012 (59)	RC	1	231	Cord blood 25(OH)D3 highest versus lowest tertile	OR	0.86 (0.74-1.00)
Litonjua, 2006 (52)	PC	2	1,290	**Maternal diet (FFQ) validated for use during pregnancy/ lowest vs. highest quartiles** : Multivitamins, copper, zinc, α- and β-carotene, β-crytoxanthin, lutein and zeaxanthin, lycopene, vitamins C, E and folic acid	OR	NS
Martindale, 2005 (15)	PC	1-2y	1,300	Total maternal intake (diet +supplements) in pregnancy/ lowest vs. highest pentile Vitamin-C	OR	1.30 (0.66-2.56)
				Maternal intake vitamin E (diet and supplement)	OR	NS

First Author and year of publication	Design	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
				Maternal intake during pregnancy highest vs lowest quartile		
				Zinc	OR	1.43 (0.81-2.52)
				β-carotene	OR	**0.52 (0.30-0.89)**
				α-carotene	OR	0.71 (0.41-1.23)
				Vitamin C	OR	0.67 (0.38-1.18)
Miyake, 2010 (48)	PC	1.5-2	763	Vitamin E	OR	0.59 (0.34-1.02)
				Maternal vitamin D intake from food during pregnancy (quartiles; 5µg/d):		
				Q3 (6.4) vs Q 1 (3.5)	OR	0.59 (0.34-1.02)
				Q2 (5.1) vs Q1 (3.5)	OR	0.63 (0.36-1.09)
				≥4.31 (25th percentile) vs <4.31	OR	**0.63 (0.41-0.98)**
Miyake, 2010 (49)	PC	1.6	763	Q4 (9.1) vs Q1 (3.5)	OR	0.67 (0.40-1.13)

First Author and year of publication	Design	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
				Maternal intake during pregnancy (highest vs lowest quartile):		
				Vitamin B2 supplement	OR	0.72 (0.35-1.49)
				Vitamin B12 supplement	OR	0.85 (0.39-1.84)
Miyake, 2011 (50)	PC	2	763	Vitamin B6 supplement	OR	1.06 (0.52-2.15)
				Maternal food consumption during the eighth month of pregnancy (unclear levels of comparison)		
				Copper	OR	0.94 (0.78-1.14)
				Magnesium	OR	**0.78 (0.63-0.97)**
				Selenium	OR	0.99 (0.81-1.21)
Nwaru, 2011 (24)	PC	5	2,441	Zinc	OR	0.92 (0.74-1.15)
				Folate	OR	0.91 (0.76-1.09)
				Vitamin A	OR	**1.12 (1.00-1.26)**
				Vitamin B2	OR	0.87 (0.73-1.03)
				Vitamin C	OR	0.91 (0.80-1.03)
				Vitamin E	OR	1.00 (0.84-1.19)

First Author and year of publication	Design	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
				Maternal intake during pregnancy (measure of comparison unclear)		
Ohya, 2011 (56)	PC	1.5, 3	1,463	Folic acid, carotene, vitamin A, retinol	OR	NS
Weisse, 2012 (41)	PC	1, 2	272	Maternal serum 25(OH)D levels at 34 weeks gestation and disease risk at age 1 and 2 years	OR	NS
				Maternal intake in pregnancy / highest vs lowest		
			316	Zinc	OR	1.73 (0.80-3.73)
			304	Vitamin C	OR	0.72 (0.33-1.57)
West, 2012 (57)	PC	1	308	Vitamin E	OR	1.42 (0.68-2.98)
				Maternal serum vitamin D during pregnancy / (quintiles; nml/L)	OR	
				Q3 (52-67) vs Q1 (min -38)		0.91 (0.70-1.18)
				Q4 (67-89) vs Q1 (min -38)	OR	0.97 (0.75-1.26)
Wills, 2013(18)	PC	7.5	4,686	Q2 (38-52) vs Q 1 (min -38)	OR	1.04 (0.81-1.34)

First Author and year of publication	Design	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
Wang, 2007 (58)	PC	0.5	1,760	Maternal calcium supplementation (maternal intake during pregnancy vs no intake during pregnancy)	OR	1.22 (0.83-1.81)

3. Infant or maternal dietary intake of vitamins and minerals and risk of food allergy

Thirteen studies investigated the association between vitamin and mineral intake and risk of FA. Figure 21 illustrates the risk of bias in studies of vitamin and mineral intake in relation to food allergy. Nearly a third of observational studies were considered to be of high overall risk of bias, and none were at low risk of bias, due to the lack of control for potential confounding. The two intervention trials were at low and unclear risk of bias respectively (Figure 22).

Figure 21 Risk of Bias in observational studies of vitamin and mineral intake and food allergy

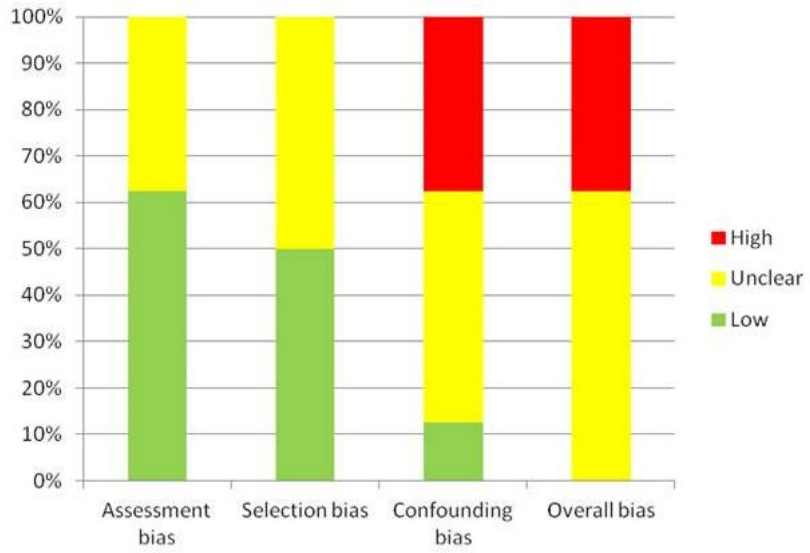
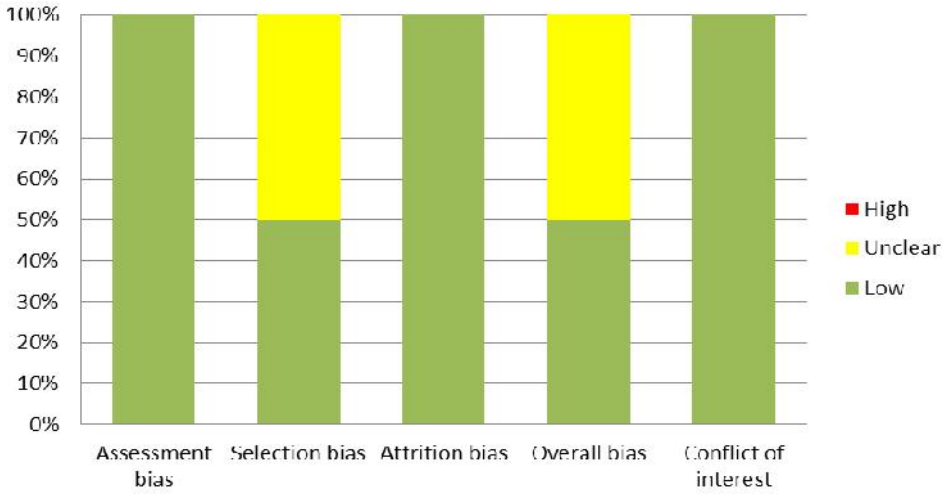


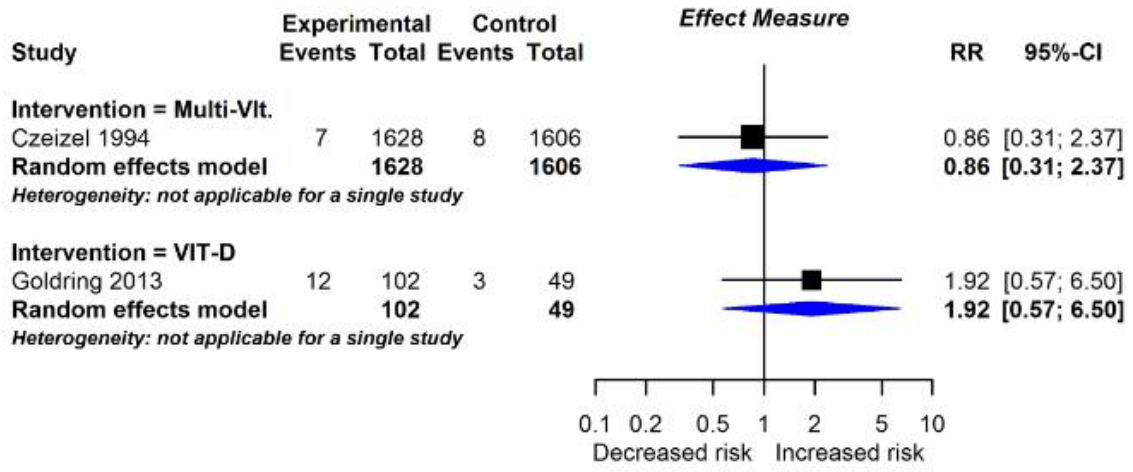
Figure 22 Risk of Bias in intervention trials of vitamins/minerals and food allergy



3.1. Intervention studies eligible for meta-analysis

We identified two intervention studies (**Czeizel 1994** and **Goldring 2013**) on multivitamins and vitamin D, respectively. There was no evidence of an association with food allergy in either study, nor was there evidence of a reduced risk of disease when the two effect sizes were combined (Figure 23). There was no heterogeneity between studies (I^2=0%). Goldring also measured food allergy from primary care record of food allergy diagnosis (study physician assessment shown in plot) and found RR 0.44 (0.07, 3.00) in that analysis.

Figure 23 Interventions with vitamins (by type) and risk of food allergy in children aged 0-4 years



3.2. Observational studies eligible for meta-analysis

We identified no observational studies with data eligible for meta-analysis.

3.3. Studies on vitamin and mineral intake and risk of food allergy which were not eligible for meta-analysis

We identified 11 observational studies that investigated the association between food allergy and vitamins or minerals (Table 4). The exposures studied included vitamin D (infant/maternal intake, serum and cord blood levels), maternal folic acid or multivitamin

supplementation, as well vitamins A, B, C, E, and minerals zinc, calcium, iron, selenium and sodium.

The nested case-control study of **Allen** (**2013**) showed that higher serum levels of vitamin D in infants was associated with a lower risk of having any food allergy at age 1 year. However, maternal vitamin D was unrelated to the risk of food allergy in this study. In the study of **Weisse (2012**), maternal and cord blood vitamin D was associated with an increased risk of food allergy within the first 2 years. Further, higher maternal vitamin D was associated with a higher risk for sensitization to food allergens at age 2 years.

The pilot case-control study of **Mullins** (**2012**) in 115 Australian children showed a non-linear relationship between serum levels of vitamin D and risk of peanut allergy: compared with the reference group (50-74.9 nmol/L), levels of 75 to 99.9 nmol/L were associated with lower risk of peanut allergy (P = 0.02). This effect was not observed at levels ≥100 nmol/L, and the risk of peanut allergy at levels less than 50 nmol/L was not significantly different from the reference group.

In the cohort study of **West** (**2012**), a higher intake of copper assessed prospectively by a food frequency questionnaire in 420 pregnant women, was associated with a reduced risk of food allergy at age 1 year. However, this was not the case for all comparison levels, and the trend was not statistically significant.

In the cohort study of **Milner** (**2004**) the authors reported that early vitamin supplementation was associated with increased risk of food allergies in exclusively formula-fed children. Vitamin supplementation at 3 years of age was associated with increased risk of food allergies, but not asthma, in both breastfed (OR: 1.62; 95% CI: 1.19-2.21) and exclusively formula-fed infants (OR: 1.39; 95% CI: 1.03-1.88).

Overall, we found no consistent evidence to suggest that infant or maternal dietary intake or supplementation with vitamins or minerals influences the risk of food allergies.

Table 4 Studies investigating the association between vitamins and minerals and food allergy which were not eligible for meta-analysis

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p<0.05)
					INFANT INTAKE OR CORD BLOOD LEVELS		
		Cow's milk allergy	1	95	**Infant intake** Iron, vitamins C, D, and E	OR	NS
Laitinen, 2005 (37)	PC	Food allergy	1	95	Calcium	OR	NS
Milner, 2004 (42)	PC	Food allergy	0-4	8285	Infant multi-vitamin intake	OR	**0.77 (0.62-0.96)**
			5-7	8285	Infant multi-vitamin intake		**0.75 (0.62-0.91)**
Liu, 2011 (21)	PC	Food allergy	0-4	649	Cord blood vitamin D intake and risk of food allergy (highest vs. lowest)	OR	1.19 (0.37-3.84)
		Cow's milk allergy	0-4	649	Cord blood vitamin D (highest vs. lowest)	OR	0.76 (0.49-1.16)
		Egg allergy	0-4	649	Cord blood vitamin D (highest vs. lowest)	OR	1.01 (0.81-1.28)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p<0.05)
					Infant plasma vitamin D intake and risk of food allergy (highest vs. lowest)	OR	0.78 (0.31-1.96)
Allen, 2013 (62)	PC	Food allergy	1	361	Vitamin D infant serum levels / 25(OH)D3 >50 vs. 25(OH)D3 ≤50 nmol/L nMol/L	OR	**0.29 (0.11-0.80)**
Oliver, 2010 (60)	NCC	Food Allergy	1	93	**Infant dietary intake:** Calcium, iron, selenium, sodium, zinc, vitamin B, vitamins A, D, and E.	OR	NS
Mullins, 2012 (64)	CC	Peanut Allergy	6	115	Vitamin D infant serum levels / 50-74.9 nmol/l vs. <50 nmol/l	OR	1.54 (0.77-3.08)
					Vitamin D infant serum levels / 75-99.9 nmol/l vs/ 50-74.9 nmol/l	OR	**0.37 (0.16-0.83)**

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p<0.05)
					MATERNAL INTAKE		
West, 2012 (57)	PC	Food allergy	1	317	Maternal intake (highest vs. lowest) Copper	OR	**0.38 (0.15-0.95)**
					Vitamin A		0.38 (0.11-1.28)
					Zinc		0.52 (0.16-1.73)
					Vitamin C		0.46 (0.16-1.36)
					Vitamin E		0.57 (0.19-1.72)
					STUDIES EXAMINING MATERNAL AND INFANT LEVELS		
Weisse, 2013 (41)	PC	Food allergy	1	272	Infant plasma vitamin D intake and risk of food allergy (highest vs. lowest)	OR	**1.92 (1.09-3.38)**
			1	272	Cord blood vitamin D intake and risk of food allergy (highest vs. lowest)	OR	1.7 (0.93-3.12)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p<0.05)
			1	272	Maternal serum 25(OH)D at 34 weeks (quartiles)	OR	1.27 (0.67-2.40)
			2	272	Maternal serum 25(OH)D at 34 weeks (quartiles)	OR	**3.66 (1.36-9.87)**
			1	272	Cord blood 25(OH)D levels (quartiles)	OR	0.92 (0.46-1.85)
			2	272	Cord blood 25(OH) D (quartiles)	OR	**4.65 (1.49-14.48)**
Allen, 2013 (62)	PC	Food allergy	1	361	Maternal multivitamin supplement intake and risk of food allergy (often vs. rare)	OR	0.9 (0.62-1.3)
Jones, 2012 (59)	RC	Food Allergy	1	146	Maternal vitamin D supplement during pregnancy (analysed in increments of 50 IU)	OR	1.08 (0.98-1.19)
				231	Cord blood 25(OH)D3 in nmol/L (continuous)	OR	NS

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p<0.05)
Allen, 2013 (62)	NCC	Food Allergy	1	2758	Additional vitamin D in pregnancy/ yes vs. no multivitamins, no additional vitamin D in pregnancy	OR	0.67 (0.35-1.28)
Grimshaw, 2012 (61)	CC	Food Allergy	2	123	Folic acid, multivitamin, vitamin D supplement during lactation / No vs yes	OR	NS
Binkley, 2011 (63)	CC	Peanut Allergy	1	1413	Folic acid supplementation before conception / - no vs. yes	OR	**1.48 (1.00-2.20)**
				1413	Folic acid supplement initiation during pregnancy / no vs. yes	OR	0.78 (0.27-2.24)

4. Infant or maternal dietary intake of vitamins and minerals and lung function

Eight observational studies and three intervention trials investigated the association between various lung function outcomes and maternal or infant intake of vitamins or minerals. Although all studies were considered to have a low risk of assessment bias, the overall bias of all included observational studies was judged to be high, due to high bias observed in the selection of participants, and to lack of adjustment for confounders in a third of studies (Figure 24); two of the intervention trials were at high risk of bias due to high loss to follow up, the other at low risk of bias (Figure 25).

Figure 24 Risk of Bias in observational studies of vitamin and mineral intake and lung function

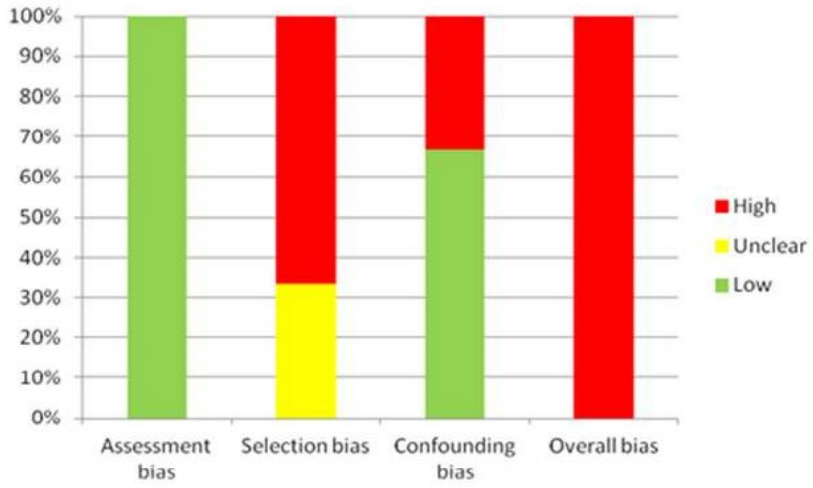
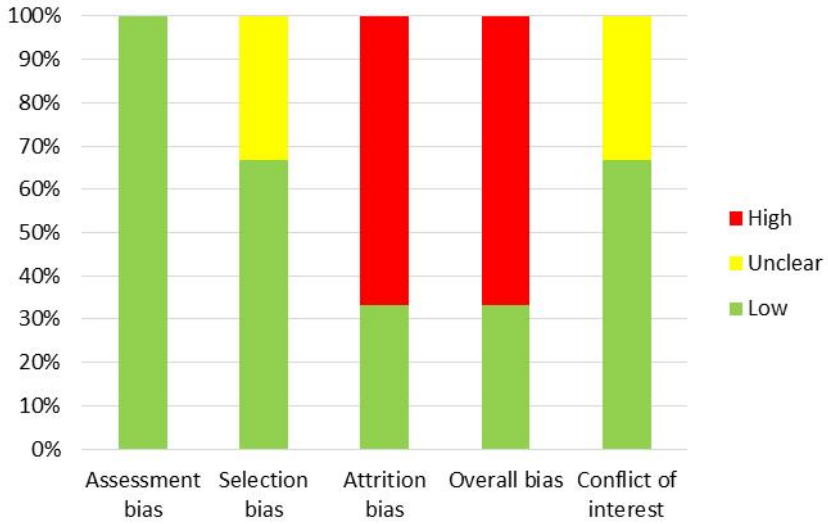


Figure 25 Risk of Bias in intervention trials of vitamins/ minerals and lung function



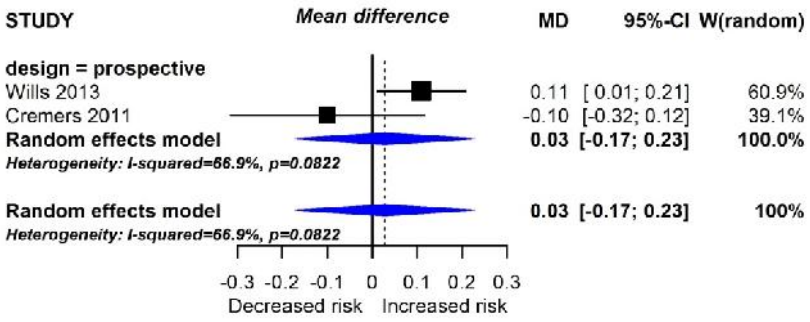
4.1. Intervention studies eligible for meta-analysis

We identified no intervention studies with data eligible for meta-analysis

4.2. Observational studies with data eligible for meta-analysis

We identified two studies which investigated the association between plasma levels of vitamin D in pregnant mothers (Figure 26) and changes in forced expiratory volume in 1 second (FEV_1). There was no evidence that maternal plasma vitamin D influences FEV_1 in children aged 5-15 years.

Figure 26 Maternal plasma vitamin D (mean difference) and lung function (FEV_1; standard deviations) in children at age 5-14 years



4.3. Studies on vitamin and mineral intake and lung function which were not eligible for meta-analysis

Three intervention studies reported data on lung function, which could not be included in meta-analyses. In the cluster RCT study of **Checkley (2010)** children whose mothers had received vitamin A had a forced expiratory volume in 1 second (FEV_1) and a forced vital capacity (FVC) that were significantly higher than those of children whose mothers had not received vitamin A supplementation, after adjustment for various potential confounders Children whose mothers had received β-carotene had adjusted FEV_1 and FVC values that were similar to those of children whose mothers had received placebo, and in neither group was there any difference in FEV1:FVC ratio or peak expiratory flow rate. **McEvoy (2014)** found significantly increased lung function (ratio of time to peak tidal expiratory flow to

expiratory time; and passive respiratory compliance per kilogram) in infants born to mothers in the intervention compared with the control group in the first 72 hours of life, but no significant difference at age 1 year. The positive findings regarding lung function from the study of Checkley were not replicated in a similar trial undertaken in Nepal using a multivitamin supplement which included a lower vitamin A dose than the trial of Checkley. **Devakumar (2015)** reported no significant difference in lung function between the children of women supplemented with multivitamins during pregnancy and a control group - FEV1 mean 1.2L SD0.2 intervention, 1.21 SD0.2 control; FVC mean 1.37L SD0.2 intervention, 1.38 SD0.2 control. We concluded that the Checkley trial findings for vitamin A were not reproduced in the trial of Devakumar using a lower vitamin A dose, were not reproduced using beta-carotene in the trial of Checkley, and were not supported by clinical evidence of differences in respiratory outcomes (see wheeze section). This finding was downgraded to no evidence due to inconsistency (-2), indirectness of the study population (-1) and imprecision (-1).

Observational studies reported inconsistent evidence for relationships between lung function and vitamin D (maternal serum or supplement intake), maternal folic acid supplementation, zinc intake (maternal and infant, including supplement use) and multivitamin use (Table 5).

In the cohort study of **Wills** (**2013**) which was carried out in a population residing in south west England, there was no evidence to suggest that maternal vitamin D blood level in pregnancy was associated with altered lung function or bronchial hyper-responsiveness measurements in the offspring measured at age 8.7 years old (n=3,728). These findings remained after adjustment for season of measurement and for other potential confounders. There was also no evidence that these relationships followed a non-linear form, and no evidence that either deficient or high concentrations of maternal vitamin D were associated with atopic or respiratory outcomes. Two other smaller studies also reported no association between maternal blood levels of vitamin D and measures of lung function in the offspring. The study of **Pike (2012)**, which included 800 pregnant mothers from Southampton, showed no significant associations between maternal late-pregnancy vitamin D status and lung function in their offspring at age 6 years. In the KOALA Birth study (**Cremers, 2011**) the authors found no association between vitamin D levels, vitamin D supplementation in childhood or recommended vitamin D dosage of ≥10 µg/day during pregnancy and lung function in children aged 6-7 years.

With regards to folic acid use (or plasma levels) in pregnant mothers, the studies of **Bekkers (2012**) and **Magdelijns (2011)** showed no evidence of an association between this exposure and measures of lung function at age 8 or 7, respectively.

Overall we found no evidence that vitamin or mineral supplementation or intake to mothers or infants influences child lung function from observational studies. We found no consistent evidence from the intervention studies that vitamin A or other vitamin supplementation during pregnancy influences lung function during childhood.

Table 5 Studies investigating the association between vitamins and minerals and lung function which were not eligible for meta-analysis

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p<0.05)
					MATERNAL INTAKE OR BLOOD LEVELS		
Checkley, 2010 (4)	cluster RCT	FEV1 (ml)	11	591/506	Maternal supplementation of vitamin A 23,300 IU (7000µg retinol equivalents) weekly from pre-conception through lactation versus peanut oil placebo	MD	**46 mls (6, 86)**
		FVC (ml)			Maternal supplementation of vitamin A 23,300 IU (7000µg retinol equivalents) weekly from pre-conception through lactation versus peanut oil placebo	MD	**46 mls (8, 84)**
		FEV1 (ml)			Maternal supplementation beta-carotene 42mg (7000µg retinol equivalents) weekly from pre-conception through lactation versus peanut oil placebo	MD	14 mls (-24, 54)
		FVC (ml)			Maternal supplementation beta-carotene 42mg (7000µg retinol equivalents) weekly from pre-conception through lactation versus peanut oil placebo	MD	17 mls (-21, 55)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p<0.05)
McEvoy, 2014 (14)	RCT	Time to peak tidal expiratory flow: expiratory time ratio(TPTEF:TE)	0	89/90	Vitamin C supplementation (500mg/d) to pregnant, smoker women compared to placebo	MD	**0.04 (0.01 – 0.06)**
			1			MD	NS
		Passive respiratory system compliance (Crs/kg)	0			MD	**0.11 (0.02 – 0.20)**
			1			MD	NS
Bekkers, 2012 (51)	PC	LF-BHR	8	3,786	Maternal vitamin or mineral supplements during pregnancy, including folic acid, pre-natal vitamins (multivitamin supplements especially for pregnant females)/ no use vs. yes Folic acid, multivitamins	OR	NS
Cremers, 2011(40)	PC	LF-FEV_1 and FVC	6.5	436	Maternal plasma vitamin D at 36 weeks gestation / Quintile 1 (21.5, 12.0-28.2) nmol/l vs. upper quintiles	β-coeff	NS
					Maternal vitamin D intake from supplements / no use vs variable amounts at 1st, 2nd or 3rd trimester	β-coeff	NS

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p<0.05)
Devereux, 2006 (16)	PC	LF	5	1,704	Maternal and children's dietary and supplement intakes of zinc were summated and energy adjusted/lowest (Q1) vs. highest (Q5) quintiles	OR	NS
Magdelijns, 2011 (39)	PC	LF-FEV_1% and FVC% predicted	7	1,902	Maternal plasma vitamin D at 36 weeks gestation / lowest vs upper quintiles	β-coeff	NS
		LF-BHR slope	6	216	Vitamin D intake during pregnancy (average total daily mcg/kg)	β-coeff	NS
Pike, 2012 (54)	PC	LF-FEV_1 or FVC (L)	6	739	Vitamin D intake or plasma levels ,during pregnancy (average total daily mcg/kg), serum levels measured as 10 nmol/litre change	β-coeff	NS
Wills, 2013 (18)	PC	Spirometry	8.7	3,728	Maternal serum vitamin D (nmol/L) in pregnancy: Higher quintiles vs lowest (Q1 min -38): Quintile 5 (89-max)	β-coeff	NS
		LF-BHR	8.7	2,409	Quintile 4 (67-89)	OR	**0.71 (0.53-0.96)**
					Quintile 3 (52-67)	OR	0.79 (0.58-1.07)
					Quintile 2 (38-52)	OR	0.87 (0.65-1.17)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p<0.05)
					Quintile 2 (38-52)	β-coeff	NS
					Quintile 3 (52-67)	β-coeff	NS
		LF-FEV_1	8.7	3728	Quintile 4 (67-89)	β-coeff	NS
					Quintile 2 (38-52)	β-coeff	NS
					Quintile 3 (52-67)	β-coeff	NS
Wills, 2013 (18)	PC	LF-FVC	8.7	3784	Quintile 4 (67-89)	β-coeff	NS

5. Infant or maternal dietary intake of vitamins and minerals and risk of wheeze

Forty studies investigated the association between intake of vitamins or minerals and risk of wheeze in childhood. Most observational studies were judged to be of low risk in all the domains assessed (Figure 27). Four of the ten intervention trials were at high risk of bias due to high loss to follow up (Figure 28).

Figure 27 Risk of Bias in observational studies of vitamin and mineral intake and wheeze

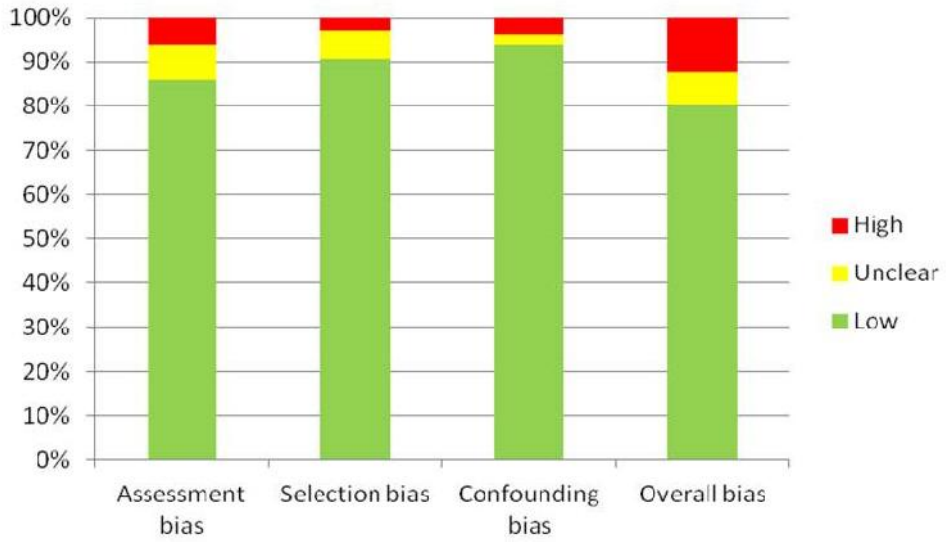
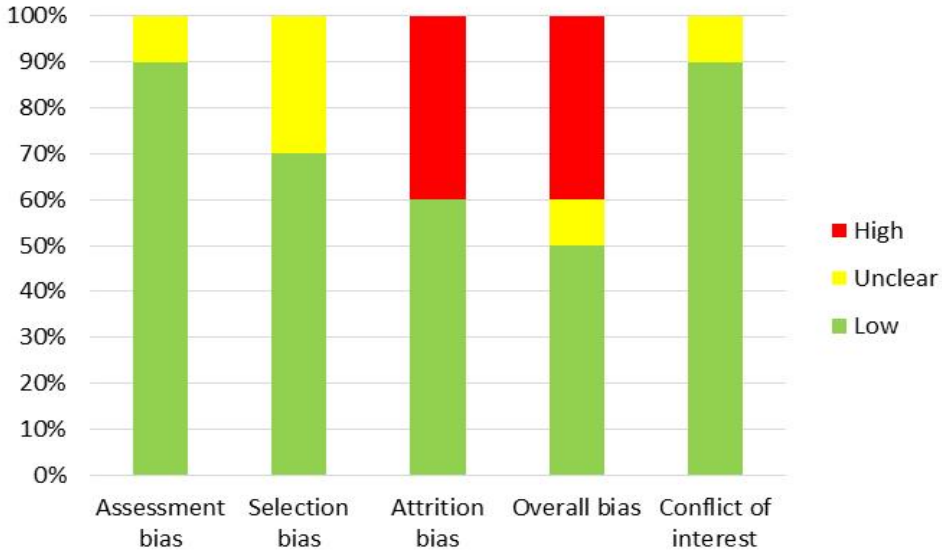


Figure 28 Risk of Bias in intervention trials of vitamins and minerals and wheeze



5.1. Intervention studies

We identified ten intervention studies. Five studies could be included in meta-analysis for the effect of vitamins on risk of wheeze at age 0-4 (Figure 29). Supplementation with vitamin D (**Goldring 2013 and Grant 2016**), vitamin C and E (**Greenough 2010 and McEvoy 2014**) or multivitamins (**Cziezel 1994**) did not demonstrate a significant effect on wheeze at age 0-4. Data from four studies (**Chawes 2016; Goldring 2013; Grant 2016; Litonjua 2016**) found no significant effect of vitamin D on risk of recurrent wheeze at age 0-4 (Figure 30). Goldring also measured current wheeze (wheeze ever is shown in Figure 29) with RR 0.98 (0.46, 2.13), and wheeze plus positive Asthma Predictive Index RR 1.00 (0.44, 2.30); and recurrent wheeze using primary healthcare record (study physician assessment is shown in Figure 30) with RR 1.48 (0.44, 5.00). Overall there was no evidence that vitamins (separately or combined) influenced the risk of wheeze outcomes at age 0-4 years in offspring. The heterogeneity across studies was moderate for both wheeze and recurrent wheeze.

Two intervention trials reported wheeze outcomes at age 5-14 years (**Checkley 2011 and Aage 2015**). No effect of maternal vitamin A supplementation on wheeze risk in offspring at age 5-14 was demonstrated (Figure 31). Checkley separately reported RR 1.37 (0.77, 2.45) with vitamin A, and RR 1.47 (0.83, 2.61) with β-carotene for current wheeze, and RR 2.66 (0.54, 13.14) with vitamin A, and RR 1.32 (0.22, 7.89) with β-carotene for recurrent wheeze.

Figure 29 Vitamin interventions (by type) and risk of wheeze in children aged 0-4 years

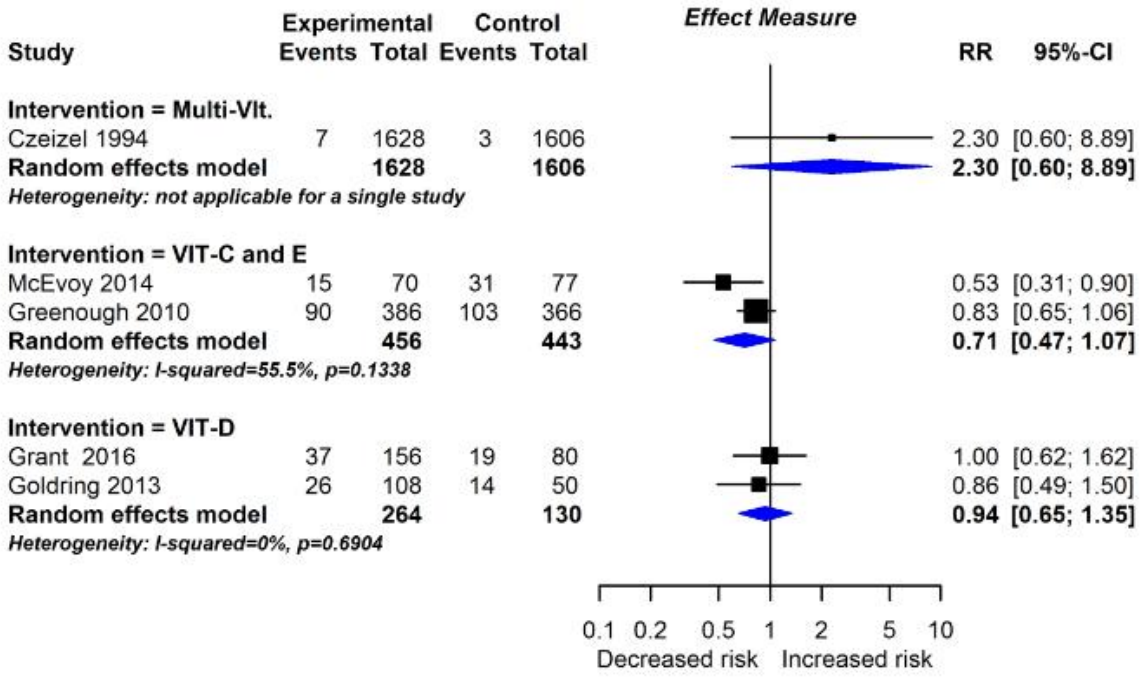


Figure 30 Vitamin interventions (by type) and risk of recurrent wheeze in children aged 0-4 years

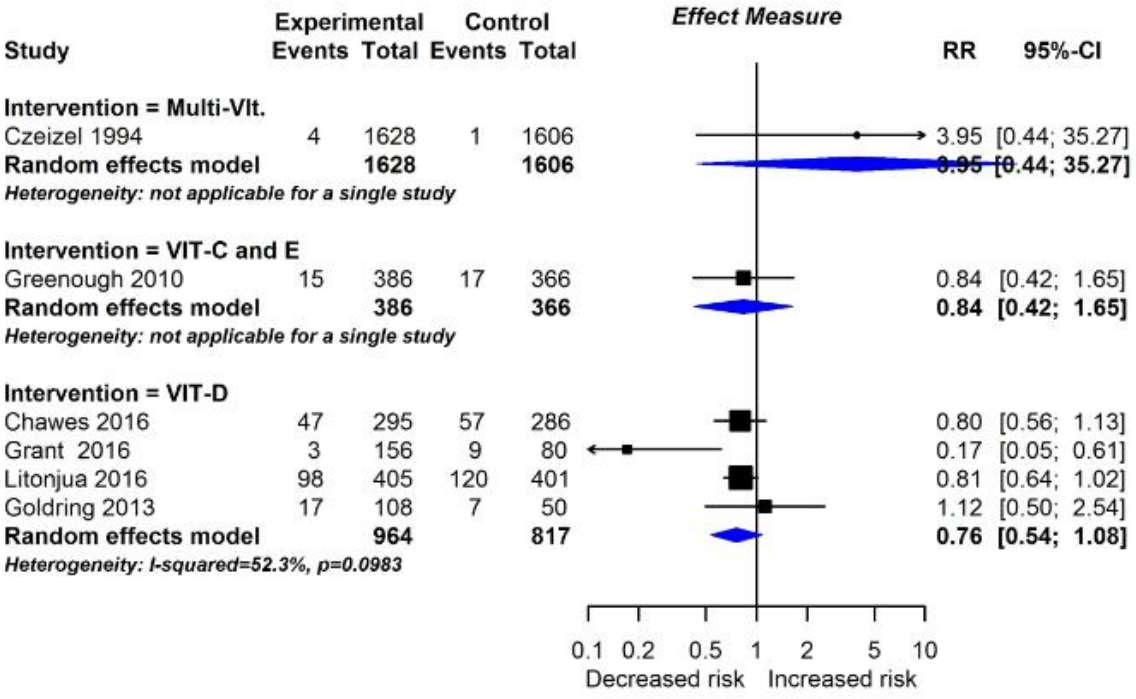
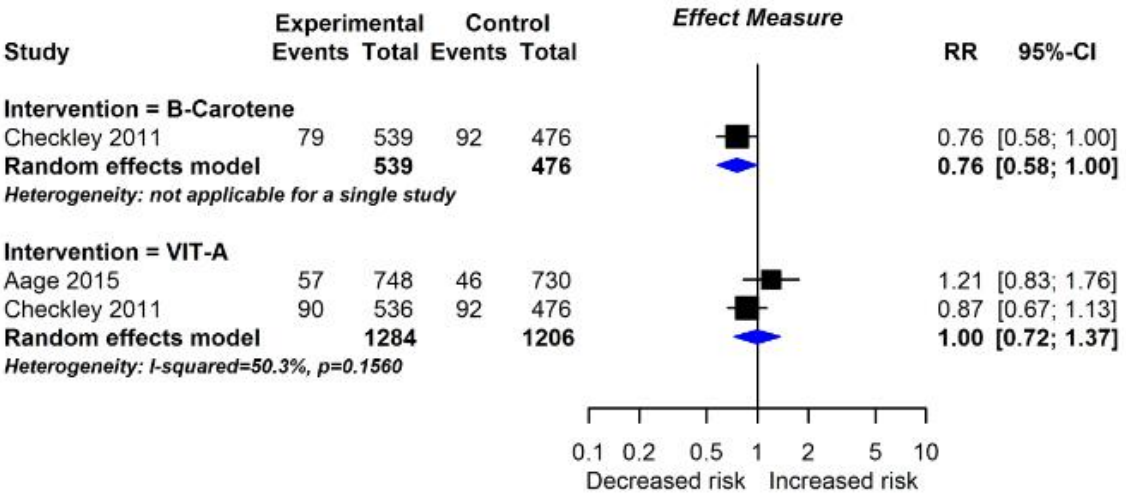


Figure 31 Vitamin interventions (by type) and risk of wheeze in children aged 5-14 years


Study
Experimental Events Total
Control Events Total
Effect Measure
RR 95%-CI
Intervention = B-Carotene
Checkley 2011 79 539 92 476 0.76 [0.58; 1.00]
Random effects model 539 476 0.76 [0.58; 1.00]
Heterogeneity: not applicable for a single study
Intervention = VIT-A
Aage 2015 57 748 46 730 1.21 [0.83; 1.76]
Checkley 2011 90 536 92 476 0.87 [0.67; 1.13]
Random effects model 1284 1206 1.00 [0.72; 1.37]
Heterogeneity: I-squared=50.3%, p=0.1560
0.1 0.2 0.5 1 2 5 10
Decreased risk
Increased risk

5.2. Observational studies with data eligible for meta-analysis

For the dietary exposures copper, zinc, folic acid, and vitamins D, C, E, and A, there were studies with comparable data for a meta-analysis. These are presented in Figures 32 to 45. With few exceptions, most of the studies showed no evidence to suggest that maternal intake, or blood/cord levels in the case of vitamin D, influence the risk of wheeze in early or later childhood. Figure 33 shows the combined effect sizes of three studies (**West 2012; Miyake 2010** and **Litonjua 2006**) that investigated the association between maternal intake of zinc and risk of wheeze in children aged 0-4 years. A higher intake of zinc was associated with a 40% reduced risk of wheeze (OR 0.60; 95% CI 0.45, 0.81). There was no heterogeneity across studies (I^2=0%).

Figure 44 shows the effect sizes of the studies of **Devereux (2006)** and **Litonjua (2006),** both of which reported a reduced risk of wheeze in children of mothers who had a higher intake of vitamin E. The overall effect showed a 53% reduction in the risk of wheeze (OR 0.47; 95% CI 0.30, 0.74). There was no evidence of heterogeneity between studies (I^2=0%).

Figure 32 Maternal copper intake (highest vs. lowest) and risk of wheeze in children aged 0 – 4 years

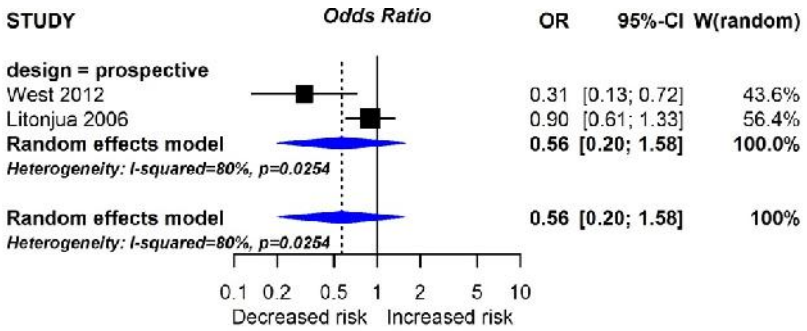


Figure 33 Maternal zinc intake (highest vs. lowest) and risk of wheeze in children at age 0-4 years

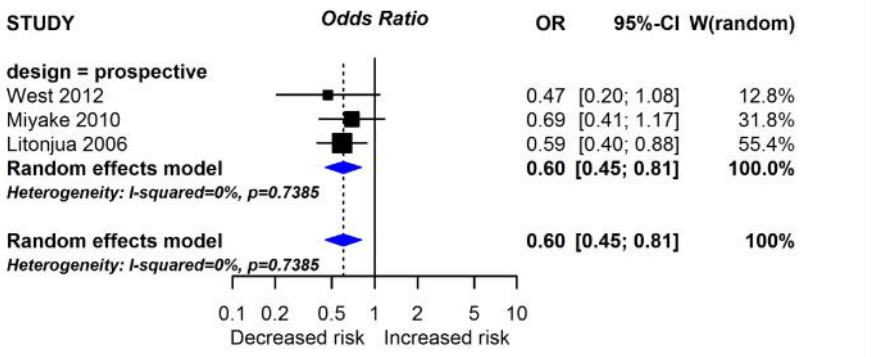


Figure 34 Maternal plasma vitamin D (highest vs. lowest) and risk of recurrent wheeze in children aged 5 – 14 years

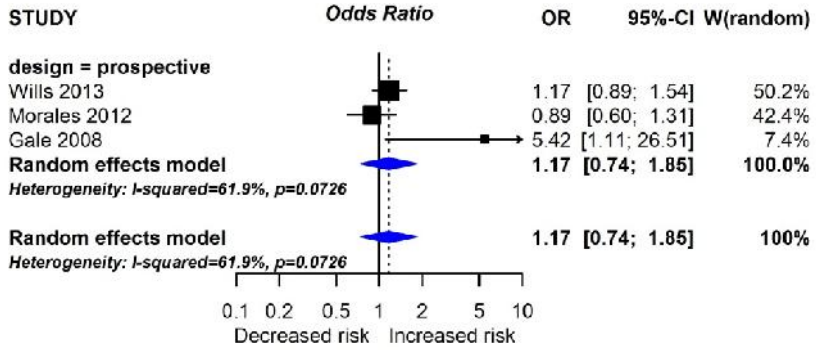


Figure 35 Maternal plasma vitamin D (per-unit increase) and risk of recurrent wheeze in children at age 5-14 years

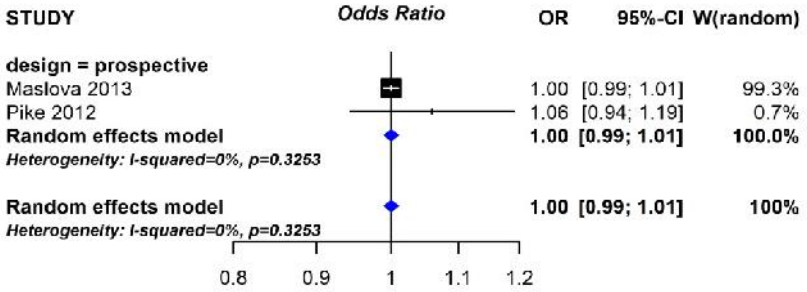


Figure 36 Maternal vitamin D intake (often vs. rare) and risk of wheeze in children aged 5 –14 years

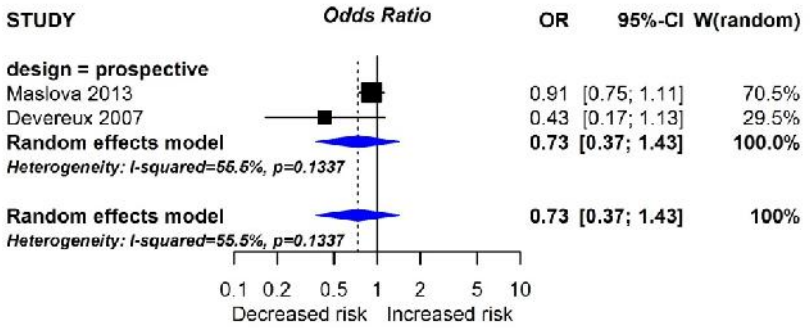


Figure 37 Maternal vitamin D intake (often vs. rare) and risk of recurrent wheeze in children aged 5 –14 years

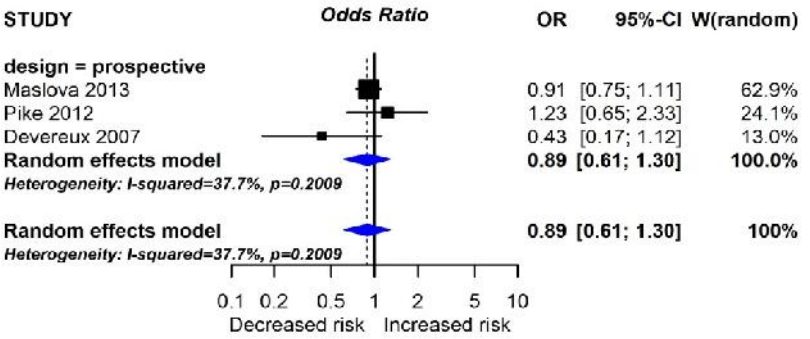


Figure 38 Maternal vitamin D intake (highest vs lowest) and risk of recurrent wheeze in children (at any age)

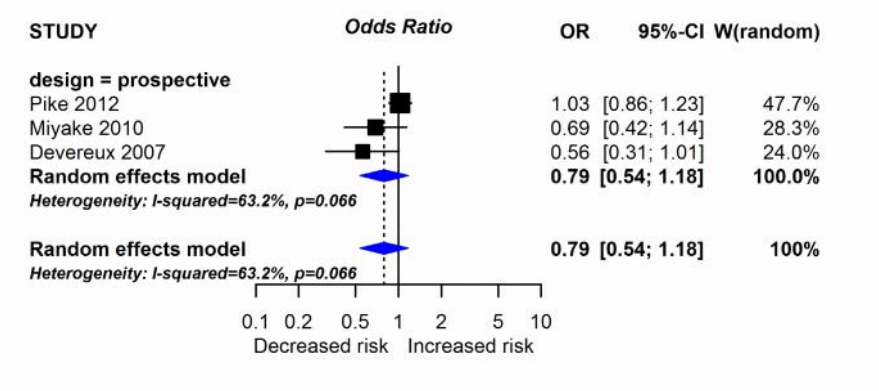


Figure 39 Cord blood vitamin D levels (highest vs. lowest) and risk of recurrent wheeze in children

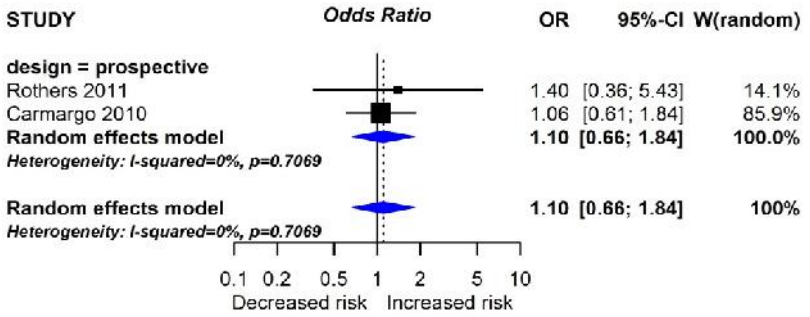


Figure 40 Maternal folic acid supplement use (often vs. rare) and risk of wheeze in children aged 0 – 4 years

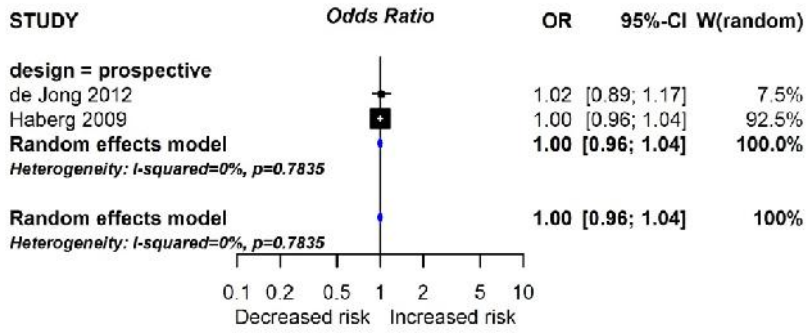


Figure 41 Maternal folic acid supplement use (highest vs lowest) and risk of wheeze in children aged 0-4 years

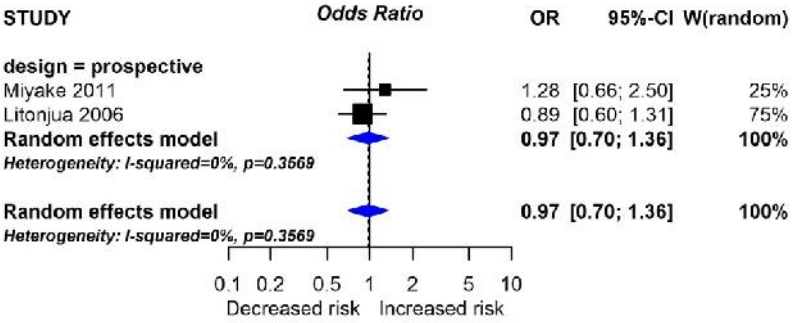


Figure 42 Maternal folic acid supplement use (often vs. rare) and risk of recurrent wheeze in children aged 5-14 years

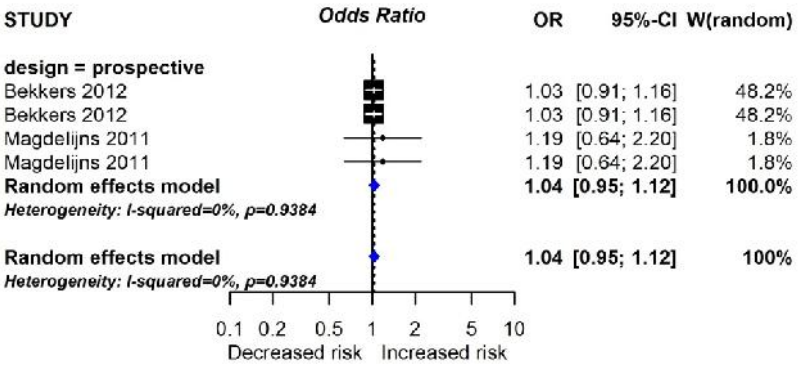


Figure 43 Maternal vitamin C intake (highest vs lowest) and risk of wheeze in children aged 0-4 years

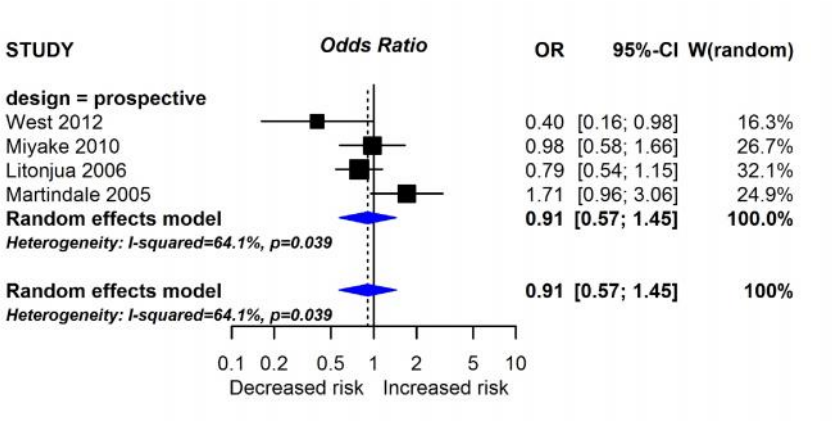


Figure 44 Maternal vitamin E intake (highest vs lowest) and risk of wheeze in children aged 0-5 years

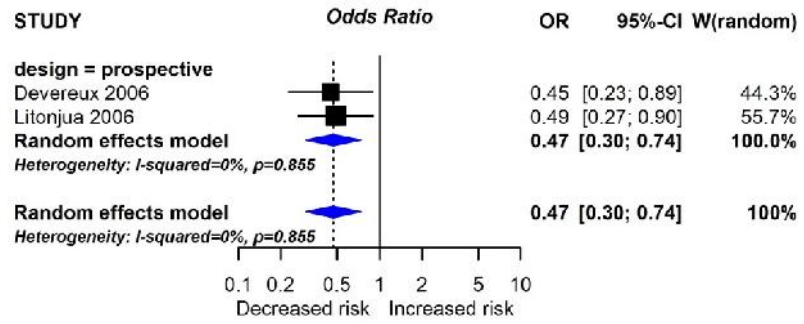
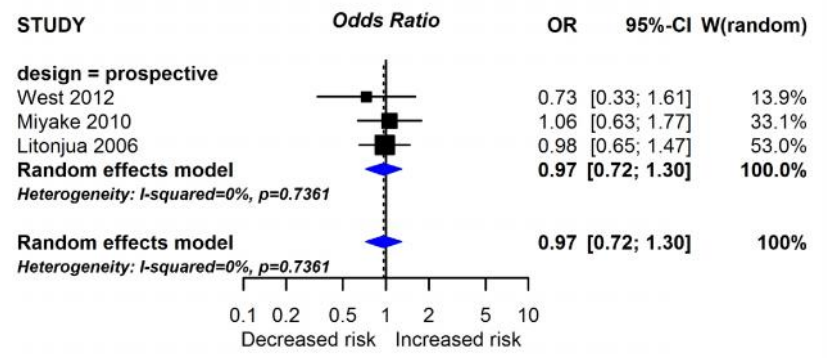


Figure 45 Maternal vitamin A intake (highest vs lowest) and risk of wheeze in children aged 0-4 years



5.3. Studies on vitamin and mineral intake and wheeze which were not eligible for meta-analysis

One intervention study reported findings that could not be included in meta-analysis. **Devakumar 2015** reported no significant difference in prevalence of wheeze or recurrent wheeze between children of women allocated multivitamins during pregnancy, and a control group – numerical data were not reported. The studies that reported data which could not be included in meta-analysis are summarised in Table 6. In observational studies Vitamin D (intake/blood) and folic acid supplementation were the most commonly studied exposures. Others included antioxidant vitamins and minerals, mostly self-reported.

With regards to vitamin D, there was no consistent evidence that maternal intake was related to a lower risk of wheeze in childhood. The studies of **Pike (2012**) and **Back (2009)** did not find an association between maternal (Pike) or infant (Back) intake and risk of wheeze or recurrent wheeze at age 6 years. The study of **Baiz (2013)** did not find an association between concentrations of vitamin D in cord blood and risk of recurrent wheeze at age 5 years. Similarly, **Wills (2013**) reported no association between maternal serum levels of vitamin D and risk of wheeze at age 7 years.

On the contrary, the study of **Devereux (2007)** reported a lower risk of wheeze in children at age 5 in pregnant mothers who had a high intake of vitamin D (when comparing highest vs lowest quintiles); the study of **Miyake (2010)** also found that a higher maternal intake of vitamin D was negatively associated with risk of wheeze at age 2. The study of **Camargo (2010)** found reduced recurrent wheeze with increased maternal vitamin D intake during pregnancy; the same authors found a similar relationship for cord-blood vitamin D levels, but only for some measures of wheezing and not for others. The studies of **Miyake 2010**, **Litonjua 2006** and the Seaton cohort (Martindale/ Devereux) all reported significantly reduced wheeze with higher estimated maternal vitamin E intake during pregnancy. However, the study of **Nwaru 2011** failed to confirm this association, and had a similar number of participants as the studies combined in meta-analysis in Figure 39. Similarly, **Nwaru 2011** failed to confirm the association between zinc intake and reduced risk of wheezing seen in Figure 31, despite including more participants in analysis than the combined studies in Figure 31.

Overall we found no consistent evidence from intervention studies to suggest that maternal vitamin supplementation during pregnancy may reduce risk of wheeze in childhood, and no consistent evidence from observational studies for a relationship between vitamin or mineral intake during pregnancy, lactation or infancy and risk of wheeze.

Table 6 Observational studies investigating the association between vitamins and minerals and wheeze which were not eligible for meta-analysis

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					INFANT OR CORD BLOOD		
	PC	Asthma-Wheeze	6	123	Infant vitamin D intake (continuous)	OR	1.06 (0.44-2.57)
Back, 2009 (20)		Rec wheeze				OR	3.16 (0.61-16.4)
Hypponen, 2004 (44)	PC	Rec wheeze	31	6722	Infant vitamin D supplementation in the first year of life – daily dose/ 2000 IU vs < 2000 IU	OR	3.91 (0.53 -29.9)
		Rec wheeze	5	239	Vitamin D in cord blood (continuous scale)	OR	1.15 (0.78-1.69)
Baiz, 2013 (29)	PC	Asthma-Wheeze	5	239	Vitamin D in cord blood (continuous scale)	OR	1.07 (0.79-1.45)
Jones, 2012 (59)	RC	Asthma-Wheeze	1	231	Cord blood 25(OH)D3 in nmol/L (continuous)	OR	NS

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					Infant vitamin supplementation (highest vs lowest quartiles):		
					α-carotene	OR	0.92 (0.63-1.34)
					b-carotene	OR	0.98 (0.65-1.47)
Litonjua, 2006 (52)	PC	Wheeze	2	1290	b-cryptoxanthin	OR	0.97 (0.67-1.41)
					Lutein and zeaxanthin	OR	0.84 (0.56-1.25)
					Lycopene	OR	0.96 (0.65-1.42)
					Vitamin C	OR	0.79 (0.54-1.15)
Litonjua, 2006 (52)	PC	Wheeze	2	1290	Vitamin E	OR	0.70 (0.48-1.03)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					MATERNAL INTAKE OR BLOOD LEVELS		
Camargo, 2007 (53)	PC	Rec wheeze	3	1194	**Maternal vitamin D intake in 1st and 2nd trimesters**:		
					Q2 (513, 446-562 IU) vs Q1 (356, 60-445 IU)	OR	**0.47 (0.28-0.77)**
					Q3 (603, 563-658) vs Q 1 (356, 60-445 IU)	OR	**0.54 (0.33-0.89)**
					Q4 (724, 659-1145 UI) vs Q1 (356, 60-445 UI	OR	**0.38 (0.22, 0.65)**
					Vitamin D intake from food only (per 100IU/d)	OR	**0.80 (0.66-0.97)**
					Total vitamin D intake	OR	**0.81 (0.71-0.93)**
					Vitamin D intake from supplements only per 100IU/d; (continuous)	OR	**0.82 (0.71-0.95)**
Camargo, 2010	PC	Rec wheeze Wheeze	1	823	Vitamin D cord blood/ ≥75 nmol/L vs. 25-74.9 nmol/L	OR	0.84 (0.55-1.29)
					Cord blood 25(OH)D in nmol/L (per ten	OR	0.98 (0.93, 1.02)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
(37)					nmol/L increase)		
Camargo, 2010 (43)	PC	Wheeze	3	823	Cord blood 25(OH)D in nmol/L (per ten nmol/L increase)	OR	**0.96 (0.91, 1.00)**
		Wheeze	5		Cord blood 25(OH)D in nmol/L (per ten nmol/L increase)	OR	**0.95 (0.91, 0.99)**
		Incident asthma	5		Cord blood 25(OH)D in nmol/L (per ten nmol/L increase)	OR	1.03 (0.97, 1.10)
Devereux, 2007 (17)	PC	Wheeze	5	1120	**Maternal vitamin D intake in 3rd trimester** (median, range): Q5 (275, 189-751 IU/d) vs Q 1 (77, 46-92 IU/d)	OR	**0.45 (0.21-0.97)**
					Q 4 (157, 142-182 IU/d) vs Q1 (77, 46-92 IU/d)	OR	0.65 (0.38-1.11)
					Q3 (128, 117-139 IU/d) vs Q1 (77, 46-92 IU/d)	OR	0.77 (0.47-1.27)
					Q2 (104, 94-115 IU/d) vs Q1 (77, 46-92 IU/d)	OR	0.84 (0.52-1.37)
Devereux, 2007 (17)	PC	Rec wheeze	5	1120	**Maternal vitamin D intake in 3rd trimester:** Q5 (157, 142-182 IU/d) vs Q1 (77, 46-92	OR	0.51 (0.22-1.20)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					IU/d)		
Devereux, 2007 (17)	PC	Rec wheeze	5	1120	Q3 (128, 117-139 IU/d) vs Q 1 (77, 46-92 IU/d)	OR	0.75 (0.35-1.61)
					Q2 (104, 94-115 IU/d) vs Q 1 (77, 46-92 IU/d)	OR	0.91 (0.44-1.88)
Erkkola, 2009 (23)	PC	Rec wheeze	5	1669	**Maternal vitamin D intake from food in pregnancy (8th month)** 2nd & 3rd Quartiles (0.31-0.54 µg/MJ) vs. 1st Quartile (<0.31 µg/MJ)	HR	1.64 (1.02-2.64)
					Vitamin D intake from supplements in pregnancy (8th month)/no use vs. use	HR	0.99 (0.62-1.57)
Gale, 2008 (30)	PC	Rec wheeze	9	178	Maternal vitamin D level in serum [nmol/L] in late pregnancy (28-42 weeks) : Q2 (30-50) vs Q 1 (<30)	OR	NS
					Q3 (51-75) vs Q1 (<30)	OR	NS

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
Magnus, 2013 (46)	NCC	Rec wheeze	3	1684/489	Plasma vitamin D at 18 weeks gestation	OR	0.96 (0.84-1.10)
Maslova, 2013 (22)	PC	Rec wheeze	7	28767	**Maternal vitamin D intake** (quintiles[IQR]) from supplements during pregnancy (µg/d) Q3 (11.7, 9.9-12.3) vs Q1 (5.5, 1.8-7.1)	RR	0.78 (0.55-1.10)
					Q2 (8.2, 7.3-9.4) vs Q1 (5.5, 1.8-7.1)	RR	0.92 (0.78-1.08)
			7	28767	Q4 (13.0, 12.4-14.0) vs Q1 (5.5, 1.8-7.1)	RR	0.92 (0.78-1.08)
			7	28767	Q5 (16.5, 14.2-27.4) vs Q 1 (5.5, 1.8-7.1)	RR	0.92 (0.78-1.08)
Maslova, 2013 (22)	PC	Rec wheeze	1.5	33425	Q3 (11.7, 9.9-12.3) vs Q1 (5.5, 1.8-7.1)	RR	0.95 (0.84-1.08)
					Vitamin D intake from food during pregnancy / ≥4.309 µcg /d vs <4.309 (25th percentile) mcg/d	OR	**0.64 (0.42-0.97)**
					Vitamin D intake / Q4 (9.1) µcg /d vs Q1 (3.5) µcg/d	OR	NS
					Vitamin D intake / Q3 (6.4) µcg/d vs Q1	OR	NS

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					(3.5) µcg/d		
Miyake, 2010 (49)	PC	Wheeze	1.6	763	Vitamin D intake / Q4 vs Q1	OR	0.69 (0.42-1.14)
Morales, 2012 (36)	PC	Wheeze	4	1223	Maternal plasma 25(OH)D3 at ~12.5 weeks gestation: Q3 (29.2-37ng/ml) vs Q1 (<21.9ng/ml)	OR	0.82 (0.54-1.25)
			4	1223	Q2 (21.9-29.1ng/ml) vs Q1 (<21.9ng/ml)	OR	0.89 (0.59-1.34)
Morales, 2012 (36)	PC	Wheeze	1	1724	Q4 (>37 ng/ml) vs Q1 (<21.9ng/ml)	OR	0.94 (0.62-1.43)
					Maternal plasma 25(OH)D3 at ~12.5 weeks gestation / Quartile 3 (29.2-37ng/ml) vs Q1 (<21.9ng/ml)	OR	0.81 (0.55-1.20)
Morales, 2012 (36)	PC	Rec wheeze	5	1233	Vitamin D plasma/Maternal plasma 25(OH)D3 at ~12.5 weeks gestation / Q2 (21.9-29.1ng/ml) vs Q1 (<21.9ng/ml)	OR	0.88 (0.60-1.29)
					Maternal vitamin D intake during pregnancy/ highest vs lowest quartile	RR	1.23 (0.65-2.33)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
Pike, 2012 (54)	PC	Rec wheeze	6	856	Maternal serum 25(OH)-D status at 34 weeks pregnancy /(continuous scale in nmol/L)	RR	NS
					Vitamin D cord blood [nml/L]:		
					50-74.9 vs. < 50	OR	2.00 (0.63-6.40)
Rothers, 2011 (34)	PC	Rec wheeze	5	194	75-99.9 vs 50-74.9	OR	1.10 (0.39-3.10)
					Maternal serum [nmol/L] vitamin D in pregnancy:		
					Quintile 3 (52-67) vs Quintile1 (min -38)	OR	0.99 (0.73-1.35)
		Wheeze	7.5	4,696	Quintile 2 (38-52) vs Quintile1 (min -38)	OR	1.03 (0.75-1.41)
					Maternal serum vitamin D in pregnancy [quintiles; nmol/L]		
Wills, 2013 (18)	PC				Q 4 (67-89) vs Q1 (min -38)	OR	0.92 (0.69-1.23)
					Q3 (52-67) vs Q1 (min -38)	OR	1.00 (0.75-1.34)
		Rec wheeze	7.5	4,648	Q2 (38-52) vs Q1 (min -38)	OR	1.02 (0.77-1.36)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					Maternal intake in pregnancy (highest vs lowest quartiles):		
					Multivitamins, α-carotene, β-carotene, β-cryptoxanthin, lutein and zeaxanthin, lycopene		NS
					Zinc	OR	**0.49 (0.28-0.87)**
Litonjua, 2006 (52)	PC	Rec wheeze	2	1,290	Vitamin E	OR	**0.49 (0.27-0.90)**
Magdelijns, 2011 (39)	PC	Wheeze	7	1,902	Folic acid supplementation before or during pregnancy, alone or with other supplements use vs no use	OR	0.99 (0.8-1.23)
Bekkers, 2012 (51)	PC	Rec wheeze	8	3,786	Folic acid supplementation during pregnancy (yes vs no)	Prevalence ratio	1.03 (0.96- 1.16)
					Vitamin and mineral intake (highest vs lowest pentile)		
					Total maternal vitamin C intake (diet and supplements)	OR	**3.00 (1.47-6.12)**
Martindale, 2005 (15)	PC	Wheeze	1-2	1,300	Total maternal vitamin E intake (diet and supplements)	OR	0.53 (0.27-1.01)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
Martindale, 2005 (15)	PC	Wheeze	1-2	1,300	Copper, magnesium, manganese, zinc, selenium, b-carotene	OR	NS
Milner, 2004 (42)	PC	Rec wheeze	0-3	8,073	Vitamin/ mineral drops given to infants at least 3 days a week / intake in the first 3 months vs no intake	OR	0.89 (0.77-10.2)
Miyake, 2010 (49)	PC	Wheeze	1.6	763	**Maternal intake during pregnancy** (highest vs lowest quartiles of intake[energy adjusted]):		
					β-carotene or α-carotene, vitamin C	OR	NS
					Vitamin D	OR	**0.48 (0.29-0.80)**
					Vitamin E intake	OR	**0.54 (0.32-0.90)**
Miyake, 2011 (50)	PC	Wheeze	2	763	Vitamins B6, B12, Folate, B2, supplementation during pregnancy (FFQ) / highest [median 1.2mg per day] vs lowest quartile [median 0.7 mg per day]	OR	NS

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
Miyake, 2010 (49)	PC	Rec wheeze	2	763	Maternal calcium intake (highest vs. lowest)	OR	**0.57 (0.33-0.99)**
Narita, 2011 (55)	PC	Wheeze	0.6, 3	1,344	Maternal consumption of calcium or vitamin D during pregnancy / highest quartile vs lowest	OR	NS
Nwaru, 2011 (24)	PC	Rec wheeze	5	2,441	**Maternal food consumption during the eighth month of pregnancy** (continuous):		
					Copper	HR	1.00 (0.71-1.41)
					Magnesium	HR	0.91 (0.59-1.41)
					Selenium	HR	1.37 (0.89-2.11)
					Zinc	HR	1.15 (0.77-1.72)
					Folate	HR	1.04 (0.71-1.52)
					Vitamin A	HR	1.20 (0.92-1.56)
					Vitamin B2	HR	1.07 (0.82-1.40)
					Vitamin C	HR	0.92 (0.69-1.22)
					Vitamin E	HR	1.02 (0.71-1.47)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
Ohya, 2011 (56)	PC	Rec wheeze	1.5, 3	1463	Iron and folic acid (unclear measure of comparison) /		NS
					Maternal intake during pregnancy (highest vs lowest quartile)		
				318	Zinc, vitamin A, vitamin E	OR	NS
West, 2012 (57)	PC	Wheeze	1	306	Vitamin C supplementation (yes/no)	OR	**0.40 (0.16-0.98)**
			3.5	490	Folic acid [Maternal intake during pregnancy] <16 weeks gestation: <100 µg/d vs. 100 µg/d	RR	1.15 (0.82-1.61)
			3.5	490	µg /day at 30-34 weeks gestation [late pregnancy] vs. early pregnancy	RR	1.32 (1.14-1.53)
Whitrow, 2009 (31)	PC	Rec wheeze	5.5	423	[Maternal intake at 30-34 weeks gestation] µg /day at 30-34 weeks gestation [early vs. late pregnancy]	RR	1.38 (1.06-1.79)

6. Infant or maternal dietary intake of vitamins and minerals and risk of allergic rhino-conjunctivitis

Eleven observational studies investigated the association between allergic rhino-conjunctivitis in relation to intake of vitamins or minerals. The assessment of risk of bias in these studies showed that all studies included some form of adjustment for confounders. Several studies were considered to have a high risk of assessment or selection bias which contributed to over two thirds of them to be considered to have a high overall risk of bias (Figure 46). Of the two intervention trials identified, one had high attrition bias (Figure 47).

Figure 46 Risk of bias in studies of vitamin and mineral intake and rhino-conjunctivitis

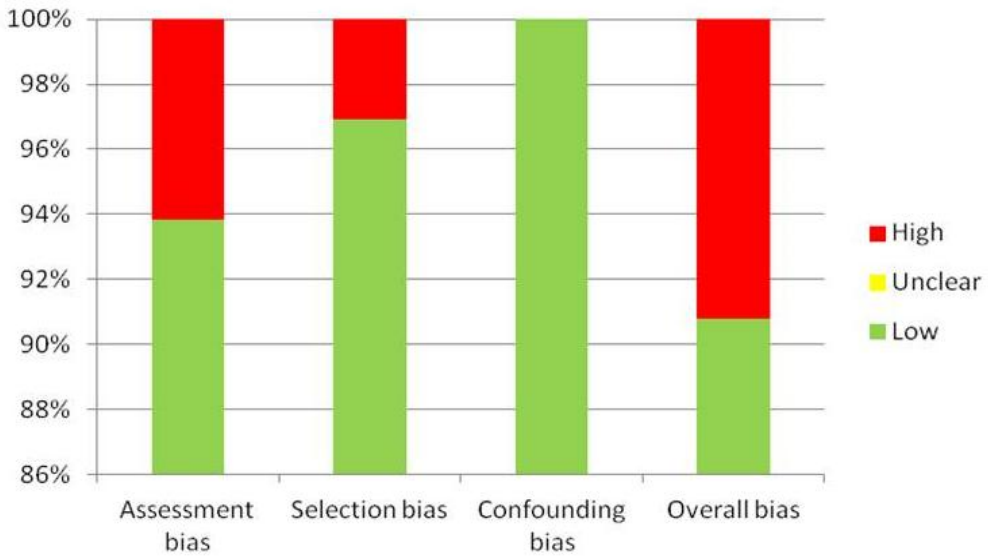
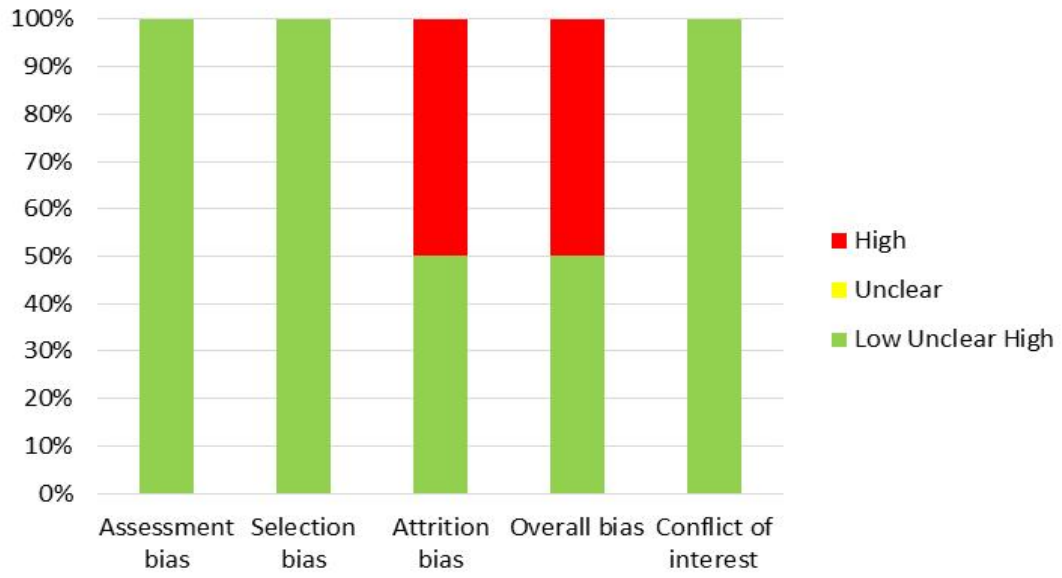


Figure 47 Risk of bias in intervention studies of vitamin and mineral intake and rhino-conjunctivitis



6.1. Intervention studies with data eligible for meta-analysis

We found no intervention studies with data eligible for meta-analysis

6.2. Observational studies with data eligible for meta-analysis

We found no observational studies with data eligible for meta-analysis

6.3. Studies on vitamin and mineral intake and rhino-conjunctivitis which were not eligible for meta-analysis

The main findings of the studies which investigated the association between the relevant exposures and rhino-conjunctivitis are summarised in Table 7. The majority of the studies investigated varying vitamin D intake or serum levels, with one observational study investigating micro-nutrients (**Nwaru 2011**).

The RCT of **Goldring (2013)** examined the effect of vitamin D supplementation during pregnancy and the risk of RC at age 3 years. They found no evidence of an effect. The RCT of **Devakumar (2015)** reported no significant difference in prevalence of RC between

children of women allocated multivitamins during pregnancy, and a control group – numerical data were not reported.

The observational studies of **Baiz (2013)**, **Maslova (2013)**, **Wills (2013)** and **Rother (2011)** showed no evidence of an association between Vitamin D and risk of RC assessed at ages 3 to 7 years of age. The study of **Hypponen (2004)** found no association between infant vitamin D supplementation and risk of adult RC (age 31 years old). In the cohort study of **Erkkola (2009)**, the authors found a negative association between maternal dietary intake of vitamin D in the last trimester and risk of RC at age 5 years. This association was not observed when vitamin D was combined with intake from supplements. There were no other significant associations in relation to other vitamins or minerals and RC.

Overall, we found no evidence to suggest that infant or maternal intake of vitamins or minerals influences the risk of RC.

Table 7 Observational studies investigating the association between vitamins and minerals and rhino-conjunctivitis which were not eligible for meta-analysis

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					INFANT INTAKE AND CORD BLOOD		
					Plasma level of 25(OH)D measured in cord blood specimens (nml/L)		
					50-74.9 vs. < 50	OR	0.91 (0.36-2.31)
Rothers, 2011 (34)	PC	RC	5	192	75-99.9 vs 50-74.9	OR	0.60 (0.20-1.80)
Back, 2009 (20)	PC	RC	5-14	123	Infant vitamin intake (highest vs. lowest)	OR	1.67 (0.6-4.61)
Baiz, 2013 (29)	PC	RC	5	239	Cord blood vitamin D (infant-1st year-blood) in ng/ml (continuous)	OR	0.99 (0.71-1.38)
Hypponen, 2004 (44)	PC	RC	31	6722	Infant vitamin D supplementation in the first year of life – daily dose / 2000 IU vs <2000 IU	OR	1.34 (0.71-2.53)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					MATERNAL INTAKE OR BLOOD LEVELS		
Goldring, 2013(11)	RCT	RC	3	120/60	Pregnant women. Single oral bolus of 200,000 IU vitamin D (cholecalciferol) at 27 weeks gestation, or daily 800IU vitamin D (ergocalciferol) from 27 weeks to delivery, versus no treatment	RR	0.76 (0.31, 1.85)
Rothers, 2011 (34)	PC	RC	5	192	Maternal vitamin D supplements and risk of rhino-conjunctivitis (high vs. lowest)	OR	2.41 (0.79-7.37)
Devereux, 2006 (16)	PC	RC	5	1704	Maternal and children's dietary and supplement intakes summated to give total nutrient intake [lowest vs. highest quintile]: Copper, Iron, magnesium, b-carotene, vitamin C	OR	NS
Erkkola, 2009 (23)	PC	RC	5	1669	Vitamin D intake in pregnancy (8th month) in µg/MJ: from food (diet)	HR	**0.85 (0.75-0.96)**

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					Maternal diet and supplements	HR	0.90 (0.79-1.02)
Erkkola, 2009 (23)	PC	RC	5	1,669	Q4 (>0.54) vs Q2 and Q3 (0.31-0.54)	HR	0.98 (0.70-1.37)
					Q2 and Q3 (0.31-0.54) vs. Q1 (<0.3)	HR	1.53 (1.14-2.06)
					Maternal vitamin D intake in pregnancy from food (in quintiles; µg/d) Q 3 (11.7, 9.9-12.3) vs Q1 (5.5, 1.8-7.1)	RR	0.90 (0.76-1.07)
					Q2 (8.2, 7.3-9.4) vs Q1 (5.5, 1.8-7.1)	RR	0.91 (0.77-1.07)
Maslova, 2013 (22)	PC	RC	7	28,545	Q 4 (13.0, 12.4-14.0) vs Q 1 (5.5, 1.8-7.1)	RR	1.05 (0.90-1.23)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					Maternal vitamin D intake in pregnancy from supplements (in quintiles; µg/d)		
					Q3 (11.7, 9.9-12.3) vs Q1 (5.5, 1.8-7.1)	RR	0.96 (0.73-1.27)
					Q 4 (13.0, 12.4-14.0) vs Q1 (5.5, 1.8-7.1)	RR	1.06 (0.89-1.26)
Maslova, 2013 (22)	PC	RC	7	28,545	Q 2 (8.2, 7.3-9.4) vs Q1 (5.5, 1.8-7.1)	RR	1.12 (0.94-1.33)
					Total maternal vitamin D intake during pregnancy (in quintiles; µg/d)		
					Q5 (16.5, 14.2-27.4) vs Q1 (5.5, 1.8-7.1)	RR	1.00 (0.84-1.19)
					Q 3 (11.7, 9.9-12.3) vs Q 1 (5.5, 1.8-7.1)	RR	1.01 (0.86-1.19)
					Q 4 (13.0, 12.4-14.0) vs Q1 (5.5, 1.8-7.1)	RR	1.02 (0.86-1.21)
					Q2 (8.2, 7.3-9.4) vs Q 1 (5.5, 1.8-7.1)	RR	1.05 (0.88-1.25)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					Maternal serum vitamin D in pregnancy (quintiles; nmol/L)/		
					Q4 (67-89) vs Q1 (min -38)	OR	0.95 (0.67-1.35)
Wills, 2013(18)	PC	RC	7.5	4,673	Q 2 (38-52) vs Q1 (min -38)	OR	1.10 (0.79-1.54)
					Q 3 (52-67) vs Q1 (min -38)	OR	1.23 (0.89-1.70)
					Maternal food consumption during the eighth month of pregnancy		
Nwaru, 2011 (24)	PC	RC	5	2,441	Copper, magnesium, selenium, zinc, folate, Vitamins A, B2, C, E	HR	NS

7. Infant or maternal dietary intake of vitamins and minerals and risk of allergic sensitisation (AS)

Eighteen studies investigated the association between intake of vitamins or minerals and risk of AS in childhood. Overall, the observational studies were almost all considered to have a low or unclear risk of bias. Most of the studies included some form of adjustment for confounders and therefore were considered to be of low risk in this domain. Some studies had unclear information about the methods of sample selection and assessment, therefore over half of the studies were considered to have an unclear overall risk of bias (Figure 48); of the six intervention trials, two had a high risk of bias due to high loss to follow up (Figure 49).

Figure 48 Risk of Bias in observational studies of vitamin and mineral intake and allergic sensitisation

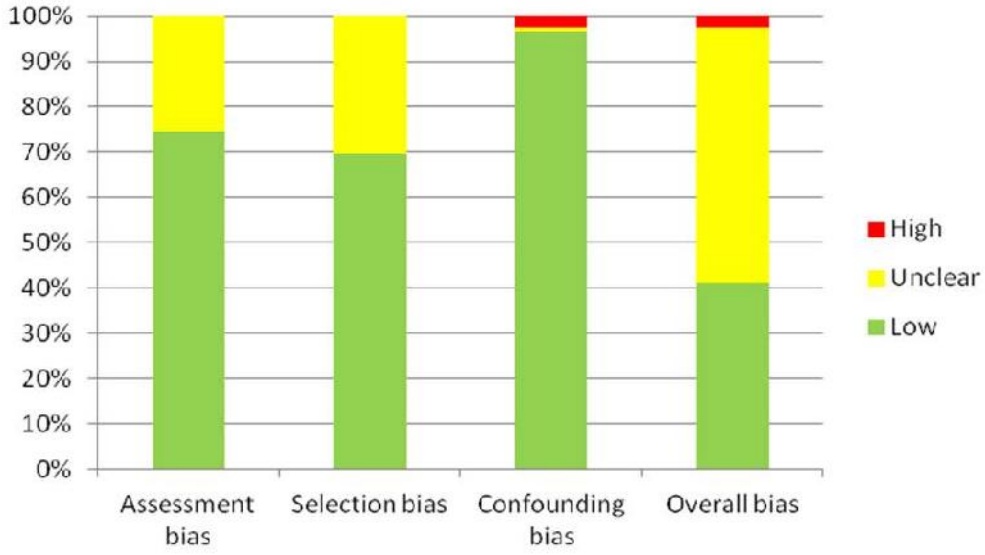
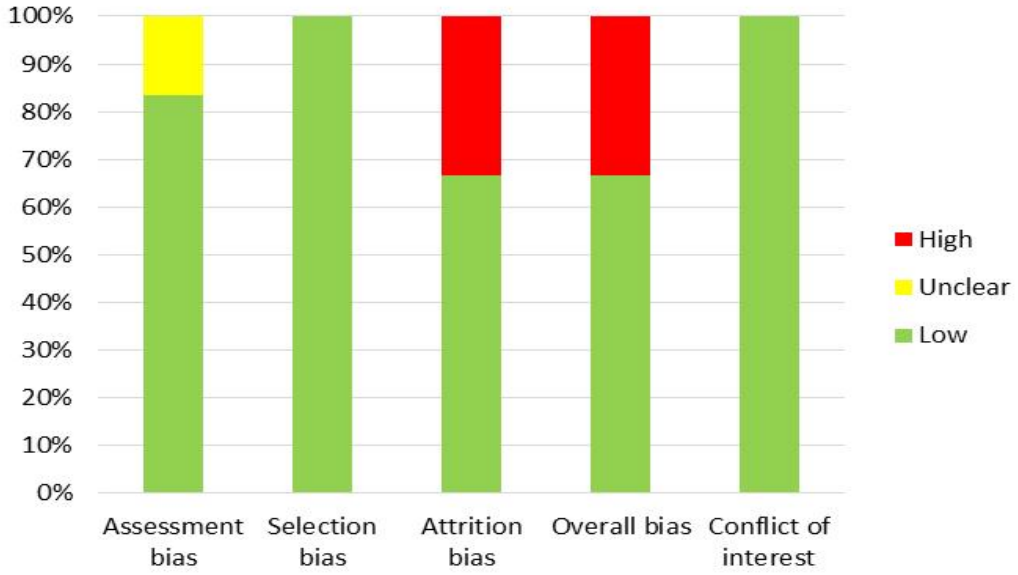


Figure 49 Risk of Bias in intervention trials of vitamins/minerals and allergic sensitisation



7.1. Intervention studies

Six intervention studies with data eligible for meta-analysis were identified. These studies demonstrated no significant effect of vitamin supplementation during pregnancy/infancy and risk of AS (**Aage 2015; Chawes 2016; Litonjua 2016**) (Figure 50) and specifically AS to aero allergens (**Kiraly 2013; Grant 2016; Goldring 2013**) (Figure 51).

Figure 50 Vitamin supplementation during pregnancy/infancy and risk of AS

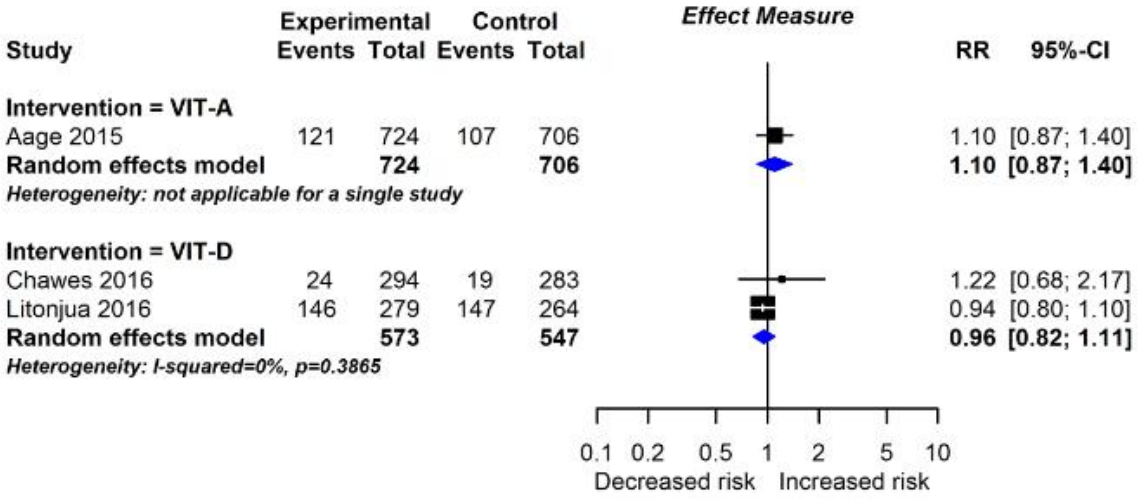
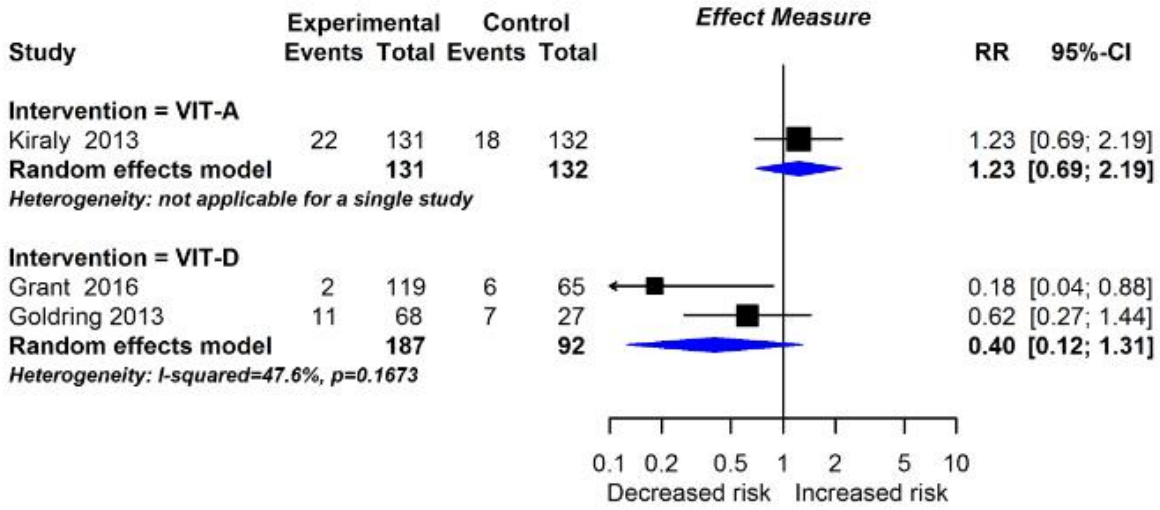


Figure 51 Vitamin supplementation during pregnancy/infancy and risk of AS to aero allergens



7.2. Observational studies with data eligible for meta-analysis

We found no observational studies with data eligible for meta-analysis

7.3. Studies on vitamin and mineral intake and allergic sensitisation which were not eligible for meta-analysis

The main findings of observational studies investigating the relationship between vitamins or minerals with AS, are presented in Table 8. The outcomes studied included specific and total IgE levels, as well as SPT. Maternal vitamin D and folic acid intake or blood levels were the commonest dietary exposures studied.

The cohort study of **Rothers (2011)** in the Tucson Infant Immune Study found that both low and high levels of cord blood vitamin D were associated with increased aeroallergen sensitization. Relative to the reference group (50-74.9 nmol/L), both low (<50 nmol/L) and high (≥ 100 nmol/L) levels were associated with increased total IgE, and detectable inhalant allergen-specific IgE at age 5 years. High cord blood levels of vitamin D were also associated with increased SPT positivity in these children. In the LINA cohort study (Lifestyle and environmental factors and their Influence on Newborns Allergy risk), **Weisse** and colleagues **(2012)** found that higher maternal blood levels of vitamin D were associated with a higher risk for sensitization against food allergens at age 2 years. The studies of **Nwaru (2010)**, **Hypponen (2004)**, **Jones (2012)** and **Pike (2012)** on maternal intake of vitamin D showed no evidence of an association with outcomes of AS.

Overall, we found no consistent evidence that minerals or vitamins are associated with risk of allergic sensitisation. We found conflicting evidence on the role of vitamin D on allergic sensitisation, which is insufficient to draw conclusions.

Table 8 Studies investigating the association between vitamins and minerals and allergic sensitization which were not eligible for meta-analysis

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					INFANT INTAKE OR CORD BLOOD LEVELS		
		SPT aero	31	4,400	Infant vitamin D supplementation in 1st year of life 2000 IU <2000 IU	OR	1.02 (0.45-2.29)
		AS any	31	4,400	Infant vitamin D intake (highest vs. lowest)	OR	**1.28 (1.06-1.56)**
Hypponen, 2004 (44)	PC	AS any	31	4,400	Infant vitamin D intake (often vs. rare)	OR	1.04 (0.75-1.45)
Jones, 2012 (59)	RC	AS	1	217	Cord blood 25(OH)D3 in nmol/L (continuous)		1.00 (0.99-1.01)
Liu, 2011(21)	PC	AS peanut	Any	123	Cord blood vitamin D (highest vs. lowest)	OR	0.55 (0.15-2.02)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					MATERNAL INTAKE OR BLOOD LEVELS		
Pike, 2012 (54)	PC	SPT any	1	635	Total energy-adjusted daily maternal vitamin D intake during pregnancy / Q3 vs Q1	RR	**1.39 (1.15-1.67)**
					Maternal serum 25(OH)D status at 34 weeks pregnancy in nmol/L (continuous)	RR	0.96 (0.89-1.03)
					Average total daily vitamin D intake during pregnancy in mcg/day (continuous)	RR	0.33 (0.10-1.07)
					Total energy-adjusted daily maternal vitamin D intake during pregnancy /Q3 vs Q1	RR	0.69 (0.43-1.11)
					Total energy-adjusted daily maternal vitamin D intake during pregnancy / Q2 vs Q1	RR	0.86 (0.53-1.40)
		SPT any	6	635	Average maternal daily vitamin D intake from FOOD during pregnancy in mcg/day (continuous)	RR	1.03 (0.95-1.12)
		AS	3	635	Maternal plasma 25(OH)D (pregnancy)	RR	0.99 (0.94-1.04)
		AS	6	635	Maternal plasma 25(OH)D (pregnancy)	RR	0.99 (0.94-1.04)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					Plasma level of 25(OH)D measured in cord blood specimens [nmol/L]:		
			2	207	50-74.9 vs. < 50	OR	0.63 (0.19-2.03)
			5	207	50-74.9 vs. < 50	OR	0.50 (0.19-1.30)
			3	207	50-74.9 vs. < 50	OR	0.38 (0.14-1.07)
Rothers, 2011 (28)	PC	sIgE aero	5	208	50-74.9 vs. < 50	OR	**0.36 (0.15-0.84)**
			1	207	50-74.9 vs. < 50	OR	0.26 (0.05-1.50)
			2	207	75-99.9 vs 50-74.9	OR	0.50 (0.10-2.50)
			1	207	75-99.9 vs 50-74.9	OR	0.90 (0.08-10.2)
			3	207	50-74.9 vs 75-99.9	OR	1.90 (0.64-5.6)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					Plasma level of 25(OH)D measured in cord blood specimens [nmol/L]:		
			5	208	75-99.9 vs 50-74.9	OR	2.10 (0.94-4.7)
			5	207	≥ 100 vs 50-74.9	OR	2.80 (0.75-10.5)
			5	207	75-99.9 vs 50-74.9	OR	**3.00 (1.13-8.0)**
Rothers, 2011 (28)	PC	sIgE aero	2	207	≥ 100 vs 50-74.9	OR	**4.70 (1.33-16.6)**
			1	207	≥ 100 vs 50-74.9	OR	**2.02 (1.23-3.32)**
			5	208	≥100 vs 50-74.9	OR	0.86 (0.61-1.21)
			5	172	50-74.9 vs. < 50	OR	0.83 (0.37-1.88)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					Plasma level of 25(OH)D measured in cord blood specimens [nmol/L]/		
		SPT aero	5	172	75-99.9 vs 50-74	OR	2.00 (0.89-4.50)
		Total-IgE	5	207	50-74.9 vs. < 50	β-coeff	NS
Rothers, 2011 (34)	PC	Total-IgE	5	207	75-99.9 vs 50-74	β-coeff	NS
			2	191	Maternal serum 25(OH)D levels at 34 weeks gestation (unclear if continuous or categorical)	OR	0.97 (0.69-1.36)
Weisse, 2012 (41)	PC		1	184	Maternal serum 25(OH)D levels at 34 weeks gestation (unclear if continuous or categorical)	OR	1.06 (0.76-1.47)
			1	184	Cord blood 25(OH)D levels (unclear if continuous or categorical)	OR	1.07 (0.74-1.54)
		Total-IgE	2	191	Cord blood 25(OH)D levels (unclear if continuous or categorical)	OR	1.07 (0.72-1.58)
		sIgE any	1	184	Maternal serum 25(OH)D levels at 34 weeks gestation	OR	0.90 (0.61-1.32)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
Weisse, 2012 (41)	PC	sIgE any	2	191	Maternal serum 25(OH)D levels at 34 weeks gestation	OR	**1.59 (1.03-2.45)**
			1	184	Cord blood 25(OH)D levels	OR	0.76 (0.49-1.18)
			2	191	Cord blood 25(OH)D levels	OR	1.60 (1.00-2.57)
Jones, 2012 (59)	RC	AS	1	146	Maternal vitamin D intake (supplementation during pregnancy) in IU (continuous)	OR	0.98 (0.90-1.07)
Goldring, 2013(11)	RCT	SPT any Total IgE	3	60/60	Pregnant women. Single oral bolus of 200,000 IU vitamin D (cholecalciferol) at 27 weeks of gestation, or daily 800IU vitamin D (ergocalciferol) from 27 weeks to delivery, or a combination of both, versus no treatment.	OR	NS
Bekkers, 2012 (51)	PC	sIgE any	8	3786	Maternal intake of specific vitamin or mineral supplements during pregnancy, including folic acid, multivitamin and vitamin B complex supplements (yes vs no)		
					Folic acid, multivitamins, vitamins B	OR	NS
					Multivitamins	OR	NS

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
			8	5368	Mothers dietary folate intake at 32 weeks gestation (yes vs no)	OR	0.98 (0.87-1.10)
Granell, 2008 (19)	PC	AS-Any	8	5368	Maternal folic acid supplementation (highest vs. lowest)	OR	**1.65 (1.07-2.54)**
Hoppu, 2000 (33)	PC	AS	Any		Maternal vitamin C intake (highest vs. lowest)	OR	0.84 (0.54 - 1.3)
Magdelijns, 2011 (39)	PC	Total-IgE	2	2465	Folic acid supplementation before or during pregnancy (questionnaire completed in weeks 14 and 34 of gestation) (use vs no use)	OR	0.72 (0.46-1.12)
Nwaru, 2010 (26)	PC	AS	5	931	Maternal consumption during t8th month pregnancy (continuous):		
					Copper mg/d	OR	1.12 (0.42-3.01)
					Zinc mg/d	OR	0.53 (0.17-1.63)
					Vitamin C mg/d	OR	1.25 (0.89-1.76)
					Vitamin D µg/day	OR	0.76 (0.49-1.17)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					Maternal consumption during t8th month pregnancy (continuous):		
					Vitamin E mg /d	OR	1.97 (0.91-4.26)
Nwaru, 2010 (26)	PC	AS	5	931	Iron - mg/day	OR	1.37 (0.54-3.49)
Devereux, 2006 (16)	PC	SPT any	5	1704	Maternal and children's dietary and supplement intakes were summated to give total nutrient intake (highest vs lowest quintile) Copper, Iron, magnesium, vitamin C	OR	NS
Nwaru, 2010 (26)	PC	AS	5	931	Maternal intake of vitamin A -µ/day	OR	0.22 (0.04-1.33)
Nwaru, 2011 (25)	PC	sIgE to cow's milk	5	652	Maternal intake during 2nd and 3rd month of breastfeeding (g/day increase in intake) Copper	OR	1.20 (0.82-1.75)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					Maternal intake during 2nd and 3rd month of breastfeeding (g/day increase in intake)		
					Selenium	OR	1.05 (0.68-1.62)
Nwaru, 2011 (25)	PC	sIgE to cow's milk	5	652	Zinc	OR	1.05 (0.73-1.51)
					Vitamin C	OR	1.11 (0.84-1.47)
					Vitamin E	OR	0.76 (0.44-1.30)
					Vitamin D	OR	1.05 (0.76-1.45)
					Maternal intake during 2nd and 3rd month of breastfeeding (g/day):		
Nwaru, 2011 (25)	PC	sIg E to egg	5	652	Copper	OR	0.87 (0.54-1.40)
					Selenium	OR	1.07 (0.68-1.68)

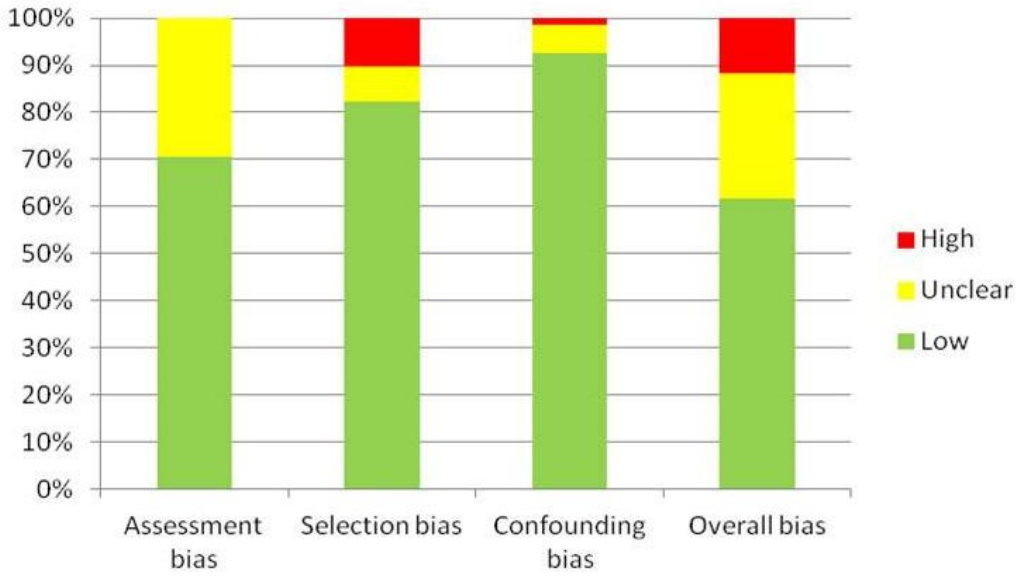
First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					Maternal intake during 2nd and 3rd month of breastfeeding (g/day):		
					Zinc	OR	0.93 (0.63-1.38)
					Vitamin C	OR	1.08 (0.82-1.42)
Nwaru, 2011 (25)	PC	sIg E to egg	5	652	Vitamin E	OR	0.81 (0.43-1.52)
					Vitamin D	OR	0.87 (0.61-1.25)
					Iron	OR	1.17 (0.88-1.55)
					Maternal intake 8th month of pregnancy / mean daily consumption (continuous)		
					Copper	OR	1.21 (0.40-3.69)
Nwaru, 2010 (26)	PC	AS	5	931	Zinc	OR	0.92 (0.25-3.37)
					Vitamin C	OR	0.83 (0.56-1.22)
					Vitamin D	OR	**0.56 (0.34-0.91)**

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					Maternal intake 8th month of pregnancy / mean daily consumption (continuous)		
					Vitamin E	OR	0.62 (0.25-1.52)
Nwaru, 2010 (26)	PC	AS	5	931	Iron	OR	1.47 (0.51-4.23)
					Vitamin A	OR	0.84 (0.56-1.27)
					Maternal vitamin intake during pregnancy:		
				307	Vitamin C	OR	0.76 (0.35-1.67)
West, 2012 (57)	PC	SPT any	1	311	Vitamin E	OR	0.64 (0.29-1.41)
		AS aero	any		Vitamin D	OR	1.54 (1.02-2.28)
					Maternal serum vitamin D in pregnancy (quintiles; nmol/L)		
West, 2012 (60)	PC	SPT aero	7.5	3652	Q4 (67-89) vs Q1 (min -38)	OR	0.92 (0.71-1.19)
					Q3 (52-67) vs Q1 (min -38)	OR	0.95 (0.73-1.24)
		SPT aero	7.5	3652	Q2 (38-52 vs Q1 (min -38)	OR	0.96 (0.74-1.25)

8. Infant or maternal dietary intake of vitamins and minerals and risk of type 1 diabetes mellitus (T1DM)

Nineteen observational studies and no intervention trials investigated the association between vitamin or mineral intake and risk of T1DM in childhood. These studies were considered to have a low risk of bias across most domains. Over 60% of the studies had a low overall risk of bias, due to appropriate account for assessment, sample selection and confounding (Figure 52).

Figure 52 Risk of Bias in studies of vitamin and mineral intake and type I diabetes mellitus



8.1. Intervention studies with data eligible for meta-analysis

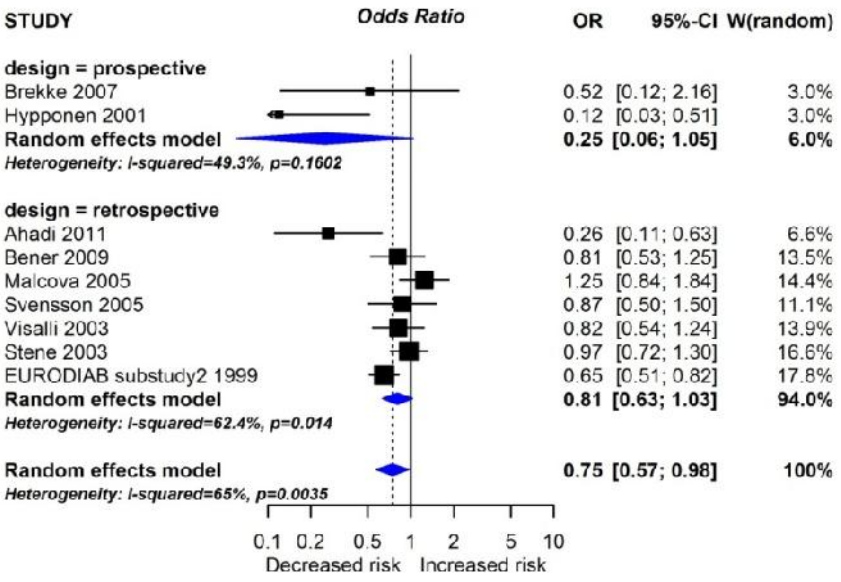
We identified no intervention studies for vitamin/mineral supplementation and TIDM.

8.2. Observational studies with data eligible for meta-analysis

Data from nine observational studies examining the association between T1DM and vitamin D were suitable for meta-analysis.

Seven case control studies and two prospective cohort studies (**Brekke 2007,** and **Hypponen 2001**) investigated the relationship of infant dietary intake of vitamin D and T1DM (Figure 53). The study of **Bekker (2007)** showed that use of supplements containing vitamin D, amongst other nutrients, during pregnancy was associated with reduced diabetes-related autoimmunity at 1 year of age, but not at 2.5 years old. The prospective cohort study of **Hypponen (2001)** showed that infant vitamin D supplementation was associated with a decreased frequency of T1DM (at age 30 years) when adjusted for neonatal, anthropometric, and social characteristics (rate ratio [RR] for regular vs no supplementation 0.12, 95% CI 0.03-0.51, and irregular vs no supplementation 0.16, 0.04-0.74). Children who regularly took the recommended dose of vitamin D (2000 IU daily) also had a reduced risk of T1DM compared with those who regularly received less than the recommended amount. The combined effect of these prospective cohorts was not statistically significant; the pooled effect of the seven retrospective studies also failed to reach statistical significance. Both analyses had significant statistical heterogeneity. When retrospective and prospective study data were pooled, which may not be appropriate due to differences in study design, the pooled association was statistically significant, but with high heterogeneity across studies (I^2=62.4%). The evidence for an association between infant vitamin D supplementation and risk of TIDM was downgraded -1 for inconsistency and -1 for imprecision leading to no conclusive evidence of an association.

Figure 53 Infant vitamin D supplementation (often vs. rare) and risk of type 1 diabetes mellitus in children



In the DAISY cohort study, **Fronczak (2003)** showed that maternal intake of vitamin D from diet was significantly associated with a decreased risk of islet auto-immunity appearance in offspring, independent of related factors such as family history of T1DM, presence of gestational diabetes mellitus, and ethnicity. The study of **Stene (2003)** found no evidence of an association between vitamin D intake and risk of T1DM. There was no evidence to suggest that maternal supplement use or plasma levels of vitamin D is associated with risk of T1DM in the offspring (Figures 53 to 56).

Figure 54 Maternal vitamin D intake (highest vs. lowest) and risk of type 1 diabetes mellitus in children at (any age)

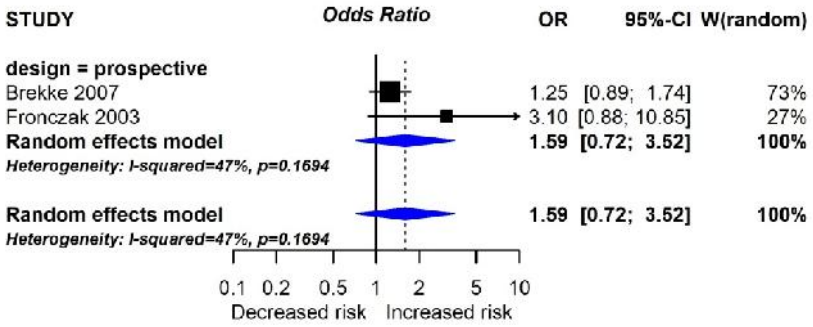


Figure 55 Maternal vitamin D supplement use (often vs. rare) and risk of type 1 diabetes mellitus in children (at any age)

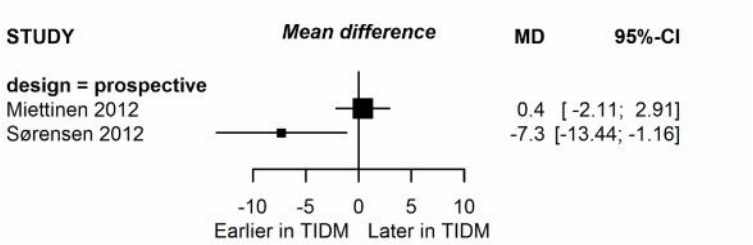
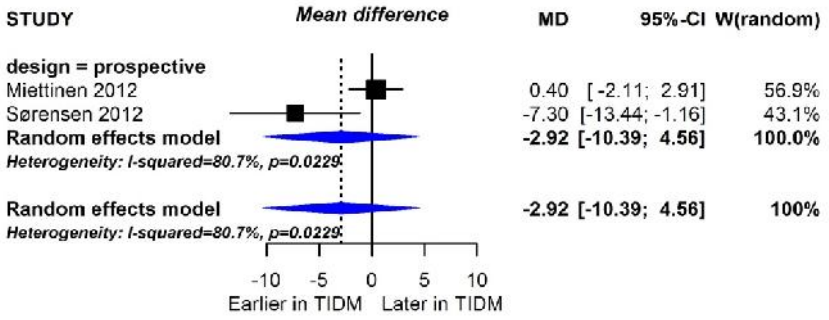


Figure 56 Maternal plasma vitamin D (mean difference) and risk of T1DM in children (at any age)



8.3. Studies on vitamin and mineral intake and T1DM which were not eligible for meta-analysis

We identified seven studies which investigated the association between various minerals and vitamins with outcomes of T1DM (Table 9). Most of the studies investigated vitamin D. The study of **Mettienen (2012)** measured serum levels of vitamin D in the first trimester of pregnancy and reported no association with risk of T1DM at age 3 years. The case-control study of **Sorensen (2012)** nested in a cohort of 29,000 Norwegian women measured serum levels of vitamin D in late pregnancy of 109 mothers with a child diagnosed with T1DM (before 15 years old) and 209 controls. Dividing the levels of maternal vitamin D into quartiles, there was a trend (although not completely linear) toward a higher risk of T1DM with lower levels of vitamin D during pregnancy. The odds of T1DM were more than twofold higher for the offspring of women with the lowest levels of vitamin D compared with the offspring of those with levels above the upper quartile. No other associations of relevance were observed.

Overall, we found no consistent evidence to suggest that infant or maternal intake of vitamins or minerals influences the risk of T1DM in the offspring.

Table 9 Studies investigating the association between vitamins and minerals and type I diabetes mellitus which were not eligible for meta-analysis

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					INFANT INTAKE OR BLOOD LEVEL		
Simpson, 2011 (67)	NCC	DM	9	128/30	Infant serum vitamin D level	HR	1.16 (0.70-1.93)
					MATERNAL INTAKE OR BLOOD LEVEL		
Uusitalo, 2008 (28)	PC	TIDM	9	3730	**Dietary intake during pregnancy** [HR is change in risk per 2-fold increase in intake, from foods plus supplements]:		
					Manganese	HR	1.03 (0.76-1.40)
					Selenium	HR	1.11 (0.75-1.64)
					Vitamin C	HR	0.96 (0.79-1.17)
					Vitamin E	HR	1.06 (0.75-1.49)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					VIT D/Maternal intake in 8th month of pregnancy [quartiles] :		
					From food Q4 vs. Q1	HR	1.17 (0.73-1.90)
		Advanced β-cell T1DM			Q3 vs. Q 1	HR	1.12 (0.69-1.82)
					Q2 vs. Q1	HR	0.74 (0.44-1.25)
Marjamaki, 2010 (27)					Total vitamin D intake (food and supplements)	HR	1.26 (0.92-1.73)
					Vitamin D from supplements	HR	1.05 (0.95-1.16)
	PC	Clinical T1DM alone	1-8y	3723	Q4 vs. Q1	HR	0.77 (0.35-1.72)
					Q3 vs. Q1	HR	0.84 (0.38-1.83)
					Q2 vs. Q1	HR	1.00 (0.48-2.11)
					Total vitamin D intake (food and supplements)	HR	1.08 (0.65-1.79)
					Vitamin D from supplements	HR	1.09 (0.99-1.20)

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
Miettinen, 2012 (69)	NCC	TIDM	3.4	686	Maternal plasma 25(OH)D levels in 1st trimester of pregnancy	OR	NS
Ashraf, 2010 (71)	CC	TIDM	1-10	195/128	Specific nutrient exposures (mother or child)	OR per SD [=540mg over 4 months] increase in exposure	NS
Stene, 2003 (78)	CC	TIDM	<15	1058	Yes vs no vitamin D supplementation during 1st year of life	OR	0.82 (0.47 -1.42)

9. Infant or maternal dietary intake of vitamins and minerals and risk of inflammatory bowel disease (IBD)

A single case control study reported infant or maternal intake of vitamins and minerals and risk of inflammatory bowel disease: the international multi-centric case-control study of **Gilat (1987)** investigated the association between risk of IBD in cases with Crohn's Disease (CD) or ulcerative colitis (UC) and use of maternal multivitamin supplements, compared to controls. The assessment of bias risk was considered unclear overall, due to lack of information on assessment and selection bias (Figure 57).

Mothers of patients with UC and CD took vitamin, mineral, and iron preparations during pregnancy significantly less frequently than mothers of controls. The authors reported that multivitamin supplementation during pregnancy was negatively associated with risk of IBD in children. We did not consider data from a single case-control study to be sufficient quality or quantity to be classed as evidence for association, and further work is needed to test the hypothesis that vitamin supplementation during pregnancy influences risk of IBD.

Overall we found no consistent evidence that maternal vitamin supplementation during pregnancy is associated with reduced UC and Crohn's disease.

Figure 57 Risk of bias in study of vitamin and mineral intake and IBD

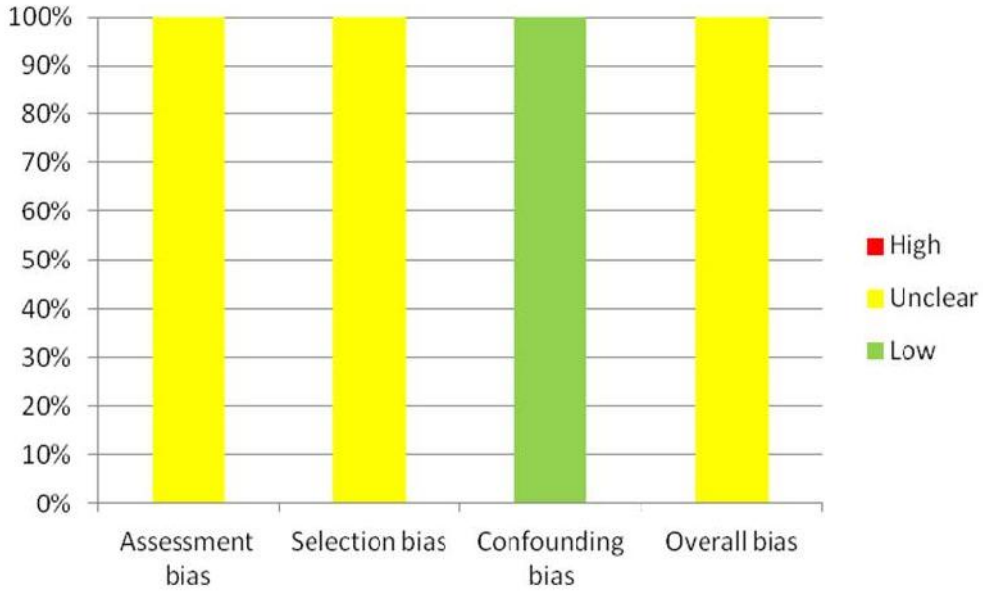


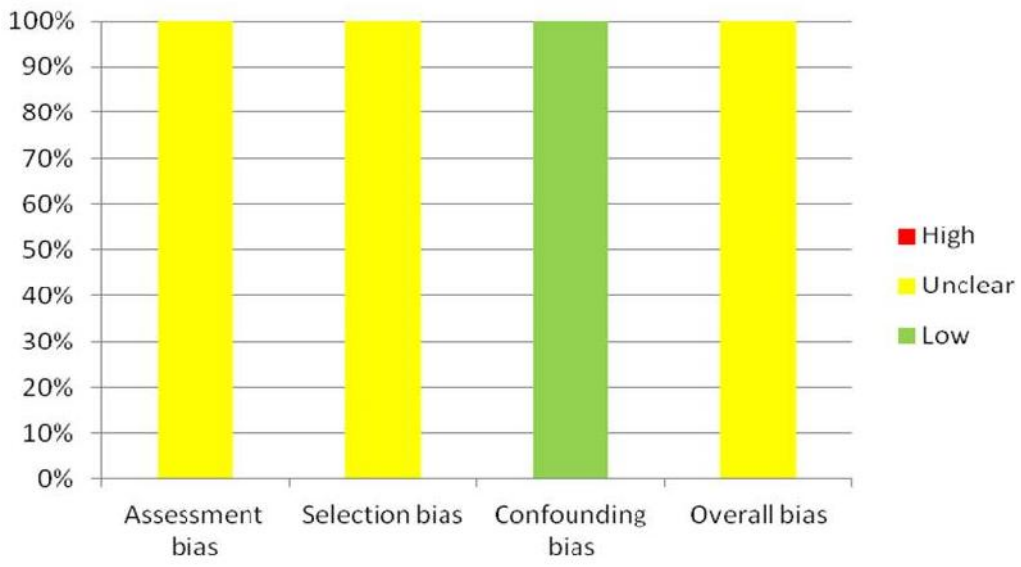
Table 10 Studies investigating the association between vitamins and minerals and inflammatory bowel disease which were not eligible for meta-analysis

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Association (bold indicates p-value <0.05)
Gilat,1987 (81)	CC	IBD	Any	167/ 337	Maternal multivitamin supplementation and risk of inflammatory bowel disease-CD) in children (often vs. rare)	OR	**0.46 (0.26-0.81)**
				128/ 251	Maternal multivitamin supplementation and risk of irritable bowel disease-UC in children (often vs. rare)	OR	**0.49 (0.25-0.99)**

10. Infant or maternal dietary intake of vitamins and minerals and risk juvenile idiopathic arthritis (JIA)

The Childhood Arthritis Risk factor Identification study (CLARITY) was set up in Australia to investigate genetic and environmental risk factors for JIA **(Ellis 2012)** in children <18 years old. In this case-control study, the authors report some of the risk factors found in the first three years of the study. The overall risk of bias was considered to be unclear (Figure 58).

Figure 58 Risk of Bias in studies of vitamin and mineral intake and JIA



Amongst the early life risk factors investigated, use of vitamin D during pregnancy was lower in case mothers (less frequent); however, these associations were not significant after adjusting for potential confounders (Table 11). There was also no evidence of difference in risk of JIA by use of maternal supplementation of folic acid, multivitamins, or calcium.

Table 11 Studies investigating the association between vitamins and minerals and juvenile idiopathic which were not eligible for meta-analysis

First Author and year of publication	Design	Outcome	Age	N/n	Dietary exposure and comparison level	Measure of association	Effect (bold indicates p-value <0.05)
					Maternal supplementation of: Iron (often vs. rare)	OR	0.82 (0.59-1.14)
					Folic acid (often vs. rare)	OR	0.82 (0.59-1.14)
					Multivitamin (often vs. rare)	OR	0.76 (0.52-1.1)
					Calcium (often vs. rare)	OR	0.61 (0.36- 1.04)
Ellis, 2012 (72)	CC	JIA	<18 years	262/458	Vitamin D (often vs. rare)	OR	0.26 (0.03-2.11)

CONCLUSION

In this systematic review of maternal and infant intake of vitamins and minerals, we found some evidence to support associations with respiratory outcomes from intervention trials, but no consistent evidence to suggest that these nutrients are related to allergic or autoimmune diseases in observational studies.

In one intervention trials there was an association between maternal vitamin A supplementation during pregnancy and increased childhood lung function, however this was not consistent with findings in another similar trial, in the same trial using another form of vitamin A (beta-carotene), or with clinical outcomes. Trials of vitamin D and risk of recurrent wheeze showed unexplained,, high heterogeneity, but overall showed no evidence of an effect.The large variations in the intake levels and the measures used to evaluate them in comparisons limited our ability to carry out meta-analyses in observational studies. However, the majority of the findings suggested that there was no association between vitamins and minerals with allergic and autoimmune outcomes.

The most common nutrients studied were vitamin D and folic acid, as well as vitamins C, E, and A, and minerals zinc and copper. With regards to vitamin D, several studies suggested that a higher intake or higher concentrations in maternal or cord blood were related to a reduced risk of atopic dermatitis, wheeze, and rhino conjunctivitis, whereas others found a positive association between increasing intake/levels of vitamin D and risk of disease. These conflicting findings may partly be explained by the various study designs and exposure and outcome assessment strategies employed in the epidemiologic studies conducted to date. In observational studies where meta-analysis was possible, we found no evidence that maternal intake of vitamin D supplements or vitamin A intake was associated with allergic or autoimmune outcomes.

We found some evidence from observational studies that infant dietary intake of vitamin D supplements was associated with a reduced risk of T1DM later in childhood, however this was downgraded for inconsistency and imprecision to no consistent evidence. Maternal dietary intake or blood levels of this vitamin were unrelated to TIDM risk. The results of our meta-analysis are in agreement with those reported in the systematic review by **Dong** *et al* (**2013**) both with regards to the lack of association between maternal intake of vitamin D and

risk of T1DM. Dong reported an association between infant vitamin D supplementation/intake and reduced TIDM (82). A more extensive systematic review by **Harvey** *et al* **(2014)** concluded that there was no evidence to support a relationship between maternal 25(OH)D status and asthma, atopy or T1DM in children, consistent with our conclusions (83). The authors also highlighted that the current evidence is limited by the observational nature of the majority of the relevant studies. We found VERY LOW (-1 imprecision) evidence from a single case control study that maternal multivitamin supplementation during pregnancy is associated with reduced inflammatory bowel disease in offspring, and no evidence to suggest that vitamin or minerals influence risk of JIA.

We found no evidence to suggest that different levels of intake of folic acid can modulate risk of allergic or autoimmune diseases. This observation was confirmed in studies where the timing of exposure studied differed. We were able to combine results from 4 studies investigating the association between maternal intake of folic acid and risk of wheeze, but there was no evidence of a relationship. One study (**Granell, 2008**) suggested that a higher intake during pregnancy was related to a higher risk of AS in the offspring, although several other studies found no indication of an association between folic acid consumption during pregnancy and AS. From a clinical point of view, the role of folic acid in protecting an adequate neural tube development in the foetus makes it a commonly used maternal supplement (before and after gestation). We found that studies investigated different timings of exposure throughout the pregnancy, as well as varying doses and frequency of supplementation. Our results are in agreement with those reported recently by **Brown** *et al* (84), which showed no evidence suggesting an association between folate consumption by the mother or the infant, and risk of allergic diseases.

Due to the observational nature of the majority of studies included in this review, dietary questionnaires were the main source to ascertain dietary intake of vitamins and minerals. The use of such instruments allows estimates of a wide range of nutrients to be derived, which was often the way in which the dietary intake of vitamins and minerals were reported in these studies. Although there were some studies finding statistically significant associations between some vitamins (e.g. vitamin C and respiratory outcomes), within the same study there were multiple comparisons being carried out. We found that none of these studies formally tested or controlled for multiple comparisons, which weakens even more any isolated statistically significant findings.

Overall, we found no consistent evidence from observational or intervention studies to suggest that maternal or infant intake of vitamins and minerals influences the risk of AD, AR, FA, AS, TIDM or JIA.

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