



Hydrolysed formula and risk of allergic or autoimmune disease: systematic review and meta-analysis

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ABSTRACT OBJECTIVE

To determine whether feeding infants with hydrolysed formula reduces their risk of allergic or autoimmune disease.

DESIGN

Systematic review and meta-analysis, as part of a series of systematic reviews commissioned by the UK Food Standards Agency to inform guidelines on infant feeding. Two authors selected studies by consensus, independently extracted data, and assessed the quality of included studies using the Cochrane risk of bias tool.

DATA SOURCES

Medline, Embase, Web of Science, CENTRAL, and LILACS searched between January 1946 and April 2015.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES

Prospective intervention trials of hydrolysed cows' milk formula compared with another hydrolysed formula, human breast milk, or a standard cows' milk formula, which reported on allergic or autoimmune disease or allergic sensitisation.

RESULTS

37 eligible intervention trials of hydrolysed formula were identified, including over 19 000 participants. There was evidence of conflict of interest and high or unclear risk of bias in most studies of allergic outcomes and evidence of publication bias for studies of eczema and wheeze. Overall there was no consistent evidence that partially or extensively hydrolysed formulas reduce risk of allergic or autoimmune outcomes in infants at high pre-existing risk of these outcomes. Odds ratios for eczema at age 0-4, compared with standard cows' milk formula, were 0.84 (95% confidence interval 0.67 to 1.07; $I^2=30\%$) for partially hydrolysed formula; 0.55 (0.28 to 1.09; $I^2=74\%$) for extensively hydrolysed casein based formula; and 1.12 (0.88 to 1.42; $I^2=0\%$) for extensively

hydrolysed whey based formula. There was no evidence to support the health claim approved by the US Food and Drug Administration that a partially hydrolysed formula could reduce the risk of eczema nor the conclusion of the Cochrane review that hydrolysed formula could allergy to cows' milk.

CONCLUSION

These findings do not support current guidelines that recommend the use of hydrolysed formula to prevent allergic disease in high risk infants.

REVIEW REGISTRATION

PROSPERO CRD42013004252.

Introduction

Immune mediated health conditions such as allergic and autoimmune diseases seem to have increased in prevalence in many countries and are leading causes of chronic illness in young people.¹ There is evidence that dietary exposures in infancy can influence the risk of these diseases, with a specific concern that early exposure to intact cows' milk protein in the form of infant formula could trigger the onset of allergic or autoimmune disease.²⁻⁴ Current infant feeding guidelines in North America, Australasia, and Europe recommend the use of hydrolysed formula in the first 4-6 months of life in place of a standard cows' milk formula for the primary prevention of allergic diseases in childhood.⁵⁻⁷ This has also been supported by the US Food and Drug Administration (FDA)⁸ and by a Cochrane systematic review.^{9,10} To inform guidelines on infant feeding in the United Kingdom, we undertook a systematic review of hydrolysed formula for preventing allergic sensitisation, allergic disease, or autoimmune disease.

Methods

This review is reported in accordance with PRISMA guidance. The review is one of a series of systematic reviews commissioned by the UK Food Standards Agency to inform UK guidelines on infant feeding, 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 "milk feeding"; CRD42013004239 "timing of allergenic food introduction"; CRD42013004252 "maternal and infant diet") on 5 August 2013, before titles were screened or studies selected from the search results. This review of hydrolysed formula is part of CRD42013004252 "maternal

WHAT IS ALREADY KNOWN ON THIS TOPIC

Breastfeeding is the optimum mode of nutrition for infants

Substitution with infant formula has been associated with allergic and autoimmune disease

International guidelines recommend use of a hydrolysed formula in place of standard infant formula for infants at risk of allergic disease to prevent eczema and allergy to cows' milk

WHAT THIS STUDY ADDS

There is no consistent evidence to support the use of hydrolysed formula for the prevention of allergic or autoimmune disease

and infant diet.” As part of this project we also searched for other systematic reviews covering the same topic published since 1 January 2011 with a revised AMSTAR score ≥ 32 .¹¹ No such reviews were identified for hydrolysed formula.

Study interventions and comparators

We included studies of any hydrolysed formula of cows' milk origin as the intervention of interest, compared with any non-hydrolysed cows' milk formula, human milk, or another type of hydrolysed cows' milk formula. Also included were studies in which hydrolysed formula was given as part of a multifaceted intervention, which we defined as an intervention with at least two other components in addition to the hydrolysed formula—for example, exclusion of allergenic food from the mother's diet, promotion of breastfeeding, delayed introduction of solid food, or measures to avoid exposure to house dust mite. We also included studies in which other interventions were applied to both intervention and control groups, such as exclusion of cows' milk from the mother's diet during lactation. Studies of hydrolysed formula of milk other than cows' milk, such as hydrolysed rice, goats' milk, or soya formula, were not included. We did not use a specific definition of partially or extensively hydrolysed formula but relied on the definition and/or trade name of formula as stated in the individual studies.

Study designs and populations

We included all intervention trials and searched for observational studies but did not extract data from these because of the evidence from intervention trials. Intervention trials were classified as randomised controlled trials, in which the method of treatment allocation was random; as quasi-randomised controlled trials, in which the method of treatment allocation was not totally random (but was thought unlikely to lead to imbalance between treatment groups in variables relevant to the outcome measures); and as controlled clinical trials, in which treatment allocation was non-random and likely to lead to imbalance between treatment groups. Controlled clinical trials were analysed separately from randomised controlled trials/quasi randomised controlled trials. We included studies of infant feeding between birth and 12 months of age and excluded studies in which infants or their mothers were defined by the presence of a pre-existing disease state, including very low birth weight or premature infants.

Study outcomes

Atopic and autoimmune outcomes were selected on the basis of their population prevalence in children and young adults in the UK and/or other affluent nations. We included diseases with a prevalence of at least one in 1000 children/adolescents or young adults (aged <40) but did not include rarer diseases. Atopic outcomes included were asthma (categorised as wheeze, recurrent wheeze, atopic wheeze, bronchial hyper-reactivity, forced vital capacity, peak

expiratory flow rate, forced expiratory volume in one second), eczema, allergic rhinitis and/or conjunctivitis, food allergy, allergic sensitisation (that is, skin prick or specific immunoglobulin E (sIgE) assessment, or total IgE level). Autoimmune outcomes included were type 1 diabetes mellitus (defined serologically and/or clinically), coeliac disease (defined serologically and/or clinically), inflammatory bowel disease, autoimmune thyroid disease, juvenile rheumatoid arthritis, vitiligo, or psoriasis. For atopic outcomes, we grouped age at assessment as 0-4, 5-14, 15-24, 25-44, 45-64, and ≥ 65 . Because of a paucity of outcome data in adults, we pooled age groups ≥ 15 . Autoimmune outcomes were not stratified for analyses by age at outcome assessment.

Data sources

The search strategies included both text terms and subject heading terms where appropriate and were initially developed for Medline and then adapted for other databases. We searched the Cochrane Library (2013, issue 7), Embase (1947 to July 2013), LILACS (1982 to July 2013), Medline (1946 to July 2013), and Web of Science (1970 to July 2013) on 25 July 2013 and reran the searches on 17 April 2015. We included all studies published up to that date and studies in progress or completed but unpublished identified through <http://apps.who.int/trialsearch/>. Peer reviewed publications and abstract publications were included 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. Authors of eligible or potentially eligible studies were not contacted for original data. We extensively piloted and refined the search strategies to optimise sensitivity, comparing search results with those of other published systematic reviews. Appendix 1 shows the Medline search strategies for the complete systematic review project.

Study selection

Seven trained researchers (RJB, VG-L, DI, NG, KJ, JC, ZR) screened titles and abstracts in duplicate. Two researchers screened titles independently and met to agree on inclusion. 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 and in April and May 2015 (RJB, TK, VG-L), with weekly team meetings to discuss uncertainties about study eligibility. The full text of all potentially eligible studies was reviewed.

Assessment of risk of bias

We assessed risk of bias in included intervention studies with 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 the outcome assessment tool (assessment bias), and

incomplete outcome data (attrition bias; considered high where <70% of randomised participants had outcome data available). We modified the tool by including an assessment of conflict of interest, judged as low when 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

DI, VG-L, RJB, and JL-B developed, piloted, and refined an Excel data extraction form. Two researchers (RJB, and TK or TA) extracted data in duplicate. Disagreements and uncertainties about data coding were discussed within the team with leads as follows: RJB (clinical queries), VG-L (dietetic queries), DI (analysis and coding queries), and JL-B (study design and statistics queries). For foreign language studies, VG-L extracted data with a native speaker of the relevant language (see acknowledgements section). We extracted all relevant data from included studies, including data that we could not meta-analyse. Data were extracted either with raw frequencies or crude or adjusted effect estimates. We undertook random effect meta-analysis. When this was not possible or not appropriate we summarised study results in a narrative table.

Data selection for analysis

We extracted outcome data that adhered to the intention to treat principle in preference to data based on per protocol analyses. When studies included multiple intervention groups, we performed pairwise comparisons in which we split the number of events and no events in the unexposed/control group to prevent double counting. When studies reported data at multiple time points within one of our predefined age groupings, we extracted the most complete dataset available, beyond the intervention period (that is, from age 1 onwards). This is the dataset with the largest denominator or when the denominator is identical for multiple time points then the largest numerator (number of events) is used. When studies reported multiple assessments of the same outcome at the same time point, we selected clinical assessments in preference to serological assessments and skin prick in preference to assessment of specific IgE of allergic sensitisation. The GINI study¹²⁻¹⁵ used generalised estimating equations (GEE) to generate odds ratios in some of their publications. This represents the most complete data available from the study, so we selected this in preference to other GINI study data analyses. Raw data or risk ratios were not given in the generalised estimating equations reports. So for analyses that include such data from the GINI study we calculated odds ratios in place of risk ratios to be able to include the most complete GINI study data available in meta-analysis. For some meta-analyses generalised estimating equation data from the GINI trial were either not reported or could not be used because of multiple

intervention groups, and in these meta-analyses we used the most complete non-generalised estimating equation data available.

Data synthesis

We presented pooled results for binary outcomes from intervention studies as risk ratios calculated from the frequencies given in the study or as odds ratios when pooled data included those from a generalised estimating equation analysis and/or adjusted effect estimates. We pooled risk ratios using the Mantel-Haenszel method (with continuity correction of 0.5 in studies with zero cell frequencies) and odds ratios using the generic inverse variance method in the statistical programme R (R version 3.1.0, 2014, www.r-project.org). Pooled data for continuous outcomes measured with similar scales are presented as mean differences with 95% confidence intervals. Heterogeneity was quantified with I^2 and classified as low (<25%), moderate (5-50%), high (50-75%), or extreme (>75%). Data were not pooled when $I^2 \geq 80\%$. We undertook subgroup analyses for meta-analyses with more than five studies and assessed for publication bias (small study bias) using funnel plots and Egger's asymmetry test when there were 10 or more studies in a meta-analysis. We undertook subgroup analyses according to low versus unclear/high overall risk of bias; high versus normal/low risk of disease; quasi-randomised controlled trial versus randomised controlled trial; low versus unclear/high risk of conflict of interest; multifaceted versus not multifaceted intervention; and casein versus whey dominant hydrolysate.

Patient involvement

The findings of this study form part of the UK government's review of advice to the general public on infant feeding. No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results.

Results

Our original search identified 16 289 original titles. Screening of titles, abstracts, and full text yielded 52 studies (37 intervention trials) of hydrolysed formula, including over 19 000 participants. There were 28 randomised controlled trials, six quasi-randomised controlled trials, and three controlled clinical trials describing allergic or autoimmune outcomes. Appendix 2 shows full details of the search results (PRISMA flow chart), and characteristics of included studies are summarised in tables A and B in appendix 3. Twenty three studies used partially hydrolysed formula, and in at least 15 cases this was one specific formula (Nan HA/Good Start/Nidina HA/Beba HA, Nestlé, Vevey, Switzerland). Eighteen studies used extensively hydrolysed formula, and five studies (three for extensively, two for partially hydrolysed formula) used hydrolysed formula as part of a multifaceted intervention. In 30 of 37 studies infants were

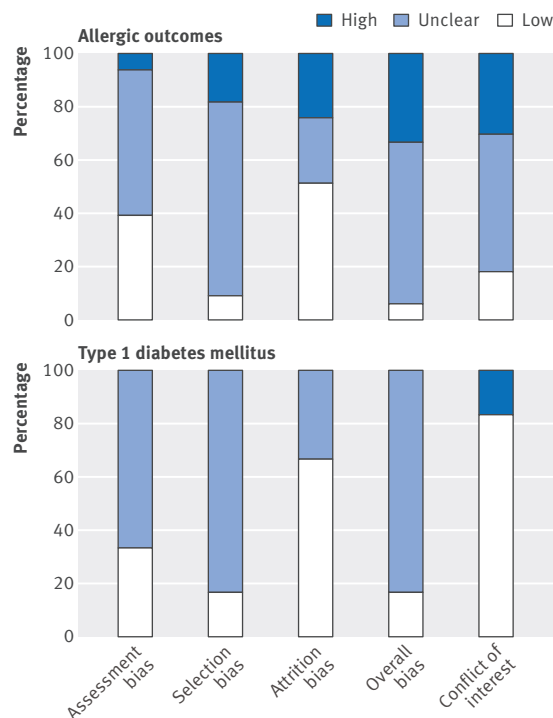


Fig 1 | Summary of risk of bias and conflict of interest in included studies reporting allergic outcomes and type 1 diabetes mellitus, showing proportion of studies with high, low, or unclear risk of bias in each domain

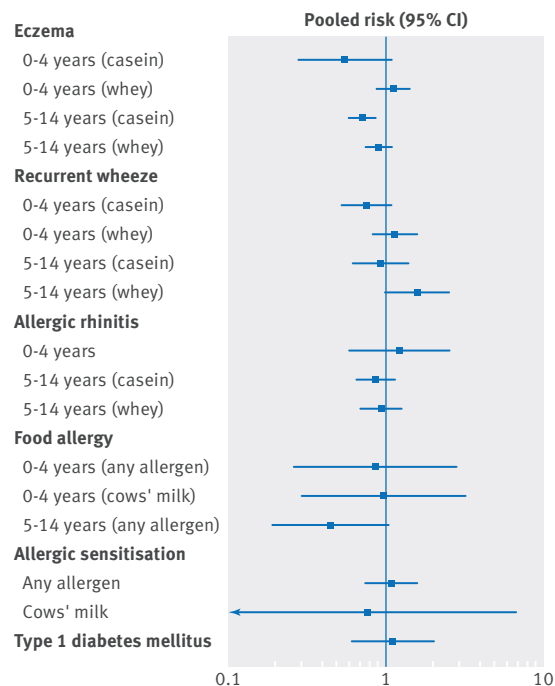


Fig 3 | Summary of treatment effects of hydrolysed formula on different outcome measures. Data shown are mean risk ratios (for allergic rhinitis at age 0-4; food allergy; allergic sensitisation; diabetes) or odds ratios (all other outcomes) with 95% confidence intervals for extensively hydrolysed formula compared with standard cows' milk formula

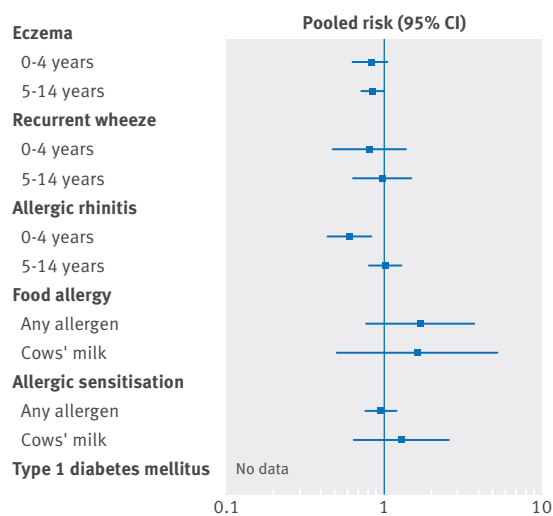


Fig 2 | Summary of treatment effects of hydrolysed formula on different outcome measures. Data shown are mean risk ratios (for allergic rhinitis at age 0-4; food allergy; allergic sensitisation; diabetes) or odds ratios (all other outcomes) with 95% confidence intervals for partially hydrolysed formula compared with standard cow's milk formula

at high risk of the relevant outcome(s) because of family history of disease in a first degree relative. Risk of bias and risk of conflict of interest were unclear or high in most studies for allergic outcomes (fig 1; table C in appendix 3), but low or unclear in most studies for autoimmune outcomes (fig 1; table D

in appendix 3). Figure 2 (partially hydrolysed formula) and figure 3 (extensively hydrolysed formula) summarise the findings of the main meta-analyses. Table 1 shows the GRADE assessment and summary of findings for key comparisons. Figures 4-7 show meta-analyses reported in table 1. The full report with a detailed description of all findings including meta-analyses and detailed methodology is available on the Food Standards Agency website (<http://www.food.gov.uk/science/research/allergy-research/fs305005>), together with an associated statement by the Committee on Toxicity (<http://cot.food.gov.uk/cotstatements>).

Risk of eczema

Twenty seven studies reported the effect of hydrolysed formula in infancy on risk of childhood eczema. The pooled data show no significant difference between extensively hydrolysed formula and standard cows' milk formula in risk of eczema at age 0-4 (odds ratio 0.84, 95% confidence interval 0.67 to 1.07; $I^2=30\%$) or age 5-14 (0.86, 0.72 to 1.02; $I^2=0\%$). Subgroup analysis suggested a significant difference in outcome according to study design or disease risk, with a more positive outcome in the single quasi-randomised controlled trial of normal risk infants. Analysis of data from randomised controlled trials for the most commonly studied partially hydrolysed formula (Nan HA/Good Start/Nidina HA/Beba HA, Nestlé, Vevey, Switzerland) showed no significant effect on risk of eczema at age 0-4 (0.94, 0.75

Table 1 | GRADE assessment and summary of key findings of review of studies of hydrolysed formula and risk of allergic or autoimmune disease

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Other considerations	Odds ratio or relative risk	GRADE of evidence
Outcome: eczema at age 0-4									
Partially hydrolysed formula:									
12 studies	11 RCT, 1 qRCT	Serious. 11 studies with high or unclear overall risk of bias, all studies with high/unclear risk of conflict of interest	Not serious. $I^2=30\%$, study estimates varying from 0.33 to 1.44; subgroup analysis suggests difference by study design or population	No	Not serious. 95% CI for OR do not exclude clinically important effect, but exclude large effect sizes and significant harmful effects	No. NB Significant risk when pHF and eHF data combined. Egger's $P<0.05$	All RCTs undertaken in populations at high risk of eczema due to family history of allergic disease	OR 0.84 (0.67 to 1.07)	Moderate
Extensively hydrolysed formula:									
6 studies, 7 interventions	6 RCT	Serious. 5 studies with high or unclear overall risk of bias, all studies with high/unclear risk of conflict of interest	Serious. $I^2=74\%$ for analysis of casein eHF; 0% for whey eHF. Study estimates varying from 0.18 to 1.26	No	Serious 95% CI for OR do not exclude large beneficial or harmful effects	Not tested ($n<10$) NB Significant risk when pHF and eHF data combined. Egger's $P<0.05$	All RCTs undertaken in populations at high risk of eczema due to family history of allergic disease	Casein eHF OR 0.55 (0.28 to 1.09), whey eHF OR 1.12 (0.88 to 1.42)	Very low
Outcome: recurrent wheeze at age 0-4									
Partially hydrolysed formula:									
5 studies	5 RCT	Serious. 4 studies with high or unclear overall risk of bias, all studies with high/unclear risk of conflict of interest	No. $I^2=15\%$, study estimates varying from 0.29 to 1.20	No	Not serious. 95% CI for OR do not exclude clinically important effect, but exclude large effect sizes	Not tested ($n<10$) NB Significant risk when pHF and eHF data are combined. Egger's $P<0.05$	All RCTs undertaken in populations at high risk of allergy due to family history of allergic disease	OR 0.82 (0.48 to 1.41)	Moderate
Extensively hydrolysed formula:									
5 studies, 6 interventions	5 RCT	Serious. 5 studies with high or unclear overall risk of bias, all studies with high/unclear risk of conflict of interest	Serious. $I^2=74\%$ for analysis of casein eHF; 0% for whey eHF. Study estimates varying from 0.18 to 1.26	Not serious. 2 studies used multifaceted interventions	Not serious. 95% CI for OR do not exclude clinically important effect, but exclude large effect sizes	Not tested ($n<10$) NB Significant risk when pHF and eHF data combined. Egger's $P<0.05$	All RCTs undertaken in populations at high risk of allergy due to family history of allergic disease	Casein eHF OR 0.76 (0.53 to 1.09), whey eHF OR 1.15 (0.84 to 1.59)	Very low
Outcome: allergic sensitisation to cows' milk at any age									
Partially hydrolysed formula:									
7 studies	7 RCT	Serious. 6 studies with high or unclear overall risk of bias, and high/unclear risk of conflict of interest	No. $I^2=0\%$, study estimates varying from 0.44 to 9.63	Not serious. 2 studies used multifaceted interventions	Not serious. 95% CI for RR do not exclude clinically important effect, but exclude very large effect sizes	Not tested ($n<10$)	All RCTs undertaken in populations at high risk of allergy due to family history of allergic disease	RR 1.30 (0.65 to 2.60)	Moderate
Extensively hydrolysed formula:									
3 studies	3 RCT	Serious. All studies with high or unclear overall risk of bias, 2 studies with high/unclear risk of conflict of interest	Serious. $I^2=77\%$, study estimates varying from 0.08 to 10.13	Not serious. 1 study used multifaceted intervention	Serious. 95% CI for RR do not exclude large effect sizes	Not tested ($n<10$)	All RCTs undertaken in populations at high risk of allergy due to family history of allergic disease	RR 0.77 (0.09 to 6.73)	Very low
Outcome: type 1 diabetes mellitus at any age									
Extensively hydrolysed formula:									
5 studies	5 RCT	Not serious. All studies had low or unclear overall risk of bias, 4 studies had low risk of conflict of interest	Not serious. $I^2=25\%$, study estimates varying from 0.62 to 2.02	No	Not serious. 95% CI for RR do not exclude clinically important effect, but exclude large effect sizes	Not tested ($n<10$)	All RCTs undertaken in populations at high genetic risk of T1DM, and 4 of 5 studies used casein eHF	RR 1.12 (0.62 to 2.02)	High

RCT=randomised controlled trial, qRCT=quasi-randomised controlled trial, pHF=partially hydrolysed formula, eHF=extensively hydrolysed formula, RR=risk ratio, OR=odds ratio.

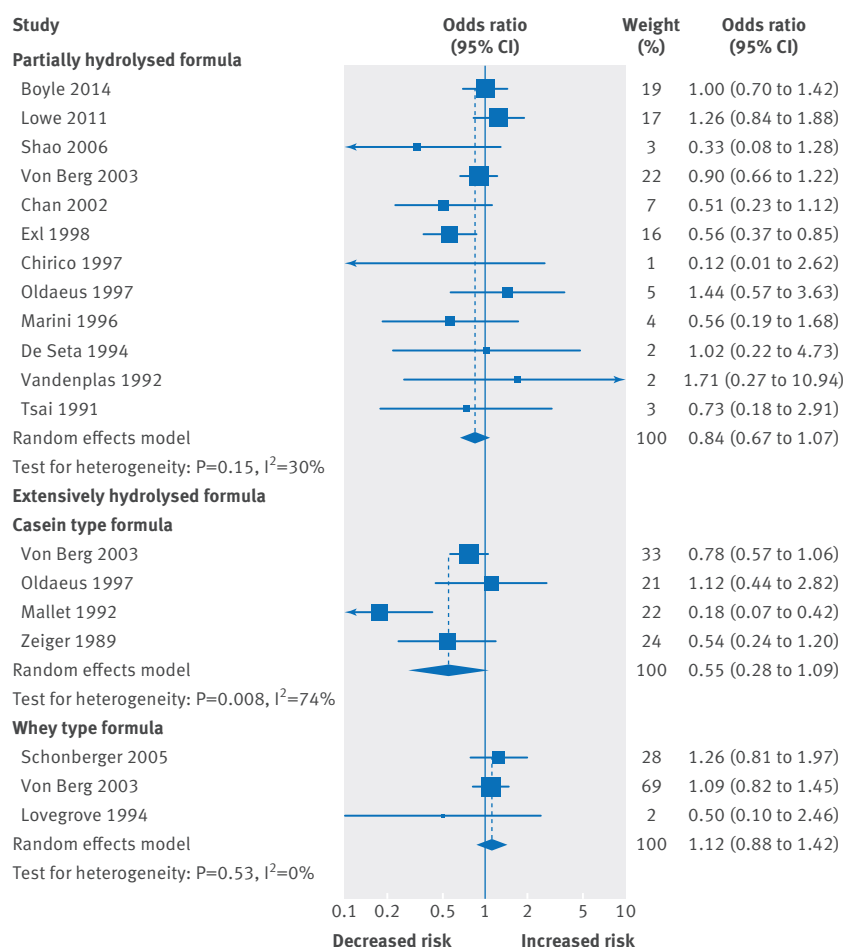


Fig 4 | Evidence from randomised or quasi-randomised controlled trials for partially hydrolysed formula and extensively hydrolysed formula compared with standard cows' milk formula for prevention of eczema in children aged ≤ 4

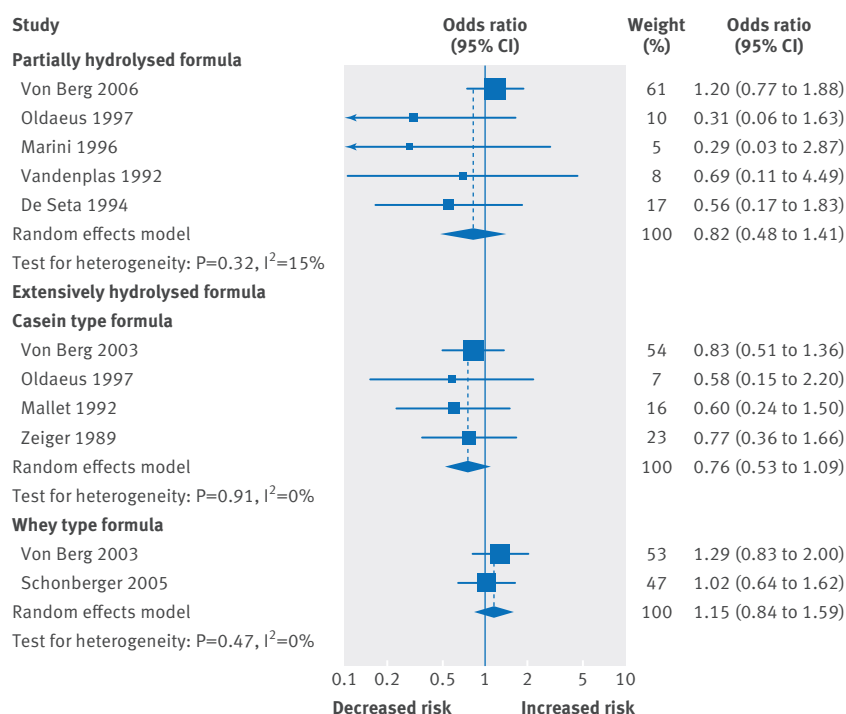


Fig 5 | Evidence from randomised controlled trials for partially hydrolysed formula and extensively hydrolysed formula compared with standard cow's milk formula, and recurrent wheezing at age ≤ 4

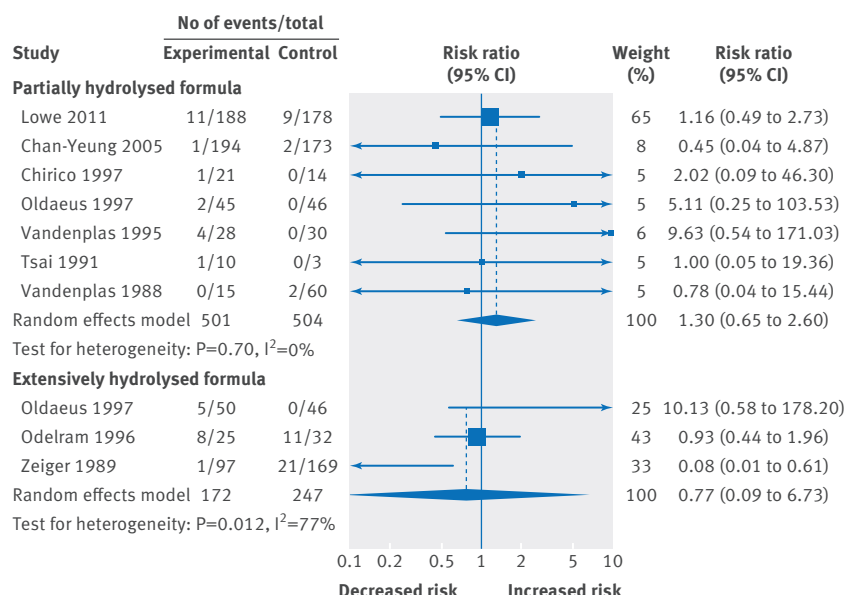


Fig 6 | Evidence from randomised controlled trials for partially hydrolysed formula and extensively hydrolysed formula compared with standard cow's milk formula, and allergic sensitisation to cows' milk

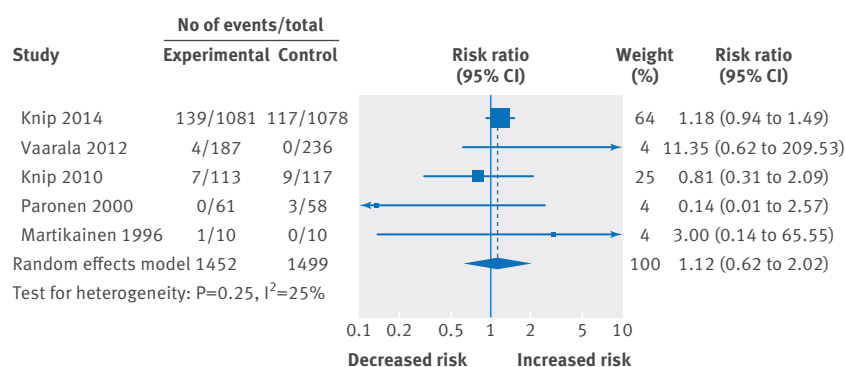


Fig 7 | Evidence from randomised controlled trials for extensively hydrolysed formula compared with standard cows' milk formula, and type 1 diabetes mellitus

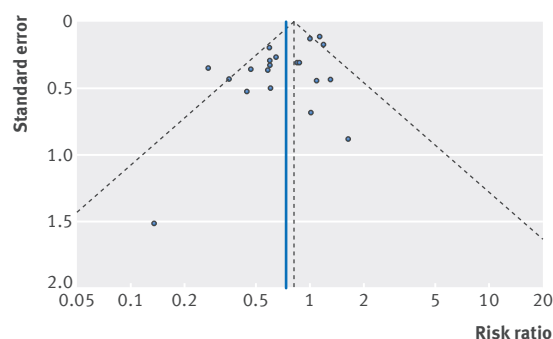


Fig 8 | Funnel plots for pooled analysis of "any hydrolysed formula" and risk of eczema showing evidence of publication bias/small study effects at age ≤ 4 (Egger's test $P=0.019$)

to 1.17; $I^2=0\%$). Though a meta-analysis of two studies on extensively hydrolysed formula found reduced odds of eczema at age 5-14 in children fed casein dominant formula during infancy (0.71, 0.59 to 0.87; $I^2=0\%$), this

effect was not seen for eczema at age 0-4 or for whey dominant formula at any age (0-4 or 5-14). Direct comparison of extensively versus partially hydrolysed formula, and casein versus whey dominant extensively hydrolysed formula, did not show a significant difference in risk of eczema at age 0-4 or 5-14. When we combined data for partially and extensively hydrolysed formula as "any hydrolysed formula" there was evidence of reduced eczema at age 0-4 (but not at age 5-14). This analysis necessitated use of per protocol data from the GINI study, had high statistical heterogeneity, and showed evidence of publication bias (fig 8).

Risk of wheeze

Twenty one studies reported the effect of hydrolysed formula in infancy on risk of wheeze or recurrent wheeze. Analysis of the outcome "wheeze" was inconclusive, with meta-analyses of partially hydrolysed formula dominated by a multifaceted intervention study in which uptake of the intervention was low and a quasi-randomised controlled trial with high risk of bias and conflict of interest. Meta-analysis of extensively hydrolysed formula was not possible because of extreme heterogeneity. Analysis of the outcome "recurrent wheeze" showed no significant difference between partially hydrolysed formula and standard cows' milk formula for recurrent wheeze at age 0-4 (odds ratio 0.82, 95% confidence interval 0.48 to 1.41; $I^2=15\%$) or age 5-14 (0.99, 0.65 to 1.51; $I^2=43\%$), and findings were also not significant for meta-analysis of casein or whey dominant extensively hydrolysed formula at ages 0-4 or 5-14. Direct comparison of extensively versus partially hydrolysed formula, and casein versus whey dominant extensively hydrolysed formula, did not show a significant difference in risk of recurrent wheeze at age 0-4 or age 5-14—this analysis necessitated use of per protocol data for the GINI study, and showed evidence of publication bias (fig 9).

Risk of allergic rhinitis

Twelve studies reported the effect of hydrolysed formula on risk of allergic rhinitis. At age 0-4 partially

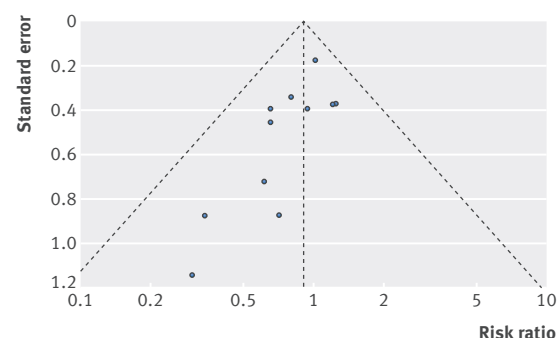


Fig 9 | Funnel plots for pooled analysis of "any hydrolysed formula" and recurrent wheeze showing evidence of publication bias/small study effects at age ≤ 4 (Egger's test $P=0.021$)

hydrolysed formula (but not extensively hydrolysed formula) was associated with significantly reduced risk of allergic rhinitis, though this meta-analysis was dominated by a multifaceted intervention study in which uptake of the intervention was low. At age 5-14 neither partially (odds ratio 1.03, 95% confidence interval 0.82 to 1.30; $I^2=0\%$) nor extensively (casein 0.87, 0.66 to 1.15; $I^2=0\%$; whey 0.93, 0.69 to 1.26; single study) hydrolysed formula were associated with a significant reduction in allergic rhinitis. Direct comparison of the two formulas, and casein versus whey dominant extensively hydrolysed formula, did not show a significant difference in risk of allergic rhinitis at age 0-4 or 5-14.

Risk of food allergy or allergic sensitisation

Thirteen and 19 studies reported the effect of hydrolysed formula on risk of food allergy and allergic sensitisation, respectively. There was no significant difference in risk of "any food allergy" with partially (risk ratio 1.73, 95% confidence interval 0.79 to 3.80; $I^2=42\%$) or extensively (0.86, 0.26 to 2.82; $I^2=42\%$) hydrolysed formula compared with standard formula at age 0-4, nor for extensively hydrolysed formula at age 5-14. We also found no difference in food allergy to cows' milk, egg, or (partially hydrolysed formula only) peanut. Direct comparison of the two formulas (egg allergy) and casein versus whey dominant extensively hydrolysed formula showed no significant difference in risk of food allergy. There was no significant difference in risk of allergic sensitisation to cows' milk with partially (1.30, 0.65 to 2.60; $I^2=0\%$) or extensively (0.77, 0.09 to 6.73; $I^2=77\%$) hydrolysed formula, and no significant difference between groups for risk of allergic sensitisation to "any allergen" or raised total IgE level.

Risk of type 1 diabetes mellitus

Six studies reported the effect of extensively hydrolysed formula compared with standard formula in infancy on risk of type 1 diabetes mellitus. There was no significant difference in risk with extensively hydrolysed formula (risk ratio 1.12, 95% confidence interval 0.62 to 2.02; $I^2=25\%$). We did not identify any studies of partially hydrolysed formula and diabetes nor of hydrolysed formula and other autoimmune outcomes.

Generalisability and study conduct

In 18 of 33 (55%) included studies reporting allergic outcomes, there were features suggesting issues with generalisability and possibly with study conduct.¹⁶ In seven studies there was either exclusive formula feeding from birth in all randomised participants¹⁷⁻²² or total cessation of breastfeeding by 14 days.²³ In five studies, randomisation and allocation of formula milk occurred early: during pregnancy,²⁴ at birth in all^{25 26} or some²⁷ participants, or in the first four days after birth in most participants.²⁸ In one study, infants were enrolled on day one, and over half were exclusively formula fed,²⁹ and in another breast milk was purposefully withheld for the first three days of life in

some infants.³⁰ In two studies breastfeeding was not mentioned,^{31 32} and in another two studies^{33 34} it was unclear whether or not the study population was selected for a high rate of early formula feeding because of insufficient information in the report. The information presented in these studies suggests the possibility that more could have been done to promote the maintenance and revival of breastfeeding in the study populations, in accordance with the International Code of Marketing of Breast-milk Substitutes.¹⁶ In the 15 remaining studies of allergic disease^{12 35-48} and in all diabetes studies^{47 49-52} there was no evidence of adverse breastfeeding outcomes in study participants.

Discussion

Principal findings

In this systematic review of hydrolysed infant formula for reducing risk of allergic or autoimmune disease we found no consistent evidence to support a protective role for partially or extensively hydrolysed formula. Our findings conflict with current international guidelines, in which hydrolysed formula is widely recommended for young formula fed infants with a family history of allergic disease.⁵⁻¹⁰ Such recommendations might therefore need revision.

Comparison with other studies

In 1936, Grulee and Sanford suggested that formula feeding could be associated with eczema,³ and more recent studies suggest that infant exposure to intact cows' milk might increase the risk of type 1 diabetes mellitus due to immunological cross reactivity between human and bovine insulin.⁴ Allergenic peptides in milk are 10-40 kDa in size, and bovine insulin is 5.8 kDa; partially and extensively hydrolysed formulas are intended to have no peptides >5 kDa and ≥ 3 kDa, respectively.⁵³ By the avoidance of exposure to insulin or allergenic peptides in milk with partially or extensively hydrolysed formula, one might in theory prevent immunological sensitisation to insulin or milk and associated diseases such as type 1 diabetes, milk allergy, and eczema. We did not, however, find consistent evidence from intervention trials to support this.

The infant feeding guidelines that recommend hydrolysed formula for allergy prevention recognise that the evidence base for such a recommendation is weak and informed by analysis of a small number of trials with high risk of bias. In the current 2006 Cochrane review Osborn and colleagues concluded that there is limited evidence to support a role for hydrolysed formula in reducing allergy to cows' milk and no evidence for other specific allergic outcomes.^{9 10} This conclusion was based on a single study,²¹ in which the selected outcome is likely to be a poor measure of allergy to cows' milk as it was reported in over 40% of the control group, and such allergy has a prevalence of 2-7.5%.⁵⁴ In our current meta-analysis of three studies reporting allergy to cows' milk, including data from the same study that

defined allergy to cows' milk as challenge proved allergy with a positive allergy test result (3% prevalence in control group), we found no evidence to support the conclusion of the Cochrane review.

International guidelines also support the use of hydrolysed formula for high risk infants to prevent eczema.⁵⁻⁷ We found no consistent evidence to support this. We did find that studies of lower quality design (controlled clinical trials and quasi-randomised controlled trials) had more positive outcomes than truly randomised controlled trials, and we found evidence of publication bias, suggesting that there could be small unpublished trials showing increased risk of eczema or recurrent wheeze associated with hydrolysed formula. The conclusions of an independent FDA review, which supported a limited health claim that a whey based partially hydrolysed formula (Good-Start, Nestlé, Vevey, Switzerland) could reduce the risk of eczema in high risk infants, also do not seem to be justified.⁸ That approval was based largely on review of the findings of the GINI study, in which per protocol analysis rather than intention to treat analysis was used to inform the FDA decision as the intention to treat analysis had not yet been published.⁸ The health claim was also approved before publication of one trial of the same formula with significantly negative results.⁴² Our own meta-analysis of published randomised controlled trials of the same partially hydrolysed formula does not support the FDA approved health claim that there is evidence for use of a whey based partially hydrolysed formula from birth to 4 months for reducing risk of eczema in healthy infants who are not exclusively breastfed and have a family history of allergy.

Strengths and limitations of the study

Many studies of allergic outcomes included in this review had unclear or high risk of bias and evidence of conflict of interest, often because of inadequate methods of randomisation and treatment allocation (selection bias) and support of the study or investigators from manufacturers of hydrolysed formula. In many cases study participants were infants with early full formula feeding, so our findings might not be applicable to populations with more typical feeding patterns.

Concerns have been raised about possible research fraud in this topic of investigation. We did not include the implicated studies, which evaluated a partially hydrolysed formula (Nan HA/Good Start/Nidina HA/Beba HA, Nestlé, Vevey, Switzerland) for preventing allergic outcomes and were led by Chandra and colleagues.⁵⁵⁻⁵⁷ Data from the Chandra studies played an important role in a 2003 Cochrane review, which concluded that hydrolysed formula reduces allergic disease.⁵⁸ Subsequent systematic reviews have excluded the Chandra data. The evidence of publication bias that we found, however, suggests that these systematic reviews might still overestimate the possibility that hydrolysed formula has beneficial effects.

Conclusions and policy implications

Our analyses suggest that current recommendations to use hydrolysed formula in place of standard cows' milk formula to prevent allergy in infants at high risk should be revised. We found no consistent evidence to support the current recommendations and found evidence of publication bias, methodological biases, and conflict of interest in those studies reporting allergic outcomes. We suggest that any future trials on hydrolysed formula should be prospectively registered, independently funded, and include adequate oversight to ensure that they do not negatively impact on breastfeeding in study participants.

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Transparency declaration: RJB affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and registered have been explained.

Data sharing: Dataset and statistical code are available from the Food Standards Agency at www.food.gov.uk

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Appendix 1: Search strategy

Appendix 2: PRISMA flowchart

Appendix 3: Supplementary tables A-D

Appendix 1: Medline Search Strategy [posted as supplied by author]

Search A [CRD42013003802 'milk feeding']

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. celiac 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

Medline Search Strategy

Search B [CRD42013004239 'timing of allergenic food introduction']

1. complementary food?.ab,ti.
2. (introduc\$ adj2 food?).ab,ti.
3. wean\$.ab,ti.
4. Weaning/
5. solid?.ab,ti.
6. semi-solid?.ab,ti.
7. baby food?.ab,ti.
8. Infant Food/
9. Infant Nutritional Physiological Phenomena/
10. breast feeding.ab,ti.
11. breastfeeding.ab,ti.
12. breast fed.ab,ti.
13. breastfed.ab,ti.
14. Breast Feeding/
15. Milk, Human/
16. formula?.ab,ti.
17. hydrolysed.ab,ti.
18. bottlefed.ab,ti.
19. bottle fed.ab,ti.
20. (bottle adj3 feed\$).ab,ti.
21. Infant Formula/
22. Bottle Feeding/
23. liquid?.ab,ti.
24. milk.ab,ti.
25. Milk/
26. egg?.ab,ti.
27. Egg Proteins/
28. Egg Proteins, Dietary/
29. nut?.ab,ti.
30. peanut?.ab,ti.
31. almond?.ab,ti.
32. (brazil? adj5 nut?).ab,ti.
33. walnut?.ab,ti.
34. pecan?.ab,ti.
35. pistachio?.ab,ti.
36. cashew?.ab,ti.
37. hazelnut?.ab,ti.
38. macadamia?.ab,ti.
39. Nuts/
40. Arachis hypogaea/
41. Prunus/
42. Bertholletia/
43. Juglans/
44. Carya/
45. Pistacia/
46. Anacardium/
47. Corylus/
48. Macadamia/

49. wheat.ab,ti.
50. Triticum/
51. soya.ab,ti.
52. Soybeans/
53. gluten\$.ab,ti.
54. Glutens/
55. fish.ab,ti.
56. Fishes/
57. 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
58. allerg\$.ab,ti.
59. asthma\$.ab,ti.
60. wheeze.ab,ti.
61. wheezing.ab,ti.
62. bronchial hyperresponsiveness.ab,ti.
63. bronchial hyperreactivity.ab,ti.
64. Forced expiratory volume.ab,ti.
65. FEV1.ab,ti.
66. "FEV 1".ab,ti.
67. "FEV0.5".ab,ti.
68. "FEV 0.5".ab,ti.
69. Forced vital capacity.ab,ti.
70. FVC.ab,ti.
71. Peak expiratory flow rate.ab,ti.
72. PEFr.ab,ti.
73. eczema.ab,ti.
74. neurodermatitis.ab,ti.
75. rhinitis.ab,ti.
76. besniers prurigo.ab,ti.
77. rhinoconjunctivitis.ab,ti.
78. hayfever.ab,ti.
79. (hay adj fever).ab,ti.
80. poll?nosis.ab,ti.
81. SAR.ab,ti.
82. (pollen adj allergy).ab,ti.
83. conjunctivitis.ab,ti.
84. immunoglobulin e.ab,ti.
85. Total IgE.ab,ti.
86. autoimmune disease?.ab,ti.
87. diabetes.ab,ti.
88. diabetic.ab,ti.
89. type 1.ab,ti.
90. c?eliac disease.ab,ti.
91. crohn\$ disease.ab,ti.
92. Inflammatory Bowel Disease?.ab,ti.
93. Ulcerative colitis.ab,ti.
94. (Lympho\$ adj3 thyroiditi\$).ab,ti.
95. (Thyroiditi\$ adj3 autoimmune).ab,ti.
96. (Hashimoto\$ adj3 (syndrome? or thyroiditi\$ or disease?)).ab,ti.
97. (Thyroiditi\$ adj3 (post-partum or postpartum)).ab,ti.

98. Graves? disease.ab,ti.
99. Basedow\$ disease.ab,ti.
100. exophthalmic goiter?.ab,ti.
101. (Still? Disease adj3 (juvenile or onset)).ab,ti.
102. (Juvenile adj3 arthriti\$).ab,ti.
103. vitiligo.ab,ti.
104. Psorias?s.ab,ti.
105. (Arthriti? adj3 Psoria\$).ab,ti.
106. atopic disease.ab,ti.
107. atopic dermatitis.ab,ti.
108. (food? adj3 sensiti\$).ab,ti.
109. (food? adj3 toleran\$).ab,ti.
110. (food? adj3 intoleran\$).ab,ti.
111. ((aero or air\$) adj3 allergen?).ab,ti.
112. (aeroallergen? adj3 sensiti\$).ab,ti.
113. (allergen? adj3 sensiti\$).ab,ti.
114. skin prick test\$.ab,ti.
115. atopy.ab,ti.
116. hypersensitiv\$.ab,ti.
117. Hypersensitivity/
118. exp Food Hypersensitivity/
119. Respiratory Hypersensitivity/
120. Asthma/
121. Bronchial Hyperreactivity/
122. Forced Expiratory Volume/
123. Vital Capacity/
124. Peak Expiratory Flow Rate/
125. Eczema/
126. Neurodermatitis/
127. Rhinitis/
128. Rhinitis, Allergic, Perennial/
129. Rhinitis, Allergic, Seasonal/
130. Conjunctivitis/
131. Immunoglobulin E/
132. Autoimmune Diseases/
133. Diabetes Mellitus, Type 1/
134. Celiac Disease/
135. Crohn Disease/
136. Inflammatory Bowel Diseases/
137. Colitis, Ulcerative/
138. Thyroiditis, Autoimmune/
139. Hashimoto Disease/
140. Postpartum Thyroiditis/
141. Graves Disease/
142. Arthritis, Juvenile Rheumatoid/
143. Vitiligo/
144. Psoriasis/
145. Arthritis, Psoriatic/
146. Dermatitis, Atopic/
147. Hypersensitivity, Immediate/
148. 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

149. infant?.ab,ti.

150. ((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.

151. ((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.

152. 150 or 151

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

154. 152 and 153

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

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

157. Infant/

158. Infant, Newborn/

159. 149 or 154 or 155 or 156 or 157 or 158

160. clinical trial?.mp.

161. random\$.mp.

162. factorial\$.mp.

163. crossover\$.mp.

164. placebo\$.mp.

165. (doubl\$ adj blind\$).mp.

166. (singl\$ adj blind\$).mp.

167. assign\$.mp.

168. volunteer\$.mp.

169. cohort stud\$.mp.

170. longitudinal\$.mp.

171. follow-up.mpp.

172. prospectiv\$.mp.

173. retrospectiv\$.mp.

174. case control.mpp.

175. case referent.mpp.

176. exp clinical trial/

177. Cross-Over Studies/

178. Placebos/

179. Double-Blind Method/

180. Single-Blind Method/

181. exp Cohort Studies/

182. case-control studies/

183. 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

184. 57 and 148 and 159 and 183

Medline Search Strategy

Search C [CRD42013004252 ‘maternal and infant diet’]

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.

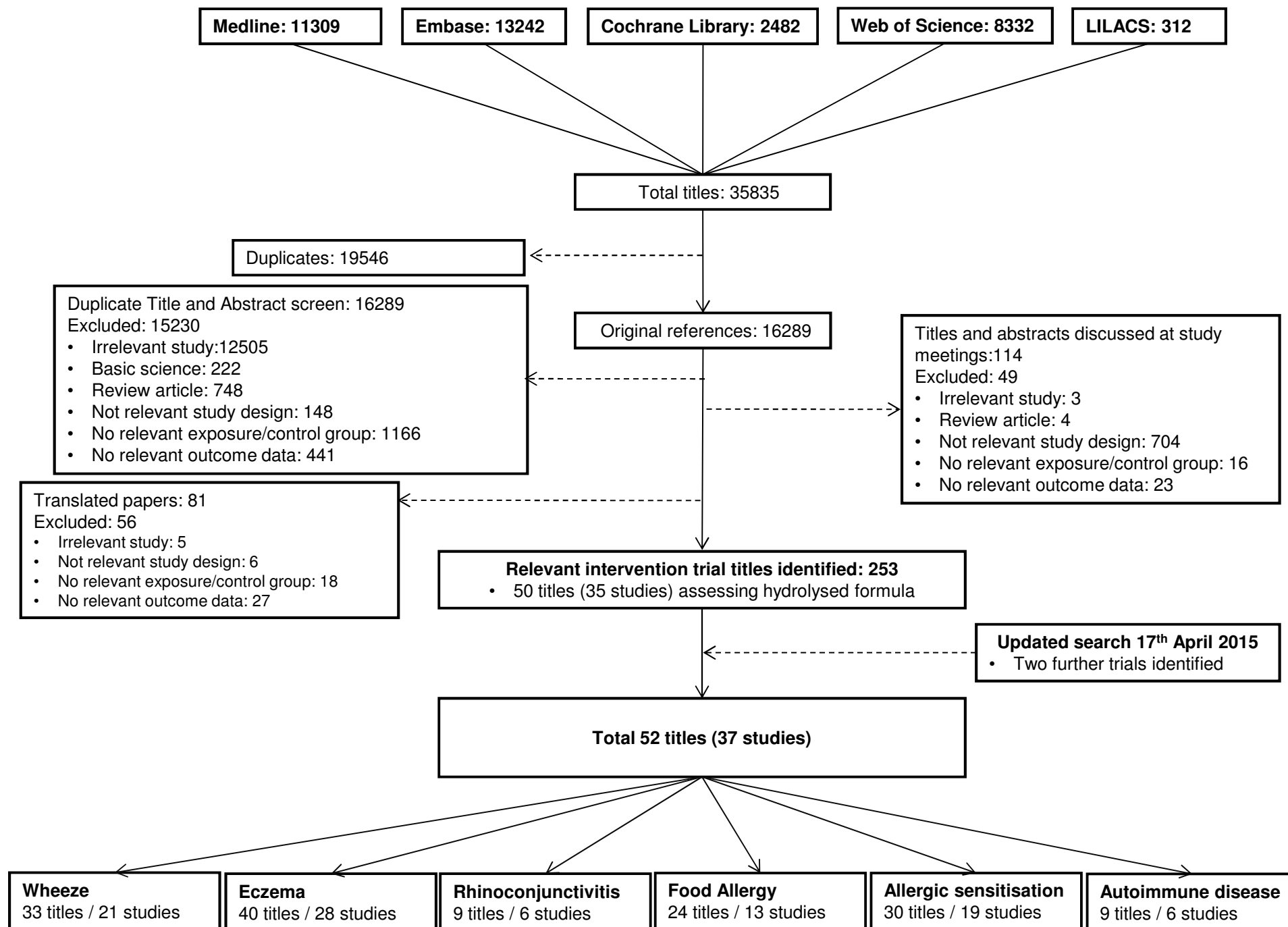
205. protein intake.ab,ti.
206. animal protein\$.ab,ti.
207. total protein\$.ab,ti.
208. vegetable protein\$.ab,ti.
209. plant protein\$.ab,ti.
210. exp Dietary Carbohydrates/
211. exp Dietary Fats/
212. exp Dietary Fiber/
213. exp Dietary Proteins/
214. exp Dietary Supplements/
215. exp Food Additives/
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



Appendix 3: Supplementary tables [posted as supplied by author]

Table A. Characteristics of Included Randomised or Quasi-Randomised Controlled Trials.

Study	Design	No. Allocated Int/Ctrl	Country	Population	Treatment	Age at outcome (yr)	Outcomes reported (assessment method)
Akerblom, 2005 [1] Knip, 2010 [2] (Nutramigen, Mead Johnson)	RCT	122/ 120	Finland	TRIGR pilot. Newborn infants with 1st degree relative with T1DM. High risk.	eHF-casein from <6 months to 6-8 months vs whey enriched CM formula (20% hydrolysed).	7, 8, 10	Diabetes Mellitus (clinical diagnosis, autoantibodies)
Becker, 2004 [3]; Chan-Yeung, 2000 [4]; Chan-Yeung 2005 [5]; Wong, 2013 [6] (Good Start, Nestlé)	RCT	281/ 268	Canada	CAPPS Study. Infants with family history of allergic conditions. High risk.	Multifaceted intervention including pHF-whey up to 12 months (only 8.3% of infants used), vs usual care/standard formula.	1, 7	Allergic Sensitisation (SPT), Allergic Rhinitis (DD), Wheeze (ISAAC and modified ECRHS), Eczema (DD), bronchial hyper-responsiveness (Metacholine PC20 <7.8), Lung function (FEV1)

Study	Design	No. Allocated Int/Ctrl	Country	Population	Treatment	Age at outcome (yr)	Outcomes reported (assessment method)
Boyle 2015 [7] (pHF, Nutricia)	RCT	432/431	Australia Singapore England and Ireland	PATCH Study. Term infants with $\geq$ one parent with allergic disease, and formula introduction <18 weeks. High risk.	pHF-whey + prebiotic, vs standard formula, from <18 to 26 weeks. Outcome reported for those starting <4 wks.	1	AD (Hanifin and Rajka criteria)
Chan, 2002 [8] (NanHA, Nestlé)	RCT	76/77	Singapore	Infants whose parents didn't intend to breastfeed/ atopy in a 1st degree relative. High risk.	pHF-whey from birth to $\geq$ 4 months, vs standard formula.	0.3, 1, 2, 2.5	Wheeze (DD), Eczema (clinical diagnosis), Allergic Sensitisation (sIgE)
Chirico, 1997 [9] (Vivena HA, Plada)	RCT	Unclear. 21/14 assessed at 6 months	Italy	Very early formula introduction. Maternal history of atopy. High risk.	pHF-whey from birth to 6 months vs standard formula.	0.5	Allergic Sensitisation (sIgE), Eczema (clinical diagnosis)

Study	Design	No. Allocated Int/Ctrl	Country	Population	Treatment	Age at outcome (yr)	Outcomes reported (assessment method)
de Seta, 1994 [10] (Nidina HA, Nestlé)	RCT	Unclear. 23/39 assessed at 2 years	Italy	Representative population of high risk infants. High risk.	pHF-whey with advice to delay CM introduction, vs standard formula from birth to 6 months.	2	Eczema (Hanifin and Rajka criteria), Wheeze (DD)
Dupont, 2009 [11] (Formula unknown)	RCT	138/141	France	Multicentre study of high risk infants. High risk.	eHF vs pHF	1	Total IgE
Halken, 1993 [12] (Nutramigen, Mead Johnson; Profylac, ALK)	RCT	59/62	Denmark	High risk infants with raised cord blood IgE. High risk.	eHF-casein vs eHF-whey , as needed to 6 months.	1.5	Eczema (DD), Wheeze (≥ 2 physician diagnosed episodes), Food allergy CM (food challenge)
Knip, 2014 [13] (Nutramigen, Mead Johnson)	RCT	2613/2543	Finland	TRIGR study. Newborn infants with 1st degree relative with T1DM. High risk.	eHF-casein from <6 months to 6-8 months vs whey enriched CM formula (20% hydrolysed).	7	Diabetes Mellitus (≥ 2 or ≥ 1 autoantibodies)

Study	Design	No. Allocated Int/Ctrl	Country	Population	Treatment	Age at outcome (yr)	Outcomes reported (assessment method)
Lovegrove, 1994 [14] (Peptijunior, Nutricia)	RCT	12/14	UK	Allergic pregnant women aged 31 ± 5 years recruited. High risk.	Multifaceted intervention including eHF-whey vs standard formula/no intervention.	0.5, 1, 1.5	Eczema (DD)
Lowe, 2011 [15] (NanHA, Nestlé)	RCT	206/206	Australia	Representative population. 1st degree relative with atopy. High Risk.	pHF-whey vs standard formula during first year.	0.5, 1, 2, 7	Eczema (DD), Allergic Rhinitis (parental report/DD), Food Allergy (parent report), Wheeze (DD), Allergic Sensitisation (SPT)
Mallet, 1992 [16] (Pregestimil, Mead Johnson)	RCT	92/85	France	Immediate family history of atopy. High Risk.	eHF-casein vs standard formula up to 4 months as needed.	0.33, 1, 2, 4	Wheeze (physician assessment), Eczema (physician assessment), Allergic Sensitisation (sIgE), Food Allergy (parent report)
Marini, 1996 [17] (Nidina HA, Nestlé)	RCT	80/75	Italy	Representative population. High Risk.	pHF-whey vs standard formula up to 5 months as needed.	1, 2, 3	Eczema (DD), Wheeze (≥ 3 physician diagnosed episodes), Allergic Rhinoconjunctivitis (≥ 3 consecutive weeks of clinical symptoms)

Study	Design	No. Allocated Int/Ctrl	Country	Population	Treatment	Age at outcome (yr)	Outcomes reported (assessment method)
Martikainen, 1996 [18]; Vaarala, 1998 [19] (Nutramigen, Mead Johnson)	RCT	10/10	Finland	Infants of mothers with diabetes. High Risk.	eHF-c vs standard formula, from < 6 until 9 months as needed.	0.5, 1	Diabetes Mellitus (clinical diagnosis, autoantibodies), Food Allergy
Moran, 1992 [20] (pHF, Mead Johnson)	RCT	Unclear. 72/65 assessed at 8 months	USA	Term infants of mothers who elected not to breast feed. Mainly urban middle class families. Normal Risk.	pHF vs standard formula, until 8 months.	0.67	Allergic Sensitisation (sIgE)
Odelram, 1996 [21] (Profylac, ALK)	RCT	~41/ ~41	Finland/ Sweden	Family history of atopy and raised cord blood IgE. High Risk.	eHFvs standard formula for the first year, as needed.	1.5	Food Allergy (physician assessment), Allergic Sensitisation (SPT, sIgE), Eczema (Seymour criteria), Allergic Rhinitis, Wheeze (≥ 2 physician diagnosed episodes)

Study	Design	No. Allocated Int/Ctrl	Country	Population	Treatment	Age at outcome (yr)	Outcomes reported (assessment method)
Oldaeus, 1997 [22]; Oldaeus, 1999 [23] (pHF or Nutramigen, both Mead Johnson)	RCT	51 pHF; 55 eHF; 49 CM	Sweden	Family history of atopy, raised cord blood IgE, maternal/infant milk/egg/fish exclusion. High Risk.	pHF or eHF-casein vs standard formula, from weaning until 9 months.	0.75, 1, 1.5	Eczema (Seymour criteria), Allergic Rhinoconjunctivitis (DD), Food Allergy (open food challenge), Wheeze (≥ 3 physician diagnosed episodes), Allergic Sensitisation (sIgE, SPT), Wheeze (parent reported)
Paronen, 2000 [24] (Nutramigen, Mead Johnson)	RCT	61/58	Finland	Newborn infants with 1st degree relative with T1DM, and high risk HLA type. High Risk.	eHF-casein vs standard formula, from <6 to 6-8 months as needed. Mean 4.8 months control/ 3.6 eHF.	2	Diabetes Mellitus (autoantibodies)
Porch, 1998 [25] (Good Start, Nestlé; Nutramigen, Mead Johnson)	RCT	59/48	USA	Formula fed from birth. At least one parent with allergy. High Risk.	pHF-whey vs eHF-casein for 1 year.	1	Eczema (DD/nurse diagnosed)

Study	Design	No. Allocated Int/Ctrl	Country	Population	Treatment	Age at outcome (yr)	Outcomes reported (assessment method)
Scalabrin, 2009 [26]; Scalabrin, 2014 [27] (pHF or Nutramigen, both Mead Johnson)	RCT	95/95	USA	Solely formula fed for ≥ 24 hours prior to 14 days age. Normal risk.	eHF-casein plus LGG vs pHF with LGG, from <14 to 120-150 days.	0.4, 5	Allergic Sensitisation (sIgE-CM), Eczema (DD), Wheeze (DD), Allergic Rhinitis (DD), Food Allergy (DD)
Schmitz, 1992 [28] (Nidal HA, Nestlé)	RCT	128/128	France	Representative population. Normal risk.	pHF-whey vs standard formula for the first 5 days.	0.25, 0.4, 1	Eczema (DD), Allergic Rhinitis (DD), Allergic Sensitisation (sIgE), Wheeze (DD)
Schonberger, 2005 [29] (Nutrilon Pepti, Nutricia)	RCT	242/234	Netherlands	PREVASC Study. Mothers with family history of asthma. High Risk.	Multifaceted intervention including eHF-whey vs standard formula to 6 months.	2	Eczema (ICHPPC), Wheeze (Dutch Guideline “Asthma in Children” and ISAAC), Allergic Sensitisation (sIgE)
Shao, 2006 [30] (Formula unknown)	RCT	23/23	China	Infants with family history of atopy. High Risk.	Multifaceted intervention including pHF-whey vs standard formula, from birth to 12 months.	1.5	Eczema (Wolkerstorfer score), Allergic Sensitisation (SPT)

Study	Design	No. Allocated Int/Ctrl	Country	Population	Treatment	Age at outcome (yr)	Outcomes reported (assessment method)
Tsai, 1991 [31] (NanHA, Nestlé)	RCT	15/18	Taiwan	Healthy term infants at risk of allergy. High Risk.	pHF-whey from 1-2 to 6 months vs standard formula.	1	Eczema (clinical symptoms), Allergic Rhinitis (clinical symptoms), Wheeze, Allergic Sensitisation (sIgE)
Vaarala, 2012 [32] (Peptidi- Tutteli, Valio)	RCT	350/389	Finland	FINDIA Study. Term infants with high risk HLA-type but no maternal diabetes. High risk.	eHF-whey vs standard formula from birth to 6 months as needed.	0.25, 0.5, 3, 6	Diabetes (autoantibodies, clinical diagnosis)
Vandenplas 1992 [33]; Vandenplas 1995 [34] (NanHA, Nestlé)	RCT	~38/~38	Belgium	Family history of atopy, and not breast fed. High Risk.	pHF-whey vs standard formula, from birth to 6 months.	0.5, 1, 3	Eczema, Allergic Rhinoconjunctivitis (clinical symptoms), Wheeze (clinical symptoms), Allergic Sensitisation (sIgE, SPT), Food Allergy

Study	Design	No. Allocated Int/Ctrl	Country	Population	Treatment	Age at outcome (yr)	Outcomes reported (assessment method)
von Berg 2003 [35], 2008 [36], 2010 [37], 2013 [38] (BebaHA, Nestlé; Nutramigen, Mead Johnson; Hipp HA, Nutricia)	RCT	eHF-w 559; eHF-c 580; pHF-w 557; CM 556	Germany	GINI Study. First degree family member with allergic disease. Representative population. High Risk.	pHF-whey , eHF-casein or eHF-whey vs standard formula to 6 months as needed. 65% introduced formula <4 weeks.	1, 3, 6, 10	Eczema (Hanifin and Rajka criteria), Food Allergy - Any (IgE and non-IgE, clinical symptoms), Wheeze (parent reported ≥ 3 episodes), Allergic Sensitisation (sIgE)
Zeiger 1989 [39], 1995 [40] (Nutramigen, Mead Johnson)	RCT	Unclear. 103/185 followed at 4 months	USA	Infants covered by Kaiser Permanente Health Plan, with an allergic parent. High Risk.	Multifaceted intervention including eHF-casein , vs no intervention/standard formula to 1 year.	2, 4, 7	Eczema (Hanifin and Rajka Criteria), Allergic Rhinoconjunctivitis (DD), Food Allergy - Any (DD), Wheeze (≥ 2 physician diagnosed episodes), Allergic Sensitisation (SPT)
Exl, 1998 [41] (Beba HA, Nestlé)	qRCT	564/ 566	Switzerland.	ZUFF Study. Representative population. Normal risk.	pHF-whey with solid foods delayed to 4 months, vs standard care.	0.1, 0.25, 0.5	Eczema (parental monitoring and DD), Wheeze

Study	Design	No. Allocated Int/Ctrl	Country	Population	Treatment	Age at outcome (yr)	Outcomes reported (assessment method)
Halken, 2000 [42] (NanHA, Nestlé)	qRCT	pHF 85; eHF-w 82; eHF-c 79	Denmark	High risk infants with raised cord blood IgE. High risk.	pHF-whey vs eHF-casein or eHF-whey from birth to 4 months as needed.	1.5	Wheeze (≥ 3 physician diagnosed episodes), Eczema (DD), Allergic Rhinoconjunctivitis (DD), Food Allergy (Parental report/challenge)
Juvonen, 1994 [43]; Juvonen, 1996 [44]; Juvonen, 1999 [45] (Nutramigen, Mead Johnson)	qRCT	~43eHF; ~58 HM, ~43 CM	Sweden	Healthy term infants. Normal risk.	eHF-casein vs standard formula or human milk, from 0 to 3 days. Exclusively breast-fed thereafter.	0.17, 0.33, 0.67, 2, 3,	Food Allergy (clinical symptoms), Eczema (physician assessment), Wheeze (physician assessment), Allergic Sensitisation (SPT, sIgE)
Nentwich, 2001 [46] (Beba HA, Nestlé; Hipp HA, Nutricia)	qRCT	37/36	Czech Republic	Term infants with an allergic first degree relative. High Risk.	pHF-whey (Beba HA) vs eHF-whey for a mean 240 days in the first year.	0.5, 1	Eczema (physician assessment), Allergic Sensitisation (sIgE)
Saarinen, 1999 [47]; Savilahti, 2009 [48] (Pepti-Junior, Nutricia)	qRCT	1737 eHF; 1789 CM; 1859 HM	Finland	Infants with formula milk before hospital discharge. Normal risk.	eHF-whey vs standard formula or human milk, from birth for mean 4 days.	2, 11.5	Food allergy - CM (food challenge), Diabetes Mellitus (clinical diagnosis)

Study	Design	No. Allocated Int/Ctrl	Country	Population	Treatment	Age at outcome (yr)	Outcomes reported (assessment method)
Vandenplas, 1988 [49] (Formula unknown)	qRCT	Unclear. 15/60 assessed at 4 months	Belgium	Infants at risk of allergy. ? not breastfed. High Risk.	Hypoallergenic formula (?pHF) vs standard formula up to 4 months.	0.33	Allergic Sensitisation (sIgE, SPT)

ICHPPC International Classification of Health Problems in Primary Care, RCT Randomised controlled trial, qRCT Quasi-randomised controlled trial, DD Doctor diagnosis (community), Physician assessment is assessment by study physician, SPT skin prick test, sIgE specific IgE, CM cow's milk formula, HM human milk, pHF partially hydrolysed formula, eHF-c extensively hydrolysed, casein based formula, eHF-w extensively hydrolysed, whey based formula. Nan HA, Beba HA, Good Start, and Nidal HA are the same product with different brand names. Hipp HA and Nutrilon Pepti are the same product with different brand names.

Table B. Characteristics of Included Controlled Clinical Trials.

Study	Design	No. Allocated Int/Ctrl	Country	Population	Treatment	Age at outcome (yr)	Outcomes reported (assessment method)
Akimoto, 1997 [51] (Nan HA, Nestlé)	CCT	~35/~98	Japan	Newborn infants. Disease risk not stated	pHF-whey from birth to 6 months if needed, vs standard infant formula	0.33, 1, 1.5, 3	Eczema (questionnaire survey), Wheeze (questionnaire survey)
Han, 2003 [52] (HA21, Maeil Dairy Industry)	CCT	~40/~40	South Korea	Healthy term infants of parents with allergic disease attending a Dairy Industry maternity school. High Risk.	pHF vs standard formula from birth to 6 months as needed.	0.5	Eczema
Willems, 1993 [50] (Nan HA, Nestlé)	CCT	~90/~90	Belgium	Infants who were not breastfed, with first degree relative affected by allergy. High Risk.	pHF-whey vs standard formula, from birth to 3 months.	1	Eczema (DD), Wheeze (DD), Allergic Rhinoconjunctivitis (DD)

CCT Controlled Clinical Trial, DD Doctor diagnosis (community), pHF partially hydrolysed formula.

Table C. Risk of Bias and Generalisability/Study Conduct Issues in Included Trials Reporting Allergic Outcomes.

Study	Assessment Bias	Selection Bias	Attrition Bias	Overall Risk of Bias	Risk of Conflict of Interest	Generalisability/Study Conduct
Becker, 2004 [3]; Chan-Yeung, 2000 [4]; Chan-Yeung 2005 [5]; Wong, 2013 [6] (Good Start, Nestlé)	Low	Low	Low	Low	Low	Low uptake of hydrolysed formula in intervention group
Boyle 2015 [7] (pHF, Nutricia)	Unclear	Unclear	Unclear	Unclear	Unclear	Nil (abstract publication only)
Chan, 2002 [8] (NanHA, Nestlé)	Unclear	Unclear	Unclear	Unclear	High <i>formula company funded study</i>	All infants exclusively formula fed
Chirico, 1997 [9] (Vivena HA, Plada)	Unclear	Unclear	Unclear	Unclear	Unclear	Infants who ‘could not be breastfed’ were randomised to different formula groups on the first day of life
de Seta, 1994 [10] (Nidina HA, Nestlé)	Unclear	Unclear	Unclear	Unclear	Unclear	Breastfeeding not mentioned – intervention group may not have been breastfed at all
Dupont, 2009 [11] (Formula unknown)	Unclear	Unclear	Unclear	Unclear	Unclear	Insufficient information to assess (abstract publication only)

Study	Assessment Bias	Selection Bias	Attrition Bias	Overall Risk of Bias	Risk of Conflict of Interest	Generalisability/Study Conduct
Halken, 1993 [12] (Nutramigen, Mead Johnson; Profylac, ALK)	Unclear	Unclear	Unclear	Unclear	Unclear	Nil
Lovegrove, 1994 [14] (Peptijunior, Nutricia)	Low	Unclear	Low	Unclear	High <i>formula company funded study and first author</i>	Nil
Lowe, 2011 [15] (NanHA, Nestlé)	Low	Unclear	Low	Unclear	High <i>formula company funded study</i>	Nil
Mallet, 1992 [16] (Pregestimil, Mead Johnson)	High <i>non-blinded study</i>	Unclear	Low	High	Unclear	Insufficient information to assess
Marini, 1996 [17] (Nidina HA, Nestlé)	Low	Unclear	Low	Unclear	Unclear	Infants were enrolled on day 1 of life, and over 50% of infants were exclusively formula fed from this time
Martikainen, 1996 [18]; Vaarala, 1998 [19] (Nutramigen, Mead Johnson)	Unclear	Unclear	Unclear	Unclear	Low	Nil

Study	Assessment Bias	Selection Bias	Attrition Bias	Overall Risk of Bias	Risk of Conflict of Interest	Generalisability/Study Conduct
Moran, 1992 [20] (pHF, Mead Johnson)	Unclear	Unclear	High ~35% <i>randomised did not contribute to outcome analysis</i>	High	High <i>single author, an employee of formula company</i>	All infants exclusively formula fed
Odelram, 1996 [21] (Profylac, ALK)	Low	Unclear	High ~31% <i>randomised did not contribute to outcome analysis</i>	High	Low	Nil
Oldaeus, 1997 [22]; Oldaeus, 1999 [23] (pHF or Nutramigen, both Mead Johnson)	Low	Unclear	Low	Unclear	Unclear	Nil
Porch, 1998 [25] (Good Start, Nestlé; Nutramigen, Mead Johnson)	Low	Unclear	Low	Unclear	High <i>formula company funded study</i>	Some infants were randomly assigned to a formula milk at birth, with formula delivered to their local neonatal unit

Study	Assessment Bias	Selection Bias	Attrition Bias	Overall Risk of Bias	Risk of Conflict of Interest	Generalisability/Study Conduct
Scalabrin, 2009 [26]; Scalabrin, 2014 [27] (pHF or Nutramigen, both Mead Johnson)	Low	Low	High ~75% <i>randomised did not contribute to outcome analysis</i>	High	High <i>some authors were employees of formula company</i>	All infants solely formula fed for at least 24 hours prior to 14 days age.
Schmitz, 1992 [28] (Nidal HA, Nestlé)	Unclear	Unclear	Unclear	Unclear	Unclear	Nil
Schonberger, 2005 [29] (Nutrilon Pepti, Nutricia)	Unclear	Unclear	Low	Unclear	Unclear	Nil
Shao, 2006 [30] (Formula unknown)	Unclear	Unclear	Low	Unclear	Unclear	Infants were randomised to formula at birth
Tsai, 1991 [31] (NanHA, Nestlé)	Unclear	Unclear	Low	Unclear	High <i>formula supplier funded study</i>	All infants were exclusively formula fed

Study	Assessment Bias	Selection Bias	Attrition Bias	Overall Risk of Bias	Risk of Conflict of Interest	Generalisability/Study Conduct
Vandenplas 1992 [33]; Vandenplas 1995 [34] (NanHA, Nestlé)	Low	Unclear	Low	Unclear	High <i>formula company undertook statistical analysis</i>	All infants were exclusively formula fed
von Berg 2003 [35], 2008 [36], 2010 [37], 2013 [38] (BebaHA, Nestlé; Nutramigen, Mead Johnson; Hipp HA, Nutricia)	Low	Low	Low	Low	Unclear	Nil
Zeiger 1989 [39], 1995 [40] (Nutramigen, Mead Johnson)	Low	Unclear	High <i>unclear how many lost to follow up early; ~40% lost to follow up between age 4 months and 4 years</i>	High	Unclear	Nil
Exl, 1998 [41] (Beba HA, Nestlé)	High <i>outcome assessment unlikely to be blinded</i>	High <i>treatment allocated according to town of birth</i>	Low	High	High <i>formula company funded study and employed most of the authors</i>	Nil

Study	Assessment Bias	Selection Bias	Attrition Bias	Overall Risk of Bias	Risk of Conflict of Interest	Generalisability/Study Conduct
Halken, 2000 [42] (NanHA, Nestlé)	Low	Unclear	Low	Unclear	Unclear	Nil
Juvonen, 1994 [43]; Juvonen, 1996 [44]; Juvonen, 1999 [45] (Nutramigen, Mead Johnson)	Unclear	High <i>treatment allocated by maternal date of birth</i>	Low	High	Low	Breastmilk was withheld for the first 3 days of life in some infants
Nentwich, 2001 [46] (Beba HA, Nestlé; Hipp HA, Nutricia)	Low	Unclear	Low	Unclear	Low	Treatment allocation during pregnancy, and participants were told the name of their allocated formula before birth
Saarinen, 1999 [47]; Savilahti, 2009 [48] (Pepti-Junior, Nutricia)	Unclear	Unclear	Low	Unclear	Low	87% of infants received supplementary feeding during their postnatal hospital stay (mean 4 days)
Vandenplas, 1988 [49] (Formula unknown)	Unclear	High <i>inclusion was chronological</i>	High <i>number randomised not stated, but expected to be high</i>	High	Unclear	All infants were exclusively formula fed from birth

Study	Assessment Bias	Selection Bias	Attrition Bias	Overall Risk of Bias	Risk of Conflict of Interest	Generalisability/Study Conduct
Akimoto, 1997 [51] (Nan HA, Nestlé)	Unclear	High <i>no information about method of treatment allocation</i>	High <i>16 participants allocated to pHF were analysed in the control group due to poor compliance</i>	High	Unclear	Breastfeeding not mentioned – intervention group may not have been breastfed at all
Han, 2003 [52] (HA21, Maeil Dairy Industry)	Unclear	High treatment allocated according to parental preference	High ~40% randomised did not contribute to outcome analysis	High	High <i>formula company provided ‘assistance to the survey’</i>	Nil
Willems, 1993 [50] (Nan HA, Nestlé)	Unclear	High <i>treatment allocated according to month of birth</i>	High ~75% randomised did not contribute to outcome analysis	High	Unclear	All infants were exclusively formula fed from birth

Nan HA, Beba HA, Good Start, and Nidal HA are the same product with different brand names. Hipp HA and Nutrilon Pepti are the same product with different brand names. Explanations are provided where judgements were made that risk of bias or conflict of interest is High.

Table D. Risk of Bias and Generalisability/Study Conduct Issues in Included Trials Reporting Autoimmune Outcomes.

Study	Assessment Bias	Selection Bias	Attrition Bias	Overall Risk of Bias	Risk of Conflict of Interest	Generalisability/Study Conduct
Akerblom, 2005 [1] Knip, 2010 [2] (Nutramigen, Mead Johnson)	Low	Unclear	Low	Unclear	Low	Nil
Knip, 2014 [13] (Nutramigen, Mead Johnson)	Low	Low	Low	Low	Low	Nil
Martikainen, 1996 [18]; Vaarala, 1998 [19] (Nutramigen, Mead Johnson)	Unclear	Unclear	Unclear	Unclear	Low	Nil
Paronen, 2000 [24] (Nutramigen, Mead Johnson)	Unclear	Unclear	Unclear	Unclear	Low	Nil
Vaarala, 2012 [32] (Peptidi-Tutteli, Valio)	Unclear	Unclear	Low	Unclear	High <i>some authors were employees of formula company</i>	Nil
Saarinen, 1999 [47]; Savilahti, 2009 [48] (Pepti-Junior, Nutricia)	Unclear	Unclear	Low	Unclear	Low	87% of infants received supplementary feeding during their postnatal hospital stay (mean 4 days)

Explanations are provided where judgements were made that risk of bias or conflict of interest is High.

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