

REVIEW

Preventing food allergy in infancy and childhood: Systematic review of randomised controlled trials

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Abstract

Background: This systematic review of ways to prevent immediate-onset/IgE-mediated food allergy will inform guidelines by the European Academy of Allergy and Immunology (EAACI).

Methods: The GRADE approach was used. Eleven databases were searched from 1946 to October 2019 for randomized controlled trials (and large prospective cohort studies in the case of breastfeeding). The studies included heterogeneous interventions, populations, and outcomes and so were summarized narratively.

Results: Forty-six studies examined interventions to reduce the risk of food allergy in infancy (up to 1 year) or early childhood. The following interventions for pregnant or breastfeeding women and/or infants may have little to no effect on preventing food allergy, but the evidence is very uncertain: dietary avoidance of food allergens, vitamin supplements, fish oil, probiotics, prebiotics, synbiotics, and emollients. Breastfeeding, hydrolyzed formulas, and avoiding cow's milk formula may not reduce the risk of cow's milk protein allergy; however, temporary supplementation with cow's milk formula in the first week of life may increase the risk of cow's milk allergy. Introducing well-cooked egg, but not pasteurized raw egg, from 4 to 6 months probably reduces the risk of hen's egg allergy. Introducing regular peanut consumption into the diet of an infant at increased risk beginning from 4 to 11 months probably results in a large reduction in peanut allergy in countries with a high prevalence. These conclusions about introducing peanut are based on moderate certainty evidence, from single trials in high-income countries.

Conclusions: Sixty percent of the included studies were published in the last 10 years, but much still remains to be understood about preventing food allergy. In particular,

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there is a need to validate the potential benefits of early introduction of food allergens in a wider range of populations.

KEYWORDS

early introduction, food allergy, IgE-mediated, immediate-onset, prevention

1 | INTRODUCTION

1.1 | Rationale

Food allergy can adversely affect people's health and quality of life.¹ In high-income countries, up to one in 10 people may be affected and rates are increasing in low-income countries.² Various strategies have been hypothesized to prevent food allergy, including breast-feeding, hydrolyzed formula, supplements, avoiding food allergens, or introducing allergens into the diet to build tolerance. However, the evidence of effectiveness remains uncertain.

In 2014, the European Academy of Allergy and Clinical Immunology (EAACI) released a food allergy prevention guideline.³ Since that time, new research has been published so EAACI is updating its guideline.

Other reviews have explored ways to prevent food allergy, but guidelines cannot be based on these alone because they focused on single interventions or included studies of widely varying design.⁴⁻¹¹ Relevant studies were included in some past reviews but excluded from others (see Appendix S5).

1.2 | Objective

The aim of this review was to assess the effectiveness of any approach (intervention) for preventing the development of immediate-onset/

Key Message

The European Academy of Allergy and Clinical Immunotherapy (EAACI) is releasing guidelines for preventing the development of immediate-onset food allergy in 2020. This systematic review to inform the guidelines found that most interventions may have little to no effect on preventing food allergy.

IgE-mediated food allergy (outcome) in infants, children, and adults (population) compared to any other intervention or placebo (comparator).

2 | METHODS

The systematic review was conducted by a task force made up of allergy, gastroenterology, primary care and dietetic clinicians, immunologists and other researchers, patient representatives, methodologists, and information specialists (all authors). The task force included members from Europe, North America, Asia, and Australasia.

The methods are briefly described here. Details are available in the published protocol¹² and via the International Prospective Register of Systematic Reviews: CRD42019127457.

2.1 | Eligibility criteria

Studies were eligible for inclusion if they met the following criteria:

- **Population:** infants (up to 1 year old), children (13 months to 17 years), and/or adults (18+ years) with or without an increased risk for developing allergic disease and with or without any sensitization or atopic manifestations. "Increased risk" was defined as having a condition associated with food allergy such as eczema or asthma or having immediate relatives with a history of any allergy, atopic dermatitis, asthma, or hay fever.¹³
- **Intervention:** any intervention to prevent the development of new cases of immediate-onset food allergy
- **Comparator:** any independent, concurrently sampled group(s) with or without a placebo, intervention, or combination of interventions
- **Outcomes:** studies that reported new cases of immediate-onset food allergy, defined as a reproducible adverse response to a food protein within hours caused by an immunologic reaction (hereafter referred to as "food allergy")
- **Timeframe:** studies published from January 1, 1946, to October 31, 2019.
- **Study types:** Published randomized controlled trials (hereafter "trials") of any size and duration were eligible. Randomized trials of breastfeeding were limited, so prospective cohort studies of breastfeeding with at least 1000 participants at general risk or at least 200 participants at increased risk of food allergy were also eligible. Only published studies available in full form were included to allow full transparency. Where repeated reports of the same study were identified, the most up-to-date publication was included unless there were more relevant details in an earlier publication. There were no language or geographical restrictions.

2.2 | Study selection and data extraction

An information specialist/methodologist (CS) developed a search strategy and searched 11 databases (Appendix S1). Two methodologists identified additional references by searching the reference lists of previous reviews, guidelines and identified studies and by seeking recommendations from experts (CS and DdS).

Two methodologists independently screened titles, abstracts, and full text (CS and DdS). Shortlisted studies were rescreened by all clinicians and patient representatives on the task force (all authors) (κ : 0.96; SE: 0.03; 95% CI: 0.90-1.00). There was agreement about all but two studies (one where the outcome measure was not clearly identified as food allergy¹⁴ and another where the extent of

randomization was uncertain¹⁵). The task force agreed by consensus to include these studies.

Data about study characteristics and outcomes were extracted into a template in triplicate independently by two methodologists (CS and DdS) and by task force members divided into small topic groups (all authors, see description below). Where relative risk (RR) estimates were not presented in the published manuscript, they were calculated based on data in the paper using the csi function in Stata v15 (StataCorp).

2.3 | Risk of bias in individual studies

Two methodologists independently assessed the risk of bias in individual studies (CS and DdS) in triplicate with small groups of task force members (all authors). Trials were assessed using the Cochrane Risk of Bias Tool 2 (ROB2).¹⁶ Prospective cohort studies were assessed using ROBINS-I.¹⁷ Arbitration was available from a senior clinician (GR), but there was 100% agreement.

2.4 | Synthesis of results and risk of bias across studies

The certainty of evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.¹⁸

The published review protocol¹² specified that meta-analysis to quantify effect size would be undertaken for outcomes with three or more studies about the same intervention in the same risk-profile population. No intervention met the criteria for meta-analysis, so results about each intervention were summarized using narrative synthesis.

Groups of clinicians and methodologists reviewed studies about approaches implemented during pregnancy and breastfeeding (CV, HS, DdS), breastfeeding (GdT, SH, DdS), supplements during infancy (PE, SA, DdS), hydrolyzed infant formula (AH, AM, RB, SH, DdS), soy formula (GR, EK, DdS), timing of cow's milk introduction (GR, KG, DdS), introduction of complementary foods (KB, KG, DdS), and multicomponent interventions (EK, GR, KG, DdS). Authors were not involved in topics where they had a potential conflict. All task force members decided on the conclusions by consensus.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist was used to structure this article.¹⁹ Although there were exceptions, minimal detailed data were available about harms for most interventions so this review focuses on reporting effectiveness.

The task force used standardized GRADE statements to narratively summarize the effect size and the certainty of the evidence.²⁰ Table 1 provides definitions of the statements used throughout this review. For example, if the relative change was of moderate size but the certainty of the effect was low, the review used the wording "X may reduce/increase food allergy slightly." If the certainty of the effect size was very low, regardless of effect size, the terminology "X may have little to no effect on food allergy but the evidence is very uncertain" was used.

3 | RESULTS

3.1 | Study characteristics

Figure 1 summarizes the number of studies screened and reasons for exclusion (see also Appendix S6). Forty-six studies were included: 41 trials and five cohort studies about breastfeeding.

65% of studies were from Europe, 20% from Australasia, 11% from Asia, 2% from North America, and 2% from Africa. 57% of the studies were published between 2010 and 2019, 13% from 2000 to 2009, and 30% prior to 2000.

All studies focused on preventing the development of food allergy in infants (up to 1 year old, 35%) or early childhood (up to 5 years, 43%) or both (22%). Almost all examined dietary strategies. 61% (28 studies) focused on those at increased risk of developing food allergy. Appendix S4 summarizes the individual studies.

57% of the studies were at high risk of bias, 33% at moderate risk, and 10% at low risk (see Appendix S2). The GRADE certainty of evidence was generally low (Appendix S3). The certainty of evidence was often downgraded due to risk of bias, indirectness, and imprecision. Studies commonly had a lack of robust diagnostic criteria, high loss to follow-up, potential confounding, and lack of blinding and were underpowered for the outcome of interest. Many of the (older) trials did not appear to be registered, meaning it was not possible to ascertain whether the food allergy outcomes presented were selectively reported.

3.2 | Overview of findings

Table 2 summarizes key outcomes, and Figure 2 lists the conclusions.

The outcome of interest was the prevention of food allergy. The studies measured this outcome in a range of ways and at a variety of time periods. Space does not permit a description of every outcome, so a selection is provided here. The online supplement summarizes the outcomes for each intervention (see Appendix S3 and Appendix S7).

3.3 | Avoiding food allergens

Avoiding potential food allergens during pregnancy, when breastfeeding or in infancy may have little to no effect on food allergy in early childhood, but the evidence is very uncertain.

There were five trials in women at increased risk, two of which focused on dietary avoidance alone and three combined with another intervention.

One trial examined avoiding cow's milk and egg during pregnancy (cumulative food allergy incidence: 0-1.5 years; RR: 1.67; 95% confidence interval (CI): 0.38-7.22, $P > .05$, very low certainty).²¹

Another examined milk and egg exclusion during the third trimester of pregnancy and while breastfeeding (cow's milk allergy cumulative incidence: 0-1.5 years; RR: 1.01, CI: 0.15-7.02, $P > .05$, low certainty).²²

Another trial examined dietary avoidance among breastfeeding women and infants for 12 months coupled with bedroom and living room treatments every 3 months (food allergy cumulative incidence: 0-1 year; RR: 0.31; CI: 0.07-1.41, $P > .05$, very low certainty).²³

Two trials combined food allergen avoidance with hydrolyzed formulas (results described in formula section).^{24,25}

3.4 | Avoiding conventional cow's milk formula

Avoiding conventional cow's milk-based formula may not reduce cow's milk protein allergy in infancy or early childhood when the formula is consumed on a recurring basis (low certainty). Seven trials examined this in general and increased risk infants^{14,26-31} (see Appendix S3 for outcomes).

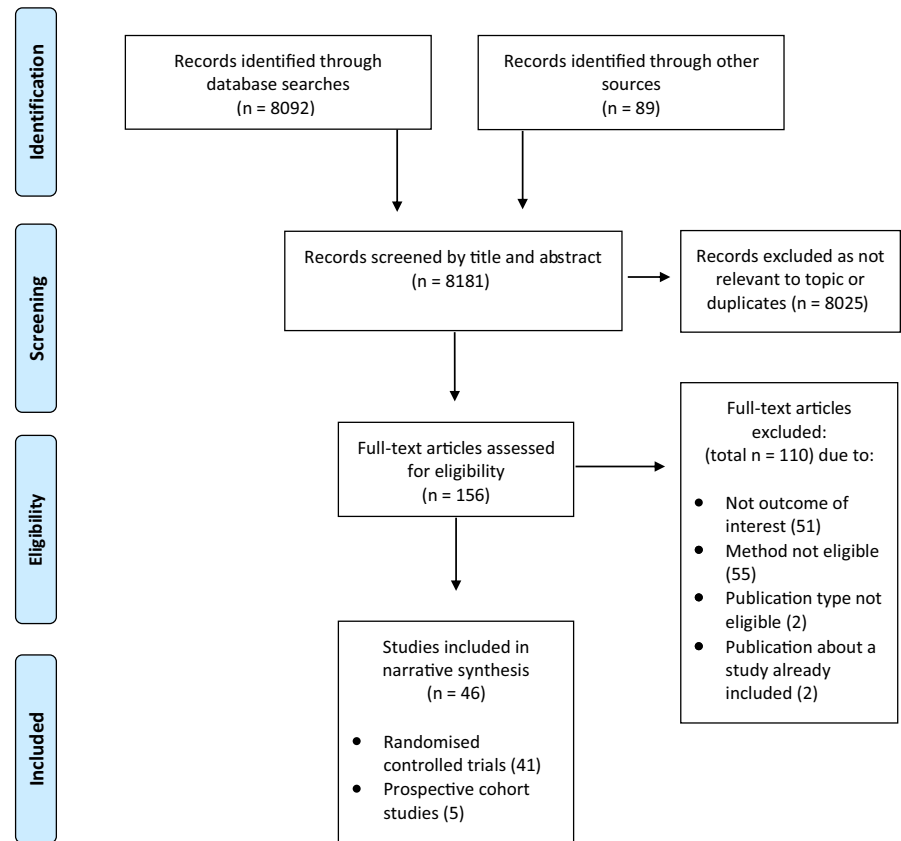
However, avoiding temporary supplementation with cow's milk formula in the first 3 days of life may result in a large decrease in the risk of cow's milk protein allergy in early childhood (1 trial, cumulative incidence: 0-2 years; RR: 0.10; CI: 0.01-0.77, $P < .05$, low certainty).³²

TABLE 1 Wording conventions used in this article to summarize effect size

Certainty of evidence	Size of effect			
	None/minor/not clinically meaningful (0%–39% relative change)	Small and important (40%–60% relative change)	Medium (61%–80% relative change)	Large (81%+ relative change)
High	X does not reduce/increase food allergy	X reduces/increases food allergy slightly	X reduces/increases food allergy	X results in a large reduction/increase in food allergy
Moderate	X probably does not reduce/increase food allergy	X probably reduces/increases food allergy slightly	X probably reduces/increases food allergy	X probably results in a large reduction/increase in food allergy
Low	X may not reduce/increase food allergy	X may reduce/increase food allergy slightly	X may reduce/increase food allergy	X may result in a large reduction/increase in food allergy
Very low	X may have little to no effect on food allergy but the evidence is very uncertain			

Note: Small, medium, and large effect sizes were all required to be deemed clinically important in order to be considered as a substantive effect.

FIGURE 1 PRISMA diagram showing study selection



3.5 | Introducing hen's egg to the infant diet

Introducing small amounts of cooked, but not pasteurized/raw, hen's egg into the infant diet as part of complementary feeding probably reduces the risk of egg allergy in infancy.

One trial in high-risk infants used cooked egg doses of 50 mg and up per day (equivalent to 1/160th of an egg) from 6 to 9 months and 250 mg per day thereafter until 12 months (egg allergy at 1 year, RR: 0.22; CI: 0.08-0.54, $P < .05$, moderate certainty)³³ This trial used much smaller amounts of egg compared to other studies.

Early introduction of pasteurized raw hen's egg powder probably does not reduce the risk of egg allergy. One trial focused on infants at general risk (1-year prevalence, RR: 3.30; CI: 0.35-31.32; $P > .05$, low certainty).³⁴ Two trials were conducted in infants at increased risk (1-year prevalence, RR: 0.75; CI: 0.48-1.17, $P > .05$ ³⁵ and RR: 0.65; CI: 0.38-1.11, $P > .05$,³⁶ low certainty).

3.6 | Introducing peanut to the infant diet

In countries with a high prevalence of peanut allergy, introducing peanut into the diet of infants at increased risk from 4 to 11 months probably results in a large reduction in peanut allergy compared to completely abstaining from peanut in the first 5 years.

Two trials introduced the equivalent of three heaped teaspoons of peanut butter per week (6g) to infants with severe eczema and/or egg allergy from 4 to 11 months (median 7.8 months) and maintained

weekly intake for 5 years. One trial included infants with positive skin prick test to peanut and one without (overall RR for peanut allergy incidence at 5 years: 0.18; CI: 0.10-0.35, $P < .05$, moderate certainty).^{37,38}

3.7 | Introducing multiple food allergens

Introducing multiple potential food allergens to the infant diet from 3 months probably does not reduce food allergy in infancy or early childhood. One trial in infants at general risk compared introducing peanut, cooked egg, cow's milk, sesame, whitefish, and wheat from 3 months vs exclusive breastfeeding to approximately 6 months (food allergy cumulative prevalence: 1-3 years; RR: 0.8; CI: 0.51-1.25, $P > .05$, low certainty). Adherence was very low.³⁹

3.8 | Breastfeeding

Breastfeeding has many benefits for infants and mothers,⁴⁰ but it may not reduce the risk of food allergy.

Five large prospective birth cohorts examined the link between breastfeeding and food allergy in general risk infants,⁴¹⁻⁴⁵ and two studies focused on infants at increased risk^{15,26} (cow's milk protein allergy RR ranged between 0.38 and 2.08, low certainty). Most studies did not include robust diagnostic criteria.

TABLE 2 Summary of effectiveness of interventions to prevent food allergy

Intervention	Timing/type	Absolute effect	Relative risk (95% CI)	Certainty of effect	Overall conclusion	Studies (participants)
Dietary avoidance of food allergens	Pregnancy	2% increase	0-1.5 y, 1.67 (0.38-7.22)	Very low	Little to no effect	1 RCT (198) ²¹
	Pregnancy and breastfeeding	0% change	Cow's milk 0-1.5 y, 1.01 (0.15-7.02)	Very low	Little to no effect	1 RCT (164) ²²
	Pregnant and/or breastfeeding women and infants	8%-11% decrease	0-1 y, 0.31 (0.07-1.41) and 1-year prevalence, 0.3 (0.12-0.77)	Very low	Little to no effect	2 RCTs (399) ^{23,24}
Avoiding standard cow's milk-based formula	Avoiding standard cow's milk formula	Range 22% decrease to 2% increase	See supplement for multiple outcomes	Low	May not reduce or increase	7 RCTs (4327) ^{14,26-31}
	Avoiding temporary supplement of cow's milk in first week of life	6% decrease	0-2 y cow's milk allergy, 0.10 (0.01-0.77)	Low	Avoiding supplementation may decrease	1 RCT (312) ³²
Introducing complementary foods	Cooked hen's egg from 6 mo	29% decrease	Egg allergy prevalence at 1 y, 0.22 (0.08-0.54)	Moderate	Probably reduces	1 RCT (147) ³³
	Raw/pasteurized egg from 4 mo	18% decrease to 2% increase	Egg allergy prevalence at 1 y, range 0.65-3.3 (see supplement)	Low	May not reduce	3 RCTs (1289) ³⁴⁻³⁶
	Peanut from median 7.8 mo in increased risk	12%-23% decrease	Peanut allergy incidence at 5 y, range 0.14-0.35	Moderate	Probably large reduction	2 RCTs (640) ^{37,38}
	6 allergenic foods from 3 mo	2% decrease	1-3 y, 0.8 (0.51-1.25)	Low	May not reduce	1 RCT (1303) ³⁹
Breastfeeding	Infancy	Range 3% decrease to 2% increase	See supplement for multiple outcomes	Low	May not reduce	7 studies (15 046) ^{15,26,41-44}
Hydrolyzed formula	Partially hydrolyzed in infancy	Range 34% decrease to 11% increase	See supplement for multiple outcomes	Low	May not reduce	5 RCTs (3572) ^{14,15,27-29}
	Extensively hydrolyzed in infancy	Range 4% decrease to 2% increase	See supplement for multiple outcomes	Low	May not reduce	5 RCTs (3221) ^{15,28-30,46}
	Hydrolyzed formula plus dietary avoidance	Range 9% to 11% decrease	0-1.5 y cow's milk allergy, 0.18 (0.01-3.37)	Very low	Little to no effect	2 RCTs (470) ^{24,25}
Soy-based formula	Infancy	1% increase	0-2 y cow's milk allergy, 1.35 (0.48-3.81)	Very low	Little to no effect	1 RCT (620) ²⁷
Vitamins	Pregnancy	6% increase	0-3 y, 1.92 (0.57-6.5)	Very low	Little to no effect	1 RCT (180) ⁴⁷
	Breastfeeding	18% increase	0-2 y, 3.42 (1.02-11.77)	Very low	Little to no effect	1 RCT (164) ⁴⁸
	Infancy	2% increase	0-1 y, 1.33 (0.76-2.33)	Very low	Little to no effect	1 RCT (975) ⁴⁹

(Continues)

TABLE 2 (Continued)

Intervention	Timing/type	Absolute effect	Relative risk (95% CI)	Certainty of effect	Overall conclusion	Studies (participants)
Fish oil	Pregnancy	Range 4% decrease to 1% increase	See supplement for multiple outcomes	Low	May not reduce	2 RCTs (789) ^{50,51}
	Pregnancy and breastfeeding	14% decrease	0-1 y, 0.13 (0.02-0.95)	Low	May decrease slightly	1 RCT (145) ⁵²
	Infancy	3% decrease	0-1 y, 0.81 (0.47-1.42)	Very low	Little to no effect	1 RCT (420) ⁵³
	Breastfeeding and infants	2% increase	0-1.5 y, 1.24 (0.62-2.50)	Low	May not reduce	1 RCT (655) ⁵⁴
Prebiotics	Infancy	12% decrease	0-1.5 y, 0.28 (0.08-1.0)	Very low	Little to no effect	1 RCT (240) ⁵⁵
Probiotics	Infancy	Range 2%–4% decrease	See supplement for multiple outcomes	Low	May not reduce	3 RCTs (563) ⁵⁶⁻⁵⁸
	Pregnancy, BF, and/or infancy	10% increase	0-2 y cow's milk allergy, 1.87 (0.74-4.69)	Very low	Little to no effect	2 RCTs (256) ^{59,60}
Prebiotics plus probiotics	Probiotics in pregnancy and infants plus prebiotic in infants	1% decrease	0-2 y, 0.89 (0.51-1.55)	Low	May not reduce	2 RCTs (1116) ^{61,62}
Other	Synbiotics	0% change	Prevalence at 1 y, 1.03 (0.63-1.68)	Low	May not reduce	1 RCT (459) ⁶³
	Emollients	2% decrease	Prevalence at 1 y, 0.81 (0.49-1.33)	Low	May not reduce	1 RCT (459) ⁶³
	Prophylactic oral immunotherapy	6% decrease	0-1 y, 0.38 (0.1-1.9)	Very low	Little to no effect	1 RCT (111) ⁶⁴
	BCG vaccination	0% change	0-13 mo, 1.48 (0.67-3.29)	Very low	Little to no effect	2 RCTs (4543) ^{65,66}

Note: The table provides the absolute and relative reductions for new cases of "food allergy" (unless allergy to a specific food is specified). Where there were multiple studies, the range of point estimate effect sizes is inserted. The outcome is cumulative incidence unless otherwise stated. There were multiple outcomes measured for most interventions, and these are listed in the Appendix S3.

- Avoiding potential food allergens during pregnancy, when breastfeeding or in infancy may have little to no effect on food allergy in early childhood but the evidence is very uncertain. The same is true of combining dietary avoidance with environmental interventions.
- Avoiding conventional cow's milk-based formula may not reduce cow's milk protein allergy in infancy or early childhood when the formula is consumed on a recurring basis. However avoiding temporary supplementation with conventional cow's milk formula in the first three days of life may result in a large decrease in the risk of food allergy in early childhood.
- Introducing small amounts of cooked, but not pasteurised or raw, hen's egg into the infant diet as part of complementary feeding probably reduces the risk of egg allergy in infancy.
- In countries with a high prevalence of peanut allergy, introducing regular peanut consumption from 4-11 months of life in infants at increased risk probably results in a large reduction in peanut allergy in early childhood compared to completely avoiding peanut for the first five years.
- Introducing multiple potential food allergens to the infant diet simultaneously from three months probably does not reduce food allergy in infancy or early childhood.
- Breastfeeding has many benefits for infants and mothers but it may not reduce the risk of food allergy or cow's milk allergy.
- Partially or extensively hydrolysed whey or casein formula may not reduce the risk of cow's milk protein allergy compared to conventional cow's milk formula. There was little to no evidence that one type of hydrolysed formula was more effective than others.
- Soy-based formula may have little to no effect on cow's milk protein allergy in early childhood but the evidence is very uncertain.
- Vitamin supplements for pregnant and/or breastfeeding women or infants may have little to no effect on food allergy in early childhood but the evidence is very uncertain.
- Fish oil supplements during pregnancy, when breastfeeding or in infancy may not reduce food allergy in infancy or early childhood. However when taken during pregnancy and continued during breastfeeding, fish oil may reduce food allergy slightly in young children at increased risk.
- Prebiotics, probiotics and synbiotics for mothers and infants may have little to no effect on food allergy in infancy and early childhood but the evidence is very uncertain.
- Non-antigen specific immune modulation through prophylactic immunotherapy or BCG vaccination for tuberculosis may have little to no effect on food allergy in infancy and early childhood but the evidence is very uncertain.

FIGURE 2 Summary of key conclusions

3.9 | Hydrolyzed infant formula

Partially or extensively hydrolyzed whey or casein formula may not reduce the risk of food allergy compared to conventional cow's milk formula. There is low certainty about this as the trials used various formulas and introduced formulas at different times and for varying durations. The diagnostic criteria for food allergy in most trials were not robust or clearly reported.

In increased risk infants, three out of four trials comparing partially hydrolyzed formula with conventional cow's milk formula found little to no effect.²⁷⁻²⁹ A small older trial that used food challenges found reduced cumulative incidence of cow's milk sensitivity (challenge-proven) at 1 year (RR: 0.36; CI: 0.15-0.89, $P < .05$, very low certainty).¹⁴

Three trials of different extensively hydrolyzed formulas found little to no effect on food allergy in infancy and early childhood (low certainty).²⁸⁻³⁰ There was little to no evidence that one type of hydrolyzed formula was more effective than others.^{15,46}

Combining dietary avoidance of food allergens plus hydrolyzed formula may have little to no effect on food allergy, but the evidence is very uncertain. In those at increased risk, one trial examined extensively hydrolyzed formula plus maternal/infant dietary avoidance (period prevalence: 0-1 year; RR: 0.3; CI: 0.12-0.77, $P < .05$, very low certainty).²⁴ Another trial combined whey extensively hydrolyzed formula for infants with an avoidance diet for mothers and infants (cow's milk allergy cumulative incidence: 0-1.5 years; RR: 0.18; CI: 0.01-3.37, $P > .05$, very low certainty).²⁵

3.10 | Soy-based formula

Soy-based formula may have little to no effect on food allergy in early childhood, but the evidence is very uncertain. One trial compared soy-based formula to cow's milk formula in infants at increased risk (cow's milk protein allergy cumulative incidence: 0-2 years; RR: 1.35; CI: 0.48-3.81, $P > .05$, very low certainty).²⁷

3.11 | Vitamin supplements

Vitamin supplements for pregnant and/or breastfeeding women or infants may have little to no effect on food allergy in early childhood, but the evidence is very uncertain.

In pregnant women at general risk, there was one trial of vitamin D daily from 27 weeks of gestation to birth (food allergy cumulative incidence: 0-3 years; RR: 1.92; CI: 0.57-6.5, $P > .05$, very low certainty).⁴⁷

In breastfeeding women whose infants were at increased risk, one trial examined 6 weeks of vitamin D supplements (food allergy cumulative incidence: 0-2 years; RR: 3.42; CI: 1.02-11.77, $P < .05$, very low certainty).⁴⁸

In infants at general risk, one trial compared a higher or lower dose of vitamin D from 2 weeks of age (food allergy cumulative incidence: 0-1 year; RR: 1.33; CI: 0.75-2.33, $P > .05$, very low certainty).⁴⁹

3.12 | Fish oil

When taken in pregnancy alone, fish oil may not reduce food allergy in infancy (1-year incidence, RR: 0.65; CI: 0.16-2.5, $P > .05$, low certainty)⁵⁰ or in early childhood (3-year incidence, RR: 1.36; CI: 0.59-3.11, $P > .05$, low certainty).⁵¹

Fish oil supplements taken by women during both pregnancy and breastfeeding may reduce food allergy slightly in young children at increased risk, but the certainty of evidence is low. There was only one relevant trial (food allergy cumulative incidence: 0-1 year; RR: 0.13; CI: 0.02-0.95, $P < .05$, low certainty).⁵²

Fish oil for infants may have little to no effect on food allergy in infancy, but the evidence is very uncertain. There was one trial in infants at increased risk (cumulative incidence: 0-1 year; RR: 0.81; CI: 0.47-1.40, $P > .05$, very low certainty).⁵³

Fish oil for mothers and infants combined may not reduce food allergy. One trial in preterm infants examined mothers taking tuna oil and infants receiving a high DHA formula if needed as a supplement (cumulative incidence of food allergy: 0-1.5 years; RR: 1.24; CI: 0.62-2.50, $P > .05$, low certainty).⁵⁴

3.13 | Prebiotics, probiotics, and synbiotics

Prebiotics, probiotics, and synbiotics for infants may have little to no effect on food allergy in infancy and early childhood, but the evidence is very uncertain.

In general risk infants, one trial of prebiotics tested formula with oligosaccharides (scGOS/lcFOS) (cumulative incidence of food allergy: 0-1.5 years compared with standard formula; RR: 0.28, CI: 0.28-1.00, $P > .05$, very low certainty).⁵⁵

Three trials examined various probiotics: *Lactobacillus acidophilus* for 6 months in general risk infants⁵⁶; *Bifidobacterium infantis* (BB-02), 155 *Streptococcus thermophilus* (TH-4), and *Bifidobacterium lactis* (BB-12) until hospital discharge in very preterm general risk infants⁵⁷; and *Bifidobacterium breve* C50 and *S thermophilus* (TH-4) for 1 year in increased risk infants⁵⁸ (see Appendix S3).

Probiotics with or without prebiotics for women and infants may have little to no effect on food allergy, but the evidence is very uncertain. For increased risk infants, one trial examined probiotics (*Lactobacillus rhamnosus* GG) taken by pregnant women and continued when breastfeeding or directly by infants for 6 months (cumulative incidence of cow's milk protein allergy: 0-2 years; RR: 1.87; CI: 0.74-4.69, $P > .05$, very low certainty).⁵⁹ Another trial examined three strains of probiotics taken for 6 weeks by pregnant women and continued for a year by infants (*B bifidum* W23, *B lactis* W52, and *Lc. lactis* W58) (data not reported, $P > .05$, very low certainty).⁶⁰

Two trials examined probiotics for women and infants combined with prebiotics for infants (*L rhamnosus* GG (ATCC53103), *L rhamnosus* LC705 (DSM 7061), *B breve* Bb99 (DSM 13692), *Propionibacterium freudenreichii* ssp *shermanii* JS (DSM 7076), and galacto-oligosaccharides) (food allergy cumulative incidence: 0-2 years; RR: 0.89; CI: 0.51-1.55, $P > .05$, low certainty overall).^{61,62}

In infants at general risk, one trial examined synbiotics (*B bifidum* OLB6378 plus fructo-oligosaccharides) from birth to 6 months (food allergy prevalence at 1 year, RR: 1.03; CI: 0.63-1.68, $P > .05$, low certainty).⁶³

3.14 | Non-antigen-specific immune modulation

Prophylactic immunotherapy or BCG vaccination for tuberculosis may have little to no effect on food allergy in infants and early childhood, but the evidence is very uncertain.

There was one trial of prophylactic house dust mite oral immunotherapy in increased risk infants (food allergy cumulative incidence: 0-1 year; RR: 0.38; CI: 0.1-1.9, $P > .05$, very low certainty).⁶⁴

There were two trials of BCG vaccination in general risk populations (food allergy prevalence at 1 year, RR: 1.17; CI: 0.55-2.48⁶⁵; cumulative prevalence: 0-13 months; RR: 1.48; CI: 0.67-3.29, $P > .05$,⁶⁶ very low certainty).

3.15 | Interventions begun in childhood and adulthood

No eligible studies were identified of interventions begun in childhood (after 1 year) or adulthood.

4 | DISCUSSION

4.1 | Summary of evidence

Figure 2 summarizes the conclusions from the review. In pregnant and breastfeeding women, the following interventions have been tested to prevent food allergy: dietary avoidance of food allergens, vitamin supplements, fish oil, and probiotics. All of these interventions may have little to no effect on food allergy, but the evidence is very uncertain.

In infants, the following interventions have been tested to prevent food allergy: breastfeeding, hydrolyzed formulas, dietary avoidance of food allergens, early introduction of food allergens, probiotics, prebiotics, synbiotics, fish oil, vitamin supplements, emollients, and environmental changes. Most of these interventions may have little to no effect on food allergy, but the evidence is very uncertain. The exception is introducing peanut and cooked egg into the infant diet around the time that complementary feeding begins. Introducing cooked egg as part of the usual infant diet probably reduces the risk of egg allergy, and feeding infants at increased risk peanut in an age-appropriate form probably results in a large reduction in peanut allergy compared to complete abstinence in populations with a high prevalence of peanut allergy.

4.2 | Comparison with previous research

At least 35 systematic reviews have examined approaches to prevent food allergy (Appendix S5), but most did not cover the wide range of interventions in the current review.

The findings of this review align with others in concluding that most interventions have limited evidence of effectiveness. This review is perhaps more conservative than some, because it took into account whether the intervention was in pregnant women, breastfeeding women, or infants and whether it was in populations at general or increased risk of food allergy. Some other reviews have combined heterogeneous interventions with different timing, doses, and population risk profiles in meta-analysis, but this may result in conclusions that are difficult to apply in practice. For instance, meta-analysis combining raw and cooked egg found a RR of 0.60 (CI 0.42-0.85)⁶⁷ The current review looked at raw and cooked egg separately, accounted for whether the population was at general or increased risk, and excluded from this analysis studies that contained multiple confounding interventions. Our conclusion is that at this stage, there is only evidence that cooked egg has a preventive effect, not raw/pasteurized egg.

Other published meta-analyses, which pooled the results from studies with different populations and interventions, support the conclusions of this review.⁶⁸ For instance, one meta-analysis concluded that hydrolyzed formulas likely do not reduce the risk of food allergy compared to standard cow's milk formula (partially hydrolyzed RR: 1.73; CI: 0.79-3.80, and extensively hydrolyzed RR: 0.86; 0.26-2.82).⁸ Another meta-analysis found that introducing peanut in the first year may reduce the risk of peanut allergy

(RR: 0.28; CI: 0.14-0.57).⁶⁹ Another meta-analysis concluded that fish oil did not reduce the risk of food allergy when started in pregnancy (OR: 0.46; CI: 0.16-1.38) or given to infants (OR: 0.34; CI: 0.10-1.15).⁷⁰ The current review adds value by compiling all the highest quality studies about multiple topics in one place and by ensuring the most up-to-date research findings are added. 60% of the studies included in this review were published in the past decade.

4.3 | Implications for practice and research

The implication for clinicians, families, and policymakers is that there is no evidence-based intervention to reduce food allergy for all infants. In those at increased risk, introducing peanut and cooked egg in the first year of life is likely to be beneficial. Large trials with longitudinal follow-up have concluded that this is safe and inexpensive to do,^{37,39} although the research is confined to high-income countries and populations with high prevalence of specific allergies. The effect appears to be specific to egg and peanut allergy. There was no significant effect on other allergies, including other food allergies. Further research is needed to confirm the generalizability of these findings in general risk populations and low- to middle-income countries.

There was a trend toward benefit when fish oil was taken by women starting in pregnancy and continuing during breastfeeding. However, this was based on one study and so could be explored further. Research could also explore the value of currently available hydrolyzed formulas, particularly as most trials did not use challenge-proven food allergy as an outcome.

The potentially harmful effects of temporary supplementation with cow's milk formula in the first week of life and the effects of hydrolyzed formula in the first 6 months of life require further research using well-defined and accepted diagnostic criteria.

4.4 | Strengths and limitations

This review was conducted by a task force of diverse clinicians, public representatives, and researchers. This was a strength because it allowed studies to be considered on clinical and methodological grounds, with robust checks by multiple experts. This also had challenges because it required consensus about study interpretation and bias from people with diverse perspectives.

This review provides the most up-to-date summary of robust research, but it has several limitations. The available evidence is heterogeneous and mostly at high risk of bias. A number of studies did not use appropriate criteria to diagnosis food allergy. Studies were often small and so may not have been powered to detect significant differences between groups. Meta-analysis was not deemed appropriate because the interventions and population risk profiles varied greatly. Very few studies reported in detail on safety outcomes or explored costs.

Not all potential preventive strategies are included in the review because only the most rigorous study designs were eligible.

Much of the evidence comes from high-income countries. Data from low- and middle-income countries are scarce. Findings may not be applicable to all regions, particularly where the infant diet is not rich in the same “allergenic” foods and allergies to peanut and egg are rare.

Food allergy is complex because the symptoms are diverse and often not specific to food allergy. Allergies can manifest in many different forms. Infants and young children sometimes outgrow their allergy, especially those who are allergic to cow's milk protein. The impact of preventive interventions can be difficult to measure because there are many confounding factors. Taking extensively hydrolyzed infant formula as an example, findings may differ depending on the type of formula, when it was introduced, the duration of use, whether it was used exclusively or in combination with other feeding, whether infants were at increased risk, whether other interventions were used simultaneously, and whether diagnostic food challenges were performed. Variations in such factors make it difficult to draw conclusions to help clinicians and families translate research findings into real-world use.

According to EAACI guidelines,⁷¹ the optimal way to diagnose food allergy is by combining relevant clinical symptoms with elimination/challenge procedures and IgE sensitization. Such diagnostic criteria were used in few studies in this review. Many studies used criteria such as parental reports. The task force took into account the diagnostic criteria used in the GRADE assessment.

5 | CONCLUSIONS

Knowing how to prevent food allergy would help to alleviate health, social, and financial impacts. Historically, efforts to prevent food allergy have relied on identifying infants at increased risk and recommending they avoid potential allergens. This approach may be out of date. Strategies to facilitate increased immunologic tolerance, including the early introduction of potential food allergens, have encouraging findings which could help to optimize community-based prevention.

Even so, this systematic review suggests that there is much left to learn about which strategies should be routinely implemented to prevent food allergy. Even in the case of early introduction of cooked egg and peanut, more research is needed to validate the trends in a variety of countries and for populations at varied risk. There is no good evidence that families should avoid food allergens or take supplements to prevent food allergy over and above a well-rounded diet for pregnant and breastfeeding women and their infants.

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CONFLICT OF INTERESTS

CS, DdS, EA, EK, HA, SA, and VV declared no potential interests. Some of the authors have professional affiliations related to the content of the review as set out below. During the conduct of the review itself, these authors were not involved in decisions about study selection, data extraction, or analysis of studies in fields where they had a declared interest. AM has received research funding from Aimmune and is a speaker for DBV, Aimmune, Mylan, ALK, and Nestle; AH is a speaker for Nestle, Bristol-Myers, and ALK; CJ is an employee of Allergy UK. Allergy UK has received funding from Abbott, Aimmune, Allergy Therapeutics, DBV, Danone, Nutricia, Mead Johnson, and Sanofi Genzyme; CV has received research funding from Thermo Fisher and is a speaker for Danone, Abbott, Nestle, and Mead Johnson; GdT is a research investigator of Aimmune, DBV, NIH (LEAP study), and Action Medical (EAT study) and is an executive member of Allergy Academy; GL is a research investigator of NIH (LEAP study) and Action Medical (EAT study); consultant for DBV, Aravex, Aimmune, ALK, Novartis, and Sanofi Genzyme; and shareholder of DBV and Mission MightyMe; GR is research investigator of NIH (LEAP study) and Action Medical (EAT study); consultant for Nutricia; and editor-in-chief of Clinical & Experimental Allergy; HS is consultant for Danone, Nestle, and Nutricia; speaker for Danone, Hipp, Nestle, and Nutricia; and editor-in-chief of Journal of Pediatric Gastroenterology and Nutrition (to June 2019); KB has received funding for research activities from Aimmune, ALK, Berliner Sparkassenstiftung, Danone, DBV, DST Diagnostic, Good Mills, Hipp, Hycor, InfectoPharm, Thermo Fisher, VDI, EU, German Research Foundation, and BMBF, and is a consultant for Aimmune, ALK, Allergopharma, Bausch & Lomb, Bencard, Danone, Hycor, Di-Text, Hammer und Rall Media, InfectoPharm, Mabyon, Meda Pharma, Mylan, Nestle, and Unilever; KG is a consultant for Nutricia, Abbott, Mead Johnson, and Reacta Biotech; RB is a consultant for Dairy Goat Cooperative and is the Senior Editor of the Cochrane Children and Families; PE has received funding for research activities from LETI, Nestle, and Thermo Fisher, and is a consultant for Danone, Novartis, ALK, DBV, Stallergenes, and Abbott and editor-in-chief of PAI; and SH is a consultant for ALK and has received research funding from ALK.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Supplementary online material

Preventing food allergy in infancy and childhood: systematic review of randomised controlled trials

This supplementary file includes the following:

S1	Search strategy	p2
S2	Risk of bias in individual studies	p6
S3	Summary of findings and evidence profiles plus narrative summary	p8
S4	Summary of individual studies	p42
S5	Studies included in other systematic reviews	p82
S6	Full text studies screened but excluded	p90
	References	p93

Throughout:

CI = confidence interval

OR = odds ratio

RCT = randomised controlled trial

RR = relative risk

SPT = skin prick test

sIgE = specific IgE

S1. Search strategy

To identify potentially relevant research, the following 11 bibliographic databases were searched for studies published from database inception to 31 October 2019:

- Cochrane Library, including:
 - o Cochrane Database of Systematic Reviews (CDSR)
 - o Database of Reviews of Effectiveness (DARE)
 - o CENTRAL (Trials)
 - o Methods Studies
 - o Health Technology Assessments (HTA)
 - o Economic Evaluations Database (EED)
- MEDLINE (OVID)
- Embase (OVID)
- CINAHL (Ebscohost, Cumulative Index to Nursing and Allied Health Literature)
- ISI Web of Science (Thomson Web of Knowledge)
- Science Citation Index and Social Sciences Citation Index
- WHOLIS (World Health Organization Library Information System)
- PAHO (Pan American Health Organization database)
- TRIP Database (www.tripdatabase.com)
- WHO ICTRP (World Health Organization International Clinical Trials Registry Platform; www.who.int/ictpr)
- US National Institutes of Health Ongoing Trials Register (Clinicaltrials.gov, NIH web)

Unpublished research was not eligible for inclusion, but trial registries were searched to identify relevant authors and studies that may since have been published.

The EAACI Guidelines Taskforce worked with a methodological team. The methodological team developed and validated a sensitive search strategy. To retrieve randomised controlled trials, the Cochrane strategy for identifying trials in MEDLINE was used: sensitivity- and precision-maximizing version.¹ The search strategy was devised on OVID MEDLINE and adapted for other databases. The search strategies are presented overleaf.

Additional references were located through the methodological team searching the reference lists of identified studies and systematic reviews and through discussion with experts in the field up. The EAACI Guidelines Taskforce contained experts active in the field from a range of disciplines and geographic locations as well as patient representative groups. The Taskforce commented on the search strategy and suggested additional studies for screening.

The methodological team identified 35 systematic reviews about relevant topics available as of 1 August 2019. These were not eligible for inclusion in the review because they used different outcome measures and combined heterogeneous interventions. However the reviews were used as a source to identify other potential studies. The EAACI Guidelines Taskforce screened studies from within these systematic reviews to identify those for further review by the methodological team. This was triangulated with screening of the same studies by the methodological team.

Search Strategy:

```

1      exp food hypersensitivity/
      (food* adj3 (allerg* or hypersensitiv* or reaction* or atop* or hyperallerg*
2      or acute sensitiv* or anaphyla*)).ti,ab.
      ((allerg* or hypersensitiv* or reaction* or atop* or hyperallerg* or acute
      sensitiv* or anaphyla*) adj3 prevent* adj3 (milk or egg* or peanut* or nut*
      or tree nut* or wheat or soy* or shellfish or fish or seafood* or kiwi fruit* or
      banana* or prevent* or diet* or nutrient or milk or meat or cow or chicken
      or corn or fruit or vege* or breastfe* or complementary food or solid or
      probiotic or prebiotic or synbiotic or formula or microbial or fish oil or
3      PUFA or omega or fatty acids or micronutrient or vitamin or skin barrier or
      high risk)).ti,ab.
4      food allerg*.mp.
5      allergy, food.mp.
6      or/1-5
7      randomized controlled trial.pt.
8      controlled clinical trial.pt.
9      randomized.ab.
10     placebo.ab.
11     clinical trials as topic.sh.
12     randomly.ab.
13     trial.ti.
14     or/7-13
15     exp animals/ not humans.sh.
16     14 not 15
17     cohort studies.pt.
18     cohort$.tw.
19     breastfe$.ab.
20     6 and 16
21     19 and 17
22     19 and 18
23     21 and 22
24     20 and 23

```

Database: Embase Classic+Embase <1947 to 2019 October 31>
Search Strategy:

```

1      exp food hypersensitivity/
2      food allerg*.mp.
3      allergy, food.mp.
4      or/1-3
5      (animal$ not human$).sh,hw.
6      4 not 5
7      random$.ti,ab. or controlled.ti.
8      *experimental design/ [EM]
9      random$.tw.
10     placebo$.tw.
11     (doubl$ adj blind$).tw.
12     (singl$ adj blind$).tw.
13     assign$.tw.
14     allocat$.tw.
15     double blind procedure/
16     randomized controlled trial/
17     single blind procedure/
18     or/7-17
19     exp cohort analysis/
20     exp longitudinal study/
21     exp prospective study/
22     exp follow-up/
23     cohort$.tw.
24     or/19-23
25     breastfe$.mp.
27     25 and 24 and 6
28     6 and 18
29     27 and 28

```

Database: CINAHL via Ebscohost Search Strategy:

```

S1    (MM "Food allergy")
S2    TI food or nutrient
S3    AB food or nutrient
S4    TI allergy or allergic or intolerant or intolerance or reaction
S5    AB allergy or allergic or hypersensitive or hypersensitivity or
      sensitive or sensitivity or intolerant or intolerance or reaction
S6    AB prevent
S7    S2 or S3
S8    S4 or S5
S9    S6 and S1
S10   S6 and S7
S11   S6 and S8
S12   S9 and A10 and A11

```

Database: ISI Web of Science: Science Citation Index, Conference Proceedings Search strategy

Topic=(food or nutrient) AND Topic=(allergy or allergic or hypersensitive or hypersensitivity or sensitive or sensitivity or intolerant or intolerance or reaction)

Databases=CPCI-S Timespan=All Years

Lemmatization=On

Topic=(food or nutrient) AND Topic=(allergy or allergic or intolerant or intolerance or reaction)

Refined by: Web of Science Categories=(ALLERGY OR IMMUNOLOGY)

Databases=CPCI-S Timespan=All Years

Lemmatization=On

Dataase: Cochrane Library Search strategy

#1 MeSH descriptor Food allergy explode all trees

#2 (food* and (allergy or allergies or allergic or allergen*))

#3 prevent*

#4 (#1 OR #2 AND #3)

Database: TRIP Database Search Strategy:

area:"Allergies and Immunology"

these words: food allerg*, prevent

Downloaded: Evidence Based Synopses, Systematic Reviews, Guidelines. All years

All other databases

food allergy and prevent*

S2. Risk of bias assessment

The risk of bias in randomised controlled trials is listed here, based on the Cochrane Risk of Bias Tool 2.

First author	Randomisation process risk of bias	Risk of bias due to assignment	Risk of bias due to missing outcome data	Risk of bias due to outcome measurement	Risk of bias due to selection of reporting	Overall risk of bias
Arshad 1992 ²	Some concerns	High	Low	Some concerns	Low	High
Bellach 2017 ³	Low	Low	Low	Low	Low	Low
D'Vaz 2012 ⁴	Low	Some concerns	Low	High	Low	High
Dissanayake 2019 ⁵	Low	Some concerns	Low	Some concerns	Low	Some concerns
Dunstan 2003 ⁶	Low	Low	Some concerns	High	High	High
Du Toit 2015, ⁷ 2016 ⁸	Low	Some concerns	Some concerns	Low	Low	Low
Falth-Magnusson 1992 ⁹	Some concerns	High	Some concerns	High	Low	High
Furuhjelm 2011 ¹⁰	Some concerns	Low	Some concerns	Some concerns	Low	Some concerns
Goldring 2013 ¹¹	Low	Low	High	High	High	High
Halken 1993 ¹²	Low	Some concerns	Low	Some concerns	Low	Some concerns
Halken 2000 ¹³	Some concerns	Low	Low	Low	Low	Some concerns
Ivakhnenko 2013 ¹⁴	Low	Low	High	High	Low	High
Kalliomaki 2003 ¹⁵	Low	Low	Some concerns	Low	Some concerns	Some concerns
Kiraly 2013 ¹⁶	Low	Some concerns	High	Some concerns	Low	High
Kukkonen 2011 ¹⁷	Some concerns	Low	High	Low	Low	High
Lilja 1989 ¹⁸	Low	Some concerns	Some concerns	Some concerns	Low	Some concerns
Lowe 2011 ¹⁹	High	Low	High	High	Low	High
Lucas 1990 ²⁰	Low	Low	Low	Low	Some concerns	Some concerns
Mallet 1992 ²¹	High	High	High	Low	Low	High
Manley 2011 ²²	Low	Low	Some concerns	Some concerns	Low	Some concerns
Marschan 2008 ²³	Low	Low	Some concerns	High	High	High
Morisset 2011 ²⁴	Low	Low	Some concerns	Low	Low	Low
Natsume 2017 ²⁵	Low	Low	Low	Low	Low	Low
Niers 2009 ²⁶	Low	Low	High	High	Low	High
Norizoe 2014 ²⁷	Low	Low	High	High	Low	High
Odelram 1996 ²⁸	Low	Low	High	High	Some concerns	High
Oldaeus 1997 ²⁹	Low	High	High	Some concerns	Low	High
Palmer 2013 ³⁰ -egg	Low	Low	High	High	Low	High
Palmer 2013 ³¹	Low	Some concerns	Some concerns	Some concerns	Low	Some concerns
Palmer 2017 ³²	Low	Low	Some concerns	Low	Low	Low
Perkin 2016 ³³	Low	Some concerns	Some concerns	Low	Some concerns	Some concerns
Plummer 2019 ³⁴	Low	Low	Low	Some concerns	Low	Some concerns
Prescott 2008 ³⁵	Low	Low	Some concerns	Some concerns	Low	Some concerns
Rosendahl 2019 ³⁶	Low	Some concerns	Low	High	Low	High
Thøstesen 2017 ³⁷	Low	Low	Low	Some concerns	Low	Some concerns
Urashima 2019 ³⁸	Low	Some concerns	Low	Low	Low	Some concerns
Vandenplas 1992 ³⁹	Some concerns	Low	Low	High	High	High
von Berg 2003 ⁴⁰	Low	Low	Some concerns	Some concerns	Low	Some concerns
Zachariassen 2011 ⁴¹	Some concerns	Low	Low	High	Low	High
Zeiger 1992 ⁴²	Low	High	High	Some concerns	Some concerns	High
Zolkipli 2015 ⁴³	Low	Low	Low	Some concerns	Low	Some concerns

The risk of bias in cohort studies is listed here, based on ROBINS-I.

	Risk of bias due to confounding	Bias in selection of participants	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Halken 2000 ^{44***}	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate
Host 1989 ⁴⁵	Serious concerns	Low	Low	Low	Low	Moderate	Low	Serious concerns
Kim 2011 ⁴⁶	Serious concerns	Low	Low	Low	Serious concerns	Serious concerns	Low	Serious concerns
Kull 2002 ⁴⁷	Serious concerns	Low	Low	Low	Serious concerns	Serious concerns	Low	Serious concerns
Saarinen 1999 ⁴⁸	Serious concerns	Low	Low	Low	Low	Serious concerns	Moderate	Serious concerns
Tariq 1998 ⁴⁹	Serious concerns	Low	Low	Low	Low	Serious concerns	Low	Serious concerns

Note: *** this reference is a randomised trial (cited as reference 13 in the table of trials), but the breastfeeding group was not randomised so for the purposes of assessing food allergy outcomes related to breastfeeding this study was treated as non-randomised.

S3. Summary of findings and evidence profiles

Note: where relative risks (RR) were not reported in the studies, they were calculated from the published data.

Avoidance of dietary food allergens in pregnant women						
People: Pregnant women whose infant will be at increased risk of food allergy						
Settings: Community						
Intervention: Avoidance of milk and egg from 28 weeks gestation to delivery						
Comparison: Usual consumption						
Outcomes	Absolute effect		Relative effect (95% CI)	Studies (and n)	Certainty of the evidence	Reference
	Without dietary avoidance	With dietary avoidance				
Food allergy cumulative incidence 0-1.5 years	3.2 per 100	5.3 per 100	RR 1.67 (0.38 to 7.22)	1 (n = 198)	Very low	Falth-Magnusson 1992
	Difference: 2.1 per 100 increase p>0.05					
Food allergy prevalence at 5 years	17.5 per 100	19.1 per 100	RR 1.09 (0.6 to 1.97)	1 (n = 198)	Very Low	Falth-Magnusson 1992
	Difference: 1.5 per 100 increase p>0.05					
Hen’s egg allergy prevalence at 5 years	0.0 per 100	7.14 per 100	RR 17.62 (1.01 to 308.42)	1 (n = 198)	Very low	Falth-Magnusson 1992
	Difference: 7.1 per 100 increase p<0.05					

Evidence profile

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
The evidence profile is the same for all three outcomes listed above						
1 RCT (n = 198)	Grade down: one study with high risk of bias	No grade change: consistent (null) results	Grade down: outcome was reported doctor diagnosis and measures were at 1.5 and 5 years which may not account for natural progression of allergy	Grade down: wide confidence intervals suggesting imprecision. Single relatively small study, few events	Uncertain but not suspected	Very low No reason to grade up based on effect size, dose response or potential effect of confounders

Avoidance of dietary food allergens in pregnant and breastfeeding women						
People: Pregnant and breastfeeding women whose infant is at increased risk of food allergy						
Settings: Community						
Intervention: Avoidance of milk and egg during last trimester and during breastfeeding						
Comparison: 2 litre milk and 1 egg per day						
Outcomes	Absolute effect		Relative effect (95% CI)	Studies (and n)	Certainty of the evidence	Reference
	Without dietary avoidance	With dietary avoidance				
Hen’s egg allergy cumulative incidence 0-1.5 years	1.2 per 100	2.5 per 100	RR 2.02 (0.19 to 21.89)	1 (n = 164)	Very low	Lilja 1989
	Difference: 1.2 per 100 increase p>0.05					
Cow’s milk allergy cumulative incidence 0-1.5 years	2.4 per 100	2.5 per 100	RR 1.01 (0.15 to 7.02)	1 (n = 164)	Very low	Lilja 1989
	Difference: 0.1 per 100 increase p>0.05					

Evidence profile

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
The evidence profile is the same for both outcomes listed above						
1 RCT (n = 164)	Grade down: moderate risk of bias	No grade change: consistent null result	Grade down: comparator egg and milk intake likely higher than in 'usual life'	Grade down: wide confidence intervals. Single relatively small study, few events	Uncertain	Very low No reason to grade up based on effect size, dose response or potential effect of confounders

Avoidance of dietary food allergens in pregnant/breastfeeding women and infants						
People: Pregnant and/or breastfeeding women and their infants at increased risk of food allergy						
Settings: Community						
Intervention: Avoidance of allergenic foods in pregnant and/or breastfeeding women and infants to 12 months						
Comparison: Usual consumption						
Outcomes	Absolute effect		Relative effect (95% CI)	Studies (and n)	Certainty of the evidence	Reference
	Without dietary avoidance	With dietary avoidance				
Food allergy cumulative incidence 0-1 year	11.3 per 100	3.5 per 100	RR 0.31 (0.07 to 1.41)	1 (n = 120)	Very low	Arshad 1992 - also included environmental intervention
	Difference: 7.8 per 100 decrease p>0.05					
Food allergy prevalence 0-1 year	16.4 per 100	5.0 per 100	RR 0.30 (0.12 to 0.77)	1 (n = 379)	Very low	Zeiger 1989 - extensively hydrolysed whey formula plus dietary avoidance by pregnant / breastfeeding women and infants vs cow's milk formula for up to one year after cessation of breastfeeding
	Difference: 11.4 per 100 decrease p>0.05					

Evidence profile

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
Both outcomes have the same evidence profile						
2 RCTs (n = 499)	Grade down: high risk of bias	No grade change: consistent result	Grade down: Multicomponent interventions (one study included environmental protection, the other hydrolysed vs conventional cow's milk formula) so applicability uncertain. Intervention required abstinence from multiple foods that may be difficult to generalise	Grade down: wide confidence intervals and areas of imprecision in measures	Not suspected	Very low No reason to grade up based on effect size, dose response or potential effect of confounders

Avoiding conventional cow’s milk formula on a recurring basis						
People: Infants at general or increased risk of food allergy						
Settings: Community						
Intervention: Avoiding conventional cow’s milk protein (formula)						
Comparison: Regular consumption of conventional cow’s milk formula						
Outcomes	Absolute effect		Relative effect (95% CI)	Studies (and n)	Certainty of the evidence	Reference
	Without cow’s milk avoidance	With cow’s milk avoidance				
Cow’s milk allergy cumulative incidence 0-1.5 years in general risk infants	4.4 per 100	3.2 per 100	RR 0.73 (0.28 to 1.87)	1 (n = 777)	Low	Lucas 1990 - Banked donor milk versus preterm formula as sole diet or as supplement to breast milk for median of 5 weeks from birth
	Difference: 1.2 per 100 decrease p>0.05					
Food allergy cumulative incidence 0-1.5 years in general risk infants	9.7 per 100	11.0 per 100	RR 1.13 (0.65 to 1.96)	1 (n = 777)	Low	Lucas 1990 – as above
	Difference: 1.3 per 100 increase p>0.05					
Food allergy prevalence at 1 year in general risk infants	0 per 100	0 per 100	RR 1.0 (0.06 to 15.78)	1 (n = 324)	Low	Zachariassen 2011 – exclusive breastfeeding vs cow’s milk-based fortifier added to breast milk for four months after discharge
	Difference: 0 per 100 decrease p>0.05					
Food allergy prevalence at 1 year in general risk infants	0 per 100	0 per 100	RR 0.93 (0.06 to 14.69)	1 (n = 324)	Low	Zachariassen 2011 – exclusive breastfeeding vs preterm formula for four months after discharge
	Difference: 0 per 100 decrease p>0.05					
Food allergy prevalence at 1 year in increased risk infants	0 per 100	1.4 per 100	Not applicable	1 (n = 177)	Low	Mallet 1992 – extensively hydrolysed formula vs cow’s milk formula for four months
	Difference: 1.4 per 100 increase p>0.05					
Food allergy cumulative incidence 0-1.5 years in increased risk infants	8.2 per 100	9.1 per 100	RR 1.11 (0.32 to 3.91)	1 (n = 155)	Very low	Oldaeus 1997 – extensively hydrolysed casein formula vs cow’s milk formula for at least three months after cessation of breastfeeding. Both groups had maternal and infant milk, egg and fish exclusion
	Difference: 0.9 per 100 increase p>0.05					
Food allergy cumulative incidence 0-1 year in increased risk infants	0.4 per 100	2.1 per 100	RR 5.3 (0.63 to 45.13)	1 (n = 2252)	Very low	Von Berg 2003 - partially hydrolysed whey formula vs cow’s milk formula for six months
	Difference: 1.7 per 100 increase p>0.05					

Cow's milk sensitivity incidence at 1 year in increased risk infants	34.29 per 100	12.5 per 100	RR 0.36 (0.13 to 1.02)	1 (n = 67)	Very low	Vandenplas 1992 - whey partially hydrolysed formula (NAN HA) exclusively vs cow's milk formula exclusively for 6 months
	Difference: 21.8 per 100 decrease p>0.05					
Cow's milk allergy cumulative incidence 0- 2 years in increased risk infants	3.1 per 100	1.6 per 100	RR 0.51 (0.13 to 1.99)	1 (n = 620)	Very low	Lowe 2011 - whey partially hydrolysed formula (NAN HA) from cessation of breastfeeding to 52 weeks vs cow's milk formula
	Difference: 1.5 per 100 decrease p>0.05					
Any food reactions cumulative incidence 0-2 years in increased risk infants	13.6 per 100	15.2 per 100	RR 1.12 (0.68 to 1.82)	1 (n = 620)	Very low	Lowe 2011 – as above
	Difference: 1.5 per 100 increase p>0.05					

Evidence profile

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
The evidence profile for all of the above outcomes related to general risk infants is the same						
Number of studies as in the summary of findings table for each outcome	Grade down: moderate and high risk of bias	No grade change	Grade down: focus was on pre-term infants	No grade change but note in one study no infant developed food allergy	Not suspected	Low No reason to grade up based on effect size, dose response or potential effect of confounders
The evidence profile for all of the above outcomes related to increased risk infants is the same (apart from one study which was not graded down for small numbers of events)						
Number of studies as in the summary of findings table for each outcome	Grade down: high risk of bias	Grade down: in some studies after the conclusion of breastfeeding so may be confounded by length of exclusive breastfeeding or other different interventions	No grade change	Grade down: small numbers of events	Not suspected	Very low No reason to grade up based on effect size, dose response or potential effect of confounders

Avoiding temporary supplementation with cow’s milk in first week of life						
People: Infants at increased risk of food allergy						
Settings: Hospital or community						
Intervention: Breastfeeding with or without amino acid-based elemental formula for at least the first 3 days of life						
Comparison: Breastfeeding supplemented with cow’s milk formula (≥5 mL/d) for the first 3 days of life						
Outcomes	Absolute effect		Relative effect (95% CI)	Studies (and n)	Certainty of the evidence	Reference
	Temporary supplement	Avoiding temporary supplement				
Food allergy cumulative incidence at 2 years	29.8 per 100	14.6 per 100	RR 0.49 (0.31 to 0.77)	1 (n = 312)	Low	Urashima 2019
	Difference: 15.2 per 100 decrease p<0.05					
Cow’s milk allergy cumulative incidence 0-2 years	6.6 per 100	0.7 per 100	RR 0.1 (0.01 to 0.77)	1 (n = 312)	Low	Urashima 2019
	Difference: 5.9 per 100 decrease p<0.05					

Evidence profile

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
The evidence profile is the same for all outcomes						
1 RCT (n = 312)	Grade down: moderate risk of bias	No grade change	Grade down: multiple interventions and timelines, making it difficult to apply findings in practice	No grade change	Uncertain	Low No reason to grade up based on effect size, dose response or potential effect of confounders

Cooked egg						
People: Infants at increased risk of food allergy						
Settings: Community						
Intervention: Cooked egg introduced from 6 months (small quantities)						
Comparison: Placebo						
Outcomes	Absolute effect		Relative effect (95% CI)	Studies (and n)	Certainty of the evidence	Reference
	Without cooked egg	With cooked egg				
Hen’s egg allergy prevalence at 1 year	37.7 per 100	8.3 per 100	RR 0.22 (0.09 to 0.54)	1 (n = 147)	Moderate	Nasume 2017
	Difference: 29.4 per 100 decrease p<0.05					

Evidence profile

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
Hen's egg allergy incidence at 1 year						
1 RCT (n = 147)	No grade change: low risk of bias	No grade change	Grade down: very small amounts of egg. May be more like immunotherapy approach	No grade change	Not suspected	Moderate No reason to grade up based on effect size, dose response or potential effect of confounders. Large effect size noted but not deemed necessary to grade up

Raw / pasteurised egg						
People: Infants at general or increased risk of food allergy						
Settings: Community						
Intervention: Pasteurised raw egg powder introduced from 4-6 months						
Comparison: Usual diet with placebo						
Outcomes	Absolute effect		Relative effect (95% CI)	Studies (and n)	Certainty of the evidence	Reference
	Without raw egg	With raw egg				
Hen's egg allergy prevalence at 1 year in increased risk infants	10.3 to 51.4 per 100	7.0 to 33.3 per 100	RR 0.65 to 0.75 (CIs 0.38 to 1.11 and 0.48 to 1.17)	2 (n = 906)	Low	Palmer 2013 Palmer 2017
	Difference: 3.3 to 18.10 per 100 decrease p>0.05					
Hen's egg allergy prevalence at 1 year in general risk infants	0.6 per 100	2.1 per 100	RR 3.3 (0.35 to 31.32)	1 (n = 383)	Low	Bellach 2017
	Difference: 1.5 per 100 increase p>0.05					

Evidence profile

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
All outcomes have the same evidence profile						
3 RCTs (n = 1289)	No grade change two studies at low risk of bias and one at high risk of bias	Grade down: variations depending on quantity / frequency. Also variations in risk profile	Grade down: drop out due to adverse events	No grade change	Not suspected	Low No reason to grade up based on effect size, dose response or potential effect of confounders

Peanut						
People: Infants at high risk of food allergy						
Settings: Community setting, countries with high prevalance of peanut allergy						
Intervention: 3 heaped teaspoons of peanut butter per week from 4-11 months to five years						
Comparison: Complete abstinence from peanut to 5 years						
Outcomes	Absolute effect		Relative effect (95% CI)	Studies (and n)	Certainty of the evidence	Reference
	Without [text]	With [text]				
Peanut allergy incidence at 5 years amongst non sensitised infants	13.7 per 100	1.9 per 100	RR 0.14 (0.05 to 0.34)	1 (n = 530)	Moderate	du Toit 2015
	Difference: 11.8 per 100 reduction p<0.05					
Peanut allergy incidence at 5 years amongst sensitised infants	35.3 per 100	12.2 per 100	RR 0.35 (0.14 to 0.85)	1 (n = 98)	Moderate	du Toit 2015
	Difference: 23.1 per 100 reduction p<0.05					

Evidence profile

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
All outcomes						
2 RCTs (n = 640)	No grade change: low risk of bias, though some issues with blinding	No grade change. Two trials reported in different populations with consistent outcomes	Grade down two levels: very high risk infants in high prevalence country. Comparison group had total abstinence from peanut for 5 years rather than usual diet	No grade change	Not suspected	Moderate Graded up based on effect size

Introduction of multiple food allergens at 3 months						
People: Infants at general risk of food allergy						
Settings: Community						
Intervention: Introduction of six food allergens from 3 months						
Comparison: Exclusive breastfeeding to 6 months						
Outcomes	Absolute effect		Relative effect (95% CI)	Studies (and n)	Certainty of the evidence	Reference
	Without allergenic foods	With allergenic foods				
Food allergy cumulative prevalence 1-3 years	7.1 per 100	5.6 per 100	RR 0.80 (0.51 to 1.25)	1 (n = 1303)	Low	Perkin 2016
	Difference: 1.6 per 100 decrease p>0.05					
Egg allergy cumulative prevalence 1-3 years	5.4 per 100	3.7 per 100	RR 0.69 (0.40 to 1.18)	1 (n = 1303)	Low	Perkin 2016
	Difference: 1.7 per 100 decrease p>0.05					
Peanut allergy cumulative prevalence 1-3 years	2.5 per 100	1.2 per 100	RR 0.49 (0.20 to 1.20)	1 (n = 1303)	Low	Perkin 2016
	Difference: 1.3 per 100 decrease p>0.05					

Evidence profile

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
All outcomes have the same evidence profile						
1 RCT (n = 1303)	Grade down: moderate risk of bias with confounders	Grade down: inconsistency in results based on per protocol or intention to treat analysis	Grade down two levels: multiple foods introduced so more difficult to assign causality. Undertaken in country with high prevalence of allergy. Issues with adherence	Grade down: issues related to loss to follow up and associated impact on imprecision	Not suspected	Low Graded up one level based on effect size and reported dose response for some food groups

Breastfeeding						
People: Infants at general risk and at high risk of food allergy						
Settings: Community						
Intervention: Breastfeeding (for varying duration)						
Comparison: Infant formula						
Outcomes	Absolute effect		Relative effect (95% CI)	Studies (and n)	Certainty of the evidence	Reference
	Without breastfeeding	With breastfeeding				
Cow’s milk allergy cumulative incidence 0-1 year	4.8 per 100	1.7 per 100	RR 0.38 (0.20 to 0.71)	1 (n = 1149)	Very low	Host 1991 – exclusive breastfeeding during first month vs not exclusive breastfeeding
	Difference: 2.8 per 100 decrease p<0.05					
Food allergy cumulative incidence 0-1 year	Range 6.0 per 100	Range 5.4 per 100	RR 0.98 (0.53 to 1.82)	2 (n = 2344)	Very low	Kim 2011 – breastfeeding 6 months or more vs less than 6 months
	Difference: 0.5 per 100 decrease p>0.05					
Food allergy cumulative incidence 0-2 years	21.5 per 100	20.0 per 100	RR 0.93 (0.8 to 1.09)	1 (n = 4089)	Very low	Kull 2002 – exclusive breastfeeding for more than 4 months vs less than 4 months
	Difference: 1.5 per 100 decrease p>0.05					
Cow’s milk allergy cumulative incidence at 2.8 years (34 months)	2.5 per 100	1.7 per 100	RR 0.71 (0.45 to 1.11)	1 (n = 6209)	Very low	Saarinen 1999 – pasteurised human milk for at least first four days of life vs cow’s milk formula
	Difference: 0.7 decrease per 100 p>0.05					
Cow’s milk allergy cumulative incidence at 2.8 years (34 months)	2.5 per 100	2.1 per 100	RR 0.86 (0.49 to 1.49)	1 (n = 6209)	Very low	Saarinen 1999 – exclusive breastfeeding for at least the first four days of life vs cow’s milk formula
	Difference: 0.4 decrease to 0.6 decrease per 100 p>0.05					
Food allergy incidence at 1 year	6.3 per 100	8.1 per 100	RR 1.29 (0.84 to 1.97)	1 (n = 1167)	Very low	Arshad 1992 – any breastfeeding vs cow’s milk formula
	Difference: 1.8 per 100 increase p>0.05					
Food allergy incidence at 4 years	3.4 per 100	2.4 per 100	21% relative reduction (CI not provided)	1 (n = 1167)	Very low	Tariq 1998 – any breastfeeding (same study as Arshad with longer follow up)
	Difference: 1 per 100 decrease p>0.05					
Cow’s milk protein allergy cumulative incidence 0-1.5 years in increased risk infants	0.6 per 100	1.3 per 100	RR 2.08 (0.22 to 19.83)	1 (n = 478)	Low	Halken 2000 – exclusive breastfeeding for 4 months vs extensively hydrolysed whey or casein formula
	Difference: 0.7 per 100 increase p>0.05					
Cow’s milk protein allergy cumulative incidence 0-1.5 years in increased risk infants	4.7 per 100	1.3 per 100	RR 0.27 (0.06 to 1.19)	1 (n = 478)	Low	Halken 2000 – exclusive breastfeeding first 4 months vs partially hydrolysed whey formula
	Difference: 3.4 per 100 decrease p>0.05					
Cow’s milk allergy	4.4 per 100	3.2 per 100	RR 0.73 (0.28 to 1.87)	1 (n =	Low	Lucas 1990 - banked

cumulative incidence 0-1.5 years in general risk infants	Difference: 1.2 per 100 decrease p>0.05			777)		donor milk versus preterm formula as sole diet or as supplement to breast milk for median of 5 weeks from birth
Food allergy cumulative incidence 0-1.5 years in general risk infants	9.7 per 100	11.0 per 100	RR 1.13 (0.65 to 1.96)	1 (n = 777)	Low	Lucas 1990 – as above
	Difference: 1.3 per 100 increase p>0.05					

Evidence profile

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
Compilation across all outcomes						
5 birth cohorts and 1 RCT with non-random breastfeeding comparison group (n = 14,269)	Grade down: five out of six studies at high risk of bias, one at moderate risk	No grade change: same direction of travel, but note some outcomes for increased risk infants and some for general risk. Heterogeneity of measures and durations. Some studies not challenge-proven	No grade change	No grade change. Multiple studies, large sample sizes, narrow confidence intervals	Not detected, multiple studies from different countries and time points	Low Graded up from #very low' as effect of residual confounders may be to underestimate effect. Broad consistency of findings across large studies from diverse populations Note: there is very low certainty in individual outcomes, but taken together the task force graded up to 'low' certainty that breastfeeding has no effect based on the number of studies, participants, precision and relative consistency of findings
The evidence profile is the same for these outcomes: cumulative incidence of cow's milk allergy 0-1 year and 0-1.5 years						
1 RCT with non-random breastfeeding comparison group (n = 478) and 1 other RCT (n = 777)	Grade down: moderate risk of bias	Grade down: comparators randomised to different formulas so difficult to compare this groups	No grade change	No grade change	Not suspected	Low No reason to grade up based on effect size, dose response or potential effect of confounders
The evidence profile is the same for all other outcomes apart from those listed above						
5 birth cohorts (n for individual outcomes as listed in summary of findings tables)	Grade down: all studies at high risk of bias, one at moderate risk	Grade down: Heterogeneity of measures and durations of breastfeeding.	Grade down: some studies not challenge-proven	No grade change. Multiple studies, large sample sizes, narrow confidence intervals	Not detected, multiple studies from different countries and time points	Very low Grading up based on potential effect of residual confounders still leaves at lowest possible grade level
Partially hydrolysed formula						
People: Infants at increased risk of food allergy						

Settings: Community						
Intervention: Partially hydrolysed formula						
Comparison: Standard cow’s milk formula (or breastfeeding or extensively hydrolysed formula)						
Outcomes	Absolute effect		Relative effect (95% CI)	Studies (and n)	Certainty of the evidence	Reference
	Without intervention	With intervention				
Cow’s milk protein allergy cumulative incidence 0-1.5 years	1.3 per 100	4.7 per 100	RR 3.64 (0.84 to 16.67)	1 (n = 478)	Low	Halken 2000 – exclusive breastfeeding vs partially hydrolysed whey formula (Nan HA) for first four months (this outcome not eligible for review as breastfeeding not randomised)
	Difference: 3.4 per 100 increase p>0.05					
Cow’s milk protein allergy cumulative incidence 0-2 years	3.1 per 100	1.6 per 100	RR 0.51 (0.13 to 1.99)	1 (n = 620)	Very low	Lowe 2011 - whey partially hydrolysed formula (NAN HA) vs cow’s milk formula from cessation of breastfeeding to 52 weeks
	Difference: 1.5 per 100 decrease p>0.05					
Food allergy cumulative incidence 0-1.5 years	8.2 per 100	19.6 per 100	RR 2.40 (0.81 to 7.15)	1 (n = 155)	Very low	Oldaeus 1997 - partially hyrdrolysed (Mead Johnson) for at least 3 months after cessation of breastfeeding vs cow’s milk formula. Both groups had maternal and infant milk, egg and fish exclusion
	Difference: 11.4 per 100 increase p>0.05					
Food allergy cumulative incidence 0-1.5 years	9.5 per 100	19.6 per 100	RR 2.06 (0.49 to 8.60)	1 (n = 155)	Very low	Oldaeus 1997 - partially hyrdrolysed (Mead Johnson) for at least 3 months after cessation of breastfeeding vs breastfeeding. Both groups had maternal and infant milk, egg and fish exclusion
	Difference: 10.1 per 100 increase p>0.05					
Cow’s milk sensitivity prevalence at 1 year	34.3 per 100	12.5 per 100	RR 0.36 (0.13 to 1.02)	1 (n = 67)	Very low	Vandenplas 1992 - partially hydrolysed whey formula exclusively (NAN HA) vs cow’s milk formula exclusively for six months
	Difference: 21.8 per 100 decrease p>0.05					
Positive challenge to cow’s milk 0-0.5 year	40.0 per 100	6.3 per 100	RR 0.16 (0.04 to 0.64)	1 (n = 67)	Very low	Vandenplas 1992 - partially hydrolysed whey formula exclusively (NAN HA) vs cow’s milk formula exclusively for six months
	Difference: 33.8 per 100 decrease p<0.05					
Cow’s milk sensitivity cumulative incidence 0-1 year (challenge proven)	49.2 per 100	15.6 per 100	RR 0.36 (0.15 to 0.89)	1 (n = 67)	Very low	Vandenplas 1992 - partially hydrolysed whey formula exclusively (NAN HA) vs cow’s milk formula exclusively for six months
	Difference: 27 per 100 decrease p>0.05					
Food allergy cumulative incidence 0-1 year	0.4 per 100	2.1 per 100	RR 5.31 (0.63 to 45.13)	1 (n = 2252)	Very low	von Berg 2003 - partially hydrolysed whey formula vs cow’s milk formula exclusively for six months
	Difference: 1.7 per 100 increase p>0.05					

Evidence profile

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
Cow's milk protein allergy cumulative incidence 0-1.5 years						
1 RCT with non-random breastfeeding comparison group (n = 478)	Grade down: moderate risk of bias	Grade down: comparators randomised to different hydrolysed formulas so difficult to compare subgroups	No grade change	No grade change	Uncertain	Low No reason to grade up based on effect size, dose response or potential effect of confounders
All other outcomes have the same evidence profile						
See summary of findings table for study numbers for each outcome	Grade down: high risk of bias, significant confounding and risk of bias from methodological flaws	Grade down: inconsistency of results and of measures	Grade down (in one instance): in one study, late introduction of formula after weaning at 3 months and combined with maternal and infant milk, egg and fish exclusion in all groups	Grade down: low numbers of events in all groups. Wide variation	Possible as manufacturer funding in this area, but not downgraded	Very low No reason to grade up based on effect size, dose response or potential effect of confounders

Extensively hydrolysed formula						
People: Infants at increased risk of food allergy						
Settings: Community						
Intervention: Extensively hydrolysed formula						
Comparison: Standard cow’s milk formula or breastfeeding or partially hydrolysed formula						
Outcomes	Absolute effect		Relative effect (95% CI)	Studies (and n)	Certainty of the evidence	Reference
	Without intervention	With intervention				
Cow’s milk allergy cumulative incidence 0-1.5 years	5.0 per 100	1.7 per 100	RR 0.34 (0.02 to 5.17)	1 (n = 158)	Low	Halken 1993 - extensively hydrolysed casein formula vs breastfeeding for first four months (this outcome not eligible for review as breastfeeding not randomised)
	Difference: 3.3 per 100 decrease p>0.05					
Cow’s milk allergy cumulative incidence 0-1.5 years	5 per 100	4.8 per 100	RR 0.97 (0.11 to 8.79)	1 (n = 158)	Low	Halken 1993 - extensively hydrolysed whey formula vs breastfeeding for first four months (this outcome not eligible for review as breastfeeding not randomised)
	Difference: 0.2 per 100 decrease p>0.05					
Cow’s milk allergy cumulative incidence 0-1.5 years	1.3 per 100	0.6 per 100	RR 0.48 (0.05 to 4.58)	1 (n = 478)	Low	Halken 2000 – extensively hydrolysed whey or casein formula (Nutramigen or Profylac) vs exclusive breastfeeding (this outcome not eligible for review as breastfeeding not randomised)
	Difference: 0.7 per 100 decrease p>0.05					
Cow’s milk allergy cumulative incidence 0-1.5 years	4.7 per 100	0.6 per 100	RR 0.13 (0.01 to 1.16)	1 (n = 478)	Low	Halken 2000 – extensively hydrolysed whey or casein formula (Nutramigen or Profylac) vs cow’s milk formula
	Difference: 4.1 per 100 decrease p>0.05					
Food allergy cumulative incidence 0-1.5 years	8.2 per 100	9.1 per 100	RR 1.11 (0.32 to 3.96)	1 (n = 155)	Low	Oldaeus 1997 – extensively hydrolysed casein formula (Nutramigen) vs cow’s milk formula for at least three months after cessation of breastfeeding. Both groups also had maternal and infant dietary avoidance of allergens
	Difference: 0.9 per 100 increase p>0.05					
Food allergy prevalence at 1 year	1.4 per 100	0.0 per 100	Not reported	1 (n = 478)	Low	Mallet 1992 – extensively hydrolysed formula vs cow’s milk formula for four months
	Difference: 1.4 per 100 increase p>0.05					
Food allergy cumulative incidence 0-1 year	0.4 per 100	0.8 per 100	RR 2.15 (0.20 to 23.57)	1 (n = 2252)	Very low	von Berg 2003 - extensively hydrolysed whey formula vs cow’s milk formula exclusively for six months
	Difference: 0.4 per 100 increase p>0.05					
Food allergy cumulative incidence 0-1 year	0.4 per 100	1.9 per 100	RR 4.88 (0.55 to 43.30)	1 (n = 2252)	Very low	von Berg 2003 - extensively hydrolysed casein formula vs cow’s milk formula exclusively for six months
	Difference: 1.5 per 100 increase p>0.05					

Evidence profile

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
All outcomes have the same evidence profile except two which was further downgraded due to higher risk of bias						
See summary of findings for individual study numbers	Grade down: moderate to high risk of bias	Grade down: comparing various types of formula to (non randomised) breastfeeding	No grade change, but note that in one study, late introduction of formula after weaning at 3 months and combined with maternal and infant milk, egg and fish exclusion in all groups	No grade change	Possible as manufacturer funding in this area, but not downgraded	Low No reason to grade up based on effect size, dose response or potential effect of confounders

Hydrolysed formula plus dietary avoidance						
People: Infants at increased risk of food allergy						
Settings: Community						
Intervention: Hydrolysed formula plus dietary avoidance of allergens in mothers and infants						
Comparison: Standard formula and no dietray avoidance						
Outcomes	Absolute effect		Relative effect (95% CI)	Studies (and n)	Certainty of the evidence	Reference
	Without intervention	With intervention				
Cow’s milk allergy cumulative incidence 0-1.5 years	9.4 per 100	0 per 100	RR 0.18 (0.01 to 3.37)	1 (n = 91)	Very low	Oldelram 1996 – extensively hydrolysed formula plus dietary avoidance in mothers and infants vs cow’s milk formula started after exclusively breastfeeding stopped and continued to one year
	Difference: 9.4 per 100 decrease p>0.05					
Period prevalance of food allergy 0-1 year	16.4 per 15	5.0 per 100	RR 0.30 (0.12 to 0.77)	1 (n = 379)	Very low	Zeiger 1992 and 1989 – extensively hydrolysed formula plus maternal and infant dietary avoidance vs cow’s milk formula for infants after exclusive breastfeeding and standard diet for mothers
	Difference: 11.4 per 100 decrease P<0.05					

Evidence profile

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
All outcomes have the same evidence profile						
2 RCTs (numbers as per summary of findings for each outcome)	Grade down: high risk of bias	Grade down: inconsistent results in subgroups	Grade down: May be linked to diagnostic criteria and timing of intervention. One study started formula late into infancy.	Grade down: Small numbers in some groups, confidence intervals wide and other data not always reported	Uncertain	Very low No reason to grade up based on effect size, dose response or potential effect of confounders

Soy-based infant formula						
People: Infants at increased risk of food allergy						
Settings: Community						
Intervention: Soy-based formula						
Comparison: Cow's milk formula						
Outcomes	Absolute effect		Relative effect (95% CI)	Studies (and n)	Certainty of the evidence	Comments
	Without Soy formula	With Soy formula				
Cow's milk protein allergy cumulative incidence 0-2 years	3.1 per 100	4.2 per 100	RR 1.35 (0.48 to 3.81)	1 (n = 620)	Very low	Lowe 2011 – soy-based versus cow's milk formula
	Difference: 1.1 per 100 increase p>0.05					
Any food reactions cumulative incidence 0-2 years	13.5 per 100	19.4 per 100	RR 1.44 (0.31 to 2.28)	1 (n = 620)	Very low	Lowe 2011 – soy-based versus cow's milk formula
	Difference: 5.9 per 100 increase p>0.05					

Evidence profile

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
Both outcomes have the same evidence profile						
1 RCT (n = 620)	Grade down two levels: high risk of bias across multiple domains. Potential confounding	No grade change	Grade down: issues with measurement approach so may not be fully applicable to food allergy	No grade change but wide confidence intervals	Not suspected	Very low No reason to grade up based on effect size, dose response or potential effect of confounders

Vitamins in pregnant women						
People: Pregnant women whose infants are at general risk of food allergy						
Settings: Community						
Intervention: Vitamin D from 27 weeks gestation to birth						
Comparison: No vitamin D						
Outcomes	Absolute effect		Relative effect (95% CI)	Studies (and n)	Certainty of the evidence	Reference
	Without vitamin D	With vitamin D				
Food allergy cumulative incidence 0-3 years	6.1 per 100	11.8 per 100	RR 1.92 (0.57 to 6.5)	1 (n = 180)	Very low	Goldring 2013
	Difference: 5.6 per 100 increase p>0.05					

Evidence profile

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
Food allergy incidence at 3 years						
1 RCT (n = 180)	Grade down: high risk of bias	No grade change: no issues with inconsistency noted	Grade down two levels: diagnostic outcome was not challenge proven and was at 3 years which may not account for natural progression of food allergy so applicability is questionable. Dose different from usual practice	No grade change: no important imprecision though one study only	Not suspected	Very low No reason to grade up based on effect size, dose response or potential effect of confounders

Vitamins in breastfeeding women						
People: Breastfeeding women whose infant is at high risk of food allergy						
Settings: Community						
Intervention: Vitamin D for six weeks						
Comparison: Placebo						
Outcomes	Absolute effect		Relative effect (95% CI)	Studies (and n)	Certainty of the evidence	Comments
	Without vitamin D	With vitamin D				
Cumulative incidence of food allergy 0- 2 years	7.5 per 100	26.5 per 100	RR 3.42 (1.02 to 11.77)	1 (n = 164)	Very low	Norizoe 2014
	Difference: 18.1 per 100 increase (p<0.05)					

Evidence profile

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
Cumulative incidence of food allergy at 2 years						
1 RCT (n = 164)	Grade down: high risk of bias across multiple domains	No grade change: no issues with inconsistency noted	Grade down: infants with facial eczema so very select group. Outcome not challenge proven (parental report of doctor diagnosis) so may not be appropriately capturing food allergy. Relatively high dose	Grade down: one relatively small study with wide confidence intervals	Not suspected	Very low No reason to grade up based on effect size, dose response or potential effect of confounders

Vitamins in infants						
People: Infants at general risk of food allergy						
Settings: Community						
Intervention: Vitamin D daily supplementation of 30 µg (1200 IU)						
Comparison: Vitamin D daily supplementation of 10 µg (400 IU)						
Outcomes	Absolute effect		Relative effect (95% CI)	Studies (and n)	Certainty of the evidence	Reference
	Without lower dose vitamin D	With high dose vitamin D				
Food allergy cumulative incidence 0-1 year	5.2 per 100	7.0 per 100	RR 1.33 (0.76 to 2.33)	1 (n = 975)	Very low	Rosendahl 2019
	Difference: 1.8 per 100 increase p>0.05					

Evidence profile

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
Food allergy cumulative incidence 0-1 year						
1 RCT (n = 975)	Grade down: high risk of bias	No grade change: trends consistent internally, not heterogeneity of concern	Grade down two levels: comparing two doses of vitamin D with no placebo so difficult to draw conclusions about impact on food allergy. Outcome not challenge proven so may not be appropriately capturing food allergy	No grade change. Single study but large, no imprecision noted	Uncertain	Very low No reason to grade up based on effect size, dose response or potential effect of confounders

Fish oil in pregnant women						
People: Pregnant women whose infants will be at increased risk of food allergy						
Settings: Community						
Intervention: Fish oil from 20 or 21 weeks until birth						
Comparison: Placebo (olive or vegetable oil)						
Outcomes	Absolute effect		Relative effect (95% CI)	Studies (and n)	Certainty of the evidence	Reference
	Without Fish oil	With Fish oil				
Food allergy incidence at 1 year	11.6 per 100	7.5 per 100	RR 0.65 (0.16 to 2.5)	1 (n = 83)	Very low	Dunstan 2003
	Difference: 4.1 per 100 decrease p>0.05					
Food allergy incidence at 3 years	2.8 per 100	3.8 per 100	RR 1.36 (0.59 to 3.11)	1 (n = 706)	Low	Palmer 2012
	Difference: 1 per 100 increase p>0.05					
Food allergy cumulative incidence 0-3 years	4.2 per 100	4.9 per 100	RR 1.2 (0.6 to 2.41)	1 (n = 706)	Low	Palmer 2013
	Difference: 0.8 per 100 increase p>0.05					

Evidence profile

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
Food allergy incidence at 1 year						
1 RCT (n = 83)	Grade down: high risk of bias	No grade change: no issues with inconsistency noted	Grade down: Outcome not challenge proven. Control group received olive oil capsules which contain some polyunsaturated fatty acids	Grade down: small single study, few events	Not suspected	Very low No reason to grade up based on effect size, dose response or potential effect of confounders
Food allergy incidence at 3 years and cumulative incidence 0-3 years						
1 RCT (n = 706)	Grade down: moderate risk of bias	No grade change: no issues with inconsistency noted	Grade down: Outcome not challenge proven	No grade change. No imprecision issues	Not suspected	Low No reason to grade up based on effect size, dose response or potential effect of confounders

Fish oil in pregnant and breastfeeding women						
People: Pregnant and breastfeeding women whose infant is at increased risk of food allergy						
Settings: Community						
Intervention: Fish oil from 25 weeks’ gestation to 3-4 months breastfeeding						
Comparison: Placebo (soy bean oil)						
Outcomes	Absolute effect		Relative effect (95% CI)	Studies (and n)	Certainty of the evidence	Reference
	Without fish oil	With fish oil				
Food allergy cumulative incidence 0- 1 year	15.4 per 100	1.9 per 100	RR 0.13 (0.02 to 0.95)	1 (n = 145)	Low	Furuhjelm 2011
	Difference: 13.5 per 100 decrease p<0.05					
Food allergy cumulative incidence 0-2 years	21.5 per 100	5.5 per 100	RR 0.21 (0.06 to 0.79)	1 (n = 145)	Low	Furuhjelm 2011
	Difference: 16.0 per 100 decrease p<0.05					

Evidence profile

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
Both outcomes above have the same evidence profile						
1 RCT (n = 145)	Grade down: moderate risk of bias	No grade change: no issues with inconsistency noted	No grade change: no indirectness	Grade down: few events, relatively small single study	Not suspected	Low No reason to grade up based on effect size, dose response or potential effect of confounders

Fish oil in infants						
People: Infants at increased risk of food allergy						
Settings: Community						
Intervention: Fish oil from birth to 6 months of age						
Comparison: Olive oil						
Outcomes	Absolute effect		Relative effect (95% CI)	Studies (and n)	Certainty of the evidence	Reference
	Without fish oil	With fish oil				
Food allergy cumulative incidence 0-1 year	15.0 per 100	12.2 per 100	RR 0.81 (0.47 to 1.42)	1 (n = 420)	Very low	D’Vaz 2012
	Difference: 2.8 per 100 decrease p>0.05					

Evidence profile

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
Food allergy incidence at 1 year						
1 RCT (n = 420)	Grade down two levels: high risk of bias across multiple domains	No grade change	Grade down: not challenge proven so may not be measuring food allergy directly	No grade change	Uncertain	Very low No reason to grade up based on effect size, dose response or potential effect of confounders

Fish oil in breastfeeding women and infants						
People: Breastfeeding women and infants at general risk of food allergy						
Settings: Community						
Intervention: Mothers took tuna oil daily. If supplementary formula was required, infants were given a high DHA pre-term formula						
Comparison: Soy oil capsules for mothers and standard diet for infants						
Outcomes	Absolute effect		Relative effect (95% CI)	Studies (and n)	Certainty of the evidence	Reference
	Without fish oil	With fish oil				
Food allergy cumulative incidence 0-1.5 years	7.0 per 100	8.7 per 100	RR 1.24 (0.62 to 2.50)	1 (n = 655)	Low	Manley 2011
	Difference: 1.7 per 100 increase p>0.05					

Evidence profile

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
Food allergy cumulative incidence 0-1.5 years						
1 RCT (n = 655)	Grade down: moderate risk of bias	No grade change	Grade down: not challenge proven so may not be assessing food allergy. Some infants in the intervention group received supplements and others did not	No grade change	Uncertain	Low No reason to grade up based on effect size, dose response or potential effect of confounders

Prebiotics for infants						
People: Infants at general risk of food allergy						
Settings: Community						
Intervention: Prebiotics in formula for at least two months						
Comparison: Standard formula or breastfeeding						
Outcomes	Absolute effect		Relative effect (95% CI)	Studies (and n)	Certainty of the evidence	Reference
	Without prebiotics	With prebiotics				
Cumulative incidence of food allergy 0-1.5 years (prebiotics vs standard formula)	17.0 per 100	4.8 per 100	RR 0.28 (0.08 to 1.00)	1 (n = 240)	Very low	Ivakhnenko 2013
	Difference: 12.1 per 100 decrease p>0.05 compared to standard formula					
Cumulative incidence of food allergy 0-1.5 years (prebiotics vs breastfeeding)	3.9 per 100	4.8 per 100	RR 1.23 (0.21 to 7.10)	1 (n = 240)	Very low	Ivakhnenko 2013
	Difference: 0.9 per 100 increase p>0.05 compared to breastfeeding					
Cumulative incidence of cow's milk protein allergy 0-1.5 years (prebiotics vs standard formula)	15.1 per 100	3.2 per 100	Not reported	1 (n = 240)	Very low	Ivakhnenko 2013
	Difference: 11.9 per 100 decrease p>0.05 compared to standard formula					

Evidence profile

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
All outcomes above have the same evidence profile						
1 RCT (n = 240)	Grade down two levels: high risk of bias across multiple domains. Compares with breastfeeding which would be a significant confounder	No change to grade	Grade down: not challenge proven so may not be accurately measuring food allergy	No grade change but limited reporting of precision	Uncertain	Very low No reason to grade up based on effect size, dose response or potential effect of confounders

Probiotics in women and infants combined						
People: Pregnant / breastfeeding women and infants at increased risk of food allergy						
Settings: Community						
Intervention: Probiotics 4-6 weeks before delivery plus probiotics for infants / when breastfeeding						
Comparison: Placebo						
Outcomes	Absolute effect		Relative effect (95% CI)	Studies (and n)	Certainty of the evidence	Reference
	Without probiotics	With probiotics				
Incidence of food allergy at 2 years	Probiotics did not reduce the incidence of food allergy at 2 years (no numerical data given)		Not given	1 (n = 156)	Very low	Niers 2009
Cumulative incidence of cow’s milk protein allergy 0-2 years	11.1 per 100	20.8 per 100	RR 1.87 (0.74 to 4.69)	1 (n = 100)	Low	Kalliomaki 2003
	Difference: 9.7 per 100 increase p>0.05					

Evidence profile

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
Incidence of food allergy at 2 years						
1 RCT (n = 156)	Grade down two levels: high risk of bias across multiple domains	No grade change	No grade change	Grade down: small single study with few events. Numerical details not provided	Not suspected	Very low No reason to grade up based on effect size, dose response or potential effect of confounders
Cumulative incidence of cow's milk protein allergy 0-2 years						
1 RCT (n = 100)	Grade down: moderate risk of bias	No grade change	No grade change	Grade down: small single study with few events. Full numerical data not provided	Not suspected	Low (very low for 4 years) No reason to grade up based on effect size, dose response or potential effect of confounders

Probiotics in infants at general risk						
People: Infants at general risk of food allergy						
Settings: Community						
Intervention: Probiotics						
Comparison: Placebo						
Outcomes	Absolute effect		Relative effect (95% CI)	Studies (and n)	Certainty of the evidence	Comments
	Without probiotics	With probiotics				
Food allergy prevalence at 2.5 years	12.3 per 100	15.8 per 100	RR 1.28 (0.57 to 2.86)	1 (n = 153)	Very low	Prescott 2008
	Difference: 3.5 per 100 decrease p>0.05					
Food allergy prevalence at 1 year	1.3 per 100	3.2 per 100	RR 2.48 (0.46 to 13.34)	1 (n = 281)	Very low	Plummer 2008
	Difference: 1.9 per 100 increase (p>0.05)					

Evidence profile

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
Food allergy prevalence at 2.5 years						
1 RCT (n = 153)	Grade down: moderate risk of bias	No change to grade	Grade down: not challenge proven so may not be adequately capturing food allergy	Grade down: few events and confidence intervals not provided	Uncertain	Very low No reason to grade up based on effect size, dose response or potential effect of confounders
Food allergy prevalence at 1 year						
1 RCT (n = 281)	Grade down: moderate risk of bias	No change to grade	Grade down: not challenge proven so may not be adequately capturing food allergy. In pre- term infants subgroup. Use probiotic combination	Grade down: single study with small number of events in each group	Uncertain	Very low No reason to grade up based on effect size, dose response or potential effect of confounders

Probiotics in infants at increased risk						
People: Infants at increased risk of food allergy						
Settings: Community						
Intervention: Probiotics added to standard formula to one year of age						
Comparison: Standard formula						
Outcomes	Absolute effect		Relative effect (95% CI)	Studies (and n)	Certainty of the evidence	Reference
	Without probiotics	With probiotics				
Cow’s milk allergy incidence at 2 years	27.3 per 100	24.5 per 100	RR 0.9 (0.47 ro 1.71)	1 (n = 129)	Low	Morisset 2011
	Difference: 2.7 per 100 decrease p>0.05					

Evidence profile

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
Cow's milk allergy incidence at 2 years						
1 RCT (n = 129)	No grade change: low risk of bias	Grade down: formula could be continued to one year so some infants likely to have received for longer duration than others	No grade change	Grade down: confidence intervals and RR not provided	Uncertain	Low No reason to grade up based on effect size, dose response or potential effect of confounders

Prebiotics plus probiotics						
People: Pregnant women plus infants at increased risk of food allergy						
Settings: Community						
Intervention: Probiotics for pregnant women during last 2-4 weeks of pregnancy plus probiotic and prebiotic for infants for 6 months						
Comparison: Placebo						
Outcomes	Absolute effect		Relative effect (95% CI)	Studies (and n)	Certainty of the evidence	Reference
	Without intervention	With intervention				
Food allergy incidence at 2 years	No significant difference between groups. Data not provided.		Not provided	1 (n = 98)	Very low	Marschan 2008
Food allergy cumulative incidence 0-2 years	7.2 per 100	6.4 per 100	0.89 (0.51 to 1.55)	1 (n = 1018)	Moderate	Kukkonen 2011
	Difference: 0.8 per 100 decrease p>0.05					

Evidence profile

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
Food allergy incidence at 2 years						
1 RCT (n = 98)	Grade down two levels: high risk of bias, subgroup analysis	No grade change	No grade change	No numerical data reported. Small single study	None suspected	Very low No reason to grade up based on effect size, dose response or potential effect of confounders
Food allergy cumulative incidence 0-2 years						
1 RCT (n = 1018)	No grade change: low risk of bias	No grade change	No grade change	Grade down: large study but precision information sparse	None suspected	Moderate No reason to grade up based on effect size, dose response or potential effect of confounders

Synbiotics						
People: Infants at general risk of food allergy						
Settings: Community						
Intervention: Synbiotic from birth to six months						
Comparison: No synbiotic						
Outcomes	Absolute effect		Relative effect (95% CI)	Studies (and n)	Certainty of the evidence	Reference
	Without Emollient	With Emollient				
Food allergy prevalence at 1 year	12.0 per 100	12.3 per 100	RR 1.03 (0.63 to 1.68)	1 (n = 459)	Low	Dissanayake 2019 – synbiotic vs no synbiotic (part of 2x2 trial with emollient)
	Difference: 0.3 per 100 increase p>0.05					

Evidence profile

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
Food allergy prevalence at 1 year						
1 RCT (n = 459)	Grade down: Moderate risk of bias	No grade change	Grade down: not challenge proven so direct measurement of food allergy uncertain	No grade change	Uncertain	Low No reason to grade up based on effect size, dose response or potential effect of confounders

Vaccination for tuberculosis						
People: Infants at general risk of food allergy						
Settings: Community						
Intervention: BCG vaccination for TB within 7 days of birth						
Comparison: Delayed BCG vaccination / no intervention						
Outcomes	Absolute effect		Relative effect (95% CI)	Studies (and n)	Certainty of the evidence	Reference
	Without early vaccination	With early vaccination				
Food allergy cumulative prevalance 0- 13 months	0.5 per 100	0.7 per 100	RR 1.48 (0.67 to 3.29)	1 (n = 4262)	Low	Thøstesen 2017
	Difference: 0.2 per 100 increase p>0.05					
Food allergy prevalance at 1 year	8.0 per 100	9.4 per 100	RR 1.17 (0.55 to 2.49)	1 (n = 281)	Low	Kiraly 2013
	Difference: 1.4 per 100 increase p>0.05					

Evidence profile

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
Both outcomes have the same evidence profile						
As per numbers in summary of findings table	Grade down: moderate to high risk of bias	No grade change: findings and groupings broadly consistent	Grade down: one study in West Africa so may not be directly applicable to high income countries. Not challenge proven. One study combined with vitamin A intervention	No grade change	Not suspected	Low No reason to grade up based on effect size, dose response or potential effect of confounders

Oral immunotherapy						
People: Infants at increased risk of food allergy						
Settings: Community						
Intervention: Prophylactic oral immunotherapy with high-dose house dust mite allergen extract						
Comparison: Placebo						
Outcomes	Absolute effect		Relative effect (95% CI)	Studies (and n)	Certainty of the evidence	Reference
	Without OIT	With OIT				
Food allergy cumulative incidence 0-1 year	9.8 per 100	3.8 per 100	RR 0.38 (0.1 to 1.9)	1 (n = 111)	Very low	Zolkipli 2015
	Difference: 6.0 per 100 decrease p>0.05					

Evidence profile

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
Food allergy cumulative incidence at 1 year						
1 RCT (n = 111)	Grade down: moderate risk of bias	No grade change	Grade down: mechanism of action for food allergy may not be directly applicable. Very high rates of food allergy	Grade down: study not powered to detect a change in this outcome	Not suspected	Very low No reason to grade up based on effect size, dose response or potential effect of confounders

Emollients						
People: Infants at general risk of food allergy						
Settings: Community						
Intervention: Emollient with or without synbiotic from birth to six months						
Comparison: No emollient						
Outcomes	Absolute effect		Relative effect (95% CI)	Studies (and n)	Certainty of the evidence	Reference
	Without Emollient	With Emollient				
Food allergy prevalence at 1 year	13.5 per 100	10.9 per 100	RR 0.81 (0.49 to 1.33)	1 (n = 459)	Low	Dissanayake 2019 – emollient vs no emollient
	Difference: 2.5 per 100 decrease p>0.05					

Evidence profile

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
Both outcomes have the same evidence profile						
1 RCT (n = 459)	Grade down: Moderate risk of bias	No grade change	Grade down: not challenge proven so direct measurement of food allergy uncertain	No grade change but confidence intervals not provided	Uncertain	Low No reason to grade up based on effect size, dose response or potential effect of confounders

S4. Summary of individual studies

Antenatal interventions

Maternal dietary avoidance during pregnancy to prevent food allergy in infants

Article	Study design	Region / country covered	Funding source	Population	Sample number	Intervention and comparator	Food allergy measure	Risk of bias	Key effectiveness findings
Falth-Magnusson 1992	RCT	Sweden	Expressen Prenatal Research Foundation, Berg Foundation, First of May Flower Annual Campaign for Children's Health, Swedish Society of Medical Sciences, Swedish Baby Food Industry Fund for Nutritional Research, Swedish Medical Research Council. Nutramigen supplied by Bristol-Myers.	Increased risk	198	Cow's milk and egg exclusion from 28 weeks gestation to delivery vs no exclusion	History of doctor diagnosed food allergy at 1.5 years and 5 years	High	At 1.5 years, there was no significant difference in food allergy between groups (RR 1.67, 95% CI 0.38 to 7.22). At 5 years there was no significant difference in food allergy between groups (RR 1.09, 95% CI 0.6 to 1.97). For egg food allergy there was an increased risk in the intervention group, but the confidence interval was wide (RR 17.62, 95% CI 1.01 to 308.42).

Supplements for pregnant women to prevent food allergy in infants

Vitamin D

Article	Study design	Region / country covered	Funding source	Population	Sample number	Intervention and comparator	Food allergy measure	Risk of bias	Key effectiveness findings
Goldring 2013	RCT	UK	Asthma UK	General risk	180 pregnant women from 27 weeks gestation, 158 infants evaluated at 3 years	800 IU ergocalciferol daily until delivery or single oral bolus of 200,000 IU cholecalciferol (intervention) vs no vitamin D	History of doctor diagnosed food allergy at 3 years (ISAAC) reported in primary care records	High	There was no significant reduction in the incidence of food allergy (12% vitamin D vs 6% control, RR 1.92, 95% CI 0.57 to 6.5, p = 0.38).

Polyunsaturated fatty acids

Article	Study design	Region / country covered	Funding source	Population	Sample number	Intervention and comparator	Food allergy measure	Risk of bias	Key effectiveness findings
Dunstan 2003	RCT	Australia	Australia National Health and Medical Research Council and Raine Medical Research Foundation	Increased risk	40 intervention and 43 comparator	3.7 g of n-3 PUFAs with 56.0% as docosahexaenoic acid (DHA) and 27.7% as eicosapentaenoic acid (EPA). The control group received 4 (1-g) capsules of olive oil per day (containing 66.6% n-9 oleic acid and <1% n-3 PUFAs)	History of food allergy at 1 year. Assessment not defined.	High	At age 1 year there was no significant difference between groups (3/40 intervention and 5/43 control, RR 0.645, 95% CI 0.16 to 2.5, $p > 0.05$).
Palmer 2013	RCT	Australia	Australian National Health and Medical Research Council; Australian Egg Corporation; treatment and placebo capsules donated by Efamol, UK.	Increased risk	368 intervention and 366 control	n-3 LCPUFA (int: 800mg DHA + 100mg EPA/day vs placebo: vegetable oil capsules	Food allergy defined as history of immediate (within 60 min) skin rash with or without respiratory symptoms, gastrointestinal symptoms or cardiovascular symptoms following ingestion. Challenges not performed.	Some concerns	At age 1 year and 3 years, there was no significant difference in food allergy between groups (1 year RR 0.91, 95% CI 0.40 to 2.07; 3 year RR 0.94, 95% CI 0.40 to 2.22, $p = 0.88$).

Interventions in breastfeeding women

Vitamins in breastfeeding women to prevent food allergy in infants

Article	Study design	Region / country covered	Funding source	Population	Sample number	Intervention and comparator	Food allergy measure	Risk of bias	Key effectiveness findings
Norizoe 2014	RCT,	Japan	Jikei University School of Medicine and St Luke's International Hospital	Increased risk	164 breastfeeding women whose infants had facial eczema at one month	Vitamin D supplements (n = 82; 800 IU/day) or placebo (n = 82) for six weeks.	Food allergy diagnosed by doctors up to age two years, reported via parental survey	High	Parental report of doctor-diagnosed food allergy was significantly more common up to age two years in the vitamin D group (10/39, 25.7%) than in the placebo group (3/40, 7.5%; risk ratio 3.42; 95% CI 1.02 to 11.77; p = 0.030). The researchers concluded that vitamin D supplementation may not decrease the severity of infantile eczema at three months of age and may increase the risk of later food allergy. No safety issues other than food allergy were identified. A large number of participants were lost to follow up.

Interventions in both pregnant and breastfeeding women

Maternal dietary avoidance during pregnancy and breastfeeding to prevent food allergy in infants

Article	Study design	Region / country covered	Funding source	Population	Sample number	Intervention and comparator	Food allergy measure	Risk of bias	Key effectiveness findings
Lilja 1989	RCT	Sweden	Not declared	Increased risk	163 women, 79 of whom had reduced intake and 83 high intake	Milk and egg exclusion during third trimester versus 1 litre milk and 1 egg per day during the last 3 months of pregnancy and while breastfeeding	Food allergy, egg allergy, milk allergy measured through skin prick test and reported symptoms, no food challenges	High	At 1.5 years, there was no difference between groups in egg allergy (RR 2.02, 95% CI 0.19 to 21.89) or cow's milk allergy (RR 0.67, 95% CI 0.2 to 2.3).

Supplements in pregnancy and breastfeeding to prevent food allergy in infants

Article	Study design	Region / country covered	Funding source	Population	Sample number	Intervention and comparator	Food allergy measure	Risk of bias	Key effectiveness findings
Furuhjelm 2011	RCT	Sweden	Funding not declared. Supplements provided by Pharma Nord.	Increased risk	145	Fish oil capsules with ω -3 FA (1.1 g DHA and 1.6 g EPA per day) or placebo soy bean oil (2.5 g LA and 0.28 g LNA per day) from 25 weeks' gestation to 3-4 months breastfeeding	Clinical examination and food-specific-positive SPT or serum IgE antibodies, followed to 2 years.	Low	At one year the period prevalence of food allergy was lower in the omega-3 group (1/52, 2%) compared to the placebo group (10/65, 15%, $p < 0.05$). At two years prevalence was 11% (6/54) in the active and 25% (16/65) in the placebo group (RR 0.45, 95% CI 0.19 to 1.07, $p < 0.05$).

Interventions in infants

Breastfeeding to prevent food allergy in infants

Note that to keep consistent terminology the words high / some concerns / low are used in the risk of bias column, however these studies were assessed using ROBINS-I which uses the terms low / moderate / serious concerns / critical. No studies were deemed critical so low = low, moderate = some concerns and high = serious concerns.

Article	Study design	Region / country covered	Funding source	Population	Sample number	Intervention and comparator	Food allergy measure	Risk of bias	Key effectiveness findings
Tariq 1998, Arshad 1992	Prospective birth cohort	UK	Isle of Wight Health Authority Trust Fund	General risk	1167 infants followed to one year (Arshad 1991) and to four years (Tariq 1998)	Breastfeeding vs cow's milk formula; no details about duration or exclusivity	Follow-up 1 year and 4 years. Food allergy defined as a history of vomiting, diarrhea, colic or rash within 4 hours of a particular food on at least 2 occasions. Food challenges were not performed. SPT with milk, egg, soya, cod, wheat, and peanut.	High	In analysis of crude data, breastfeeding was not associated with reduced incidence of food allergy (6.3% of formula fed and 8.0% of breastfed infants, $p>0.05$) at one year but these data were not adjusted for confounders. At four year follow-up (Tariq 1998) food allergy incidence was 2.4% of 667 formula fed and 3.4% of 419 breastfed infants ($p>0.05$) but these data were not adjusted for confounders.

Article	Study design	Region / country covered	Funding source	Population	Sample number	Intervention and comparator	Food allergy measure	Risk of bias	Key effectiveness findings
Halken 2000	RCT with non random breastfed group (non random for the purposes of this intervention / outcome comparison)	Denmark	Not commercial. Companies provided formulas	Increased risk infants	478 infants	232 were exclusively breastfed (non randomised group) The comparator was extensively hydrolysed whey vs casein formula (Nutramigen or Profylac) vs partially hydrolysed whey formula (Nan HA)	Clinical evaluation of allergic symptoms. Food allergy / cow's milk allergy defined by challenges. Followed to 18 months	Some concerns (quasi random, but non-random for this intervention)	At 12 and 18 months, there was no difference in parental-reported and documented cow's milk allergy between those exclusively breastfed vs those receiving formula. At 18 months, the cumulative incidence of confirmed cow's milk protein allergy was 1.3% in exclusively breastfed infants (3/232), 0.6% in infants fed extensively hydrolysed formula (1/161) and 4.7% in infants fed partially hydrolysed formula (4/85) ($p > 0.05$ for hydrolysed formula vs breastfeeding).

Article	Study design	Region / country covered	Funding source	Population	Sample number	Intervention and comparator	Food allergy measure	Risk of bias	Key effectiveness findings
Host 1989 and 1991	Prospective birth cohort	Denmark	Non-commercial Private funding: Mrs and Mr CO Hansen, Research Foundation of Odense University Hospital	General risk	1749 newborns	Breastfeeding vs cow's milk formula in first month of life (not interventional)	Cow's milk allergy at 12 and 18 months. All with symptoms suspicious of cow's milk allergy were investigated clinically and with open food challenges.	High	Infants fed cow's milk formula solely or mainly during the first month(s) had a higher incidence of cow's milk allergy compared to exclusively breastfed infants (1+ months, 4.5% (n=15) vs 1.7% (n=24)). All who developed cow's milk protein allergy (n 39) received supplements of conventional cow's milk based formula during the first five days of life (39/1539) vs none of those 210 who did not receive such supplement (p < 0.05).
Kim 2011	Prospective birth cohort	Korea	Korean Ministry of Environment and Dairy Goat Co-operative (NZ) Ltd	General risk	1177 of 1664 followed up	Duration and exclusivity of breastfeeding	Telephone interviews at 4, 8 and 12 months. Food allergy defined as repetitive convincing history of immediate reactions. Challenges not performed	High	62 (5.3%) had food allergy, nearly all with skin symptoms. The duration of exclusive breastfeeding (< 6 vs ≥ 6 months) was not associated with food allergy (adjusted OR 1.02, 95% CI 0.55 to 1.88).

Article	Study design	Region / country covered	Funding source	Population	Sample number	Intervention and comparator	Food allergy measure	Risk of bias	Key effectiveness findings
Kull 2002, 2010	Prospective birth cohort	Sweden	Swedish Asthma and Allergy Association and the Swedish Foundation for Health Care Science and Allergy Research	General risk	3791 out of 4089 investigated at 4 years of age and at 8 years	Exclusive breastfeeding; partial breastfeeding, for greater than or less than four months	At four years, doctor diagnosed food allergy or food allergy reported by symptoms having appeared directly after food consumption. Challenges not performed	High	There was no association between breastfeeding and food allergy, whether breastfeeding was exclusive or partial and whether it continued for more than four months. At 8 years the cumulative adjusted odds ratio for exclusive breastfeeding for at least four months vs not was 0.93 for various food allergens (0.72 to 1.21).
Lucas 1990	RCT	UK	Not stated	General risk, pre-term infants	777 preterm infants	Trial 1: banked donor milk versus preterm formula as sole diet versus preterm formula as supplement to breast milk for median of 5 weeks. Trial 2: term versus preterm formula	Food allergy, followed to 18 months. Observed symptoms with some controlled challenges	Some concerns	Feeding preterm babies formula based on cow's milk, including pre-term formula with high protein content, did not increase the overall risk of food allergy. At 18 months there were no differences in food allergy between babies who received human milk and those who received cow's milk (all food allergy odds ratio 1.3, 95% CI 0.6 to 2.1; cow's milk reactions odds ratio 0.7, 95% CI 0.3 to 1.9).

Saarinen 1999	Prospective birth cohort with random cluster allocation to formula groups (by month of birth / hospital)	Finland	Nutricia Limited; Valio Limited, Research Funds of Helsinki University Central Hospital and Jorvi Hospital; Foundation for Paediatric Research, Helsinki; Sigrid Juselius Foundation.	General risk	6209 unselected healthy full-term infants,	824 children exclusively breastfed compared to supplementing with formula in first four days of life. Those who needed formula top up to or instead of breastfeeding were assigned to receive cow's milk formula (1758), pasteurised human milk (1844) or whey hydrolysate formula (1715) if needed. Allocation by month of birth and hospital.	Parent reported cow's milk protein allergy (urticaria, atopic dermatitis, vomiting, diarrhea, poor gain in weight, allergic rhinitis or wheezing). Then elimination diet and an open cow's milk challenge. SPT and sIgE. Follow up to 18-34 months	High	Breastfeeding did not decrease the incidence of cow's milk protein allergy compared to formula feeding. Cumulative incidence of cow's milk protein allergy was 2.1% in those exclusively breastfed vs 2.4%, 1.7% and 1.5% respectively of those receiving cow's milk formula, pasteurised human milk and whey hydrolysate in the first four days (p-value not reported for breastfeeding vs all others). The incidence of cow's milk allergy was 3.3% (43/1304), 2.3% (32/1403), 2.0% (26/1311) and 2.6% (17/643) among infants exposed to conventional cow's milk formula, pasteurized human milk, whey hydrolysate formula vs exclusively breastfed the first eight weeks respectively. Supplementing breastfeeding with conventional cow's milk based formula in the first four days of life increased the risk of developing cow's milk allergy (OR 1.54; 95% CI, 1.53-3.52).
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Hydrolysed formula

Article	Study design	Region / country covered	Funding source	Population	Sample number	Intervention and comparator	Food allergy measure	Risk of bias	Key effectiveness findings
Halken 1993	RCT With non random breastfed group	Denmark	Not commercial Companies provided formulas	Increased risk infants	159 infants	Extensively hydrolysed whey formula versus partially hydrolysed whey formula versus extensively hydrolysed casein formula to supplement breastfeeding in the first 4 months	Clinical evaluation of allergic symptoms. Food allergy and cow's milk protein allergy defined by challenges. All challenges were open, but with equivocal results the challenge was repeated and eventually blind. Followed to 18 months	Some concerns	There were no differences in the incidence of food allergy or cow's milk allergy between the extensively hydrolysed whey and casein formulas (or the non random breastfed group). 2% (1/59) of those fed casein hydrolysate, 5% (3/62) of those fed ultrafiltrated whey hydrolysate and 5% (1/20) of those breastfed (non-randomised group) had cow's milk allergy ($p>0.05$).

Article	Study design	Region / country covered	Funding source	Population	Sample number	Intervention and comparator	Food allergy measure	Risk of bias	Key effectiveness findings
Halken 2000	RCT with non random breastfed group	Denmark	Not commercial. Companies provided formula	Increased risk infants	478 infants	Extensively hydrolysed whey vs partially hydrolysed whey vs extensively hydrolysed casein formula for the first four months if breastfeeding was not sufficient. 232 were exclusively breastfed (non randomised group)	Clinical evaluation of allergic symptoms. Food allergy / cow's milk allergy defined by challenges. Followed to 18 months	Some concerns (randomised by date of birth: quasi random for this intervention / outcome)	At 18 months, the cumulative incidence of confirmed cow's milk allergy was 1.3% in exclusively breastfed infants (3/232), 0.6% in infants fed extensively hydrolysed formula (1/161) and 4.7% in infants fed partially hydrolysed formula (4/85) ($p = 0.05$ for partial vs extensively hydrolysed formula, $p > 0.05$ for hydrolysed formula vs breastfeeding). There was no difference in the incidence of cow's milk protein allergy among infants fed whey (0/82 = 0%) or casein (2/79=2.5%) based extensively hydrolysed formulas.

Article	Study design	Region / country covered	Funding source	Population	Sample number	Intervention and comparator	Food allergy measure	Risk of bias	Key effectiveness findings
Lowe 2011	RCT	Australia	Nestle Australia	Increased risk infants	620 infants at increased risk followed	Whey partially hydrolysed formula (NAN HA) vs soy vs cow's milk formula allocated at cessation of breastfeeding At study start two arms: soy vs conventional cow's milk formula. After 6 months changed to three arms including a third arm with partially hydrolysed whey formula (Nan HA)	Parental report of allergic manifestations using telephone interviews every 4 weeks. Followed up to 2 years. Skin prick test performed. Challenges not performed	High (Approximately 50% received some allocated formula by 4 months; 16% did not receive allocated treatment; intervention stopped at 6 months. Definition of food allergy poor; may be discrepancies between other data published about this study)	Use of partially hydrolysed whey formula or soy formula did not decrease the risk of allergic symptoms or food allergy at two years compared to cow's milk. Unadjusted cumulative prevalence of cow's milk allergy at 2 years was 3.1 % (26/193) vs 1.6% (3/191) (OR 0.50; 95% CI 0.12 to 2.02) in the conventional formula vs the partially hydrolysed group. No adjusted results.

Article	Study design	Region / country covered	Funding source	Population	Sample number	Intervention and comparator	Food allergy measure	Risk of bias	Key effectiveness findings
Mallet 1992	RCT	France	Not commercial	Increased risk	177 infants, with 124 followed up at 2 years and 139 at 4 years	Extensively hydrolysed casein (Pregestimil, n = 92) vs standard cow's milk formula (n = 85) up to 4 months as needed	Clinical evaluation at 4 months, 12 months, 2 years, 4 years. Food allergy defined as 'obvious cow's milk protein allergy verified by type I reagenic allergy or malabsorption' reported at 1 year. Oral challenges not performed	High (Investigators not blinded, challenges not described, food allergy outcome insufficient, underpowered for food allergy)	At one year the prevalence of food allergy was too low to show significant differences between groups (1% hydrolysed formula alone versus 0% hydrolysed formula plus breastfeeding versus 0% adapted cow's milk formula alone or with breastfeeding).

Article	Study design	Region / country covered	Funding source	Population	Sample number	Intervention and comparator	Food allergy measure	Risk of bias	Key effectiveness findings
Oldaeus 1997 1999	RCT	Sweden	Mead-Johnson	Increased risk	155 (51 partially hydrolysed, 55 extensively hydrolysed, 49 cow's milk formula). 21 exclusively breastfed until 9 months. 141 completed follow-up at 18 months	Extensively hydrolysed casein formula (Nutramigen) vs partially hydrolysed (Mead Johnson) vs cow's milk formula for at least 3 months after cessation of breastfeeding until at least 9 months. This was combined with maternal and infant milk, egg and fish exclusion in all groups	'Gastrointestinal allergy', clinical evaluation of symptoms and oral challenges, sIgE, skin prick test, unclear which symptoms were measured	High (combined intervention, late introduction and long duration of formula, mean introduction of formula at 3-4 months, confounders not described)	No difference in food allergy / gastrointestinal allergy between groups: 10% (5/55), 21% (10/51), 8% (4/49) and 10% (2/21) in the groups receiving extensively hydrolyzed, partially hydrolysed conventional formula or breastmilk The authors reported no difference between groups in cumulative prevalence of positive skin prick tests for food allergy outcomes (relative risk data not provided).

Article	Study design	Region / country covered	Funding source	Population	Sample number	Intervention and comparator	Food allergy measure	Risk of bias	Key effectiveness findings
Vandenplas 1992	RCT	Belgium	Nestle	Increased risk	67/75 infants included and followed to 1 year.	Whey partially hydrolysed formula (NAN HA) vs adapted cow's milk formula (NAN) exclusively for 6 months	Cow's milk allergy, challenge proven (open) Cow's milk 'sensitivity' was defined by confirmed atopic symptoms (eczema, wheezing, rhinitis, vomiting, diarrhea and colic, when other causes were excluded) and positive elimination challenge procedures (interpreted by the reviewers to be equivalent to cow's milk protein allergy for the purposes of this review, but the article itself did not clearly define 'allergy')	High (Small sample, open challenge, various outcomes reported)	The authors state that the incidence of cow's milk protein sensitivity at one year was 15.6% in the hydrolysate group (five infants: two during exclusive hydrolysate feeding and three after age of 6 months) compared with 42.8% in the adapted formula group (15 infants: 14 during exclusive Nan administration and one after the age of 6 months), $p < 0.05$. From birth to 6 months, the total number of participants with positive challenge to cow's milk was 2/32 in the intervention group and 14/35 in the control group ($p=0.0011$). Between 6 to 12 months there was no difference between groups in new cases of challenge proven cow's milk protein allergy (3/32 vs 1/35, $p > 0.05$) or allergy to egg, fish, orange or banana.

Article	Study design	Region / country covered	Funding source	Population	Sample number	Intervention and comparator	Food allergy measure	Risk of bias	Key effectiveness findings
von Berg 2003	RCT	Germany	German Ministry of Education	Increased risk	2252: eHFw 559 eHFc 580 pHFw 557 CM 556.	Randomly assigned at birth to one of 4 blinded formulas: CMF, partially hydrolysed whey formula, extensively hydrolysed whey formula, and extensively hydrolysed casein formula (eHF-C). Exclusive BF for 4 months in 889, 865 with follow-up 1 year.	Clinical evaluation of IgE and non IgE food allergy. Standard elimination / challenge procedure. Food allergy only assessed if gastrointestinal symptoms (FA-GIT).	Some concerns (Combined primary outcome, food allergy outcome not sufficient, 13% dropped out and 13% excluded from analyses due to non-compliance)	Partially hydrolysed formula and extensively hydrolysed casein formula were less likely to result in allergic symptoms overall than cow's milk formula, but the impact specific to food allergy / cow's milk allergy was not clear. FA_GIT diagnosed in 1/256 (0.4%) in CMF, 5/241 (5%) in pHFw, in 2/238 (0.8%) in eHFw and in 4/210 (1.9%) in the eHFc group. Combining the HF groups resulted no - significant (p 0.53) reduction in FA-GIT

See also tables related to combined interventions for other studies related to formula.

Soy formula

Article	Study design	Region / country covered	Funding source	Population	Sample number	Intervention and comparator	Food allergy measure	Risk of bias	Key effectiveness findings
Lowe 2011	RCT	Australia	Nestle Australia	Increased risk infants	620 infants at increased risk followed at 6, 12 and 24 months and to 2 years; 575 followed to 2 years	Whey partially hydrolysed formula (NAN HA) vs soy vs cow's milk formula allocated at cessation of breastfeeding	Parental report of allergy using telephone interviews every 4 weeks. skin prick test, reaction within 2 hours of ingesting food	High (16% did not receive allocated treatment, intervention stopped at 6 months)	Use of soy formula did not decrease the risk of cow's milk protein allergy. The odds ratio of soy compared to cow's milk formula for any food reactions within the first two years was 1.54 (95% CI 0.89 to 2.67) and for cow's milk protein 1.46 (0.46 to 4.00).

Supplements for infants to prevent food allergy in infants

Vitamins

Article	Study design	Region / country covered	Funding source	Population	Sample number	Intervention and comparator	Food allergy measure	Risk of bias	Key effectiveness findings
Rosendahl 2019	RCT	Finland	Unknown	General risk	975 infants	Daily vitamin D supplementation of 10 µg (400 IU) or 30 µg (1200 IU) from the age of 2 weeks	Reported food allergy at 12 months, including cow's milk protein allergy. No challenges performed	High	At 12 months there was no difference between groups in reported food allergy apart from cow's milk protein allergy where there was a trend towards greater occurrence in infants administered 30µg vitamin D compared with the 10µg dose (odds ratio 2.23; 95% CI 1.00 to 4.96).
Kiraly 2013	RCT	West Africa	Unknown	General risk, low birth weight infants	281	Early or delayed (usual policy) BCG vaccination. A subgroup was randomly assigned to vitamin A or placebo in a two-by-two factorial design. Follow-up occurred at age 3-9 years.	Reported symptoms of food allergy was a secondary outcome. Skin prick test for reaction to foods. 3-9 year follow up	High	There was no difference between groups in symptoms of food allergy or skin prick test outcomes (p>0.05).

Polyunsaturated fatty acids

Article	Study design	Region / country covered	Funding source	Population	Sample number	Intervention and comparator	Food allergy measure	Risk of bias	Key effectiveness findings
D'Vaz 2012	RCT	Australia	National Health and Medical Research Council of Australia	Increased risk (mothers with allergic disease and restricted fish intake)	420 (218 active group, 202 placebo group)	Daily capsules with 650mg fish oil or olive oil (controls) from birth to 6 months of age	Food allergy assessed by history and skin prick testing. Not challenge proven. Evaluated at 6 and 12 months	High	Fish oil supplements did not reduce the risk of food allergy at one year (19/156 vs 25/167 control; RR 0.81, 95% CI 0.46 to 1.21).

Prebiotics

Article	Study design	Region / country covered	Funding source	Population	Sample number	Intervention and comparator	Food allergy measure	Risk of bias	Key effectiveness findings
Ivakhnenko 2013	RCT	Ukraine	Lviv National Medical University	General risk	240 healthy infants, 166 followed up	Breastfeeding; formula with oligosaccharides (scGOS/lcFOS); or standard formula. Infants not being breastfed were randomised to a formula type. Mothers were asked to use the feeding method for at least two months.	Gastrointestinal symptoms of food allergy as reported by parents; allergic reactions to cow's milk reported by parents and in health records. Follow up to 18 months	High (High loss to follow up, food allergy not mentioned as outcome measure but results reported, non defined outcome measure)	At 18 month follow up, infants fed breast milk or supplemented formula had less allergic reactions to food compared to infants fed standard formula (3.92% breastfeeding, 4.84% supplemented formula and 16.98% standard formula, $p<0.05$). Infants fed breast milk or supplemented formula had less allergic reactions to cow's milk compared to infants fed standard formula (1.96% breastfeeding, 3.23% supplemented formula and 15.09% standard formula, $p<0.05$).

Probiotics

Article	Study design	Region / country covered	Funding source	Population	Sample number	Intervention and comparator	Food allergy measure	Risk of bias	Key effectiveness findings
Morisset 2011	RCT	France	Bledina, France (Danone group).	Increased risk infants (family history of allergy)	129 infants; AG (n=66, of which 53 completed the study), placebo group (n=63, of which 55 completed the study)	Standard infant formula fermented with heat-killed Bifidobacterium breve C50 (4.2×10^9 bacteria per 100 g of powder formula) and Streptococcus thermophilus 065 (3.8×10^7 bacteria per 100g of powder formula) from birth until 1 year of age. Comparator: Standard infant formula	Challenge proven cow's milk allergy in the first 24 months of age	Low	Infant formula supplemented with probiotics did not reduce the incidence of cow's milk allergy compared to standard formula (13% versus 15% controls, $p = 1.0$).
Plummer 2019	RCT	Australia	Unknown	General risk	281 preterm infants (subset of larger trial)	Probiotic combination or placebo from soon after birth until discharge from hospital or term corrected age, whichever was earlier	Food allergy assessed at 12 months by questionnaire, clinical examination and skin prick tests to common allergens	Some concerns	There was no difference between prebiotics and placebo in the prevalence of food allergy (4/124 vs 2/154, 3% vs 1%, $p > 0.05$)

Article	Study design	Region / country covered	Funding source	Population	Sample number	Intervention and comparator	Food allergy measure	Risk of bias	Key effectiveness findings
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Prescott 2008	RCT	Australia	National Health and Medical Research Council of Australia, Child Health Research Foundation of Western Australia, Probiomics	General risk infants	153 infants monitored up to 2.5 years of age; active group (n=77); placebo group (n=76)	3 x 10 ⁹ Lactobacillus acidophilus probiotic strain (LAFTI, L10/LAVRI-A1) given daily orally for the first 6 months in maltodextrin as stable freeze dried powder (in sachet packets), dissolved in 1-2ml sterile water. Placebo: maltodextrin alone	2.5 year follow up. Food allergy not challenge proven. Diagnosis based on consistent clinical history and IgE sensitisation	Some concerns	Probiotic supplementation did not reduce the risk of food allergy in the first 2.5 years versus placebo (12/76, 16% vs 9/73, 12%, p > 0.05).
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Timing of introduction of complementary foods to prevent food allergy in infants

Timing of introducing combination of allergenic foods

Article	Study design	Region / country covered	Funding source	Population	Sample number	Intervention and comparator	Food allergy measure	Risk of bias	Key effectiveness findings
Perkin 2016	RCT	UK	UK Food Standards Agency	General risk population, exclusively breastfed to 3 months with intention to breastfeed until 6 months of age	1303 infants aged 3 months, 1106 followed up	Introduction of six foods at 3 months (cow's milk, hen egg, peanut, whitefish, sesame, wheat) in addition to breastfeeding until 6 months of age; 2g protein of each food given twice a week. Comparator was exclusive breastfeeding to 6 months of age	Prevalence of IgE-mediated allergy to any of the six allergenic foods between 1 and 3 years of age. Food challenge	Some concerns	In intention-to-treat analysis, there was no difference between groups in food allergy prevalence at age 1 to 3 years (5.6% early introduction versus 7.1% standard-introduction, RR 0.8, 95% CI 0.51 to 1.25, $p>0.05$). In per-protocol analysis, the prevalence of any food allergy was lower in the early-introduction group (2.4% vs 7.3%, $p = 0.01$) along with the prevalence of peanut allergy (0% vs 2.5%, $p = 0.003$) and egg allergy (1.4% vs 5.5%, $p = 0.009$). There was no difference between groups in milk, sesame, fish or wheat allergy. In the per protocol analysis, consuming 2g per week of peanut or egg-white protein was associated with a significantly lower prevalence of these respective allergies compared to lower consumption. Early introduction of all six foods was difficult for participants to achieve (low adherence) but was safe.

Introducing hen's egg

Article	Study design	Region / country	Funding source	Population	Sample number	Intervention / comparator	Food allergy measure	Risk of bias	Key effectiveness findings
Bellach 2017	RCT	Germany	US Food Allergy & Anaphylaxis Network, Prevention and Information Network for Allergy/Asthma	General risk	383 infants aged 4 to 6 months negative for specific IgE to egg	Pasteurised egg powder (n=184) to age 12 months. Controls received rice powder (n=199) to age 12 months.	Hen's egg allergy (secondary outcome) was confirmed by double-blind, placebo-controlled food challenge tests	Low	Introducing hen's egg between 4 to 6 months did not reduce egg allergy at 12 months of age (2.1% vs 0.6% placebo, relative risk, 3.30; 95% CI 0.35 to 31.32; p = 0.35). 7.1% of the early introduction group reacted to egg. There was one FPIES and 2 anaphylaxis episodes in the early introduction group (out of 142 participants). Among 406 screened infants, 23 (5.7%) had hen's egg-specific IgE before randomisation.
Palmer 2013	RCT	Australia	Women's and Children's Hospital Foundation; Ilhan Food Allergy Foundation	Increased risk (eczema)	86 infants	Pasteurized egg powder (n= 49) given daily between ages 4-8 months. Controls received rice powder (n=37) given daily between ages 4-8 months	Observed pasteurised raw egg challenge and skin prick tests at 12 months	High (adherence to intervention)	At 12 months, there was no difference in IgE-mediated egg allergy (33% vs 51% controls; relative risk 0.65; 95% CI 0.38 to 1.11; p = 0.11). 31% [15/49] of infants randomised to receive egg had an allergic reaction to the egg powder and did not continue powder ingestion.
Palmer 2017	RCT	Australia	Australian National Health and Medical Research Council	Increased risk (atopic mother but no personal history of eczema)	820 infants aged 4-6 months	Pasteurised egg powder (n=407) from 4 to age 10 months. Controls had rice powder (n=413) to age 10 months.	Pasteurised raw egg challenge at age 12 months	Low	There was no difference between groups in infants with IgE-mediated egg allergy (egg group 7.0% vs control 10.3%; adjusted relative risk 0.75; 95% CI 0.48 to 1.17; p = 0.20). A higher proportion of infants in the egg group stopped taking the study powder because of a confirmed allergic reaction (25 of 407 [6.1%] compared with 6 of 413 [1.5%]).

Article	Study design	Region / country covered	Funding source	Population	Sample number	Intervention and comparator	Food allergy measure	Risk of bias	Key effectiveness findings
Natsume 2017	RCT	Japan	Ministry of Health, Labour and Welfare, and National Centre for Child Health and Development, Japan	Increased risk (eczema)	147 infants	50mg of heated egg powder per day from 6 months to 9 months of age and 250 mg per day thereafter until 12 months (n= 73). Controls had matched pumpkin powder (n=74) until 12 months of age.	Hen's egg allergy confirmed by open oral food challenges at 12 months of age, assessed blindly	Low	The intervention group was less likely to develop egg allergy. Five (8%) of 60 participants had an allergy to heated egg in the egg group compared with 23 (38%) of 61 in the placebo group (risk ratio 0.221, 95% CI 0.090 to 0.543, p=0.0001). This study used smaller amounts of egg than other studies and used heated egg.

Introducing peanut

Article	Study design	Region / country covered	Funding source	Population	Sample number	Intervention and comparator	Food allergy measure	Risk of bias	Key effectiveness findings
Du Toit 2015 and 2016	RCT	UK	ITN, US	Increased risk infants (severe eczema or egg allergy or both) The study included two independently randomised and controlled groups: one sensitised to peanut and one not, each with its own control group.	640 infants between 4 and 11 months old (mean 7.8 months), assigned to separate study cohorts on the basis of pre-existing sensitivity to peanut extract, which was determined with the use of a skin-prick test	Peanut consumption until age 5 years; 6g peanut protein per week. Then avoidance from 5 years. The comparison group avoided peanuts until after 6 years	Double-blind, placebo-controlled peanut challenge at 5 and 6 years. Follow up of 460 children	Low (Groups not blinded, challenges were)	Among the 530 infants in the intention-to-treat population who initially had negative results on the skin-prick test, the prevalence of peanut allergy at 5 years of age was 13.7% in the avoidance group and 1.9% in the consumption group ($p < 0.001$). Among the 98 participants in the intention-to-treat population who initially had positive skin prick test results, the prevalence of peanut allergy was 35.3% in the avoidance group and 10.6% in the consumption group ($p = 0.004$). The reduction in confirmed peanut allergy remained after all participants then avoided peanut for a year (18.6% control vs 4.8% peanut, $p < 0.001$).

Introduction of cow's milk

Article	Study design	Region / country covered	Funding source	Population	Sample number	Intervention and comparator	Food allergy measure	Risk of bias	Key effectiveness findings
Lowe 2011	RCT	Australia	Nestle Australia	Increased risk infants	620 infants at increased risk followed at 6, 12 and 24 months and to 2 years; 575 followed to 2 years	Whey partially hydrolysed formula (NAN HA) vs soy vs cow's milk formula allocated at cessation of breastfeeding	Parental report of allergy using telephone interviews every 4 weeks. skin prick test, reaction within 2 hours of ingesting food	High (50% and 16% did not receive allocated treatment at 4 months and when, intervention stopped at 6 months, respectively)	Delaying the introduction of cow's milk by using soy or whey partially hydrolysed formula after breastfeeding did not decrease the risk of food allergy. The odds ratio of soy compared to cow's milk formula for any food reactions within the first two years was 1.54 (95% CI 0.89 to 2.67) and for cow's milk protein 1.46 (0.46 to 4.00).
Lucas 1990	RCT	UK	Not stated	General risk, pre-term infants	777 preterm infants	Trial 1: banked donor milk versus preterm formula as sole diet versus preterm formula as supplement to breast milk for median of 5 weeks. Trial 2: term versus preterm formula	Food allergy, followed to 18 months. Observed symptoms with some controlled challenges	Some concerns	Feeding preterm babies formula based on cow's milk, including pre-term formula with high protein content, did not increase the overall risk of food allergy. At 18 months there were no differences in food allergy between babies who received human milk and those who received cow's milk (all food allergy odds ratio 1.3, 95% CI 0.6 to 2.1; cow's milk reactions odds ratio 0.7, 95% CI 0.3 to 1.9).

Article	Study design	Region / country covered	Funding source	Population	Sample number	Intervention and comparator	Food allergy measure	Risk of bias	Key effectiveness findings
Urashima 2019	RCT	Japan	Unknown	Increased risk	312 infants	Breastfeeding with or without amino acid-based elemental formula for at least the first 3 days of life vs or breastfeeding supplemented with cow's milk formula (≥ 5 mL/d) from the first day of life to 5 months of age	Immediate-type food allergy diagnosed by oral food challenge test or triggered by food ingestion, with food-specific IgE levels of at least 0.35 UA/mL at two years	Some concerns	Prevalence of immediate-type food allergy at two years was lower in the breastfeeding / elemental formula group than in the group who received cow's milk formula supplements (2.6% vs 13.2%, RR 0.20, 95% CI, 0.07-0.57).
Zachariassen 2011	RCT	Denmark	Not commercial	General risk, very preterm	324 very preterm infants (gestational age 24-32 weeks)	Cow's milk-based human milk fortifier added to mother's breast milk versus exclusive breastfeeding versus (for those not breastfeeding) cow's milk-based preterm formula for 4 months after discharge	Reported food allergy at one year	High	No infant developed food allergy. There were no differences between groups.

See also studies related to hydrolysed formula which contain relevant data.

Non-antigen specific immune modulation to prevent food allergy in infants

Article	Study design	Region / country covered	Funding source	Population	Sample number	Intervention and comparator	Food allergy measure	Risk of bias	Key effectiveness findings
Kiraly 2013	RCT	West Africa	Unknown	General risk, low birth weight infants	281	Early or delayed (usual policy) BCG vaccination. A subgroup was randomly assigned to vitamin A or placebo in a two-by-two factorial design. Follow-up occurred at age 3-9 years.	Reported symptoms of food allergy was a secondary outcome. Skin prick test for reaction to foods. 3-9 year follow up	High	There was no difference between groups in symptoms of food allergy or skin prick test outcomes ($p>0.05$).

Article	Study design	Region / country covered	Funding source	Population	Sample number	Intervention and comparator	Food allergy measure	Risk of bias	Key effectiveness findings
Thøstesen 2017	RCT	Denmark	Danmarks Grundforskningsfond, Augustinus Fonden; Udviklingsraadet of Sygehus Lillebaelt; Direktør Jacob Madsen og Hustru Olga Madsens Fond; Forskningsfonden of Sygehus Lillebaelt; The Højmosegaard grant; The A. P. Møller Foundation for the Advancement of Medical Science	General risk	4,262 infants	Within 7 days of birth at three Danish hospitals, 4,262 newborns of 4,184 mothers were randomised to BCG vaccination or to a no-intervention control group. Exclusion criteria were gestational age <32 weeks, birth weight <1000g and known immuno-deficiency.	Food allergy at 13 months of age suspected by doctors or parents. Telephone interviews were conducted at 3 and 13 months. Doctor-diagnosed food allergy required a confirmative answer to the question "Has a doctor said that your child has food allergy?" Subgroups were offered blood sampling at 13 months. sIgE	Some concerns	BCG neonatal vaccination had no effect on suspected food allergy at 13 months (relative risk 1.48, 95% CI 0.67 to 3.29). The interaction for ethnicity in the effect of BCG on suspicion of food allergy was significant.
Zolkipli 2015	RCT	UK	UK National Institute for Health Research	Increased risk	111 infants less than 1 year old at increased risk of atopy (2 or more first degree relatives with allergic disease) and with negative skin prick tests to common allergens at randomisation	Infants were randomised to prophylactic oral immuno-therapy with high-dose house dust mite allergen extract or placebo twice daily for 12 months.	Food allergy, skin prick test, specific IgE. Children were assessed every three months for one year. Challenges not performed	Some concerns	The study found no effect on food allergy, but was not powered to detect this. There were no differences between the intervention and placebo groups in the number or nature of adverse effects. The intervention was well tolerated.

Other interventions to prevent food allergy in infants

Article	Study design	Region / country covered	Funding source	Population	Sample number	Intervention and comparator	Food allergy measure	Risk of bias	Key effectiveness findings
Dissanayake 2019	RCT	Japan	Unknown	General risk	459 infants	2 x 2 factorial design with emollient, synbiotic (combination of prebiotic and probiotic), both or neither. The intervention was carried out from birth up to 6 months of age.	Food allergy reported in questionnaires at 1, 6, 9 and 12 months of age, sIgE	Some concerns	Neither the emollient nor the synbiotic, alone or in combination, reduced food allergy at one year of age.

Interventions in pregnant / breastfeeding women and infants

Dietary avoidance in mothers and infants coupled with environmental interventions

Article	Study design	Region / country covered	Funding source	Population	Sample number	Intervention and comparator	Food allergy measure	Risk of bias	Key effectiveness findings
Arshad 1992	RCT	UK	Not known	Increased risk (family history of atopy and high (greater than 0.5 kU/l) cord-blood concentrations of total IgE)	120 infants	In the active group (n = 58), breastfeeding mothers avoided allergenic foods (milk, egg, fish, and nuts) and avoided feeding their infants these foods and soya, wheat, and orange up to the age of 12 months; the infants' bedrooms and living rooms were treated with an acaricidal powder and foam every 3 months. The control group had an unrestricted diet and no environmental interventions.	A paediatric allergy specialist unaware of group assignment examined the infants for allergic disorders at 10-12 months. Food allergy (named food intolerance) defined as a history of vomiting, diarrhoea, colic or rash with 4 h of ingestion of a recognized food allergen combined with a positive open challenge	High (food allergy not main outcome, small sample, combined intervention)	At one year there was no difference between groups in food allergy (2/58 = 3% intervention vs 7/62 = 11% controls, OR 3.29, 95% CI 0.6 to 17.3).

Hydrolysed formula plus dietary avoidance

Article	Study design	Region / country covered	Funding source	Population	Sample number	Intervention and comparator	Food allergy measure	Risk of bias	Key effectiveness findings
Odelram 1996	RCT	Sweden and Finland	Swedish Medical Research Council, Swedish National Association for the Prevention of Asthma and Allergy, Medical Research Fund of the County of Ostergotland, the King Gustaf Vth 80-Year Anniversary Fund, Odd Fellows Foundation, Fison's Scientific Fund, Swedish Association for Allergology.	Increased risk family history + IgE	91 infants	Extensively hydrolysed ultrafiltered cow's milk whey formula (Profylac) (n = 32) versus cow's milk formula (n = 39) started after exclusive breastfeeding ended at 6 months and continued up to 1 year of age as needed. Lactating mothers avoided milk, egg and fish as did infants up to one year.	Cow's milk allergy was evaluated by physician assessment, using history, single-blind challenge and allergy testing (SPT and sIgE) at 1.5 years, and included IgE and non-IgE milk allergy.	High	There was no significant difference in cow's milk protein allergy between groups (relative risk 0.18, 95% CI 0.01, 3.37). None of 25 infants evaluated in the intervention group developed cow's milk allergy, compared with 3 of 32 infants in the control group, but this was not statistically significant.

Zeiger 1989 1992 and 1995	RCT	USA	Not commercial	Increased risk (parental history)	288/379 infants followed up to two years, 165 infants followed to seven years	Following or to supplement breastfeeding, extensively hydrolysed formula (Nutramigen) vs cow's milk formula as needed up to 1 year combined with maternal avoidance of cow's milk, egg and peanut in last trimester and during breastfeeding and infant food- allergen avoidance of cow's milk to 1 year, egg to 2 years and peanut and fish to 3 years in intervention group. Usual diet in control group.	Food allergy and cow's milk allergy clinical evaluation at 4, 12 months 1, 2, 3, 4 and 7 years including double blind food challenge and skin prick tests	High (Follow up 76%)	The combined intervention of extensively hydrolysed formula and maternal/infant dietary avoidance was associated with reduced cow's milk allergy at 4 and 12 months. There was a lower cumulative prevalence of food allergy in the intervention group compared with the control group from 1 to 2 years and at 4 years. There was no difference between groups in the period prevalence at 3 and 4 years. At seven years, follow up was low and there was no significant difference (relative risk 0.45, 95% CI 0.19 to 1.04).
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Probiotics for mothers and infants with or without prebiotics for infants

Article	Study design	Region / country covered	Funding source	Population	Sample number	Intervention and comparator	Food allergy measure	Risk of bias	Key effectiveness findings
Kalliomaki 2003	RCT	Finland	Finnish Foundation for Paediatric Research, National Technology Agency of Finland, Allergy Research Foundation	Increased risk (family history of atopic disease)	100 infants were monitored up to 4 years of age; (active group n=50, placebo, n=50)	Mothers took two capsules of 1×10^{10} CFU of Lactobacillus GG daily for 4 weeks before expected delivery. Postnatally for 6 months, either the mother (during breastfeeding) or the infant consumed the same probiotic. Placebo was daily intake of two capsules of microcrystalline cellulose	Challenge proven allergy to cow's milk protein in the first 4 years	Some concerns	Probiotics did not reduce the risk of cow's milk protein allergy. (Cumulative incidence at 2 years 6/54 placebo children vs 11/53 lactobacillus, $p=0.17$). In two children in each group ($p=0.98$), the symptoms persisted up to the age of 4 years.

Article	Study design	Region / country covered	Funding source	Population	Sample number	Intervention and comparator	Food allergy measure	Risk of bias	Key effectiveness findings
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Kukkonen 2011	RCT	Finland	Helsinki University Central Hospital Research Funds, Valio Ltd	Increased risk population (at least one of the child's parents had a doctor-diagnosed allergic disease)	1018 infants; active group n=506, of which 445 completed 2 years of follow-up; placebo group n=461, of which 464 completed 2 years of follow-up	From the 36 th week of gestation, mothers in the active group took twice daily a capsule containing Lactobacillus rhamnosus GG (ATCC53103) 5x10 ⁹ CFU, L. rhamnosus LC705 (DSM 7061) 5x10 ⁹ CFU, Bifidobacterium breve Bb99 (DSM 13692), 2x10 ⁸ CFU, and Propionibacterium freudenreichii ssp. Shermanii JS (DSM 7076) 2x10 ⁸ CFU. Their infants then received daily the 4 probiotic strains mixed with an adequate amount of liquid containing prebiotic galacto-oligosaccharides (0.8 g/day) in a teaspoon. Placebo was inert cellulose capsules	Challenge proven allergy in the first 2 years	Low	Compared with placebo, probiotic plus prebiotic treatment had no effect on food allergy at two years (6% probiotics plus prebiotics versus 7% controls, p > 0.05).
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Article	Study design	Region / country covered	Funding source	Population	Sample number	Intervention and comparator	Food allergy measure	Risk of bias	Key effectiveness findings
Marschan 2008	RCT	Finland	Valio Limited, Research Foundation of Orion Corporation, Espoo, Foundation for Pediatric Research, Finland; Sigrid Juselius Foundation, Research Fund of the Helsinki University Central Hospital.	Increased risk population (at least one of the child's parents had a doctor-diagnosed allergic disease)	98 infants	Probiotics for mothers during last 2-4 weeks of pregnancy plus probiotic and prebiotic for infants for 6 months versus placebo for mothers and infants. Active group took two capsules a day [Lactobacillus rhamnosus GG (ATCC 53103) 5×10^9 CFU, L. rhamnosus LC705 5×10^9 CFU, Bifidobacterium breve Bb 99 2×10^8 CFU, and Propionibacterium freudenreichii sp. Shermanii JS 2×10^9 CFU in a capsule]. Infants received the same capsules once a day but mixed with sugar syrup containing 0.8 g of prebiotic sugars (galacto-oligosaccharides).	Challenge proven food allergy, followed to 2 years	High	There was no significant difference between groups in food allergy prevalence.

Article	Study design	Region / country covered	Funding source	Population	Sample number	Intervention and comparator	Food allergy measure	Risk of bias	Key effectiveness findings
Niers 2009	RCT,	The Netherlands	Wilhelmina Children Hospital. University Medical Centre Utrecht	Increased risk population (at least one of the child's parents had a doctor-diagnosed allergic disease)	156 infants (active n=78, of which 50 completed 2-year-follow-up, placebo group n=78, of which 48 completed 2-year-follow-up)	Pregnant women took probiotic bacteria during the last 6 weeks of pregnancy. Infants took it for 12 months. Probiotic comprised once daily 3×10^9 CFU (1×10^9 CFU of each strain: B. bifidum W23, Bifidobacterium lactis W52, and Lc. Lactis W58) of freeze dried probiotic mixture. Placebo consisted of the carrier of the probiotic product: rice starch and maltodextran.	Specific IgE and skin prick test and history in the first 2 years, parent diary of 'symptoms indicative of food allergy'.	High (loss to follow up)	Probiotics did not reduce the incidence of food allergy at 2 years (no numerical data given).

Fish oil for breastfeeding mothers and infants

Article	Study design	Region / country covered	Funding source	Population	Sample number	Intervention and comparator	Food allergy measure	Risk of bias	Key effectiveness findings
Manley 2011	RCT	Australia	Unknown	General risk	655 pre-term infants < 33 weeks gestation	High docosahexaenoic acid (DHA) vs standard diet. Infants consumed expressed breast milk from mothers taking either tuna oil (high-DHA diet, six 500mg capsules daily) or soy oil (standard-DHA) capsules. If supplementary formula was required, the high DHA group were given a high DHA pre-term formula.	Parental reported food allergy. Follow up to 18 months	Some concerns	There was no effect on parental reported food allergy at 18 months.

S5. Studies included in other systematic reviews

The table below lists other systematic reviews identified as of August 2019 that include studies about preventing food allergy. It sets out the potentially relevant studies included in those reviews. Studies eligible for the current review are in green. This shows that whilst a number of reviews have been conducted about relevant interventions, these reviews included studies that did not have food allergy as an outcome or study designs that were not randomised. The reason that studies whose full text was excluded is in the table overleaf (S6). Any studies not listed in that table were excluded due to not having food allergy as an outcome or not being an eligible study design.

		Reviews																																				
Studies included in reviews		Al-Saud 2018 ⁵⁰	Anadan 2009 ⁵¹	Arnoldussen 1997	Boyle 2016 ⁵²	Burgess 2019 ⁵³	Chmielewska 2017 ⁵⁴	Cuello-Garcia 2010 ⁵⁵	Cuello-Garcia 2015 ⁵⁶	de Silva 2014 ⁵⁷	Garcia Larsen 2018 ⁵⁸	Gunaratne 2015 ⁵⁹	Gungor 2019 ⁶⁰	Hays 2015	Ierodiakonou 2016 ⁶¹	Klemens 2011 ⁶²	Kong 2014 ⁶³	Kramer 2012	Larson 2017 ⁶⁴	Lodge 2013 ⁶⁵	Lodge 2015 ⁶⁶	Osborn 2006 ⁶⁷	Osborn 2018 ⁶⁸	Osborn 2013 ⁶⁹	Recto 2017 ⁷⁰	Schindler 2016 ⁷¹	Schneider Chafen 2010 ⁷²	Schneider Chafen 2010b ⁷³	Szajewska 2010	Tang 2012	Tarini 2006	Vandenplas 2014 ⁷⁴	Vandenplas 2019 ⁷⁵	Victoria 2016 ⁷⁶	Yepes-Nuñez 2018 ⁷⁷	Zhang 2017 ⁷⁸		
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Studies included in reviews	Al-Saud 2018 ⁵⁰	Anadan 2009 ⁵¹	Arnoldussen 1997	Boyle 2016 ⁵²	Burgess 2019 ⁵³	Chmielewska 2017 ⁵⁴	Cuello-Garcia 2010 ⁵⁵	Cuello-Garcia 2015 ⁵⁶	de Silva 2014 ⁵⁷	Garcia Larsen 2018 ⁵⁸	Gunaratne 2015 ⁵⁹	Gungor 2019 ⁶⁰	Hays 2015	Ierodiakonou 2016 ⁶¹	Klemens 2011 ⁶²	Kong 2014 ⁶³	Kramer 2012	Larson 2017 ⁶⁴	Lodge 2013 ⁶⁵	Lodge 2015 ⁶⁶	Osborn 2006 ⁶⁷	Osborn 2018 ⁶⁸	Osborn 2013 ⁶⁹	Recto 2017 ⁷⁰	Schindler 2016 ⁷¹	Schneider Chafen 2010 ⁷²	Schneider Chafen 2010b ⁷³	Szajewska 2010	Tang 2012	Tarini 2006	Vandenplas 2014 ⁷⁴	Vandenplas 2019 ⁷⁵	Victoria 2016 ⁷⁶	Yepes-Nuñez 2018 ⁷⁷	Zhang 2017 ⁷⁸		
Grimshaw 2013												✓																									
Gruber 2010																			✓																		
Gruskay 1982																				✓																	
Gustafsson 2000									✓	✓			✓																								
Halken 1992									✓				✓																								
Halken 1993									✓				✓																								
Halken 1994													✓																								
Halken 2000									✓				✓									✓							✓								
Halmerbauer 2002									✓																		✓										
Halpern 1973																				✓																	
Hascoet 2011							✓																														
Hattevig 1989									✓	✓																	✓										
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Hikino 2001										✓		✓								✓																	
Hill 2000																				✓																	
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Host 1991										✓			✓																								
Huurre 2008							✓		✓																		✓										
Ivakhnenko 2013																✓																					
Jelding-Dannemand 2015																																					✓
Johnston 1966									✓													✓															
Joseph 2011																																					

Studies included in reviews	Al-Saud 2018 ⁵⁰	Anadan 2009 ⁵¹	Arnoldussen 1997	Boyle 2016 ⁵²	Burgess 2019 ⁵³	Chmielewska 2017 ⁵⁴	Cuello-Garcia 2010 ⁵⁵	Cuello-Garcia 2015 ⁵⁶	de Silva 2014 ⁵⁷	Garcia Larsen 2018 ⁵⁸	Gunaratne 2015 ⁵⁹	Gungor 2019 ⁶⁰	Hays 2015	Ierodiakonou 2016 ⁶¹	Klemens 2011 ⁶²	Kong 2014 ⁶³	Kramer 2012	Larson 2017 ⁶⁴	Lodge 2013 ⁶⁵	Lodge 2015 ⁶⁶	Osborn 2006 ⁶⁷	Osborn 2018 ⁶⁸	Osborn 2013 ⁶⁹	Recto 2017 ⁷⁰	Schindler 2016 ⁷¹	Schneider Chafen 2010 ⁷²	Schneider Chafen 2010b ⁷³	Szajewska 2010	Tang 2012	Tarini 2006	Vandenplas 2014 ⁷⁴	Vandenplas 2019 ⁷⁵	Victoria 2016 ⁷⁶	Yepes-Nuñez 2018 ⁷⁷	Zhang 2017 ⁷⁸			
Juvonen 1994, 1996, 1999				✓																		✓																
Kajosaari 1983, 1994									✓	✓																✓						✓						
Kajosaari 1991									✓																						✓							
Kalliomaki 2001								✓								✓																						
Kalliomaki 2003							✓	✓								✓																						
Kalliomaki 2007								✓	✓							✓																						
Kemeny 1991										✓																												
Kim 2010										✓																												
Kim 2011								✓		✓																												
Kiraly 2013									✓																													
Kjellman 1979									✓													✓																
Klemens								✓																														
Kljakovic 2009																				✓																		
Koplin 2010										✓										✓																		
Kopp 2008								✓																														
Kramer 2009								✓	✓																													
Kuitunen 2009								✓	✓	✓						✓											✓											
Kukkonen 2007								✓	✓							✓																						
Kukkonen 2011																✓																						
Kull 2002										✓																												
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Kull 2010																																						

Studies included in reviews	Al-Saud 2018 ⁵⁰	Anadan 2009 ⁵¹	Arnoldussen 1997	Boyle 2016 ⁵²	Burgess 2019 ⁵³	Chmielewska 2017 ⁵⁴	Cuello-Garcia 2010 ⁵⁵	Cuello-Garcia 2015 ⁵⁶	de Silva 2014 ⁵⁷	Garcia Larsen 2018 ⁵⁸	Gunaratne 2015 ⁵⁹	Gungor 2019 ⁶⁰	Hays 2015	Ierodiakonou 2016 ⁶¹	Klemens 2011 ⁶²	Kong 2014 ⁶³	Kramer 2012	Larson 2017 ⁶⁴	Lodge 2013 ⁶⁵	Lodge 2015 ⁶⁶	Osborn 2006 ⁶⁷	Osborn 2018 ⁶⁸	Osborn 2013 ⁶⁹	Recto 2017 ⁷⁰	Schindler 2016 ⁷¹	Schneider Chafen 2010 ⁷²	Schneider Chafen 2010b ⁷³	Szajewska 2010	Tang 2012	Tarini 2006	Vandenplas 2014 ⁷⁴	Vandenplas 2019 ⁷⁵	Victoria 2016 ⁷⁶	Yepes-Nuñez 2018 ⁷⁷	Zhang 2017 ⁷⁸		
Kumar 2010																				✓																✓	
Kusunoki 2010																																					
Lack 2003										✓																											
Lau 2012										✓																											
Lauritzen 2005		✓		✓					✓		✓				✓											✓											
Lilja 1989, 1991									✓	✓																											
Lindfors, 1988 and 1992									✓				✓																								
Lodinova-Zadnikova 2010								✓																													
Lovegrove 1994									✓	✓																											
Lowe 2011				✓					✓																												
Lucas 1990									✓				✓																								
Luccioli 2014																																					
Makrides 2010										✓																											
Mallet 1992				✓					✓																												
Manley 2011									✓																		✓										
Marini 1996									✓																				✓								
Marschan 2008								✓	✓							✓													✓								
Matheson 2007									✓	✓																											
McGowan 2015																																					✓
Merrett 1988									✓																												✓
Mihrshahi 2007									✓																												

Studies included in reviews	Al-Saud 2018 ⁵⁰	Anadan 2009 ⁵¹	Arnoldussen 1997	Boyle 2016 ⁵²	Burgess 2019 ⁵³	Chmielewska 2017 ⁵⁴	Cuello-Garcia 2010 ⁵⁵	Cuello-Garcia 2015 ⁵⁶	de Silva 2014 ⁵⁷	Garcia Larsen 2018 ⁵⁸	Gunaratne 2015 ⁵⁹	Gungor 2019 ⁶⁰	Hays 2015	Ierodiakonou 2016 ⁶¹	Klemens 2011 ⁶²	Kong 2014 ⁶³	Kramer 2012	Larson 2017 ⁶⁴	Lodge 2013 ⁶⁵	Lodge 2015 ⁶⁶	Osborn 2006 ⁶⁷	Osborn 2018 ⁶⁸	Osborn 2013 ⁶⁹	Recto 2017 ⁷⁰	Schindler 2016 ⁷¹	Schneider Chafen 2010 ⁷²	Schneider Chafen 2010b ⁷³	Szajewska 2010	Tang 2012	Tarini 2006	Vandenplas 2014 ⁷⁴	Vandenplas 2019 ⁷⁵	Victoria 2016 ⁷⁶	Yepes-Nuñez 2018 ⁷⁷	Zhang 2017 ⁷⁸		
Milner 2004									✓											✓																	
Miskelly 1988								✓													✓																
Morisset 2008							✓																														
Morisset 2011								✓	✓																												
Natsume 2017									✓																												
Nentwich 2001																													✓								
Niers 2009								✓		✓																											
Noakes 2012																																					
Norizoe 2014																																					✓
Nwaru 2010																✓																					
Nwaru 2013																✓																					
Odelram 1996				✓					✓				✓														✓										
Oldaeus 1997				✓					✓														✓														
Ou 2012								✓																													
Palmer 2013	✓			✓					✓																												
Palmer 2013 (PUFA)											✓																										
Palmer 2017	✓																																				
Perkin 2016	✓																																				
Pesonen 2006										✓										✓																	
Poole 2006												✓								✓																	
Poysa 1991																																					
Prescott 2008								✓	✓	✓																											
Rautava, 2002																											✓										
Rosendahl 2019																																					
Saarinen 1995, 1979									✓	✓			✓																								
Saarinen				✓				✓					✓										✓														

Studies included in reviews	Al-Saud 2018 ⁵⁰	Anadan 2009 ⁵¹	Arnoldussen 1997	Boyle 2016 ⁵²	Burgess 2019 ⁵³	Chmielewska 2017 ⁵⁴	Cuello-Garcia 2010 ⁵⁵	Cuello-Garcia 2015 ⁵⁶	de Silva 2014 ⁵⁷	Garcia Larsen 2018 ⁵⁸	Gunaratne 2015 ⁵⁹	Gungor 2019 ⁶⁰	Hays 2015	Ierodiakonou 2016 ⁶¹	Klemens 2011 ⁶²	Kong 2014 ⁶³	Kramer 2012	Larson 2017 ⁶⁴	Lodge 2013 ⁶⁵	Lodge 2015 ⁶⁶	Osborn 2006 ⁶⁷	Osborn 2018 ⁶⁸	Osborn 2013 ⁶⁹	Recto 2017 ⁷⁰	Schindler 2016 ⁷¹	Schneider Chafen 2010 ⁷²	Schneider Chafen 2010b ⁷³	Szajewska 2010	Tang 2012	Tarini 2006	Vandenplas 2014 ⁷⁴	Vandenplas 2019 ⁷⁵	Victoria 2016 ⁷⁶	Yepes-Nuñez 2018 ⁷⁷	Zhang 2017 ⁷⁸		
1999, 2000																																					
Sausenthaler 2007									✓																												
Sausenthaler 2011									✓																												
Schneider Chafen 2010									✓																												
Schneider Chafen 2010b									✓																												
Schoetzau 2002																																					
Scott 2012									✓																												
Sigurs 1992																										✓											
Sirivimonpan 2014																																					
Snijders 2008																																					
Soh 2009								✓		✓																											
Steenhuis 2008			✓																																		
Stelmach 2014																				✓																	
Szajewska 2004																										✓											
Tan 2017																																					
Tariq 1998													✓																								
Taylor 2007								✓																													
Thøstesen 2017									✓																												
Tsai 1991																													✓								
Vandenplas 1986													✓																✓								

Studies included in reviews	Al-Saud 2018 ⁵⁰	Anadan 2009 ⁵¹	Arnoldussen 1997	Boyle 2016 ⁵²	Burgess 2019 ⁵³	Chmielewska 2017 ⁵⁴	Cuello-Garcia 2010 ⁵⁵	Cuello-Garcia 2015 ⁵⁶	de Silva 2014 ⁵⁷	Garcia Larsen 2018 ⁵⁸	Gunaratne 2015 ⁵⁹	Gungor 2019 ⁶⁰	Hays 2015	Ierodiakonou 2016 ⁶¹	Klemens 2011 ⁶²	Kong 2014 ⁶³	Kramer 2012	Larson 2017 ⁶⁴	Lodge 2013 ⁶⁵	Lodge 2015 ⁶⁶	Osborn 2006 ⁶⁷	Osborn 2018 ⁶⁸	Osborn 2013 ⁶⁹	Recto 2017 ⁷⁰	Schindler 2016 ⁷¹	Schneider Chafen 2010 ⁷²	Schneider Chafen 2010b ⁷³	Szajewska 2010	Tang 2012	Tarini 2006	Vandenplas 2014 ⁷⁴	Vandenplas 2019 ⁷⁵	Victoria 2016 ⁷⁶	Yepes-Nuñez 2018 ⁷⁷	Zhang 2017 ⁷⁸			
Vandenplas 1992, 1995				✓					✓													✓							✓									
Venter 2009									✓	✓																												
Venter 2010																																						
von Berg 2003, 2008				✓					✓													✓					✓		✓									
West 2009								✓		✓																												
Wetzig 2000									✓				✓																									
Wickens 2012								✓		✓																												
Wong 2013																✓																						
Zachariassen 2011																																						
Zeiger 1989, 1992, 1994				✓					✓	✓																												
Zolkipli 2015																																						
Zutavern 2006, 2008																✓																						

S6. Full text studies considered for the review but excluded

The table below lists studies that were considered for inclusion by reviewing the full text, but that did not meet the eligibility criteria.

Article	Reason excluded
Abrahamsson 2007	Outcome not eligible: no data on food allergy, only sensitisation to food allergens
Allen 2010	Outcome not eligible: study designed for eczema. No data on food allergy
Allen 2012	Outcome not eligible: study designed for eczema. No data on food allergy
Allen 2013	Method not eligible: case control
Alm 1997	Method not eligible: retrospective
Almqvist 2007	Outcome not eligible: did not look at food allergy specifically
Arshad 2007	Outcome not eligible: food sensitisation only
Bardare 1993	Method not eligible: not randomised with only 2 of 3 participating hospitals delivering the intervention
Bedolla Barajas 2016	Method not eligible: cross-sectional study
Besednjak-Kocijancic 2010	Method not eligible: abstract of a cohort study
Birch 2010	Outcome not eligible: did not look at food allergy specifically only as part of wider allergy outcome
Brown 1969	Outcome not eligible: food allergy not reported
Bruno 1993	Method not eligible: cohort study
Burr 1993	Outcome not eligible: food allergy not reported
Chan 2002	Outcome not eligible: food sensitisation only
Chandra 1997	Method not eligible: studies discredited
Chirico 1997	Outcome not eligible: food allergy not reported
D'Agata 1996	Method not eligible: not randomised
de Jong 1998	Outcome not eligible: food allergy not reported
de Jong 2002	Outcome not eligible: food allergy not reported
de Seta 1994	Method not eligible: not randomised
Du Toit 2008	Method not eligible: cross-sectional study
Ehlaye 2008	Outcome not eligible: food allergy not assessed
Goksor 2011	Publication type not eligible: abstract only
Gorissen 2014	Duplication of a study by the same group included
Grimshaw 2013	Method not eligible: case-control study
Gruber 2010	Outcome not eligible: sensitisation
Gruskay 1982	Outcome not eligible: food allergy not reported
Gustafsson 2000	Method not eligible: sample of 100 high risk children, not minimum of 200 required
Halken 1992	Method not eligible: non randomised with intervention group compared to a control group born a few years earlier
Halmerbauer 2002	Outcome not eligible: food sensitisation only
Halpern 1973	Method not eligible: quasi randomised
Hascoet 2011	Outcome not eligible: study designed for eczema. No data on food allergy
Hattevig 1989	Method not eligible: not randomised controlled trial (controlled clinical trial)
Hesselmar 2010	Method not eligible: cohort study
Hikino 2001	Method not eligible: cross sectional study in low birth weight infants
Hill 2000	Publication type not eligible: unpublished, randomisation not standard
Host 1988	Method not eligible: cohort study
Huurre 2008	Outcome not eligible: did not assess food allergy, only sensitisation
Jelding-Dannemand 2015	Outcome not eligible: examined allergic sensitisation
Johnston 1966	Outcome not eligible: food allergy not reported
Joseph 2011	Method not eligible: cohort study with food sensitisation as outcome

Article	Reason excluded
Juvonen 1994, 1996, 1999	Method not eligible: quasi randomised design
Kajosaari 1991	Method not eligible: sample size less than 200 in high risk group
Kajosaari 1983, 1994	Method not eligible: non randomised comparison
Kalliomaki 2001	Outcome not eligible: no data on food allergy only on sensitisation to food allergens
Kalliomaki 2007	Outcome not eligible: no data on food allergy, only on sensitisation to food allergens
Kemeny 1991	Method not eligible: sample size of 200 in undifferentiated population, not minimum of 1000 required for breastfeeding
Kim 2010	Outcome not eligible: no data on food allergy, only on sensitisation to food allergens
Kjellman 1979	Outcome not eligible: intolerance focus, randomisation allocation unclear
Klemens	Outcome not eligible: did not report on food allergy
Kljakovic 2009	Outcome not eligible: assesses peanut allergy risk and management, cross sectional
Koplin 2010	Method not eligible: cross-sectional study
Kopp 2008	Outcome not eligible: no data on food allergy, only on sensitisation to food allergens
Kramer 2009	Outcome not eligible: no data on food allergy
Kuitunen 2009	Outcome not eligible: no data on food allergy
Kukkonen 2007	Outcome not eligible: study designed for eczema. No data on food allergy
Kull 2006	Method not eligible: case control / birth cohort
Kull 2010	Outcome not eligible: no data on food allergy, only sensitisation
Kumar 2010	Method not eligible: cohort study
Kusunoki 2010	Method not eligible: cross sectional survey in childhood
Lack 2003	Method not eligible: case-control study on peanut allergy
Lau 2012	Outcome not eligible: no data on food allergy, only on sensitisation to food allergens
Lauritzen 2005	Outcome not eligible: did not report on food allergy
Lilja 1991	Outcome not eligible: not specific to food allergy
Lindfors, 1988 and 1992	Method not eligible: cohort study
Lodinova-Zadnikova 2010	Method not eligible: not randomised controlled trial
Lovegrove 1994	Method not eligible: not fully randomised
Luccioli 2014	Method not eligible: cross sectional, not prospective cohort study
Marini 1996	Outcome not eligible: food allergy not an outcome, not randomised
Matheson 2007	Method not eligible: retrospective data about early feeding
Matsumoto 2019	Method not eligible: retrospective
McGowan 2015	Method not eligible: cohort study
Merrett 1988	Outcome not eligible: food allergy not reported
Mihrshahi 2007	Method not eligible: cohort study
Milner 2004	Method not eligible: cohort study
Miskelly 1988	Outcome not eligible: food sensitisation only
Morisset 2008	Publication type not eligible: abstract only
Nentwich 2001	Outcome not eligible: food sensitisation only
Netea 2019	Method not eligible: review
Noakes 2012	Outcome not eligible: did not assess food allergy
Nwaru 2010	Method not eligible: cohort study
Nwaru 2013	Method not eligible: cohort study
Ou 2012	Outcome not eligible: no data on food allergy, only on sensitisation to food allergens
Pesonen 2006	Method not eligible: sample size for breastfeeding smaller than 1000 in undifferentiated population

Article	Reason excluded
Poole 2006	Method not eligible: cohort study
Poysa 1991	Method not eligible: cohort study
Rautava, 2002	Outcome not eligible: not food allergy
Saarinén 1995, 1979	Method not eligible: sample size for breastfeeding smaller than 1000 in undifferentiated population
Sausenthaler 2007	Method not eligible: not randomised controlled trial (prospective cohort)
Sausenthaler 2011	Method not eligible: cohort study
Schoetzau 2002	Method not eligible: cohort study with atopic dermatitis as the main outcome
Scott 2012	Outcome not eligible: food sensitisation only
Sirivimonpan 2014	Method not eligible: abstract of a case control study
Snijders 2008	Method not eligible: cohort study
Soh 2009	Outcome not eligible: no data on food allergy, only on sensitisation to food allergens
Steenhuis 2008	Outcome not eligible: food allergy alone not an outcome, reported 'reaction to food'
Stelmach 2014	Method not eligible: cross sectional, sample < 1000
Szajewska 2004	Outcome not eligible: food allergy alone not reported
Tan 2017	Outcome not eligible: sensitisation
Taylor 2007	Outcome not eligible: no data on food allergy, only on sensitisation to food allergens
Tsai 1991	Outcome not eligible: food sensitisation only
Tsuang 2019	Intervention not eligible: not prevention
Vandenplas 1986	Method not eligible: <1000 for prospective breastfeeding cohort
Venter 2009	Method not eligible: cohort study
Venter 2010	Method not eligible: abstract of a cohort study
West 2009	Outcome not eligible: study designed for eczema. No data on food allergy
Wetzig 2000	Outcome not eligible: no data on food allergy, only sensitisation
Wickens 2012	Outcome not eligible: study designed for eczema and "atopy". No specific data on food allergy. "Atopy to food allergens" mentioned but not defined
Wong 2013	Method not eligible: abstract of a intervention study
Zutavern 2006, 2008	Method not eligible: cohort study

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