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Probiotics in infants for prevention of allergic disease (Review)

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[Intervention Review]

Probiotics in infants for prevention of allergic disease

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ABSTRACT

Rationale

This is an update of a Cochrane review first published in 2007.

Allergic disease and food allergy are prevalent, and contribute to a significant burden of disease on the individual, their family and the healthcare system. Probiotics are live bacteria that colonise the gastrointestinal tract, and have been studied in many clinical trials for preventing allergic conditions.

Objectives

To evaluate the benefits and harms of a probiotic, or a probiotic with added prebiotic ('synbiotic'), compared with control (placebo or no treatment) for preventing allergic diseases (asthma, eczema, allergic rhinitis) and dietary allergies in infants by two years of age.

Search methods

We searched CENTRAL, MEDLINE, Embase and trial registries in December 2023. We reviewed the reference lists of studies selected for inclusion in this review, and systematic reviews on similar topics. We manually searched conference abstracts.

Eligibility criteria

We included randomised controlled trials that compared a probiotic to a control, or a probiotic added to a prebiotic ('synbiotic'). We included enterally fed infants in the first six months of life without clinical evidence of allergic disease. We included probiotics added to human milk or infant formula, added in the manufacturing process or given separately.

Outcomes

Infant incidence by two years of age and childhood incidence (up to 10 years of age or up to the age of latest report between 2 and 10 years) of specific allergic diseases, including: asthma, eczema, allergic rhinitis, immunoglobulin E (IgE)-mediated food allergy, IgE-mediated cow's milk protein allergy. Events of anaphylaxis and potential harms including adverse effects, harms or infection with probiotic bacteria.

Risk of bias

We used the Cochrane RoB 2 tool to assess bias in the studies.

Synthesis methods

We used the random-effects (Mantel-Haenszel) model for meta-analysis where possible. Where this was not possible due to the nature of the data, we synthesised and interpreted individual studies separately. We used GRADE to assess the certainty of evidence for each outcome.

Included studies

We included 24 studies (7077 mother–infant pairs). The studies were conducted in many parts of the world, including the USA, Europe, South Korea, Japan, Singapore and Australia, with most being conducted in Europe. Studies were published between 2001 and 2020. As some studies measured outcomes such as eczema using different criteria, we made assumptions to allow us to combine data.

Synthesis of results

Probiotics may result in little to no difference in asthma (risk ratio (RR) 0.96, 95% confidence interval (CI) 0.65 to 1.44; 4 studies, 954 participants; low-certainty evidence), allergic rhinitis (RR 0.89, 95% CI 0.45 to 1.77; 5 studies, 1045 participants; low-certainty evidence) and IgE-mediated cow's milk protein allergy (RR 0.99, 95% CI 0.82 to 1.20; 4 studies, 259 participants; low-certainty evidence) by two years of age. Probiotics may result in a slight reduction in eczema by two years of age (RR 0.87, 95% CI 0.78 to 0.97; 18 studies, 3494 participants; low-certainty evidence); however, sensitivity analysis of the studies at low risk of bias showed little or no difference in eczema by two years of age (RR 0.86, 95% CI 0.69 to 1.07; 4 studies, 892 participants). Probiotic supplementation may have little to no effect on the incidence of food allergy by two years, but the evidence is very uncertain (RR 1.12, 95% CI 0.57 to 2.20; 3 studies, 857 participants; very low-certainty evidence).

The evidence is very uncertain about the effect of synbiotics on eczema by two years of age (RR 0.88, 95% CI 0.52 to 1.47; 3 studies, 1235 participants; very low-certainty evidence). Synbiotics may result in little to no difference in food allergy by two years of age (RR 1.06, 95% CI 0.55 to 2.07; 1 study, 223 participants; low-certainty evidence). There were no data for the effect of synbiotics on asthma, allergic rhinitis and IgE-mediated cow's milk protein allergy by two years of age.

Probiotic or synbiotic supplementation may result in little to no difference in potential harms including adverse effects, harms or infection with probiotic bacteria at any point during the study intervention by two years of age. There were no serious adverse events related to probiotics or synbiotics reported.

We had some concerns about risk of bias for most studies, with only a few judged at low risk of bias. Some studies had a high risk of bias due to unclear randomisation, missing data and lack of prespecified intentions. Estimates were often imprecise, with wide CIs due to limited events. The limited data prevented subgroup analyses on infant risk factors and feeding methods for outcomes other than the effect of probiotics on eczema. Only three studies assessed synbiotic supplementation, leaving their role in allergic disease prevention uncertain. The included studies were mainly in high-income countries in many different areas of the world, but may have limited applicability to other regions.

Authors' conclusions

There is insufficient evidence to make conclusions about the effect of probiotics and synbiotics on preventing the development of allergic diseases by two years of age and during childhood up to 10 years of age. Although there were no serious adverse events reported for the use of probiotics in infants, incorporating probiotics and synbiotics into routine practice requires further information to support their use.

Funding

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Registration

Protocol (2007) available via https://doi.org/10.1002/14651858.CD006475.

Original review (2007) available via https://doi.org/10.1002/14651858.CD006475.pub2.

PLAIN LANGUAGE SUMMARY

Does giving a probiotic supplement to infants reduce allergies?

Key messages

- Probiotics (live bacteria that provide health benefits to the digestive tract) given to newborns as a supplement or added to infant formula in the first six months of life may slightly reduce the development of eczema (dry, itchy and inflamed skin) in infants by the age of two years, but there are not enough good-quality studies to be certain about the result.
- Probiotics may have little to no effect on the development of allergic diseases such as asthma (a respiratory condition with symptoms like cough, wheezing, chest tightness and breathlessness) and allergic rhinitis (often called hay fever), and dietary allergies (to food and cow's milk) during infancy.

- The effects of synbiotics (a mixture of probiotics and prebiotics (non-digestible fibres that help bacteria grow)) are uncertain.

What are allergies?

Allergies to certain foods, such as cow's milk, peanuts and eggs, as well as non-food allergies, are common. Some infants become sensitive to foods, including cow's milk, through their digestive tract. This may be affected by the bacteria in the digestive tract. Other infants may become sensitive through the skin. Sensitisation to allergens (the component that causes the allergic reaction) tends to follow a pattern, with allergies to food occurring in the first two to three years of life, followed by indoor allergens (for example, house dust mites and pets) and subsequently outdoor allergens (for example, rye and Timothy grass) that present as asthma, eczema or allergic rhinitis.

How can they be prevented?

Probiotics are helpful to the live gut bacteria that live in the digestive tract, and there is interest in whether probiotics might prevent sensitisation to allergens that lead to food allergies and non-food allergies.

What did we do?

We wanted to find out the impact of giving probiotics or synbiotics (probiotics with added prebiotics (non-digestible fibres that help bacteria grow)) to infants in the first six months of life compared to giving a placebo (pretend treatment) or no treatment, on preventing the development of allergic diseases, including asthma, eczema, allergic rhinitis, food allergy and cow's milk allergy.

We searched for studies that gave infants probiotics or synbiotics as an intervention compared with no probiotics or synbiotics during the first six months of life. We compared and summarised the results of these studies and rated our confidence in the evidence, based on factors such as study methods and sizes.

What did we find?

We included 24 studies that involved 7077 mother–infant pairs.

Probiotics may result in little to no difference in asthma, allergic rhinitis and cow's milk allergy by two years of age. Probiotics may slightly reduce eczema by two years of age, but there were not enough good-quality studies for us to be certain about the result. Probiotics may have little to no effect on the occurrence of food allergy by two years of age, but the evidence is very uncertain.

The evidence is very uncertain about the effect of synbiotics on eczema by two years of age. Synbiotics may result in little to no difference in food allergy by two years of age. We found no data for the effect of synbiotics on asthma, allergic rhinitis and cow's milk allergy by two years of age.

Probiotic or synbiotic supplementation may result in little to no difference in potential unwanted effects, including infection with probiotic bacteria by two years of age. There were no serious unwanted effects related to the use of probiotics or synbiotics reported.

What are the limitations of the evidence?

We had some concerns about how some of the studies were conducted. Not all the studies provided data about everything that we were interested in. Most studies looked at probiotics and reported on eczema. There were not enough studies for us to be certain about the effects of probiotics and synbiotics on other allergic diseases and dietary allergies.

How up to date is this evidence?

The evidence is up to date to December 2023.

SUMMARY OF FINDINGS

Summary of findings 1. Probiotic compared with no probiotic in infants for preventing allergic disease by two years of age

Probiotic compared with no probiotic in infants for preventing allergic disease by two years of age

Patient or population: infants < 6 months of age (both at risk of developing allergic disease and infants not selected for risk of allergy)
Setting: outpatients in perinatal hospitals, medical centres or antenatal care clinics in Europe, the US, Asia (Japan, Korea, Singapore), Australia and New Zealand
Intervention: probiotic
Comparison: no probiotic (placebo or no treatment)

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)		Certainty of the evidence (GRADE)	What happens?
		Without probiotic	With probiotic		
Asthma by 2 years of age physician diagnosed or from past medical history № of participants: 954 (4 RCTs)	**RR 0.96** (0.65 to 1.44)	96 per 1000	92 per 1000 (62 to 138)	⊕⊕⊖⊖ **Low**[a,b,c]	Probiotic may result in little to no difference in asthma by 2 years of age.
Eczema by 2 years of age SCORAD, measured on a scale from 0 to 103, < 25 mild, > 50 severe *or* UK Working Party's Diagnostic Criteria measured on pruritus + 3 minor skin features № of participants: 3494 (18 RCTs)	**RR 0.87** (0.78 to 0.97)	232 per 1000	281 per 1000 (252 to 313)	⊕⊕⊖⊖ **Low**[d,e]	Probiotic may result in a slight reduction in eczema by 2 years of age.
Allergic rhinitis by 2 years of age physician diagnosed or from past medical history № of participants: 1045 (5 RCTs)	**RR 0.89** (0.45 to 1.77)	34 per 1000	30 per 1000 (15 to 60)	⊕⊕⊖⊖ **Low**[a,b,c]	Probiotic may result in little to no difference in allergic rhinitis by 2 years of age.
Food allergy by 2 years of age physician diagnosed food allergy with or without a positive SPT (> 0) or serological testing for specific IgE or failed oral allergen tolerance test (symptoms of mild allergic reaction including itchiness, rashes, mild difficulty breathing, requiring antihistamine) № of participants: 857	**RR 1.12** (0.57 to 2.20)	94 per 1000	106 per 1000 (54 to 208)	⊕⊖⊖⊖ **Very low**[a,b,c,f]	Probiotics may have little or no effect on the incidence of food allergy by 2 years of age, but the evidence is very uncertain.

(3 RCTs)					
Cow's milk protein allergy by 2 years of age physician diagnosed cow's milk protein allergy with or without a positive SPT (> 0) or serological testing for specific IgE or failed oral allergen tolerance test (symptoms of mild allergic reaction including itchiness, rashes, mild difficulty breathing, requiring antihistamine) № of participants: 259 (4 RCTs)	**RR 0.99** (0.82 to 1.20)	148 per 1000	147 per 1000 (122 to 178)	⊕⊕⊖⊖ **Low**[c,g,h]	Probiotic may result in little to no difference in cow's milk protein allergy by 2 years of age.
Potential harms by 2 years of age including adverse effects, harms or infection with probiotic bacteria at any point during the study intervention by 2 years of age, assessed by participant interviews/surveys № of participants: 2405 (11 RCTs)	2 studies reported no serious adverse events that could be related to the study formula and no difference in mild adverse events in infants receiving study formula with or without probiotics. 1 study reported 1 adverse event in 1 infant in the intervention group who experienced gastro-oesophageal reflux whose relationship with the study formula was undetermined. 5 studies reported no difference in mild adverse events. 1 study reported no serious adverse events with no mention of mild adverse events. 1 study reported no serious adverse events; however, 2 infants in the intervention group experienced mild gastrointestinal complaints leading to withdrawal and 1 infant in the control group was diagnosed with eczema who was recommended by their own physician to discontinue the study. 1 study reported no serious adverse events but noted fewer events of rash development in infants of the intervention group in first 3 months of supplementation. 1 study reported significantly lowered respiratory potential allergic adverse events in the intervention group. Another study reported 2 possible mild adverse reactions (regurgitation) in the intervention group that resolved upon discontinued administration.			⊕⊕⊖⊖ **Low**[g,i]	Probiotic may result in little to no difference in potential harms including adverse effects, harms or infection with probiotic bacteria at any point during the study intervention by 2 years of age.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **IgE:** immunoglobulin E; **RCT:** randomised controlled trial; **RR:** risk ratio; **SCORAD:** SCORing Atopic Dermatitis; **SPT:** Skin Prick Test.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level for most studies being at some concern of overall risk of bias.
[b]Downgraded one level for imprecision of effect estimate due to wide confidence intervals.
[c]Too few studies to reliably assess publication bias.
[d]Downgraded one level for most studies being at some concern of overall risk of bias (10 studies) or high overall risk of bias (4 studies).
[e]Downgraded one level for sensitivity analysis of studies with low risk of bias showed no effect (RR 0.86, 95% CI 0.69 to 1.07; 4 studies), reducing confidence in the overall estimate.
[f]Downgraded one level as moderate heterogeneity amongst studies. Allen 2014 showed possible benefit, Plummer 2020 suggested potential harm, Taylor 2006 showed no clear benefit or harm.
[g]Downgraded one level for studies being at some concern of overall risk of bias or high overall risk of bias.
[h]Downgraded one level for imprecision due to confidence intervals encompassing both potential benefit and harm.
[i]Downgraded one level as narrative synthesis was conducted, estimates were not precise.

Summary of findings 2. Synbiotic compared with no synbiotic in infants for preventing allergic disease by two years

Synbiotic compared with no synbiotic in infants for preventing allergic disease by two years of age

Patient or population: infants < 6 months of age (both at risk of developing allergic disease and infants not selected for risk of allergy)
Setting: outpatients in perinatal hospitals, medical centres or antenatal care clinics in Europe, the US, Asia (Japan, Korea, Singapore), Australia and New Zealand
Intervention: synbiotic
Comparison: no synbiotic (placebo and no treatment)

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)		Certainty of the evidence (GRADE)	What happens?
		Without synbiotic	With synbiotic		
Asthma by 2 years of age physician diagnosed or from past medical history	This outcome was not reported.				
Eczema by 2 years of age SCORAD, measured on a scale from 0 to 103, < 25 mild, > 50 severe *or* UK Working Party's Diagnostic Criteria measured on pruritus + 3 minor skin features № of participants: 1235 (3 RCTs)	**RR 0.88** (0.52 to 1.47)	300 per 1000	264 per 1000 (156 to 441)	⊕⊖⊖⊖ **Very low**[a,b,c,d]	The evidence is very uncertain about the effect of synbiotic on eczema by 2 years of age.
Allergic rhinitis by 2 years of age physician diagnosed or from past medical history	This outcome was not reported.				

Food allergy by 2 years of age physician diagnosed food allergy with or without a positive SPT (> 0) or serological testing for specific IgE or failed oral allergen tolerance test (symptoms of mild allergic reaction including itchiness, rashes, mild difficulty breathing, requiring antihistamine) № of participants: 223 (1 RCT)	**RR 1.06** (0.55 to 2.07)	130 per 1000	138 per 1000 (72 to 270)	⊕⊕⊖⊖ **Low**[a,c,d]	Synbiotic may result in little to no difference in food allergy by 2 years of age.
Cow's milk protein allergy by 2 years of age physician diagnosed cow's milk protein allergy with or without a positive SPT (> 0) or serological testing for specific IgE or failed oral allergen tolerance test (symptoms of mild allergic reaction including itchiness, rashes, mild difficulty breathing, requiring antihistamine)	This outcome was not reported.				
Potential harms by 2 years of age Potential harms including adverse effects, harms or infection with synbiotic bacteria at any point during the study intervention by 2 years of age, assessed by participant interviews/surveys	1 study had no adverse effects to the interventions reported. 1 study reported minor adverse effects including abdominal discomfort, vomiting and excessive crying in both intervention and control groups.			⊕⊕⊖⊖ **Low**[a,d,e]	Synbiotic may result in little to no difference in potential harms including adverse effects, harms or infection with probiotic bacteria at any point during the study intervention by 2 years of age.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **IgE:** immunoglobulin E; **RCT:** randomised controlled trial; **RR:** risk ratio; **SCORAD:** SCORing Atopic Dermatitis; **SPT:** Skin Prick Test.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level for studies being some concern of overall risk of bias or high overall risk of bias.
[b]Downgraded one level for substantial heterogeneity between studies. Dissanayake 2018 showed no significant effect, Kukkonen 2006 suggested a significant benefit, Rozé 2012 suggested potential benefit but wide confidence intervals.
[c]Downgraded one level for imprecision of effect estimate due to wide confidence intervals.

[d]Too few studies to reliably assess publication bias.
[e]Downgraded one level as narrative synthesis was conducted, estimates were not precise.

BACKGROUND

Description of the condition

Allergic diseases and immunoglobulin E (IgE)-mediated food allergy are prevalent [1, 2, 3, 4]. Genetic susceptibility plays a large role in the development of allergic disease. Approximately 10% of children without an allergic first-degree relative (parent or sibling) develop allergic disease, compared with 20% to 30% of children with an allergic first-degree relative, and 40% to 50% of children with two affected relatives [5, 6, 7]. Infants commonly present with symptoms and signs of atopic (IgE-mediated allergic) eczema, gastrointestinal symptoms and recurrent wheezing. Asthma and rhinoconjunctivitis become prevalent in later childhood. Sensitisation to allergens tends to follow a characteristic pattern [1], with sensitisation to food allergens in the first two to three years of life, followed by indoor allergens (e.g. house dust mites and pets) and subsequently outdoor allergens (e.g. rye and Timothy grass) [8].

Description of the intervention and how it might work

A major focus of current research is the mechanisms for developing immune tolerance and allergen sensitisation in the foetus and newborn, and primary prevention strategies [9, 10]. Probiotics are live bacteria that colonise the gastrointestinal tract [5]. They have anti-inflammatory properties associated with changes in cytokine expression that could facilitate Type 1-helper cell immune response [11, 12], which could inhibit the development of allergic Type 2-helper cell response and IgE antibody production.

An altered microbial exposure in the gastrointestinal tract may be partly responsible for the increase of allergic diseases in populations with a western lifestyle [7]. Breastfeeding promotes the colonisation of bifidobacteria and lactobacilli that inhibit the growth of pathogenic micro-organisms and compete with potentially pathogenic bacteria for nutrients and epithelial adhesion sites. The gastrointestinal flora may modulate mucosal physiology, barrier function, and systemic immunological and inflammatory responses [7, 13, 14]. The efficiency of this gastrointestinal barrier is reduced in the newborn period [15]. Perinatal risk factors reported for asthma and allergic disease have included prematurity [16, 17], and foetal growth restriction [16], both of which are associated with an immature and potentially injured gastrointestinal mucosal barrier. The composition of the intestinal microflora may be different in people with atopic eczema, and such differences may precede the development of eczema. The most consistent finding in such studies is a reduced proportion of bifidobacteria species in the faeces of infants with eczema [18, 19], and atopic sensitisation [20], but not in the faeces of children with symptoms of asthma [19]. This has led to the development of strategies aimed at manipulating bacterial colonisation in formula-fed infants, including the use of prebiotics and probiotics.

Why it is important to do this review

Allergic diseases contribute to a significant burden of disease on the individual, their families and the healthcare system. For infants and children, allergic diseases can impact their perception of well-being and limit their open experience of life [21]. There is no current consensus for preventing the development of allergic disease [3, 22]. Recent research has explored the use of probiotics and prebiotics as potential prevention strategies for allergic diseases with mixed results [23, 24, 25, 26, 27, 28]. There are ongoing clinical trials evaluating the effect of prebiotics and probiotics on allergic disease at all ages, from infancy to adults.

This is an update of a Cochrane review first published in 2007 [29]. This updated systematic review focusses on the evidence for using probiotics (probiotics only and synbiotics) in infants to prevent allergic disease and IgE-mediated food allergy. A separate Cochrane review examines the effects of prebiotics (prebiotics only and synbiotics) compared with no prebiotics in infants for the prevention of allergic disease and IgE-mediated food allergies [30].

OBJECTIVES

To evaluate the benefits and harms of a probiotic, or a probiotic with added prebiotic ('synbiotic'), compared with control (placebo or no treatment) for preventing allergic diseases (asthma, eczema, allergic rhinitis) and dietary allergies in infants by two years of age.

METHODS

In this update of the review, we made the following changes to the published protocol [31], and the published review [29]. We changed the review title as the review focused on allergic disease and no longer reported on food hypersensitivity and growth data. Food hypersensitivity was removed from all descriptions of participants. We changed the objectives of the review, critical outcomes and other outcomes, as the review now focusses on allergic disease and no longer reports on food hypersensitivity and growth data. Seven of the 12 included studies from the published review have been excluded following the change in review title, objectives, and critical and important outcomes (see Excluded studies).

Potential harms including adverse effects, harms or infection with probiotic bacteria and cases of anaphylaxis have been included as an outcome. We added summary of findings tables, and included full risk of bias tables.

We updated PICO-S elements, data extraction and synthesis methods to cover all points. We took into consideration the suggested wording from the *Cochrane Handbook for Systematic Reviews of Interventions* [32].

We followed the Methodological Expectations for Cochrane Intervention Reviews when conducting the review [33], and PRISMA 2020 for the reporting [34].

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) that compared the use of a probiotic to a control (placebo or no treatment), or used a probiotic combined with a prebiotic ('synbiotic').

We excluded quasi-RCTs due to a risk of selection bias. We focused on RCTs that were adequately randomised.

We excluded cluster-RCTs due to a risk of selection bias and potential imbalance between study arms. We focused on RCTs that were adequately randomised with well-balanced groups.

Types of participants

We included enterally fed infants in the first six months of life without clinical evidence of allergic disease or IgE-mediated food

allergy, both with and without risk factors for allergy and IgE-mediated food allergy. Participants in the included studies were outpatients. For any studies with subsets of eligible participants, we explored the effect of these subsets as part of the sensitivity analysis.

Types of interventions

We included probiotics added to human milk or infant formula, and synbiotics added to human milk or infant formula separately. We included studies that provided probiotic or synbiotic supplementation during the first six months of the infant's life (the frequency of supplementation may have been different based on the probiotic or synbiotic investigated in the study).

We compared:

- probiotics versus control (placebo or no treatment);
- synbiotics versus control (placebo or no treatment).

Outcome measures

The outcome measures were as described below. The following outcome measures did not form part of the eligibility criteria.

Critical outcomes

- Infant incidence (by two years of age) of specific allergic diseases including:
  - asthma;
  - eczema;
  - allergic rhinitis.
- Infant incidence of IgE-mediated food allergy.
- Infant incidence of IgE-mediated cow's milk protein allergy.
- Potential harms including adverse effects, harms or infection with probiotic/synbiotic bacteria reported by two years of age.

Definitions of allergic disease and IgE-mediated food allergy had to be consistent with the 'Revised nomenclature for allergy for global use: report of the Nomenclature Review Committee of the World Allergy Organization, October 2003' [35]. Specific allergies were identified as atopic when confirmed by demonstration of an IgE response, either through skin testing or serological testing for specific IgE (e.g. radioallergosorbent test or enzyme-labelled anti-human test or Pharmacia CAP system).

Important outcomes

- Childhood incidence (by 10 years of age or up to the age of latest report between 2 and 10 years) of specific allergic diseases including:
  - asthma;
  - eczema;
  - allergic rhinitis.
- Anaphylaxis reported at any point during the study.
- Potential harms including adverse effects, harms or infection with probiotic/synbiotic bacteria reported by 10 years of age or up to the age of latest report between 2 and 10 years.

A specific allergic disease or IgE-mediated food allergy may be diagnosed on the basis of:

- history of recurrent and persistent symptoms typical of the allergic disease or IgE-mediated food allergy;
- a clinician diagnosis of allergic disease or food intolerance based on clinical findings supported by the above history;
- clinical allergic disease and IgE-mediated food allergy confirmed by testing, including detection of allergen sensitisation by either skin testing or serological testing for specific IgE (e.g. radioallergosorbent test or enzyme-labelled anti-human test or CAP system), asthma confirmed by respiratory function testing for presence of bronchial hyper-responsiveness, and food allergy confirmed by elimination/challenge *and* detection of allergen sensitisation:
  - eczema: measured on a scale from 0 to 103, less than 25 mild, greater than 50 severe *or* UK Working Party's Diagnostic Criteria [36] measured on pruritus plus three minor skin features;
  - food or cow's milk protein allergy: physician-diagnosed allergy based on history with a positive Skin Prick Test (SPT) (greater than 0) or positive SPT to food allergen or cow's milk protein containing allergen or serological testing for specific IgE or failed oral allergen tolerance test (symptoms of mild allergic reaction including itchiness, rashes, mild difficulty breathing, requiring antihistamine; severe allergic reaction include anaphylaxis).

We used the following definitions of age of allergic disease:

- infant allergic disease incidence: allergic disease occurring up to two years of age;
- childhood allergic disease incidence: allergic disease occurring up to 10 years of age (or up to age of latest report between 2 and 10 years);
- childhood allergic disease prevalence: new-onset allergic disease reported that was present between two and 10 years of age;
- adolescent allergic disease: allergic disease present from 10 to 18 years of age;
- adult allergic disease: allergic disease present after 18 years of age.

We used the following definitions for method of infant feeding:

- infants fed predominately human milk: 50% or greater of the infants in the study were breastfed for any duration of time;
- infants fed predominately cow's milk formula: less than 50% of the infants in the study were breastfed for any duration of time.

Search methods for identification of studies

Electronic searches

Two searches were run for this review; one written by clinical authors (EH, HZW) and run in January and June 2023; the other by an Information Specialist (MF), run 15 December 2023. The Information Specialist revised strategies to ensure consistent translation of concepts and to increase the sensitivity of search terms. The search by clinical authors used CINAHL, but CINAHL was omitted from the December 2023 search because it is not a mandatory database according to the *Cochrane Handbook for Systematic Reviews of Interventions* [37]. There were no date, language or publication type limits in the following databases.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2023, Issue 12)

- Ovid MEDLINE All, 1947 to 13 December 2023
- Ovid Embase, 1974 to 13 December 2023

Our search strategies are available in Supplementary material 1.

Searching other resources

We searched the following clinical trial registries for ongoing or recently completed trials on 15 December 2023.

- US National Library of Medicine's trial registry (https://clinicaltrials.gov)
- World Health Organization's International Clinical Trials Registry Platform (https://www.who.int/clinical-trials-registry-platform/the-ictrp-search-portal)
- ISRCTN Registry (https://www.isrctn.com/)

We undertook reference checking of systematic reviews investigating probiotics and allergic disease [24, 30, 38, 39, 40, 41, 42, 43]; and of the studies we identified for inclusion in this review. We also searched for publications related to (cited by or citing) the primary studies identified for inclusion in this review.

We searched the conference abstracts of the Pediatric Academic Societies (1998 to 2022) and the Perinatal Society of Australia and New Zealand (1998 to 2022).

We contacted expert informants to identify additional studies relevant to the area.

Data collection and analysis

We collected information regarding the method of randomisation, blinding, intervention, stratification and whether the trial was single or multicentre for each included study. We noted information regarding trial participants, including number of participants, strain of probiotic or synbiotic used and duration of intervention. We analysed the clinical outcomes listed in the Outcome measures. We entered and cross-checked data using Review Manager [44].

Selection of studies

We screened search results using two methods: Cochrane's Screen4Me and author assessment. Screen4Me includes three levels of assessment for identifying non-RCT records. Of these three levels, we used two: Known Assessments and RCT Classifier. Information about the performance of Screen4Me is found in the following publications [45, 46, 47, 48].

We placed references categorised as non-RCTs in the irrelevant segment of Covidence [49]. This approach ensures references are available for deduplication purposes when searches are updated; and files containing references excluded by Screen4Me are maintained for cross-checking should a potentially relevant study appear to have been missed by the search. Two review authors (EH, HZW) independently screened references remaining after Screen4Me classification. Two review authors (EH, HZW) independently assessed the full-texts for references retained following title/abstract review. At any point in the screening process, we resolved disagreements through discussion or with input from a third review author (JS). Where a review author was involved in a study identified during title/abstract or full-text review, other review authors made decisions regarding inclusion. The selection process is reported in Results.

In cases where study reports did not include sufficient information, or where we had questions about the study, we contacted, or attempted to contact, study authors to request clarification or data.

We documented the reasons for excluding studies during the review of full texts (Supplementary material 3). We collated multiple reports of the same study so that each study, rather than each report or reference, was the unit of interest in the review. We grouped related reports under a single study ID. We provided any information we could obtain about ongoing studies. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram [50, 51].

Data extraction and management

Two review authors (EH, HZW) independently extracted the data using a data extraction form integrated with a modified version of the Cochrane Effective Practice and Organisation of Care Group data collection checklist [52]. We piloted the form within the review team, using a sample of included studies. We extracted the following characteristics from each included study.

- Administrative details: study author(s); published or unpublished; year of publication; year in which study was conducted; presence of vested interest by study authors; details of other relevant papers cited.
- Study characteristics: study design type, study duration, completeness of follow-up (e.g. greater than 80%), informed consent.
- Participants: number randomised, number lost to follow-up/withdrawal, number analysed, inclusion criteria and exclusion criteria.
- Interventions: initiation, dose and duration of administration.
- Outcomes as mentioned above under Outcome measures.

We compared data and resolved differences by consensus in consultation with a senior review author (JS).

We described ongoing studies identified by our search and documented available information such as the primary author, research question(s), methods and outcome measures, together with an estimate of the anticipated reporting date (Supplementary material 5).

Risk of bias assessment in included studies

In this update, we adopted the Cochrane RoB 2 tool (a change from the previous review) [53]. Two review authors (EH, HZW) independently assessed the risk of bias (low, some concern, high) of all included trials, for the following domains.

- Bias arising from the randomisation process
- Bias due to deviations from intended interventions
- Bias due to missing outcome data
- Bias in measurement of the outcome
- Bias in selection of the reported result

We evaluated the effect of assignment to the intervention at baseline, regardless of whether the intervention was received as intended (the intention-to-treat effect), as this reflects the real-world applicability of the intervention. We considered deviations from intended interventions under the second domain of RoB 2,

ensuring that any issues related to non-adherence or cross-over were appropriately addressed in the overall assessment.

We resolved any disagreements by discussion with a senior review author (JS). See Supplementary material 6 for a more detailed description of the risk of bias for each domain.

Two review authors (EH, HZW) independently assessed the risk of bias due to missing results in a synthesis by visual inspection of forest plots and described the direction and magnitude of effects and the degree of overlap between confidence intervals (CIs). We also considered the statistics generated in forest plots that measured statistical heterogeneity. We resolved any disagreement by discussion with a senior review author (JS).

If any queries arose, or in cases for which additional data were required, one review author (HZW) contacted the study investigators/authors for clarification. Detailed risk of bias assessment data with consensus responses to the signalling questions can be provided on request.

Measures of treatment effect

We performed statistical analyses using Review Manager [44], in accordance with the standard methods of Cochrane Neonatal.

Dichotomous data

We analysed dichotomous data using risk ratios (RR), risk difference (RD) and the number needed to treat for an additional beneficial outcome (NNTB), or the number needed to treat for an additional harmful outcome (NNTH) if there was a significant reduction (or increase) in RD. We reported the 95% CIs on all estimates.

Continuous data

We analysed continuous data using mean difference (MD) when trials measured the outcomes in the same way. We used the standardised mean difference (SMD) to combine trials that measured the same outcome but used different methods. Where trials reported continuous data as the median and interquartile range (IQR) and data passed the test of skewness, we converted the median to mean and estimated the standard deviation as IQR/1.35. We reported the 95% CIs on all estimates.

Unit of analysis issues

The unit of randomisation was the intended unit of analysis, and we expect this to be individual infants. We performed primary analysis per individual randomised. We included any trials that had multiple arms compared against the same control condition in the same meta-analysis. The groups were either combined to create a single pair-wise comparison, or selected for one pair of interventions with the others excluded. In cases where intervention arms were not suitable for combination, we selected the most clinically relevant comparison based on criteria such as intervention similarity.

In the meta-analysis and data synthesis, we only included the first-phase data from cross-over trials.

Dealing with missing data

Where feasible, we conducted analyses on an intention-to-treat basis for all outcomes. Where possible, we analysed all participants in the treatment group to which they were randomised, regardless of the actual treatment received. If we identified important missing data (in the outcomes) or unclear data, we requested the missing data from the authors, when possible, by contacting the original investigators. We made explicit the assumptions of any methods used to deal with missing data.

In the case that data were missing and could not be derived or obtained from the original investigators, we assessed the effect of included trials with substantial (e.g. greater than 20% losses) through sensitivity analyses. The sensitivity analysis aimed to assess how sensitive the results were to reasonable changes in assumptions resulting from data imputation. We addressed the potential impact of missing data on the findings of the review in the Discussion.

Reporting bias assessment

Two review authors (EH, HZW) independently assessed reporting bias by comparing the stated primary and secondary outcomes and reported outcomes. Where study protocols were available, we compared them with full publications to determine the likelihood of reporting bias. We planned to investigate reporting biases (such as publication bias) using funnel plots only for studies with at least 10 studies included in the meta-analysis. We assessed funnel plot asymmetry visually. When there was asymmetry, we performed an exploratory analysis to investigate it. For continuous outcomes, we planned to use the test proposed by Egger and colleagues [54], and for dichotomous outcomes, we used the test proposed by Harbord and colleagues [55]. We resolved any disagreement by discussion with a senior review author (JS).

Synthesis methods

We performed a meta-analysis using Review Manager [44]. We included studies of probiotic or synbiotic interventions delivered enterally to infants in the first six months of life with control (placebo or no treatment):

- probiotics compared with control;
- synbiotics compared with control.

For categorical outcomes, we calculated the typical estimates of RR and RD, each with its 95% CIs. For continuous outcomes, we planned to calculate the MD or SMD, each with its 95% CIs.

We used a random-effects model due to the larger numbers of studies/events, where there was likely to be heterogeneity related to different interventions, populations and measurement tools. We analysed and interpreted individual trials separately when we judged meta-analysis to be inappropriate.

We described the clinical diversity and methodological variability of the evidence narratively and in tables. The tables included data on study characteristics such as design features, population characteristics and intervention details. The Mantel-Haenszel method was used as the method has been shown to have better statistical properties when there are few events and is useful for analysis of dichotomous outcomes.

To assess statistical heterogeneity, we visually inspected forest plots and described the direction and magnitude of effects and the degree of overlap between CIs. We also considered the statistics generated in forest plots that measured statistical heterogeneity. We examined data for heterogeneity using the Chi^2 test for heterogeneity. Heterogeneity is reported where there was an I^2

statistic of 40% or greater or the Chi^2 P value was 0.1 or less. Heterogeneity was quantified using the I^2 statistic.

We graded heterogeneity as:

- 0% to 40% may not be important;
- 30% to 60% may represent moderate heterogeneity;
- 50% to 90% may represent substantial heterogeneity;
- greater than 75% may represent considerable heterogeneity.

We used a rough guideline to interpret the I^2 value rather than a simple threshold, and our interpretation took into account an understanding that measures of heterogeneity (I^2 and Tau statistics) were estimated with high uncertainty when the number of studies was small [56].

Investigation of heterogeneity and subgroup analysis

We explored sources of heterogeneity in a subgroup analysis when there were at least 10 studies for an outcome (see Investigation of heterogeneity and subgroup analysis).

When subgroup comparisons were possible, we conducted stratified meta-analysis and a formal statistical test for interaction to examine whether subgroup differences could account for effect heterogeneity (e.g. Cochran's Q test, meta-regression) [32, 57].

Given the potential differences in the intervention effectiveness related to specific probiotics or synbiotics, risk of allergy (at least one first-degree relative with allergic disease or not selected on basis of heredity), method of infant feeding (predominately human milk or predominately cow's milk formula), the effect on eczema (by two years of age and during childhood (up to 10 years of age or up to the age of latest report between 2 and 10 years)), we planned to conduct subgroup comparisons to see if the intervention was more effective for the following groups for subgroup analysis where data were available. We decided to focus on eczema as clinical signs of food hypersensitivity and allergy are often associated with allergic immune response and a mediating factor of eczema [58, 59].

We conducted the following subgroup analyses of factors that may contribute to heterogeneity in the effects of the intervention on eczema.

- Risk of allergy: infant and childhood incidence of infants at high risk of allergy (at least one first-degree relative with allergic disease)
- Risk of allergy: infant incidence of infants at low risk of allergy, or not selected on the basis of heredity
- Method of infant feeding: infant and childhood incidence of infants fed predominately human milk, measured as greater than 50% of participants were fed human milk for some period of time during the study
- Method of infant feeding: infant incidence of infants fed predominately cow's milk formula, measured as greater than 50% of participants were fed cow's milk formula for some period of time during the study
- Probiotic type: infants fed probiotics with *Lacticaseibacillus rhamnosus* (*L rhamnosus*) compared with not containing *L rhamnosus*
- Period of supplementation: participants who received antenatal probiotic complementation compared with no antenatal probiotic supplementation

Summary of subgroup analyses rationale (see details discussed in the Background section).

- Risk of allergy: genetic susceptibility plays a large role in the development of allergic disease [5, 6, 7]
- Method of infant feeding: breastfeeding promotes the colonisation of bacteria that inhibit the growth of pathogenic micro-organisms in the gastrointestinal tract. This establishment of gastrointestinal flora may modulate barrier function and systemic immunological and inflammatory responses that contribute to the development of allergic disease [13, 14].

Equity-related assessment

No equity-related assessment was completed.

Sensitivity analysis

We performed a sensitivity analysis for outcomes with at least five trials to determine if the findings were affected by risk of bias, excluding studies with high risk of overall bias. We conducted a sensitivity analysis for eczema to explore the different definitions of eczema, specifically the differentiation between atopic dermatitis and atopic eczema, defined as eczema with a positive SPT (greater than 0) to one or more allergen, physician assessed or serological testing for specific IgE.

Given that there is no formal statistical test that can be used for sensitivity analysis, we made informal comparisons between the different ways of estimating the effect under different assumptions. We did not use changes in P values to judge whether there was a difference between the main analysis and sensitivity analysis, since statistical significance may be lost with fewer studies included.

Certainty of the evidence assessment

We used the GRADE approach, as outlined in the *GRADE Handbook* [60], to assess the certainty of evidence for the following (clinically relevant) outcomes. Outcomes of infant incidence of allergic disease, food allergy, cow's milk allergy and potential harms including anaphylaxis were measured as incidence by two years of age. We prioritised measures for eczema over other definitions of eczema, including atopic eczema. Food allergy as an overall measure was prioritised and not split into specific foods.

- Infant incidence (by two years of age) of specific allergic disease including:
  - asthma: physician diagnosed or from past medical history;
  - eczema: SCORAD, measured on a scale from 0 to 103, less than 25 mild, greater than 50 severe *or* UK Working Party's Diagnostic Criteria measured on pruritus plus three minor skin features;
  - allergic rhinitis: physician diagnosed or from past medical history.
- Infant incidence of IgE-mediated food allergy: physician diagnosed food allergy with a positive SPT (greater than 0) or serological testing for specific IgE or failed oral allergen tolerance test (symptoms of mild allergic reaction

including itchiness, rashes, mild difficulty breathing, requiring antihistamine; severe allergic reaction include anaphylaxis).
- Infant incidence of IgE-mediated cow's milk protein allergy: physician diagnosed cow's milk protein allergy with a positive SPT (greater than 0) or serological testing for specific IgE or failed oral allergen tolerance test (symptoms of mild allergic reaction including itchiness, rashes, mild difficulty breathing, requiring antihistamine; severe allergic reaction include anaphylaxis).
- Potential harms including adverse effects, harms or infection with probiotic bacteria assessed by participant interviews/ surveys.

Two review authors (EH, HZW) independently assessed the certainty of the evidence for each of the outcomes above. We considered evidence from RCTs as high certainty but downgraded the evidence one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates and presence of publication bias. We resolved any disagreement by discussion with a senior review author (JS).

We used GRADEpro GDT to create two summary of findings tables to report the certainty of the evidence for the following comparisons [61].

- Probiotic compared with no probiotic in infants for preventing allergic disease by two years of age (Summary of findings 1).
- Synbiotic compared with no symbiotic in infants for preventing allergic disease by two years of age (Summary of findings 2).

The GRADE approach results in an assessment of the certainty of a body of evidence as one of four grades.

- High certainty: further research is very unlikely to change our confidence in the estimate of effect.
- Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low certainty: we are very uncertain about the estimate.

Consumer involvement

Consumers were not involved in this review.

RESULTS

Description of studies

We included the results of the search for this review update in the study flow diagram (Figure 1).

Figure 1. Flow diagram: 2024 review update

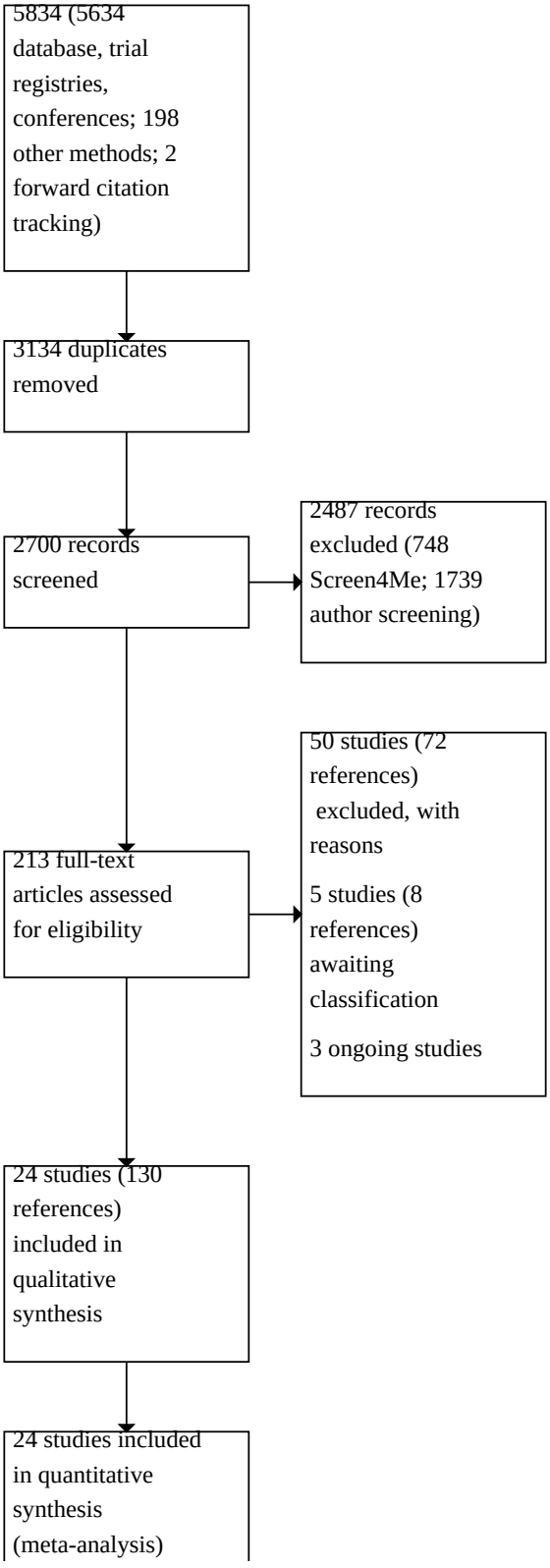


Figure 1. (Continued)

synthesis
(meta-analysis)

For the included studies, see Supplementary material 2 and Table 1.

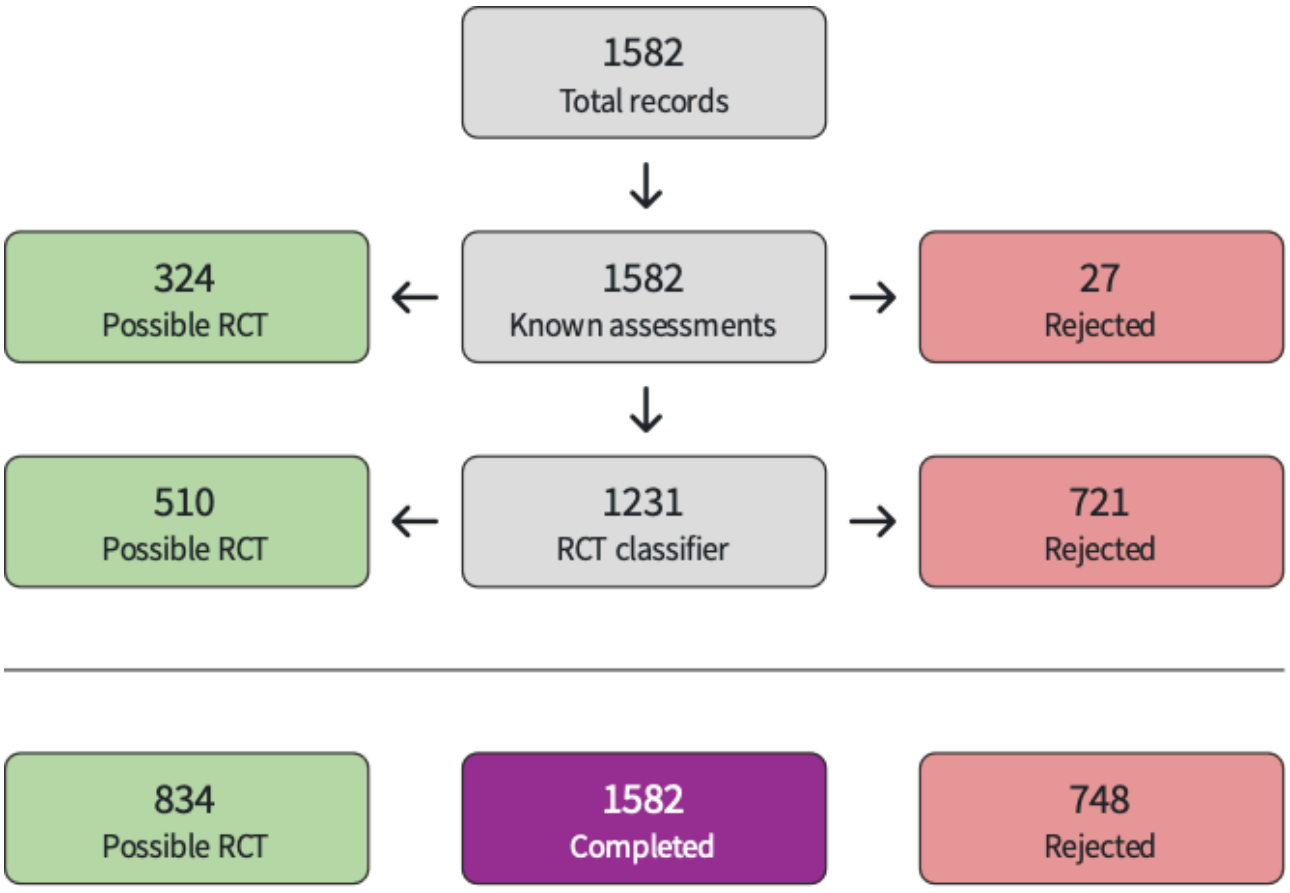
See Supplementary material 3 for characteristics of excluded studies, Supplementary material 4 for characteristics of studies awaiting classification and Supplementary material 5 for characteristics of ongoing studies.

Results of the search

The searches identified 5834 references. After removing 3134 duplicates, 2700 references were available for screening. We excluded 2487 references based on title/abstract screening (748 using Screen4Me; 1739 by author screening). We reviewed 213 full-text and trial registry records. We included 24 studies (19 new for this update) (130 references); we excluded 50 studies (26 new for this update) (72 references); identified three ongoing studies; and categorised five studies (8 references) as awaiting classification as we await information from study authors. Two of the five studies awaiting classification were published after editorial assessment of this manuscript; these studies will be assessed for eligibility in an update of this review.

Details of study flow and selection are available in Figure 1; details of Screen4Me are available in Figure 2.

Figure 2. Screen4Me, *Copyright © 2024 Cochrane: reproduced with permission;* S4M run in December 2023.



Included studies

We included 24 studies enroling 7077 mother–infant pairs and assessing allergic disease outcomes in this review.

Nineteen of 24 studies are new to this update (Allen 2014 [62, 63, 64]; Cabana 2007 [65, 66, 67, 68, 69, 70, 71]; Dissanayake 2018 [72, 73, 74]; Hascoët 2011 [75]; Kim 2010 [76, 77, 78]; Kopp 2008 [79, 80]; Lau 2012 [81, 82, 83]; Morisset 2011 [84, 85]; Niers 2009 [86, 87, 88, 89, 90]; Ortiz-Andrellucchi 2008 [91]; Plummer 2020 [92, 93, 94, 95,

96, 97]; Rozé 2012 [98]; Savino 2010 [99]; Scalabrin 2009 [100, 101]; Soh 2009 [102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114]; Taipale 2011 [115, 116]; Vlieger 2009 [117]; West 2008 [118, 119, 120, 121]; Wickens 2008 [122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133]); the remaining five were included in the original review (Abrahamsson 2007 [134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144]; Kalliomaki 2001 [145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157]; Kukkonen 2006 [158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182]; Rautava 2006 [183, 184]; Taylor 2006 [185, 186, 187, 188, 189, 190, 191]).

We reclassified and excluded six studies included in the original review and provided the reasons in Excluded studies (Bin-Nun 2005 [192]; Brunser 2006 [193, 194]; Lin 2005 [195]; Puccio 2007 [196]; Saavedra 2004 [197]; Vendt 2006 [198]).

One study included in the original review, Rautava and colleagues [199], has been added as a secondary reference to Kalliomaki 2001, which reported the same clinical trial participant cohort.

Detailed characteristics of the included studies are reported in Supplementary material 2.

Participants

- Twelve studies enroled term or near-term infants at high risk of allergy or food hypersensitivity (infants with at least one first-degree relative with a history of allergy or food hypersensitivity) (Abrahamsson 2007; Cabana 2007; Kalliomaki 2001; Kim 2010; Kopp 2008; Kukkonen 2006; Lau 2012; Morisset 2011; Niers 2009; Soh 2009; Taylor 2006; Wickens 2008).
- One study reported the outcomes of 108 infants at high risk of allergy separately (these infants were included in this subgroup analysis) (West 2008).
- Twelve studies enroled infants not selected on the basis of a family history of allergy or food hypersensitivity (Allen 2014; Dissanayake 2018; Hascoët 2011; Ortiz-Andrellucchi 2008; Plummer 2020; Rautava 2006; Rozé 2012; Savino 2010; Scalabrin 2009; Taipale 2011; Vlieger 2009; West 2008).
- The infants enroled in one study had symptoms of 'infantile colic' but were not suspected of having allergies (Savino 2010).
- One study enroled very preterm infants to evaluate the effect of postnatal probiotics on the development of allergic disease (Plummer 2020).
- One study enroled infants at a low risk of allergy or food hypersensitivity (Ortiz-Andrellucchi 2008). They excluded women with pre-existing allergies.
- Fourteen studies enroled infants starting breastfeeding with high rates of maintenance of breastfeeding (Abrahamsson 2007; Cabana 2007; Kalliomaki 2001; Kim 2010; Kopp 2008; Niers 2009; Ortiz-Andrellucchi 2008; Plummer 2020; Rautava 2006; Savino 2010; Soh 2009; Taipale 2011; Taylor 2006; Wickens 2008).
- Seven studies enroled infants receiving prolonged cow's milk formula feeding (Allen 2014; Dissanayake 2018; Hascoët 2011; Morisset 2011; Rozé 2012; Soh 2009; Vlieger 2009).
- One study compared infants receiving study formula with control formula and breastfeeding (Hascoët 2011).
- One study encouraged mothers who wanted to breastfeed to do so; most infants were reported to be formula-fed (Morisset 2011).

Interventions

- All 24 studies used prolonged supplementation of infant feeds with probiotic supplements.
- Four studies used synbiotics (Dissanayake 2018; Kukkonen 2006; Rozé 2012; Vlieger 2009).
- Eight studies also provided probiotic supplements to pregnant women (Abrahamsson 2007; Allen 2014; Kalliomaki 2001; Kim 2010; Kopp 2008; Kukkonen 2006; Niers 2009; Wickens 2008), of which five continued to supplement breastfeeding mothers (Abrahamsson 2007; Kalliomaki 2001; Kim 2010; Kopp 2008; Wickens 2008).
- Sixteen studies supplied the intervention to infants only (Cabana 2007; Dissanayake 2018; Hascoët 2011; Lau 2012; Morisset 2011; Ortiz-Andrellucchi 2008; Plummer 2020; Rautava 2006; Rozé 2012; Savino 2010; Scalabrin 2009; Soh 2009; Taipale 2011; Taylor 2006; Vlieger 2009; West 2008).

Outcomes

Most common primary outcomes included the following.

- Eczema in the first two years conducted by a paediatrician, trained nurse or clinician — assessed by the SCORAD system.
- Asthma in the first two years diagnosed by a physician or from past medical history.
- Allergic rhinitis in the first two years diagnosed by a physician or from past medical history.
- Food allergy in the first two years — physician diagnosed food allergy with or without a positive SPT (greater than 0) or serological testing for specific IgE or failed oral allergen tolerance test (symptoms of mild allergic reaction including itchiness, rashes, mild difficulty breathing, requiring antihistamine).
- Cow's milk protein allergy in the first two years — physician-diagnosed cow's milk protein allergy with or without a positive SPT (greater than 0) or serological testing for specific IgE or failed oral allergen tolerance test (symptoms of mild allergic reaction including itchiness, rashes, mild difficulty breathing, requiring antihistamine).
- Potential harms in the first two years including adverse effects, harms or infection with probiotic bacteria at any point during the study intervention by two years of age, assessed by participant interviews/surveys.

Detailed primary outcomes, other outcomes and definitions are reported in Supplementary material 2.

Excluded studies

See Supplementary material 3.

We excluded 50 studies (72 references) for the following reasons.

- Twenty-five studies did not measure the relevant outcomes (Bakker-Zierikzee 2005 [200, 201]; Bin-Nun 2005; Brunser 2006; Chouraqui 2004 [202]; Dani 2002 [203]; Durack 2015 [204, 205]; Harvey 2014 [206, 207, 208] (study 1); Huet 2006 [209]; Huoman 2021 [210]; Kankaanpaa 2002 [211]; Kocourková 2007 [212]; Lin 2005; Manzoni 2006 [213, 214]; Marzotto 2006 [215]; Mohan 2006 [216, 217]; Puccio 2007; Rio 2004 [218]; Roggero 2020 [219]; Saavedra 2004; Savino 2007 [220]; Shamir 2005 [221]; Thibault 2004 [222]; Vendt 2006; Weizman 2006 [223]; Wu 2012 [224]).

- Sixteen studies enroled infants with clinical evidence of allergic disease or IgE-mediated food allergy (Aldaghi 2022 [225]; Bi 2021 [226]; Brouwer 2006 [227]; Harvey 2014 (study 2); Isolauri 2000 [228]; Kirjavainen 2002 [229]; Kirjavainen 2003 [230]; Lin 2012 [231]; Majamaa 1997 [232]; Pohjavuori 2004 [233]; Rosenfeldt 2003 [234]; Rosenfeldt 2004 [235]; Sistek 2006 [236]; Torii 2011 [237]; Viljanen 2005 [238, 239, 240]; Weston 2005 [241, 242]).
- Five studies provided the intervention to pregnant mothers and not to infants directly postnatally (Barthow 2016 [243]; Boyle 2008 [244, 245, 246, 247, 248]; Dotterud 2010 [249, 250, 251, 252]; Ou 2012 [253, 254, 255]; Rautava 2012 [256]).
- Two studies did not meet the criteria for an RCT (Damm 2017 [257, 258]; Lodinová-Žádníková 2003 [259, 260]).
- Three studies did not provide the intervention of interest, including probiotics or synbiotics (Arvola 2006 [261]; Huurre 2008 [262, 263]; Lodinová-Žádníková 2010 [264]).

Studies awaiting classification

Five studies are awaiting classification.

Of these, two have no assessable allergy outcomes, and we are awaiting data.

- De Leon 2007 [265] enroled healthy term infants at high risk of developing allergic disease.
- Simon 2006 [266] enroled full-term infants with a family history of atopic disease.

Three studies were completed after our search date and during editorial assessment of this manuscript and will be considered for inclusion in an update of this review.

- NCT04662619 [267, 268] enroled healthy term infants with at least one first-degree relative with a history of atopic disease.
- Shen 2024 [269, 270] enroled healthy infants, two groups received probiotics and one group received regular formula.
- Tyrsin 2024 [271, 272] enroled breastfed infants with "colic, constipation, diarrhea, or regurgitation, either individually or in combination."

See Supplementary material 4.

Characteristics of ongoing studies

We categorised three studies as ongoing.

- One study plans to enrol healthy, full-term infants at risk of developing atopic disease receiving hydrolysed protein and breast milk with prebiotic and probiotic or intact protein and breast milk with prebiotic and probiotic or exclusively breast milk (NCT03489733 [273])
- One study includes three parts, with part B enroling infants at 14 days of life or less to receive a daily dosage of placebo mixed with milk, formula or a milk product for 28 days (NCT05003804 [274]).
- One study plans to enrol healthy infants to receive probiotics with vitamin D_3 daily or vitamin D_3 only for 90 days (NCT04741971 [275])

See Supplementary material 5.

Risk of bias in included studies

The risk of bias in the included studies is presented in Figure 3. Details of the methodological quality of each study are described in the Supplementary material 2.

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

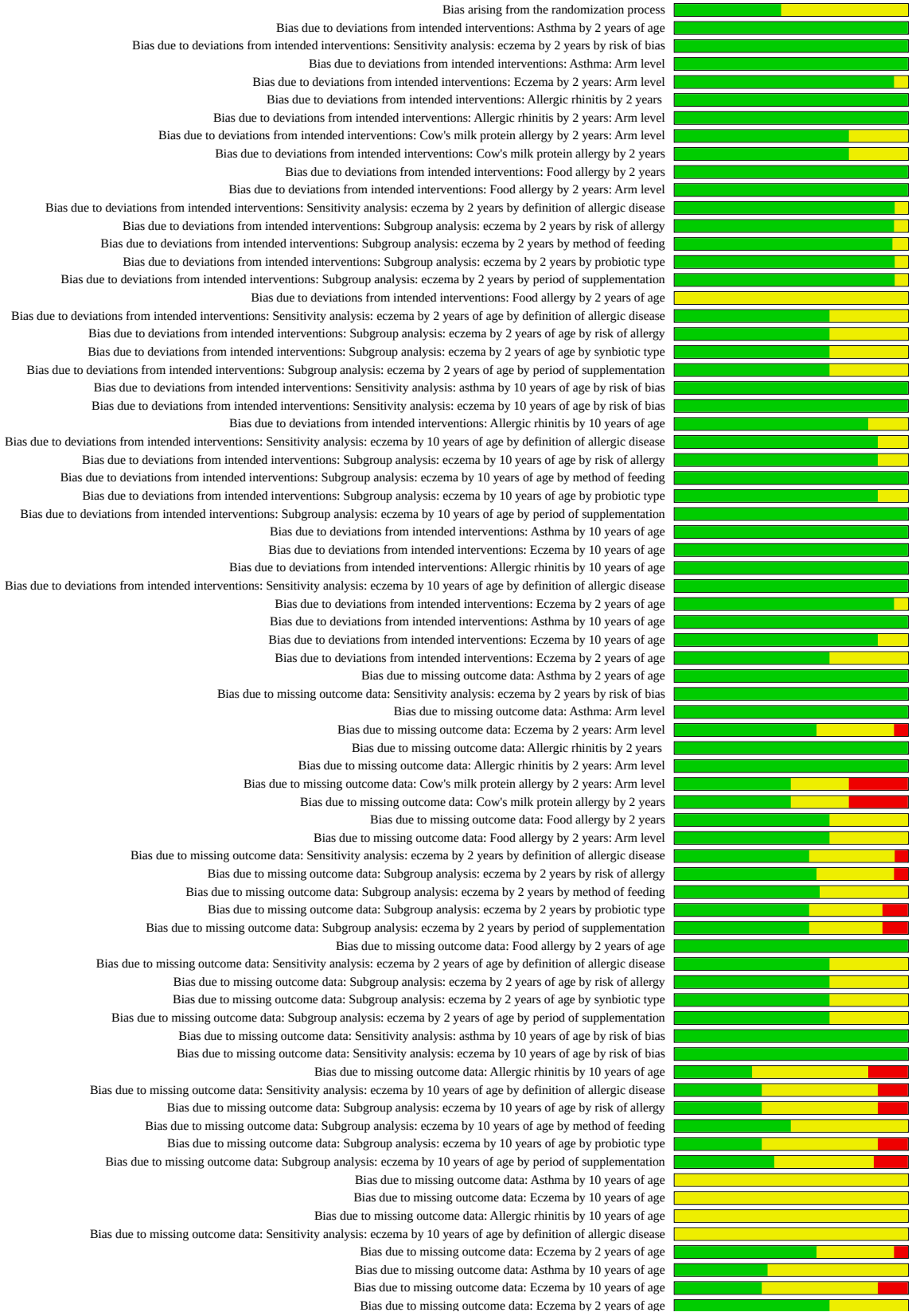
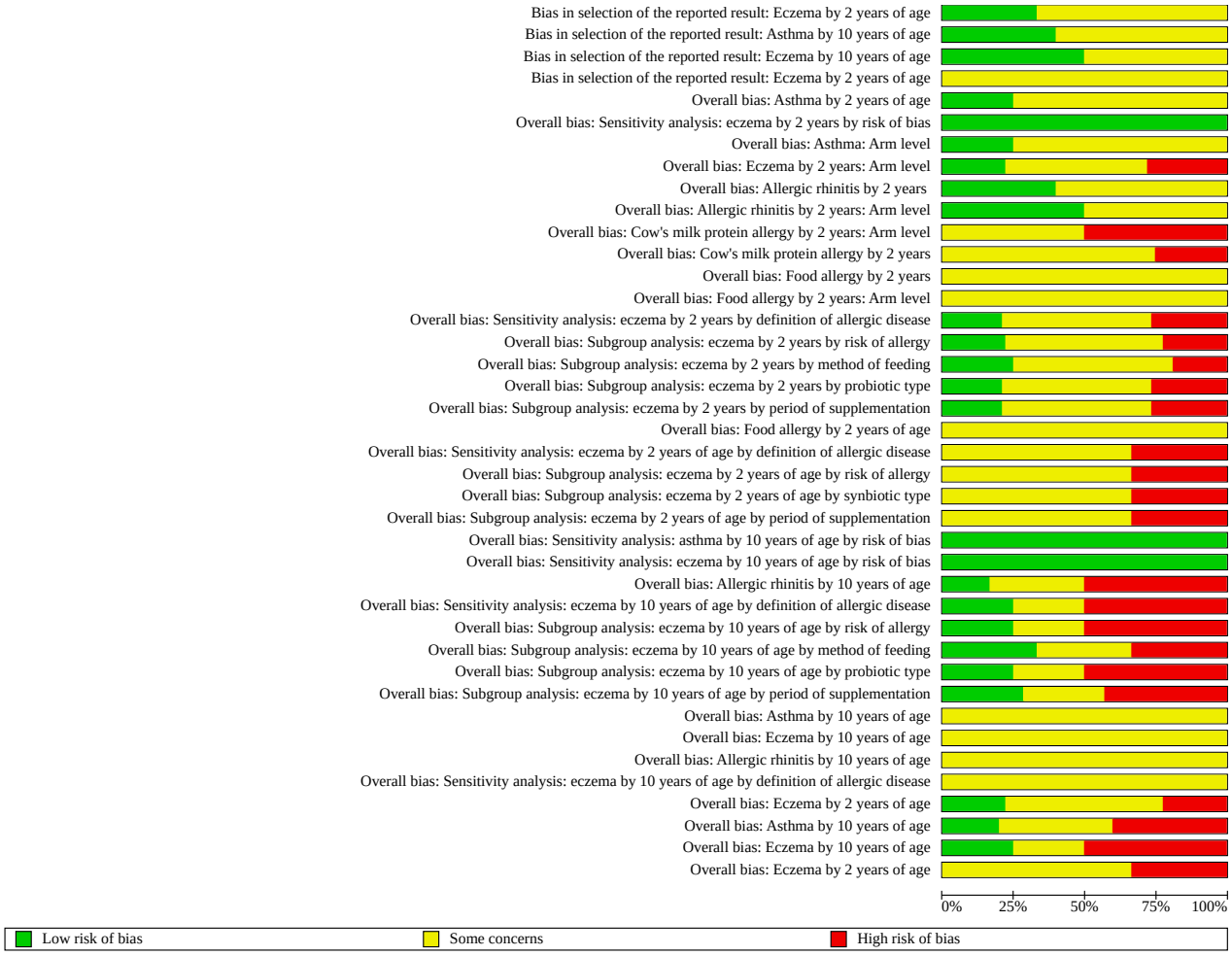


Figure 3. (Continued)

Figure 3. (Continued)



Bias arising from the randomisation process

We judged bias arising from the randomisation process to be low in 11 studies. We judged bias arising from the randomisation process to be uncertain in 11 studies because the allocation concealment or random sequence generation was not described (Hascoët 2011; Kalliomaki 2001; Kopp 2008; Lau 2012; Niers 2009; Rozé 2012; Scalabrin 2009; Soh 2009; Taipale 2011; Vlieger 2009; West 2008). Bias was uncertain in Kim 2010 because of potentially clinically significant although not statistically significant differences between groups after randomisation. Bias was uncertain in Taylor 2006 because of significant differences in birth length and birth head circumference between groups analysed.

Bias due to deviations from intended interventions

We judged 20 studies at low risk of bias due to deviations from intended interventions. We judged bias due to deviations from intended interventions to be uncertain in two studies because they conducted a per-protocol analysis (Kopp 2008; Morisset 2011). Bias was uncertain in Dissanayake 2018 because the study used no treatment as the control group. Bias was uncertain in Scalabrin 2009 because details of blinding were not reported.

Bias due to missing outcome data

We judged 16 studies at low risk of bias. We judged bias due to missing outcome data to be uncertain in seven studies because the studies did not report whether dropouts were related to specific outcomes or the reason for missing data or because of high number of dropouts, although the reasons were described to be unrelated to study interventions (Kalliomaki 2001; Kim 2010; Kopp 2008; Niers 2009; Ortiz-Andrellucchi 2008; Plummer 2020; Rozé 2012). We judged bias due to missing outcome data to be high in Lau 2012 because 24 participants discontinued due to adverse events but there were no details of whether adverse events were related to study outcomes. We judged bias to be high in Taipale 2011 due to potentially clinically important differences between groups as analysed after substantial losses with reasons for dropout was not described.

Two studies were at uncertain bias due to missing outcome data for childhood incidence of atopic disease due to a large number of loss to follow-up in a five-year follow-up study, dropout rates not related to health outcomes (Scalabrin 2009; Taylor 2006). Bias due to missing outcome data was high in Cabana 2007 for childhood incidence of atopic disease because of the large number of dropouts for five-year follow-up with reasons not reported.

Bias in measurement of the outcome

We judged 23 studies at low risk of bias. We judged Allen 2014 to be at uncertain risk of bias in measurement of the outcome because of potential recall bias and delayed follow-up in children seen up to, but not including, three years of age.

Bias in selection of the reported result

We judged eight studies at low risk of bias in selection of the reported results. We judged 15 studies to be at uncertain risk of bias in selection of the report result because prespecified analysis plan was not available (Allen 2014; Dissanayake 2018; Hascoët 2011; Kim 2010; Kopp 2008; Kukkonen 2006; Lau 2012; Niers 2009; Ortiz-Andrellucchi 2008; Rautava 2006; Rozé 2012; Soh 2009; Taylor 2006; Vlieger 2009; West 2008). Bias was uncertain in Taipale 2011 because allergic disease was not described as an outcome on prespecified analysis plan.

Synthesis of results

Critical outcomes

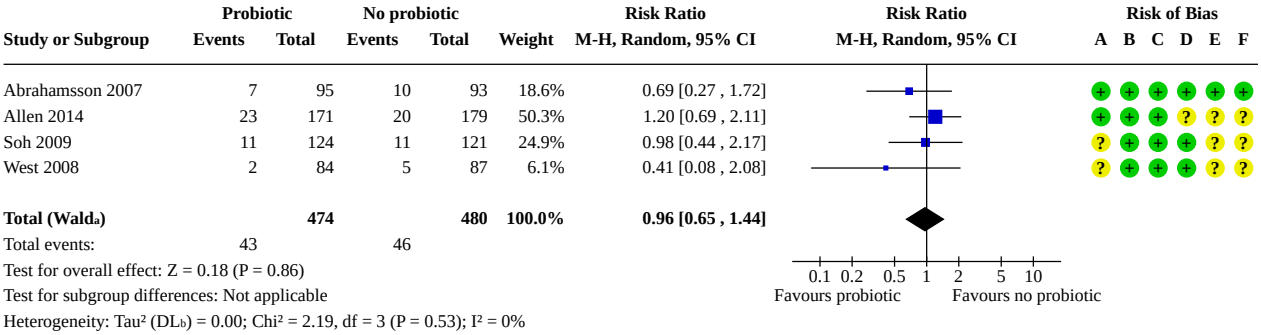
Probiotic compared with no probiotic

See Summary of findings 1.

Asthma by two years of age

Four studies reported this outcome (Abrahamsson 2007; Allen 2014; Soh 2009; West 2008). Probiotic may result in little to no difference in asthma by two years of age (RR 0.96, 95% CI 0.65 to 1.44; I^2 = 0%; 4 studies, 954 participants; low-certainty evidence; Figure 4).

Figure 4. Asthma by 2 years of age



Footnotes

[a]CI calculated by Wald-type method.
[b]Tau² calculated by DerSimonian and Laird method.

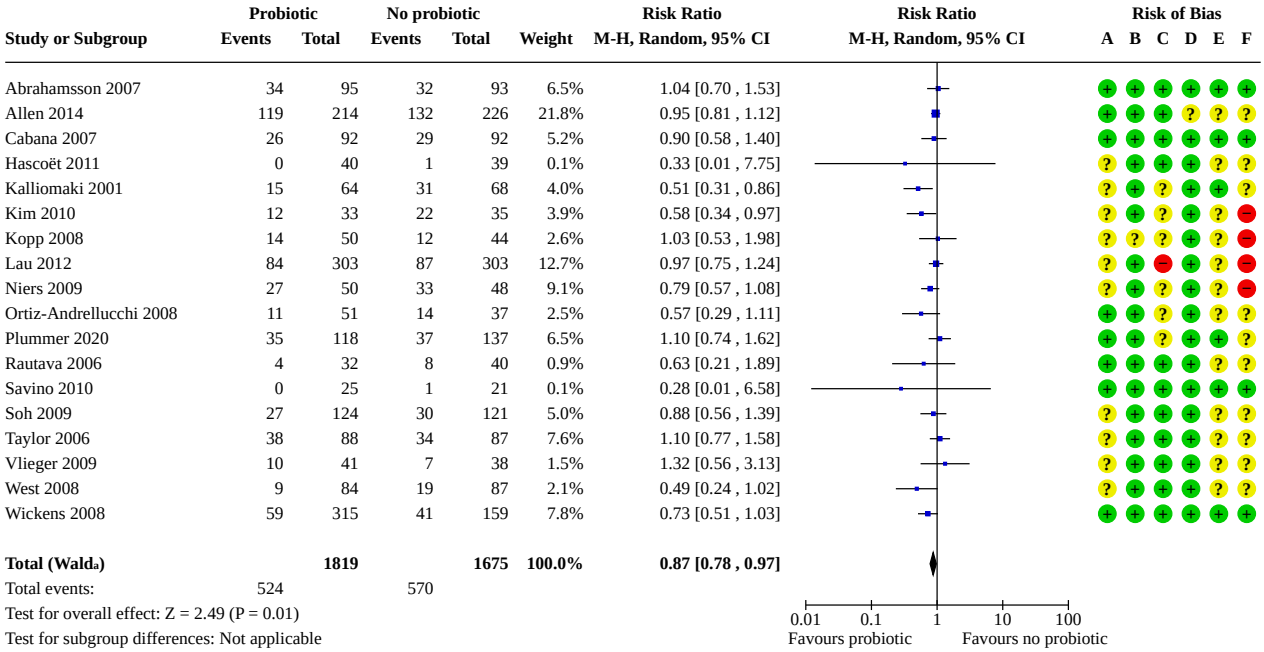
Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Eczema by two years of age

Eighteen studies reported this outcome (Abrahamsson 2007; Allen 2014; Cabana 2007; Hascoët 2011; Kalliomaki 2001; Kim 2010; Kopp 2008; Lau 2012; Niers 2009; Ortiz-Andrellucchi 2008; Plummer 2020; Rautava 2006; Savino 2010; Soh 2009; Taylor 2006; Vlieger 2009; West 2008; Wickens 2008). Probiotic may result in a slight reduction in eczema by two years of age (RR 0.87, 95% CI 0.78 to 0.97; I^2 = 14%; 18 studies, 3494 participants; low-certainty evidence; Figure 5). We did not detect any substantial risk of publication bias (Figure 6).

Figure 5. Eczema by 2 years of age



Test for overall effect: Z = 2.49 (P = 0.01)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (DL[b]) = 0.01; Chi² = 19.74, df = 17 (P = 0.29); I² = 14%

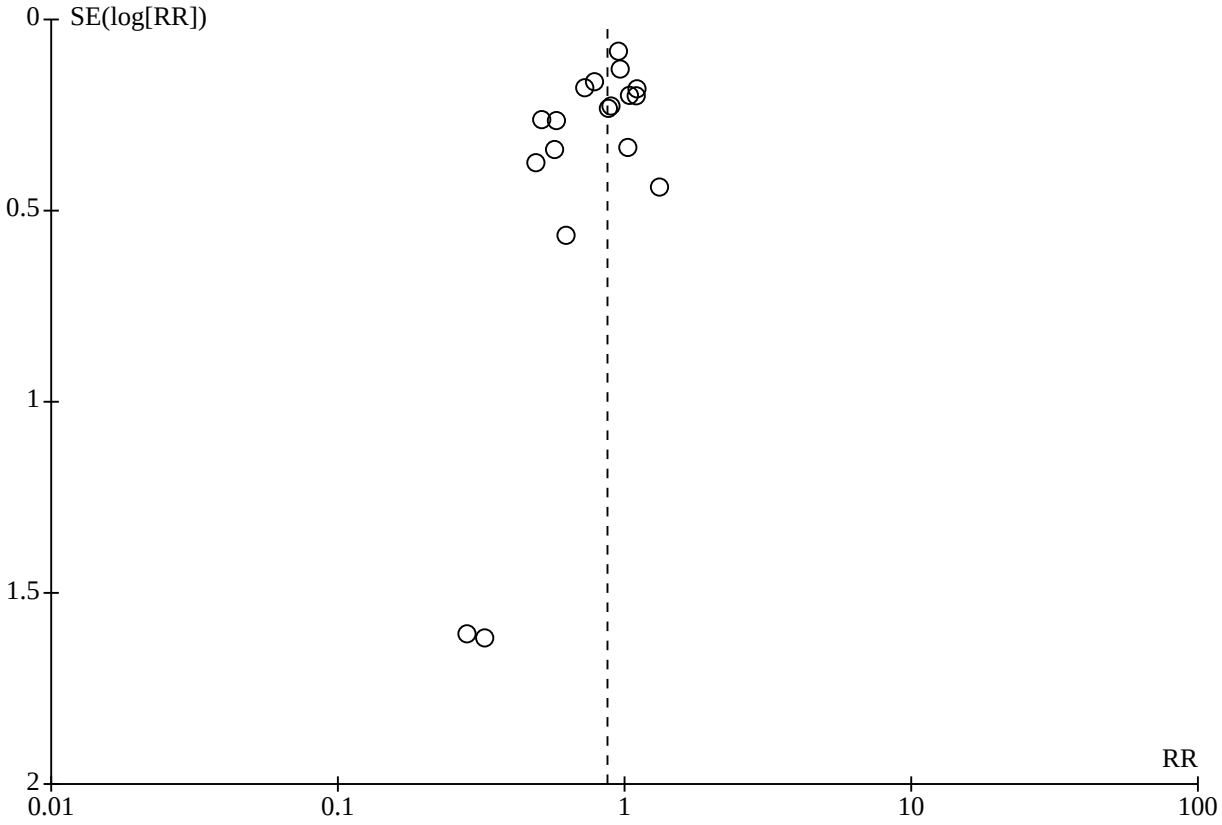
Footnotes

[a]CI calculated by Wald-type method.
[b]Tau² calculated by DerSimonian and Laird method.

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Figure 6. Funnel plot: probiotics versus no probiotics - eczema by 2 years



Subgroup analyses

See Supplementary material 7.

Infants at high risk of allergy versus infants not selected for risk of allergy: the test for subgroup difference was not significant (P = 0.60, I^2 = 0%; Analysis 1.8).

Infants fed predominately human milk versus infants fed predominantly cow's milk formula: the test for subgroup difference was not significant (P = 0.22, I^2 = 34.2%; Analysis 1.9).

Infants given probiotic containing *L rhamnosus* versus infants given probiotic not containing *L rhamnosus*: the test for subgroup difference was not significant (P = 0.10, I^2 = 64.0%; Analysis 1.10).

Mothers of infants who received antenatal probiotic versus mothers of infants who did not receive antenatal probiotic: the test for subgroup difference was not significant (P = 0.25, I^2 = 24.9%; Analysis 1.11).

Sensitivity analyses

See Supplementary material 7 and Supplementary material 9.

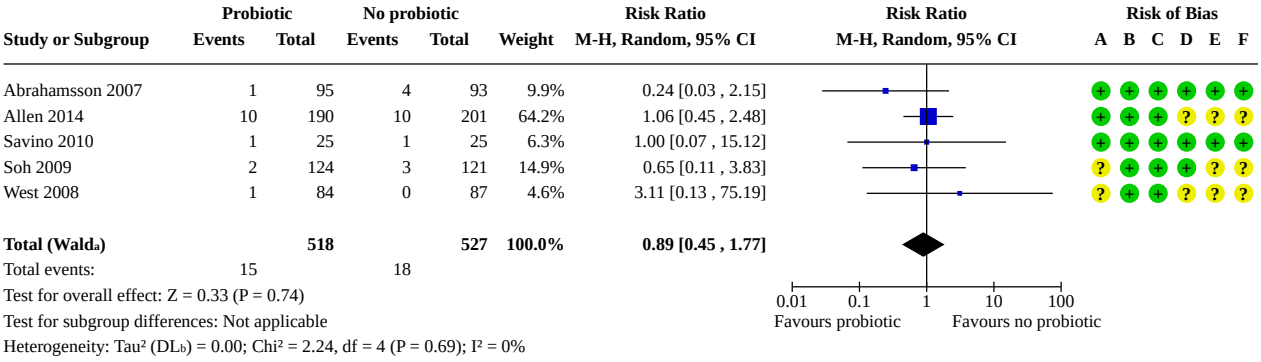
Sensitivity analyses reinforced the importance of differentiating between eczema types as probiotic supplementation may result in slight reduction in general eczema but very uncertain effects on atopic eczema by two years of age.

Sensitivity analysis of the studies at low risk of bias showed little or no difference in eczema by two years of age (RR 0.86, 95% CI 0.69 to 1.07; 4 studies, 892 participants).

Allergic rhinitis by two years of age

Five studies reported this outcome (Abrahamsson 2007; Allen 2014; Savino 2010; Soh 2009; West 2008). Probiotic may result in little to no difference in allergic rhinitis by two years of age (RR 0.89, 95% CI 0.45 to 1.77; I^2 = 0%; 5 studies, 1045 participants; low-certainty evidence; Figure 7).

Figure 7. Allergic rhinitis by 2 years of age



Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions

(C) Bias due to missing outcome data

(D) Bias in measurement of the outcome

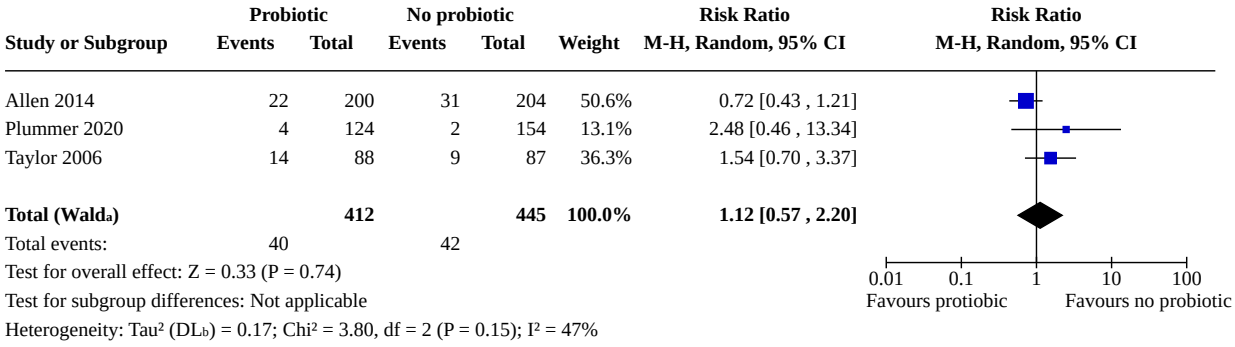
(E) Bias in selection of the reported result

(F) Overall bias

Immunoglobulin E-mediated food allergy by two years of age

Three studies reported this outcome (Allen 2014; Plummer 2020; Taylor 2006). Probiotic supplementation may have little to no effect on the incidence of food allergy during infancy, but the evidence is very uncertain (RR 1.12, 95% CI 0.57 to 2.20; I^2 = 47%; 3 studies, 857 participants; very low-certainty evidence; Figure 8).

Figure 8. Food allergy by 2 years of age



Footnotes

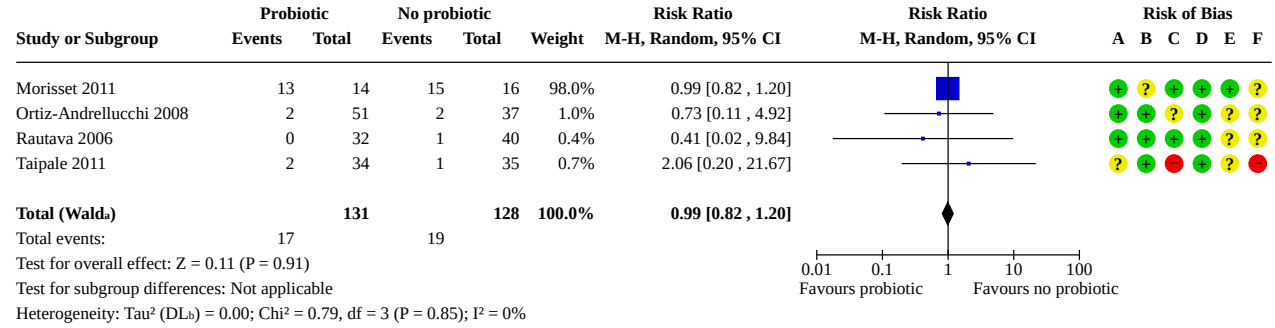
[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Immunoglobulin E-mediated cow's milk protein allergy by two years of age

Four studies reported this outcome (Morisset 2011; Ortiz-Andrellucchi 2008; Rautava 2006; Taipale 2011). Probiotic may result in little to no difference in cow's milk protein allergy by two years of age (RR 0.99, 95% CI 0.82 to 1.20; I^2 = 0%; 4 studies, 259 participants; low-certainty evidence; Figure 9).

Figure 9. Cow's milk protein allergy by 2 years of age



Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions

(C) Bias due to missing outcome data

(D) Bias in measurement of the outcome

(E) Bias in selection of the reported result

(F) Overall bias

Potential harms including adverse effects, harms or infection with probiotic bacteria by two years of age

Probiotic may result in little to no difference in potential harms including adverse effects, harms or infection with probiotic bacteria at any point during the study intervention by two years of age (11 studies, 2405 infants; low-certainty evidence; narrative synthesis).

Abrahamsson 2007 reported no difference in the cumulative incidence of mild adverse events (spitting-up, colic and constipation) during the first 12 months of age. There were no serious adverse effects reported.

Allen 2014 previously reported that probiotic supplementation was not associated with adverse effects in mothers or their infants during the first 12 months of age. There were two possible adverse reactions with infants experiencing regurgitation, after which administration was discontinued following the symptoms.

Cabana 2007 reported no major adverse events in infants supplemented with probiotics and infants who were not supplemented with probiotics up to five years of age.

Hascoët 2011 reported no significant difference in adverse events in infants receiving study formula with or without probiotics during the first four months of age. Symptoms of digestive tolerance (frequency of vomiting, spitting-up, crying, being fussy, colic and flatulence) were not significantly different among the groups.

Kopp 2008 reported there were no notable adverse effects attributable to the supplementation of probiotics during the first 24 months of age.

Lau 2012 reported no difference in adverse event prevalence between groups at all time points at one year, two years and three years of age.

Morisset 2011 reported that infants in the intervention group showed a significantly lower proportion of respiratory potential allergic adverse events at 12 months and 24 months compared with the control group. There was no significant difference for general intensity of potential allergic adverse events.

Savino 2010 reported similar gastrointestinal function between intervention and control groups on day 21 of the study. Adverse events, including rhinitis, eczema, fever, otalgy and gastro-oesophageal reflux reported during the study, were deemed unrelated to the study product.

Scalabrin 2009 reported a similar incidence of adverse events between the intervention and control groups through 120 days of age. Serious adverse events were unrelated to study formulas except for one infant in the intervention group with gastro-oesophageal reflux whose relationship with the study formula was undetermined.

Taipale 2011 reported no serious adverse effects during the administration period (first six to eight months of life). Two infants in the intervention group withdrew due to gastrointestinal complaints. One infant in the control group was diagnosed with atopic eczema and recommended by their family physician to discontinue the study.

Vlieger 2009 reported no serious adverse events that could be related to the study formula during the first six months of life. Infants in the intervention group had fewer events of rash development in the first three months of intervention. There were no differences in other adverse effects between groups during the first and second semesters of the intervention.

Synbiotic compared with no synbiotic

See Summary of findings 2.

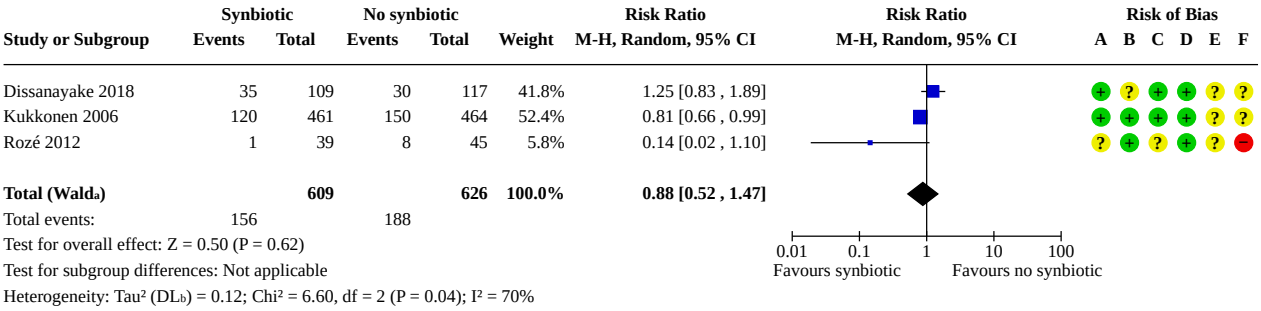
Asthma by two years of age

No studies reported data on this outcome.

Eczema by two years of age

Three studies reported this outcome (Dissanayake 2018; Kukkonen 2006; Rozé 2012). The evidence is very uncertain about the effect of synbiotic on eczema by two years of age (RR 0.88, 95% CI 0.52 to 1.47; I^2 = 70%; 3 studies, 1235 participants; very low-certainty evidence; Figure 10).

Figure 10. Eczema by 2 years of age



Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Subgroup analyses

See Supplementary material 7.

Infants at high risk of allergy versus infants not selected for risk of allergy: the test for subgroup difference was not significant (P = 0.71, I^2 = 0%; Analysis 2.4).

Infants fed predominately human milk versus infants fed predominantly cow's milk formula: no data available.

Infants given synbiotic containing *L rhamnosus* versus infants given synbiotic not containing *L rhamnosus*: the test for subgroup difference was not significant (P = 0.23, I^2 = 29.3%; Analysis 2.5).

Mothers of infants who received antenatal synbiotic versus mothers of infants who did not receive antenatal synbiotic: the test for subgroup difference was not significant (P = 0.71, I^2 = 0%; Analysis 2.6).

Sensitivity analysis

See Supplementary material 7 and Supplementary material 9.

Sensitivity analyses reinforce the importance of differentiating between eczema types as the evidence is very uncertain about the effect of synbiotic on general eczema, but may result in a slight reduction in the incidence of atopic eczema by two years of age. However, the evidence was limited to one study reporting this outcome.

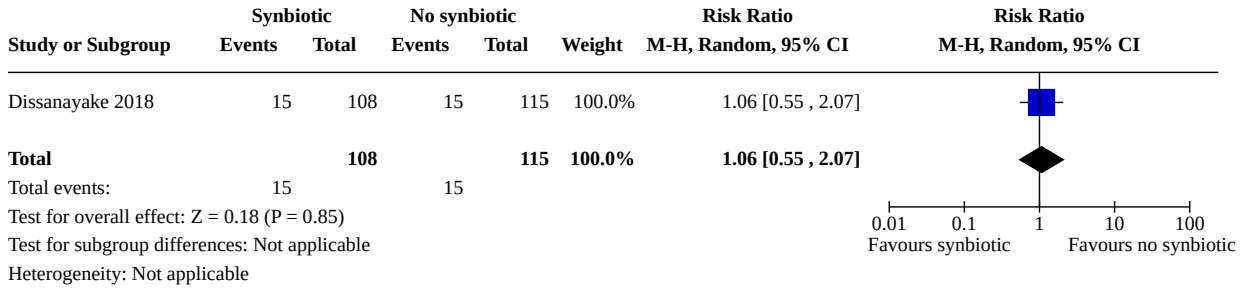
Allergic rhinitis by two years of age

No studies reported data on this outcome.

Immunoglobulin E-mediated food allergy by two years of age

One study reported this outcome (Dissanayake 2018). Synbiotic may result in little to no difference in food allergy by two years of age (RR 1.06, 95% CI 0.55 to 2.07; 1 study, 223 participants; low-certainty evidence; Figure 11).

Figure 11. Food allergy by 2 years of age



Immunoglobulin E-mediated cow's milk protein allergy by two years of age

No studies reported data on this outcome.

Potential harms including adverse effects, harms or infection with probiotic bacteria by two years of age

Synbiotic may result in little to no difference in potential harms, including adverse effects, harms or infection with probiotic bacteria at any point during the study intervention by two years of age (2 studies, 1497 participants; low-certainty evidence; narrative synthesis).

Dissanayake 2018 reported no adverse effects to the interventions during the study.

Kukkonen 2006 reported minor adverse effects (abdominal discomfort, vomiting and excessive crying) in both the intervention group (55 participants) and the control group (58 participants).

Important outcomes

Probiotic compared with no probiotic

See Supplementary material 7.

Asthma by 10 years of age

Five studies reported this outcome (Abrahamsson 2007; Kalliomaki 2001; Niers 2009; Soh 2009; Taylor 2006). Probiotic may result in little to no effect in asthma by 10 years of age (RR 1.08, 95% CI 0.79 to 1.49; I^2 = 0%; 5 studies, 778 participants; Analysis 3.1).

Sensitivity analysis: asthma by 10 years by risk of bias

See Supplementary material 9.

Eczema by 10 years of age

Eight studies reported this outcome (Abrahamsson 2007; Kalliomaki 2001; Lau 2012; Niers 2009; Scalabrin 2009; Soh 2009; Taylor 2006; Wickens 2008). Probiotic may result in little to no effect in eczema by 10 years of age (RR 0.89, 95% CI 0.76 to 1.05; I^2 = 42%; 8 studies, 1965 participants; Analysis 3.2).

Infants at high risk of allergy versus infants not selected for risk of allergy: the test for subgroup difference was not significant (P = 0.18, I^2 = 44.2%; Analysis 3.7).

Infants fed predominately human milk versus infants fed predominantly cow's milk formula: the test for subgroup difference was not significant (P = 0.66, I^2 = 0%; Analysis 3.8).

Infants given probiotic containing *L rhamnosus* versus infants given probiotic not containing *L rhamnosus*: the test for subgroup difference was not significant (P = 0.06, I^2 = 71.8%; Analysis 3.9).

Mothers of infants who received antenatal probiotic versus mothers of infants who did not receive antenatal probiotic: the test for subgroup difference was not significant (P = 0.25, I^2 = 25.3%; Analysis 3.10).

Sensitivity analysis: eczema by 10 years by definition of allergic disease

See Supplementary material 9.

Sensitivity analysis: eczema by 10 years by risk of bias

See Supplementary material 9.

Allergic rhinitis by 10 years of age

Six studies reported this outcome (Abrahamsson 2007; Cabana 2007; Kalliomaki 2001; Niers 2009; Scalabrin 2009; Soh 2009). Probiotic may result in little to no effect in allergic rhinitis by 10 years of age (RR 1.11, 95% CI 0.75 to 1.66; I^2 = 21%; 6 studies, 912 participants; Analysis 3.3).

Anaphylaxis

No studies reported data on this outcome.

Potential harms including adverse effects, harms or infection with probiotic bacteria

Three studies reported this outcome.

Abrahamsson 2007 reported no serious adverse events in follow-up at seven years.

Lau 2012 reported no difference in adverse event prevalence between groups at all time points at one year, two years and three years of age.

Scalabrin 2009 reported the incidence of viral skin infection in the intervention group was significantly higher through year three. No serious adverse events correlated to consumption of intervention through year five.

In summary, probiotic may result in little to no difference in potential harms including adverse effects, harms or infection with probiotic bacteria at any point during the study intervention by 10 years of age (3 studies, 1124 participants; low-certainty evidence; narrative synthesis).

Synbiotic compared with no synbiotic

Asthma by 10 years of age

One study reported this outcome (Kukkonen 2006). The evidence is very uncertain about the effect of synbiotic on asthma by 10 years of age (RR 0.92, 95% CI 0.66 to 1.29; 1 study, 891 infants; Analysis 4.1).

Eczema by 10 years

One study reported this outcome (Kukkonen 2006). The evidence is very uncertain about the effect of synbiotic on eczema by 10 years of age (RR 0.91, 95% CI 0.78 to 1.06; 1 study, 891 infants; Analysis 4.2).

Sensitivity analysis: eczema by 10 years by risk of bias

See Supplementary material 9.

Allergic rhinitis by 10 years

One study reported this outcome (Kukkonen 2006). The evidence is very uncertain about the effect of synbiotic on allergic rhinitis by 10 years of age (RR 1.08, 95% CI 0.83 to 1.41; 1 study, 891 infants; Analysis 4.3).

Anaphylaxis

No studies reported data on this outcome.

Potential harms including adverse effects, harms or infection with probiotic bacteria

No studies reported this outcome.

Reporting biases

We were unable to pool more than 10 studies for most of the comparisons; we did not create a funnel plot to explore possible small-study and publication biases for these comparisons.

Funnel plot analysis of infant incidence of eczema by two years of age for infants with probiotic versus no probiotic supplementation did not suggest any substantial risk of publication bias (Figure 6).

DISCUSSION

Summary of main results

We included 24 RCTs, enroling 7077 mother–infant pairs in this updated review. Five of the studies were previously included in the published review [29], and 19 are new to this update. The population included all infants less than six months of age (both at risk of developing allergic disease and infants not selected for risk of allergy) for varying durations of probiotic, synbiotic or no probiotic (placebo or no treatment) supplementation in outpatient settings.

We identified three ongoing trials in this update. It is unclear whether the inclusion of these studies may influence the findings, conclusions and implications for research as reported in the review due to lack of data reported to date.

Probiotic compared with no probiotic

Probiotic may result in little to no difference in asthma, allergic rhinitis and IgE-mediated cow's milk protein allergy by two years of age. Probiotic may have little to no effect on the incidence of food allergy during infancy, but the evidence is very uncertain.

Probiotic may result in a slight reduction in eczema by two years of age; however, the sensitivity analysis of the studies at low risk of bias showed little to no difference in eczema by two years of age.

There were no serious adverse events that could be related to study intervention of probiotic reported. Studies reported mild adverse events that may be related to the study intervention of probiotics were no different between groups. In summary, probiotic may result in little to no difference in potential harms including adverse effects, harms or infection with probiotic bacteria at any point during the study intervention by two years of age.

Synbiotic compared with no synbiotic

The evidence is very uncertain about the effect of synbiotic on eczema by two years of age.

Synbiotics may result in little to no difference in food allergy by two years of age.

There were no data for the effect of synbiotics on asthma, allergic rhinitis and IgE-mediated cow's milk protein allergy by two years of age.

There were no serious adverse events related to study intervention of synbiotics reported. Synbiotics may result in little to no difference in potential harms including adverse effects, harms or infection with probiotic bacteria at any point during the study intervention by two years of age.

Limitations of the evidence included in the review

For certainty of the evidence, see Summary of findings 1 and Summary of findings 2.

The overall certainty of evidence according to the GRADE approach ranged from very low to low. Some studies had overall high risk of bias due to unclear allocation/randomisation processes, risk of bias from missing data and some concern over lack of prespecified intentions available. Most studies were judged to have overall some concern of risk of bias with only a few judged at overall low risk of bias.

Many outcome estimates were downgraded because of imprecision of estimates due to a smaller number of events leading to wide CIs. Not all studies reported the critical outcomes of interest, but most studies did report on eczema as a primary outcome (18 studies that used probiotics as an intervention, 3 studies that used synbiotics as an intervention). A sensitivity analysis including only studies at low risk of bias assessing the effect of probiotic on risk of eczema by two years of age suggested that study quality may have influenced the effect observed in the primary analysis. The certainty of evidence was downgraded due to risk of bias and inconsistency, reducing confidence in the generalisability of the effect estimations. Inconsistencies in this outcome may also reflect variation in how the presence of eczema was defined across included studies as no uniform diagnostic threshold was applied in this review.

Most included studies reported on the incidence of eczema as a primary outcome. However, there were limited data reported on the outcome of other allergic diseases such as allergic rhinitis, food allergy and cow's milk protein allergy. We were unable to undertake appropriate subgroup analyses to assess differences in

effect for infants with varying risk factors and feeding methods during childhood and adolescence due to limited data. Of the 24 studies included, only three studies reported the effect of synbiotic compared with no synbiotics; therefore, the effect of synbiotics on prevention of allergic disease remains unclear. The studies identified were conducted in many parts of the world, including the US, Europe, Asia (South Korea, Japan and Singapore) and Australia. With most studies being conducted in high-income countries, the applicability of our findings to other areas of the world remains unclear.

Limitations of the review processes

This review searched for published and unpublished studies, assessed the evidence for publication bias, extracted data using appropriately prespecified criteria for allergic diseases and IgE-mediated allergies, performed subgroup analyses to explore potential causes of heterogeneity and performed sensitivity analysis to explore the effect of study methodology. The data presented are from the intention-to-treat analyses reported from the trials or independently obtained from the study authors, reducing the potential for selection bias.

In this update, the critical and important outcomes of the review have been updated and may be considered as a source of bias. The differences between protocol and review update have been described in the Methods.

We made every effort to minimise bias in the review process. Two review authors independently performed study selection, extraction and assessment of biases, with any differences resolved by consensus and disagreements resolved by discussion with a senior review author. Two review authors independently assessed all included studies for the risk of bias using the RoB 2 tool [53]; we resolved disagreements by discussion with a senior review author to minimise the risk of bias in the review process.

There are numerous trials of probiotics that did not investigate allergic diseases outside of eczema including asthma and allergic rhinitis or food and cow's milk protein allergy (see table in Supplementary material 3). There was an insufficient number of studies available to investigate the potential risk of publication bias for all outcomes except eczema. We were unable to perform sensitivity analyses for several outcomes due to the small number of studies available. A number of studies reported outcomes for general eczema and atopic eczema. We performed a sensitivity analysis to investigate any potential effects that the definition of eczema may have had on the outcome, which revealed the importance of differentiating between eczema types as the evidence may be conflicting. However, this sensitivity analysis was limited by the small number of studies available (see table in Supplementary material 9).

Agreements and disagreements with other studies or reviews

Systematic reviews on the use of probiotics for eczema prevention have reported inconsistent results. Some reviews reported significant reductions in eczema risk with antenatal and postnatal probiotic use [276, 277], while others, including Cochrane reviews, found no effect on eczema treatment or severity [41].

Our findings are consistent with reviews indicating some reductions in eczema by two years of age with probiotic supplementation, but minimal impact on other allergic outcomes such as food allergies, allergic rhinitis and asthma [39, 43, 278]. The evidence reported in this review is very uncertain about the effect of synbiotics on eczema by two years of age. There is currently limited evidence to recommend the administration of synbiotics (and probiotics) in the prevention of allergic disease in children [279, 280].

In this review, we found that there were no serious adverse events and no significant differences in mild adverse reactions between the intervention and control groups. The absence of significant adverse events supports probiotics being well tolerated and associated with low risk of adverse events [281]. However, there is limited high-quality evidence available to conclude the clinical benefit of probiotic supplementation in infancy.

Differences in findings across systematic reviews may stem from the inclusion of "different strains, periods of intervention, and duration of supplementation (that) have hampered any definitive conclusions on the clinical impact of probiotics and/or prebiotics" for the prevention of allergic diseases [278]. Additionally, the heterogeneity across studies, particularly regarding strain combinations and varying risk of allergic disease, makes it difficult to establish recommendations. Our review includes studies up to 2023, capturing more recent trials compared to earlier reviews, which may contribute to differences in conclusions [39, 41, 43, 276, 277]. The evidence for the use of probiotics and synbiotics for allergic disease prevention has varied conclusions, highlighting the need for well-designed studies assessing the effects of both probiotics and synbiotics for allergy prevention.

AUTHORS' CONCLUSIONS

Implications for practice

Probiotic supplementation given to infants during the first six months of life may result in a slight reduction in the risk of eczema by two years of age, but may have little to no effect on other allergic diseases, including asthma, allergic rhinitis and immunoglobulin E-mediated cow's milk protein allergy by two years of age. Probiotics may have little to no effect on the incidence of food allergy by two years, but the evidence is very uncertain.

The effects of synbiotic supplementation during the first six months of life remain uncertain for eczema by two years of age and may result in little to no difference in immunoglobulin E-mediated food allergy by two years of age. There were no studies available that reported the effect of synbiotics on outcomes of asthma, allergic rhinitis and cow's milk protein allergy.

The available evidence showed no serious adverse events and no significant difference in mild adverse reactions between infants who received probiotic/synbiotic supplementation during the first six months of life.

However, there is insufficient evidence to conclude the effect of probiotics and synbiotics on preventing the development of allergic diseases during infancy and childhood. Although there were no serious adverse events reported for the use of probiotics in infants, incorporating probiotics and synbiotics into routine practice requires further information to support their use.

Implications for research

The prevalence of allergic disease is increasing in some areas of the world while stabilising in other areas [1, 2, 282, 283]. Nonetheless, allergic disease is one of the most common long-term health conditions in children. It contributes to a significant burden of disease on the individual, their families and the healthcare system. Unfortunately, there is currently no consensus for preventing the development of allergic diseases [3, 22], highlighting the importance of further study.

We identified three ongoing trials and five trials awaiting classification in this update. It is unclear whether the inclusion of these studies may influence the findings, conclusions and implications for research as reported in the review as no data have been reported to date.

The current evidence is limited by small sample sizes, inconsistent reporting and several studies being of some concern or high risk of bias. Many outcomes were downgraded due to imprecision and wide confidence intervals. Future research with standardised outcome measures including consistent eczema definitions is needed. There is the need for independent, adequately powered randomised controlled trials to determine the effect of probiotic or synbiotic supplementation in infants for the prevention of allergic diseases beyond eczema. Future randomised controlled trials conducted in different countries will improve the applicability to diverse populations. Additionally, as only three studies investigated synbiotic supplementation, further trials are needed to determine the role of synbiotics in the prevention of allergic disease.

SUPPLEMENTARY MATERIALS

Supplementary materials are available with the online version of this article: 10.1002/14651858.CD006475.pub2.

Supplementary material 1 Search strategies

Supplementary material 2 Characteristics of included studies

Supplementary material 3 Characteristics of excluded studies

Supplementary material 4 Characteristics of studies awaiting classification

Supplementary material 5 Characteristics of ongoing studies

Supplementary material 6 Risk of bias

Supplementary material 7 Analyses

Supplementary material 8 Data package

Supplementary material 9 Sensitivity analysis of primary and secondary outcomes

ADDITIONAL INFORMATION

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The methods section of this review is based on a standard template used by Cochrane Neonatal.

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- Sign-off Editor (final editorial decision): Robert Boyle, Imperial College London, UK
- Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Liz Bickerdike, Cochrane Central Editorial Service
- Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments and supported editorial team): Addie-Ann Smyth, Cochrane Central Editorial Service
- Copy Editor (copy editing and production): Anne Lawson, Cochrane Central Production Service
- Peer-reviewers (provided comments and recommended an editorial decision): Associate Professor Jennifer Koplin, University of Queensland (clinical/content review), Louisa Bontz-Goldbach (consumer review), Jo-Ana Chase, Cochrane Evidence Production and Methods Directorate (methods review), Steve McDonald, Cochrane Australia (search review)

Contributions of authors

HZW: assessed studies for eligibility, performed critical appraisal of eligible studies and data extraction, and formed a consensus on the conclusions for the 2023 review update; contacted authors of papers for additional information, entered data into Review Manager, analysed data, interpreted data; lead author in writing the 2023 review update.

EH: assessed studies for eligibility, performed critical appraisal of eligible studies and data extraction, and formed a consensus on the conclusions for the 2023 review update.

MF: wrote search strategies, search methods, results of search and PRISMA; and contributed to writing the review.

JS: contributed to cross-checking eligibility as a senior reviewer; involved in discussions during disagreements of critical appraisal of eligible studies and data extraction as a senior review author in the 2023 review update; and contributed to writing the review.

DO: wrote the published protocol and published review [29]; provided guidance and advice towards writing the review.

All authors reviewed and approved the manuscript.

Declarations of interest

HZW: none.

EH: none.

MF is employed by the Cochrane Neonatal Group, but did not participate in the editorial appraisal or acceptance of this review.

JS: none.

DO is a Senior Editor for the Cochrane Neonatal Group, but did not participate in the editorial appraisal or acceptance of this review.

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Registration and protocol

Protocol (2007): doi.org/10.1002/14651858.CD006475

Original review (2007): doi.org/10.1002/14651858.CD006475.pub2

Data, code and other materials

As part of the published Cochrane review, the following are made available for download for users of the Cochrane Library: full search strategies for each database; full citations of each unique report for all studies included, ongoing or awaiting classification, or excluded at the full-text screen, in the final review; study data, including study information, study arms, and study results or test data; consensus risk of bias assessments; and analysis data, including overall estimates and settings, subgroup estimates, and individual data rows. Appropriate permissions have been obtained for such use. Analyses and data management were conducted within Cochrane's authoring tool, Review Manager, using the inbuilt computation methods. Template data extraction forms from Covidence are available from the authors on reasonable request.

For data package details, see Supplementary material 8.

What's new

Date	Event	Description
13 June 2025	New search has been performed	Search updated December 2023; 12 new studies included (24 in total), 50 excluded, five awaiting classification, and three ongoing.
13 June 2025	New citation required and conclusions have changed	This review has been substantially updated with new studies and updated conclusion. EH, MF and HZW have been added as primary review authors, DO and JS are listed as senior review authors. Changes to methods included updated search dates, full risk of bias table and added summary of findings tables. The 2023 review update does not report on 'all allergic diseases' and food hypersensitivity as a primary outcome, urticaria is no longer reported as a secondary outcome.

History

Protocol first published: Issue 2, 2007
Review first published: Issue 4, 2007

Date	Event	Description
16 September 2009	New search has been performed	Substantive update Sept 2009
14 September 2009	New search has been performed	This updates the review "Probiotics in infants for prevention of allergic disease and food hypersensitivity" published in the Cochrane Database of Systematic Reviews, Issue 4, 2007 [29]. The review has been substantially updated with new studies and updated conclusion.
25 August 2008	Amended	Converted to new review format.
16 June 2007	New citation required and conclusions have changed	Substantive amendment

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ADDITIONAL TABLES

Table 1. Summary of included studies

Study	Infant allergy risk	Probiotic 1 (with/without prebiotic)	Probiotic 2	Control	Infant feeding	Duration
Abrahamsson 2007	1st-degree allergic relative	*L reuteri* 1 × 10^8 cfu/day suspended in coconut and peanut oil	—	Placebo: coconut and peanut oil	Predominately breastfed, weaned to hydrolysed formula if needed	Pregnancy: 4 weeks before delivery Infant: to 12 months
Allen 2014	Infants with and without 1st-degree allergic relative	*L salivarius* 6.25 × 10^9 cfu/day, *L paracasei* 1.25 × 10^9 cfu/day, *B infantis* 1.25 × 10^9 cfu/day and *B bifidum* 1.25 × 10^9 cfu/day	—	Placebo: maltodextrin	Predominately formula-fed	Pregnancy: 36 weeks' gestation until delivery Infant: from birth to 6 months
Cabana 2007	1st-degree allergic relative	*L rhamnosus* GG 1 × 10^9 cfu/day with inulin 225 mg	—	Placebo: inulin 325 mg	Predominately breastfed	Infant: from birth to 6 months

Table 1. Summary of included studies *(Continued)*

Dissanayake 2018	Healthy full-term infants	*B bifidum* 7 × 10^9 cfu/g combined with fructo-oligosaccharides 0.5 g twice a day	—	No treatment	Predominately formula-fed	Infant: to 6 months
Hascoët 2011	Healthy full-term infants	*B longum* 2 × 10^7 cfu/g in cow's milk formula	—	Placebo: cow's milk formula	Compared infants exclusively cow's milk formula-fed versus exclusively breastfed	Infant: up to 4 months
Kalliomaki 2001	1st-degree allergic relative	*L rhamnosus* GG 1 × 10^{10} cfu/day	—	Placebo: microcrystalline cellulose	Breastfed, weaned to formula if needed	Pregnancy: 2–4 weeks before delivery Infant: to 6 months
Kim 2010	1st-degree allergic relative	*B bifidum* 1.6 × 10^9 cfu/day, *B lactis* 1.6 × 10^9 cfu/day and *L acidophilus* 1.6 × 10^9 cfu/day in maltodextrin and alpha-corn	—	Placebo: maltodextrin and alpha-corn	Predominately breastfed	Pregnancy: 8 weeks before the expected delivery to 3 months after delivery Infant: to 4–6 months
Kopp 2008	1st-degree allergic relative	*L rhamnosus* GG 5 × 10^9 cfu/day	—	Placebo: microcrystalline cellulose	Breastfed, weaned to formula if needed	Pregnancy: 4–6 weeks before delivery Infant: to 6 months
Kukkonen 2006	1st-degree allergic relative	*L rhamnosus* GG 5 × 1 0^9 cfu/day; *L rhamnosus* LC705 5 × 10^9 cfu/day; *B breve* Bb99 2 × 10^8 cfu/day; *P freudenreichii* 2 × 10^9 cfu/day; GOS 0.8 g	—	Placebo: microcrystalline cellulose (mothers) or sugar syrup (infants)	Did not describe percentage of breastfed infants	Pregnancy: 4–6 weeks before delivery Infant: to 6 months
Lau 2012	1st-degree allergic relative	Non-pathogenic Gram-negative *E coli* Symbio and non-pathogenic Gram-positive *Enterococcus faecalis* Symbio (1.5–4.5 × 10^7 bacteria/mL) with a daily dosage of 3 × 0.7 mL, 3 times a day	—	Placebo: lactose monohydrate, sodium chloride, potassium chloride, magnesium sulphate, distilled water	Did not describe percentage of breastfed infants	Infant: week 5 to end of month 7
Morisset 2011	1st-degree allergic relative	*B breve* C50 (4.2 × 10^9 bacteria per 100 g of powder formula) and *S thermophilus* 065 (3.84 × 10^7 bacteria per 100 g of powder formula)	—	Placebo: control formula	Predominately breastfed	Infant: to end of breastfeeding Partial breastfeeding: to 12 months

Table 1. Summary of included studies *(Continued)*

Niers 2009	1st-degree allergic relative	*B bifidum* 1×10^9 cfu; *B lactis* W52 1×10^9 cfu (previously classified as *B infantis*), and *L lactis* 1×10^9 cfu in rice starch and maltodextrin	—	Placebo: rice starch and maltodextrin	Predominately breastfed	Pregnancy: last 6 weeks Infants: to 12 months
Ortiz-Andrellucchi 2008	No family history allergy	*L casei* dose not reported	—	Placebo: irradiated treatment product	Predominately breastfed, weaned to formula if needed	Infant: to 6 weeks
Plummer 2020	Not selected on basis of risk of allergy	*B infantis* 300×10^6 cfu, *S thermophilus* 350×10^6 cfu, and *B lactis* 350×10^6 cfu per 1.5 g in a maltodextrin base powder daily	—	Placebo maltodextrin powder	Predominately breastfed	Preterm infants: to discharge from hospital or 40 weeks' corrected age
Rautava 2006	Not selected on basis of risk of allergy	*L rhamnosus* GG and *B lactis* 1×10^{10} cfu/day	—	Placebo: (microcrystalline cellulose)	Compared infants breastfed and formula-fed, predominately breastfed	Infant: to 12 months
Rozé 2012	Not selected on basis of risk of allergy	*L rhamnosus*, *B infantis* and prebiotics: 96% GOS and 4% short-chain fructo-oligosaccharides	—	Placebo: control formula	Predominately formula-fed	Infant: to 6 months
Savino 2010	Breastfed infants diagnosed with infantile colic	*L reuteri* 10^8 cfu/day in sunflower oil and medium-chain triglyceride oil	—	Placebo: sunflower oil and medium-chain triglyceride oil	Predominately breastfed	Infant: for 21 days
Scalabrin 2009	Healthy term infants	Extensively hydrolysed casein formula supplemented with LGG 1×10^8 cfu/g	Partially hydrolysed whey: casein formula supplemented with LGG 1×10^8 cfu/g	Extensively hydrolysed casein formula	Formula-fed	Infant: for 120 days
Soh 2009	1st-degree allergic relative	*B longum 1* $\times 10^7$ cfu/g and *L rhamnosus* 2×10^7 cfu/g in cow's milk formula	—	Placebo: cow's milk formula	Predominately breastfed with added cow's milk formula	Infant: to 6 months
Taipale 2011	Healthy full-term infants	*B animalis* BB-12 10×10^9 cfu/day in xylitol tablet	—	Placebo: xylitol tablet	Predominately breastfed	Infant: 1–2 months to 8 months
Taylor 2006	1st-degree allergic relative	*L acidophilus* 3×10^9 cfu in water	—	Placebo: maltodextrin	Predominately breastfed, weaned to formula if needed	Infant: to 6 months

Table 1. Summary of included studies *(Continued)*

Vlieger 2009	Healthy term infants	*B animalis* 1×10^7 cfu/g and *L paracasei* 1×10^7 cfu/g in cow's milk formula with GOS 2.4 g/L	—	Placebo: cow's milk formula with GOS 2.4 g/L	Predominately cow's milk formula-fed	Infant: to 3 months
West 2008	Not selected on the basis of risk of allergy	*L paracasei* F19 1×10^8 cfu/serving in cereals containing milk proteins	—	Placebo: cereal without probiotic	Weaning to cereals. Did not describe percentage breastfed	Infant: 4–13 months
Wickens 2008	1st-degree allergic relative	*L rhamnosus* HN001 6×10^9 cfu	*B lactis* HN019 9×10^9 cfu	Placebo (dextran, salt and yeast extract).	Predominately breastfed, weaned to formula if needed	Pregnancy: 2–5 weeks before delivery Mother: 6 months if breastfeeding Infant: 0–2 years

B: *Bifidobacterium*; cfu: colony-forming unit; *E*: *Escherichia*; GOS: galacto-oligosaccharides; *L*: *Lactobacillus*; LGG: *Lactobacillus rhamnosus* GG; *P*: *Propionibacterium*; *S*: *Streptococcus*; W52: 52 weeks.

INDEX TERMS

Medical Subject Headings (MeSH)

Food Hypersensitivity [prevention & control]; Hypersensitivity [*prevention & control]; Milk Hypersensitivity [prevention & control]; Probiotics [adverse effects] [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans; Infant; Infant, Newborn