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BACKGROUND INFORMATION

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

1. Authors' full names

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3. Statement of author contributions

The EAACI task force was chaired by SH and AM and coordinated by GR. All authors jointly developed the content for this article. CS and DdS undertook searches and study selection, did preliminary quality appraisal for clinical review, extracted data, summarised findings and developed and refined the draft. SH, GR and AM critically reviewed the content. EK extracted additional data. All other authors contributed further refinements and quality assured the material in writing and verbally. GR, SH and AM acted as the final decision makers and guarantors.

All authors have made substantial contributions to the conception and design of this paper, collated and analysed data, been involved in drafting the manuscript or revising it critically for important intellectual content, given approval for publication and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

4. Running title, not exceeding 40 characters and spaces

Preventing food allergy: systematic review

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6. Word count; number of tables and figures

Abstract: 280 words
Main text: 6,943 words

Tables: 2
Figures: 2

This article covers 26 different interventions, which is why the article is over the usual word limit. The editorial team gave permission to submit a longer article. Only a sentence or short paragraph has been included about each intervention. Extra words have been added to accommodate the peer reviewers' requests. Inserting the numerical findings of each study into the main text (as requested by the reviewers) rather than including in a table has added significant words.

7. Material in the electronic repository, if applicable

Two online supplementary files.

JOURNAL ARTICLE

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

i. Statement with potential conflict of interests related to the manuscript content

The following authors declared no potential interests: CS, DdS, EA, EK, HA, SA, VV.

Some of the authors have professional affiliations related to the content of the review as set out below. During the conduct of the review itself, these authors were not involved in decisions about study selection, data extraction or analysis of studies in fields where they had a declared interest.

AM: Research: Aimmune; Speaker: DVB, Aimmune, Mylan, ALK, Nestle;

AH: Speaker: Nestle, Bristol-Myers, ALK;

CJ: Employee of Allergy UK. Allergy UK has received funding from Abbott, Aimmune, Allergy Therpeutics, DBV, Danone, Nutricia, Mead Johnson, Sanofi-Genzyme;

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GL: Research: NIH (LEAP study), Action Medical (EAT study). Consultant: DBV, Aravex, Aimmune, ALK, Novartis, Sanofi-Genzyme. Shareholder: DBV, Mission Mighty Me;

GR: Research: NIH (LEAP study), Action Medical (EAT study). Consultant: Nutricia. Editor: Editor in Chief, Clinical & Experimental Allergy;

HS: Consultant: Danone, Nestle, Nutricia. Speaker: Danone, Hipp, Nestle, Nutricia,. Editor: Journal of Ped Gastroenterology and Nutrition (to June 2019);

KB: Research: Aimmune, ALK, Berliner Sparkasson Stiftung, Danone, DBV, DST Diagnostic, Good Mills, Hipp, Hycor, Infectopharm, ThermoFisher, VDI, EU, German Research Foundation, BMBF. Consultant: AImmune, ALK, Allergopharma, Bausch & Lomb, Bencard, Danone, Hycor, Di-Text, Hammer und Rall Media, Infectopharm, Mabylon, Meda Pharma, Mylan, Nestle, Unilever;

KG: Consultant: Nutricia, Abbott, Mead Johnson, Reacta Biotech;

RB: Consultant: Diary Goat Cooperative, Cochrane Children and Families.

PE: Research: LETI, Nestle, ThermoFisher. Consultant: Danone, Novartis, ALK, DBV, Stallergens, Abbott. Editor: Editor in Chief PAI;

SH: Consultant: ALK. Research: ALK.

ii. Financial support

The European Academy of Allergy and Clinical Immunology (EAACI) funded the systematic review as a source of evidence to support the development of food allergy prevention guidelines. The funder had no role in the development of the protocol for the systematic review, the conduct or analysis of the review or the preparation or publication of the manuscript. The funder had no role in the decision to submit the review for publication.

iii. Abstract and keywords

Background

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

Methods

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

Results

Forty-six studies examined interventions to reduce the risk of food allergy in infancy (up to one year) or early childhood. The following interventions for pregnant or breastfeeding women and/or infants may have little to no effect on preventing food allergy but the evidence is very uncertain: dietary avoidance of food allergens, vitamin supplements, fish oil, probiotics, prebiotics, synbiotics and emollients.

Breastfeeding, hydrolysed formulas and avoiding cow's milk formula may not reduce the risk of cow's milk protein allergy, however temporary supplementation with cow's milk formula in the first week of life may increase the risk of cow's milk allergy.

Introducing well-cooked egg, but not pasteurised raw egg, from four to six months probably reduces the risk of hen's egg allergy. Introducing regular peanut consumption into the diet of an infant at increased risk beginning from four to 11 months probably results in a large reduction in peanut allergy in countries with a high prevalence. These conclusions are based on moderate certainty evidence, from single trials in high-income countries.

Conclusions

Sixty percent of the included studies were published in the last ten years, but much still remains to be understood about preventing food allergy. In particular, there is a need to validate the potential benefits of early introduction of food allergens in a wider range of populations.

Keywords: Food allergy, IgE-mediated, Prevention, Immediate-onset, Early introduction

iv. Main text

INTRODUCTION

Rationale

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

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

Other reviews have explored ways to prevent food allergy but guidelines cannot be based on these alone because they focused on single interventions or included studies of widely varying design.[4,5,6,7,8,9,10,11] Relevant studies were included in some past reviews but excluded from others (see online supplement S5).

Objective

The aim of this review was to assess the effectiveness of any approach (intervention) for preventing the development of immediate-onset / IgE-mediated food allergy (outcome) in infants, children and adults (population) compared to any other intervention or placebo (comparator).

METHODS

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

The methods are briefly described here. Details are available in the published protocol[12] and via the International Prospective Register of Systematic Reviews: CRD42019127457.

Eligibility criteria

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

- Population: infants (up to one year old), children (13 months to 17 years) and/or adults (18+ years) with or without an increased risk for developing allergic disease and with or without any sensitisation or atopic manifestations. 'Increased risk' was defined as having a condition associated with food allergy such as eczema or asthma or having immediate relatives with a history of any allergy, atopic dermatitis, asthma or hay fever.[13]

- Intervention: any intervention to prevent the development of new cases of immediate-onset food allergy

- Comparator: any independent, concurrently sampled group(s) with or without a placebo, intervention, or combination of interventions

- Outcomes: studies that reported new cases of immediate-onset food allergy, defined as a reproducible adverse response to a food protein within hours caused by an immunological reaction (hereafter referred to as 'food allergy')

- Timeframe: studies published from 1 January 1946 to 31 October 2019.

- Study types: published randomised controlled trials (hereafter 'trials') of any size and duration were eligible. Randomised trials of breastfeeding were limited so prospective cohort studies of breastfeeding with at least 1,000 participants at general risk or at least 200 participants at increased risk of food allergy were also eligible. Only published studies available in full form were included to allow full transparency. Where repeated reports of the same study were identified, the most up-to-date publication was included unless there were more relevant details in an earlier publication. There were no language or geographical restrictions.

Study selection and data extraction

An information specialist/methodologist (CS) developed a search strategy and searched 11 databases (online supplement S1). Two methodologists identified additional references by searching the reference lists of 35 previous reviews, guidelines and identified studies and seeking recommendations from experts (CS, DdS).

Two methodologists independently screened titles, abstracts and full text (CS, DdS). Shortlisted studies were rescreened by all clinicians and patient representatives on the task force (all authors) (kappa 0.96, SE 0.03, 95% CI 0.90 to 1.00). There was agreement about all but two studies (one where the outcome measure was not clearly identified as food allergy[14] and another where the extent of randomisation was uncertain[15]). The task force agreed by consensus to include these studies.

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

Risk of bias in individual studies

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

Synthesis of results and risk of bias across studies

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

The published review protocol[12] specified that meta-analysis to quantify effect size would be undertaken for outcomes with three or more studies about the same intervention in the same risk-

profile population. No intervention met the criteria for meta-analysis so results about each intervention were summarised using narrative synthesis.

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

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

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

RESULTS

Study characteristics

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

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

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

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

Overview of findings

Table 2 summarises key outcomes and Figure 2 lists the conclusions.

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

Avoiding food allergens

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

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

One trial examined avoiding cow's milk and egg during pregnancy (cumulative food allergy incidence 0-1.5 years RR 1.67, 95% confidence interval (CI) 0.38 to 7.22, p>0.05, very low certainty).[21]

Another examined milk and egg exclusion during the third trimester of pregnancy and whilst breastfeeding (cow's milk allergy cumulative incidence 0-1.5 years RR 1.01, CI 0.15 to 7.02, p>0.05, low certainty).[22]

Another trial examined dietary avoidance amongst breastfeeding women and infants for 12 months coupled with bedroom and living room treatments every three months (food allergy cumulative incidence 0-1 year RR 0.31, CI 0.07 to 1.41, p>0.05, very low certainty).[23]

Two trials combined food allergen avoidance with hydrolysed formulas (results described in formula section).[45,46]

Avoiding conventional cow's milk formula

Avoiding conventional cow's milk-based formula may not reduce cow's milk protein allergy in infancy or early childhood when the formula is consumed on a recurring basis (low certainty).

Seven trials examined this in general and increased risk infants[14,24,25,26,27,28,29] (see online supplement S3 for outcomes).

However avoiding temporary supplementation with cow's milk formula in the first three days of life may result in a large decrease in the risk of cow's milk protein allergy in early childhood (1 trial, cumulative incidence 0-2 years RR 0.10, CI 0.01 to 0.77, p<0.05, low certainty).[30]

Introducing hen's egg to the infant diet

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

One trial in high risk infants used cooked egg doses of 50mg and up per day (equivalent to 1/160th of an egg) from six to nine months and 250mg per day thereafter until 12 months (egg allergy at 1 year RR 0.22, CI 0.08 to 0.54, p<0.05, moderate certainty)[31] This trial used much smaller amounts of egg compared to other studies.

Early introduction of pasteurised raw hen's egg powder probably does not reduce the risk of egg allergy. One trial focused on infants at general risk (1 year prevalence RR 3.30; CI 0.35 to 31.32; p>0.05, low certainty).[32] Two trials were conducted in infants at increased risk (1 year prevalence RR 0.75; CI 0.48 to 1.17, p>0.05[33] and RR 0.65; CI 0.38 to 1.11, p>0.05,[34] low certainty).

Introducing peanut to the infant diet

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

Two trials introduced the equivalent of three heaped teaspoons of peanut butter per week (6g) to infants with severe eczema and/or egg allergy from four to 11 months (median 7.8 months) and maintained weekly intake for five years. One trial included infants with positive skin prick test to peanut and one without (overall RR for peanut allergy incidence at 5 years 0.18, CI 0.10 to 0.35, p<0.05, moderate certainty).[35,36]

Introducing multiple food allergens

Introducing multiple potential food allergens to the infant diet from three months probably does not reduce food allergy in infancy or early childhood. One trial in infants at general risk compared introducing peanut, cooked egg, cow's milk, sesame, whitefish, and wheat from three months versus exclusive breastfeeding to approximately six months (food allergy cumulative prevalence 1-3 years RR 0.8, CI 0.51 to 1.25, p>0.05, low certainty). Adherence was very low.[37]

Breastfeeding

Breastfeeding has many benefits for infants and mothers[38] but it may not reduce the risk of food allergy.

Five large prospective birth cohorts examined the link between breastfeeding and food allergy in general risk infants[39,40,41,42,43] and two studies focused on infants at increased risk[15,24] (cow's milk protein allergy RR ranged between 0.38 and 2.08, low certainty). Most studies did not include robust diagnostic criteria.

Hydrolysed infant formula

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

In increased risk infants, three out of four trials comparing partially hydrolysed formula with conventional cow's milk formula found little to no effect.[25-27] A small older trial that used food challenges found reduced cumulative incidence of cow's milk sensitivity (challenge-proven) at one year (RR 0.36, CI 0.15 to 0.89, p<0.05, very low certainty).[14]

Three trials of different extensively hydrolysed formulas found little to no effect on food allergy in infancy and early childhood (low certainty).[26-28] There was little to no evidence that one type of hydrolysed formula was more effective than others.[15,44]

Combining dietary avoidance of food allergens plus hydrolysed formula may have little to no effect on food allergy but the evidence is very uncertain. In those at increased risk, one trial examined extensively hydrolysed formula plus maternal/infant dietary avoidance (period prevalence 0-1 year RR 0.3, CI 0.12 to 0.77, p<0.05, very low certainty).[45] Another trial combined whey extensively hydrolysed formula for infants with an avoidance diet for mothers and infants (cow's milk allergy cumulative incidence 0-1.5 years RR 0.18, CI 0.01 to 3.37, p>0.05, very low certainty).[46]

Soy-based formula

Soy-based formula may have little to no effect on food allergy in early childhood but the evidence is very uncertain. One trial compared soy-based formula to cow's milk formula in infants at increased risk (cow's milk protein allergy cumulative incidence 0-2 years RR 1.35, CI 0.48 to 3.81, p>0.05, very low certainty).[25]

Vitamin supplements

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

In pregnant women at general risk, there was one trial of vitamin D daily from 27 weeks gestation to birth (food allergy cumulative incidence 0-3 years RR 1.92, CI 0.57 to 6.5, p>0.05, very low certainty).[47]

In breastfeeding women whose infants were at increased risk, one trial examined 6 weeks of vitamin D supplements (food allergy cumulative incidence 0-2 years RR 3.42, CI 1.02 to 11.77, p<0.05, very low certainty).[48]

In infants at general risk one trial compared a higher or lower dose of vitamin D from two weeks of age (food allergy cumulative incidence 0-1 year 1.33, CI 0.75 to 2.33, p>0.05, very low certainty).[49]

Fish oil

When taken in pregnancy alone, fish oil may not reduce food allergy in infancy (1 year incidence RR 0.65, CI 0.16 to 2.5, p>0.05, low certainty)[50] or in early childhood (3 year incidence RR 1.36, CI 0.59 to 3.11, p>0.05, low certainty).[51]

Fish oil supplements taken by women during both pregnancy and breastfeeding may reduce food allergy slightly in young children at increased risk, but the certainty of evidence is low. There was only one relevant trial (food allergy cumulative incidence 0-1 year RR 0.13, CI 0.02 to 0.95, p<0.05, low certainty).[52]

Fish oil for infants may have little to no effect on food allergy in infancy but the evidence is very uncertain. There was one trial in infants at increased risk (cumulative incidence 0-1 year RR 0.81, CI 0.47 to 1.40, p>0.05, very low certainty).[53]

Fish oil for mothers and infants combined may not reduce food allergy. One trial in pre-term infants examined mothers taking tuna oil and infants receiving a high DHA formula if needed as a supplement (cumulative incidence of food allergy 0-1.5 years 1.24, CI 0.62 to 2.50, p>0.05, low certainty).[54]

Prebiotics, probiotics and synbiotics

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

In general risk infants, one trial of prebiotics tested formula with oligosaccharides (scGOS/lcFOS) (cumulative incidence food allergy 0-1.5 years compared with standard formula 0.28, CI 0.28 to 1.00, p>0.05, very low certainty).[55]

Three trials examined various probiotics: *Lactobacillus acidophilus* for six months in general risk infants,[56] *Bifidobacterium infantis (BB-02), 155 Streptococcus thermophilus (TH-4)* and *Bifidobacterium lactis (BB-12)* until hospital discharge in very preterm general risk infants[57] and *Bifidobacterium breve C50* and *Streptococcus thermophilus (TH-4)* for one year in increased risk infants[58] (see online supplement S3).

Probiotics with or without prebiotics for women and infants may have little to no effect on food allergy but the evidence is very uncertain. For increased risk infants, one trial examined probiotics (*Lactobacillus rhamnosus GG*) taken by pregnant women and continued when breastfeeding or directly by infants for six months (cumulative incidence of cow's milk protein allergy 0-2 years RR 1.87, CI 0.74 to 4.69, p>0.05, very low certainty).[59] Another trial examined three strains of probiotics taken for six weeks by pregnant women and continued for a year by infants (*B. bifidum W23, Bifidobacterium lactis W52* and *Lc. lactis W58*) (data not reported, p>0.05, very low certainty).[60]

Two trials examined probiotics for women and infants combined with prebiotics for infants (*Lactobacillus rhamnosus GG (ATCC53103), L. rhamnosus LC705 (DSM 7061), Bifidobacterium breve Bb99 (DSM 13692), Propionibacterium freudenreichii ssp. shermanii JS (DSM 7076),* galacto-oligosaccarides) (food allergy cumulative incidence 0-2 years RR 0.89, CI 0.51 to 1.55, p>0.05, low certainty overall).[61,62]

In infants at general risk, one trial examined synbiotics (*Bifidobacterium bifidum OLB6378* plus fructo-oligosaccharides) from birth to six months (food allergy prevalence at 1 year RR 1.03, CI 0.63 to 1.68, p>0.05, low certainty).[63]

Non-antigen specific immune modulation

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

There was one trial of prophylactic house dust mite oral immunotherapy in increased risk infants (food allergy cumulative incidence 0-1 year 0.38, CI 0.1 to 1.9, p>0.05, very low certainty).[64]

There were two trials of BCG vaccination in general risk populations (food allergy prevalence at 1 year 1.17, CI 0.55 to 2.48;[65] cumulative prevalence 0-13 months RR 1.48, CI 0.67 to 3.29, p>0.05,[66] very low certainty).

Interventions begun in childhood and adulthood

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

DISCUSSION

Summary of evidence

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

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

Comparison with previous research

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

The findings of this review align with others in concluding that most interventions have limited evidence of effectiveness. This review is perhaps more conservative than some, because it took into account whether the intervention was in pregnant women, breastfeeding women or infants and whether it was in populations at general or increased risk of food allergy. Some other reviews have combined heterogeneous interventions with different timing, doses and population risk profiles in meta-analysis, but this may result in conclusions that are difficult to apply in practice. For instance, meta-analysis combining raw and cooked egg found a RR of 0.60 (CI 0.42 to 0.85)[67] The current review looked at raw and cooked egg separately, accounted for whether the population was at general or increased risk and excluded from this analysis studies that contained

multiple confounding interventions. Our conclusion is that at this stage there is only evidence that cooked egg has a preventive effect, not raw/pasteurised egg.

Other published meta-analyses, which pooled the results from studies with different populations and interventions, support the conclusions of this review.[68] For instance one meta-analysis concluded that hydrolysed formulas likely do not reduce the risk of food allergy compared to standard cow's milk formula (partially hydrolysed RR 1.73, CI 0.79 to 3.80, extensively hydrolysed RR 0.86, 0.26 to 2.82).[8] Another meta-analysis found that introducing peanut in the first year may reduce the risk of peanut allergy (RR 0.28, CI 0.14 to 0.57).[69] Another meta-analysis concluded that fish oil did not reduce the risk of food allergy when started in pregnancy (OR 0.46, CI 0.16 to 1.38) or given to infants (OR 0.34, CI 0.10 to 1.15).[70] The current review adds value by compiling all the highest quality studies about multiple topics in one place and by ensuring the most up-to-date research findings are added. 60% of the studies included in this review were published in the past decade.

Implications for practice and research

The implication for clinicians, families and policy-makers is that there is no evidence-based intervention to reduce food allergy for all infants. In those at increased risk, introducing peanut and cooked egg in the first year of life is likely to be beneficial. Large trials with longitudinal follow-up have concluded that this is safe and inexpensive to do,[35,37] although the research is confined to high-income countries and populations with high prevalence of specific allergies. The effect appears to be specific to egg and peanut allergy. There was no significant effect on other allergies, including other food allergies. Further research is needed to confirm the generalisability of these findings in general risk populations and low to middle-income countries.

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

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

Strengths and limitations

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

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

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

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

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

interventions were used simultaneously and whether diagnostic food challenges were performed. Variations in such factors make it difficult to draw conclusions to help clinicians and families translate research findings into real world use.

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

Conclusions

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

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

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vi. Figure legends

Figure 1: PRISMA diagram showing study selection

Figure 2: Summary of key conclusions

vii. Tables

Table 1: Wording conventions used in this article to summarise effect size

Certainty of evidence	Size of effect			
	None / minor / not clinically meaningful (0% to 39% relative change)	Small and important (40% to 60% relative change)	Medium (61% to 80% relative change)	Large (81%+ relative change)
High	X does not reduce / increase food allergy	X reduces / increases food allergy slightly	X reduces / increases food allergy	X results in a large reduction / increase in food allergy
Moderate	X probably does not reduce / increase food allergy	X probably reduces / increases food allergy slightly	X probably reduces / increases food allergy	X probably results in a large reduction / increase in food

				allergy
Low	X may not reduce / increase food allergy	X may reduce / increase food allergy slightly	X may reduce / increase food allergy	X may result in a large reduction / increase in food allergy
Very low	X may have little to no effect on food allergy but the evidence is very uncertain			

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

Table 2: Summary of effectiveness of interventions to prevent food allergy

Intervention	Timing/type	Absolute effect	Relative risk (95% CI)	Certainty of effect	Overall conclusion	Studies (participants)
Dietary avoidance of food allergens	Pregnancy	2% increase	0-1.5 years 1.67 (0.38 to 7.22)	Very low	Little to no effect	1 RCT (198)[21]
	Pregnancy and breastfeeding	0% change	Cow's milk 0-1.5 years 1.01 (0.15 to 7.02)	Very low	Little to no effect	1 RCT (164)[22]
	Pregnant and/or breastfeeding women and infants	8% to 11% decrease	0-1 year 0.31 (0.07 to 1.41) and 1 year prevalence 0.3 (0.12 to 0.77)	Very low	Little to no effect	2 RCTs (399)[23,45]
Avoiding standard cow's milk-based formula	Avoiding standard cow's milk formula	Range 22% decrease to 2% increase	See supplement for multiple outcomes	Low	May not reduce or increase	7 RCTs (4327)[14,24-29]
	Avoiding temporary supplement of cow's milk in first week of life	6% decrease	0-2 years cow's milk allergy 0.10 (0.01 to 0.77)	Low	Avoiding supplementation may decrease	1 RCT (312)[30]
Introducing complementary foods	Cooked hen's egg from 6 months	29% decrease	Egg allergy prevalence at 1 year 0.22 (0.08 to 0.54)	Moderate	Probably reduces	1 RCT (147)[31]
	Raw / pasteurised egg from 4 months	18% decrease to 2% increase	Egg allergy prevalence at 1 year range 0.65 to 3.3 (see supplement)	Low	May not reduce	3 RCTs (1289) [32-34]
	Peanut from median 7.8 months in increased risk	12% to 23% decrease	Peanut allergy incidence at 5 years range 0.14 to 0.35	Moderate	Probably large reduction	2 RCTs (640)[35,36]
	6 allergenic foods from 3 months	2% decrease	1-3 years 0.8 (0.51 to 1.25)	Low	May not reduce	1 RCT (1303)[37]
Breastfeeding	Infancy	Range 3% decrease to 2% increase	See supplement for multiple outcomes	Low	May not reduce	7 studies (15046)[15,24,39-42]
Hydrolysed formula	Partially hydrolysed in infancy	Range 34% decrease to 11% increase	See supplement for multiple outcomes	Low	May not reduce	5 RCTs (3572)[14,15,25-27]
	Extensively hydrolysed in infancy	Range 4% decrease to 2% increase	See supplement for multiple outcomes	Low	May not reduce	5 RCTs (3221)[15,26-28,44]
	Hydrolysed formula plus dietary avoidance	Range 9% to 11% decrease	0-1.5 years cow's milk allergy 0.18 (0.01 to 3.37)	Very low	Little to no effect	2 RCTs (470)[45,46]
Soy-based formula	Infancy	1% increase	0-2 years cow's milk allergy 1.35 (0.48 to 3.81)	Very low	Little to no effect	1 RCT (620)[25]

Intervention	Timing/type	Absolute effect	Relative risk (95% CI)	Certainty of effect	Overall conclusion	Studies (participants)
Vitamins	Pregnancy	6% increase	0-3 years 1.92 (0.57 to 6.5)	Very low	Little to no effect	1 RCT (180)[47]
	Breastfeeding	18% increase	0-2 years 3.42 (1.02 to 11.77)	Very low	Little to no effect	1 RCT (164)[48]
	Infancy	2% increase	0-1 year 1.33 (0.76 to 2.33)	Very low	Little to no effect	1 RCT (975)[49]
Fish oil	Pregnancy	Range 4% decrease to 1% increase	See supplement for multiple outcomes	Low	May not reduce	2 RCTs (789)[50,51]
	Pregnancy and breastfeeding	14% decrease	0-1 year 0.13 (0.02 to 0.95)	Low	May decrease slightly	1 RCT (145)[52]
	Infancy	3% decrease	0-1 year 0.81 (0.47 to 1.42)	Very low	Little to no effect	1 RCT (420)[53]
	Breastfeeding and infants	2% increase	0-1.5 years 1.24 (0.62 to 2.50)	Low	May not reduce	1 RCT (655)[54]
Prebiotics	Infancy	12% decrease	0-1.5 years 0.28 (0.08 to 1.0)	Very low	Little to no effect	1 RCT (240)[55]
Probiotics	Infancy	Range 2% to 4% decrease	See supplement for multiple outcomes	Low	May not reduce	3 RCTs (563)[56-58]
	Pregnancy, BF and/or infancy	10% increase	0-2 years cow's milk allergy 1.87 (0.74 to 4.69)	Very low	Little to no effect	2 RCTs (256)[59,60]
Prebiotics plus probiotics	Probiotics in pregnancy and infants plus prebiotic in infants	1% decrease	0-2 years 0.89 (0.51 to 1.55)	Low	May not reduce	2 RCTs (1116)[61,62]
Other	Synbiotics	0% change	Prevalence 1 year 1.03 (0.63 to 1.68)	Low	May not reduce	1 RCT (459)[63]
	Emollients	2% decrease	Prevalence 1 year 0.81 (0.49 to 1.33)	Low	May not reduce	1 RCT (459)[63]
	Prophylactic oral immunotherapy	6% decrease	0-1 year 0.38 (0.1 to 1.9)	Very low	Little to no effect	1 RCT (111)[64]
	BCG vaccination	0% change	0-13 months 1.48 (0.67 to 3.29)	Very low	Little to no effect	2 RCTs (4543)[65,66]

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

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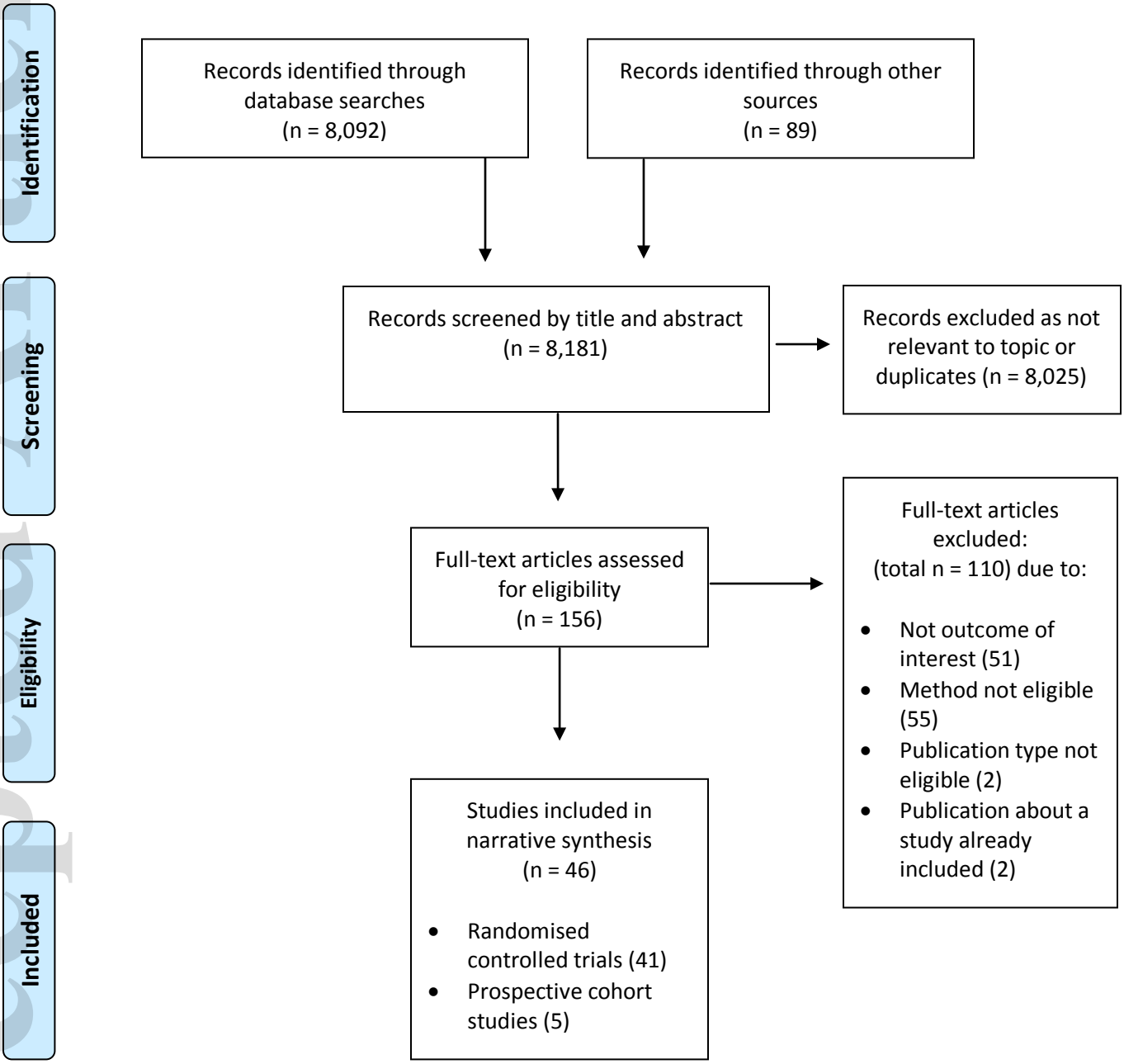

Figure 2: Summary of key conclusions

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