

REVIEW ARTICLE

Primary prevention of food allergy in children and adults: systematic review

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Abstract

Background: Food allergies can have serious physical, social, and financial consequences. This systematic review examined ways to prevent the development of food allergy in children and adults.

Methods: Seven bibliographic databases were searched from their inception to September 30, 2012, for systematic reviews, randomized controlled trials, quasi-randomized controlled trials, controlled clinical trials, controlled before-and-after studies, interrupted time series studies, and prospective cohort studies. Experts were consulted for additional studies. There were no language or geographic restrictions. Two reviewers appraised the studies using appropriate tools. Data were not suitable for meta-analysis due to heterogeneity, so were narratively synthesized.

Results: Seventy-four studies were included, one-third of which were of high quality. There was no good evidence to recommend that pregnant or breastfeeding women should change their diet or take supplements to prevent allergies in infants at high or normal risk. There were mixed findings about the preventive benefits of breastfeeding for infants at high or normal risk, but there was evidence to recommend avoiding cow's milk and substituting with extensively or partially hydrolyzed whey or casein formulas for infants at high risk for the first 4 months. Soy milk and delaying the introduction of solid foods beyond 4 months did not have preventive benefits in those at high or normal risk. There was very little evidence about strategies for preventing food allergy in older children or adults.

Conclusions: There is much to learn about preventing food allergy, and this is a priority given the high societal and healthcare costs involved.

People with food allergies suffer symptoms that affect both their health and lifestyle, so there is considerable interest in ways to reduce the risk of developing a food allergy. The causes of food allergy are likely related to both genetic factors and environmental exposure (1, 2). Genetic factors are not modifiable so strategies to prevent food allergy have focused on limiting early exposure to potential allergens antenatally or during breastfeeding, by changing what mothers eat in the hope that this will limit allergen exposure to their babies or boost protective mechanisms (3, 4). Prevention strategies may also directly target the infant formula and foods that babies and children consume (5). This review summarizes evidence about the most effective ways to prevent food allergy in children and adults.

The European Academy of Allergy and Clinical Immunology (EAACI) is developing *EAACI Guidelines for Food Allergy and Anaphylaxis*. This systematic review is one of the seven interlinked syntheses undertaken to provide a state-of-the-art synopsis of the evidence base in relation to the epidemiology, prevention, diagnosis, management, and impact on quality of life, which will be used to inform clinical recommendations.

Methods

Protocol and registration

The review was registered with the International Prospective Register of Systematic Reviews. The protocol has been published previously (6), so only brief details about the methodology are provided here.

Search strategy

The following databases were searched: Cochrane Library; MEDLINE, Embase, CINAHL, ISI Web of Science, TRIP Database, and Clinicaltrials.gov. Experts in the field were contacted for additional studies. Further details are included in the review protocol (6).

Inclusion and exclusion criteria

This review focused solely on studies that were primarily concerned with preventing sensitization to food(s) and/or the development of food allergy. Studies seeking to prevent potential manifestations of food allergy such as atopic eczema/dermatitis or asthma, but not including an explicit diagnosis of sensitization to food or food allergy, were not included.

Systematic reviews and meta-analyses, randomized controlled trials, quasi-randomized controlled trials, controlled clinical trials, controlled before-and-after studies, interrupted time series studies, and prospective cohort studies published up until 30 September 2012, were eligible. No language restrictions were applied and, where possible, relevant studies in languages other than English were translated.

Study selection

The titles and abstracts of articles were checked by two independent reviewers and categorized as included, not included, and unsure (DdS and MG). Full-text copies of potentially

relevant studies were obtained, and their eligibility for inclusion was independently assessed by two reviewers (DdS and MG). Any discrepancies were resolved by consensus or discussion with other reviewers (SH and AS).

Risk of bias assessment

Risk of bias was independently carried out by two reviewers (DdS and MG) using adapted versions of the Critical Appraisal Skills Programme (CASP) tool and the Cochrane Effective Practice and Organisation of Care Group (EPOC) Risk of Bias tools. An overall grading of high, medium, or low quality was assigned to each study.

Analysis, synthesis, and reporting

Two reviewers independently used a customized data extraction form to obtain data from each study (DdS and MG). Discrepancies were resolved by discussion. Experts in the field checked all of the data extraction for accuracy and relevance (SH and AH). Meta-analysis was not appropriate because the studies were heterogeneous in focus, design, target populations, and interventions. Findings were synthesized narratively by grouping studies according to intervention and target population. These syntheses were checked by a group of methodologists and experts to ensure accuracy and relevance.

Results

Study selection and characteristics

Figure 1 shows the PRISMA flowchart. Seventy-four studies were included, comprising 15 systematic reviews (20%), 32 randomized controlled trials (43%), nine nonrandomized comparative studies (12%), and 19 cohort studies (25%). Based on the risk of bias assessment, 25 of the studies were deemed to be of high quality (34%), 19 were of moderate quality (26%), and 30 were of low quality (40%), often due to small sample sizes or nonrandomized designs. Further details about each study are available in the online Supporting Information.

Most studies focused on preventing the development of food allergy from an early age (i.e., in unborn children and infants). Many studies focused on babies at high risk due to having a family history of allergy or atopy. Throughout the review, the term 'at high risk' is used as an abbreviation to mean that infants had an increased risk of developing food allergy or atopy due to a familial history of allergic disease. Table 1 summarizes the key findings.

Prevention strategies in pregnant women

High-risk families

Unborn children may be sensitized to the foods their mothers' consume (7, 8). Investigations have therefore been undertaken to establish whether avoiding particularly allergenic foods during pregnancy has an impact on the development of food allergy in their offspring, but the answer remains unclear. A systematic review (9) and two randomized controlled trials found no benefit from restricting common food allergens among pregnant women (10, 11).

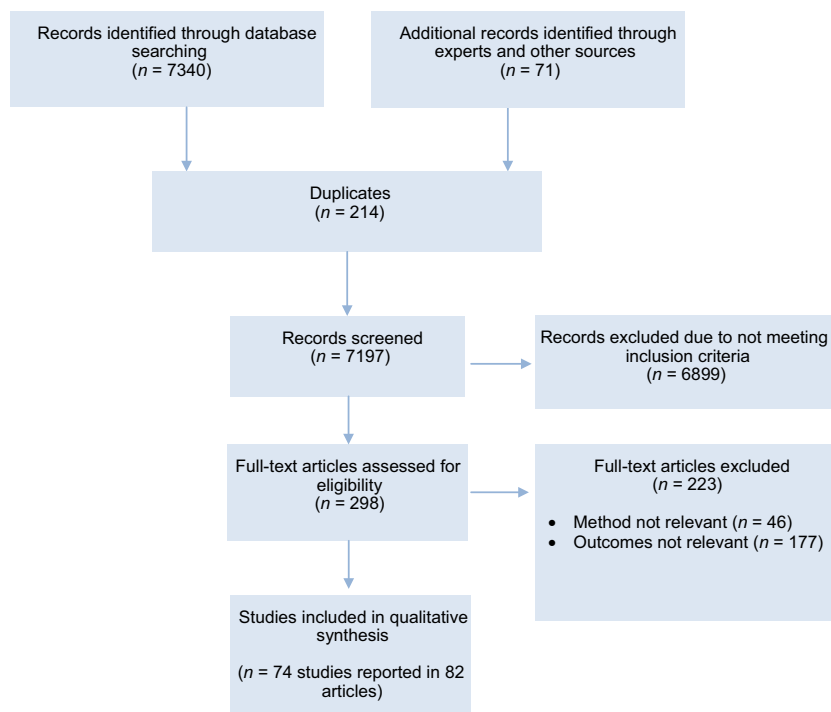


Figure 1 PRISMA flow diagram for selection of studies

Supplements to modulate the developing immune system are another approach that has received interest. Fish oil supplements may be worthy of further investigation because two randomized controlled trials suggested trends toward reduced sensitization to egg (12, 13), although there was no beneficial impact demonstrated on the development of food allergy (14). There was insufficient evidence about probiotics, with just one inconclusive trial identified about this (15).

Normal-risk families

In unselected populations, one study with results from two cohort studies suggested that what women eat during pregnancy may impact on food sensitization in infants. High maternal celery and citrus fruit intake increased infant sensitization to food (16, 17), but these studies have not been replicated and did not focus on allergy development, so there is no strong evidence to recommend changes to the diet of pregnant women to prevent food allergy in infants.

Prevention strategies for breastfeeding mothers

High-risk families

It has been hypothesized that mothers may inadvertently sensitize their children to certain foods through breast milk (18, 19), but there is little evidence that changing what mothers consume when breastfeeding prevents food allergy in infants. Two nonrandomized comparisons found that maternal dietary changes while breastfeeding may not prevent food allergies in high-risk infants (20, 21), and one trial of probiotics found no benefit (22).

Normal-risk families

One systematic review (23) and two randomized controlled trials (24, 25) found no differences in most infant allergy outcomes from fish oil supplements taken by unselected populations of breastfeeding women.

Prevention during infancy

High-risk families

More research has been published about preventive strategies targeting infants. Although breastfeeding is widely promoted and has many other benefits (26, 27), there is insufficient evidence to draw conclusions about its impact on preventing food allergies in high-risk infants. One systematic review identified many studies suggesting a benefit from exclusive and nonexclusive breastfeeding (1); in contrast, however, two cohort studies suggested that extended exclusive breastfeeding may increase the likelihood of sensitization or food allergy in infants at high risk (28, 29).

There is more positive evidence about the benefits of alternatives to cow's milk formula for babies at high risk. Two systematic reviews and three randomized trials suggested that extensively hydrolyzed whey or casein formula may have a protective effect (1, 30–33) although the evidence was conflicting (34).

Partially hydrolyzed infant formula also appears to have a protective effect. Although a small number of studies failed to find any benefit (35), two systematic reviews, two randomized controlled trials, and two nonrandomized comparisons found that partially hydrolyzed formula may protect against

Table 1 Summary of key evidence about prevention strategies

| Strategies | Studies | % high quality | Findings about preventive effects in those at high risk | Findings for normal risk or unselected populations |
|---|---------|----------------|--|---|
| Antenatal strategies | | | | |
| Maternal diet | 5 | 20 | One systematic review (9) and two randomized trials (10, 11) found no benefit | One study with results from two cohort studies found that different aspects of maternal diet may be associated with an increased risk of food allergy. High maternal celery and citrus fruit intake increased sensitization to food in infants (16, 17) |
| Maternal fish oil supplements | 2 | 50 | Two randomized trials suggested a preventive effect against egg sensitization (12, 13) | |
| Maternal probiotic supplements | 1 | 100 | One randomized trial found a benefit for sensitization, but was inconclusive overall (15) | |
| Strategies targeting breastfeeding mothers | | | | |
| Diet when breastfeeding | 2 | 0 | Two nonrandomized comparisons found no evidence of a protective effect for food allergy (20, 21) | |
| Probiotics when breastfeeding | 1 | 100 | One randomized trial found no protective effect (22) | |
| Fish oil when breastfeeding | 3 | 67 | | One systematic review (23) and two randomized trials found no good evidence of a benefit (24, 25) |
| Strategies targeting infants | | | | |
| Breastfeeding | 11 | 9 | One systematic review found that most studies of breastfeeding in those at high risk identified a protective benefit (1). Two cohort studies suggested no benefit and that exclusively breastfeeding may even increase the risk of food allergy (28, 29) | One systematic review (1) and three cohort studies found that breastfeeding was associated with a reduced risk of sensitization or food allergy (58–60), three cohort studies suggested an increased risk (61–63), and three cohorts found no association (64–66) |
| Alternatives to cows' milk formula | 18 | 44 | Two systematic reviews and four randomized trials found a benefit from extensively hydrolyzed whey or casein formula, (1, 30–33) although one study found no benefit (34). Two systematic reviews, two randomized trials, and two nonrandomized comparisons found a benefit from partially hydrolyzed formula compared with cows' milk formula (36–41). One randomized trial and one nonrandomized study found no effect (34, 35). One systematic review (36) and two randomized trials found no benefit from soy-based formula (43, 44) | |
| Infant prebiotic supplements | 2 | 50 | | One systematic review found insufficient evidence (67), and one trial found no benefits (68) |
| Infant probiotic supplements | 7 | 86 | Four trials found no evidence of a benefit (45–48) | Two systematic reviews (69, 70) and one trial (71) found no evidence of a benefit. |

Table 1 (Continued)

| Strategies | Studies | % high quality | Findings about preventive effects in those at high risk | Findings for normal risk or unselected populations |
|---|---------|----------------|--|--|
| Other supplements | 2 | 0 | | One trial and one cohort study found no evidence to recommend other supplements (72, 73) |
| Age at introduction of solid foods | 7 | 14 | Two cohort studies found no benefit from delaying the introduction of solid foods longer than 4 months (49, 50) | One systematic review (17) and two cohort studies found no benefit of delaying the introduction of solid foods longer than 4 months (17, 75). Two cohort studies found reduced food allergy when solids were introduced earlier than 4 months (64, 76) |
| Exposure to food allergens | 6 | 33 | One randomized trial found no benefit from withholding cows' milk or foods made with cow's milk during the first 4 months of infancy (51) | One systematic review and one trial found that exposure to cows' milk protein the first days of life did not alter the risk, (66, 78) but one trial and one cohort studies suggested an increased risk of cows' milk allergy (66, 78). One cohort study found that consumption of fish during infancy may protect against food allergy or sensitization (80) |
| Multifaceted strategies combining changes to environment and diet | 9 | 33 | Two randomized trials, two nonrandomized comparisons, and one cohort study found a benefit from combining dietary and environmental strategies (53–57). Two systematic reviews found insufficient evidence to make firm recommendations about preventive strategies (83, 84) | |
| Strategies for older children and adults | | | | |
| Vaccinations | 1 | 100 | | One systematic review found that BCG vaccinations had no protective effect against food allergy (80) |
| Supplements | 2 | 50 | | One review found no benefit from fish oil supplements (81). One cohort study found that taking vitamins before age five may protect against food allergy (82) |

food allergy compared with standard cow's milk formula (36–41). There appeared to be little difference between whey- or casein-based formulations or between partially or extensively hydrolyzed formulas.

There was no evidence to support soy-based formulas. One systematic review (42) and two randomized trials (43, 44) found that soy-based formulas may not protect against food allergies compared with cow's milk formula or other alternatives.

It is also unlikely that probiotic supplements confer preventive benefits during infancy. Four randomized controlled

trials found no benefit for preventing food allergy or sensitization (45–48).

Another strategy is to delay the introduction of solid foods. Infants may not need, or may not be physiologically ready to eat, solid foods until after the age of 4–6 months, but two cohort studies found that delaying the introduction of solid foods longer than 4 months did not seem to confer any protective benefits (49, 50). Another cohort study found that avoiding cow's milk or foods containing cow's milk for 4 months had no impact (51).

Although the quality of evidence is low, there is some evidence from six studies to suggest that combining dietary with environmental modifications during infancy may be useful (52–57). Further research in this area is needed because there are few data about specific food allergy outcomes, and it is difficult to differentiate cause-and-effect relationships.

Normal-risk families

The evidence about preventive strategies for infants in unselected populations or those at normal risk is also mixed. One systematic review (1) and three cohort studies found that breastfeeding was associated with a reduced risk of food allergy or sensitization in childhood (58–60), three cohort studies suggested an increased risk (61–63), and three cohort studies found no association in unselected populations (64–66).

There is no evidence to support prebiotics or probiotics to prevent food allergy in unselected or mixed-risk populations. One systematic review (67) found insufficient evidence, and one trial found no benefits from prebiotics (68). Two systematic reviews (69, 70) and one randomized trial (71) found no benefit from probiotics in unselected or mixed populations. One randomized trial (72) and one cohort study found no evidence to recommend other supplements (73).

One systematic review (74) and two cohort studies found that introducing solid foods after 4 months did not protect against food allergy in unselected populations (17, 75). Two cohort studies found reduced food allergy when solids were introduced earlier than 4 months (64, 76).

Studies have investigated whether exposure to cow's milk proteins in the first 3 days of life may protect against sensitization to foods. Two randomized controlled trials found that early exposure to cow's milk protein did not alter the risk of atopic symptoms (77, 78), but one cohort study and one randomized controlled trial suggested an increased risk of cow's milk allergy if children in unselected populations were fed cow's milk protein early (28, 66).

There is little other evidence about avoiding potential food allergens, although one cohort study found that consuming fish during infancy may protect against food allergy or sensitization (79).

Prevention during childhood and adulthood

Very little has been published about strategies to prevent food allergy development in children and adults, and all available studies are in unselected populations. One systematic review found that BCG vaccinations for children had no protective effect against food allergy (80), and another systematic review found no protective benefit from fish oil supplements for children and adults (81). A cohort study found that taking vitamins before age five may protect against food allergy, but the quality of this type of evidence is low (82).

Discussion

Statement of principal findings

This comprehensive and rigorously undertaken review indicates that there is much still to learn about how to prevent

the development of food allergy. Overall, the evidence is not strong enough to recommend changing the diet or supplements of pregnant or breastfeeding women at normal or high risk. While breastfeeding may have many other benefits, the evidence in relation to the prevention of food allergy is not strong. This to a large extent reflects the ethical challenges of randomizing infants to a nonbreastfeeding arm. There is more evidence about the benefits of alternatives to cow's milk formula for babies at high risk. Extensively hydrolyzed whey or casein formula and partially hydrolyzed formula may have a protective effect, but it appears that soy formula does not protect against food allergies. Probiotics do not seem to be protective in infants at high or normal risk, and neither does delaying the introduction of solid foods until later than the recommended minimum weaning age. Combining dietary with environmental modifications during infancy may be the best way forward for infants at high risk.

Strengths and limitations

This review included the most up-to-date research about preventing food allergy, with studies from Europe, North America, Asia, and Australasia. It was conducted using stringent international standards and drew on a substantially greater evidence base than previous reviews (83, 84).

However, the studies included were heterogeneous, and as a result, it was not appropriate to quantitatively synthesize this evidence. The inclusion criteria meant that studies about manifestations of food allergy such as atopic eczema, dermatitis, and asthma were not included unless food allergy or sensitization was also studied as an outcome. Furthermore, due to the mixed findings and small evidence base, we were unable to draw conclusions about the comparative benefits and risks of different prevention approaches, or to quantify potential effects.

There are also limitations with the studies themselves. To date, the focus of research has largely been on preventing IgE-mediated food allergy rather than on non-IgE-mediated food allergy. Many studies are small, short term and focus on the surrogate measure of food sensitization rather than food allergy. Sensitization may be a normal, harmless, and transitory phenomenon, which does not necessarily correlate with allergic disease.

Another issue is the extent to which research provides meaningful information for clinical practice. For example, many infants and young children grow out of their food allergy, especially those who are allergic to cow's milk protein during the first 3–5 years of life. To provide useful information, studies should include follow-ups from birth at regular intervals during the first years of life, as well as when the children have symptoms suggestive of food allergy. This would help to avoid claims that an intervention makes a difference when any change is merely a function of the natural course of the condition's progression.

Conclusions

Finding ways to prevent the development of food allergy would significantly reduce morbidity and costs of managing this

disorder (85). The evidence suggests that some interventions are unlikely to be useful, such as changing the diet or supplements of pregnant or breastfeeding women. However, other strategies appear more promising. There is evidence to support alternatives to cow's milk formula for babies at high risk, although changes to infant diet such as delaying the introduction of solid foods are unlikely to protect against food allergy. Combining environmental with dietary changes is feasible, but there is much work to be performed to identify the most effective strategies.

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Author contributions

AS, AM, DdS, and GR conceived this review. The review was undertaken by DdS, MG, and colleagues at The Evi-

dence Centre. DdS led the drafting of the manuscript, and all authors commented on the drafts of the manuscript and agreed the final version. SH provided detailed feedback at each stage. This review was undertaken as part of a series managed by SSP and overseen by AS.

Conflicts of interest

K. Grimshaw has received payment for attending and presenting at conferences hosted by Nutricia Ltd. L. O'Mahony has been a consultant to Alimentary Health Ltd. C. Venter has produced educational material for Danone, Mead Johnson and Nestlé and has received research funding from Ther-mofischer, Danone and Mead Johnson. The other authors of the paper declare no conflict of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Studies included in the systematic review.

Table S2. Quality assessment of systematic reviews.

Table S3. Quality assessment of primary studies.

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