Managing Food Allergy: Ga2len Guideline 2022

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Online supplement 1: methods used to compile evidence

This supplement sets out the methods we used to identify and compile evidence to inform our recommendations.

We undertook two systematic reviews and three rapid reviews using a systematic search strategy.

Protocols

Clinicians, patient representatives and methodologists worked together to agree and prioritize key questions of interest. These are listed in Box 2 in the main text. For each review question we agreed a protocol, setting out the population of interest, intervention, comparator, outcomes and search strategy.

Table S1.1 summarizes key points. The full protocols are available on request from the authors.

We undertook systematic reviews about allergen immunotherapy and biological therapies. We undertook rapid reviews about dietary interventions, risk identification and education. We used the same systematic search approach, but the rapid reviews used a simplified risk of bias assessment and the certainty of evidence was judged largely on the risk of bias in those reviews.

Study selection

An information specialist searched 6 databases for studies published between the beginning of the database and 30 April 2021 (CINAHL, Cochrane Library, EMBASE, ISI Web of Science, MEDLINE, Scopus). For the education topic, PsychInfo and ERIC were also searched. The search was updated to 30 September 2021 for biological therapies. There were no language or geographic restrictions.

The taskforce also reviewed the reference lists of reviews, guidelines and identified studies and contacted experts in the field for additional research.

Two methodologists independently screened the titles, abstracts and full text of potentially relevant studies. Shortlisted studies were rescreened by clinicians, allied health professionals and patient representatives (all authors) to reach consensus about what to include.

The Task Force divided into five working groups, with one group taking responsibility for each of the key clinical questions that we prioritized. Each working group rescreened the full text of potentially relevant papers and searched for others that met the inclusion criteria.

The inclusion criteria are listed in Table S1.1.

All reviews excluded studies of people with lactose intolerance or coeliac disease, all other reactions to food that have sometimes been referred to as ‘food intolerance’ and studies about other potential manifestations of food allergy such as eczema where there was not an explicit diagnosis of food allergy or a reported history of food allergy. Non-systematic reviews, discussion papers, non-research letters and editorials, case studies, observational studies (except for risk identification), animal studies, abstracts, studies not available in full form and unpublished material were excluded.

Where repeated reports of the same study were identified, we included and cited the most up-to-date or detailed unless there was a good clinical reason to include earlier write ups of the studies.

Data extraction

For all reviews, pairs of Task Force members extracted study characteristics and outcomes independently using a bespoke form. We compared the results to reach consensus. A senior clinician acted as an arbitrator if needed, but there was consensus.

The data extracted included citation details, country, population characteristics / subgroups, sample size, intervention, food allergens, efficacy and safety outcomes and outcome measurement approach, including time period.

Risk of bias in individual studies
Pairs of Task Force members and methodologists independently assessed the risk of bias in individual studies using the Cochrane Risk of Bias tool 2 (ROB2) for randomized controlled trials and ROBIN I for non-randomized studies. Arbitration was available if needed from a senior clinician but there was agreement in the risk of bias assessments.

In our rapid reviews we used all the category headings for ROB2 and ROBIN I, but the assessments were not independently agreed with methodologists.

Randomized controlled trials were assessed focusing on bias due to the (i) randomization process; (ii) assignment / deviations from intended group; (iii) missing data; (iv) outcome measurement; and (v) reporting. Each factor was rated as at low, moderate or high risk of bias, then an overall rating was assigned.

Non-randomized studies were assessed focusing on bias due to the (i) confounding (non-comparable groups); (ii) participant selection; (iii) how interventions were defined; (iv) changes from the intended intervention; (v) missing data; (vi) outcome measurement; and (vii) reporting. Each factor was rated as at low, moderate or high risk of bias, then an overall rating was assigned.

Synthesis of results
Table S1.2 gives the page numbers for where components of the AGREE II framework are summarized. We used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach to synthesize data about each outcome.

In the systematic review about immunotherapy, we pooled intention-to-treat data using random effects Mantel-Haenszel meta-analysis (Revman 5.4) because the studies included different populations, regimes and time periods and to avoid overweighting large but imprecise studies. We divided studies based on the food allergy and immunotherapy administration route. We undertook subgroup analysis based on risk of bias, age, allergy severity, comparator and threshold tolerated. In sensitivity analysis, we used a continuity correction (adding 0.05 to numerators and denominators) where there were no events in each study arm for severe or life-threatening events, anaphylaxis and adrenaline use.

In this system review we also used funnel plots to help assess publication bias. We quantified the heterogeneity of studies using the I2 statistic, with values less than 25% indicating low heterogeneity. We weighed up all of this information when creating evidence profiles and summary of findings tables.

In all of our other reviews, we synthesized the findings narratively because the data were insufficient or too heterogeneous to undertake meta-analysis.

All Task Force members developed conclusions by consensus, recognizing any potential conflicts of interest, which were declared in advance. We used standardized GRADE statements to summarize the conclusions. We used tables to summarize key findings and the other factors that we considered when creating recommendations. These are presented in Supplements 2-6.

TABLE S1.1: SCOPE OF THE REVIEWS

Characteristic	Education	Dietary interventions	Immunotherapy	Biological therapies	Risk identification
Review type	Rapid	Rapid	Systematic	Systematic	Rapid
Population	People reported with food allergy.	People diagnosed with food allergy	People with IgE-mediated food allergy confirmed with food challenge	People with IgE-mediated food allergy confirmed with food challenge	People with IgE-mediated food allergy or FPIES, confirmed with food challenge
Intervention	Education about managing food allergy for affected individuals and their family members	Any dietary interventions including elimination diets, infant formulas and supplements	Allergen immunotherapy alone or with a biological therapy; any route of administration	Biological therapy alone	Any predictor associated with more severe outcomes due to acute reactions: hospitalization, intensive care admission, death
Comparator	No intervention, another educational intervention or 'routine management'	Any comparator, placebo, no active intervention or 'routine management'	Placebo or no active intervention or 'routine management' as long as routine management did not involve an active treatment agent	Placebo or no active intervention or 'routine management' as long as routine management did not involve an active treatment agent	Not applicable
Outcomes of interest	Quality of life Effectiveness (improved knowledge or confidence) Adverse events (including anxiety Cost-effectiveness	Quality of life Effectiveness (fewer allergic reactions, tolerance) Adverse events (including growth, reactions) Tolerance development Cost-effectiveness	Quality of life Effectiveness (desensitization, sustained unresponsiveness) Adverse events Cost-effectiveness	Quality of life Effectiveness (tolerance) Adverse events Cost-effectiveness	Morbidity or mortality
Study types	Randomized controlled trials or prospective non-randomized studies with a simultaneous comparison group published in full as articles or research letters	Randomized controlled trials or prospective non-randomized studies with a simultaneous comparison group published in full as articles or research letters	Randomized controlled trials published in full as articles or research letters	Randomized controlled trials or controlled clinical trials published in full as articles or research letters	Systematic reviews; randomized controlled trials or controlled clinical trials; cohort studies with >50 blinded food challenges or >100 open food challenges; case-control studies with >100 cases; case series with >500 cases; for fatal or near-fatal outcomes, case series with n≥15. All reports published in full as articles or research letters
Databases searched	CINAHL, Cochrane Library, Embase, ERIC, ISI Web of Science, MEDLINE, PsychInfo, Scopus	CINAHL, Cochrane Library, Embase, ISI Web of Science, MEDLINE, Scopus	CINAHL, Cochrane Library, Embase, ISI Web of Science, MEDLINE, Scopus	CINAHL, Cochrane Library, Embase, ISI Web of Science, MEDLINE, Scopus	CINAHL, Cochrane Library, Embase, ISI Web of Science, MEDLINE, Scopus

SEARCH STRATEGIES

Dietary and education

Question
Which educational interventions and dietary interventions for people with food allergy are effective and cost-effective?

Inclusion criteria

- Study design: systematic reviews (to help identify other relevant studies only), randomised controlled trials, or controlled clinical trials (simultaneous control group, but not necessarily randomly assigned, includes quasi randomised, not before and after studies). Published as full article or research letter, not abstract
- Population: people with IgE-mediated or non-IgE-mediated food allergy. No requirement to confirm at outset by food challenge
- Intervention: any educational intervention for people with food allergy (not professionals); any dietary intervention for people with food allergy
- Comparator: placebo, routine management or other intervention
- Outcomes: efficacy, quality of life, adverse effects from intervention, cost-effectiveness
- Timeframe: Published from the beginning of databases (1946) to 30 April 2021

Search strategy for CINAHL, Cochrane Library, ISI Web of Science

(Food hypersensitivity or food allergy or milk allergy or egg allergy or nut allergy or peanut allergy or tree nut allergy or hazelnut allergy or legumes allergy or wheat allergy or soy allergy or fish allergy or seafood allergy or shellfish allergy or kiwi allergy or apple allergy or peach allergy or additives hypersensitivity or additives allergy or IgE)

AND

(educat* or info* or train* or course or simulation or leaflet or book* or online or peer or aid or visual or graphic or counsel* or psycho-social or social or diet* or formula* or probiotic* or avoid* or eliminat* or hydroly* or food label or psychologic*)

AND

(Intervention stud* or experimental stud* or trial or clinical trial* or randomi* controlled trial or random allocation or single blind method or double blind method or triple blind method or random* or quasi* or controlled clinical trial or economic evaluation* or cost effective* analys* or cost analys* or cost benefit analys* or cost utility analys* or cost consequence analys* or finances or quality of life or efficacy or desensiti* or sustained unresponsiveness)

Search strategy for MEDLINE and EMBASE

1. exp Food Hypersensitivity/
2. exp Milk Hypersensitivity/
3. exp Egg Hypersensitivity/
4. exp Peanut Hypersensitivity/
5. exp Tree nut Hypersensitivity/
6. exp Nut Hypersensitivity/
7. ((food or milk or egg or peanut or tree nut or hazelnut or brazil nut or walnut or chestnut or pistachio or almond or legumes or wheat or rice or soy or fish or seafood or shellfish or shrimp or lobster or crab or crawfish or kiwi or apple or peach or apricot or cherry or pear or plum or tomato

or green pea or potato or carrot or parsley or celery or additives or IgE) adj3 (allerg* or hypersensitivit*)).mp.
8. or/1-7
9. (educat* or info* or train* or course or simulation or leaflet or book* or online or peer or aid or visual or graphic or counsel* or psycho-social or social or diet* or formula* or probiotic* or avoid* or eliminat* or hydroly* or food label or psychologic*)
10. 8 and 9
11. exp Intervention Studies/
12. Intervention Studies.mp.
13. Experimental stud*.mp.
14. exp Clinical Trial/
15. Trial.mp.
16. Systematic review.mp.
17. Randomi?ed Controlled Trial.mp.
18. exp Placebos/
19. Placebos.mp.
20. exp Random Allocation/
21. Random Allocation.mp.
22. exp Double-Blind Method/
23. Double-Blind Method.mp.
24. Double-Blind design.mp.
25. exp Single-Blind Method/
26. Single-Blind Method.mp.
27. Single-Blind design.mp.
28. Random*.mp.
29. Quasi random*.mp.
30. Controlled clinical trial.mp.
31. Comparison.mp
32.. Cost.mp.
33. Exp Health care Costs/
34. Economic evaluation*.mp.
35. ((cost effective* adj1 analys*) or cost minimi?ation analys* or cost benefit analys* or cost utility analys* or cost consequence analys* or finances).mp.
36. Quality of life.mp.
37. Efficacy.mp.
38. Effective*.mp.
39. Or/11-38
40. 10 and 39

Risk

Inclusion criteria

Population: People with IgE-mediated food allergy or FPIES, confirmed either by food challenge or clinician-assessed history of severe reaction (e.g. anaphylaxis).
Study focus: Any predictor associated with more severe outcomes due to acute reactions: hospitalization, intensive care admission, death.
Outcomes: severe anaphylaxis; morbidity or mortality
See Table S1.1 for details of study types.

There were no language restrictions.

Search strategy

MEDLINE, EMBASE and the Cochrane Register of Controlled Trials were searched including all primary records from 1 January 2010 until 31 August 2021. Search strategy:

1. sever*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy] AND (food or peanut or milk or egg or wheat or LTP or nut or fish or seafood or crustac*).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy] AND allergy.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy]
2. limit 1 to human
3. (systematic or review or randomised or randomized or control* or placebo or cohort or observational or registry).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy]
4. 2 and 3

The reference lists of included studies and review articles were also reviewed to identify other relevant studies.

TABLE S1.2: LOCATION OF AGREE II POINTS IN THE GUIDELINE

Area	Location in guideline
DOMAIN 1. SCOPE AND PURPOSE	
1. The overall objective(s) of the guideline is (are) specifically described.	Introduction - final paragraph
2. The health question(s) covered by the guideline is (are) specifically described.	Box 2
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Introduction - final paragraph
DOMAIN 2. STAKEHOLDER INVOLVEMENT	
4. The guideline development group includes individuals from all relevant professional groups.	Methods - Approach to developing guideline
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Methods - Approach to developing guideline
6. The target users of the guideline are clearly defined.	Introduction - final paragraph
DOMAIN 3. RIGOUR OF DEVELOPMENT	
7. Systematic methods were used to search for evidence.	Methods - Review of the evidence
8. The criteria for selecting the evidence are clearly described.	Methods - Review of the evidence; Supplement 1 – Study selection; Table S1.1
9. The strengths and limitations of the body of evidence are clearly described.	Supplement 1 - Risk of bias in individual studies
10. The methods for formulating the recommendations are clearly described.	Methods - Review of the evidence; Supplement 1 - Synthesis of results
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Methods - Review of the evidence and S2 to 6 tables of benefits and risks
12. There is an explicit link between the recommendations and the supporting evidence.	Guideline recommendations; Tables S2.1, S3.1, S4.1, S5.1
13. The guideline has been externally reviewed by experts prior to its publication.	Methods - Peer review and public comment
14. A procedure for updating the guideline is provided.	Methods - Updating the guidelines
DOMAIN 4. CLARITY OF PRESENTATION	
15. The recommendations are specific and unambiguous.	Table 2
16. The different options for management of the condition or health issue are clearly presented.	Guideline recommendations
17. Key recommendations are easily identifiable.	Table 2
DOMAIN 5. APPLICABILITY	
18. The guideline describes facilitators and barriers to its application.	Table 4
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Table 4
20. The potential resource implications of applying the recommendations have been considered.	Table 4
21. The guideline presents monitoring and/or auditing criteria.	Table 4
DOMAIN 6. EDITORIAL INDEPENDENCE	
22. The views of the funding body have not influenced the content of the guideline.	Methods - Editorial independence and managing conflicts
23. Competing interests of guideline development group members have been recorded and addressed.	Methods - Editorial independence and managing conflicts

Online supplement 2: dietary interventions

TABLE S2.1: JUSTIFICATION FOR ELIMINATION DIET RECOMMENDATIONS

The GA²LEN Task Force suggests that people with a documented food allergy avoid the offending food unless their individual circumstances and risks allow for some consumption, as advised by their healthcare professional. We suggest that most breastfeeding mothers whose infants have a food allergy do not need to avoid the offending food themselves, though in rare cases this might be considered.

Intervention	Evidence of effectiveness	Benefits versus harms	Patient/care giver values	Feasibility and cost issues
Elimination diet for children and adults with any food allergy	Avoiding the offending food likely reduces reactions and symptoms, but the certainty of evidence is low due to few studies directly examining elimination diets. This means we cannot make a strong recommendation in favor of elimination diets. Most of the available evidence is in children with milk or egg allergy. 2 trials[1,2] (n = 296) and 2 non-randomized comparisons[3,4] (n = 93) found that eliminating hen's egg or cow's milk reduced reactions and/or improved symptoms in children. These studies and others about immunotherapy and infant formula focused on other interventions and used elimination diets as the control group.	Elimination diets are commonly recommended. The benefits, such as avoiding anaphylaxis and other symptoms from accidental exposure, [5,6] outweigh potential risks to nutrition and growth as long as people exclude only the offending food and do not have an unnecessarily strict diet. We make a conditional recommendation in favor of eliminating the allergen in recognition of the importance of avoiding severe reactions, but also the need to take into account people's individual reaction thresholds and risk of severe reactions and the need to maintain appropriate nutrition and unnecessarily strict diets.	Based on feedback from people with food allergy and their care givers and expert experience, people generally accept the need to avoid offending foods. However, it can be difficult to follow an elimination diet daily and this can impact on anxiety and social activities. It is therefore important to take an individualized approach when considering the extent of avoidance. This is why we do not make a strong recommendation in favor of universal avoidance.	Based on feedback from people with food allergy and care givers and expert experience, it is feasible to adhere to an avoidance diet if a) food allergy is formally diagnosed b) there is a thorough allergy diet history c) people with food allergy receive support from appropriate professionals such as a dietitian It can be costly to use substitute foods such as hypoallergenic milk formulas or gluten free alternatives. Reimbursement strategies differ by country. Therefore, it is important to focus on avoiding only the offending food. Heating some foods such as cow's milk and hen's egg may reduce the allergenicity and allow some people to consume products.[7,8] Young children with allergies to foods such as cow's milk and hen's egg may develop tolerance over time so diagnosis should be checked regularly to avoid unnecessarily long elimination diets.
Elimination diet in breastfeeding mothers whose infant has a food allergy	We found no eligible studies about the effectiveness of breastfeeding mothers avoiding the offending food if their infants had a food allergy. Our guidance on maternal dietary avoidance is therefore based on expert opinion and experience.	Breast-feeding is the best source of nutrition for infants. Clinical experience suggests that benefits of maternal avoidance do not outweigh potential harms such as reduced nutrition for the mother which can negatively impact on breastfeeding.[9]	Based on feedback from care givers and expert experience, it can be difficult for mothers to follow an elimination diet and this can impact on anxiety and social activities.	There is a fiscal burden with elimination diets. Feasibility issues may also lead mothers to consider reducing breastfeeding, which may in turn lead to increased costs for breastmilk substitutes. Very few infants react to the small amounts of food proteins in breastmilk.[10-12] In rare cases where a reaction is suspected while exclusively breastfed, the mother could try avoiding the offending food, with advice about maintaining nutrition for breastfeeding.

TABLE S2.2: JUSTIFICATION FOR INFANT FORMULA RECOMMENDATIONS

The GA²LEN Task Force suggests that most infants (aged 0-1 years) diagnosed with cow's milk allergy who need a breastmilk alternative use a documented hypoallergenic extensively hydrolyzed cow's milk formula, or an amino-acid based formula if better tolerated or more appropriate. We suggest against using partially hydrolyzed cow's milk formula, mammalian milks and, also for infants under 6 months, against soy-based formula.

The GA²LEN Task Force makes no recommendation for or against hydrolyzed plant-based formulas including rice hydrolysates that have been evaluated so far for managing food allergy in infancy.

Intervention	Evidence of effectiveness	Benefits versus harms	Patient/care giver values	Feasibility and cost issues
Extensively hydrolyzed cow's milk based infant formula documented to be hypoallergenic	Extensively hydrolyzed cow's milk formula may reduce symptoms and reactions for infants with cow's milk allergy. There is moderate certainty about this evidence, but some of the evidence is indirect or limited. We identified 10 trials (n = 705)[13-22] and 2 non-randomized comparisons (n = 38),[23,24] measuring the impact on cow's milk allergy symptoms. Extensively hydrolyzed cow's milk formula reduced allergy symptoms, but the trials compared different formulas and various comparators. We cannot say that one type of extensively hydrolyzed cow's milk formula is more effective than others. Some of these studies included other interventions such as pre/probiotics.	The benefits outweigh possible harms. Two additional studies were identified after we reviewed the evidence.[25,26] The trials did not identify any significant adverse effects. Different extensively hydrolysed cows' milk formulas are not identical and are heterogenic in composition.[27] The AAP and EAACI criteria for a product to be designated hypoallergenic is tolerance in 90% of children with cow's milk allergy.[28,29] Extensively hydrolyzed formulas that are documented hypoallergenic are well tolerated and do not negatively affect nutrition or growth.[30,31] The EU Commission and EFSA, FDA and AAP define hypoallergenic formulas as 'food for special medical purposes' and must fulfil the nutritional requirements of products classified as 'infant formula' WHO warns that any supplement may reduce breastfeeding.[32]	Breastfeeding is preferable, but when this is not possible the best alternative should be chosen based on a family's individual circumstances and preferences. The taste of the extensively hydrolyzed cow's milk based differs between brands. Two studies suggested that the palatability of whey based extensively hydrolysed formulas containing lactose may be more palatable.[33,34] If a child does not accept hypoallergenic products, the following could be tried: (i) mix and titrate the formula with breastmilk (do not store in mixed format to prevent autodigestion); (ii) mix and titrate with current formula if symptoms are not severe on current infant formula; (iii) use (alcohol free) vanilla drops to flavor the formula; (iv) a ready to feed formula may be better tolerated than a powdered one; (v) as a last resort, a few drops of milk shake syrups can be used for a few days; (vi) offer the formula in a cup/beaker or sippy cup in children who can use these.	Breastfeeding is low cost. Breast milk substitutes vary in cost and between countries. The price of extensively hydrolyzed formula may be higher than regular cow's milk based infant formula. Reimbursement differs in different countries.

Intervention	Evidence of effectiveness	Benefits versus harms	Patient/care giver values	Feasibility and cost issues
Amino acid-based infant formula	Amino acid-based formula may reduce symptoms and reactions for infants with cow's milk allergy. There is moderate certainty about this evidence, but some of the evidence is indirect or limited. 7 trials (n = 465)[35-41] and 1 non-randomized comparison (n = 18)[42] found a reduction in symptoms and allergic reactions from amino acid-based formula. The trials compared different formula with various comparators. Some were in children who did not tolerate extensively hydrolyzed formula and had poorer growth.	The benefits outweigh possible harms for selected children. Studies included in our rapid review found that amino acid-based formula supports normal growth[43-46] and may support longitudinal catch-up growth.[47,48] WHO warns that any supplement may reduce breastfeeding.[32] There are no data that suggest that amino acid-based formula delays the development of tolerance to cow's milk according to one study published after our review of the evidence.[49]	Breastfeeding is preferable, but when this is not possible the best alternative should be chosen based on a family's individual circumstances and preferences. We do not have evidence about the values and preferences of people with food allergy and care givers related to amino acid-based formulas to inform this recommendation. The formulas were well tolerated in most studies, but there is some experience that the taste can be off putting for some, particularly in older infants.	Amino acid-based formula is usually more expensive than other formulas so we do not suggest this as the first option to try in most cases. Reimbursement varies between countries We suggest this option for infants whose symptoms are not fully resolved with extensively hydrolyzed formula, those infants who are not thriving on extensively hydrolysed formula,[50] those eliminating multiple foods, those with severe complex gastrointestinal food allergies, eosinophilic esophagitis or symptoms while exclusively breastfeeding.
Partially hydrolyzed cow's milk based infant formula	There is very low certainty evidence about the effectiveness of partially hydrolyzed formula for managing cow's milk allergy in infants. 1 non-randomized comparison (n = 20) found no reduction in symptoms, and an increase in reactions to a partially hydrolyzed formula compared to extensively hydrolyzed formula.[51]	The possible harms, including risk of anaphylaxis, outweigh benefits. A number of publications that did not meet the eligibility criteria for our rapid review reported increased allergic reactions to partially hydrolyzed formula.[52-55]	Some infants may like the taste of partially hydrolyzed formula better than extensively hydrolyzed formula, but this is not a reason for recommending it as a way of managing food allergy. 'The product chosen has to be effective and safe.	The price may be higher than regular formula, but lower than extensively hydrolyzed formulas. Reimbursement varies between countries. Individual evaluation is important because some infants with a high threshold to cow's milk and mild symptoms may tolerate these products. However we do not suggest them for routine use, and these products should be used only after a careful individual assessment and advice from a healthcare professional.

Intervention	Evidence of effectiveness	Benefits versus harms	Patient/care giver values	Feasibility and cost issues
Mammalian milk such as goat and ass	There is very low certainty of evidence about the effectiveness of milk from other mammals for managing cow's milk allergy in infants 1 trial (n = 28) found no reduction in cow's milk allergy symptoms when using goats' milk whereas ass milk was better tolerated.[56]	The possible harms, including risk of anaphylaxis, outweigh benefits. There is a high degree of cross reactivity with cow's milk proteins, especially for goats milk (89%), whereas it is a lower (4-17%) for heated donkeys' milk or camels' milk.[57] Some observational or poor quality studies which did not meet our criteria for inclusion suggested that goat's milk may be associated with increased allergic reactions, including anaphylaxis, in a high proportion of children with cow's milk allergy.[57-61] The products may not be nutritionally sufficient. Other safe products are available.	We do not have evidence about the values and preferences of patients and caregivers to inform this recommendation.	In some countries these milks may be inexpensive compared to some alternatives but they may also be difficult to access in other countries. We suggest that these should only be used to manage cow's milk allergy in special circumstances and with caution. Further, they should be used only after 1 year of age, from advice from a healthcare professional and under supervision of the nutrition and growth of the child.

Intervention	Evidence of effectiveness	Benefits versus harms	Patient/care giver values	Feasibility and cost issues
Plant based infant formulas such as soy formula or partially hydrolyzed rice formula	We cannot draw conclusions about plant based hydrolyzed infant formulas for managing cow's milk allergy in infants because we have low certainty in the evidence. 3 trials (n = 350) found that soy-protein based infant formula reduced symptoms.[62-64] But 1 trial (n = 38)[65] and 3 non-randomized comparisons (n = 350) found no improvement in symptoms or tolerance with soy based infant formula compared to extensively hydrolyzed cow's milk[66,67] , or partially hydrolyzed rice formula.[68] Another trial (n = 92) found that partially hydrolyzed rice formula was as effective and well tolerated as extensively hydrolyzed cow's milk formula.[69] 1 trial (n = 52) found that almond drink was as effective as extensively hydrolyzed cow's milk and soy formulas.[70] We found no trials investigating the effect or safety of hydrolyzed soy-protein based formula	The possible harms outweigh benefits from some plant-based drinks/formulas. Plant based formulas have no nutritional advantage over cow's milk formulas. Position papers not eligible for our review report potential negative effects on growth and other adverse effects of plant-based drinks.[71,72] Soy-protein based formulas contain high concentrations of phytate, aluminum and phytoestrogens (isoflavones) which might have detrimental effects in the first 6 months of life.[72,73] Soy also contains glucose which may affect a baby's teeth. One trial of soy-protein based formula included in our review found allergic reactions to the formula, especially in infants younger than 6 months. After 6 months this was rare.[74,75] Studies have generally not found reduced growth in cow's milk allergic infants fed soy-protein based formula or rice hydrolysate.[76,77] Other safe products are available. There are concerns about possible arsenic levels in rice drinks.[78]	Families may wish to consider soy-protein based formula or rice based hydrolysates for infants who cannot have dairy-based products because of cultural, medical or religious reasons such as a vegan lifestyle, persistent lactose intolerance or galactosemia. In this case, the potential benefits and harms of soy and rice formulas/ hydrolysates should be discussed fully. For these families, infant soy based formulas could be considered, but preferably not until after 6 months of age; soy drinks are not appropriate. When breastmilk is not available a hydrolyzed rice formula can be used from birth.	Soy-protein based formulas and other plant based formulas are available in many countries, but are more expensive than breastfeeding and more expensive than cow's milk-based formula, though cheaper than extensively hydrolyzed cow's milk based and amino-acid infant formulas. Access to other plant-based infant formulas varies in different parts of the world. Other plant based drinks/formulas than soy- and rice based infant formulas, cannot replace breastfeeding or other infant formulas, but may be used as supplement after the age of one year.

Intervention	Evidence of effectiveness	Benefits versus harms	Patient/care giver values	Feasibility and cost issues
Other infant drinks / formulas: Chicken-based formula Home made meat based formula	There is very low certainty evidence about the effectiveness of other infant drinks/formulas. 2 trials found that chicken based formula was associated with fewer allergic reactions in infants with cow's milk allergy than soy formula (n = 38)[79] and extensively hydrolyzed cow's milk formula (n = 67).[80] 1 non-randomized comparison found that a home-made meat-based formula reduced the severity of atopic dermatitis induced by various foods (not solely cow's milk).[81]	There is insufficient evidence upon which to weigh up the potential harms versus benefits in food allergy so it is not possible to make an evidence-based recommendation about other infant drinks/formulas. There are risks related to home-made based formula outside of food allergy, which include nutritional content, renal solute load, osmolality and dehydration, food safety and allergic reactions due to ingredients.	We have no information about patient and care giver preferences and values related to other infant drinks.	Access to and use of other infant drinks / formulas varies in different parts of the world. It is probably not feasible in most places to use them routinely.

TABLE S2.3: JUSTIFICATION FOR SUPPLEMENTS RECOMMENDATION

The GA²LEN Task Force makes no recommendation for or against any prebiotics, probiotics or synbiotics that have been evaluated so far for managing food allergy, whether used as a supplement or added to formula.

Intervention	Evidence of effectiveness	Benefits versus harms	Patient/care giver values	Feasibility and cost issues
Probiotics as supplement	We found insufficient evidence to draw conclusions. The certainty of evidence was very low. We found 5 trials (n = 401), each about a different probiotic strain or combination of strains in people of different ages and with various food allergies. The strains assessed are listed in the supplementary tables. 2 trials found that probiotic supplements were associated with a slight reduction in food allergy symptoms[82,83] and 3 did not.[84-86]	We found insufficient evidence to draw conclusions. Of the 5 trials we identified, 4 did not provide data about adverse events and 1 found no difference in adverse events with probiotics.	There is limited evidence about patient and care giver preferences, and these preferences are likely to vary between individuals. Of the 5 trials we identified, none reported on quality of life.	There may be access and cost issues which preclude recommending this intervention routinely. There are a variety of strains and many have not been evaluated so far in clinical trials. Not all probiotics are the same. Each needs to be evaluated separately for its efficacy and safety
Probiotics added to infant formula for infants with cow's milk protein allergy	We found insufficient evidence to draw conclusions. The certainty of evidence was very low. We found 1 trial and 2 non-randomized comparisons of adding LGG to extensively hydrolyzed casein formula (n = 535) which resulted in small reductions in symptoms and suggested faster development of tolerance.[87-89] 3 trials of extensively hydrolyzed whey formula found that various probiotics were not associated with reduced symptoms (n = 95).[90-92] The strains assessed are listed in the supplementary tables. 2 trials comparing extensively hydrolyzed whey and casein formula found that adding various probiotics did not improve symptoms or tolerance (n = 191).[93,94]	We found insufficient evidence to draw conclusions. The trials reported that there were no adverse events from treatment. In some cases the potential benefits may outweigh the risks, except in immuno-compromised infants, but there is very low certainty of evidence and it is not advisable to group findings about different strains and different types of formula together.	There is limited evidence about patient and care giver preferences, and these preferences are likely to vary between individuals.	There may be access and cost issues which preclude recommending this intervention routinely. There are a variety of strains and many have not been evaluated so far in clinical trials. Not all probiotics are the same. Each needs to be evaluated separately for its efficacy and safety

Intervention	Evidence of effectiveness	Benefits versus harms	Patient/care giver values	Feasibility and cost issues
Prebiotics as supplement	We found insufficient evidence to draw conclusions. We identified no trials meeting our eligibility criteria.	We found insufficient evidence to draw conclusions.	There is limited evidence about patient and care giver preferences, and these preferences are likely to vary between individuals.	There may be access and cost issues which preclude recommending this intervention routinely. There are a variety of strains and many have not been evaluated so far in clinical trials.
Prebiotics added to infant formula	We found insufficient evidence to draw conclusions. We identified no trials meeting our eligibility criteria.	We found insufficient evidence to draw conclusions. One study not eligible for our review found no significant adverse events.[95]	There is limited evidence about patient and care giver preferences, and these preferences are likely to vary between individuals.	There may be access and cost issues which preclude recommending this intervention routinely. There are a variety of strains and many have not been evaluated so far in clinical trials.
Synbiotics as supplement	We found insufficient evidence to draw conclusions. We identified no trials meeting our eligibility criteria.	We found insufficient evidence to draw conclusions.	There is limited evidence about patient and care giver preferences, and these preferences are likely to vary between individuals.	There may be access and cost issues which preclude recommending this intervention routinely. There are a variety of strains and many have not been evaluated so far in clinical trials.
Synbiotics added to infant formula	We found insufficient evidence to draw conclusions. The certainty of evidence was very low. 1 trial of amino acid-based formula found that adding synbiotics did not improve symptoms (n = 110).[96] The strains assessed are listed in the supplementary tables.	We found insufficient evidence to draw conclusions. There was no negative impact on growth.	There is limited evidence about patient and care giver preferences, and these preferences are likely to vary between individuals.	There may be access and cost issues which preclude recommending this intervention routinely. There are a variety of strains and many have not been evaluated so far in clinical trials. Not all synbiotics are the same. Each needs to be evaluated separately for its efficacy and safety.

TABLE S2.4: NUMBER OF STUDIES SCREENED, INCLUDED AND EXCLUDED

Number of potential studies identified by database searches	2,135
Number of additional potential studies identified through other sources	12
Total number of studies screened once duplicates were removed	2,147
Number of studies shortlisted for full text review	50
Number of studies excluded after full text review	11
Number and type of studies included	39 (30 RCTs, 9 CCTs)

Note: see the end of this supplement for a list of the studies we excluded after screening the full text.

TABLE S2.5: DETAILS OF STUDIES INCLUDED

Study	Contributed to recommendation	Study type	Risk of bias	Region	Funding source	Total participants	Age	Allergy type	Severity of allergy	Intervention	Comparator
Agostoni 2007	Formula	CCT	Moderate	Europe	None	160	<5y	Cow's milk, soy	Moderate to severe	Soy formula	Casein hydrolysate or rice hydrolysate
Berni Canani 2012	Pre/pro/synbiotics	RCT	Moderate	Europe	Industry	55	<5y	Cow's milk	Moderate	Cow's milk formula and Lactobacillus rhamnosus GG	Free diet
Berni Canani 2013	Formula Pre/pro/synbiotics	CCT	High	Europe	None	260	<5y	Cow's milk	Moderate	Extensively hydrolyzed with LGG or amino acid-based formula or hydrolyzed rice formula or soy formula	Extensively hydrolyzed cow's milk formula
Berni Canani 2017	Formula Pre/pro/synbiotics	RCT	Moderate	Europe	Industry	220	<5y	Cow's milk	Moderate	Extensively hydrolyzed casein formula with Lactobacillus rhamnososus GG	Extensively hydrolyzed casein formula
Brouwer 2006	Pre/pro/synbiotics	RCT	High	Europe	Not industry	50	<5y	Cow's milk	Unknown	Extensively hydrolyzed whey formula with Lactobacillus rhamnosis or Lactobacillus GG.	Extensively hydrolyzed whey formula

Study	Contributed to recommendation	Study type	Risk of bias	Region	Funding source	Total participants	Age	Allergy type	Severity of allergy	Intervention	Comparator
Burks 2015	Formula Pre/pro/synbiotics	RCT	Low	USA	Industry	110	<5y	Cow's milk	Moderate	Formula with synbiotic blend: prebiotics: chicory-derived neutral oligofructose, long-chain inulin and pectin-derived acidic oligosaccharide. Combined with probiotic Bifidobacterium breve M-16V.	Amino acid-based formula
Caffarelli 2002	Formula	CCT	High	Europe	Unknown	20	<5y	Cow's milk	Moderate	Soy formula	Extensively hydrolyzed whey formula, partially hydrolyzed whey formula, extensively hydrolyzed casein formula, amino acid-based formula and cow's milk
Canani 2017	Formula	RCT	High	Europe	Industry	40	<5y	Cow's milk	Moderate	Amino acid-based formula	Extensively hydrolyzed whey formula

Study	Contributed to recommendation	Study type	Risk of bias	Region	Funding source	Total participants	Age	Allergy type	Severity of allergy	Intervention	Comparator
Candy 2018	Pre/pro/synbiotics	RCT	Moderate	Europe	Industry	71	<5y	Cow's milk	Moderate	Amino acid-based formula with synbiotic: prebiotic blend of chicory-derived neutral oligofructose and long-chain inulin and probiotic strain Bifidobacterium breve M-16V	Amino acid-based formula
Cantani 2006	Diet	CCT	High	Europe	None	51	<5y	Cow's milk, hen's egg	Unknown	Specific elimination diet	No intervention
DuPont 2014 Hol 2008 DuPont 2015 BJN	Formula	RCT	Low	Europe	Industry	75	<5y	Cow's milk	Unknown	Amino acid-based formula	Amino-acid formula
DuPont 2015	Formula	RCT	Low	Europe	Not industry	66	<5y	Cow's milk	Unknown	Extensively hydrlyzed casein based	Standard formula
Esmaeilzadeh 2018	Diet	RCT	High	Middle East	None	84	<5y	Cow's milk	Severe	Baked muffin followed by baked pizza	No intervention
Flinterman 2007	Pre/pro/synbiotics	RCT	High	Europe	Industry	13	<5y	Cow's milk, egg, peanut	Unknown	Probiotic strains (Lactobacillus (L.) acidophilus W55, L. casei W56, L. salivarius W57, Lactococcus (Lc.) lactis W58, Bifidobacterium (B.) infantis W52, B. lactis W18 and B. longum W51	Placebo
Helin 2002	Pre/pro/synbiotics	RCT	Low	Europe	Industry	36	13+ y	Apple	Mild	Lactobacillus rhamnosus	No intervention

Study	Contributed to recommendation	Study type	Risk of bias	Region	Funding source	Total participants	Age	Allergy type	Severity of allergy	Intervention	Comparator
Hill 1995	Formula	CCT	High	Australasia	None	18	<5y	Cow's milk, hen's egg, wheat, soy, peanut, mixed	Moderate	Soy formula	Casein hydrolysate, or whey hydrolysate formula
Isolauri 1995	Formula	CCT	High	Europe	None	45	<5y	Cow's milk, hen's egg, wheat	Moderate	Amino acid-based formula	Extensively hydrolyzed whey formula
Ivakhnenko 2013 and Ivakhnenko 2013	Pre/pro/synbiotics	RCT	High	Europe	None	60	<5y	Cow's milk	Moderate	Probiotics: Bifidobacterium lactis BB-12 and Streptococcus thermophilus TH-4	No intervention
Jirapinyo 2007	Formula	RCT	Moderate	Asia	Not industry	38	<5y	Cow's milk	Moderate	Chicken based formula	Soy formula
Jirapinyo 2012	Formula	RCT	High	Asia	Not industry	67	<5y	Cow's milk	Moderate	Chicken based formula	Extensively hydrolyzed casein formula
Kirjavainen 2003	Formula Pre/pro/synbiotics	RCT	High	Europe	Not industry	45	<5y	Cow's milk	Unknown	Extensively hydrolyzed whey formula with viable LGG or with heat inactivated LGG;	Extensively hydrolyzed whey formula
Klemola 2002 and Klemola 2005	Formula	RCT	Moderate	Europe	Industry	170	<5y	Cow's milk	Moderate	Soy formula	Extensively hydrolyzed whey formula
Majamaa 1997	Pre/pro/synbiotics	RCT	High	Europe	Not industry	27	<5y	Cow's milk	Moderate	Extensively hydrolyzed formula with probiotic: Lactobacillus GG	Extensively hydrolyzed formula

Study	Contributed to recommendation	Study type	Risk of bias	Region	Funding source	Total participants	Age	Allergy type	Severity of allergy	Intervention	Comparator
McLeish 1995	Formula	RCT	High	Europe	None	40	<5y	Cow's milk	Moderate	Amino acid-based formula	Extensively hydrolyzed whey formula
Niggemann 2001	Formula	RCT	High	Europe	Industry	73	<5y	Cow's milk	Moderate	Amino acid-based formula	Extensively hydrolyzed formula
Niggemann 2008	Formula	RCT	Low	Europe	Industry	65	<5y	Cow's milk	Moderate	Extensively hydrolyzed formula	Amino acid-based formula
Nowak-Wegrzyn 2015	Formula	RCT	Moderate	USA	Industry	37	<5y	Cow's milk	Unknown	New amino acid-based formula	Amino acid formula
Payot 2018	Formula	RCT	High	Europe	Industry	34	<5y	Cow's milk and mixed	Moderate	Amino acid-based yoghurt texture formula	Amino acid-based formula
Reche 2010	Formula	RCT	High	Europe	Industry	92	<5y	Cow's milk	Unknown	Hydrolyzed rice formula	Extensively hydrolyzed formula
Salpietro 2005	Formula	RCT	Low	Europe	None	52	<5y	Cow's milk	Moderate	Almond milk or, soy milk formula	Extensively hydrolyzed cow's milk formula
Savino 2005	Formula	CCT	High	Europe	None	88	<5y	Cow's milk	Unknown	Rice- based hydrolysate formula, soy formula, extensively hydrolyzed casein formula	Free diet
Seppo 2005	Formula	RCT	High	Europe	Not industry	168	<5y	Cow's milk	Mild	Soy formula	Extensively hydrolyzed whey formula
Sistek 2006	Pre/pro/synbiotics	RCT	Moderate	Australasia	Not industry	62	0-12y	Mixed	Unknown	Probiotics (Lactobacillus rhamnosus and Bifidobacteria lactis)	Placebo
Terheggen-Lagro 2002	Formula	RCT	Low	Europe	Industry	30	<5y	Cow's milk	Unknown	Extensively hydrolyzed casein based formula with amino acids	Standard formula

Study	Contributed to recommendation	Study type	Risk of bias	Region	Funding source	Total participants	Age	Allergy type	Severity of allergy	Intervention	Comparator
Terracciano 2010	Formula	CCT	Moderate	Europe	Unknown	72	<5y	Cow's milk	Moderate	Soy formula or rice hydrolysate formula	Cows' milk extensively hydrolyzed formula
Vandenplas 2013	Formula Pre/pro/synbiotics	RCT	High	Europe	Industry	116	<5y	Cow's milk	Mild	Extensively hydrolyzed whey formula with Bifidobacteium lactis	Extensively hydrolyzed casein formula with Lactobcilus GG
Viljanen 2005 PAI and Viljanen 2005	Pre/pro/synbiotics	RCT	Moderate	Europe	industry	230	<5y	Cow's milk	Moderate	Lactobacillus rhamnosus OR a mixture of probiotics: LGG 5x10^9 cfu, L. rhamnosus LC705 5x10^9cfu, Bifidobacterium breve Bbi99 2x10^8 cfu, and Propionibacterium freudenreichii ssp. Shermanii JS 2 x 10^9 cfu,	Placebo
Vita 2007	Formula	RCT	Moderate	Europe	None	28	<5y	Cow's milk	Moderate	Goat's milk	Ass' milk

Note: CCT = controlled clinical trial (non-randomized); RCT = randomized controlled trial

TABLE S2.6: SUMMARY OF RISK OF BIAS

Risk of bias in randomized trials

Study	Randomization process risk of bias	Risk of bias due to assignment	Risk of bias due to missing outcome data	Risk of bias due to outcome measurement	Risk of bias due to reported results	Overall risk of bias
Berni Canani 2012	Low	Low	Low	Low	Low	Low
Berni Canani 2017	Low	Low	Moderate	Low	Moderate	Moderate
Brouwer 2006	Low	Low	Low	High	Low	High
Burks 2015	Low	Low	Low	Low	Low	Low
Canani 2017	High	Moderate	Low	Moderate	Low	High
Candy 2018	Low	Moderate	Low	Low	Moderate	Moderate
DuPont 2014 Hol 2008 DuPont 2015 BJN	Low	Low	Low	Low	Low	Low
DuPont 2015	Low	Low	Low	Low	Low	Low
Esmaeilzadeh 2018	High	Moderate	Low	Moderate	Moderate	High
Flinterman 2007	High	Low	High	Low	Low	High
Helin 2002	Unclear	Low	Low	Low	Low	Low
Ivakhnenko 2013 and Ivakhnenko 2013	High	Low	Moderate	High	High	High
Jirapinyo 2007	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Jirapinyo 2012	High	Moderate	Moderate	High	Moderate	High
Kirjavainen 2003	High	Unclear	Unclear	Low	Low	High
Klemola 2002 and Klemola 2005	Low	Moderate	Low	Moderate	Moderate	Moderate
Majamaa 1997	High	High	Moderate	High	High	High
McLeish 1995	High	Low	High	Low	Low	High
Niggemann 2001	High	Moderate	Unclear	Moderate	Moderate	High
Niggemann 2008	Low	Low	Low	Low	Low	Low
Nowak-Wegrzyn 2015	Moderate	Low	Low	Low	Low	Moderate
Payot 2018	Low	High	Low	Low	Low	High
Reche 2010	Moderate	High	Low	Low	Low	High

Study	Randomization process risk of bias	Risk of bias due to assignment	Risk of bias due to missing outcome data	Risk of bias due to outcome measurement	Risk of bias due to reported results	Overall risk of bias
Salpietro 2005	Low	Low	Low	Low	Low	Low
Seppo 2005	Low	High	High	High	Moderate	High
Sistek 2006	Low	Moderate	Low	Low	Moderate	Moderate
Terheggen-Lagro 2002	Low	Low	Low	Low	Low	Low
Vandenplas 2013	Low	Low	High	Low	Moderate	High
Viljanen 2005 PAI and Viljanen 2005	Low	Moderate	Moderate	Low	Moderate	Moderate
Vita 2007	Low	Moderate	Low	Low	Low	Moderate

Risk of bias in non-randomized comparison studies

Study	Confounding	Selection issues	Issues defining interventions	Changes from intended interventions	Missing data	Measurement issues	Selective reporting	Overall risk of bias
Agostoni 2007	Low	Low	Low	Low	Low	Moderate	Moderate	Moderate
Berni Canani 2013	High	High	Low	Low	Moderate	Moderate	Low	Moderate
Caffarelli 2002	Low	Low	High	High	High	Low	Moderate	High
Cantani 2006	High	High	Low	Moderate	Low	Low	High	High
Hill 1995	Moderate	Low	Moderate	Low	High	Low	Low	High
Isolauri 1995	High	High	Low	Low	Low	Moderate	Low	High
Savino 2005	High	Moderate	Low	Moderate	Low	Low	High	High
Terracciano 2010	Low	Moderate	Low	Low	Low	Low	Low	Moderate

TABLE S2.7: REASONS WHY STUDIES SCREENED AS FULL TEXT WERE EXCLUDED

Note: many other studies were excluded after screening titles and abstracts

Study	Reason not eligible
Agata 1993	No control group with food allergy
Berni Canani R, Nocerino R, Leone L, Di Costanzo M, Terrin G, Passariello A, Cosenza L, Troncone R. Tolerance to a new free amino acid-based formula in children with IgE or non-IgE-mediated cow's milk allergy: a randomized controlled clinical trial. BMC Pediatr 2013;13:24.	Not RCT or CCT. All enrolled children had same study intervention/
Chafen JJ, Newberry SJ, Riedl MA, Bravata DM, Maglione M, Suttorp MJ, Sundaram V, Paige NM, Towfigh A, Hulley BJ, Shekelle PG. Diagnosing and managing common food allergies: a systematic review. JAMA 2010;303(18):1848-56	Systematic review. Studies eligible for this review were extracted individually.
de Silva D, Geromi M, Panesar SS, Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Cardona V, Dubois AE, Halken S, Host A, Poulsen LK, Van Ree R, Vlieg-Boerstra BJ, Agache I, Sheikh A. Acute and long-term management of food allergy: systematic review. Allergy 2014;69(2):159-67.	Systematic review. Studies eligible for this review extracted individually
Fiocchi A, Sarratud P, Terracciano L, Vacca E, Bernardini R, Fuggetta D, Ballabio C, Duranti M, Magni C, Restani P. Assessment of the tolerance to lupine-enriched pasta in peanut-allergic children. Clin Exp Allergy 2009;39(7):1045-51.	Not RCT or CCT. Investigated lupine tolerance in a group of children allergic to peanut
Giampietro PG, Kjellman NI, Oldaeus G, Wouters-Wesseling W, Businco L. Hypoallergenicity of an extensively hydrolyzed whey formula. Pediatr Allergy Immunol 2001;12(2):83-6.	Not RCT or CCT
Gorelova ZhIu, Ladodo KS, Levachev MM, Lupinovich VL, Mamonova LG, Orlova SV, Balabolkin II, Zadkova GF, Arutiunova MB. Role of polyunsaturated fatty acids in diet therapy of children with allergic diseases. Vopr Pitan 1999;68(1):31-5.	Text in Russian. Appeared not to be RCT or CCT
Halken S, PAI 1993, Safety of a new, ultrafiltrated whey hydrolysate formula in children with cow milk allergy: a clinical investigation. Pediatr Allergy Immunol 1993;4(2):53-9.	Not RCT or CCT
Hill DJ, Murch SH, Rafferty K, Wallis P, Green CJ. The efficacy of amino acid-based formulas in relieving the symptoms of cow's milk allergy: a systematic review. Clin Exp Allergy 2007	Systematic review. Studies eligible for this review extracted individually
Inuo C, Tanaka K, Nakajima Y, Yamawaki K, Matsubara T, Iwamoto H, Tsuge I, Urisu A, Kondo Y. Tolerability of partially and extensively hydrolyzed milk formulas in children with cow's milk allergy. Asia Pac J Clin Nutr 2019;28(1):49-56.	Outcome not relevant
Luniakov AS, Shirina LI, Kruglik VI, Shatskaia NG. Use of new domestic foodstuffs in the treatment of digestive system diseases with food intolerance. Vopr Pitan 1993;(5):25-7.	Text in Russian. Appeared not to be RCT or CCT
Paparo L, Nocerino R, Bruno C, Di Scala C, Cosenza L, Bedogni G, Di Costanzo M, Mennini M, D'Argenio V, Salvatore F, Berni Canani R. Randomized controlled trial	Outcome not relevant

Study	Reason not eligible
on the influence of dietary intervention on epigenetic mechanisms in children with cow's milk allergy: the EPICMA study. Sci Rep 2019;9(1):2828.	
Pohjavuori E, Viljanen M, Korpela R, Kuitunen M, Tiittanen M, Vaarala O, Savilahti E. Lactobacillus GG effect in increasing IFN-gamma production in infants with cow's milk allergy. J Allergy Clin Immunol 2004;114(1):131-6.	Outcome not relevant
Qamer S, Deshmukh M, Patole S. Probiotics for cow's milk protein allergy: a systematic review of randomized controlled trials. Eur J Pediatr 2019;178(8):1139-1149.	Systematic review. Studies eligible for this review extracted individually
Sampson HA, Bernhisel-Broadbent J, Yang E, Scanlon SM. Safety of casein hydrolysate formula in children with cow milk allergy. J Pediatr 1991;118(4 Pt 1):520-5.	Not RCT or CCT
Sampson HA, James JM, Bernhisel-Broadbent J. Safety of an amino acid-derived infant formula in children allergic to cow milk. Pediatrics 1992;90(3):463-5.	Not RCT or CCT
Santos SCD, Konstantyner T, Cocco RR. Effects of probiotics in the treatment of food hypersensitivity in children: a systematic review. Allergol Immunopathol 2020;48(1):95-104.	Systematic review. Studies eligible for this review extracted individually
Scalabrin D, Harris C, Johnston WH, Berseth CL. Long-term safety assessment in children who received hydrolyzed protein formulas with Lactobacillus rhamnosus GG: a 5-year follow-up. Eur J Pediatr 2017;176(2):217-224.	Not eligible for our review. Investigated healthy children, no food allergy
Scott JF, Hammond MI, Nedorost ST. Food avoidance diets for dermatitis. Curr Allergy Asthma Rep 2015;15(10):60.	Systematic review. Not relevant. On dermatitis, not food allergy
Stróżyk A, Horvath A, Meyer R, Szajewska H. Efficacy and safety of hydrolyzed formulas for cow's milk allergy management: A systematic review of randomized controlled trials. Clin Exp Allergy 2020;50(7):766-779.	Systematic review. Studies eligible for this review extracted individually
Tang ML, Ponsonby AL, Orsini F, Tey D, Robinson M, Su EL, Licciardi P, Burks W, Donath S. Administration of a probiotic with peanut oral immunotherapy: A randomized trial. J Allergy Clin Immunol. 2015;135(3):737-44.e8.	Not eligible for our review. Study is about OIT
Zibaee S, Hosseini SM, Yousefi M, Taghipour A, Kiani MA, Noras MR. Nutritional and therapeutic characteristics of camel milk in children: a systematic review. Electron Physician 2015;7(7):1523-8.	Systematic review. No studies eligible for this review included.

Online supplement 3: allergen immunotherapy

This supplement summarises our reasoning behind recommendations about allergen immunotherapy. The recommendation justifications are summarised first, followed by details about the studies we included in drawing our conclusions.

TABLE S3.1: JUSTIFICATION OF RECOMMENDATION FOR PEANUT ORAL IMMUNOTHERAPY

The GA2LEN Task Force recommends offering peanut oral immunotherapy under specialist supervision with standardized evidence-based protocols using peanut products (or licensed pharmaceutical products, where appropriate), to selected children (aged 4+ years) with clinically diagnosed, severe, IgE-mediated, peanut allergy to increase the amount of peanut tolerated while on therapy.

Intervention	Evidence of effectiveness	Benefits versus harms	Patient/care giver values	Feasibility and cost
OIT in children with peanut allergy	We have high certainty evidence that children with IgE-mediated allergy to peanuts tolerate significantly more peanut while on therapy (RR 6.50, 95%CI 3.31-12.75, N=888) (desensitization).[97] The number needed to treat to achieve 1 child tolerating 300mg or 1000mg peanut protein as a single dose while on therapy was 2. There is low certainty evidence that this benefit persists after therapy discontinues (RR 8.75, 1.24-61.57, n=85). The impact on quality of life is unclear due to very low certainty evidence.	Overall, the benefits of OIT for peanut allergy outweigh the risks in selected children. There was no difference in adverse events between the OIT and control group (RR 1.07, 95% CI 0.99 to 1.16, n=953). Severe reactions were rare and not significantly different between OIT and control groups (RR 1.55, 95%CI 0.69 to 3.48, n=950).[97] However, some studies have excluded extremely allergic individuals so safety in these individuals is unclear A systematic review meta-analysed the different quality of life outcomes used in OIT studies. They found a -0.56 (95%CI -0.92 to -0.20) standardised mean difference between active and control, which means that immunotherapy may improve quality of life.[98] Eosinophilic esophagitis has been reported in relation to OIT, although its prevalence is unknown due to a high rate of transient abdominal symptoms compatible with EoE[99,100] but endoscopic confirmation lacking in most of these individuals.	OIT needs a considerable investment in time from the family. It may also be associated with local adverse effects so some families may prefer to avoid peanut instead. Adherence is important and should be considered especially with adolescents. However, desensitization may be valuable to people with food allergy as it reduces the chance of experiencing a reaction with packaged foodstuffs containing peanut accidentally.[105] Although OIT is associated with adverse events, care givers report that these events are “expected” during the treatment and families are well trained and closely monitored to deal with them better than with the uncertainty of unexpected reactions of full avoidance.[106] However there is likely a need for lifetime therapy given the low rate of sustained unresponsiveness.[97]	A pharmaceutical product has been licensed in Europe and the United States. Many other groups have used non-pharmaceutical formulations.[103,104,107] In some EU countries only licensed products will be allowed . This is based on the consideration that they have been developed according to Good manufacturing practice (GMP) for ensuring consistency of allergen content and biologic potency across the doses and product batches. Treatment is usually given daily, for years, and this represents a significant burden, which may result in lack of adherence and subsequent loss of protection and rise in accidental reactions.[108-109] In the mid/long term, the taste of the treatment may become an issue.[107] Treatment needs to be provided in an appropriate setting by experienced doctors but these centres are not equally distributed,

Intervention	Evidence of effectiveness	Benefits versus harms	Patient/care giver values	Feasibility and cost
		The baseline reactivity threshold of people included in most trials is very low, ranging from 10mg[101] up to 122mg[102] of peanut protein. It is unclear whether the risk/benefit balance remains the same in people with higher reactivity thresholds Given the logistics around peanut oral immunotherapy and the potential for reactions, we consider that it is indicated in children with severe peanut allergy. This includes those with a substantial risk of severe reactions and those with substantially impaired quality of life. This has to be a shared judgement between the healthcare professional and family. There is some evidence that OIT may reduce the severity of the reactions in addition to increasing the threshold for reaction.[101,103,104]		leading to inequity in access to treatment.[110] Some precautions when administering the treatment are significantly limiting: avoiding exercise/hot shower, infections, intake of NSAIDs, fasting or other cofactors.[111] One US health economics study estimated a high incremental cost effectiveness ratio of $255 431 for an 80 year time horizon based on societal costs, but this has not been replicated.[112]

TABLE S3.2: JUSTIFICATION OF RECOMMENDATION FOR PEANUT EPICUTANEOUS IMMUNOTHERAPY

The GA2LEN Task Force suggests offering peanut epicutaneous immunotherapy under specialist supervision using licensed pharmaceutical products if they become available to selected children aged 4-11 years with clinically diagnosed, severe, IgE-mediated, peanut allergy to increase the amount of peanut tolerated while on therapy.

Intervention	Evidence of effectiveness	Benefits versus harms	Patient/care giver values	Feasibility and cost
EPIT in children with peanut allergy	This recommendation is based on moderate certainty evidence for individuals with IgE-mediated allergy to peanuts tolerating significantly more peanut while on therapy (RR 2.63, 95%CI 1.79 to 3.84, n=651).[97] The effectiveness appears to be less both in magnitude and in number needed to treat than for peanut OIT There is no controlled data focused on sustained unresponsiveness). The impact on quality of life was unclear due to very low quality of evidence. One study demonstrated a small improvement in quality of life compared to placebo.[113]	Overall, the benefits of EPIT for peanut allergy may outweigh the risks in children with severe allergy. A conditional rather than a strong recommendation is made for EPIT as the magnitude of the benefit is not as large as for peanut OIT and the evidence is less certain. It also needs a pharmaceutical product and one is not currently licensed nor available. The vast majority of adverse events are local reactions. Severe reactions are rare. The peanut EPIT safety profile may be better than for OIT so this approach could be considered for children with severe allergy when the treatment becomes available.	Although there are no data on sustained unresponsiveness, extrapolation from other forms of allergen immunotherapy suggests that lifelong therapy will be required for maintained effectiveness. Although EPIT is less demanding for people, such a commitment may not suit everyone. Some may find it easier to avoid peanuts.	The EPIT approach necessitates a pharmaceutical preparation. This comes with increased cost, potentially reducing access to the approach. A product is not currently available commercially and none has been approved by a regulatory authority. Given the mechanism of delivery, other products (should they become available) may not be comparable.

TABLE S3.3: JUSTIFICATION OF RECOMMENDATION FOR EGG AND MILK OIT

The GA2LEN Task Force suggests offering oral immunotherapy under specialist supervision with standardized evidence-based protocols using food products to selected children (aged 4+ years) with clinically diagnosed persistent severe IgE-mediated hen's egg or cow's milk allergy to increase the amount of allergen tolerated while on therapy.

Intervention	Evidence of effectiveness	Benefits versus harms	Patient/care giver values	Feasibility and cost
OIT for children with hen's egg allergy	There is moderate certainty evidence that children aged 3-15 years with IgE-mediated allergy to hen's egg tolerated significantly more hen's egg while on therapy (RR 8.91, 95%CI 4.42-17.95, n=259, 5 studies).[97] There is low certainty evidence that this benefit persists after therapy is discontinued (RR 7.12, 1.73-29.36, n=91, 2 studies).[97] The impact on quality of life unclear due to very low quality of evidence.	Overall, the benefits of OIT for hen's egg allergy outweigh the risks in children with severe egg allergy. Severe means that they are at risk of severe reactions involving cardiorespiratory issues or are suffering from substantially impaired quality of life as a result of their allergy. The points in the general indications and contraindications Table should be noted (see Box 4 of main text) . OIT for hen's egg allergy increases the proportion of children who experience adverse events compared to an elimination diet (RR 7.01, 95%CI 2.49 to 19.75, n=291). Severe reactions and the use of adrenaline were rare and not significantly increased in the OIT group (risk difference 0.05, 95%CI 0.00 to 0.11, n=211 and 0.05, 95%CI -0.01 to 0.11, n=186 respectively). There were no life-threatening reactions.[97] Young children and older children up to 8-10 years old are likely to outgrow their egg allergy if sensitization levels are low so the benefit of the intervention may be lower for them. There is no evidence to whether raw or cooked egg should be recommended, although most of the evidence is for raw egg. Theoretically cooked egg OIT would offer less protection against large amounts of ovalbumin.	OIT needs a considerable investment in time from people with food allergy and their care givers. It may also be associated with local adverse effects so some people with food allergy and their care givers may prefer to avoid hen's egg instead. Care givers of young children may prefer to wait to see if they outgrow their egg allergy. The decision to commence OIT should therefore be individualized using a shared decision making processes with people with food allergy and their care givers. People with egg allergy may have a preference for not eating large amounts of raw egg. Cooked egg may be simpler to manage.	There are no standardized products or harmonized protocols for egg OIT. Real-life studies have found that it is feasible to use grocery bought food, which is low cost and easily accessible.[114-118] For countries that do not allow a non-pharmaceutical based approach, a pharmaceutical based product is not yet available and will likely be expensive. This is likely to make this approach less feasible. Even in countries that allow a non-pharmaceutical based approach, the lack of allergy specialists limit the possibility of offering the treatment to all that would desire it. The use of raw material poses a risk of Salmonella infection unless this is pasteurized.

Intervention	Evidence of effectiveness	Benefits versus harms	Patient/care giver values	Feasibility and cost
OIT for children with cow's milk allergy	This recommendation is based on moderate certainty evidence for children with IgE-mediated allergy to cow's milk tolerating significantly more milk while on therapy (RR 5.67, 95%CI 1.92 to 16.71, n=249). There is considerable heterogeneity between studies.[97] There was no randomized controlled evidence focused on sustained unresponsiveness or quality of life.	Overall, the benefits of oral immunotherapy for cow's milk allergy outweighs the risks in children at risk. OIT for cow's milk allergy increases the proportion of children who experience adverse events compared to placebo or an elimination diet (RR 3.94, 95%CI 2.06 to 7.51, n=220). Severe reactions and the use of adrenaline were rare and not significantly different in OIT and control groups (risk difference 0.01, 95%CI -0.04 to 0.05 and 0.04, 95% CI 0.03 to 0.11 respectively). Only 1 life-threatening reactions was reported.[97] Eosinophilic esophagitis has been seen in around 5% of individuals undergoing milk OIT in real life studies.[119,120]	OIT needs a considerable investment in time from the family. It may also be associated with adverse effects so some families may prefer to avoid cow's milk instead. Most younger children outgrow their cow's milk allergy. Care givers are often interested in a treatment for cow's milk allergy as milk is so common in the diet so that accidental exposures are common. Milk is the main cause number of anaphylaxis in children in Europe. The decision to commence OIT should be individualized using a shared decision making processes with people with food allergy and their care givers.	There is considerable experience with oral immunotherapy for cow's milk allergy.[110] Real-life studies have found that it is feasible to use grocery bought food, which is low cost and easily accessible.[114-118] For countries that do not allow non-pharmaceutical based approach, a pharmaceutical based product is not yet available and will likely be expensive, making this approach less available. Even in countries that allow a non-pharmaceutical based approach, the lack of allergy resources and specialists limit the possibility of offering the treatment to all that would desire it. In contrast to what happens with peanut and egg, administering very small amounts of milk in the first stages of the treatment is relatively easy.

TABLE S3.4: JUSTIFICATION FOR NOT RECOMMENDING FOR OR AGAINST OTHER IMMUNOTHERAPY

Intervention	Evidence of effectiveness	Benefits versus harms	Patient/care giver values	Feasibility and cost
OIT for adults with IgE-mediated peanut allergy	We make no recommendation for or against OIT in adults with hen's egg allergy because there is insufficient evidence to draw conclusions. The certainty of evidence is very low.[97]	There was insufficient evidence available to weigh up benefits versus hams. The intervention could be considered in adults with food allergy where the likely benefit outweighs potential adverse effects.	The burden of the treatment probably is likely to be higher in adults because of the high number of visits to the allergy centre for dosing clashing against working duties. Additionally, adults are likely to have adapted to their peanut allergy such that its impact is minimised.	A pharmaceutical product is licensed in Europe and the United States for children. The same comments as in Table S3.1 related to children apply here.
EPIT for adolescents and adults with peanut allergy	We make no recommendation for or against EPIT in adolescents and adults with peanut allergy because there is insufficient evidence to draw conclusions. The certainty of evidence is very low.[97] Data from two studies found no significant impact on peanut allergy in a small number of adults.[121,122]	There was insufficient evidence available to weigh up benefits versus hams	No data available.	The EPIT approach necessitates a pharmaceutical preparation. This comes with increased cost potentially reducing access to the approach. A product is not currently available commercially and none has been approved by a regulatory authority. Given the mechanism of delivery, other products (should they become available) may not be comparable.
SCIT for patients of any age with peanut allergy	We make no recommendation for or against SCIT in people with peanut allergy because there is insufficient evidence to draw conclusions. The certainty of evidence is very low.[97]	Only 2 very small trials assessed the effectiveness of SCIT for peanut allergy.[123,124] Both had a high rate of systemic reactions making SCIT unacceptable for routine use in people with peanut allergy.	No data available, but may be of interest to people with peanut allergy as treatment could be given once per week or month.	Existing studies are almost 30 years old and used aqueous extracts. New forms of subcutaneous immunotherapy may be possible.
SLIT for patients of any age with peanut allergy	We make no recommendation for or against SLIT in patents with peanut allergy because there is insufficient evidence to draw conclusions. The certainty of evidence is very low.[97]	Adverse effects are predominately local. There are much less than for oral immunotherapy and no reactions required adrenaline injection.[97]	No data available	No specific product available outside the research setting.

Intervention	Evidence of effectiveness	Benefits versus harms	Patient/care giver values	Feasibility and cost
OIT for adults with IgE-mediated hen's egg allergy	We make no recommendation for or against OIT in adults with hen's egg allergy because there is insufficient evidence to draw conclusions. The certainty of evidence is very low.[97]	There was insufficient evidence available to weigh up benefits versus hams. The intervention could be considered in adults where the likely benefit outweighs potential adverse effects.	Given the very low likelihood of spontaneous resolution and the ubiquitous nature of egg in our diet, adults may be keen to at least attempt desensitization.	The same comments as in Table S3.2 related to children apply here.
EPIT for patients of any age with cow's milk allergy	We make no recommendation for or against EPIT in patents with cow's milk because there is insufficient evidence to draw conclusions. The certainty of evidence is very low.[97] We identified only one trial.	There was insufficient evidence available to weigh up benefits versus hams. 1 small trial found slightly more adverse events with active doses compared to placebo.[125]	No data available	There is no commercially available product.
SLIIT for patients of any age with cow's milk allergy	We make no recommendation for or against EPIT in patents with cow's milk because there is insufficient evidence to draw conclusions. The certainty of evidence is very low.[97] We identified only one trial.	There was insufficient evidence available to weigh up benefits versus hams.	No data available	There is no commercially available product.

Intervention	Evidence of effectiveness	Benefits versus harms	Patient/care giver values	Feasibility and cost
AIT for other food allergies	We make no recommendation for or against any form of immunotherapy in patents with other food allergies because there is insufficient evidence to draw conclusions. The certainty of evidence is very low.[97] The few randomized trials available focused on wheat,[126] hazelnut[127] and peach[128] plus a study that included participants with milk, egg, fish or apple allergy (Patriarca 1998).	AIT should only be considered in people with other food allergies where the likely benefit outweighs potential adverse effects. In general, immunotherapy was associated with increased adverse reactions compared to the comparator group.[97] There is no evidence to date that OIT would not be effective or would pose significantly more risk with other food allergens than with egg, peanut and cow's milk, but robust evidence is lacking.	We do not know to what extent we can extrapolate results from one food to another. The decision to offer AIT will be influenced by people with food allergy and their care givers' tolerance to uncertainty. The impact on quality of life of people with atypical food allergens can be worsened by a greater lack of control, labelling and social recognition of these rarer allergens.	Many people have food allergies to uncommon foods for which we are unlikely to ever have high quality data, thus raising questions in terms of equity in access. Commercial products are unlikely to be developed for all the potential food allergies. Non-randomized studies have shown the feasibility of OIT with various grocery bought food including almond, apple, cashew, fish, hazelnut, orange, mustard, peach juice, pecan, pistachio, sesame, shrimp, soy, walnut, wheat, barley, brazil nuts, sunflower, buckwheat, chickpea, chicken, potato, yellow pea, lentils, chia seed, linseed, macadamia, oat, pineapple, pine nuts and scallops.

TABLE S3.5: NUMBER OF STUDIES SCREENED, INCLUDED AND EXCLUDED

Number of potential studies identified by database searches	12,723
Number of additional potential studies identified through other sources	119
Total number of studies screened once duplicates were removed	12,842
Number of studies shortlisted for full text review	48
Number of studies excluded after full text review	11
Number and type of studies included	37

Note: see the end of this supplement for a list of the studies we excluded after screening the full text.

TABLE S3.6: DETAILS OF STUDIES INCLUDED

Study	Allergy type	Admin route	Overall risk of bias	Region	Industry sponsored	Total participants began	Main population	Allergy severity	Raw or cooked	Duration in weeks, inc maintenance	Comparator
Akashi 2017	Egg	Oral	Moderate	Asia	Yes	36	Children	Mild / moderate	Raw	27	Elimination
Anagnostou 2014	Peanut	Oral	Moderate	Europe	No	99	Children	Mixed	Roasted	27	Elimination
Bird 2018	Peanut	Oral	Low	USA	Yes	55	Mixed	Moderate	Roasted	24	Placebo
Blumchen 2019 / Trendelenburg 2020	Peanut	Oral	Low	Europe	No	62	Children	Mixed	Roasted	68	Placebo
Caminiti 2009	Milk	Oral	High	Europe	No	6	Children	Severe	Raw	18	Placebo
Caminiti 2015	Egg	Oral	Low	Europe	No	31	Children	Mild / moderate	Raw	16	Placebo
Chinthrajah 2019	Peanut	Oral	Low	USA	No	120	Children	Mixed	Roasted	156	Placebo
Dello Iacono 2013	Egg	Oral	Moderate	Europe	No	20	Children	Severe	Raw	27	Elimination
Dupont 2010	Milk	Epicutaneous	Moderate	Europe	Yes	19	Mixed	Mixed	Raw	12	Placebo
Enrique 2005	Hazelnut	Sublingual	Moderate	Europe	No	23	Adults	Mixed	Raw	11	Placebo
Escudero 2015	Egg	Oral	Moderate	Europe	No	61	Children	Mixed	Raw	13	Elimination
Fauquert 2018	Peanut	Oral	Moderate	Europe	No	30	Children	Mixed	Roasted	24	Placebo
Fernández-Rivas 2009	Peach	Sublingual	Moderate	Europe	Yes	55	Adults	Mixed	Raw	29	Placebo
Fleischer 2013	Peanut	Sublingual	Low	USA	No	40	Adults	Mild / moderate	Raw	44	Placebo
Fleischer 2019 / DunnGalvin 2021	Peanut	Epicutaneous	Low	Multiple	Yes	356	Children	Mild / moderate	Raw	52	Placebo
Itoh-Nagato 2018	Egg	Oral	Moderate	Asia	No	45	Children	Mixed	Roasted	13	Elimination
Jones 2017	Peanut	Epicutaneous	Low	USA	Yes	74	Mixed	Mild / moderate	Raw	52	Placebo
Keet 2012	Milk	OIT vs SLIT	Moderate	USA	No	30	Children	Mixed	Raw	80	OIT vs SLIT
Lee 2013	Milk	Oral	High	Asia	No	31	Infants	Mixed	Raw	27	Elimination
Longo 2008	Milk	Oral	Moderate	Europe	Not reported	60	Children	Severe	Raw	52	Elimination
Martín-Muñoz 2019	Egg	Oral	Moderate	Europe	No	101	Children	Mixed	Raw	52	Elimination
Martorell 2011	Milk	Oral	High	Europe	Not reported	60	Infants	Mild / moderate	Raw	52	Elimination

Study	Allergy type	Admin route	Overall risk of bias	Region	Industry sponsored	Total participants began	Main population	Allergy severity	Raw or cooked	Duration in weeks, inc maintenance	Comparator
Morisset 2007	Milk	Oral	High	Europe	Not reported	42	Mixed	Mild / moderate	Raw	13	Elimination
Narisety 2015	Peanut	OIT vs SLIT	Moderate	USA	No	21	Mixed	Mild / moderate	Raw	52	OIT vs SLIT
Nowak-Węgrzyn 2019	Wheat	Oral	Moderate	USA	Yes	46	Mixed	Mild / moderate	Raw	52	Placebo
O'B Hourihane 2020	Peanut	Oral	Low	Europe	Yes	175	Children	Mixed	Raw	40	Placebo
Oppenheimer 1992	Peanut	Subcutaneous	High	USA	No	8	Mixed	Severe	Raw	5	Placebo
Pajno 2010	Milk	Oral	Moderate	Europe	No	30	Children	Mixed	Raw	18	Placebo
Patriarca 1998	Multiple	Oral	High	Europe	Not reported	24	Children	Mixed	Raw	27	Elimination
Pérez-Rangel 2017	Egg	Oral	High	Europe	Yes	33	Children	Mild / moderate	Raw	23	Elimination
Salmivesi 2013	Milk	Oral	High	Europe	No	28	Children	Mixed	Raw	23	Placebo
Sampson 2017	Peanut	Epicutaneous	Low	Multiple	Yes	221	Mixed	Mixed	Raw	52	Placebo
Skripak 2008	Milk	Oral	Moderate	USA	No	20	Children	Mild / moderate	Raw	23	Placebo
Staden 2007	Multiple	Oral	Moderate	Europe	No	45	Children	Mild / moderate	Raw	72	Elimination
Takahasi 2017	Milk	Oral + omalizumab	High	Japan	No	16	Children	Severe	Cooked	8 weeks omalizumab first then 16 weeks	Elimination
Vickery 2018	Peanut	Oral	Low	Multiple	Yes	555	Children	Mixed	Roasted	52	Placebo

TABLE S3.7: SUMMARY OF RISK OF BIAS

Risk of bias assessment – peanut

Citation	Randomization process risk of bias	Risk of bias due to assignment	Risk of bias due to missing outcome data	Risk of bias due to outcome measurement	Risk of bias due to selective reporting	Overall risk of bias
Anagnostou 2014	Low	Low	Moderate/High	Moderate	Low	Moderate
Bird 2018	Low	Low	Low	Low	Low	Low
Blumchen 2019	Low	Low	Low	Low	Low	Low
Chinthrajah 2019	Low	Low	Low	Low	Low	Low
Fauquert 2018	Low	Low	Low	Moderate	Low	Moderate
Fleischer 2013	Low	Low	Low	Low	Unclear	Low
Fleischer 2019	Low	Low	Low	Low	Low	Low
Jones 2017	Low	Low	Low	Low	Low	Low
Hourihane 2020	Low	Low	Low	Low	Low	Low
Oppenheimer 1992	Low	High	High	High	High	High
Sampson 2017.	Low	Low	Low	Low	Low	Low
Vickery 2018.	Low	Low	Low	Low	Low	Low

Risk of bias assessment - cow's milk

Citation	Randomization process risk of bias	Risk of bias due to assignment	Risk of bias due to missing outcome data	Risk of bias due to outcome measurement	Risk of bias due to selective reporting	Overall risk of bias
Caminiti 2015	Low	Low	Low	Low	Low	Low
Dupont 2010	Unclear	Low	Low	Moderate	Low	Moderate
Lee 2013	Unclear	Moderate	Moderate	High	Unclear	High
Longo 2008	Low	Moderate	Low	Moderate	Unclear	Moderate
Martorell 2011	Low	Moderate	Low	High	Moderate	High
Morisset 2007	Low	High	Moderate	Moderate	Moderate	High
Pajno 2010	Low	Moderate	Low	Moderate	Moderate	Moderate
Salmivesi 2013	Unclear	Low	Moderate	High	Unclear	High
Skripak 2008	Unclear	Low	Moderate	Moderate	Unclear	Moderate

Risk of bias assessment - hen's egg

Citation	Randomization process risk of bias	Risk of bias due to assignment	Risk of bias due to missing outcome data	Risk of bias due to outcome measurement	Risk of bias due to selective reporting	Overall risk of bias
Akashi 2017	Low	Low	Moderate	Moderate	Low	Moderate
Caminiti 2009	Unclear	Low	High	High	Moderate	High
Dello Iacono 2013	Low	Moderate	Low	Moderate	Low	Moderate
Escudero 2015	Low	Low	Low	Moderate	Unclear	Moderate
Itoh-Nagato 2018	Low	Moderate	Low	Moderate	Moderate	Moderate
Martín-Muñoz 2019	Low	Low	Moderate	Moderate	Moderate	Moderate
Pérez-Rangel 2017	Low	Moderate	Low	High	Low	High

Risk of bias assessment - other allergens

Citation	Randomization process risk of bias	Risk of bias due to assignment	Risk of bias due to missing outcome data	Risk of bias due to outcome measurement	Risk of bias due to selective reporting	Overall risk of bias
Enrique 2005	Unclear	Low	Low	Moderate	Moderate	Moderate
Patriarca 1998	Moderate	High	Low	High	Moderate	High
Staden 2007	Unclear	Moderate	Moderate	Moderate	Low	Moderate
Fernández-Rivas 2009	Low	Low	Moderate	Moderate	Moderate	Moderate
Nowak-Węgrzyn 2019	Unclear	Low	Low	Moderate	Low	Moderate

Risk of bias assessment – direct comparison of administration routes

Citation	Randomization process risk of bias	Risk of bias due to assignment	Risk of bias due to missing outcome data	Risk of bias due to outcome measurement	Risk of bias due to selective reporting	Overall risk of bias
Keet 2012	Low	Moderate	Low	Low	Unclear	Moderate
Narisety 2015	Unclear	Low	Low	Moderate	Moderate	Moderate

Risk of bias assessment - immunotherapy plus biological

Citation	Randomization process risk of bias	Risk of bias due to assignment	Risk of bias due to missing outcome data	Risk of bias due to outcome measurement	Risk of bias due to selective reporting	Overall risk of bias
Takahashi 2017	Low	Moderate	Low	High	Moderate	High

TABLE S3.8: REASONS WHY STUDIES SCREENED AS FULL TEXT WERE EXCLUDED

Note: many other studies were excluded based on titles and abstracts and these are not listed here.

Study	Reason not eligible for inclusion
Burks AW, Jones SM, Wood RA, Fleischer DM, Sicherer SH, Lindblad RW, Stablein D, Henning AK, Vickery BP, Liu AH, Scurlock AM, Shreffler WG, Plaut M, Sampson HA. Oral immunotherapy for treatment of egg allergy in children. N Engl J Med 2012;367(3):233-43.	No baseline food challenge. Eligibility determined based on clinical history of egg allergy and a serum egg-specific IgE.
Fuentes-Aparicio V, Alvarez-Perea A, Infante S, Zapatero L, D'Oleo A, Alonso-Lebrero E. Specific oral tolerance induction in paediatric patients with persistent egg allergy. Allergol Immunopathol 2013;41(3):143-50.	Baseline challenge only performed on those who had not suffered clinical episodes within the previous 3 months. In intervention group baseline open challenge performed in 27/40. In control group open challenge performed at baseline in all. No follow up challenge reported with control group. 21.8% of controls developed spontaneous tolerance to egg vs 92.5% tolerance in intervention group ($p < 0.0001$). Includes data on adverse events for intervention group, not controls.
García BE, González-Mancebo E, Barber D, Martín S, Tabar AI, Díaz de Durana AM, Garrido-Fernández S, Salcedo G, Rico P, Fernández-Rivas M. Sublingual immunotherapy in peach allergy: monitoring molecular sensitizations and reactivity to apple fruit and Platanus pollen. J Investig Allergol Clin Immunol 2010;20(6):514-20.	Does not include outcomes of interest to the review. Explores skin reactivity using skin prick tests. No follow up food challenge
Giavi S, Vissers YM, Muraro A, Lauener R, Konstantinopoulos AP, Mercenier A, Wermeille A, Lazzarotto F, Frei R, Bonaguro R, Summermatter S, Nutten S, Papadopoulos NG. Oral immunotherapy with low allergenic hydrolyzed egg in egg allergic children. Allergy 2016;71(11):1575-1584.	Baseline challenge not performed in all.
Jones SM, Agbotounou WK, Fleischer DM, Burks AW, Pesek RD, Harris MW, Martin L, Thebault C, Ruban C, Benhamou PH. Safety of epicutaneous immunotherapy for the treatment of peanut allergy: A phase 1 study using the Viaskin patch. J Allergy Clin Immunol 2016;137(4):1258-1261.e10.	No baseline food challenge.
MacGinnitie AJ, Rachid R, Gragg H, Little SV, Lakin P, Cianferoni A, Heimall J, Makhija M, Robison R, Chinthrajah RS, Lee J, Lebovidge J, Dominguez T, Rooney C, Lewis MO, Koss J, Burke-Roberts E, Chin K, Logvinenko T, Pongracic JA, Umetsu DT, Spergel J, Nadeau KC, Schneider LC. Omalizumab facilitates rapid oral desensitization for peanut allergy. J Allergy Clin Immunol 2017;139(3):873-881.e8.	All receive immunotherapy. Randomization is between omalizumab and placebo.

Study	Reason not eligible for inclusion
Meglio P, Giampietro PG, Carello R, Gabriele I, Avitabile S, Galli E. Oral food desensitization in children with IgE-mediated hen's egg allergy: a new protocol with raw hen's egg. Pediatr Allergy Immunol 2013;24(1):75-83.	Oral challenge OR convincing history were inclusion criteria. 3/20 were included based on history, not challenge.
Reier-Nilsen T, Carlsen KCL, Michelsen MM, Drottning S, Carlsen KH, Zhang C, Borres MP, Håland G. Parent and child perception of quality of life in a randomized controlled peanut oral immunotherapy trial. Pediatr Allergy Immunol 2019;30(6):638-645. AND Reier-Nilsen T, Michelsen MM, Lodrup Carlsen KC, Carlsen K-H, Mowinckel P, Nygaard UC, Namork E, Borres MP, Håland G. Feasibility of desensitizing children highly allergic to peanut by high-dose oral immunotherapy. Allergy 2019; 74: 337–48.	No outcomes in these papers relevant to the review. Measures quality of life but not with the tool listed as required in review protocol. Measured with the PedsQL 4.0. Adverse events reported for intervention group only / no control data.
Palosuo K, Karisola P, Savinko T, Fyhrquist N, Alenius H, Mäkelä MJ. A randomized, open-label trial of hen's egg oral immunotherapy: efficacy and humoral immune responses in 50 children. J Allergy Clin Immunol Pract (Published online ahead of print January 2021).	Compares 6 months of avoidance with 8 months of immunotherapy. However 8 months immunotherapy group also includes avoidance for 6 months then starting immunotherapy. No direct comparison between avoidance and immunotherapy.
Varshney P, Jones SM, Scurlock AM, Perry TT, Kemper A, Steele P, Hiegel A, Kamilaris J, Carlisle S, Yue X, Kulis M, Pons L, Vickery B, Burks AW. A randomized controlled study of peanut oral immunotherapy: clinical desensitization and modulation of the allergic response. J Allergy Clin Immunol 2011;127(3):654-60.	No challenge at baseline, only skin prick test.
Wood RA, Kim JS, Lindblad R, Nadeau K, Henning AK, Dawson P, Plaut M, Sampson HA. A randomized, double-blind, placebo-controlled study of omalizumab combined with oral immunotherapy for the treatment of cow's milk allergy. J Allergy Clin Immunol 2016;137(4):1103-1110.e11.	All receive immunotherapy. Randomization is between omalizumab and placebo.

Online supplement 4: biological therapies

This supplement provides evidence in support of our conclusions about biological therapies. The first tables summarise our reasoning. This is followed by details about the studies we included in drawing our conclusions.

TABLE S4.1: RECOMMENDATION JUSTIFICATION FOR OMALIZUMAB

The GA^{2}LEN Task Force makes no recommendation for or against offering omalizumab for treating food allergy.

Intervention	Evidence of effectiveness	Benefits versus harms	Patient/care giver values	Feasibility and cost issues
Omalizumab monotherapy	There is very low certainty evidence about the effectiveness of omalizumab monotherapy. Therefore, we cannot recommend for or against this as a routine treatment option for people with food allergy. 1 one very small trial found no statistically significant difference in peanut tolerance amongst adults with peanut allergy, but there were positive trends.[129]	There is insufficient information to weigh up benefits versus potential harms. In the one trial that met our inclusion criteria, omalizumab was well tolerated. Other observational studies and descriptive reviews suggests improved tolerance and quality of life so it is possible that benefits outweigh harms.[130,131] Clinicians may wish to consider whether individuals would benefit with omalizumab as a specialist treatment. However, based on controlled trials, there is not yet enough certainty of evidence to say that omalizumab should be universally considered at this stage.	We have no information about the views of people with food allergy about omalizumab.	There is no robust evidence about the feasibility or cost effectiveness of omalizumab for food allergy. Similarly to other monoclonal antibodies, omalizumab may more likely to provide value for money for people with severe food allergy at high risk of anaphylaxis. Many people have multiple allergic manifestations. Omalizumab is already licensed for treating severe asthma. The potential added benefit for food allergy may be a consideration when deciding whether or not to commence someone with asthma on a biological therapy. A higher affinity monoclonal anti-IgE therapy (Ligelizumab) is now being investigated for food allergy

TABLE S4.2: RECOMMENDATION JUSTIFICATION FOR ETOKIMAB

The GA^{2}LEN Task Force makes no recommendation for or against offering etokimab for treating food allergy.

Intervention	Evidence of effectiveness	Benefits versus harms	Patient/care giver values	Feasibility and cost issues
Etokimab monotherapy	There is very low certainty evidence about the effectiveness of etokimab monotherapy. Therefore, we cannot recommend for or against this as a routine treatment option for people with food allergy. 1 one small trial found a trend towards improved tolerance of peanut amongst adults with peanut allergy who had a single dose of intravenous etokimab.[132]	There is insufficient information to weigh up benefits versus potential harms. In the one trial we identified, etokimab was well tolerated.	We have no information about people with food allergy and their care givers' views about etokimab.	There is no robust evidence about the feasibility or cost effectiveness of etokimab. Similarly to other monoclonal antibodies, etokimab may more likely to provide value for money for people with severe food allergy at high risk of anaphylaxis. Clinicians may wish to consider whether individuals would benefit with etokimab as a specialist treatment. However, based on controlled trials, there is not yet enough certainty of evidence to say that etokimab should be universally considered at this stage. Large randomized trials with standardised measures are needed to determine efficacy and the most suitable candidates, doses and durations of treatment.

TABLE S4.3: RECOMMENDATION JUSTIFICATION FOR OTHER BIOLOGICAL MONOTHERAPY

The GA^{2}LEN Task Force makes no recommendation for or against offering TNX-901 to patients with food allergy and as this therapy is not available, we do not mention it in the guideline

Intervention	Evidence of effectiveness	Benefits versus harms	Patient/care giver values	Feasibility and cost issues
TNX-901 monotherapy	There is very low certainty evidence about the effectiveness of TNX-901 therapy and this drug has been withdrawn from development. Therefore, we cannot recommend for or against this as a routine treatment option for people with food allergy. 1 trial found that TNX-901 (monoclonal anti-IgE therapy) did not increase the proportion of adults able to tolerate peanut.[133]	There is insufficient information to weigh up benefits versus potential harms.	We have no information about people with food allergy and their care givers' views.	This therapy was an experimental molecule which is not being further developed for the pharmaceutical market so we do not cover it in the guideline. New monoclonal antibodies with higher affinity to free circulating serum IgE are currently available.

TABLE S4.4: NUMBER OF STUDIES SCREENED, INCLUDED AND EXCLUDED

Number of potential studies identified by database searches	4,560
Number of additional potential studies identified through other sources	24
Total number of studies screened once duplicates were removed	4,574
Number of studies shortlisted for full text review	5
Number of studies excluded after full text review	2
Number and type of studies included	3 RCTs

Note: see the end of this supplement for a list of the studies we excluded after screening the full text.

TABLE S4.5: DETAILS OF STUDIES INCLUDED

Citation	Study type	Risk of bias	Country	Funding source	Total participants	Age	Allergy type	Severity of allergy	Biological tested	Biological dose and duration	Comparator
Chinthrajah 2019	RCT	Moderate	USA	Industry and non industry	20	Adults. Median age (range): intervention 27 years (19 to 54); placebo 22 years (18 to 50)	Peanut	Not specified Appears moderate.	Etokimab	Single dose of etokimab, 300mg/100 mL i.v.	Placebo
Leung 2003	RCT	Low	USA	Industry and non industry	84	13+ years Eligible: 12 to 60 years, included 13 to 59	Peanut	Moderate to severe	TNX-901 (humanized IgG1 monoclonal antibody against IgE)	150mg, 300mg, or 450mg of TNX-901 subcutaneously every 4 weeks for 4 doses.	Placebo
Sampson 2011	RCT	Moderate	USA	Industry	14	Mixed 5 to 12 (50%) and 13+ years (50%) Range 6 to 75 years	Peanut	Not specified	Omalizumab	Dose based on total IgE levels and body weight. Treatment was 20 to 22 weeks every 2 to 4 weeks. Dose was a minimum of 0.016 mg/kg/IgE (IU/mL) every 4 weeks. Those requiring more than a 300mg dose had the dose divided and given every 2 weeks.	Placebo

TABLE S4.6: SUMMARY OF RISK OF BIAS

Study	Randomization process risk of bias	Risk of bias due to assignment	Risk of bias due to missing outcome data	Risk of bias due to outcome measurement	Risk of bias due to reported results	Overall risk of bias
Chinthrajah 2019	Unclear	Low	Moderate	Moderate	Moderate	Moderate
Leung 2003	Low	Low	Low	Low	Low	Low
Sampson 2011	Unclear	Low	High	Low	Low	Moderate

TABLE S4.7: REASONS WHY STUDIES SCREENED AS FULL TEXT WERE EXCLUDED

Study	Reason not eligible
Cavagni 1989	Not biological therapy
Leung 2004	Same study as Leung 2003

Online supplement 5: educating individuals with food allergy and families

TABLE S5.1: JUSTIFICATION OF BEST PRACTICE STATEMENT ABOUT EDUCATION

It is good practice to offer structured education to people with food allergy and their family about managing food allergy routinely and in an emergency, tailored to their age group and individual needs.

Intervention	Evidence of effectiveness	Benefits versus harms	Patient / care giver values	Feasibility and cost
Written information	We found insufficient evidence to draw conclusions about providing written information for people with food allergy. The certainty of evidence was very low. 1 trial (n = 75) found that providing written dietary advice to children with nut allergy did not change their behavior or improve quality of life.[134]	We found limited robust evidence to help weigh up the evidence of the benefits versus potential harms of education for people with food allergy and their family members. Observational studies and reviews not eligible for inclusion in our rapid review suggest the potential for improved knowledge and reduced anxiety from some forms of education about managing food allergy.[140,141] In children and adults with other conditions, education that incorporates psychological, motivational or behavioral change concepts has been found to reduce anxiety and improve people's confidence to self-manage[142,143] but there is limited evidence about these types of interventions for people with food allergy. There may be some risk of harm from education such as the potential to increase anxiety if information is not provided with appropriate support or phrased in a sensitive manner. There is also a small risk of over-confidence leading to a potential risk of inappropriate exposure to food allergens. Online resources and mobile apps that people access may not be quality assured.[144,145] On balance it is likely that the benefits of person-centered tailored education outweigh	People with food allergy and care givers often identify gaps in their knowledge about managing food allergy[146,147] and welcome education from professionals as they otherwise rely on information from friends and family or unofficial online sources.[148,149] The most appropriate education will depend on the person's age, context and individual needs. For instance some may value taking part in group education sessions whereas others may prefer a structured online program or mobile phone app. It would likely be useful to have a range of education options available to address individual preferences and ways of learning.	It is feasible and need not be costly to provide all with some form of education tailored to their individual needs and stage of life. Education with psychological components need not be delivered by clinical psychologists. Motivational and behavior change principles can be used by a wide range of professionals, after minimal training.[150] Observational studies and reviews not eligible for inclusion in our rapid review highlight gaps in non-specialist clinicians' and teachers' knowledge about how to educate people about managing food allergy.[151-154]
Education using psychological / behavioral change principles	We found insufficient evidence to draw conclusions about education using psychological, motivational or behavioral change principles. The certainty of evidence was very low. 1 trial (n = 200) of a single-session of cognitive behavioral therapy with communication about risks did not reduce anxiety in mothers of children with food allergy, but a subgroup with the highest initial anxiety had improvements at 6 weeks.[135] 1 trial (n = 50) found that describing potential non-life-threatening 'symptoms' of oral immunotherapy in positive terms rather than as negative side effects reduced anxiety and increased compliance amongst children with peanut allergy.[136]			
Group education	We found insufficient evidence to draw conclusions about group education for people with food allergy. The certainty of evidence was very low. 1 trial of two 3-hour training sessions for adults with severe food allergy and care givers of children with severe food allergy found improved knowledge and			

Intervention	Evidence of effectiveness	Benefits versus harms	Patient / care giver values	Feasibility and cost
	competence in managing anaphylaxis (n = 92 with food allergy or family members).[137]	the risks, but there is not enough evidence to recommend one form of education over others.		
Education including practical components	We found insufficient evidence to draw conclusions about practical education strategies for people with food allergy. The certainty of evidence was very low. 1 trial (n = 60) found that adolescents with peanut allergy and their care givers felt more comfortable with adrenaline autoinjectors after supervised practice, but there were no significant improvements in anxiety or quality of life.[138] 1 trial (n = 60) found that encouraging children to hold nuts that they were not allergic to did not reduce anxiety or improve quality of life in children with nut allergy.[139]			

TABLE S5.2: NUMBER OF STUDIES SCREENED, INCLUDED AND EXCLUDED

Number of potential studies identified by database searches	1,401
Number of additional potential studies identified through other sources	3
Total number of studies screened once duplicates were removed	1,404
Number of studies shortlisted for full text review	14
Number of studies excluded after full text review	8
Number and type of studies included	6 RCTS

Note: see the end of this supplement for a list of the studies we excluded after screening the full text.

TABLE S5.3: DETAILS OF STUDIES INCLUDED

Study	Study type	Risk of bias	Region	Funding source	Total participants	Age	Allergy type	Severity of allergy	Intervention	Comparator
Boyle 2017	RCT	Moderate	Europe	Non-industry	200 mothers of children with food allergy	Adults	Various	Mild to severe	Single-session cognitive behavioral therapy including risk communication	Standard care.
Brockow 2015	RCT	Moderate	Europe	Non-industry	183 total, of which 19 adults with food allergy and 73 parents of children with food allergy	Adults	Various	Severe	2 sessions of group education, each 3 hours long	Standard education about adrenaline autoinjectors
Howe 2019	RCT	Moderate	USA	Non-industry	50	7 to 17 years	Peanut	Severe	People with food allergy and their families informed that non-life-threatening symptoms during oral immunotherapy were positive (could signal desensitization)	Informed that non-life-threatening symptoms during oral immunotherapy were negative (side effects of treatment)
Norman 2016	RCT	Moderate	Australasia	Not industry	75	2-16 years	Nut	Severe	Written instructions to eat non-allergic nuts, recipe booklet and monthly reminder text messages	Standard verbal dietary advice
Shemesh 2017	RCT	High	USA	Non-industry	60	13 to 17 years and their parents	Peanut	Mild to severe	Supervised 'practice' injection of needle into thigh	Standard education about adrenaline autoinjectors
Weinberger 2019	RCT	High	US	Not stated	60	9 to 17 years	Nuts and peanuts	Mild to severe	Education plus supervised touching of nuts that children were not allergic to	Education alone

TABLE S5.4: RISK OF BIAS ASSESSMENT

Study	Randomization process risk of bias	Risk of bias due to assignment	Risk of bias due to missing outcome data	Risk of bias due to outcome measurement	Risk of bias due to reported results	Overall risk of bias
Boyle 2017	Low	Low	Low	Moderate	Low	Moderate
Brockow 2015	Low	Low	Low	Moderate	Low	Moderate
Howe 2019	Low	Low	Low	Moderate	Low	Moderate
Norman 2016	Low	Low	Moderate	Moderate	Low	Moderate
Shemesh 2017	Low	Low	High	Moderate	Moderate	High
Weinberger 2019.	Unclear	Low	High	Moderate	Low	High

TABLE S5.5: REASONS WHY STUDIES SCREENED AS FULL TEXT WERE EXCLUDED

Study	Reason not eligible
Baptist AP,et al. A self-regulation intervention can improve quality of life for families with food allergy. J Allergy Clin Immunol 2012;130(1):263-5.e6.	Not education
Fernandez-Mendez F et al Learning and treatment of anaphylaxis by laypeople: a simulation study using pupilar technology. Biomed Res Int 2017;2017:9837508.	Not people with food allergy or family
Hernandez-Munoz LU et al. Evaluation of AllergiSense smartphone tools for adrenaline injection training. IEEE J Biomed Health Inform 2017;21(1):272-282.	Not people with food allergy or family
LeBovidge JS et al Evaluating a handbook for parents of children with food allergy: a randomized clinical trial. Ann Allergy Asthma Immunol. 2016;116(3):230-236.e1.	Not educational (instructional guide)
Sugunasingha N, Jones FW, Jones CJ. Interventions for caregivers of children with food allergy: A systematic review. Pediatr Allergy Immunol 2020;31(7):805-812.	Systematic review - not primary study. No relevant studies included for our review
Vazquez-Ortiz M, Understanding the challenges faced by adolescents and young adults with allergic conditions: A systematic review. Allergy 2020;75(8):1850-1880.	Systematic review - not primary study. No relevant studies included for our review
Young I, A systematic review and meta-regression of the knowledge, practices, and training of restaurant and food service personnel toward food allergies and Celiac disease. PLoS One 2018;13(9):e0203496.	Systematic review - not primary study. No relevant studies included for our review

Online supplement 6: risk identification and management

This supplement provides evidence in support of our conclusions about risk identification and management. The first tables summarize our reasoning. This is followed by details about the studies we included in drawing our conclusions.

TABLE S6.1: JUSTIFICATION FOR BEST PRACTICE STATEMENT ABOUT ADOLESCENTS

Adolescents and young adults with food allergy are at increased risk of severe reactions, so it is good practice to put into place effective risk management and transition strategies.

Evidence of impact	Benefits versus harms	Patient / care giver values	Feasibility and cost
Teenagers and young adults are at increased risk of severe reactions. Fatality data from France, UK and Australia have indicated these age groups are at higher risk of fatal anaphylaxis, although very low risk overall.[155,156,157] This cannot solely be attributed to risk-taking behavior, suggesting an age-specific vulnerability to severe outcomes from food-induced allergic reactions. There is also evidence of increased risk of ICU admission in teenagers.[158] Data from unintended allergic reactions due to food occurring in the community are also consistent with this age-related risk.[159] With respect to food challenges (FC), data are less consistent, with some studies reporting an association between severity and age,[160] but not others,[161] although reaction severity at FC is limited due to the manner in which FC are performed). Many studies do not distinguish between reactions due to food and non-food triggers, which is likely to be an important confounder.	Specific interventions targeting teenagers and young adults are unlikely to be harmful where strategies are intended to increase self-efficacy (confidence in managing food allergy) rather than increase anxiety. However, there is an absence of evidence as to whether such interventions reduce risk of severe reactions. Targeting children and young people as part of transitioning care may be advantageous, although given the resource limitations of most healthcare environments, targeting a specific age group may result in less care to others.	"Transitioning" has been identified as an important area for support, both by young people and their families.[162]	Targeting of educational strategies to specific ages may be a more efficient use of limited resources, however this should not be at the expense of education to other individuals at risk of food-anaphylaxis.

TABLE S6.2: JUSTIFICATION OF BEST PRACTICE STATEMENT ABOUT ASTHMA MANAGEMENT

It is good practice to optimise asthma control in people with food allergy as this reduces morbidity and mortality due to asthma. It *might* reduce the risk of severe food-induced allergic reactions, though the evidence about this is unclear.

Evidence of impact	Benefits versus harms	Patient / care giver values	Feasibility and cost
Data from fatality registries indicate that while asthma is a common comorbidity (in >80% of fatalities), only in the minority of cases is there evidence of prior, poorly controlled asthma. For non-fatal anaphylaxis, evidence is inconsistent. Some studies report a weak-moderate association between a diagnosis of asthma and[159,163-167] while others do not.[168-172] Data may be inconsistent even within the same datasets,[165,169] depending on how severity is assigned. A systematic review and meta-analysis of 13 studies included only 2 studies specifically on food-induced anaphylaxis. The reviewers found an increase in reaction severity with asthma diagnosis (OR 1.89; 95%CI, 1.26-2.83); however the analysis was limited by medium-high risk of bias, incomplete search strategy and significant study heterogeneity.[173] Most studies in this area are at moderate-high risk of bias and do not assess asthma control at time of reaction. One study found that a diagnosis of asthma does not impact on mortality in children admitted to PICU for anaphylaxis.[158]	Data relating to the association between asthma severity, asthma control and severity of food-induced allergic reactions are inconsistent. However, achieving good asthma control in food-allergic patients will reduce morbidity/mortality due to asthma. This is an important outcome which, in turn, may reduce the risk of severe food-induced allergic reactions due to unintended exposure, but the evidence about this is unclear.	Achieving good asthma control is important to individuals with asthma, and is associated with improvements in health-related quality of life, but we cannot say that this has direct impacts on the risk of severe reactions in people with food allergy.	Achieving good asthma control is important and cost-effective as a means to reduce the morbidity and mortality associated with asthma, but we have no evidence about the feasibility and cost of asthma control for addressing severe reactions to food.

TABLE S6.3: JUSTIFICATION OF BEST PRACTICE ABOUT PREDICTION

It is good practice for clinicians to consider the severity of previous symptoms and the likely triggering dose when evaluating the risk of anaphylaxis, though there is not always a clear relationship. Allergen-specific IgE levels alone are not useful in predicting risk of anaphylaxis.

Evidence of impact	Benefits versus harms	Patient / care giver values	Feasibility and cost
The relationship between dose/level of exposure and severity of food reactions is complex and unclear.[174] However, people with food allergy who experience only mild symptoms to large levels of exposure are probably less likely to have severe reactions to low levels of exposure. There is no evidence that people who react to very low levels of allergen are at greater risk of anaphylaxis.[175] A previous review concluded that there are currently no predictors of clinical utility to inform future risk severity.[176] Our rapid review did not identify any evidence to contradict this. Prior history of anaphylaxis implies potential for future anaphylaxis, but level (dose) of exposure is a clear confounder in predicting future risk,[174] which probably explains why prior history of anaphylaxis often does not correspond to anaphylaxis at food challenge.[161,163,170,177] Most fatal food anaphylaxis events occur in people without a prior history of anaphylaxis.[176] People with only oral allergy symptoms (OAS) to low levels of exposure cannot be assumed to have pollen food allergy syndrome on that basis alone. OAS is not synonymous with Pollen Food Allergy Syndrome (PFAS). In general, people with PFAS are at lower risk of anaphylaxis,[176] although patients with poly-sensitization may be at greater risk than mono-sensitized individuals.[178] There are emerging data about cofactors, although some studies have found no clear impact on severity.[171] In general, IgE sensitization does not predict the severity of reactions. For peanut allergy, IgE to Ara h 2 is not predictive of severity.[159,170,179,180] Some studies have concluded that IgE sensitization (skin prick testing, serum IgE to food allergens	Providing false reassurance to individuals with food allergy and their care givers about future risk can be harmful, however clinicians must also provide information that does not overstate risk. Food allergy is associated with issues of trust and miscommunication regarding allergen labelling. It is vital that people are provided with reliable and accurate information by healthcare professionals. Absence of prior anaphylaxis does not exclude future risk of anaphylaxis. However, the vast majority of anaphylaxis reactions are not severe and respond to 1-2 doses of rescue adrenaline. People with a history of anaphylaxis tend to have higher levels of IgE-sensitization than those without, at least for peanut. However the overlap is so extensive that in practice, these biomarkers are not helpful in predicting life-threatening allergic reactions. The risk is that patients with low levels of IgE-sensitization might be falsely reassured they cannot have anaphylaxis, while those with high levels are wrongly counselled that they are at high risk of severe reactions	Informing people who react with significant symptoms to very low levels of exposure that they are not at greater risk of severe reactions may help alleviate anxiety and counteract the impact of a diagnosis of food allergy on quality of life. This also holds true in terms of interpreting the degree of IgE-sensitization correctly.	In people where the there is a lack of information over the dose needed to cause symptoms, undertaking a supervised food challenge may result in a significant improve in self-efficacy and quality of life measures.[192] He cost-effectiveness of such interventions has not been evaluated. For most foods, there is no strong evidence that evaluation of IgE-components is helpful to predict risk of severity and inform changes in management. IgE-testing (including, for some food allergens, component-resolved diagnostics) may be cost-effective in distinguishing between IgE-sensitization with non-reactivity and true clinical allergy, but not in determining severity.

or components) or basophil activation are correlated with anaphylaxis at food challenge.[181-184] However, these analyses included non-reactive (but sensitized) individuals and those reacting with non-severe reactions. This skews the analysis and significantly over-estimates the specificity of the test.[185] Including IgE-sensitization in a model to predict severity in peanut-allergic individuals did not significantly improve predictive value compared to using clinical determinants alone.[186] Some IgE-markers (e.g. Ara h 2 for peanut, Jug r 1 and Jug r 4 for walnut, Cor a 9/14 for hazelnut) imply a higher risk of systemic reaction, but do not differentiate between anaphylaxis and non-anaphylactic systemic skin reactions.[187-189] Sensitization to LTPs without clinical reactivity is now frequently reported,[176] and there is some evidence that polysensitization to Bet v 1 homologues in LTP-sensitized individuals can moderate severity.[190] The Task Force noted anecdotal reports that mono-sensitization to LTP may be associated with greater risk of severity, particularly in central Europe. Conversely, mono-sensitization to Bet v 1 homologues (e.g. Ara h 8 in peanut allergy) can imply PFAS and a lower risk of anaphylaxis when present in the context of low or absent sensitization to other components. However, this may not be true for other allergens (e.g. Cor a 1 in hazelnut allergy), where it is not uncommon for individuals with monosensitization to Cor a 1 to be at significant risk of systemic reactions,[191] possibly due to the presence of IgE-sensitization to other undetected components.			

TABLE S6.4: NUMBER OF STUDIES SCREENED, INCLUDED AND EXCLUDED

Number of potential studies identified by database searches	3142
Number of additional potential studies identified through other sources	27
Total number of studies screened once duplicates were removed	3169
Number of studies shortlisted for full text review	99
Number of studies excluded after full text review	16
Number and type of studies included	Total 83: 4 systematic reviews, 1 RCT and 78 observational studies

Note: see the end of this supplement for a list of the studies we excluded after screening the full text.

TABLE S6.5: DETAILS OF STUDIES INCLUDED

Citation	Study type	Risk of bias	Country	Funding source	Total no. participants		Age	Allergy type	Severity Definition
					Overall	"Severe" group			
Taylor 2010	DBPCFC Retrospective	Moderate	France	Industry and non-industry	286	40	≤48 y Median 7.0 y	Peanut	Astier Grade 4/5
Pastorello 2011	Prospective cohort	High	Italy	Industry and non-industry	148	72	13-62 y Median 37 y	Peach	Systemic symptoms
Calvani 2011	Retrospective case series (consecutive recruitment)	Moderate	Italy	Industry	163 included (21 excluded: incomplete data)	36	≤18 y Median 4y	Any food	Sampson grade 4/5
Huang 2012	Retrospective case series	High	USA	Non-industry	192 (152 to food)	15	≤18 y Median 8 y	Any food	Brown Grade 3
Neuman-Sunshine 2012	Retrospective case series	High	USA	Non-industry	782	164	≤16 y	Peanut	CVS/resp or symptoms from 3+ organs
Eller 2012	Open and blinded FC, retrospective	Moderate	Denmark	Internal	487	Not stated	6m – 74 y [0.5–73.5]	Egg, milk, hazelnut, peanut	Sampson grade 4/5
Nguyen-Luu 2012	Retrospective case series	High	Canada	Non-industry	1411	N/A	Children, mean 7.1 y	Peanut	Severe as per Hourihane 1997
Rolinck-Werninghaus 2012	DBPCFC, prospective	Moderate	Germany	Internal funds	869	51	≤16 y Median 1 y	Egg, milk, soy, wheat	Sampson grade 4/5
Cianferoni 2012	Open FC, retrospective	High	USA	Not stated	983	111	Mean 5 y	Egg, milk, peanut	2+ organs requiring treatment
Vetander 2012	Retrospective case series	Moderate	Sweden	Internal	371	128	≤17 y Mean 6 y	All foods	EAACI 2007
Eller 2013	Open and blinded FC, retrospective	Moderate	Denmark	Industry + internal	175	Not stated	1-26 y Mean 5.6 y	Peanut	Sampson grade 4/5
Masthoff 2013	DBPCFC, retrospective	High	Netherlands	Industry	161	79	Median 7y (children) 27y (adults)	Hazelnut	Any objective symptoms

Citation	Study type	Risk of bias	Country	Funding source	Total no. participants		Age	Allergy type	Severity Definition
					Overall	"Severe" group			
van Erp 2013	DBPCFC, retrospective	Low	Netherlands	Internal	109	24	Median 6.7y (IQR 5-9.5)	Peanut	Sampson grade 4/5
Brown 2013	Prospective cohort	Low	Australia	Non-industry	412 131 food	97 19 food	3-99 years Median 36 y IQR 24-50y	All foods	Brown Grade 3
Libbers 2013	DBPCFC, retrospective	Moderate	Netherlands	Not stated	59	Not stated	Children	Egg	Study-defined
Klemens 2013	DBPCFC, retrospective	Moderate	Netherlands	Internal	93	Not stated	Mean 30 y (sd ± 12.5)	Peanut	Adapted from Mueller grade 3/4
Mulla 2013	State-wide hospital data	Moderate	USA	Internal	2410 (all trigger)	Not stated	Median 50 y	All foods	ICU or mechanical ventilation
Johnson 2014	Retrospective case series	Moderate	Sweden	Non-industry + internal	578	239	Median 5.9 y IQR 2.3-12y	All foods	NIAID with adrenaline treatment
Vetander 2014	Retrospective case series	Moderate	Sweden	Internal	358	20	≤17 y Mean 5 y	All foods	EAACI 2007
Clark 2014	Retrospective case series	High	USA	Not stated	11,972 (20% food)	2622	Adults + children	All foods	Hospital/ICU admission
Jerschow 2014	Fatality case series	Low	USA	Internal	164	164	Adults + children	All foods	Fatal anaphylaxis
Xu 2014	Fatality case series	Moderate	Canada	Internal	40	40	9-78 y Mean 32 y	All foods	Fatal anaphylaxis
Nassiri 2015	Anaphylaxis registry	High	Europe	Not stated	1222	116	Adults + children	All foods	Mueller
Turner 2015	Fatality case series	Moderate	UK	Non-industry	124	124	Adults + children	All foods	Fatal anaphylaxis
Song 2015	Prospective DBPCFC	Moderate	USA	Industry and non industry	58	Not stated	12-45 y	Nuts, seafood, sesame	Sampson Grade
Kukkonen 2015	Prospective DBPCFC	Moderate	Finland	Non-industry	69	25	6-18y	Peanut	Hourihane 2005
Francuzik 2015	Anaphylaxis registry	Moderate	Europe	Internal	5765	116	Adults + children	All triggers (not just food)	Brown, Ring+Messmer

Citation	Study type	Risk of bias	Country	Funding source	Total no. participants		Age	Allergy type	Severity Definition
					Overall	"Severe" group			
Uasuf 2015	Retrospective case series	High	Italy	Not stated	133	23	Adults	Peach	Mueller Grade 3/4
De Schryver 2016	Retrospective case series	High	Canada	Industry and non industry	164	Not stated	2-12y Mean 7y	All foods	Brown
Deschildre 2016	Prospective cohort	Moderate	France, Belgium, Luxemburg	Non-industry	669	200	Median 9y (IQR 6-13) 14% >16y	Peanut	2+ organs or anaphylaxis
Grabenhenrich 2016	Anaphylaxis registry	Moderate	Europe	Internal	1970 1092 food	18 food	≤18 y	All triggers (not just food)	Ring+Messmer Grade 3+ICU or Grade 4
Jiang 2016	Retrospective case series	High	China	Non-industry	1501 food	737	0.4-75 y Mean 30y	All foods	Life-threatening anaphylaxis
Mullins 2016	Fatality case series	Moderate	Australia	Non-industry	22	22	4-66 y Median 28y	All foods	Fatal anaphylaxis
Versluis 2016	Retrospective cohort	High	Netherlands	Industry and non industry	496	258	Mean 33 y (sd 12.5)	All foods	Mueller grade 3/4
Stensgaard 2017	Cross-sectional study	High	Denmark	Not stated	369	N/A	Mean 15 y (sd 8.1 y)	Peanut, hazelnut, egg,	N/A
Chan 2017	Open FC, prospective	Low	Australia	Non-industry	726	19	Age 1-4y	Peanut, egg, sesame	Anaphylaxis (ASCIA)
Abrams 2017	Open FC, retrospective	High	Canada	Internal	104	20	≤18y Median 5.5y	All foods	Study-defined anaphylaxis
Motosue 2017	Retrospective case series	High	USA	Internal	10464	591	Adults + children	All foods	Hospital/ICU admission
Nieto-Nieto 2017	Population hospital data	Moderate	Spain	Internal	5261				ICU/mechanical ventilation
Yanagida 2017	DBPCFC, retrospective	Moderate	Japan	Non-industry	393	98	Children >5y Median 8.3y	Milk, egg, wheat, peanu	Study-defined
Datema 2018	DBPCFC, prospective	Moderate	Europe	Non-industry	423 87 with FC	116 32 FC	Adults + children	Hazelnut	Study-defined anaphylaxis

Citation	Study type	Risk of bias	Country	Funding source	Total no. participants		Age	Allergy type	Severity Definition
					Overall	"Severe" group			
Reier-Nilsen 2018	DBPCFC, prospective	Moderate	Norway	Industry and non-industry	96	Not stated	5-15 y Median 9.7y	Peanut	EAACI 2007, Sampson
Worm 2018	Anaphylaxis registry	Moderate	Europe	Internal	2588 food	953	Children + Adults	All foods	Ring & Messmer
Pettersson 2018	DBPCFC, prospective	Moderate	Netherlands	Internal	734	270	≤18y Median 6y	Milk, egg, peanut, hazelnut, cashew	Astier Grade 4
Kennard 2018	Retrospective case series	High	UK	Internal	132	87	Adults	WDEIA	Brown
Dua 2018	Open+blinded FC, prospective	Low	UK	Non-industry	160	14	Adults	Peanut	Ewan & Clark
Christensen 2018	Open FC, prospective	Low	Denmark	Internal	71 46 with +ve FC	Not stated	20-73 y Mean, 43y	WDEIA	Sampson
Chinthrajah 2018	DBPCFC, prospective	Moderate	USA	Non-industry	120	22	4-18 y Median 11y	Peanut	Study-defined
Pouessel 2018	Prospective cohort	Moderate	France	Not stated	62	44	Children	All foods	Ring & Messmer Grade 3/4 with ICU
Arkwright 2018	Open+blinded FC, retrospective	Moderate	UK, Ireland, Australia	Non-industry	525	55	Children	Peanut	Anaphylaxis (ASCIA)
Purington 2018	DBPCFC, retrospective	Moderate	USA	Non-industry	410	98	1-52y Median 9y	All foods	Study-defined
Versluis 2019	Prospective cohort	Moderate	Netherlands	Industry and non-industry	157	41	18-70y Mean 35y	All foods	Mueller grade 3/4
Datema 2019	Open+blinded FC, retrospective	Moderate	Denmark	Industry and non-industry	181	118	0.6-27 y Mean 6.5 y	Peanut	Sampson grade 3/4
Tejedor-Alonso 2019	Systematic review	Low-moderate	Variable	Internal	15 studies 15,072 patients	Not stated	Not stated	All foods	Varied with study
Pouessel 2019[a,b]	Case series	Moderate	France	Industry and non-industry	18	18	6-62y Median 15y	All foods	Fatal anaphylaxis, PICU admission

Citation	Study type	Risk of bias	Country	Funding source	Total no. participants		Age	Allergy type	Severity Definition
					Overall	"Severe" group			
Ballmer-Weber 2019	Open+blinded FC, prospective	Moderate	Switzerland, Germany, and Spain	Incomplete declaration	91 15 DBPCFC 46 open FC 30 anaphylaxis	70 40 with FC	Children + Adults	Walnut	Systemic reaction
Ramsey 2019	Case series -ICU data	Moderate	USA, Canada	Internal	1989	19	Children	All foods	ICU admission
Dua 2019	RCT	Low	UK	Non-industry	100	Not stated	Adults	Peanut	Adrenaline use
Francuzik 2019	Anaphylaxis registry	Moderate	Europe	Internal	5765 1162 food	42 9 food	Adults + children	All triggers	3+ doses of adrenaline
Shaker 2020	Systematic review	Low	Variable	Internal	32 studies	Not stated	Adults + children	All triggers	Biphasic anaphylaxis
Poirot 2020	Fatality case series	Moderate	USA	Internal	24	24	Adults + children	All foods	Fatal anaphylaxis
Kiewiet 2020	Retrospective case series	Moderate	Sweden	Non-industry	128	60	19-76 y Median 51y	Alpha-gal (meat)	Study-defined
Santos 2020	Open FC, prospective	Moderate	UK	Non-industry	117	13	5-6 y	Peanut	CTCAE grade severe
Olabarri 2020	Prospective cohort	Moderate	Spain	Non-industry	453 episodes of anaphylaxis 396 due to food	61	Median 5 y (IQR 2-9 y)	All foods	2+ doses of adrenaline, biphasic reaction, intubation, ICU
Kraft 2020	Anaphylaxis registry	Moderate	Europe	Internal	9171 3343 food	435 158 food	Adults + children	All triggers	Biphasic reaction
Su 2020	Retrospective case series	Moderate	USA	Non-industry	203	19	Adults + children	All triggers	Poor weight gain
Kaur 2021	Open FC, prospective	Moderate	Australia	Internal	89	30	Median 9 y (IQR 6-12y)	Peanut	Study-defined
Goldberg 2021	Open FC, prospective	Moderate	Israel	Internal	120	60	Median 8 y (IQR 6-11y)	Walnut	WAO 2010

Citation	Study type	Risk of bias	Country	Funding source	Total no. participants		Age	Allergy type	Severity Definition
					Overall	"Severe" group			
Tejedor-Alonso 2021	Systematic review	Low-moderate	Variable	Internal	13 studies	Not stated	Not stated	All triggers	Varied with study
Yonkof 2021	Open FC, retrospective	Moderate	USA	Internal	158	Not stated	Children	Egg, milk, nuts	NIAID
Maris 2021	Anaphylaxis registry	HIgh	Europe	Internal	1962	304	≤17 years	All foods	Ring & Messmer G3/4
Baseggio Conrado 2021	Fatality case series	Moderate	UK	Non-industry	187	187	Adults + children	All foods	Fatal anaphylaxis
Miceli Sopo 2021	Open FC (FPIES), retrospective	Moderate	Italy	Not stated	91 48 with +ve FC	4	≤10y Mean 2y	All foods	ICON FPIES guideline
Gabrielli 2021a	Case registry (prospective+ retrospective)	Moderate	Canada	Non-industry	3498 2769 food	240	Median 8y (IQR 3-16y) 20% ≥16y	All triggers	EAACI 2007; admission±ICU
Gabrielli 2021b	Case registry (prospective+ retrospective)	Moderate	Canada	Non-industry	250	27	Median 10y (IQR 3-23y)	Fruit only	EAACI 2007
Lyons 2021	Prospective cohort	Moderate	Europe	Non-industry	531 336 with probable FA	90	Mean 30y (sd ±13.9 y) 15% <18y	Walnut	Study-defined anaphylaxis
Kraft 2021	Anaphylaxis registry	High	Europe	Internal	1691 250 wheat	667 153 wheat	13+ y	Wheat	Brown
Lam 2021	Population hospital data	Moderate	UK	Internal	15,405	N/A	Adults + children	All foods	Hospital admission
Turner 2021	DBPCFC, prospective	Low	UK, Spain	Non-industry	83	16	Children 6-18 y, median 10 y	Cow's Milk	Anaphylaxis (WAO 2020)
Baseggio Conrado 2021	Systematic review	Low	Variable	Internal	65 studies	Not stated	Adults + children	All triggers	Study-defined anaphylaxis
Kennedy 2021	Open FC, retrospective	High	USA	Internal	675	128	≤18 y Medial 6 y	All foods	Study-defined

TABLE S6.6: SUMMARY OF RISK OF BIAS

Study	Selection bias	External validity*	Case definition valid?	Data collection valid and systematic?	Recall bias	Internal validity**	Overall risk of bias
Taylor et al, 2010	Low	+	++	+	Low	+	Low
Pastorello 2011	Moderate	±	±	±	High	±	High
Calvani 2011	Moderate	+	+	±	Moderate	+	Moderate
Huang 2012	Moderate	±	+	±	High	±	High
Neuman-Sunshine 2012	Moderate	±	+	±	High	±	High
Eller 2012	Moderate	+	++	+	Low	+	Moderate
Nguyen-Luu 2012	High	±	+	+	High	±	High
Rolinck-Werninghaus 2012	Moderate	+	++	++	Low	++	Moderate
Cianferoni 2012	Moderate	±	±	±	Moderate	±	High
Vetander 2012	Moderate	+	+	±	Moderate	±	Moderate
Eller 2013	Moderate	+	++	+	Low	+	Moderate
Masthoff 2013	High	±	±	+	Moderate	±	High
van Erp 2013	Low	+	+	+	Low	++	Low
Brown 2013	Low	++	++	+	Low	++	Low
Libbers 2013	Moderate	+	+	+	Low	+	Moderate
Klemens 2013	Moderate	+	+	+	Low	++	Moderate
Mulla 2013	Moderate	+	±	+	Moderate	±	Moderate
Johnson 2014	Moderate	+	±	±	Moderate	+	Moderate
Vetander 2014	Low	+	+	+	Moderate	+	Moderate
Clark 2014	High	±	±	+	Moderate	±	High
Jerschow 2014	Moderate	+	++	+	Low	+	Low
Xu 2014	Moderate	±	++	+	Moderate	+	Moderate
Nassiri 2015	Moderate	±	+	±	High	±	High
Turner 2015	Moderate	+	++	+	Low	+	Moderate
Song 2015	Moderate	±	+	+	Low	+	Moderate
Kukkonen 2015	Moderate	+	+	+	Low	+	Moderate
Francuzik 2015	Moderate	±	+	+	Moderate	±	Moderate
De Schryver 2016	High	±	+	±	Low	-	High
Deschildre 2016	Moderate	±	+	±	Moderate	±	Moderate
Uasuf 2015	Moderate	±	+	±	High	±	High
Grabenhenrich 2016	Moderate	±	+	+	Moderate	±	Moderate
Jiang 2016	High	±	+	±	High	-	High
Mullins 2016	Moderate	+	++	+	Low	+	Moderate
Versluis 2016	Moderate	±	±	+	High	±	High
Stensgaard 2017	High	±	±	±	High	+	High
Chan 2017	Low	++	+	++	Low	+	Low
Abrams 2017	High	±	+	+	Moderate	+	High
Motosue 2017	High	+	±	±	Low	±	High

Study	Selection bias	External validity*	Case definition valid?	Data collection valid and systematic?	Recall bias	Internal validity**	Overall risk of bias
Nieto-Nieto 2017	Moderate	+	±	+	Moderate	±	Moderate
Yanagida 2017	Moderate	+	±	+	Low	+	Moderate
Datema 2018	Moderate	±	+	+	Low	+	Moderate
Reier-Nilsen 2018	Moderate	±	+	++	Low	+	Moderate
Worm 2018	Moderate	±	+	+	Moderate	±	Moderate
Pettersson 2018	Moderate	+	+	+	Low	+	Moderate
Kennard 2018	High	±	+	±	High	+	High
Dua 2018	Moderate	+	+	+	Low	+	Low
Christensen 2018	Moderate	+	+	+	Low	+	Low
Chinthrajah 2018	Moderate	±	+	+	Low	+	Moderate
Pouessel 2018	Moderate	±	+	±	Moderate	±	Moderate
Arkwright 2018	Moderate	±	+	±	Moderate	±	Moderate
Purington 2018	Moderate	±	+	+	Moderate	±	Moderate
Versluis 2019	Moderate	±	+	+	Low	+	Moderate
Datema 2019	Moderate	+	++	+	Low	+	Moderate
Tejedor-Alonso 2019	N/A	N/A	+	±	N/A	+	Low-moderate
Pouessel 2019	Moderate	+	++	+	Low	+	Moderate
Ballmer-Weber 2019	Moderate	+	±	+	Moderate	+	Moderate
Ramsey 2019	Moderate	+	+	+	Low	+	Moderate
Dua 2019	Moderate	+	+	++	Low	++	Low
Francuzik 2019	Moderate	±	+	+	Moderate	±	Moderate
Shaker 2020	N/A	+	+	+	N/A	+	Low
Poirot 2020	Moderate	+	+	±	Low	+	Moderate
Kiewiet 2020	Moderate	±	+	+	Moderate	±	Moderate
Santos 2020	Moderate	+	±	+	Low	±	Moderate
Olabarri 2020	Moderate	+	+	±	Low	+	Moderate
Kraft 2020	Moderate	±	+	+	Moderate	±	Moderate
Su 2020	Moderate	+	±	±	Low	+	Moderate
Kaur 2021	Moderate	+	+	+	Low	+	Moderate
Goldberg 2021	Moderate	±	+	+	Low	+	Moderate
Tejedor-Alonso 2021	N/A	N/A	+	±	N/A	+	Low-moderate
Yonkof 2021	High	±	+	+	Low	+	Moderate
Maris 2021	Moderate	±	±	±	Moderate	±	High
Baseggio Conrado 2021	Moderate	+	++	+	Low	+	Moderate
Miceli Sopo 2021	Moderate	+	+	+	Moderate	+	Moderate
Gabrielli 2021a	Moderate	++	+	+	Low	+	Moderate
Gabrielli 2021b	Moderate	++	+	+	Low	+	Moderate
Lyons 2021	Moderate	±	+	++	Moderate	++	Moderate
Lam 2021	Moderate	+	±	+	Moderate	+	Moderate
Turner 2021	Moderate	+	+	++	Low	++	Low

Study	Selection bias	External validity*	Case definition valid?	Data collection valid and systematic?	Recall bias	Internal validity**	Overall risk of bias
Kraft 2021	Moderate	±	±	±	Moderate	±	High
Baseggio Conrado 2021	Moderate	++	±	±	Low	+	Moderate
Kennedy 2021	High	+	+	±	Moderate	±	High
Datema 2021	Moderate	±	±	+	Moderate	+	Moderate

*External validity assesses whether selection bias impacts on whether the study data are generalizable to the overall food-allergic population, and described as ++ (all or most of the criteria have been fulfilled, and where not the conclusions are very unlikely to alter), + (some criteria have been fulfilled, and where not fulfilled or adequately described, the conclusions are unlikely to alter), − (few or no checklist criteria fulfilled). **Internal validity reflects the degree of systematic data collection and how this data was sourced (e.g. direct from patients, contemporaneous medical notes, historical case notes)

TABLE S6.7: REASONS WHY STUDIES SCREENED AS FULL TEXT WERE EXCLUDED

Study	Reason not eligible
Ballini et al. Frequency of positive oral food challenges and their outcomes in the allergy unit of a tertiary-care pediatric hospital. Allergol Immunopathol (Madr). 2021;49(3):120-130.	Only 14 positive challenges FPIES challenges reported No robust analysis of severity for OFC for IgE-mediated food allergy
Blazowski et al. Food allergy endotype with high risk of severe anaphylaxis in children-Monosensitization to cashew 2S albumin Ana o 3. Allergy 2019;74(10):1945-1955.	Unclear how many individuals with anaphylaxis included. “Severe” anaphylaxis cohort included 77 children.
Buka et al. Anaphylaxis and ethnicity: higher incidence in British South Asians. Allergy. 2015;70(12):1580-7.	Only 38 reactions to food included.
Hompes et al. Elicitors and co-factors in food-induced anaphylaxis in adults. Clin Transl Allergy. 2013 Nov 21;3(1):38.	<50 food-allergic individuals with positive FC included.
Kim et al. Clinical Manifestations and Risk Factors of Anaphylaxis in Pollen-Food Allergy Syndrome. Yonsei Med J. 2019;60:960-968.	No FC reported, and <500 participants.
Klingebiel et al. Pru p 7 sensitization is a predominant cause of severe, cypress pollen-associated peach allergy. Clin Exp Allergy 2019;49(4):526-536.	Only 78 patients with prior anaphylaxis included (<100).
Kotaniemi-Syrjänen et al. Likelihood of Immediate Food Challenge Reactions Varies by Age, History, Allergens, and Levels of Sensitization. Pediatric Allergy, Immunology, and Pulmonology 2017.45-52.	No analyses in terms of severity following FC.
Lee et al. Antihypertensive medication use is associated with increased organ system involvement and hospitalization in emergency department patients with anaphylaxis. JACI 2013;131(4):1103-8.	Only 82 (<100) food-allergic individuals with anaphylaxis included.
Masthoff et al. Diagnostic value of hazelnut allergy tests including rCor a 1 spiking in double-blind challenged children. Allergy. 2012;67:521-7.	Only 32 objective reactions to hazelnut included
Sahiner et al. Serum basal tryptase may be a good marker for predicting the risk of anaphylaxis in children with food allergy. Allergy. 2014;69(2):265-8.	<100 food-allergic individuals with anaphylaxis included.
Sala-Cunill et al. Usefulness and limitations of sequential serum tryptase for the diagnosis of anaphylaxis in 102 patients. Int Arch Allergy Immunol. 2013;160(2):192-9.	Only 35 reactions to food included.

Study	Reason not eligible
Sánchez-Ruano et al. Clinical utility of microarray B-cell epitope mapping in food allergies: A systematic review. Pediatr Allergy Immunol. 2020;31(2):175-185.	No analyses relating to severity reported.
Santos et al. Distinct parameters of the basophil activation test reflect the severity and threshold of allergic reactions to peanut. JACI 2015;135(1):179-86.	Overlap with Santos et al 2020
Srivastava et al. Systemic reactions and anaphylaxis with an acute serum tryptase ≥14 µg/L: retrospective characterization of etiology, severity and adherence to NICE guidelines for serial tryptase measurements and specialist referral. J Clin Pathol. 2014;67(7):614-9.	Only 10 reactions to food included.
Ta et al. Use of Specific IgE and Skin Prick Test to Determine Clinical Reaction Severity. Br J Med Med Res. 2011;1(4):410-429.	N=24 only
Wang et al. Food Protein-Induced Enterocolitis Syndrome Food Challenges: Experience from a Large Referral Center. JACI Pract. 2019 Feb;7(2):444-450.	Only 30 challenges positive (<50), with most FC undertaken to demonstrate resolution. Analysis of risk factors for historical severity not possible.

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