EAACI Food Allergy and Anaphylaxis Guidelines

Primary prevention of food allergy

Short title: EAACI Food Allergy Primary Prevention Guideline

Key words: infants, children, adults, primary prevention, food allergy, EAACI

Words: approximately 4500 (Max. 4500)
Abstract

Food allergy can have significant effects on morbidity and quality of life and can be costly in terms of medical visits and treatments. Therefore, there is considerable interest in approaches that may reduce the risk of developing food allergy. This Guideline has been prepared by the European Academy of Allergy and Clinical Immunology’s (EAACI) Taskforce on Prevention and is part of the EAACI Guidelines for Food Allergy and Anaphylaxis. It aims to provide evidence-based recommendations for primary prevention of food allergy. A wide range of antenatal, perinatal, neonatal and childhood strategies have been investigated, and the effectiveness and safety of these strategies have been assessed and synthesized in a systematic review.

Based on this evidence families can be provided with some advice about preventing food allergy, particularly amongst infants at high-risk for development of allergic disease. The advice for all mothers include a normal healthy diet without restrictions during pregnancy and lactation. For all infants exclusive breastfeeding is recommended for the first 4-6 months of life. If breastfeeding is insufficient or not possible for the first four months, infants at high-risk can be recommended a hypoallergenic formula with a documented preventive effect for the first 4 months. There is no need to avoid introducing complementary foods beyond four months, and the present evidence does not justify recommendations about either withholding or encouraging exposure to potentially allergenic foods after four months of age once weaning has commenced, irrespective of atopic heredity. There is no evidence for the use of supplements such as prebiotics or probiotics for food allergy prevention.
Background

Food allergy can have a significant effect on people’s morbidity and quality of life, and can be costly in terms of medical visits and treatments. Given the morbidity resulting from food allergy, there is considerable scientific, professional and lay interest in approaches that may reduce the risk of developing food allergy. This Guideline has been prepared by the European Academy of Allergy and Clinical Immunology’s (EAACI) Taskforce on Prevention and is part of the EAACI Guidelines for Food Allergy and Anaphylaxis. This Guideline aims to provide evidence-based recommendations for primary prevention of food allergy. The primary audience is allergists throughout Europe, but it is also likely to be of relevance to all other healthcare professionals (e.g. doctors, nurses, pharmacists and paramedics) in hospitals and primary care.

The causes of food allergy are likely to reflect an interaction between genetic factors and environmental exposure. Genetic factors are currently not modifiable, so strategies to prevent food allergy have tended to focus on early likely exposures to the food proteins most likely to be involved in its pathogenesis. This may occur antenatally or during breastfeeding, by focusing on the maternal diet, or it may be by directly targeting infant nutrition. In addition, there has been a focus on other nutritional factors or supplements that may modify the immune system in a positive direction.

In this guideline, primary prevention of food allergy is defined as prevention of development of food allergy. A wide range of antenatal, perinatal, neonatal and childhood strategies have been investigated, and the development of the Guideline has been informed by a systematic review of primary prevention of food allergy examining strategies for the primary prevention of food allergy in children and adults[1]. This systematic review includes only studies with food allergy or food sensitization as outcomes. In instances where there is a lack of clear or consistent evidence, the findings of the literature review have been supplemented with expert consensual opinion. Even though only studies where food allergy or food sensitization was an outcome were included, other possible atopic/allergic symptoms such as atopic dermatitis are also reported. Not all studies reported on confirmed food allergy or sensitization to foods, and some reported food allergy in a combined outcome with other allergies.

Methods
This guideline was produced using the Appraisal of Guidelines for Research & Evaluation (AGREE II) approach [2;3]. This is a structured approach to guideline production that is designed to ensure appropriate representation of the full range of stakeholders, a careful search for and critical appraisal of the relevant literature, a systematic approach to the formulation and presentation of recommendations, and steps to ensure that the risk of bias is minimized at each step of the process. We provide below an overview of the approach used.

Clarifying the scope and purpose of the Guideline
This process began in January 2012 with a meeting to discuss the overall approach to guideline development, including detailed discussions on the main aims of the guidelines, the target conditions, clarifying the target populations, to whom the recommendations applied, agreeing the intended end-user group, and ensuring adequate professional and lay representation in the guideline development process.

Ensuring appropriate stakeholder involvement
Participants represented a range of European countries, and disciplinary and clinical backgrounds (including medical secondary care, primary care and nursing), and patient groups. The Prevention Task Force continued to work together over the ensuing 18 months through email discussions, teleconferences and face-to-face meetings.

Systematic review of the evidence
The initial full range of questions that were considered important were rationalized through several rounds of iteration to agree to one key over-arching question (Box 1) that were then pursued through a formal protocol [4] to a systematic review of the evidence [1].

Seven bibliographic databases were searched from their inception to September 30, 2012 for systematic reviews, randomized controlled trials, quasi-randomized controlled trials, controlled clinical trials, controlled before-and-after studies, interrupted time series and cohort studies. Cohort studies were included due to an inability to randomize with interventions such as breastfeeding. Excluded were reviews, discussion papers, non-research letters and editorials, qualitative studies, case studies, case series and animal studies.

Formulating recommendations
We used the GRADE approach to translate the key findings from these systematic reviews into evidence-linked recommendations [5] (Box 2). This involved formulating clear recommendations and making clear the strength of evidence underpinning each recommendation. This ranged from consistent evidence derived from systematic reviews of randomized controlled trials through to evidence derived from expert consensus. Experts identified the resource implications of implementing the recommendations, barriers and facilitators to the implementation of each recommendation, advice on approaches to implementing the recommendations and suggested audit criteria that can help with assessing organizational compliance with each recommendation.

**Peer review**

A draft of this Guideline was externally peer-reviewed by experts from a range of organizations, countries and professional backgrounds. All feedback was considered by the Prevention Task Force and, where appropriate, final revisions were made according to the feedback received.

**Identification of evidence gaps**

The process of developing this guideline has identified a number of evidence gaps and we plan in future to prioritize the questions that the Prevention Task Force believes should be most urgently addressed.

**Editorial independence and managing conflict of interests**

The production of this guideline was funded and supported by EAACI. The funders did not have any influence on the guideline production process, its contents or on the decision to publish. Conflicts of interest statements were completed by all members of the Task Force and these were taken into account by Task Force chair as recommendations were formulated.

**Updating the Guideline**

We plan to update this guideline in 2017 unless there are important advances before then.

**Challenges in interpreting the evidence**

Food allergy is a complex topic because the symptoms are diverse and allergies can manifest in many different forms. In children only around one third of parental reported food allergy can be confirmed when appropriately investigated. In the population S IgE sensitization to foods is not always associated with clinical reactions and food allergy [6-10]. So the diagnostic accuracy is suboptimal when based solely on history and/or sensitization; a food allergy diagnosis needs to be
confirmed by controlled elimination and challenge procedures when possible. Unfortunately, most studies on prevention of food allergy rely on reported reactions or low-level sensitization to foods. Moreover, it is important to be aware of the natural course of food allergy, since food allergies develop in the order of exposure to different foods and many children with food allergies, e.g. cow’s milk allergy, develop tolerance during the first years of life. Therefore, it is important to investigate specific food allergies in the relevant age groups when they experience symptoms suggestive for food allergy, and to investigate the specific food allergens that are relevant. Finally, most studies are not sufficiently powered to detect clinical important reductions of the incidence of food allergy. It is not ethical to randomize mothers to breastfeeding their infants and evidence on this topic has therefore been based on high-quality observational studies. However, exclusively breastfed children may be not comparable to others due to self-selection and these mothers may be more motivated to exclusively breastfeed due to atopic heredity or early symptoms in their children. Thus, there may be a risk of reverse causation, which is not taken into consideration in most studies.

It is important to note that the quality assessment in the systematic review was, in keeping with standard practice, undertaken on methodological grounds, rather than on the clinical relevance or overall validity of the studies. When extracting the relevant evidence for the guidelines it is also important to evaluate the scientific quality and clinical relevance of the studies. Thus, for these recommendations on primary prevention of food allergy the above mentioned factors have been considered alongside the formal methodological quality assessment, and experimental studies reporting on confirmed food allergy are ranked highest, whereas studies with self-reported food allergy, atopic symptoms (which may represent food allergy) and sensitization as outcomes are included but are ascribed a lower validity. Studies reporting only retrospective data are not included due to their high risk of bias.

Primary prevention

Box 1 Key terms
| **High risk:** | In the literature defined as infants / children having at least one parent and/or sibling with a history of allergic disease sometimes also supplemented with an elevated cord blood IgE. Here we are defining high-risk as having one or two parents and/or older siblings with a history of allergic disease. |
| **Unselected:** | Infants and children in an unselected population including families with and without allergic diseases i.e. low risk as well as high risk infants / children |
| **Infancy:** | In the literature used to describe either first month or first year; here infancy is defined as the first year of life. |
| **Children:** | Here defined as after one year of life. |
| **Sensitization:** | A positive skin prick test and/or detectable specific IgE irrespective of method or cut-off values and irrespective of clinical reactions |
| **Food allergy:** | Adverse reaction to a food allergen caused by immunological reactions |
| **Proven food allergy:** | Food allergy documented by controlled elimination / challenge procedures |

Almost all of the studies focused on dietary strategies of some type. The studies can be conceptually divided into those which target pregnant women (dietary restrictions and supplements), those which target mothers while breastfeeding (dietary restrictions and supplements) and those which target infants directly (breastfeeding and exclusive breastfeeding, cow’s milk formula substitutes, supplements, delaying the introduction of complementary foods and dietary restrictions). Other preventive initiatives included vaccinations and multifaceted strategies combining dietary and environmental changes or targeting both mothers and infants simultaneously.

Almost all of the studies focused on preventing the development of food allergy from an early age i.e. antenatal and infancy. Many studies focused on infants at high-risk due to having a family history of allergic disease.

**Antenatal prevention**
Overall, there is no evidence to recommend that women modify their diet during pregnancy or take any supplements such as probiotics in order to prevent food allergy in their infants / children (B).

High-risk families
Currently the evidence supporting the role of specific dietary modifications during pregnancy to prevent food allergy in high-risk infants/children is lacking.
A systematic review [11][SR35] and two randomized controlled trials [12;13] found no benefit from restricting common food allergens among pregnant women.
Fish oil supplements may deserve further investigation as two randomized controlled trials suggested trends towards reduced sensitization to egg [14-16].
One trial found that probiotic supplementation during pregnancy among high-risk families reduced allergic sensitization, but there was no evidence specific to food sensitization or food allergy [17].

Unselected families
In an unselected population, one cohort study indicated that maternal intake of foods rich in n-6 polyunsaturated fatty acids and allergenic foods during late pregnancy may increase the risk of childhood sensitization, as opposed to foods rich in n-3 polyunsaturated fatty acids. Also high intake of celery and citrus fruits was associated with an increase in food sensitization, but there were no data on food allergy [18].

Prevention strategies for breastfeeding mothers
There is no evidence to recommend that breastfeeding women modify their diet or take any supplements such as probiotics in order to prevent food allergy in their infants / children (B).

High-risk families
There is no evidence to support intervention strategies for breastfeeding mothers. Two low quality non-randomized comparisons found that *maternal dietary changes* i.e. avoidance of the allergenic foods while breastfeeding may not prevent food allergies in infants [19;20].
One randomized trial found no effect on food sensitization from probiotic supplement during late pregnancy and lactation [21;22].

Unselected families

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

Prevention strategies during infancy

Breastfeeding

Breastfeeding has many benefits for mother and child and is therefore recommended for all infants. There is a small amount of evidence to support breastfeeding as a means of preventing the development of food allergy (C).

The immunomodulatory components e.g. long chain fatty acid content and human milk oligosaccharides in breast milk may differ from one mother to another, making it more complex to study the effect of breast milk per se on allergy prevention [26-28].

High-risk families

Although breastfeeding is widely promoted and has many other benefits, there is limited evidence to draw firm conclusions about the benefit for food allergies among infants at high-risk. One systematic review [29] found that most studies identified some benefit of breastfeeding. One randomized trial of preterm infants indicated a lower risk for cow’s milk protein allergy in high-risk infants fed human bank milk as compared to preterm or term formula[30]. However, one cohort study found that those who were exclusively breastfed for five months or more were more likely to be sensitized to eggs at one year, but not at two years; no data on food allergy was included [31].Another study found that breastfeeding for 6 months or more and introducing solid foods after 3 months was associated with an increased risk for atopy including food sensitization at 5 years [32]). However, the latter study was a part of a trial including other interventions, which makes it difficult to evaluate the effect of breastfeeding.

Unselected families
The evidence is also mixed in unselected populations or those at normal risk. One systematic review [29](SR 56) and four cohort studies[33-36] found that breastfeeding was associated with a reduced risk of food allergy or sensitization in childhood, three found no association in unselected populations[37-39]R 6 but one was not powered at food allergy prevention [37],and another was not targeted at food allergy[39]. Furthermore, one cohort study suggested an increased risk for self-reported food allergy in those with high-risk only [40].

**Alternatives to cow’s milk formula for infants**

There is evidence to recommend that hypoallergenic hydrolyzed cow’s milk based formulas with proven clinical preventive efficacy, are used for infants at high risk, for the first four months, if breastfeeding is insufficient or not possible (B).

**High-risk families**

There is more positive evidence about the benefits of alternatives to cow’s milk formula for infants. Two systematic reviews[29;41] (SR 73, 74), four randomized trials [42-46] and two non-randomized trials suggested that extensively hydrolyzed whey or casein formulas may have a protective effect, although two other randomized comparisons failed to find a benefit [47;48]. However, in one of these, the children were breastfed for a long period and the formula was introduced after the age of 6 months[47]. Another randomized trial combining extensively hydrolyzed casein based formula with avoidance of some foods for varying periods and maternal diet, also found a benefit of extensively hydrolyzed casein based formula on food allergy until three years of life[49-51]. In one of the systematic reviews food allergy were not reported separately, only as part of atopic symptoms[41]. The Swedish study [47]reported on symptoms suggestive of food allergy, whereas the others reported on confirmed food allergy.

**Partially hydrolyzed infant formula** also appears to have a protective effect. Two systematic reviews[52;53], two randomized controlled trials[45;54] and two non-randomized comparisons [55;56] found that partially hydrolyzed formula may protect against food allergy, and the latter two found that food allergy symptoms or sensitization may be reduced when compared to standard cow’s milk formula. One randomized trial [57] and one non-randomized comparison[58] failed to find any benefit. However, in one [57] outcomes were only assessed by telephone interview.
A few studies have compared the possible preventive effect of extensively and partially hydrolyzed formulas. They indicate that the preventive efficacy is dependent on the specific formula studied. The degree of hydrolysis alone may not correlate with the efficacy of prevention of food allergy [59] and also different extensively hydrolyzed formulas may have different effects. Thus, an extensively hydrolyzed whey formula used in the German GINI study was not effective for prevention, whereas another extensively hydrolyzed whey formula was effective in other studies and extensively hydrolysed casein formula has been effective in several studies. A few studies indicated that some extensively hydrolysed formulas (based on casein or whey) might have a better preventive effect as compared to partially hydrolyzed whey formula [42] or a blend of casein and whey [44], though a metaanalysis found no significant difference [53].

There was no evidence to support the use of soy-based formulas in allergy prevention. One systematic review [60] and two randomized trials [57;61] found that soy-based formulas might not protect against food allergies when compared to cow’s milk formula or to other alternatives. However, in one of the latter [57] outcome were assessed by telephone interview.

**Unselected families**

There are no available data as these studies have not been performed.

**Dietary supplements**

There is no evidence to recommend pre- or probiotics or other dietary supplements based on particular nutrients to prevent food allergy (B).

**Probiotic supplements**

**High-risk families**

Probiotic supplements have been tested during infancy, but there is little evidence to support their effectiveness. Four randomized controlled trials [62-65] found no benefit against food allergy or sensitization.

**Unselected families**

There is no evidence to support prebiotics or probiotics to prevent food allergy in unselected or mixed-risk populations. One systematic review [66] found insufficient evidence about the benefits of prebiotics in infant formula and one randomized trial using a particular blend of neutral oligosaccharides and pectin-derived acidic oligosaccharides [67] found benefit for eczema but not...
for food sensitization. Two systematic reviews [68;69] and one randomized trial using Lactobacillus
and Bifidobacterium Lactis [70] found no benefit of using probiotics in unselected or mixed
populations.

Other supplements

One randomized trial [71] found no evidence to recommend or avoid cow’s milk based human
milk fortifier in premature infants, though the study may not be powered for food allergy as an
outcome. One cohort study [72] found no evidence to recommend or avoid vitamin A and D as
water-soluble or in peanut oil.

Introduction of complementary foods

There is insufficient evidence to make specific recommendations about the timing of the
introduction of complementary foods and individual solid foods in regards of food allergy
prevention (C). However, a few studies indicate that it might be an advantage not to introduce
solids before 4 months of age (C). In addition, other aspects have to be considered, such as the
infant’s developmental readiness, parental opinion/needs, the nutritional needs and the risk for
developing very selective eating habits. Therefore, we recommend introducing complementary
foods from 4-6 months of age according to standard local practices and the needs of the infant,
irrespective of atopic heredity.

High-risk families

Another strategy has been to delay the introduction of solid foods. Infants may not need or may
not be developmentally ready to start eating solid foods until sometime within the age range of 4-
6 months, so this period of ‘four to six months’ is often considered to as an appropriate minimum
weaning age. Some research suggests that introducing solid foods earlier than four months may
increase the risk of food sensitization in infants with a family history of allergy. However, delaying
the introduction of solid foods beyond four months does not seem to confer any additional
protective benefits. Two low quality cohort studies [73;74] found no evidence that introducing
solid foods after four months in high-risk infants prevented food allergy. This finding is supported
by the low prevalence of food allergy in randomized trials on hydrolyzed formulas without
delaying introduction of solid foods after 4 - 6 months [42;43].

Unselected families
One systematic review [75] and two cohort studies [76;77] found that introducing solid foods after four months did not protect against food allergy; but one of these [76] found that introduction of solid foods before week 17 increased the risk of later allergy. Two cohort studies found reduced food sensitization when solids were introduced earlier than four months [37;78], in the latter only in those at high-risk.

**Introduction of potential food allergens**

The timing of potential food allergen introduction may be important, but there is insufficient evidence in this regard, and the present evidence does not justify recommendations about either withholding or encouraging exposure to potentially allergenic foods during infancy (B-C).

Therefore, for primary prevention we recommend no withholding or encouraging exposure to “highly allergenic” foods such as cow’s milk, hens egg and peanuts irrespective of atopic heredity, once weaning has commenced.

Two randomized controlled trials[79-81] found that there was no increased risk of food allergy from early exposure to cow’s milk protein in the first three days of life, but in one [79;80]the diagnostic criteria for food allergy was week and not documented by challenges while the other one[81] the symptoms were unspecific and food allergy was not reported. Another randomized trial [82] and one cohort study [36] suggested an increased risk of confirmed cow’s milk allergy if children in unselected populations were fed cow’s milk protein in the first few days.

There is little additional evidence about avoiding potential food allergens. One cohort study found [83] that consuming fish regularly during the first year of life may protect against food allergy or sensitization.

In another large cross-sectional study, not included in the review because of its design, comparing Israeli and UK Jewish children, the prevalence of peanut allergy was 10-fold higher in the UK than in Israel whereas the median monthly consumption of peanuts in Israeli infants was very high but absent in the UK [84]. This is an interesting association, which has to be confirmed in further studies [85].

**Combining dietary with environmental modifications**
Although the quality of evidence is low, there is some evidence from six studies [86-92] to suggest that combining dietary with different environmental recommendations or modifications during infancy for high-risk families may be useful (B). Further research in this area would be helpful because there are few data about specific food allergy outcomes and it is difficult to differentiate cause and effect relationships in the available literature.

Prevention strategies during childhood and adulthood

Very little has been published about strategies to prevent food allergy targeting children and adults, and all available studies are in unselected populations. One systematic review [93] found that BCG vaccinations had no protective effect against food allergy and another systematic review [94] found no protective benefit from fish oil supplements. A cohort study [95] found that taking vitamins before age five may protect against food allergy, but the quality of evidence is very low (C).

Conclusions and future perspectives

Based on this evidence families can be provided with some practical advice about preventing food allergy, particularly amongst infants at high-risk due to parent and/or older siblings with allergic disease (Box 3). The advice for all mothers includes the consumption of a normal healthy diet without restrictions during pregnancy and lactation. For all infants exclusive breastfeeding is recommended for the first 4-6 months of life. If breastfeeding is insufficient or not possible for the first four months, infants at high-risk can be recommended a hypoallergenic formula with documented preventive effect (i.e. documented in research trials) to the infant for the first 4 months of life. There is no need to avoid introducing complementary foods beyond four months or for infants and children to take supplements such as prebiotics or probiotics. In addition, the present evidence does not justify recommendations about either withholding or encouraging exposure to potentially allergenic foods after the age of 4 months irrespective of atopic heredity, once weaning has commenced.

Although no cost-effect or cost-benefit analysis has been published, the above recommendations seem to be easy to follow, at low cost and have a low potential for harm (D).
Whilst considering these recommendations, it should be remembered that just because there is a lack of evidence about some topics, it does not necessarily mean they are not useful, merely that there is yet insufficient proof of any potential benefit. In this regard, there is a need for future studies.

Acknowledgements

Authors’ contribution

Conflicts of interest
Box 1. Key over-arching question addressed in the supporting systematic reviews [4]

- What is the effectiveness of approaches for the primary prevention of food allergy?

Box 2. Assigning levels of evidence and recommendations [5]

**Level of evidence**

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level I</td>
<td>Systematic reviews, meta-analysis, randomized control trials</td>
</tr>
<tr>
<td>Level II</td>
<td>Two groups, non-randomized studies (e.g. cohort, case-control)</td>
</tr>
<tr>
<td>Level III</td>
<td>One-group non-randomized (e.g. before and after, pre test and post test)</td>
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<tr>
<td>Level IV</td>
<td>Descriptive studies that include analysis of outcomes (single-subject design, case-series)</td>
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<tr>
<td>Level V</td>
<td>Case reports and expert opinion that include narrative literature, reviews and consensus statements</td>
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**Grades of recommendation**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
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<tbody>
<tr>
<td>Grade A</td>
<td>Consistent level I studies</td>
</tr>
<tr>
<td>Grade B</td>
<td>Consistent level II or III studies or extrapolations from Level I studies</td>
</tr>
<tr>
<td>Grade C</td>
<td>Level IV studies or extrapolations from level II or III studies</td>
</tr>
<tr>
<td>Grade D</td>
<td>Level V evidence or troublingly inconsistent or inconclusive studies at any level</td>
</tr>
<tr>
<td>Recommendations</td>
<td>Evidence level</td>
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<tr>
<td>-------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td><strong>No dietary restrictions for all pregnant or the lactating mother for allergy preventive purposes</strong></td>
<td>I–II</td>
</tr>
<tr>
<td>High-risk infants should receive a hypoallergenic formula with documented preventive effect for the first 4 months, whereas other infants should receive a standard formula. After the age of 4 months a standard cow’s milk based formula is recommended according to standard nutrition recommendations, irrespective of atopic heredity</td>
<td>I</td>
</tr>
<tr>
<td><strong>Introduction of complementary foods after the age of 4 months according to normal standard weaning practices and nutrition recommendations, for all children irrespective of atopic heredity</strong></td>
<td>II–III</td>
</tr>
<tr>
<td><strong>No special dietary restrictions after the age of 4 months for infants with high risk for development of allergic disease</strong></td>
<td>II–III</td>
</tr>
<tr>
<td>No withholding or encouraging exposure to “highly allergenic” foods such as cow’s milk, hens egg and peanuts irrespective of atopic heredity, once weaning has commenced</td>
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### Box 4: Gaps in the evidence

<table>
<thead>
<tr>
<th>Gaps in the evidence</th>
<th>Plan to address</th>
<th>Priority</th>
</tr>
</thead>
<tbody>
<tr>
<td>The effect of timing of weaning and introduction of different food antigens - while breastfeeding versus while not breastfeeding.</td>
<td>Prospective randomised controlled study with sufficient power and well accepted diagnostic criteria. Probably difficult to address sufficiently, at least in countries with high rate of breastfeeding.</td>
<td>1</td>
</tr>
<tr>
<td>The effect of maternal nutrition and environmental exposures during pregnancy and lactation on development of food allergy in the child.</td>
<td>Prospective randomised controlled study with sufficient power and well accepted diagnostic criteria.</td>
<td>2</td>
</tr>
<tr>
<td>The preventive effect of different hydrolysed formulas on food allergy including long term effects.</td>
<td>Prospective randomised controlled study with sufficient power and well accepted diagnostic criteria. Europe wide cohort study looking at the ongoing childhood diet and allergy development (EuroPrevall follow-up, IFAAM)</td>
<td>3</td>
</tr>
<tr>
<td>The effect of pre- and probiotics on the incidence and prognosis of food allergy.</td>
<td>Prospective randomised controlled study with sufficient power and well accepted diagnostic criteria.</td>
<td>4</td>
</tr>
</tbody>
</table>
### Barriers and facilitators to implementation, audit criteria and resource implications of recommendations

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Evidence level</th>
<th>Grade</th>
<th>Key ref</th>
<th>Barriers to implementation</th>
<th>Facilitators to implementation</th>
<th>Audit criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendation 1</strong>&lt;br&gt;No dietary restrictions for all pregnant or the lactating mother for allergy preventive purposes</td>
<td>I - II</td>
<td>B</td>
<td>Kramer MS, 2012&lt;br&gt;Muraro A, III, 2004&lt;br&gt;Lilja G, 1991&lt;br&gt;Fälth-Magnusson K, 1992&lt;br&gt;Sausenthaler S, 2007&lt;br&gt;Sausenthaler S, 2011</td>
<td>Should be none</td>
<td>It is not an intervention, but normal unrestricted diet for women</td>
<td>All pregnant and lactating women should have no dietary restriction to prevent allergy in their children</td>
</tr>
<tr>
<td><strong>Recommendation 2</strong>&lt;br&gt;Exclusive breastfeeding is recommended for all infants for the first 4-6 months</td>
<td>II - III</td>
<td>C</td>
<td>Van Odijk, 2003&lt;br&gt;Muraro A, III, 2004&lt;br&gt;Kull I, 2010&lt;br&gt;Schoetzau A, 2002&lt;br&gt;Venter C, 2009&lt;br&gt;Saarinen KM, 1999&lt;br&gt;Saarinen KM, 2000&lt;br&gt;Høst A, 1988,&lt;br&gt;Lucas A, 1990</td>
<td>Lack of support at the nursery, from family and friends&lt;br&gt;Lack of maternity leave</td>
<td>Breastfeeding is a general recommendation for nutrition of infants and young children&lt;br&gt;Human milk provides the nutritional needs for normal children until the age of 4-6 months&lt;br&gt;Very few contraindications to breastfeeding&lt;br&gt;It is easy and cheap</td>
<td>≥ 75 % of all infants are breastfed for ≥ the first 4 months</td>
</tr>
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</table>
### Recommendations

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Evidence level</th>
<th>Grade</th>
<th>Key ref</th>
<th>Barriers to implementation</th>
<th>Facilitators to implementation</th>
<th>Audit criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendation 3</strong>&lt;br&gt; If breastfeeding is insufficient or not possible: High-risk infants should receive a hypoallergenic formula with documented preventive effect for the first 4 months, whereas other infants should receive a standard formula. After the age of 4 months a standard cow’s milk based formula is recommended according to standard nutrition recommendations, irrespective of atopic heredity</td>
<td>I</td>
<td>A  – B</td>
<td>Muraro A, III, 2004, Van Odijk 2003 Osborn DA, 2003 Zeiger RS, 1989, 1992, 1995 Halken S, 1993, 2000 Odelram H, 1996 Oldaeus G, 1997 Von Berg A, 2003 Von Berg A, 2008</td>
<td>Limited access to documented hypoallergenic formulas with documented preventive effect Costs for documented hypoallergenic formulas with documented preventive effect</td>
<td>It is a very little restrictive intervention Limited need for hypoallergenic formula in breastfed children</td>
<td>≥ 75 % high risk infants are breastfed for ≥ the first 4 months ≥ 75 % high risk infants have documented hypoallergenic formula if needed in the first 4 months ≥ 75 % high risk infants ≥ 4 month are offered normal and adequate nutrition without restrictions for preventive purposes</td>
</tr>
<tr>
<td><strong>Recommendation 4</strong>&lt;br&gt; Introduction of complementary foods after the age of 4 months according to normal standard weaning practices and nutrition recommendations, for all children irrespective of atopic heredity</td>
<td>II – III</td>
<td>C</td>
<td>Tarini BA, 2006 Sausenthaler S, 2011 Schoetzau A, 2002 Venter C, 2009 Joseph CL, 2011 Kull I, 2006</td>
<td>Little, if any Misleading advice</td>
<td>This is normal nutritional practice adequate for the particular age</td>
<td>≥ 90 % of all infants and children avoid unnecessary dietary restrictions</td>
</tr>
<tr>
<td><strong>Recommendation 5</strong>&lt;br&gt; No special dietary restrictions after the age of 4 months for infants with high risk for development of allergic disease No withholding or encouraging exposure to “highly allergenic” foods such as cow’s milk, hens egg and peanuts irrespective of atopic heredity, once weaning has commenced</td>
<td>II – III</td>
<td>C</td>
<td>As for recommendation 3+4</td>
<td>Little if any Misleading advice</td>
<td>This is normal nutritional practice adequate for the particular age</td>
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</tr>
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Reference List


