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Modifying the infant's diet to prevent food allergy

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Abstract (175 words)

Recommendations and guidelines on the prevention of food allergy have changed in recent decades. The aim of this review of the current evidence and on-going studies is to provide a comprehensive picture of the current state of the art in this field for healthcare professionals. It was undertaken as part of the European Union funded iFAAM (Integrated Approaches to Food Allergy and Allergen Management) study. This is a wide-ranging project bringing together expertise across the breadth of food allergy research. Specifically, the review discusses dietary manipulation in food allergy prevention and covers the possible preventive strategies of allergen avoidance, early allergen introduction, general nutrition and supplements as well as other strategies such as pre- and probiotics.. The review concludes that despite agreement that allergen avoidance strategies should not be undertaken for allergy prevention, there is currently no consensus regarding what actions should be recommended beyond exclusive breastfeeding for the first 4-6 months of life. Recent and up-coming trial results, which are detailed in this review, should help inform the debate and add clarity to the topic.

Introduction

Food allergy affects all ages and has serious health consequences.[1] There has been speculation of its pathophysiology with research focussing on prevention. Additionally, there have been numerous recommendations from groups ranging from national health bodies to mothers' "blogs" on how to prevent food allergy. This advice has changed over time causing confusion amongst healthcare professionals and the lay public.

A further complication is the differing terminology used to define food reactions [2,3] This leads to conditions with differing immunological mechanisms being considered together under an umbrella term of 'food allergy' hindering identification of causative factors due to heterogeneity of cases studied.

This manuscript aims to present an up to date review of current understanding of primary and secondary IgE-mediated food allergy prevention in relation to infant feeding (Figure 1). The recent publications of important randomised controlled trials (RCTs) makes this a timely review delivering a critical and independent overview of current evidence.

Figure 1 Algorithm of the three stages of allergy prevention

Allergenic food avoidance

In 1906, the principle that an allergic reaction occurred on the second and subsequent exposures to the allergen following initial allergen priming was first proposed. This led to the concept that exposure to the food allergen early in an infant's immunological development was important in food allergy initiation [4]. As knowledge in the field of immunology developed with

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3 the concept of immunological sensitisation and the discovery of IgE it became clear that the first
4 exposure could be in-utero or during breast-feeding. Consequently allergen avoidance became
5 the primary strategy for allergy prevention with an idealised strategy for allergy prevention being
6 published in 1983.[5] It aimed to avoid intra-uterine and post-natal sensitisation by minimising
7 exposure to sensitising proteins during the third trimester of pregnancy, during lactation by
8 recommending exclusive breast feeding of the infant (or fed an extensively hydrolysed infant
9 formula) until 6 months of age. It then advocated the introduction of 'relatively non-allergenic
10 foods' with milk, corn, citrus, legumes, egg, peanuts and fish introduction being delayed until 1
11 to 3 years of age. RCTs using this strategy initially had encouraging results[6-9] so the concept
12 of allergen avoidance for food allergy prevention continued into the late 1990's with national and
13 regional guidelines supporting these recommendations.[10,11]
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28 Early this century, allergy prevention research focussed on pregnancy,[12,13] environmental
29 factors,[14,15] and infant feeding strategies.[16] Related research suggested acquiring
30 tolerance to foreign (food) proteins was an active rather than a passive process.[17,18]
31 Consequently, early introduction of allergenic foods into the diet ought not to lead to
32 sensitisation or allergic disease.[19-21] This meant avoidance as an allergy prevention strategy
33 was questioned. Additionally, newer publications from observational birth cohort studies[22-25]
34 and subsequent systematic review[1] suggested evidence for recommending avoidance
35 strategies in pregnancy and lactation was lacking and delaying solid introduction did not appear
36 to protect against food allergy. Consequently, the latest recommendation for allergy prevention
37 by the European Academy of Allergy and Clinical Immunology (EAACI) does not support
38 avoidance as an allergy prevention strategy during pregnancy, lactation or complementary
39 feeding.[26] The American Academy of Pediatrics (AAP),[27] the Australasian Society of Clinical
40 Immunology and Allergy (ASCI)[28] and other national bodies[29,30] have similar views.
41 EAACI does however state that "current evidence does not justify any recommendations about
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3 either withholding or encouraging exposure to potentially allergenic foods after 4 months once
4 weaning has commenced".[26]
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7 8 **Introduction of allergenic foods** 9

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11 The World Health Organisation (WHO) recommendation for exclusive breastfeeding for the first
12 six months with complementary feeding thereafter alongside breastfeeding to two years of age
13 remains the basis for infant feeding recommendations in the UK and around much of the world
14 but it should be remembered that their primary aim was to reduce GI infections and allergy
15 prevention was not considered.[31] The European Society for Paediatric Gastroenterology,
16 Hepatology and Nutrition (ESPGHAN) committee recommends exclusive or full breastfeeding
17 for about six months as a desirable goal. It also adds that complementary feeding should not
18 start before 17 weeks but should have started by 26 weeks.[32] Meanwhile, advice from the
19 USA and Australia states solid food introduction, including allergenic foods, may begin between
20 four and six months.[27,28] Feeding recommendations relating to allergenic foods also
21 differs.[33] In practice, reported feeding practices vary, for example, 4% of infants are first
22 introduced to solids before 4 months of age in Australia and Greece compared to 43% in the UK
23 (Table 1).
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Table 1. International reported practices of food introduction in infants

Country	Year Data collected	Reference	Proportion of infants introduced to solids before 4 months	Proportion of infants introduced to solids after 6 months	Proportion of infants introduced to allergenic foods before 6 months	Proportion of infants introduced to allergenic foods by 8-10 months
Australia	2008-2010	Koplin et al 2010[34]	4%	5%		
France	2003-2006	de Lauzon-Guillain et al Am J Clin Nutr 2013[35]	~30%	~30%		
Germany	2002-2006	Tromp et al Arch Pediatr Adolesc Med 2011[36]		55%	69% Cows milk; 21% Hen's egg; 15% Peanut; 13% Tree nuts; 29% Soy	
Greece	2005-2007	de Lauzon-Guillain et al Am J Clin Nutr 2013[35]	~4%	~10%		
Ireland	2008-2012	O'Donovan et al (37)	18% (<17weeks)	3% (>26 weeks)	57% cow's milk; 57% gluten [Wheat (39%); Barley (13%); Rye (16%)]; 40% soy, 8% egg; 6% fish; 6% kiwi.	n/a
Portugal	2005-2006	De Lauzon-Guillain et al Am J Clin Nutr 2013[35]	~5%	~20%		

UK	2010* [‡] 2006- 2008 [†]	*Lennox et al 2011[38]; *McAndrew et al IFS 2010[39]; Grimshaw KE and Roberts G (40)	43%* 36.6% [†]	1.7% [†]	54% Cows milk; 42% wheat; 10% Hens egg; 19% Fish; 6% Kiwi; 0.5% Peanut [†]	8% (peanut) [‡]
USA	2005- 2007	Luccioli et al Pediatrics 2014[41]	34%		70% Cows milk; 0.9% Hens egg; 0.5% Peanut; 0.7% Soy; 0.2% Fish	

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3 Several observational studies have examined the association between age of complementary
4 feeding and allergy development.[24,34,42-44] Unfortunately interpretation of these studies is
5 limited by their heterogeneity, particularly regarding breastfeeding duration. This may prove to
6 be more important than the duration of exclusive breastfeeding since there is emerging data of
7 a possible protective effect on the development of allergy of solid introduction with concurrent
8 breastfeeding, [44, 45]. This supports the WHO recommendation that solid introduction should
9 ideally take place alongside continued breastfeeding. [31] Additionally, there is initial evidence
10 that introducing allergens as complementary foods and as part of a healthy diet is also
11 protective. [46, 47] However, even well designed observational birth cohort studies cannot
12 determine causality, only associations. Nevertheless, anecdotal or observational evidence
13 points to lower allergy rates in countries where consumption of dietary allergens as
14 complementary foods starts at an earlier age.[42-44;48]4 Evidence from large-scale RCTs is
15 required to assess whether there is a causal relationship between early consumption and
16 reduced food allergy risk and a number of RCTs have been established with the aim of
17 addressing this.

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37 Three of these RCTs have reported fully: STAR, LEAP and EAT studies. The STAR study
38 enrolled 86 high-risk infants aged 4 to 6 months with moderate/severe eczema[49]. Of the
39 infants randomised to receive egg powder, 31% had an allergic reaction to the egg powder
40 leading to the study being stopped prematurely. At 12 months of age, there was a trend in this
41 small study towards fewer infants randomised to the egg ingestion group being diagnosed with
42 IgE mediated food allergy (33% versus 51%, $p=0.11$).

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Initial findings from the LEAP study, which enrolled 530 high-risk infants with moderate/severe
eczema and/or egg allergy aged 4 to 11 months, have been reported [50]. They demonstrated
that of infants randomised to open-label peanut consumption, 1.9% had peanut allergy

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3 determined by double-blind, placebo-controlled challenge at age 5 years compared to 13.7% in
4 the control group who avoided peanuts ($p < 0.001$). In a second group of 98 high-risk infants from
5 the LEAP study with a 1-4mm skin prick test wheal to peanut, 10.6% of the early consumption
6 group developed peanut allergy compared to 35.3% in the avoidance group ($p = 0.004$). The
7 findings from this study led to a consensus communication giving interim guidance on early
8 peanut introduction and the prevention of peanut allergy in high-risk infants.[51] Recently a
9 follow up to the LEAP study ("LEAP-ON" Study) has been published [52]. The participants were
10 reassessed for peanut allergy after all being on a peanut avoidance diet for a year. Peanut
11 allergy at 6 years continued to be much more prevalent in the LEAP avoiders than consumers
12 (18.6% versus 4.8%, $p < 0.001$) and there was no increase in peanut allergy in the LEAP
13 consumption arm. These results suggest that early introduction of peanut into the diet may
14 induce long term tolerance.
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30 The EAT study focused on the early introduction of six common food allergens into the diet of
31 1303 breastfed 3 month old infants recruited from a general (not high-risk) population. [53] In
32 an intention to treat analysis, 7.1% of the standard introduction group and 5.6% of the early
33 introduction group developed food allergy to one or more of the six intervention foods (peanut,
34 egg, cows milk, sesame, white fish and wheat) up to 3 years of age ($p = 0.32$). However, when
35 the analysis was adjusted for adherence to early introduction, there was a statistically significant
36 reduction in food allergy in the early introduction group (6.4% versus 2.4%, $p = 0.03$), suggesting
37 introduction of sufficient amounts of allergenic foods into the infant diet from three to six months
38 alongside continued breastfeeding may be effective in food allergy prevention. However, the
39 poor adherence to study protocol emphasises the challenges around introducing solids into the
40 diets of infants under six months of age.
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3 Four of the five on-going studies have been completed but their findings have not yet been
4 published. The final two will be completed over the next few years (Table 2). The four
5 completed studies all looked at early introduction of egg in the general population (HEAP) and in
6 children at moderate-risk of developing an allergy (BEAT, PETIT and STEP). They have similar
7 study designs and large enrolment numbers. HEAP has reported limited results in a conference
8 abstract [54] and symposium presentation with a conclusion that early consumption of hens egg
9 was not effective in preventing hens egg allergy, but full results are awaited. BEAT and PETIT
10 have also made a preliminary reports in abstract form. PETIT reported a scheduled interim
11 analysis which showed a significant difference in prevalence of egg allergy in the intention-to-
12 treat analysis (37.7% in placebo group and 8.3% in egg group ($p=0.0013$) with no significant
13 difference in adverse events between the groups.[55] BEAT findings showed a significant
14 reduction in egg skin test sensitisation rates and higher egg specific IgG4/IgE in infants who
15 had egg introduced between 4-6 months compared with those introduced after 8 months. They
16 reported no difference in clinical egg allergy and a significant rate of egg allergic reactions on
17 initial exposure in the infants randomised to receive egg, suggesting many at risk infants may
18 already be allergic and not be amenable to early introduction of egg by 4-5 months of age. [56]
19 The PEAAD Study will look at early peanut consumption in infants with eczema and a high risk
20 of developing a peanut allergy. Children in this study are not randomly assigned to the
21 intervention/control groups, instead, the carer chooses whether their child will consume or avoid
22 peanut. The age when children begin peanut consumption is wider than in the LEAP Study thus
23 providing data on the impact of peanut introduction beyond the first year of life. Finally, the
24 PreventADALL study will assess the impact of the introduction of four allergenic foods by 4
25 months, and/or emollient use to 9 months of age on food allergy development. All these studies
26 address slightly different populations in terms of allergy risk, resulting in a broad picture across
27 the atopic risk spectrum. Data from all these trials will be brought together in the EU-funded
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3 Integrated Food Allergy and Allergen Management (iFAAM) project to provide advice on allergy
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5 prevention strategies for clinicians and families.
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Table 2. Summary of current studies investigating the hypothesis that the early introduction of allergenic foods can induce oral tolerance

Name of Trial	Country (institution)	Allergen(s) of interest	Population	Study details	Study status
Enquiring About Tolerance (EAT)	UK (Kings College, London)	Cows' milk, hens' egg, peanut, cod, sesame, wheat	General population	<ul style="list-style-type: none"> Open-label RCT n = 1106 Enrolled at 3 months of age then consumption of 6 allergenic foods until 6 months or exclusive breastfeeding until 6 months of age Outcome: prevalence of IgE-mediated food allergy to any of the 6 allergenic foods between 1 and 3 years of age 	Reported
Learning Early About Peanut allergy (LEAP)	UK (Kings College, London)	Peanut	High-risk (infants with moderate / severe eczema and / or egg allergy)	<ul style="list-style-type: none"> Open-label RCT n = 640 Enrolled at 4-11 months then peanut consumption or avoidance until age 5 Outcome: prevalence of DBPCFC confirmed peanut allergy at 5 years of age 	Reported
Hens' Egg Allergy Prevention (HEAP)	Germany (Charite Hospital, Berlin)	Hens' egg	General population	<ul style="list-style-type: none"> RCT, placebo controlled n ~ 800 Enrolled at 4-6 months then consumption of egg powder or placebo until 12 months of age Outcome: prevalence of IgE-mediated egg allergy at 12 months of age 	Completed. Abstract presented [54]
Preventing Peanut Allergy in Atopic Dermatitis (PEAAD)	Germany (Charite Hospital, Berlin)	Peanut	High-risk (infants with atopic dermatitis)	<ul style="list-style-type: none"> Non-randomized, self-selected n~460 Enrolled at 5-30 months of age then peanut consumption or avoidance for 1 year Outcome: prevalence of IgE-mediated peanut allergy after 1 year of enrolment 	Ongoing
Prevention of egg allergy in infants with atopic dermatitis (PETIT)	Japan (National Center for child Health and Development, Japan)	Hens' egg	High-risk (infants with atopic dermatitis)	<ul style="list-style-type: none"> RCT, placebo controlled n ~ 200 Enrolled at 4-6 months then consumption of egg powder or placebo until 12 months of age Outcome: prevalence of IgE-mediated egg allergy at 12 months of age 	Completed. Abstract presented
Solids Timing for Allergy Research	Australia (University of	Hens' egg	High-risk (infants with moderate /	<ul style="list-style-type: none"> RCT, placebo controlled n = 86 	Reported

(STAR)	Western Australia)		severe eczema)	<ul style="list-style-type: none"> Enrolled at 4-6 months of age then consumption of egg powder or placebo until 8 months of age Outcome: prevalence of IgE-mediated egg allergy at 12 months of age 	
Starting Time for Egg Protein (STEP)	Australia (University of Western Australia)	Hens' egg	Moderate-risk (infants without eczema but atopic mothers)	<ul style="list-style-type: none"> RCT, placebo controlled n~1500 Enrolled at 4-6 months of age then consumption of egg powder or placebo until 12 months of age Outcome: prevalence of IgE-mediated egg allergy at 12 months of age 	Completed
Beating Egg Allergy (BEAT)	Australia (Sydney University (Children's Hospital,)	Hens' egg	Moderate-risk (sibling / parent with allergy)	<ul style="list-style-type: none"> RCT, placebo controlled n~290 Enrolled at 4 months of age then consumption of egg powder or placebo until 8 months of age Outcome: primary- egg white sensitisation. Secondary-prevalence of IgE-mediated egg allergy at 12 months of age 	Completed
Preventing atopic dermatitis and allergies in children (PreventADALL)	Norway (Oslo University Hospital)	Hen's egg, milk, wheat, peanut	General population	<ul style="list-style-type: none"> Open label RCT with four arms: observation, early introduction by 4 months, skin care, both early introduction and skin care N=5200 Outcome: food allergy, atopic dermatitis 	Ongoing

Micronutrients and allergy prevention

Since most food allergens are proteins, these have usually been the focus of food allergy prevention research. However, with increased knowledge of the role of macro- and micro-nutrients in immunological processes, there is increasing interest in the relationship between dietary nutrients and the development of allergic conditions. Observational data linking delayed allergen introduction and increased allergy rates may also be explained by the reduced intake of immunologically active nutrients.[19,34,57,58] Polyunsaturated fatty acids (PUFAs), antioxidants (selenium, vitamins A, C, E and β -carotene), vitamin D, iron, zinc and folate are of particular interest for allergy prevention.[59-67]

To date, PUFAs have been the most extensively studied immuno-modulatory nutrient. Observational studies have related increased intake of omega-3-rich foods during pregnancy, lactation and infancy with decreased risk of allergic disease.[58,67] However, interventional study findings have been inconsistent, possibly due to small sample sizes and heterogeneous allergy outcomes. A recent Cochrane review looked at eight randomised control trials of omega-3 PUFA supplementation during pregnancy (5 trials), lactation (2 trials) or both (1 trial). Supplementation showed a clear reduction in any IgE mediated allergy in children aged 12-36 months but not beyond 36 months. For specific allergies there was no clear difference for food allergies at 12-36 months but a clear reduction was seen for children up to 12 months of age. The author conclude "there is limited evidence to support maternal n-3 LCPUFA supplementation during pregnancy and/or lactation for reducing allergic disease in children".[68] Large intervention trials (completed or on-going; Table 3) may further clarify the association between PUFAs and food allergy development.[69-72]

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3 Vitamin D has received considerable attention in recent years with a suggestion that vitamin D
4 supplementation and/or food fortification is the cause of increasing allergic disease
5 prevalence[73] with observed associations between high maternal and infant vitamin D status
6 and allergic disease[74,75] supporting this theory. Conversely, latitudinal differences in auto-
7 injector prescriptions for food-induced anaphylaxis [76] and hypoallergenic infant formula
8 use[77] have suggested a causal link with low vitamin D status. Associations between vitamin D
9 intake and status and allergic disease risk are from a diverse literature, including cross-
10 sectional, case-control and cohort studies, with variable outcome definitions, analytical
11 procedures and study quality.[74,75,78-81] However, the HealthNuts study, which used a
12 validated food allergy outcome measure, showed that low vitamin D status may be a risk factor
13 for infant food allergy.[82] The VITALITY trial (NCT02112734) is currently looking at the impact
14 of infant vitamin D supplementation on food allergy prevalence at 1 year.

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30 Lower intakes of antioxidants are suggested to reduce antioxidant defences and increase the
31 risk of atopic disease.[83-87] In particular, vitamins A, E and C and zinc may confer some
32 protection. However, appropriately designed controlled studies are required to establish if there
33 is a causal relationship.[88]

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40 Differing reports of observed associations between immune-modulatory nutrients and allergic
41 disease may be explained by the fact that the whole diet rather than one particular nutrient
42 modifies immunological function. This hypothesis is supported by a number of studies that have
43 found an association between the whole diet, (including diversity), and allergic disease.[46, 47,
44 89-90] Additionally, recent research demonstrated that an infant diet consisting of high levels of
45 fruits, vegetables, and home-prepared foods was associated with less food allergy by the age of
46 2 years.[46] This inverse association with processed foods has been observed elsewhere[89]
47 and may be due to the higher microbial load of home processed foods compared to
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3 commercially prepared foods[92] or that home processed fruits and vegetables are good
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5 sources of naturally occurring prebiotics. Both are thought to modify immune function.[93]
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8 **Other strategies for preventing food allergy**

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10 *Hypoallergenic infant formula*

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14 In new-borns, the mucosal barrier is immature and large quantities of macromolecules cross the
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16 epithelium into systemic circulation. Intestinal permeability reduces with age but in the first few
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18 months of life when combined with the immature status of the immune system, it is considered a
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20 risk factor for food allergy development and this is the period when standard infant formula is
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22 given if breastfeeding isn't possible. Therefore, if breastfeeding isn't possible, it is
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24 recommended that high-risk children (parent or sibling with a history of allergy) use a
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26 hypoallergenic cow's milk protein (HA) formula to avoid early exposure to intact milk
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28 allergens.[27,28]
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33 HA formulas are processed to reduce the allergenicity of milk proteins by 'snipping' them into
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35 smaller pieces (peptides). They are differentiated into extensively and partially hydrolysed
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37 formulas (eHF and pHF respectively). eHF contain predominantly small milk-derived peptides
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39 with almost no allergenicity, whereas pHFs also contain larger milk-derived peptides. eHFs were
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41 originally produced to treat milk-allergic infants but are now also used for allergy
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43 prevention,[94,95] whereas pHFs are produced only for allergy prevention.
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47 Studies indicate that some pHF and eHF can reduce the risk of food allergy development but
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49 other studies failed to demonstrate a protective effect.[26] Consequently, there is debate as to
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51 which is the best formula for allergy prevention as reflected by differing national and
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53 professional body recommendations[25-29] and individual clinicians' opinions.[96,97]
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3 However, a recent systematic review and meta-analysis, using a rigorous approach, failed to
4 find a beneficial effect of hypoallergenic infant formulas on food allergy.[98] The authors
5 highlighted that many studies were at uncertain or high risk of bias, they also found evidence of
6 publication bias. They argued that earlier reviews have been influenced by the more positive
7 results from lower quality design studies. Since it appears preventive efficacy is highly
8 dependent on the specific formula studied, the EAACI guidelines group recommended the use
9 of HA formulas with a *documented* preventive effect for high-risk children in the first 4 months of
10 life only.[26] No studies show a preventive effect in low-risk children.
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24 *Prebiotics and probiotics*

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27 The microbiota of infants with atopic disease is both quantitatively and qualitatively different[99]
28 from their non-atopic counterparts, with decreased populations of beneficial bacteria
29 (bifidobacteria, bacteroides, and lactobacilli and higher numbers of coliforms and *S.*
30 *aureus*.[100]. This has promoted research into the role of intestinal microbiota in the
31 development of immune tolerance. Lower consumption of prebiotics (fibre/indigestible dietary
32 components) are suggested to lead to less favourable colonization patterns which may be
33 implicated in the loss or inability to develop oral tolerance. Neonatal prebiotic supplementation
34 trials have failed to show any effect of prebiotics on food allergy development but have shown
35 favourable results on other allergic outcomes such as eczema. [101] RCTs assessing the
36 effects of probiotics in the prevention of eczema, and/or food allergy have reported differing
37 findings.[102-10106]. The most up to date Cochrane review on the subject states that further
38 research is needed before probiotic use can be recommended for allergy prevention.[107]
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41 However, a recent World Allergy Organisation (WAO) systematic review has suggested using
42 probiotics in infants at high risk of allergy due to the “likely net benefit” from the prevention of
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3 eczema seen with the use of probiotics.[108] The guideline panel did however acknowledge that
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5 their recommendation was supported by very low quality evidence demonstrating a need for
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7 high quality intervention trials and there a number of these ongoing (Table 3) which may provide
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9 further insight in the future. These studies will also provide information on which strains may be
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11 the most effective for allergy prevention and what dose is required as these are important
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13 factors to consider and about which there is currently very little information.
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Table 3. Intervention trials with food allergy as a primary or secondary outcome

Nutrient	Study Name	Location	Recruitment Status	Identifier
Vitamin D	The VITALITY trial	Australia	Recruiting	NCT02112734
Vitamin A	Vitamin A supplementation at birth and atopy in childhood	Guinea Bissau	Active	NCT01779180
PUFAs	DHA to optimise mother infant outcomes (DOMInO) trial	Australia	Completed	ACTRN12605000569606
PUFAs	The infant fish oil supplementation (IFOS) trial	Australia	Active	ACTRN12606000281594
PUFAs	Can supplementation with <i>Lactobacillus reuteri</i> and Omega-3 fatty acids during pregnancy and lactation reduce the risk of allergic disease in infancy? (PROOM-3)*	Sweden	Recruiting	NCT01542970
Probiotics	Primary prevention of atopic disease by perinatal administration of probiotics	Netherlands	Completed	NCT00200954
Probiotics	Influence of probiotics on atopy, immunological responses and gut microflora, follow-up to 5 years	Singapore	Completed	NCT00365469
Probiotics	Microbiota as a potential target for food allergy	Italy	Recruiting	NCT02087930
Probiotics	Effect of lactobacillus GG on atopic march	Italy	Recruiting	NCT01891916
Prebiotic	Prebiotics in the prevention of atopy (PIPA)	Italy	Completed	NCT02116452

† atopic sensitization; Se: selenium; Fe: Iron; Zn: Zinc

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Figure 2 Early factors and mechanisms that interact to prevent or favour the development of an allergic response to a food protein

Confidential: For Review Only

Summary and conclusions

This review covered a number of approaches to prevent the development of food allergy. These are likely to interact. Figure 2 summarises how factors (including prenatal factors which have not been considered in this review) may interact to prevent or promote the food allergy development. Unlike in previous decades, national recommendations for food allergy prevention strategies now largely agree, particularly concerning hypoallergenic formula use and not delaying the introduction of allergenic foods. [26-29] However, while there is consensus that avoidance strategies are ineffective, guidelines do not provide any alternative strategies. There is a call for more high-quality data from robust RCTs. Some has already been provided and appears to support the concept that early consumption of allergenic food promotes the development of immune tolerance and a recent consensus statement supports this[47]. However, before recommendations are updated, it is important to understand how best to introduce preventive interventions in a community context, particularly since there may be significant numbers of children already sensitised by the time they are weaned. Given their different intervention strategies and populations investigated, combining the new RCT data into meta- or pooled analyses, will broaden their informational scope, and this is planned as part of the iFAAM study. However, even pooled, they may not provide data as to what dose of allergenic food should be given and for how long. Data from on-going studies on solid food introduction and nutritional supplementation may also provide a broader understanding of food allergy prevention. As studies have generally only focused on IgE mediated food allergy, their findings may not be applicable to preventing the development of non-IgE mediated food allergy conditions such as eosinophilic oesophagitis and food protein induced enterocolitis syndrome. Aetiology data for these conditions are lacking and RCTs similar to those carried out for IgE-mediated disease should be a future research priority in the field of food allergy.

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10 11 12 13 **Authors Contributions**

14 GR, KG and KL planned the manuscript. All the authors contributed to drafting the manuscript and reviewing the
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30 31 32 33 **Competing Interests**

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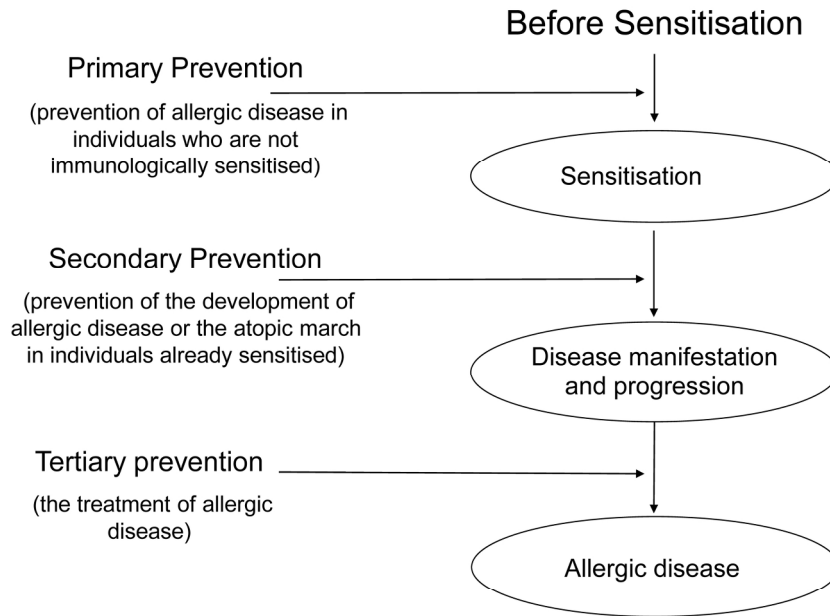
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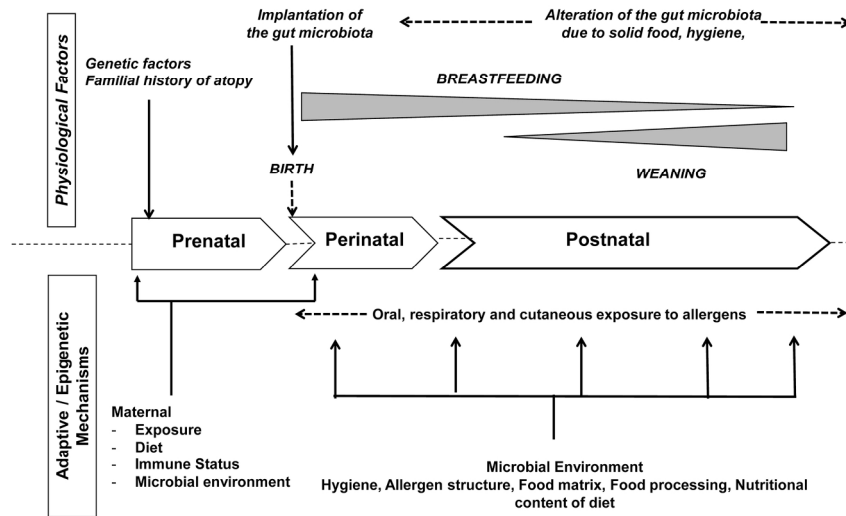
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