

ORIGINAL ARTICLE

Epidemiology of Allergic Disease

Can dietary strategies in early life prevent childhood food allergy? A report from two iFAAM workshops

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Abstract

Food allergy affects a small but significant number of children and adults. Food allergy is responsible for considerable morbidity and is the commonest cause of anaphylaxis in children. One of the aims of the European Union-funded “Integrated Approaches to Food Allergen and Allergy Risk Management” (iFAAM) project was to improve our understanding of the best way to prevent the development of food allergy. Groups within the project worked on integrating the current prevention evidence base as well as generating new data to move our understanding forward. This paper from the iFAAM project is a unique addition to the literature on this topic as it not only outlines the recently published randomized controlled trials (as have previous reviews) but also summarizes two iFAAM-associated project workshops. These workshops focused on how we may be able to use dietary strategies in early life to prevent the development of food allergy and summarized the range of opinions amongst experts in this controversial area.

Roberts and Grimshaw equally contributed to this study.

KEYWORDS

diet, food allergy, nutrition, prevention

1 | INTRODUCTION

Food allergy represents a considerable burden to affected individuals. Around 5% of preschool children and between 0.3% and 5.6% of older children and adults in Europe have food allergy.¹⁻⁵ Typical causative allergens are hen's egg, cow's milk, peanuts, tree nuts, wheat, soya, shellfish and fish.^{1,2} Food allergy is the commonest cause of anaphylaxis,⁶ a systematic and potentially life-threatening systemic allergic reaction.⁷ Current management strategies for food allergy revolve around avoidance of the causative allergen and rescue therapy for reactions.⁷ Avoidance of foods that are often a ubiquitous part of our diet is challenging, resulting in inconvenience to the individual and their family. Inconvenience also results from the need to carry rescue therapy, such as adrenaline auto-injectors. Although with adequate avoidance strategies, allergic reactions are infrequent, food allergy can result in considerable anxiety mainly due to their unpredictability.⁸ Therefore, food allergy represents a considerable burden to individuals, families and society.

In the past, the prevailing hypothesis to explain the aetiology of food allergy was that early ingestion of allergenic foods would result in the development of food allergy in at-risk individuals. The widely accepted approach to reducing the likelihood of an infant developing food allergy was therefore to delay the introduction of dietary allergens into their diet.⁹⁻¹¹ The failure of these avoidance strategies to reduce the incidence of food allergy has led to a reassessment and the formulation of the dual exposure hypothesis.¹² This reassessment developed from a number of different lines of evidence and suggests that initial contact of an allergenic food via the gastrointestinal tract in early life leads to development of tolerance; this contrasts with when initial contact is via eczematous skin when allergic hypersensitivity is likely to develop. This new hypothesis has led to a number of randomized controlled trials to assess whether the dietary introduction of allergens at 4-6 months leads to a reduction in the development of clinical food allergy. A number of these trials have now reported.

Integrated Approaches to Food Allergen and Allergy Risk Management (iFAAM) was a European Union-funded FP7 project. iFAAM aimed to reduce the burden of food allergy through a number of integrated activities. The project evaluated the evidence relating to the development of food allergy to improve our approach to the prevention of food allergy. This paper is a summary from two iFAAM workshops held on 12 December 2016 and 19 to 20 April 2018. The aims of these workshops were to review the recent key data on the prevention of food allergy; to make recommendations on the best approach to utilize infant diet to prevent food allergy; and to consider what gaps remain in the evidence base. The discussion was focused on the introduction of complementary solid foods into the infant diet with "early" defined as less than 26 weeks of life. Participants were all involved in iFAAM and represented the breadth of stakeholders and

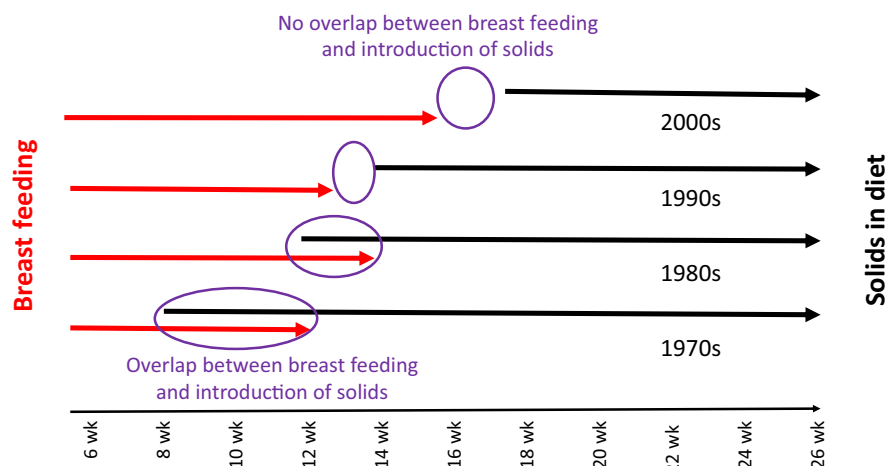
range of opinions in this area, for example paediatricians, dietitians, patient group representatives and food scientists.

2 | POTENTIAL IMPACT OF ALTERING THE AGE OF INTRODUCTION OF ALLERGENIC SOLIDS ON INFANT NUTRITION

In making recommendations about infant diet, a holistic view is required, as positive impacts in one clinical area may need to be balanced with negative ones in another. This can be seen by the effect of feeding recommendations on the overall composition of the infant diet. Historically, infants were breastfed for their first year of life with solids introduced once they were able to physically eat, for example being able to hold head up independently. Initiation rates and duration of breastfeeding started to decline in many European countries in the 1950s (Figure 1). At that time, complementary foods could be started from as early as 6-8 weeks of age. From the 1970s, there were recommendations to introduce complementary foods later.^{13,14} In 2003, the World Health Organization recommended exclusive breastfeeding until 26 weeks of age with continued breastfeeding until two years of age.¹⁵ In practice, this is rarely achieved in many countries in the developed world.⁸ Where breastfeeding is not prolonged, delaying the introduction of complementary foods means that there is less or even no overlap between breastfeeding and the introduction of solids and this may have a detrimental effect on allergy development.¹¹ Additionally, guidelines may be directed at particular population groups (eg high-risk infants) but are followed by all population groups.^{9,10}

The format in which a food is eaten is very important for infants and is affected by their age. Consequently, this needs to be considered when deciding how to introduce allergenic foods into the diet. For example, egg is traditionally introduced into an infant's diet in a well-cooked format to overcome texture issues and is consequently given at a relatively low dose. This observation is supported by available trial data, which demonstrates that cooked egg is much better tolerated than raw egg and is consumed in lower doses.¹⁶ Likewise, the choking risk with peanuts also needs to be considered, and children under 5 years of age should only consume these in a ground/smooth format such as peanut butter or satay sauce. Consideration is also needed to ensure that any recommended changes to the infant diet are in line with local dietary practice. For example, peanuts are not part of the local diet in many areas of the world. Finally, the impact of any recommendations requires reflection to ensure that it has no negative nutritional or dietary consequences. For example, peanuts formulated as peanut puffs have a relatively high sodium chloride and fat content and nutritional data from the LEAP study showed that the early introduction did have a major impact

FIGURE 1 Illustration of the historic trends in breastfeeding and the introduction of allergenic solids into the infant diet in the United Kingdom. The figure illustrates the typical timelines for breastfeeding and the introduction of solids into the infant diet in the last 4 decades in the United Kingdom where the LEAP and EAT were undertaken.^{13,14,21-23} However, an overlap between breastfeeding and the introduction of solids can still be seen in other European countries such as Norway and Denmark²⁴



on the relative intake of key nutrients, although no adverse effects on growth were found.¹⁷ Peanut would be better introduced as part of the protein content of meals rather than as a snack to reduce the potential for an infant having too much protein, protein-associated fat and sodium chloride in their diet which have long-term health consequences including obesity in later life.¹⁸ Finally, there is a need to look for potential long-term consequences as our dietary experience as infants affects our long-term diet and therefore health.¹⁹

All these factors demonstrate why it is important that one clinical speciality should not drive public nutrition recommendations. The European Society of Paediatric Gastroenterology and Nutrition has published updated recommendations on complementary feeding.²⁰ They recommended that “exclusive or full breast-feeding should be promoted for at least 4 months and exclusive or predominant breast-feeding for approximately 6 months is a desirable goal.” Additionally, they recommend that “complementary foods should not be introduced before 4 months but should not be delayed beyond 6 months.” They explain that they base these recommendations on when an infant has the necessary maturity in gastrointestinal, renal and motor function to safely consume complementary foods.

3 | RANDOMIZED CONTROLLED PREVENTION TRIALS FOCUSED ON EARLY INTRODUCTION OF ALLERGENIC SOLIDS

A literature search was undertaken in MEDLINE and EMBASE ([food allergy or hypersensitivity or intolerance] and [prevention] and [SIGN randomized controlled trial search strategy²⁵]). Additionally, Clinicaltrials.gov, www.clinicaltrialsregister.eu, www.controlled-trials.com and <http://www.anzctr.org.au> were searched for ongoing or planned randomized controlled trials (18 April 2018) and rerun for any new studies (7 December 2019). A total of 7 randomized studies focusing on the question of whether the early introduction of allergenic solids might prevent the development of food allergy have been published; a further one is ongoing (Table 1). Most of the studies focus on egg,^{16,26-29} one has focused on peanuts,^{30,31} and one on

multiple foods.³² One trial of multiple food allergies (PreventADALL) is still ongoing.³³ Lastly, there is one non-randomized trial on peanut allergy in high-risk infants (PEAP) which is also ongoing.³⁴ To understand these studies fully, a number of different aspects need to be understood:

Population—studies have focused on either a high-risk group,^{16,26,30,31} moderate-risk group^{27,28} or a general population.^{29,32,33} High risk has been defined as the presence of moderate to severe eczema, which is known to be associated with food allergy.³⁵ Moderate risk has been defined as a first-degree relative with allergy.^{27,28} Some studies have aimed to recruit a general population although inevitably, those enrolled are likely to be more at risk than a truly representative general population.^{29,32,33} Studies based on an at-risk population have a better chance of identifying any preventative impact of an intervention as more individuals develop food allergy than in the general population. There is though a possibility that such high-risk infants have already developed food allergy. The successful impact of the LEAP intervention in sensitized infants (SPT < 4 mm) would argue against this at least for peanut allergy. In the STAR study,²⁶ which did not screen for sensitization prior to inclusion in the study, many infants reacted to the egg intervention and these infants had significantly higher SpIgE to egg at recruitment than those who did not react. However in the HEAP study,²⁹ only infants who were not sensitized were included and there were still frequent reactions to the egg intervention; this was not seen in the PETIT study¹⁶ who did not screen by egg-specific IgE prior to inclusion. The likely explanation for this difference was the use of small doses of heated hen's egg in the PETIT study.

Intervention—foods have been introduced in a number of formats and doses. For the egg interventions, a number of studies used a format that appears to be similar to raw egg in terms of allergenicity.^{16,27-29} But the EAT and PETIT studies used a cooked form of egg.^{16,32} Interestingly, it appears introduction of the “raw” egg into the infant diet does not prevent the development of egg allergy and results in lots of allergic side effects. Meanwhile, introduction of the cooked form into the infant diet possibly results in a reduction in the development of egg allergy and has been well tolerated.

TABLE 1 Summary of randomized controlled studies investigating the impact of early introduction of allergenic foods on prevention of food allergy

Name of trial	Country (institution)	Population
Egg		
Hens' Egg Allergy Prevention (HEAP) Bellach et al ²⁹	Germany (Charité Universitätsmedizin Berlin, Germany)	General population, non-sensitized (screened at recruitment)
Prevention of egg allergy in infants with atopic dermatitis (PETIT) Natsume et al ¹⁶	Japan (National Centre for Child Health and Development, Japan)	High risk (infants with atopic dermatitis)
Solids Timing for Allergy Research (STAR) Palmer et al 2013 ²⁶	Australia (University of Western Australia)	High risk (infants with moderate/severe eczema)
Starting Time for Egg Protein (STEP) Palmer et al 2016 ²⁷	Australia (University of Western Australia)	Moderate risk (infants without eczema but atopic mothers)
Beating Egg Allergy (BEAT) Tan et al ²⁸	Australia (Sydney University Children's Hospital)	Moderate risk (sibling/parent with allergy). SPT to egg < 2mm
Peanut		
Learning Early About Peanut Allergy (LEAP) Du Toit et al ^{30,31}	United Kingdom (Kings College, London)	High risk (infants with moderate/severe eczema and/or egg allergy). SPT to peanut < 4mm
Multiple foods		
Enquiring About Tolerance (EAT) Perkin et al ³²	United Kingdom (Kings College, London)	General population
Preventing Atopic Dermatitis and ALLergies in children (PreventADALL) ³³	Norway (Oslo University Hospital)	General population

Note: DBPCFC, double-blind, placebo-controlled food challenge; ITT, intention to treat; PP, per protocol; RCT, randomized controlled trial.

Study details	Results
• RCT, placebo-controlled • n = 383 • Enrolled at 4-6 months and then consumption of egg powder ("pasteurized egg white" equal in its allergenicity to raw hen's egg) or placebo until 12 months of age; started with 800-mg egg protein three times a week, increasing to 1.6g in week 2 and 2.5g in week 3. • Outcome: primary: prevalence of egg sensitization; secondary: placebo-controlled challenge proven IgE-mediated egg allergy at 12 months of age	At 12 months, there was a non-significant difference in egg sensitization (2.6% control vs 5.6% egg, $P = .24$) and egg allergy (0.6% control vs 2.1% egg, $P = .35$) between the groups in ITT analyses; many infants reacted to the intervention.
• RCT, placebo-controlled • N = 147 • Enrolled at 4-6 months and then consumption of "heated egg powder" or placebo; started on a very small amount (25 mg of egg protein daily increasing to 125 mg from 9 months) • Outcome: prevalence of open challenge proven IgE-mediated egg allergy at 12 months of age	Recruited finished early after an interim analysis; intervention leads to a significant reduction in egg allergy (38% control vs 8% egg, $P = .0001$); no major safety issues.
• RCT, placebo-controlled • n = 86 • Enrolled at 4-6 months of age and then consumption of egg powder ("pasteurized raw whole egg powder") or placebo until 8 months of age; 900-mg egg proteins given daily • Outcome: prevalence of open challenge proven IgE-mediated egg allergy at 12 months of age	A third of infants randomized to egg reacted to the intervention; at 12 months, there was a non-significant difference in egg allergy between the groups in the intervention group (51% control vs 33% egg, ITT analysis, $P = .11$).
• RCT, placebo-controlled • N = 804 • Enrolled at 4-6 months of age and then consumption of pasteurized raw whole egg powder or placebo until 12 months of age • Outcome: prevalence of challenge proven IgE-mediated egg allergy at 12 months of age	At 12 months, there was a non-significant increase in IgE-mediated egg allergy in the control group compared to the intervention group (10.3% control vs 7.0% egg, $P = .20$); there were a number of allergic reactions to the intervention.
• RCT, placebo-controlled • N = 319 • Enrolled at 4 months of age and then consumption of pasteurized whole egg powder or placebo until 8 months of age • Outcome: primary egg white sensitization; secondary: prevalence of IgE-mediated egg allergy at 12 months of age	Early introduction of egg was associated with a reduction in sensitization at 12 months (20% control vs 11% egg, $P = .03$). There was no effect on the proportion of children with probable egg allergy. A number of infants reacted to the intervention.
• Open-label RCT • n = 640 • Enrolled at 4-11 months (mean age 7.8 months) then peanut consumption or avoidance until age 5; 6-g peanut protein per week • Outcome: prevalence of DBPCFC confirmed peanut allergy at 5 years of age	Significant reduction at 60 months in ITT analysis (13.7% control vs 1.9% overall, $P < .001$) regardless of presence of initial (cutaneous) sensitization; no significant between-group differences in serious adverse events. Significant reduction was still seen after both groups and then avoided peanut for a year (18.6% control vs 4.8% peanut, ITT analysis, $P < .001$).
• Cows' milk, hens' egg, peanut, cod, sesame, wheat • Open-label RCT • n = 1106 • Enrolled at 3 months of age and then consumption of 6 allergenic foods until 6 months or exclusive breastfeeding until 6 months of age; 2-g protein of each food given twice a week • Outcome: prevalence of IgE-mediated food allergy to any of the 6 allergenic foods between 1 and 3 years of age	Non-significant reduction in ITT analysis (7.1% control vs 5.6% intervention, $P = .32$). In PP analysis, a significant reduction was seen for any food allergy (7.3% control vs 2.4% intervention, $P = .01$), peanut (2.5% control vs 0% peanut, $P = .003$) and egg allergy (5.5% control vs 1.4% egg, $P = .009$)
• Hen's egg, milk, wheat, peanut • Open-label RCT with four arms: observation, early introduction by 4 months, skincare, both early introduction and skincare • N = 2500 • Outcome: food allergy, atopic dermatitis	Ongoing

One challenge here though is that it is difficult to standardize the degree of cooking. Other factors may also be important, for example the matrix (Table 2). Dose-wise, studies have used a wide range of amount of food. Most of the egg studies have used an amount equivalent to approximately $\frac{1}{2}$ -1 egg per week.^{26-29,32} The exception is the PETIT study, which started with a low daily egg protein intake (equivalent to 1/20th of an egg a week) from 6-9 months, followed by daily intake equivalent to a $\frac{1}{4}$ of an egg a week from 10-12 months, and was associated with a very large reduction in egg allergy.¹⁶ It is important to note that the hen's egg in the PETIT and EAT studies was well cooked. For the peanut studies, the LEAP study gave 6-g peanut protein per week,^{30,31} whereas the EAT study used 4 g of peanut protein.³²

Timing of introduction of allergen solid(s)—the egg studies have all introduced this allergen at 4-6 months of age,²²⁻²⁶ whilst the peanut study introduced the allergen from 4-11 months (mean 7.8 months).^{27,28} In the EAT study, allergenic foods were introduced between 4 and 6 months except for cow's milk which was introduced from 3 months.²⁹

Comparator—only some of the studies had a double-blind design²⁶⁻²⁹; the other randomized controlled trials were open in design.²⁶⁻²⁸ Without blinding, there is a potential for reporting bias; to overcome this, the primary outcome needs to be objective and robust. The success of the randomization also needs to be examined; for example, there was an imbalance in baseline sensitization to egg in the PETIT study although a *post hoc* analysis did suggest that this did not affect the result.¹⁶

Outcomes—the patient relevant outcome is food allergy which is assessed in most studies²⁶⁻³²; only some used a double-blind challenge protocol.²⁵⁻²⁸ Challenge results can be difficult to define accurately in small infants. Several studies have used sensitization as their primary outcome^{28,29}; given the data that sensitized infants can be protected from developing food allergy,^{30,31} it is difficult to know how to interpret these sensitization results in isolation from accompanying challenge results.

4 | SYNTHESIS OF THE RANDOMIZED CONTROL PREVENTION TRIALS

A systematic review and meta-analysis of these randomized controlled prevention trials have been published.³⁶ Level of risk for developing food allergy differed between these populations and can be seen in Table 1. An updated figure from the review is reproduced as shown in Figure 2. The analyses suggest that the early introduction of peanut and egg is effective in preventing the development of peanut and egg allergy, respectively. The PETIT study is a cause of much of the heterogeneity,¹⁶ and it has been criticized given that it was stopped early, after an interim analysis, when the two groups were unbalanced for the presence of specific IgE to egg.^{36,37} However, meta-analysis of the egg studies remains positive for a preventative effect even if the PETIT study is removed from the analysis. These updated data give a number needed to treat

to prevent egg and peanut allergy of 28 and 18, respectively. The analysis for milk allergy failed to demonstrate that early introduction is an effective preventative strategy.

Updated from Ierodiakonou et al³⁶ where results for egg, milk and peanut allergy are presented separately. Error bars represent 95% confidence intervals.

A subsequent systematic review and meta-analysis of studies looking at early introduction of egg and allergy development indicated that neither the total amount nor pre-treatment of egg showed any effect on egg allergy development at the age of 12 months. The authors propose that further studies should be performed to generate stronger data.³⁵

5 | INTERPRETATION OF THE RANDOMIZED CONTROLLED PREVENTION TRIAL DATA

For egg, milk and peanut, there are important limitations in the currently available data. There is heterogeneity in both the egg and peanut analyses. For egg, this is largely explained by the imbalance in risk factors for egg allergy at baseline in the PETIT study, the early termination of recruitment in this trial and the usage of very different amounts of the allergen.¹⁶ For peanut, the heterogeneity may be explained by very different adherence to the intervention seen in the LEAP and EAT studies and also the different population groups (Table 1).³⁰⁻³² The data for peanut allergy are based on two studies from one institution, and it remains to be seen whether the findings are generalizable to other countries with different breastfeeding initiation rates and durations, different prevalence of eczema and different household peanut consumption. Peanut allergy is also not seen in many countries. We do not have data for other allergenic foods. Lastly, we need to consider the potential for adverse consequences of the early introduction of allergenic solids; this is discussed in the next section.

So whilst there appears to be a proof of concept that early introduction of allergenic solids in the right amounts, in the right formulation and at the right time can reduce the development of food allergy in infants, important gaps in the evidence base remain (Table 2). The heterogeneity of the published studies is a particular concern with differences in the included populations, format and dose of the intervention and how "early" was defined. This heterogeneity could be used to optimize the approach, but a definitive study would then be required to assess this strategy.

6 | CAN WE EXTRAPOLATE FROM THE AVAILABLE EVIDENCE TO OTHER FOOD GROUPS?

Allergic reactions to different foods present very differently. Although their presentation is usually temporally associated with when that food group first appears in the diet, it is possible that clinically relevant allergy

TABLE 2 Research gaps

Gap	Approach to closing gap	Priority
General considerations		
Evidence that early introduction of solids is beneficial for low-risk infants	Needs very large randomized controlled trial in a low-risk population and in different countries as current observational data are confounded by socio-economic factors	+
How early should allergenic solids be introduced into the infant diet? For example < 4 better than 4 or 5 months?	Randomized controlled trial but impact likely to be different for different foods so trials need to be powered to look at specific foods	+
Appropriate format (eg raw, cooked) and dosage of the food	Secondary analysis of published trials to assess optimal format and dose. Further assessment of hypothesized optimal approach in a randomized controlled trial	++
Lack of evidence on how food processing and the food matrix may affect the prevention of food allergy	Further studies need to control for a potential matrix effect	+
Potential role of maternal consumption and transfer of dietary protein to infant via breast milk on the prevention of food allergy	Future trials need to control for or investigate the potential impact of maternal consumption of allergenic foods on the prevention of food allergy	+
The longevity of any preventative impact	Ongoing follow-up of randomized controlled trials. Before-after controlled trials	+
Evidence that allergenic solid introduction with concurrent breastfeeding is protective	Need to examine in data sets of the existing RCT studies, or to be examined in future studies	++
Short-term nutritional safety of early introduction of allergenic solids	Nutritional consequences of infant dietary interventions need to be assessed. Need to examine EAT (and other RCT) data sets	+++
Long-term safety of early introduction of allergenic solids, eg hypertension, obesity and diabetes	This requires long-term follow-up of randomized controlled trial participants, potentially using routine health data. Alternatively, before-after controlled trial approach could be used	++
Egg		
Best dose and format of egg.	Positive studies use a wide variety of doses and formats of egg, need a comparative randomized controlled trial to assess the best approach	+++
Peanut		
Replication of LEAP data in other countries with a high, moderate and low prevalence of peanut allergy and different cultural practices around infant feeding	Multi-centre randomized controlled trial building on LEAP study protocols	++
Other foods		
Will the LEAP approach work for tree nuts?	Multi-centre randomized controlled trial building on LEAP study protocols	++
Effective preventative approach for cow's milk allerg.	Perhaps a clinical trial of early introduction of cow's milk alongside breastfeeding	+
Lack of evidence about the best time to introduce other food allergens	Further randomized controlled trials	+

develops sometime before the first known ingestion. This may be different for different foods. For example, trials have demonstrated that peanut interventions are well tolerated even by sensitized infants up to 11 months of age,³⁰⁻³² whereas many younger infants have allergic reactions with the raw pasteurized egg intervention.^{26,29} However, this difference may just as easily be due to the form the foods were ingested and how the infants were screened prior to inclusion in the study.

Additionally, there may be different "windows of opportunity" for prevention to different allergenic foods during childhood.

Also, whether or not the allergy is outgrown and the speed that this happens is very variable making extrapolation to other foods problematic. However, the mechanisms that underlie tolerance are likely to be similar for all foods and will involve either clonal deletion, clonal anergy or suppression. At present, we can only compare early introduction of different foods in the EAT study³² and this was underpowered to look individually at the less prevalent food allergies. We need more evidence for all the food groups (Table 2).

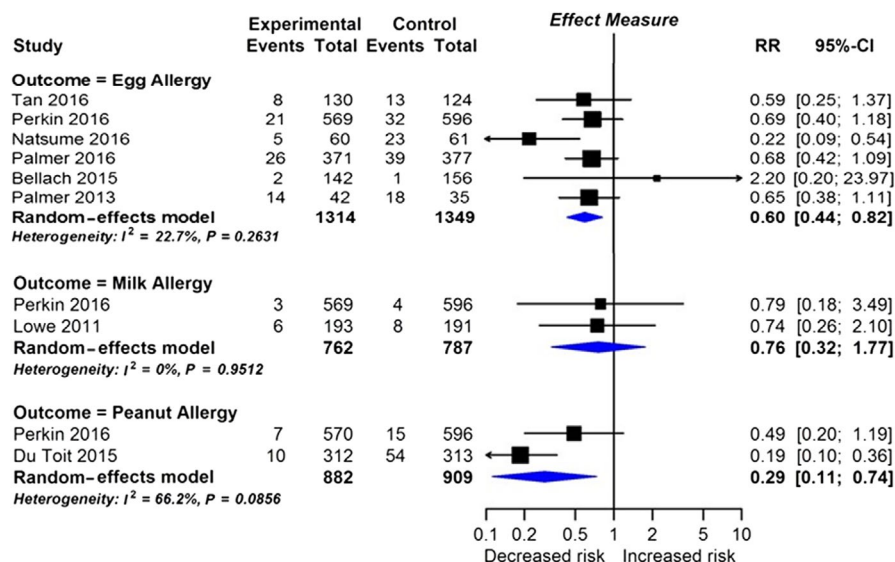


FIGURE 2 Meta-analysis of randomized controlled prevention studies

7 | IS THERE ADEQUATE EVIDENCE TO MAKE RECOMMENDATIONS ABOUT THE BEST APPROACH FOR SOLID INTRODUCTION AND ALLERGY PREVENTION?

Participants at the first workshop (2016) were asked to consider, in four small groups, whether there was sufficient current evidence to make recommendations about the age of introduction of complementary solids into the infant diet to reduce the likelihood of developing food allergy. In the second workshop, groups were asked to consider (a) the definition of a high-risk infant; (b) when foods should be introduced to low-risk infants; (c) when foods should be introduced to high-risk infants; (d) what are the potential consequences of early introduction of allergenic foods; (e) should different foods be introduced at different ages and (f) in what format should foods be introduced.

There was agreement by participants at the 2018 workshop that there is a paucity of evidence to be able to define absolutely high(er) risk populations for the development of food allergy. However, it was thought that whilst a family history of allergies is widely acknowledged to increase the risk of food allergy development, there are other factors such as early-onset eczema, ethnicity and geography that also have an effect and need to be considered.

All the participants at the first workshop (2016) agreed that breastfeeding should be recommended until at least 6 months of age, not based on its impact on food allergy but due to its other proven health benefits. The most recent systematic review on this topic compared maternal and infant outcomes with exclusive breastfeeding for 6 months vs 3-4 months.³⁸ A total of 23 eligible studies (11 from low- and 12 from high-income countries) were included. Some benefits for exclusive breastfeeding for 6 months were seen, for example reduced gastrointestinal infection even in high-income countries. A weakness of the evidence base is that most of the studies are observational with no randomized controlled trials in high-income countries. Moreover, exclusive breastfeeding duration in these

studies was often determined by the introduction of breast milk substitutes rather than introduction of solids, and it is unclear whether early introduction of solid foods on its own increases risk for gastrointestinal infection. At the second workshop (2018), the question of breastfeeding duration for allergy protection was not discussed directly but continuing to breastfeed, whilst introducing solids into the diet was recommended by the many participants when answering the other questions (detailed above).

In 2016, all the discussion groups discussed when the allergenic foods should be introduced into the infant diet. For egg, most thought that it could be introduced into the diet of all infants from 4-6 months of age, when they are developmentally ready. Given the trial evidence, it was agreed that this should probably be in small amounts of the well-cooked or baked form that is appropriate within the local diet. However, one group believed that the heterogeneity in the design of the completed trials and the relatively high number of adverse reactions meant that firm conclusions could not be made. Pragmatically, this results in a time frame around 4-6 months of age. The lack of consensus between the workshop participants indicated the need for additional data focused on the format and dosage of egg used in the intervention (Table 2). Since the first workshop, two international consensus documents have made recommendations for egg. The Asia Pacific Association of Pediatric Allergy, Respiratory & Immunology (APAPARI) consensus statement says that high-risk infants with severe eczema should first be assessed by an allergy specialist if parents want to introduce egg from 5-6 months of age.³⁹ Meanwhile, the Australian Society of Clinical Immunology and Allergy (ASCI) states "all infants should be given allergenic solid foods including peanut butter, cooked egg, dairy and wheat products in the first year of life".⁴⁰ The participants at the second workshop (2018) reached a consensus that egg should be introduced first in the heated or cooked form, after the establishment of weaning by the introduction of low allergenic foods, for example fruit and vegetables between 4 and 6 months of age.

For peanut, there was no consensus in either of the discussion groups. One group thought that the peanuts should be introduced

into the diet of infants in the general population from around 4 months based on the evidence of benefit from the LEAP study^{30,31} and lack of evidence of harm in the EAT study.³² Another group believed that data from the LEAP and EAT studies³⁰⁻³² were sufficient to recommend introducing peanuts into the diet of infants with severe eczema and/or hens egg allergy from the age of 4-11 months after testing for sensitization to peanut in the United Kingdom. They restricted their recommendation because of the selected population recruited into LEAP,^{30,31} the lack of replication in the intention-to-treat analysis in the EAT study³² and lack of evidence from outside of the United Kingdom. This is similar to the stance taken by an international consensus group,⁴¹ ESPGHAN,²⁰ the Australian society,⁴⁰ BSACI^{42,43} and Asian Association (where peanut prevalence is high)³⁹ although these extend their recommendations to all countries with a high prevalence of peanut allergy. The more recent US National Institute of Allergy and Infectious Diseases extends the recommendations of peanut introduction of around 6 months to infants at moderate and low risk of developing peanut allergy, however, only in accordance with family preferences and cultural practice.⁴⁴ Other discussion groups agreed that peanut should be introduced into the infant diet once they are developmentally ready and other solids have been introduced; they thought that this would ideally be 4-6 months of age given the potential risk of increased risk of peanut allergy if introduction is delayed. The range of views clearly identifies that this is still a topic where there is a substantial gap in available evidence with the perceived need for confirmatory data from inside and outside the United Kingdom and in low-risk infants (Table 2). Finally, the US National Institute of Allergy and Infectious Diseases has suggested that in countries where peanut products are not widely consumed by adults, early dietary introduction of peanut could lead to an increase in sensitization and allergic manifestations.⁴⁴ This fact was mentioned in the discussion at the 2018 workshop when answering the question of what are the potential adverse consequences of early introduction of allergenic foods. Other potential adverse consequences were given as allergic reactions (including anaphylaxis) and more rarely FPIES and EoE, increased risk of sensitization, and the adverse impact on other eating patterns and nutritional intake.

For allergenic foods, the 2018 workshop reached consensus that allergenic foods should be introduced at around the same time as other complementary foods are introduced as per country-specific recommendations and culinary and family practices. However, it was thought that there were insufficient data to make recommendations about when other allergenic foods should be introduced into the infant diet, a further gap in the evidence base (Table 2).

8 | SUMMARY AND FUTURE PERSPECTIVES

Over the last years, we have seen some initial attempts to assess the role of early allergen introduction on food allergy development with intervention trials. Data are now available for egg with some also for

peanut and milk allergy. Delaying the introduction of egg or peanut to the infant diet also appears to increase their risk for egg or peanut allergy. This may be particularly relevant for infants at high risk for developing food allergy, such as those with early-onset troublesome eczema.

The randomized controlled trial data suggest that the early introduction of egg into the infant diet might be associated with the development of less egg allergy. However, questions remain given the heterogeneity in the format and dosage of egg used in different studies plus many infants reacted to the intervention with sometimes life-threatening symptoms. The majority of participants in the workshop thought that there was sufficient evidence to recommend that cooked egg should be introduced into the diet of all infants from 4-6 months of age, when they are developmentally ready, to reduce the likelihood of egg allergy developing. However, others thought that the heterogeneity in trial designs and results precluded any preventative recommendations. A further large trial using a cooked form of egg is clearly required to resolve this.

There is clear evidence of benefit from the early introduction of peanut in one study but limited replication data and no data from outside of the United Kingdom. Although national and European government and academy organizations have used these data to make wide-ranging recommendations, consensus was not achieved in either of the workshops. Many participants were concerned by the lack of replication data and the generalizability of the results. Given the potential for the early introduction of peanuts into the diet as being a very successful public health preventative strategy, there is obviously an urgent need for a replication study in a more general risk population outside of the United Kingdom.

There are obvious gaps in the evidence base for other foods although foods such as tree nuts represent important causes of food allergy. We have still much to understand about how the infant diet can be modified to reduce the likelihood of developing food allergy. However, we do have the basis to plan and conduct the much needed further trials using the best methodological approach possible. We also need to understand any potential adverse nutritional consequences of altering the infant diet and any long-term impact, both positive and potentially negative, of such strategies.

There remains the challenge as to how to advise the families of infants who are at low, medium and high risk of developing food allergies. There was a consensus at the 2016 workshop that we should be advising that infants are breastfed for at least 6 months but not for any impact on food allergy. The 2018 workshop added that cooked egg can be introduced between 4 and 6 months of age and peanut may be introduced between 4 and 11 months if culturally appropriate. There are now international guidelines^{20,39-44} that recommend the early introduction of peanuts into the infant diet to prevent allergy in countries with a high prevalence of peanut allergy, but how this is achieved differs according to whether they are considered to be at high risk of developing food allergy. An alternative approach is to return to the situation where there is no deliberate delay of introducing any food to an infant, but to introduce it when

they are developmentally ready (rather than delaying introduction), this will usually be when they are 4–6 months of age.

ACKNOWLEDGEMENTS

This report was generated as part of the EU iFAAM project: Integrated Approaches to Food Allergen and Allergy Risk Management (Grant Agreement No. 312147) and an iFAAM workshop held at the UK Food Standards Agency. We would like to acknowledge the assistance of the UK Food Standards Agency in hosting the workshop. Liz Kendall and Erin Oliver from the Food Standards Agency and Rachel Elsom from Public Health England were observers at the workshop. We would also like to acknowledge the support of ILSI in arranging the second workshop.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

- Nwaru BI, Hickstein L, Panesar SS, et al. Prevalence of common food allergies in Europe: a systematic review and meta-analysis. *Allergy*. 2014;69:992-1007.
- Nwaru BI, Hickstein L, Panesar SS, et al. The epidemiology of food allergy in Europe: a systematic review and meta-analysis. *Allergy*. 2014;69:62-75.
- Schoemaker AA, Sprickelman AB, Grimshaw KE, et al. Incidence and natural history of challenge-proven cows milk allergy in European children- EuroPrevall birth cohort. *Allergy*. 2015;70(8):963-972.
- Xepapadaki P, Fiocchi A, Grabenhenrich L, et al. Incidence and natural history of hen's egg allergy in the first 2 years of life—the EuroPrevall birth cohort study. *Allergy*. 2016;71:350-357.
- Lyons SA, Burney PGJ, Ballmer-Weber BK, et al. Food allergy in adults: substantial variation in prevalence and causative foods across Europe. *J Allergy Clin Immunol Pract*. 2019;7(6):1920-1928.
- Panesar SS, Javad S, de Silva D, et al. The epidemiology of anaphylaxis in Europe: a systematic review. *Allergy*. 2013;68:1353-1361.
- Muraro A, Roberts G, Worm M, et al. Anaphylaxis: guidelines from the European academy of allergy and clinical immunology. *Allergy*. 2014;69:1026-1045.
- Salvilla SA, Dubois AEJ, Flokstra-de Blok BMJ, et al. Disease-specific health-related quality of life (HRQL) instruments for IgE-mediated food allergy. *Allergy*. 2014;69:834-844.
- Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment. Peanut allergy. 1998. <https://cot.food.gov.uk/committee/committee-on-toxicity/cotreports/cotwgreports/cotpeanutallergy> (last accessed 13th January 2019).
- Kleinman RE. American academy of pediatrics recommendations for complementary feeding. *Pediatrics*. 2000;106:127.
- Grimshaw K, Logan K, O'Donovan S, et al. Modifying the infant's diet to prevent food allergy. *Arch Dis Child*. 2017;102:179-186.
- du Toit G, Tsakok T, Lack S, Lack G. Prevention of food allergy. *J Allergy Clin Immunol*. 2016;137(4):998-1010.
- Department of Health and Social Security. Present-Day Practice in Infant Feeding. London: HMSO, 1980. Report on Health and Social Subjects:20.
- Pipes PL. Chapter 7 Infant feeding and nutrition. *Nutrition in Infancy and Childhood*. St. Louis, MO: Pub The C.V. Mosby Company; 1981.
- World Health Organisation. Infant and Young Child Feeding. Geneva 2009. <https://www.ncbi.nlm.nih.gov/books/NBK148965/> (last accessed 13th January 2019).
- Natsume O, Kabashima S, Nakazato J, et al. Two-step egg introduction for prevention of egg allergy in high-risk infants with eczema (PETIT): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2017;389:276-286.
- Feeney M, Du Toit G, Roberts G, et al. Impact of peanut consumption in The LEAP Study: feasibility, growth and nutrition. *J Allergy Clin Immunol*. 2016;138:1108-1118.
- Pimpin L, Jebb S, Johnson L, Wardle J, Ambrosini G. Dietary Protein intake is associated with body mass index and weight up to 5 years of age in a prospective cohort of twins. *Am J Clin Nutr*. 2016;103:389-397.
- Maslin K, Grimshaw K, Oliver E, et al. Taste preference, food neophobia and nutritional intake in children consuming a cows' milk exclusion diet: a prospective study. *J Hum Nutr Diet*. 2016;29:786-796.
- Fewtrell M, Bronsky J, Campoy C, et al. Complementary feeding: a position paper by the European society for paediatric gastroenterology, hepatology, and nutrition (ESPGHAN) committee on nutrition. *J Pediatr Gastroenterol Nutr*. 2017;64(1):119-132.
- Department of Health and Social Security. Present-Day Practice in Infant Feeding. London: HMSO, 1974. Report on Health and Social Subjects:9.
- United Kingdom Infant Feeding Study 2010 Consolidated results. <https://digital.nhs.uk/data-and-information/publications/statistical/infant-feeding-survey/infant-feeding-survey-uk-2010> (Last accessed 13th January 2019).
- Office of Population Censuses and Surveys (OPCS). Infant feeding Report 1975.
- Lund-Blix NA, Sander SD, Størdal K, et al. Infant feeding and risk of type 1 diabetes in two large scandinavian birth cohorts. *Diabetes Care*. 2017;40:920-927.
- <https://www.sign.ac.uk/search-filters.html>, last accessed 13th January 2019.
- Palmer DJ, Metcalfe J, Makrides M, et al. Early regular egg exposure in infants with eczema: a randomized controlled trial. *J Allergy Clin Immunol*. 2013;132(2):387-392.
- Palmer DJ, Sullivan TR, Gold MS, Prescott SL, Makrides M. Randomized controlled trial of early regular egg intake to prevent egg allergy. *J Allergy Clin Immunol*. 2017;139:1600-1607.
- Tan JWL, Valerio C, Barnes EH, et al. A randomized trial of egg introduction from 4 months of age in infants at risk for egg allergy. *J Allergy Clin Immunol*. 2017;139:1621-1628.
- Bellach J, Schwarz V, Ahrens B, et al. Randomized placebo-controlled trial of hen's egg consumption for primary prevention in infants. *J Allergy Clin Immunol*. 2017;139:1591-1599.
- Du Toit G, Roberts G, Sayre PH, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med*. 2015;372(2):803-813.
- Du Toit G, Sayre PH, Roberts G, et al. Effect of avoidance on peanut allergy after early peanut consumption. *N Engl J Med*. 2016;374(15):1435-1443.
- Perkin MR, Logan K, Tseng A, et al. Randomized trial of introduction of allergenic foods in breast-fed infants. *N Engl J Med*. 2016;374(18):1733-1743.
- Preventing Atopic Dermatitis and Allergies in Children (PreventADALL). <https://clinicaltrials.gov/ct2/show/NCT02449850> (last accessed 13th January 2019).

34. Prevention of peanut allergy by early consumption – a prospective study (PEAP) <http://apps.who.int/trialsearch/Trial2.aspx?TrialID=DRKS00005487>.
35. Tsakok T, Marrs T, Mohsin M, et al. Does atopic dermatitis cause food allergy? A systematic review. *J Allergy Clin Immunol*. 2016;137(4):1071-1078.
36. Ierodiakonou D, Garcia-Larsen V, Logan A, et al. Timing of allergenic food introduction to the infant diet and risk of allergic or autoimmune disease: a systematic review and meta-analysis. *JAMA*. 2016;316(11):1181-1192.
37. Roberts G. Another step towards prevention of food allergy. *Lancet*. 2017;389:230-231.
38. Kramer MS, Kakuma R. Optimal duration of exclusive breastfeeding. *Cochrane Database Syst Rev*. 2012;(8). <https://doi.org/10.1002/14651858.CD003517.pub2>
39. Tham EH, Shek LP, Van Bever HP, et al. Early introduction of allergenic foods for the prevention of food allergy from an Asian perspective—An Asia Pacific Association of Pediatric Allergy, Respiratory & Immunology (APAPARI) consensus statement. *Pediatr Allergy Immunol*. 2017;29:1-10.
40. Australasian Society of Clinical Immunology and Allergy. Infant Feeding and Allergy Prevention in children (Position Statement). 2016. www.allergy.org.au/images/pcc/ASCIAGuidelines_infant_feeding_and_allergy_prevention.pdf. Accessed Jan 2019.
41. Fleischer DM, Sicherer S, Greenhawt M, et al. Consensus communication on early peanut introduction and the prevention of peanut allergy in high-risk infants. *J Allergy Clin Immunol*. 2015;136:258-261.
42. British Society of Allergy and Clinical Immunology. Infant feeding and allergy prevention 2018 <https://www.bsaci.org/pdf/Infant-feeding-and-allergy-prevention-PARENTS-FINAL-booklet.pdf>. Accessed Jan 2019.
43. Turner PJ, Feeney M, Meyer R, Perkin MR, Fox AT. Implementing primary prevention of food allergy in infants: New BSACI guidance published. *Clin Exp Allergy*. 2018;48:912-915.
44. Togias A, Cooper SF, Acebal ML, et al. Addendum guidelines for the prevention of peanut allergy in the United States. *Pediatr Dermatol*. 2017;34(1):5-12.

How to cite this article: Roberts G, Grimshaw K, Beyer K, et al. Can dietary strategies in early life prevent childhood food allergy? A report from two iFAAM workshops. *Clin Exp Allergy*. 2019;49:1567-1577. <https://doi.org/10.1111/cea.13515>