



Doctor, when should I feed solid foods to my infant?

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Purpose of review

Modalities and timing of the introduction of solid foods to infants may influence growth, obesity, atherosclerosis, hyperlipidemia, hypertension, diabetes, and metabolic disease. The most debated effects of solid foods introduction are those on the development of food allergy.

Recent findings

For the first time, in recent years prospective studies have been published about the effects of early vs. delayed introduction of allergenic foods into the infants' diet on food allergy. According to these studies, the early introduction of peanut may be a powerful protecting factor against peanut allergy in some risk categories. This seems not be true for wheat, cow's milk, sesame, and whitefish. The effect of early introduction of egg on egg allergy are controversial.

Summary

The recent studies have changed the practice recommendations given by healthcare providers to families. We review the modifications of the recommendations of international societies on the introduction of solid foods, both to the general population and to infants at risk for allergy.

Keywords

egg allergy, food allergy, infancy, peanut allergy

INTRODUCTION

The modalities and timing of weaning may influence not only the optimal growth and development, but also the later establishment of obesity, atherosclerosis, hyperlipidemia, hypertension, diabetes, and metabolic disease [1–4]. However, the most debated effects of solid foods introduction are those on the development of food allergy. Recent data have changed the common wisdom, modifying the practice recommendations given by healthcare providers to families. We review here how the recommendations of international societies on weaning, both to the general population and to infants at risk for allergy, have changed in the last few years.

IS MY BABY AT RISK FOR ALLERGY?

According to all current guidelines, an infant is defined as at risk for allergy when 'at least one first-degree relative has a history of allergic disease' [5,6], in particular allergic rhinitis, asthma, eczema, or food allergy [7,8^{***}]. This definition is not universally adopted throughout studies (Table 1)

[9–14,15^{***},16–18]. Thus, the results of each study will not be directly applicable outside the specific risk profile assessed, nor to all risk categories.

THE PARADIGM SHIFT FROM AVOIDANCE TO EQUIPOISE: 2000–2014

Years ago, the recommendations on weaning children 'at risk for allergy' were based on the concept that delaying allergenic food exposure was beneficial. This assumption was based on two prospective studies suggesting that food allergy [9] and

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KEY POINTS

- It is an exciting time for food allergy prevention! It used to be proposed by delaying the introduction of allergenic foods.
- This prohibitionistic approach has been challenged by a series of studies unable to confirm associations between delayed introduction of solids in infants and the incidence of atopic disease.
- The recent publication of prospective studies has reversed the approach, proposing to introduce early peanuts and milk, to reduce peanut and milk allergies.
- The application of the results of individual studies should take into account the context of the study, the population studied, and the allergy risk factors included.
- New guidelines are being now produced but their application requires continuous monitoring and tracking, so that early signs of adverse outcomes can be remedied and early signs of benefit can be further expanded and disseminated.

eczema [10] in childhood were postponed by a late introduction of specific foods. Contemporaneous studies, showing a reduced incidence of cow's milk allergy (CMA) and eczema due to milk allergen reduction in children at risk [19], corroborated the idea that the earlier the allergen was introduced, the more probable was break of tolerance and inception of food allergy. This concept became part of the

infant feeding policies in Europe [20], Australia [21], and the U.S. [22]. The last prohibitionist statement was the American College of Allergy Asthma and Immunology (ACAAI) Food Allergy Committee Consensus Document, published as Continuous Medical Education review in 2006 [23].

Starting 2004, the 'avoid specific food allergens for prevention' paradigm was challenged by a series of epidemiological studies [24–32] unable to confirm associations between late introduction of solids and the development of eczema, food allergy, or asthma. Despite their noninterventional nature, these studies produced a mass of data robust enough to convince many academic bodies to temper their recommendations to delay weaning in at-risk populations. After 2005, there was a shift from a prohibitionist to an equipoise behavior (Fig. 1) [33]. In 2005, Australians revised their infant feeding guidelines, raising concerns about the lack of good evidence to support food allergen avoidance practices [34]. In 2008, the American Academy of Pediatrics (AAP) report on weaning replaced its earlier policy statement, indicating that there was not enough evidence to maintain any prohibitionist recommendation [5]. The European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) Committee on Nutrition gave similar recommendations, suggesting to wean not before the 17th, but not after the 26th week of life [35]. Same suggestions were given by the UK Department of Health [36], indicating peanuts, nuts, seeds, milk, eggs, wheat, fish, or shellfish be introduced

Table 1. Allergy risk categories and clinical outcomes in trials on the effect of the introduction of specific solid foods to infants

Author	Type of risk included	Outcomes evaluated
Saariinen 1980 [9]	Open population	Food allergy (positive challenge)
Kajosaari 1983 [10]	Both parents allergic	Eczema; food allergy (clinical judgment)
Zeiger 1989 [11]; Zeiger 1995 [12]	One parent atopic	Atopic dermatitis, urticaria/angioedema, allergic rhinitis, asthma (clinical judgment), food allergy (50% clinical judgment, 50% DBPCFC)
Halken 2000 [13]	Both parents allergic or one parent/ sibling allergic + CB IgE ≥ 0.3 kU/L	Asthma, recurrent wheezy bronchitis, atopic dermatitis, allergic rhinoconjunctivitis, at least two episodes of allergic urticarial, food allergy, cow's milk allergy
Palmer 2013 (STAR) [14]	'High risk' – infants with moderate to severe eczema (SCORAD > 15)	IgE-mediated egg allergy at 12 months of age (positive SPT and egg challenge)
Lack 2015 (LEAP) [15**]	'High risk' – 4–8-month-old children with eczema and/or egg allergy	Peanut allergy at 5 years of age (OFC)
Lack 2009 (EAT) [16]	Normal risk – general population	IgE-mediated food allergy to any of six foods: cow's milk, egg, wheat, sesame, fish, and peanut at 1–3 years of age (OFC)
Palmer 2010 (STEP) [17]	'Intermediate risk' – maternal history of allergy + positive maternal SPT	IgE-mediated egg allergy at 12 months of age (positive SPT and egg challenge)
Campbell 2011 (BEAT) [18]	'Intermediate risk' – first degree relative with atopy	IgE-sensitization to egg (SPT at 8 and 12 months of age)

In italic, the ongoing – not yet published – studies. CB, cord blood; DBPCFC, double-blind, placebo-controlled food challenge; EAT, Enquiring About Tolerance; IgE, immunoglobulin E; LEAP, Learning Early about Peanut Allergy; OFC, oral food challenge; SCORAD, SCORing Atopic Dermatitis; SPT, skin-prick test.

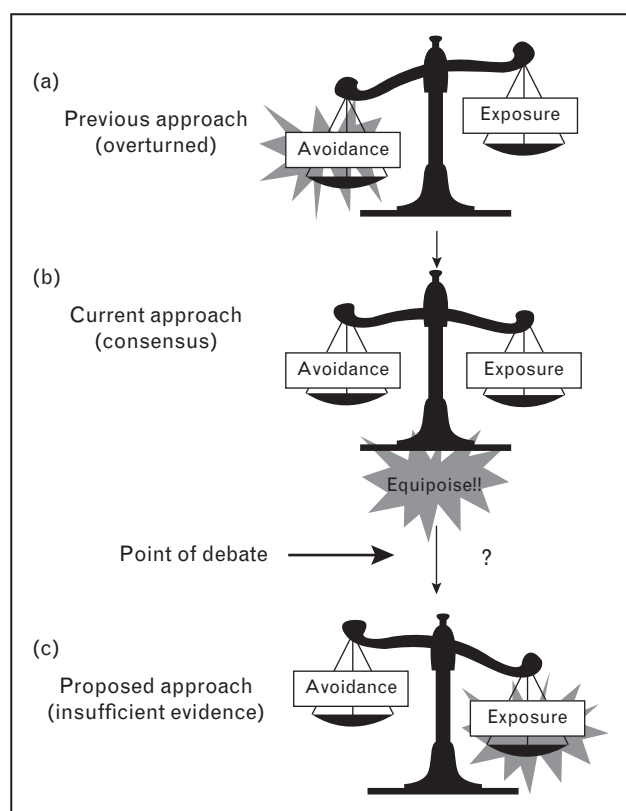


FIGURE 1. From prevention by avoidance to equipoise. Are we going towards exposure as preventive mean for food allergy? Reproduced with permission [33].

freely after 6 months of age to all children. Canadians acknowledged in their guidelines that ‘there is no conclusive evidence that delaying the introduction of eggs, fish, and nuts beyond 4–6 months of age helps to avoid food allergies’ [37]. In 2014, the European Academy of Allergy, Asthma and Clinical Immunology (EAACI) came up with recommendations for the prevention of food allergy indicating to ‘not deny or encourage exposure to highly allergenic foods deemed as cow’s milk, hen eggs, and peanuts as soon as it started weaning’ [6]. The American Academy of Allergy, Asthma and Immunology (AAAAI) suggested to wean between 4 and 6 months of age, providing formal recommendations about how and when to introduce the main allergenic foods (cow’s milk, egg, soy, wheat, peanut, tree nuts, fish, and shellfish) [38]. They also indicated scenarios in which a consultation with an allergist for development of a personalized plan for food introduction would be sought.

Probably the most influential document in this field was the National Institute for Allergy and Infectious Diseases (NIAID) sponsored expert panel guideline [7]. Based on a full meta-analysis and, following the Grading of Recommendations Assessment, Development and Evaluation (GRADE)

method, it found insufficient evidence to support the association between delayed weaning in infants and the incidence of atopic disease. The meta-analysis did not consider the 1980’s studies, but indicated that similar studies published in the 1990’s are of poor or fair quality [39]. All the changes in the guidelines have been recently reviewed [40].

TOWARDS EARLY EXPOSURE?

Some epidemiological studies not only found ineffectiveness of the prohibitionist approach, but suggested to hasten allergen exposure. The authors of an Australian cross-sectional study [41] of children with normal allergy risk (HealthNuts) asked for a change in guidelines, because the introduction of cooked egg at 4–6 months of age might protect against egg allergy. The Finnish Type 1 Diabetes Prediction and Prevention nutrition study [42] showed that early introduction of oats (<5.5 months) was associated with reduced rate of asthma, whereas early introduction of fish (<8 months) was associated with a reduced rate of rhinitis. From the same cohort, an analysis of 994 infants associated early introduction of cereals, fish, and egg with a decreased rate of asthma, allergic rhinitis, and atopic sensitization in childhood [43]. Finally, a questionnaire-based Israeli-UK study [44] found peanut allergy rates higher in the UK, in which the consumption was far lower. The authors raised the question whether early introduction, rather than avoidance, of allergenic foods would promote oral tolerance.

RECENT INTERVENTIONAL STUDIES [45]

Around the time of the ACAAI consensus document [23] it became clear that prospective, interventional studies must be planned to solve the question. The first, specifically designed to this end, was the Learning Early about Peanut Allergy (LEAP) trial, registered in 2006. It aimed to evaluate whether early exposure to peanuts protects from developing peanut allergy in ‘high risk’ children [15²²,46]. The single-center trial was powered to include 640 infants aged 4–11 months. High risk was defined as severe eczema and/or egg allergy (Table 1). Children with a positive skin-prick test (SPT) for peanut with a wheal of more than 4 mm in diameter (irrespective if they were allergic to peanut or not), those with a sound suspicion of peanut allergy, and peanut allergy in a care provider or a current household member were excluded. Also excluded were children with a diagnosis of persistent asthma, whereas children with recurrent wheezing were admitted [46]. Thus, not only infants displaying

other risk factors (for instance CMA, mild to moderate eczema, familial history of allergy) were not specifically targeted, but those at very high risk of food allergy were excluded. Infants were openly randomized to consume at least 6 g of peanut protein per week, distributed in three or more meals, until they reached 60 months of age, or to avoid peanuts until 60 months of age. The primary outcome was peanut allergy at 60 months of age, determined by oral food challenge (OFC). Markers of sensitization were evaluated yearly by SPT and peanut-specific immunoglobulin E (IgE). Peanut-specific immunoglobulin G (IgG) and IgG4 antibodies were also measured at each visit. Enrolled children were stratified into infants with a negative result on the initial SPT with peanut (542, 530 of which completed the study) and children already sensitized but not allergic (98, all evaluated at 60 months). The former was evaluated for primary prevention of peanut allergy, the latter for secondary prevention. Globally, 57 participants (9 randomly assigned to consumption and 48 to avoidance) developed peanut allergy, a 17.2% rate in the avoidance and a 3.2% in the consumption group (Fig. 2) [15²²].

The reduction was found both in the primary (6.0% prevalence in the avoidance vs. 1.0% in the consumption group, $P=0.008$) and secondary prevention group (33.1 vs. 6.8%, $P<0.001$). The results stand also in the per-protocol analysis and after a worst-case imputation analysis, assuming that participants with missing data in the peanut-consumption group would have been allergic to peanuts and participants with missing data in the peanut-avoidance group would not. These results correspond to a 14% absolute risk reduction for peanut allergy, a number needed to treat of 7.1 to prevent peanut allergy in one child, and a relative risk reduction of 81%. From an immunological point

of view, the avoidance group showed a significant increase in SPT wheal size starting at 12 months, particularly children who were allergic to peanuts at month 60. Peanut-specific IgE did not show statistical differences at 12, 30, and 60 months. Fewer participants in the consumption group displayed very high specific IgE levels at these time points, but globally the avoidance group presented with lower levels (Fig. 3) [47]. Levels of peanut-specific IgG and IgG4, higher in the consumption group, reflected exposure.

LEAP trial has been rightly defined a milestone, opening the way to 'do something to reverse the increasing prevalence of peanut allergy' [48]. The intervention proved effective with an 86% reduction in peanut allergy at 5 years in primary prevention and a 70% reduction in secondary prevention. Although the study was not placebo-controlled, the message that early oral introduction of peanuts could prevent peanut allergy in high-risk infants stands very clearly. At least for this allergen, avoidance is associated with a greater frequency of food allergy than consumption. Naturally the LEAP study does not evaluate the use of different doses, the minimal length of exposure necessary to induce the tolerogenic effect, the potential risks of premature discontinuation or sporadic feeding of peanut, nor the duration of the effect. This last question is initially addressed by the LEAP-on trial, a follow-up study [49²³] aimed to evaluate the persistent tolerance to peanut after 12 months of cessation of peanut consumption in the LEAP study population. Among the 550 participants, 18.6% in the peanut-avoidance group and 4.8% in the peanut-consumption group had peanut allergy ($P<0.001$) (Fig. 4). The findings remained significant after worst-case imputation. In the peanut consumption group, the percentage of participants with peanut allergy rose from 3.6% at 60 months to 4.8% at 72 months

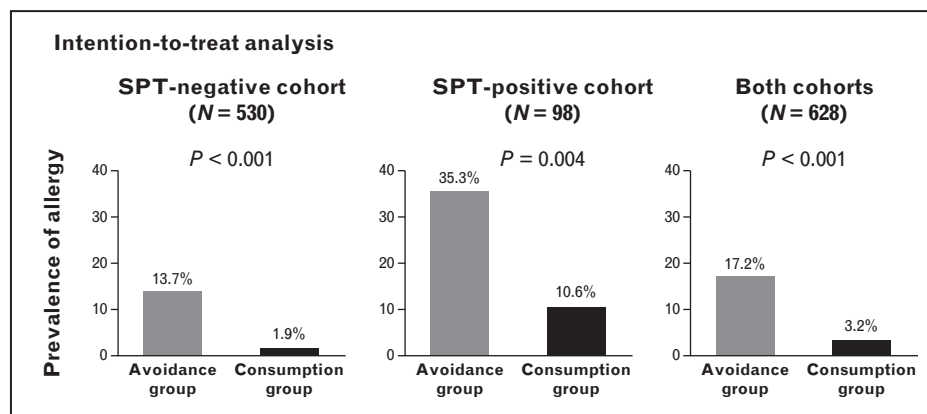


FIGURE 2. LEAP study: prevalence of peanut allergy at 60 months of age among participants who had a negative result on the skin-prick test at baseline, among those who had a positive result at baseline, and in both groups combined, in the intention-to-treat analysis. Reproduced with permission [15²²]. LEAP, Learning Early about Peanut Allergy.

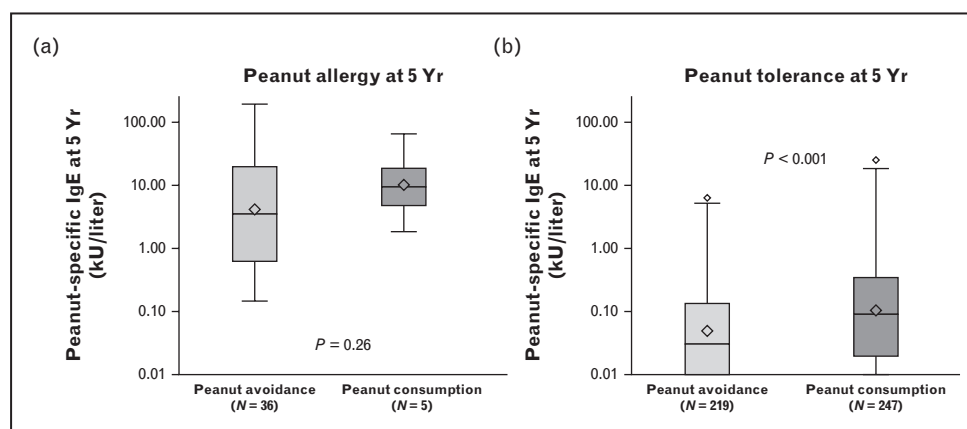


FIGURE 3. Peanut-specific IgE in the LEAP study. Reproduced with permission [47]. IgE, immunoglobulin E; LEAP, Learning Early about Peanut Allergy.

($P = ns$). In the peanut-avoidance group, the percentage rose from 17.2 to 19.2% ($P = ns$). Thus, unresponsiveness to peanut induced by early consumption persists after 12 months of avoidance; whether it persists over the course of many years remains to be evaluated.

Following a similar pattern with a wider approach, the Enquiring About Tolerance study, registered in 2009, aims to examine the effect of early consumption of potentially allergenic foods on IgE-mediated allergy. It aimed to include 2500 infants [16]. The intervention arm introduced egg, wheat, peanuts, cow's milk, sesame, and whitefish between 3 and 6 months of age while the control group did it after 6 months of age. Food allergy to one or more of the six intervention foods developed in 7.1% of the participants in the standard-

introduction group (42 of 595 participants) and in 5.6% of those in the early-introduction group (32 of 567 participants) ($P = 0.32$). In the intention to treat analysis, no differences were found for single foods (Fig. 5). The per-protocol analysis identified a significantly lower proportion of any food allergy in the early-introduction group (2.4 vs. 7.3%, $P = 0.01$), due in particular to a lower prevalence of peanut (0 vs. 2.5%, $P = 0.003$) and egg allergy (1.4 vs. 5.5%, $P = 0.009$). No significant effects were found for milk, sesame, fish, and wheat. The author reports practical difficulties in getting an early introduction of all six foods [50[■]].

Other studies have been conceived in Europe and Australia. The Hen's Egg Allergy Prevention (HEAP) study [51] aimed to evaluate egg allergy at 12 months of age in 800 children, randomized to receive either hen's egg or a placebo at 4–6 months of age. The STAR trial (registered in 2009 in Australia) aimed to an 'high-risk' group of 226 infants with moderate to severe eczema, divided into an intervention group (consuming daily egg powder from 4 until 8 months of age, and introducing cooked egg from 8 months of age) and a control group, consuming daily placebo and introducing cooked egg from 8 months of age [52]. Of the planned number of children, only 86 were recruited, 49 randomized to the egg group, and 37 randomized to placebo. The results were not conclusive. The proportion of infants receiving a diagnosis of IgE-mediated egg allergy at 12 months of age was lower in the egg group (33%) than in the control group (51%) (Fig. 6a); however, the difference did not reach statistical significance (Fig. 6b) [14]. The authors commented that the trend for lower incidence of egg allergy in the egg exposed reduces previous concerns that early introduction of this allergenic food would be associated with increased egg allergy risk, but no conclusion can be drawn in

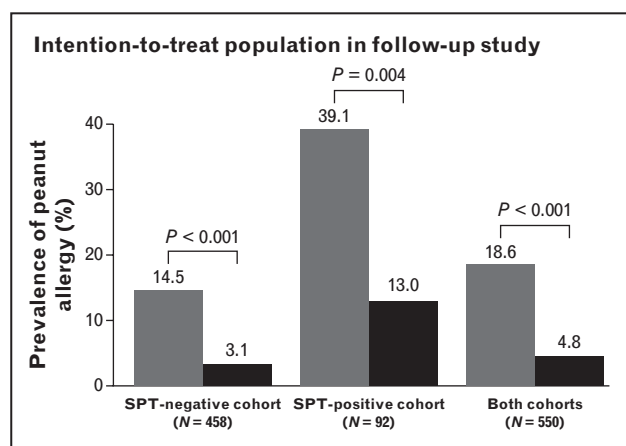


FIGURE 4. LEAP-on study: prevalence of peanut allergy at 72 months of age among participants who had a negative result on the skin-prick test at baseline, among those who had a positive result at baseline, and in both groups combined. Intention-to-treat analysis. Reproduced with permission [48]. LEAP, Learning Early about Peanut Allergy.

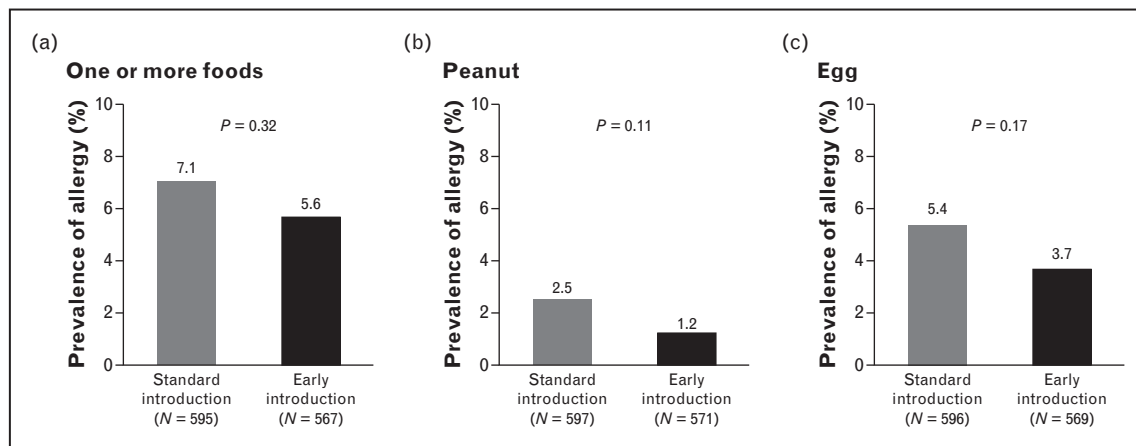


FIGURE 5. EAT study: prevalence of IgE-mediated food allergy to six early-intervention foods (peanut, cooked egg, cow's milk, sesame, whitefish, and wheat; Panel a), to peanut (panel b), and to egg (panel c). Reproduced with permission [49]. EAT, Enquiring About Tolerance; IgE, immunoglobulin E.

the opposite direction. They underline that, given the observation of sensitization to egg before its introduction, the roots of food sensitization seem to start well before weaning.

The STEP study, registered in 2010, is designed for 1500 'intermediate risk' infants without eczema but with atopic mothers (history of allergy along with positive SPT in the mothers). The group has been randomly exposed to daily consumption of egg or placebo from 4 to 6 months until 10 months of age, then egg is freely introduced [17]. Both STAR

and STEP studies target IgE-mediated egg allergy at 12 months of age, based on positive SPT and egg challenge. A similar trial is ongoing in Japan (JPRN-UMIN000008673, not accessible).

The BEAT study [18] (Beating Egg Allergy Trial) is also intended for 'intermediate risk' infants (first degree relative with atopy) exposed to daily consumption of egg protein from 4 to 6 months until 8 months of age vs. not-exposed to egg until 8 months of age, then introduced to 'normal unrestricted diet'. The outcome in this case is egg

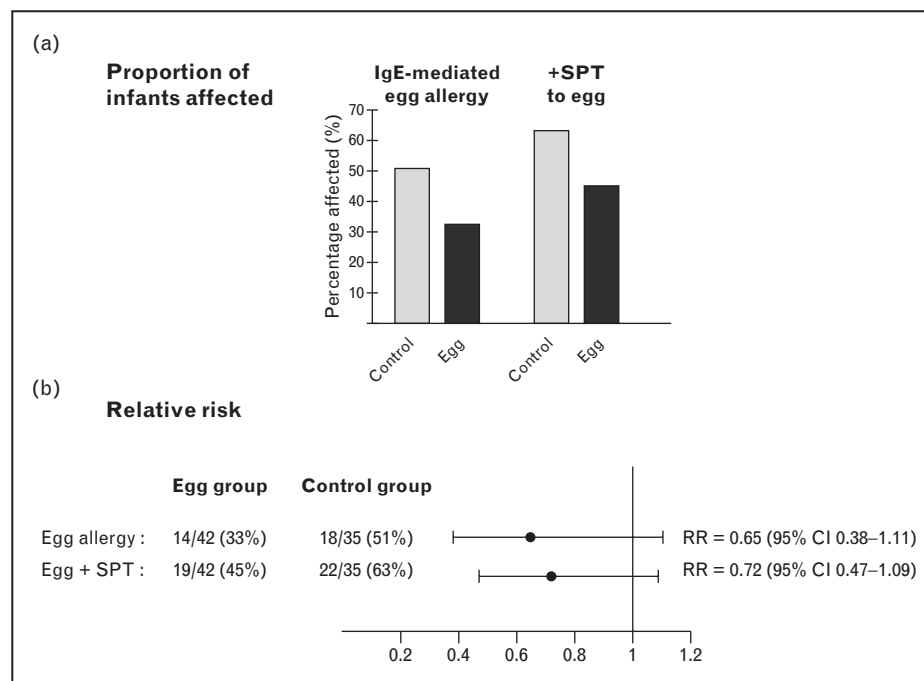


FIGURE 6. IgE-mediated egg allergy and positive SPT response (+SPT) to egg at 12 months of age: (a) proportion of infants and (b) RR between the egg and control groups. Reproduced with permission [51]. IgE, immunoglobulin E.

sensitization measured by SPT at 8 and 12 months of age.

SHOULD WE MOVE TOWARDS AN EXPOSURE APPROACH FOR ALL COMPLEMENTARY FOODS?

The evidence from the LEAP study was judged compelling enough by the scientific allergy societies over the world to take the decision to highlight its practical effects. Waiting for more formal guidelines, the World Allergy Organization and nine other scientific societies jointly published a Consensus Communication highlighting the necessity to support early peanut introduction in at-risk infants [53]. According to the document:

- (1) Pediatricians and allergists should recommend introducing peanut-containing products into the diets of 'high-risk' infants early in life (between 4 and 11 months of age) in countries where peanut allergy is prevalent.
- (2) Infants with early-onset atopic disease might benefit from evaluation by an allergist or trained physician to diagnose any food allergy and assist in implementing these suggestions.
- (3) Evaluation of such patients might consist of performing peanut skin testing, in-office observed peanut ingestion, or both, as deemed appropriate after discussion with the family.
- (4) The clinician can perform an observed peanut challenge for those with evidence of a positive peanut skin test response to determine whether they are clinically reactive before initiating at-home peanut introduction.
- (5) If the child is not allergic to peanut, this food should be consumed at least three times a week, for the amount of at least 6g, up to 6 years.

This advice is generating a series of discussions about its applicability, risks, and opportunities for extension to the various risk categories in different settings [54–57]. Currently, an expert group convened by NIAID is in the final stages of issuing addendum guidelines to supplement to the NIAID expert panel guidelines.

CONCLUSION

A new time has come, rich with new perspectives in food allergy prevention. Many possibilities are now on the table when we face a pregnant or recent mother of a child at risk. The approach to peanut introduction has changed because of more recent evidence, but it has not yet been put to the test (we have no outcomes of the dissemination of the new

approach yet). The approach to the introduction of other solids remains open to evaluation. More extensive guidelines will be announced in the near future from the NIAID expert panel on food allergy and EAACI Guidelines Group with their multidisciplinary stakeholders [53].

As we have learned from previous guidelines on prevention, exemplified by the World Allergy Organization-Driven Guidelines on Allergic Disease: Prevention (GLAD-P) [8²²,58], interpreting individual studies relies on the context of the study and the population studied as regards to their risk factors. This may render the comparison among studies difficult. The experts do their best in drafting guidelines based on their interpretation of the data, aided by the established GRADE system, and their own personal experiences. The ultimate test, however, is the improvement of the health of the population at risk upon widespread implementation of the new guidelines. This requires continuous monitoring and tracking, so that early signs of adverse outcomes can be remedied and early signs of benefit can be further expanded and disseminated.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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