

## Prevention of food allergy: Beyond peanut



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**Key words:** Food allergy prevention, egg allergy, early introduction

Prevention of peanut allergy has entered mainstream practice with the publication of the landmark Learning Early About Peanut (LEAP) and LEAP-ON studies and the addendum guidelines updating recommendations about early peanut introduction.<sup>1</sup> Comparatively less is known about how to prevent other allergies beyond peanut, the subject of this article. Although observational studies can contribute important insights, the main focus of this review will be randomized controlled trials (RCTs) and meta-analyses of interventional studies in which the outcome of interest is clinical food allergy.

## EARLY INTRODUCTION OF EGG

Cooking changes the allergenicity of hen's egg proteins, an important consideration that must be applied to the review and interpretation of egg prevention literature. Taking observational and interventional studies with all types of egg protein into account, a recent meta-analysis concluded with moderate certainty that early egg (and peanut) introduction at 4 to 6 months was associated with reduced egg (and peanut) allergy,<sup>2</sup> and the strength of this evidence has led some allergy societies to endorse early egg introduction along with early peanut introduction. Stratifying cohorts as very high risk (moderate-to-severe atopic dermatitis [AD]), high risk (primary relative with atopy), and normal risk (unselected population), the number needed to treat to prevent egg allergy was estimated at 5, 23, and 42, respectively,<sup>2</sup> although it should be noted that risk stratification strategies are not well validated. However, prospective interventional trials have used different types of egg proteins, which might

have contributed to differing results and in some cases safety concerns. We will first review data from studies using cooked egg, which for practical reasons is most likely to be the form accepted for real-world use.

Two trials used heated egg protein and showed significant benefit of early egg introduction without significant safety concerns. Infants enrolled in the Enquiring About Tolerance (EAT) trial in the United Kingdom were introduced to a small hard-boiled egg in addition to milk, peanut, sesame, whitefish, and wheat at between 3 and 5 months of age.<sup>1</sup> Although there was no difference in the intention-to-treat (ITT) population between early introduction versus standard introduction groups in the rate of food allergy to any food between 1 and 3 years of age, the per-protocol (PP) analysis demonstrated a protective benefit of early feeding against the development of any food allergy and specifically peanut and egg allergies. The prevalence of egg allergy in the PP analysis was significantly decreased in those able to ingest at least 2 g/wk of hard-boiled egg; however, protocol adherence with egg was the most difficult allergen to maintain in the infant diet, with only 43% of infants included in the PP analysis.

In the Japanese Prevention of Egg Allergy Tiny Amount Intake (PETIT) trial, infants with AD were enrolled at 4 to 5 months and given 25 mg of egg protein in the form of heated egg powder or placebo daily from 6 to 9 months.<sup>3</sup> The dose was increased to 125 mg of heated egg protein or placebo from 9 to 12 months. At 12 months, infants were challenged with the same heated egg product. The trial was stopped early after an unplanned interim efficacy analysis demonstrated a protective benefit in the intervention group (8% rate of egg allergy in the intervention group compared with 38% in the placebo group). Infants were not tested for reactivity to less-cooked forms of egg.

Four other prospective placebo-controlled RCTs have used raw egg protein, which is thought to be more allergenic than heated egg: the Solids Timing for Allergy Research (STAR) trial, Starting Time of Egg Protein (STEP) trial, and Beating Egg Allergy Trial (BEAT), all of which were conducted in Australia, and the Hen's Egg Allergy Prevention (HEAP) trial, which was conducted in Germany.<sup>4-7</sup> The HEAP trial was the only trial to sample the general population. The STAR trial, STEP trial, and BEAT intervened in what were considered to be higher-risk populations based on either the presence of AD (STAR trial), maternal atopy (STEP trial), or atopy in a first-degree relative (BEAT). BEAT was the only trial of the 4 to show a significant reduction in sensitization to egg white at 12 months, but oral food challenges were not conducted. A lower proportion of infants in the STAR trial were given a diagnosis of IgE-mediated egg allergy compared with the control cohort, but the difference was not significant; however, the trial was not sufficiently powered to rule out a significant difference. It should be noted that data from the STEP trial were not available and thus were not included in the previously mentioned meta-analysis.

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Disclosure of potential conflict of interest: J. A. Bird reports grants, personal fees and other from DBV Technologies, personal fees and non-financial support from Food Allergy Research and Education, grants from Nestle Health Sciences, personal fees from Nutricia North America, personal fees from Pharm-Olam International LTD, grants and personal fees from Aimmune Therapeutics, personal fees from Pfizer Pharmaceuticals, and personal fees from Allergy Therapeutics, Ltd, outside the submitted work. C. Parrish reports personal fees and non-financial support from Aimmune Therapeutics, and non-financial support from DBV Technologies, outside the submitted work. B. P. Vickery reports personal fees from Aimmune Therapeutics and ThermoFisher, and advisory board membership at Aimmune and Food Allergy Research and Education, outside the submitted work. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication September 18, 2018; revised December 31, 2018; accepted for publication December 31, 2018.

Available online January 4, 2019.

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J Allergy Clin Immunol 2019;143:545-7.

0091-6749/\$36.00

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<https://doi.org/10.1016/j.jaci.2018.12.993>

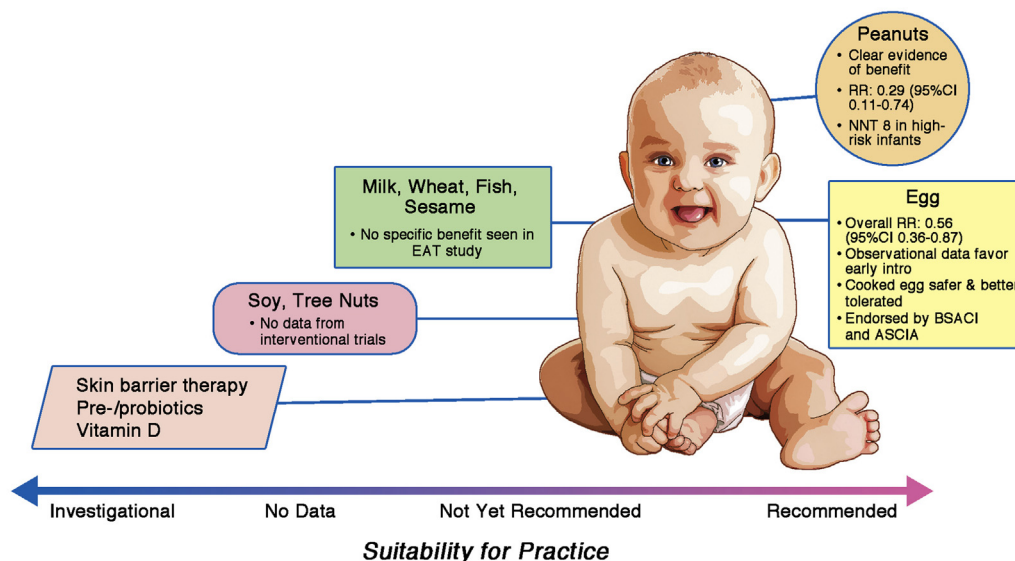


**FIG 1.** Suitability for the practice of allergen-specific and nonspecific prevention strategies. RR, Relative risk.

Egg allergy at study entry was the greatest limiting factor encountered by trials other than the PETIT trial. The STAR trial cohort selected children with moderate-to-severe AD and found that 31% of 4-month-old infants randomized to egg had an allergic reaction to egg powder before initiating therapy.<sup>4</sup> Despite enrolling children from the general population, the HEAP trial found that 5.7% (23/406) of participants already had sensitization to egg at screening.<sup>5</sup> Seventeen of 23 underwent a challenge, and 16 were confirmed to be allergic, including 11 with anaphylaxis. One third of the allergic infants did not have AD or any history of atopy that might suggest a greater risk of reacting, highlighting the concern that allergic reactions, some severe, can occur unexpectedly in infants with first exposure to unheated egg protein in an unmonitored setting. Fourteen (8.5%) infants in the BEAT cohort reacted to egg within 1 week of intervention.<sup>7</sup> A confirmed allergic reaction led to study discontinuation in 6.1% of participants in the egg group in the STEP trial.<sup>6</sup>

As of this writing, the Australasian Society of Clinical Immunology and Allergy (ASCIA; <https://www.allergy.org.au/patients/allergy-prevention/ascia-how-to-introduce-solid-foods-to-babies>) and the British Society of Allergy and Clinical Immunology (BSACI; <https://www.bsaci.org/about/early-feeding-guidance>), but not North American societies, have endorsed early introduction of egg to prevent egg allergy. ASCIA recommends introduction of hard-boiled egg, and BSACI allows for scrambled egg, omelet, or soft or hard-boiled egg if produced under strict food safety controls to minimize risk of microbial contamination. It appears that introduction of raw egg, especially in high-risk infants, can lead to a significant number of reactions, and cooked egg is more likely to be introduced into the diet and tolerated. However, it is important to balance the apparent benefit of early cooked egg with the knowledge that this has been demonstrated in only 1 placebo-controlled RCT; that the benefit was determined based on results of a challenge to the same heated material after reduction in allergenicity rather than a real-world egg serving with intact epitopes; that the heated egg protein was administered

in small measured amounts and gradually increased rather than given *ad libitum*; and that the trial was unfortunately stopped early as a result of an unplanned interim efficacy analysis, which is not a recommended procedure and was noted by Roberts in the editorial accompanying the publication as a problem that could limit the size of the observed effect by at least 50%. A large, multicenter, properly powered study of a widely available heated egg product that tests full egg tolerance and is allowed to proceed to completion would generate important and decisive additional data. Also, because the development of egg allergy in some children can occur before developmental skills allow for appropriate oral feeding, future investigations might need to consider approaches incorporating egg protein into formula or expressed breast milk as a method of safe exposure to egg earlier in life. It is important to note that there have been no studies suggesting that delayed introduction of egg provides any protective benefit; and for those able to introduce allergenic solids into the diet, especially infants with AD, the overall data suggest that introduction of egg is likely to provide protective benefit.

## FOODS OTHER THAN EGG AND PEANUT

Data for early introduction of other food proteins are limited. As mentioned, the EAT trial evaluated early introduction of 6 allergenic foods into the diets of breast-fed infants from an unselected population, starting with milk protein (yogurt) at age 3 months.<sup>1</sup> Sesame, fish, wheat, peanut, and egg were subsequently introduced by 5 months. There was no apparent PP benefit for milk, sesame, fish, or wheat seen in the EAT trial; similarly, a meta-analysis found no effect on the prevention of milk, fish, or wheat allergy with early introduction.<sup>2</sup> In a prospective cohort, Katz et al<sup>8</sup> reported that cow's milk allergy developed in only 0.05% of infants who were started on regular cow's milk protein formula in the first 14 days of life versus 1.75% who were started on formula between 105 and 194 days of life. There are no data on prevention of tree nut allergies. Ongoing trials will provide

additional insight into the timing and potential benefits of early introduction of allergenic solids (Preventing AD and Allergies in Children, NCT02449850; Preventing Peanut Allergy and Atopic Dermatitis [PEAAD, Germany]).

## ALTERNATIVE PREVENTION STRATEGIES

The approaches outlined above rely on feeding allergenic proteins to induce tolerance. The EAT trial experience illustrates the challenge of feeding young infants multiple solid foods, and because of the disparate timing of specific allergy development, early introduction in its current form might not be practical for every food and every infant. Other approaches to food allergy prevention might be necessary, such as aggressive control of eczema early in life, based on the dual-exposure hypothesis/atopic march.<sup>1</sup>

Other approaches that have also been considered include the manipulation of microbial populations (with prebiotics or probiotics) and fish oil or vitamin D supplementation ([clinicaltrials.gov](https://clinicaltrials.gov); NCT02112734) based on HealthNuts data that infants with vitamin D levels of 50 nmol/L or less at 12 months had an increased risk of peanut and egg allergies.<sup>9</sup> A recent systematic review of vitamin D supplementation concluded that limited information is available addressing primary prevention of atopic disease with vitamin D, and its role in prevention remains uncertain.<sup>10</sup> It should be noted that several published studies in these areas showed no effect, and none can be considered useful yet clinically. There is no evidence that maternal dietary restrictions or hypoallergenic milk formulas affect the onset of food allergy.

## CONCLUSIONS

A recent meta-analysis found that early feeding with egg and peanut, but not other potentially allergenic foods, led to a significant reduction in egg and peanut allergy. Careful review of the egg prevention RCTs suggests that cooked egg products might be safer and better tolerated than raw egg products, although more definitive evidence would be helpful. On the basis

of these data, allergy societies outside of North America have endorsed early feeding of cooked egg. There is concern that medicalizing infant feeding practices is unnecessary and also that no data exist to support delayed introduction. Perhaps the best recommendation might be the common-sense approach suggested by the ASCIA, which states, "When your infant is ready, introduce foods according to what the family eats, regardless of whether the food is considered to be a common food allergen." Additional study of the allergen-specific and nonspecific prevention strategies depicted in [Fig 1](#) is urgently needed to form population-based recommendations for other foods.

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