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Unscrambling egg allergies: Examining the impact of introduction timing of egg protein on the development of food allergies

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Abstract

Objective: To assess the efficacy of early egg protein introduction in the reduction of later childhood egg allergy development. **Design:** Systematic literature review. **Methods:** Searches were done using PubMed and cross referenced with articles on UpToDate, using the search strings 'egg', 'allergy', 'randomized controlled trial', 'early', and 'introduction'. Our inclusion criteria included: published in the last 5 years, human trial, randomized controlled trials only. **Results:** Our selection process yielded 3 quality studies: the "Beating Egg Allergy Trial" (BEAT)[1], "Start time of egg protein to prevent egg allergy" (STEP)[2], and "Two-step Egg Introduction for Prevention of Egg Allergy in High-risk Infants With Eczema" (PETIT)[3], which are discussed below. **Conclusion:** These studies found a minor reduction in the development of severe egg allergies in the experimental group as compared to the control group but were hampered by data collection issues and the limitations of their statistical analysis. Further research is necessary to understand the impact introduction timing of allergenic foods on the development of severe food allergies.

Introduction

Food allergies in children have been increasing in prevalence in the United States over the past several decades.[4] Egg allergy is the second most common food allergy in children after cow's milk.[5] It is estimated that 1.3% of US children under the age of five have an allergy to eggs with the majority of those being IgE-mediated allergies.[5,6] Given the increasing prevalence of food allergies, along with the risk of life-threatening anaphylaxis carried by IgE-mediated egg allergy, there is a growing need for research regarding mitigation and prevention of egg allergy development in young children.

Strategic timing of introduction of allergenic foods to a child's system is one means by which parents and clinicians have sought to reduce the risk of allergy development. Recommendations regarding timing of allergenic food introduction has varied significantly over the past few decades.[5] In 2000, the American Academy of Pediatrics (AAP) recommended delaying introduction of eggs to high-risk children (those with eczema or a family history of food allergy) until age two.[5] Eight years later, after additional studies found that delayed introduction may actually contribute to increased allergy risk, those guidelines were revised, stating there was insufficient evidence to recommend any specific timeline for allergenic food introduction.[5] Research has continued in this area, and while the AAP now recommends early introduction of peanuts, it offers no additional guidance for eggs.[7]

Recent studies have reached conflicting conclusions about the efficacy of early introduction of egg for prevention of egg allergy development. The purpose of this review is to compare existing research regarding early egg introduction and determine if this strategy is a safe and effective approach for use in at-risk infants.

Methods

Inclusion/exclusion criteria

We searched for studies that utilized randomized controlled trials to introduce eggs to infants and documented the rate of development of egg allergy between the control and experimental groups. We excluded studies published before 2015, as well as studies that included foods besides eggs, studies that included children older than 12 months of age at the time of egg exposure, or studies that had less than 100 participants. See Figure 1.

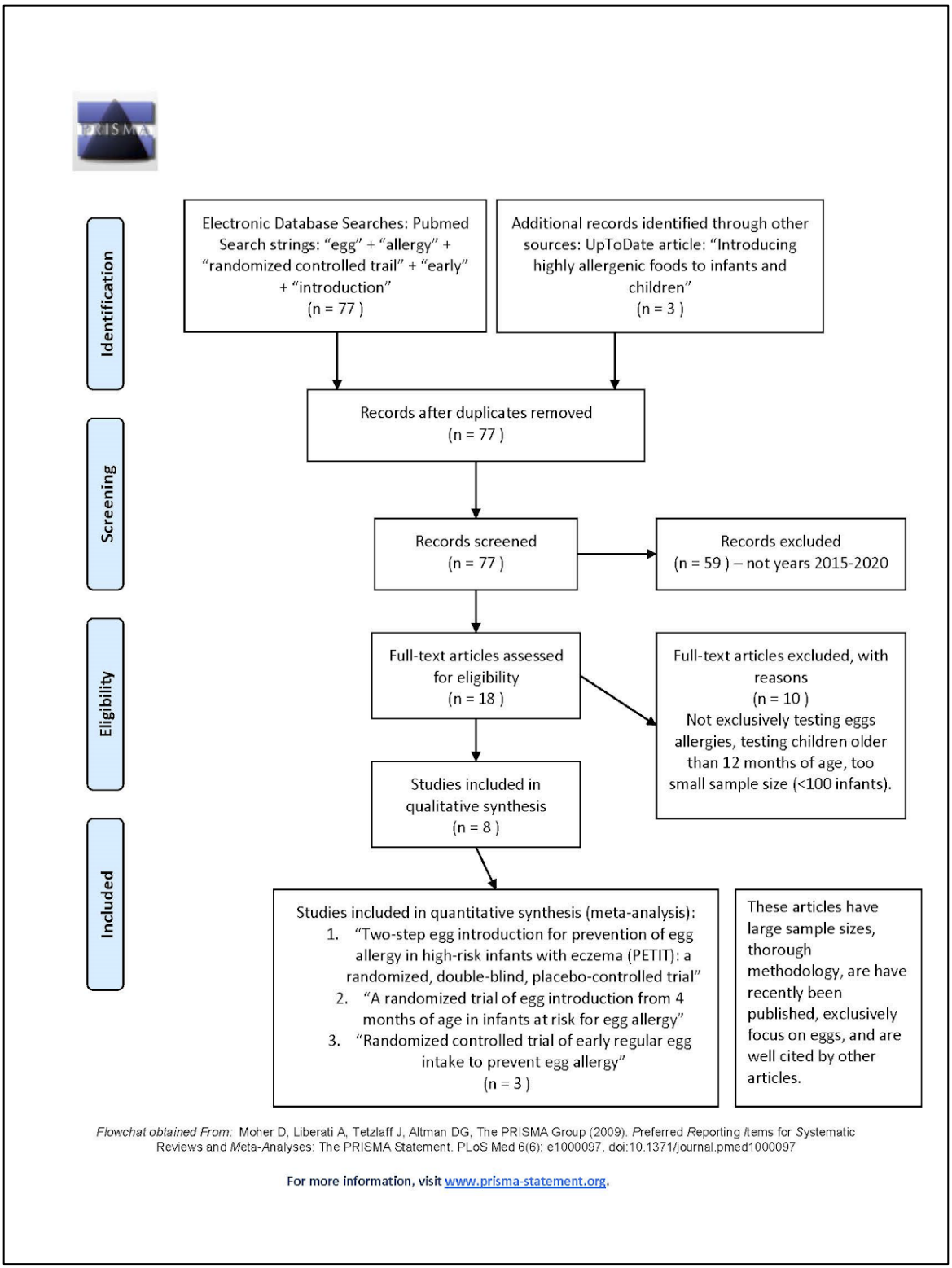

Figure 1. PRISMA

Databases

We utilized PubMed to search for our articles. Our search strings included: 'egg', 'allergy', 'randomized controlled trial', 'early', and 'introduction'. Three articles that were obtained as a result of these search terms were also cited in an UpToDate article that had been another source of our research, he title of which was "Introducing highly allergenic foods to infants and children."[8]

Quality assessment criteria

The studies that we included in our final analysis had several shared qualities (see Table 1). Firstly, they were all large, randomized controlled studies, with the BEAT trial having 319 participants, the STEP trial having 820 participants, and the PETIT trial having 147 participants. They all included infants with risk factors for the development of future egg allergies, including a history of diagnosed atopic disease such as eczema, allergic rhinitis, asthma, or who had mothers with a history of atopic disease. Study participants were screened via history taking for pre-existing allergies to egg protein and excluded if they had a history of egg allergy, in one study infants were excluded if they had any prior ingestion of egg, in another prospective participants were excluded if they had started on solid foods before the age of 4 months. All three of our studies introduced egg protein on a daily basis starting from 6 months until 1 year of age, at which they were tested for the development of IgE mediated allergy to egg protein via a combination of serum immunoglobulin testing and skin prick testing. All of the studies used both per-protocol and intention to treat analysis in their discussion of the data.

	BEAT	**STEP**	**PETIT**
Age range	4 mos at start	4 – 6.5 mos at start	- 4 – 5 mos at enrollment - 6 mos at start of participation
At-risk criteria	At least one 1st-degree relative w/ hx of atopic dz (food allergy, asthma, eczema, allergic rhinitis)	Infants w/ atopic mothers (hx of medically dx'd allergic dz w/ sensitization to at least 1 common aeroallergen)	Atopic dermatitis
Exclusion	Infants w/ >/=2mm skin prick response to commercial egg white	- Infants with hx of allergic disease (e.g. eczema) or any previous ingestion of egg - infants who started solids before 4mos - infants with congenital or acquired disease or developmental disorder likely to impact feeding	- prior ingestion of egg - history of immediate allergic reaction to egg - history of non-immediate allergic reaction to a specific type of food - complications of severe disease

Allergen introduction	350mg (0.35g) egg protein daily (via pasteurized whole egg powder) until 12mos	400mg (0.4g) pasteurized raw whole egg protein daily until 12mos	- from 6mos – 9mos old: 25mg (0.025g) heated egg protein - from 9mos – 12 mos old: 125mg (0.125g) heated egg protein
Primary Outcome	Proportion of infants in each group sensitized to egg white on skin prick test at 12 mos	IgE-mediated egg allergy at 12mos defined as allergic reaction to oral egg challenge *and* positive skin prick test	Proportion of participants with hen's egg allergy confirmed by oral food challenge at 12 mos
Secondary Outcomes	- egg allergy at oral food challenge at 12 mos - serum IgE, IgG4 levels - presence of eczema at 8 & 12 mos - SCORAD score at 8 & 12 mos - skin prick response to other allergenic foods at 12 mos	- serum IgE and IgG4 levels - sensitization to egg via positive skin prick test (without allergic response during oral challenge) - sensitization to peanut - development of atopic eczema or wheezing	- Serum IgE, IgG1, IgG4, IgA levels - SCORAD score - POEM score
Type of study	Randomized, placebo-controlled, double-blind, single-site trial	Randomized, placebo-controlled, double-blind, multi-center trial	Randomized, placebo-controlled, double-blind trial
Analysis	PP and FAS both used	ITT and PP both used	ITT and PP

Table 1. Study characteristics

Statistical methods overview

The BEAT trial analyzed their results with odds ratios (OR), relative risk reduction (RRR), absolute risk reduction (ARR), and number needed to treat (NNT). The STEP trail used both intention to treat (ITT) and per protocol (PP) analysis to assess their data, as well as ARR. The PETIT trial used RR, OR, ARR, and NNT to generate their findings.

Results

Study 1: Randomized Controlled Trial of Early Regular Egg Intake to Prevent Egg Allergy ("Starting Time of Egg Protein" trial or STEP)

Objective:
To determine if consumption of egg protein on a regular basis between the ages of 4-6 months reduces the risk of IgE-mediated egg allergy in children of mothers with atopic disease.

Design:
This was a double-blind, randomized, placebo-controlled study of 820 singleton infants of mothers with diagnosed atopic disease. Participants were recruited from two major medical centers in Australia. All

infants were between the ages of 4-6.5 months. Infants were excluded if they had a history of allergic disease themselves, had any previous ingestion of egg, had any feeding difficulties or any medical issues that predisposed them to such.

Infants were randomized to either the control or experimental group. Infants in the experimental group were fed whole 400g of pasteurized whole egg protein in powdered form daily, mixed with their normal solid food. Control group infants were fed a control (no egg) powder daily, also mixed with their normal solid food. To facilitate blinding of all involved parties, the intervention and control powders where combined with other powdered baby food flavors and packaged identically. The powders were administered up until the age of 10 months, during which all infants were otherwise maintained on a strict egg-free diet. At 10 months, diets of all infants were liberalized to include egg-containing foods.

Infants were assessed for egg sensitivity at 12 months via skin prick tests, blood tests for egg-specific IgE and IgG_4 serum antibody concentrations, and supervised oral egg challenge (with half an egg).

Results:
According to intention to treat analysis, 7% of infants in the experimental group had IgE-mediated egg allergy at 12 months based on failed oral egg challenge compared to 10.3% in the control group (p=0.20). When per-protocol analysis was applied, these numbers changed to 3% (experimental) compared to 9.9% (control), p=.002. Infants in the experimental group also had higher levels of egg-specific IgE at 12 months compared to infants in the control group (OR=2.73, p=0.03). The authors conclude that early and regular introduction of egg intake does not significantly alter the risk of egg allergy development by age 12 months in this infant population.

Critique:
This study has several strengths. In addition to its double-blinded, randomized, controlled design, it also appears to be free of funding biases, supported solely by grant money from the Australian National Health and Medical Research Council. Additionally, there was a 95% completion rate, which is impressive considering the duration of the study and the population involved. One weakness, however, is that the authors were unable to reach their initial enrollment goal, which left the study underpowered. As a result, they are less able to demonstrate significant experimental benefit.

<u>Study 2:</u> A Randomized Trial of Egg Introduction From 4 Months of Age in Infants at Risk for Egg Allergy ("Beating Egg Allergy Trial" or BEAT)

Objective:
To determine if introduction of egg between the ages of 4-6 months reduces sensitization to eggs at 12 months in infants at risk of egg allergy.

Design:
This was a double-blind, randomized, placebo-controlled single-site study conducted in Sydney, Australia, involving infants who had at least one first degree relative with a history of atopic disease. 332 infants were screened via skin prick test at 4 months of age for sensitivity to egg and those with a reaction of >/=2mm were excluded from the study, resulting in a total of 319 participants for randomization.

Infants were randomized via computerized block method to either the control or experimental group. Infants in the experimental group were fed 350mg of pasteurized whole egg protein in powdered form

daily. Control group infants were fed a placebo rice powder. The two types of powder were packaged identically to maintain blinding. The intervention period lasted from age 4 months until age 8 months at which point the diets of all participants were liberalized to include other egg-containing foods at the parents' discretion. Daily food diaries were provided for the parents of all infants to document adherence to protocol and any adverse events.

Assessments were completed at 3 separate intervals: 4, 8, and 12 months of age. These included evaluation for eczema and growth parameters. At 12 months, all participants were assessed for sensitivity to egg via a skin prick test. Those infants with a response of >/=3mm were also given a supervised oral food challenge to assess response. Serum egg-specific IgE and IgG_4 levels were also drawn.

Results:
Using full analysis set (FAS) analysis, 10.7% of infants in the experimental group were sensitized to egg white via skin prick test at 12 months compared to 20.5% in the control group, resulting in an odds ratio of 0.46 (p=.03) and an absolute risk reduction of 9.8% and number needed to treat of 11. Per protocol analysis mirror these results (OR=0.24, p=.0015). Infants in the experimental group had statistically significantly higher IgG_4levels than infants in the control group (p<.0001) but there was no difference in egg-specific IgE levels between groups.

Critique:
Like the STEP study, one of the strengths of the BEAT trial is its double-blinded, randomized, controlled design. It also does not appear to have a funding source bias as it was supported by grants from a philanthropic organization, The Ilhan Food Allergy Foundation and the Children's Hospital at Westmead Allergy and Immunology research fund. One significant weakness, however, is the significant attrition rate, with 20% of participants lost to follow-up by the study's completion. The loss was equal in both arms of the study but prevented the authors from being able to use more robust analyses to assess their findings.

<u>Study 3:</u> Two-step Egg Introduction for Prevention of Egg Allergy in High-risk Infants with Eczema (PETIT): a Randomised, Double-Blind, Placebo-controlled Trial

Objective:
To determine if stepwise introduction of eggs to 6-month-old infants with eczema, combined with eczema treatment, prevents egg allergy at 12 months of age.

Design:
This was a double-blind, randomized, placebo-controlled study conducted in Japan, with 147 infants with eczema. Infants were enrolled between the ages of 4-5 months and study protocol was initiated at 6 months of age. Prior ingestion of egg, history of food allergy, preterm delivery, and complications associated with any severe disease were all considered criteria for exclusion.

Infants were randomized to experimental and control groups via computerized block assignment. Infants in the experimental group were fed 25mg of powdered egg protein mixed with powdered squash daily from ages 6-9 months, before stepping up to 125mg powdered egg protein mixed with powdered squash for months 9-12. Infants in the placebo group also received two different doses of placebo squash powder to be consumed in the same amounts for the same frequencies and durations. Study

powder consumption was recorded each day by the infants' caregivers. Caregivers were instructed to maintain the infants on egg-free diets for the duration of their study participation.

The infants' eczema was treated throughout the course of the study with regular outpatient visits to monitor their disease and alter therapies as appropriate. Topical corticosteroids as well as non-medicated ointments or emollients were used, depending on disease severity. The goal was to achieve remission in each child, if possible.
At 12 months of age, each infant participated in a supervised oral food challenge of 7g of heated whole-egg powder. Serum concentrations of egg-specific IgE, IgG_1, IgG_4, and IgA were also measured at that time. Eczema severity scales were measured at enrollment and 12 months as well.

Results:
8% of infants in the experimental group demonstrated an allergic reaction to the oral food challenge at 12 months compared to 38% of infants in the experimental group, with a relative risk of 0.22 ($p=0.0001$) and a number needed to treat of 3.4. Serum concentrations of egg-specific IgE were lower in the experimental group than the placebo group ($p<0.03$), whereas serum concentrations of egg-specific IgG_1, IgG_4, and IgA were higher in the experimental group.

Critique:
Similar to the STEP and BEAT studies, the PETIT trial has strengths in its design (double-blind, randomized, controlled) as well as its lack of funding bias (supported by grants from both the Japanese Ministry of Health, Labour, and Welfare and the National Centre for Child Health and Development). Its major limitation, however, is the fact that it was terminated early. Although it was terminated due to benefit, this prevented the researchers from enrolling a large sample size and collecting a greater number of data points. As a result, their findings, as the authors readily acknowledge in their paper, may skew more positively.

Discussion

IgE-mediated egg allergy poses a significant health risk to children with eczema or who have a family history of atopic disease. Exploring strategies that could help prevent development of IgE-mediated reactions to egg is important to help guide parents of these children as they begin introducing solid foods. In this review, we examined three large studies in an effort to determine if there is sufficient evidence to definitively support early egg introduction. Upon careful examination of their collective results, while there is no evidence of significant risk associated with early egg introduction, there appears to be only minimal benefit with regards to preventing egg allergy development in this population.

Each study measured primary outcomes at 12 months via slightly varying but overlapping assessment methods (see Table 2). As secondary measures, all three studies also measured serum IgE and IgG_4 levels and assessed the infants for eczema at 12 months. The BEAT and PETIT studies found a reduction in the proportion of infants sensitized to egg in the experimental group, with NNTs of 11 and 3.4, respectively. The STEP study, however, found no significant difference between control and experimental groups, though their statistics did favor the experimental group when per-protocol analysis was employed. All three studies also showed an increase in egg-specific serum IgG_4 levels in the experimental groups at 12 months, an indicator of allergic desensitization to egg in those participants.

	Primary Outcome	p value	RR	ARR	OR	NNT
PETIT	Hen's egg allergy w/ oral food challenge at 12 mos	0.0001	0.22	29.4%	0.113	3.4
BEAT	Sensitization to egg via skin prick test at 12 mos	0.03	0.55	9.8%	0.46	11
STEP	Allergic reaction to oral egg challenge ***and*** (+) skin prick test at 12 mos	0.2	0.75	3.3%	0.65	30.3

Table 2. Primary outcome data across studies

Each study had its own limitations with regards to validity. For example, The BEAT study had a 20% loss to follow-up. The loss was equal between control and experimental groups but is still a significant portion of missing data that resulted in the use of "full analysis set" and per-protocol analyses rather than the more comprehensive intention-to-treat analysis format. The STEP trial authors were unable to reach their initial sample size goal which limited their ability to show more statistically significant benefits. As such, their results can only indicate a lack of harm, rather than a definitive benefit. Finally, the PETIT trial was stopped early due to the degree of clinical benefit at the time of the first interim analysis. While this seems like a strongly favorable development, it halted further enrollment and also curtailed data gathering, such that the results presented may skew more positively for early introduction than may have been seen if the study had reached a larger sample size and proceeded to its original completion date.

Positively, all three studies were funded by research grants from national health organizations, large medical centers, or philanthropic organizations. There does not appear to be any bias with regards to funding source. In addition, all used randomized, placebo-controlled, double-blinded designs. The randomization and blinding procedures were outlined in detail for each study with satisfactory descriptions of efforts employed to maintain blinding for the duration of each months-long trial. Finally, all studies completed multiple post-hoc analyses in an effort to investigate any unintended between-group differences generated by the randomization process.

This trio of studies is judged to be grossly homogenous with regards to design, methods, ages of participants, and outcomes measured. There is heterogeneity, however, with regards to how each study defined "at-risk for egg allergy", the volume of egg introduced to the experimental group, and the degree of egg-related diet restriction placed on study participants. The PETIT trial is the only one that specifically enrolled infants who already carried a diagnosis of atopy. In contrast, the STEP trial excluded infants who had been previously diagnosed with allergic disease and, like the BEAT trial, defined "at-risk" in terms of family history instead. Egg protein dosing in the experimental groups ranged from 25 – 400mg daily across studies. Parents of infants in all three studies were instructed not to give their infants any other egg-containing foods during the initial months of the trial, however, eventual liberalization of diets to include egg-containing items was encouraged at 8 and 10 months in the BEAT and STEP trials, respectively, while parents in the PETIT trial were instructed to maintain strict egg restrictions for the duration of the study. It is uncertain if these differences are significant enough to influence a comparison of their findings.

There are several limitations to this review and its generalizability based on the individual studies included. For instance, only the STEP trial included infants who already demonstrated sensitization to egg at the time of enrollment. Under normal circumstances, parents will not know whether their child already possesses an egg sensitivity when they begin to transition to solids, so it would likely have been more useful from an extrapolation standpoint to have a larger pool of infants

with pre-introduction sensitivity included. Generalizability may be further limited by selection bias as parents who are able to participate in a multi-month research trial may not be truly representative of the greater population. One further potential criticism may be that these studies were completed in other countries and, as a result, may be less generalizable to children in the U.S.; however, egg allergy prevalence in Australia, where both the BEAT and STEP trials were completed, is nearly identical to prevalence in the U.S.[9]

Conclusion

A meta-analysis of current research indicates that there may be a minor benefit in the early introduction of egg protein to prevent egg allergy, but the results are hindered by some limits of statistical analysis and study follow through. As a result, it is difficult to state the exact role introduction timing plays in the development of egg allergy. This is not to say the immunological theories that underpin are without merit or do not deserve further inquiry, rather that as of yet there is not a preponderance of evidence necessary to definitively state the role that early introduction of egg protein plays in the development of the egg allergies. Further research is needed with larger sample sizes, intention-to-treat analysis, true double-blind study structure, and wider ranges of dose amounts and patterns of administration to establish any generalizable guidance for mass consumption by parents. The studies in our analysis all administered egg protein in tiny quantities and in a powdered form, which was easier to manage experimentally but that does not reflect the forms of eggs that are actually consumed by the general population, which may have impacted the results as well. At present, the most that can be definitely said about the role of early egg protein introduction in infants is that it does not seem to increase the development of severe egg allergy when compared to delayed introduction and may be associated with a slight decrease in the development of egg allergies.

It is clear that the development of life-threatening food allergies is an increasing challenge for populations across developed countries, and that it is influenced by a complex and poorly understood set of factors, of which the timing of food introduction is only one. Extensive research is necessary to tease out the complicated ways that food, environment, medications, and the immune system interact to lead to the development of severe food and environmental allergies. If current trends hold, severe environmental and food allergies will only continue to become more prevalent both within developed countries and among countries that are becoming more developed. And it is clear that as a 'western lifestyle' becomes the norm across many parts of the globe, western health problems such as diabetes, dyslipidemia, and yes, food allergies, are likely to spread with them. The benefits of understanding these systems thoroughly include an increased quality of life for children with food allergies, reduced medical expenses, and ideally the prevention of food allergies in the first place. The risks of such research are low and can be managed in research and clinical settings with proper participant education and follow up.

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