

Another step towards prevention of food allergy



Food allergy is an important clinical problem, which has a large impact on family life, particularly in childhood, where 3–4% of children are affected.¹ Attempts to prevent the development of food allergy have focused on the avoidance of allergenic foods in infancy. The failure of this approach has led to various trials^{2,3} assessing whether or not the early introduction of allergenic foods into the diet might paradoxically succeed.

Previously, the Solids Timing for Allergy Research (STAR) study⁴ randomly allocated high-risk infants to 6 g of raw egg protein per week (approximately 1 large egg) or placebo from 4 months of age. A trend of reduced development of egg allergy was noted, but a third of participants reacted to the intervention. In the Enquiring About Tolerance (EAT) study,⁵ infants were randomly allocated to early introduction of various foods, including one small egg per week from 3 to 4 months of age. A per-protocol, but not an intention-to-treat, analysis showed a significant reduction in egg allergy. Last, in the Hen's Egg Allergy Prevention (HEAP) study,⁶ high-risk infants were randomly allocated to raw eggs (initially 2.5 g per week) or placebo from 4 to 6 months of age. No difference was noted between the groups at follow-up, but many infants were already egg allergic at enrolment. Despite the negative results, these studies provided a glimmer of hope that very early introduction of egg into the diet might prevent the development of egg allergy.

In *The Lancet*, Osamu Natsume and colleagues⁷ describe another approach to prevent development of egg allergy. They randomly allocated high-risk infants aged 4–5 months to very small quantities (0.2–1.1 g per week) of cooked egg or placebo. The Independent Data and Safety Monitoring Committee terminated the study when a scheduled interim analysis found a highly significant reduction in egg allergy in the egg group, halfway through recruitment. Challenge-proven egg allergy was found in five (8%) of 60 participants in the egg group and 23 (38%) of 61 in the placebo group ($p=0.0001$). This finding gives a number needed to treat to prevent egg allergy of 3.40 (95% CI 2.30–6.52).

Although this preventive strategy looks effective, caution is required when the results of a study that has been prematurely stopped are interpreted. For example, authors of a systematic review⁸ have suggested that

such trials overestimate the effect size by 50%. Also, few participants were randomised to treatment, meaning that important adverse events might not have been seen. Stopping a trial early for benefit is not generally recommended.

The different results in these egg allergy prevention studies suggest that differences in study populations or the specific interventions might predict efficacy. By contrast with the other studies, specifically HEAP, excluded infants who were already sensitised to eggs because of concern that they were already irreversibly committed to developing egg allergy. Although findings from the other three studies showed a significant or partly significant reduction in egg allergy, findings from the HEAP study showed no difference. So the very infants destined to develop an egg allergy might have been excluded in the HEAP study. Egg allergy also seems to be preventable even when allergic sensitisation has already developed.

Infants who are already sensitised to eggs are more likely to have an allergic reaction with ingestion of eggs, as seen in the STAR study.⁴ The egg product used in the STAR and HEAP studies was allergenically equivalent to raw egg. A potential way to reduce the likelihood of reactions is to use a heat-treated egg protein with lower allergenicity than seen with raw egg. Few reactions to the egg were seen in the EAT study⁵ and the study by Natsume and colleagues,⁷ probably because the egg was cooked. Findings from the EAT study suggested that ingestion of at least 2 g of egg

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protein per week is effective in prevention of development of egg allergy in infants. However, the study by Natsume and colleagues suggests that ten times less egg protein is equally effective; this finding is important, as a smaller dose is also much less likely to cause an allergic reaction in infants who are already sensitised to eggs.

Although caution is needed because of the early termination of the study by Natsume and colleagues and the previous negative studies, promise exists that small quantities of cooked egg introduced very early into the infant diet might be an effective preventive strategy. Further studies are required in larger populations with different diets and environmental exposures to show the generalisability and safety of this potential population preventative strategy. Some of these issues are discussed in detail in a systematic review.⁹

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