

CORRESPONDENCE

Introducing Allergenic Foods in Infants

TO THE EDITOR: Perkin and colleagues (May 5 issue)¹ find no evidence of efficacy of the early introduction of allergenic foods for the prevention of food allergy in the intention-to-treat analysis of their randomized trial. An apparent protective effect in the per-protocol analysis could be explained by the higher rate of nonadherence to the early-introduction protocol among infants in whom allergy symptoms developed (Table S14 in the Supplementary Appendix, available with the full text of the article at NEJM.org).

A potential explanation for the lack of efficacy of the intervention is that there is little difference between the standard-introduction group and the early-introduction group in the actual age at which allergenic foods were introduced. In the early-introduction group, the median age of the infants was approximately 20 weeks. Introduction of these foods was permitted from 6 months of age in the standard-introduction group, but the median age at introduction in this group is not presented — an important missing piece of information. It may be that although the delayed introduction of allergenic foods (e.g., >12 months of age) is associated with a higher risk of food allergy than early introduction, as was shown in the Learning Early about Peanut Allergy (LEAP) trial,² the introduction of such foods at 5 months of age provides little additional benefit as compared with introduction in the second 6 months of life.

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No potential conflict of interest relevant to this letter was reported.

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2. 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;372:803-13.

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TO THE EDITOR: In Table S8 in the Supplementary Appendix of the article by Perkin et al., parental reporting at 4 to 6 months of age shows a significantly higher rate of IgE and non-IgE type symptoms in the early-introduction group than in the standard-introduction group. The food-protein-induced enterocolitis syndrome (FPIES) during the first 5 months of life occurred in 7 participants in the early-introduction group (with cooked egg in 6 participants) but in only 3 in the standard-introduction group (no one with egg) (Table S9 in the Supplementary Appendix). The rate of FPIES in the early-introduction group was 1.4% (7 of 486 participants), which is higher than expected¹⁻³ because data from population-based birth-cohort studies showed a prevalence of FPIES of 0.3% associated with cow's milk proteins² and also showed that egg has not been identified as a prevalent causative agent.³ These data suggest that the early introduction of cooked egg may be related to the occurrence of FPIES.

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No potential conflict of interest relevant to this letter was reported.

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3. Mehr S, Frith K, Campbell DE. Epidemiology of food protein-induced enterocolitis syndrome. *Curr Opin Allergy Clin Immunol* 2014;14:208-16.

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TO THE EDITOR: It is unfortunate when clinical trials must be done to find out what we already knew. Perkin et al. introduced allergenic foods to infants at 3 months of age and found this to be not only safe but protective, at least for those who completed the trial. When my daughters were born, in the 1970s, it was common practice to start introducing nonallergenic foods as early as 1 month of age, with higher-protein foods

added at 4 months. Their whole generation grew up without a lot of food allergy.

Then opinion changed, on the basis of scant evidence,¹ and by 1991 less than 20% of 2-month-old infants were getting semisolid food, as compared with more than 70% in 1976.² When my daughters visited, I could not feed my grandchildren bananas at 6 weeks of age, even though their mothers enjoyed them in their infancy. An entire generation attests to the safety and benefits of early introduction of solid foods.

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No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: Allen and Koplin hypothesize that the apparent protective effect in the Enquiring about Tolerance (EAT) trial in the per-protocol analysis could be explained by a higher rate of nonadherence among infants in the early-introduction group whose parents reported food-allergy symptoms than among infants in the early-introduction group whose parents did not report such symptoms. This was not the case. Although a higher rate of nonadherence did occur among infants whose parents reported symptoms, the rate of challenge-proven food allergy among participants in the early-introduction group who did not adhere to the protocol was almost identical to the rate among participants in the standard-introduction group who adhered to the protocol (Table S10A in the Supplementary Appendix of our article).

The introduction of peanut in the standard-introduction group between 7 and 12 months of age was minimal. Although egg did start to be introduced in the standard-introduction group after 6 months, the frequency of consumption in the early-introduction group remained significantly higher at every month between 7 months and 12 months ($P < 0.005$ for all comparisons). The EAT trial showed that it is not just the introduction of allergenic food but the consumption

of it in sufficient quantity that may induce a protective effect.

The prevalence of FPIES-like reactions in the early-introduction group was 7 of 652 participants (1.1%; 95% confidence interval, 0.4 to 2.2), not 7 of 486. No cohort study has systematically recorded the prevalence of FPIES with regard to multiple foods, and hence the true prevalence of FPIES is unknown.¹ We state in the Supplementary Appendix of our article that the cases we observed were FPIES-like, because we did not undertake confirmatory challenges immediately for FPIES-like reactions (on safety grounds), hence the true rate of FPIES in our trial may have been somewhat lower.

It has been suggested that differences in reported foods causing FPIES might simply reflect cultural differences in how early they are introduced, with rice and grains being introduced early in the United States and fish early in Italy, with correspondingly more reports of FPIES with these foods in the respective countries.² However, it is interesting to note that no FPIES-like reactions were reported for milk or fish in the early-introduction group. It remains to be seen what two other unpublished studies that are introducing egg early, the Beating Egg Allergy Trial and the Starting Time for Egg Protein trial (Australian New Zealand Clinical Trials Registry numbers, ACTRN12611000535976 and ACTRN12610000388011, respectively), will show.

Although we would not endorse the introduction of solid food from 1 month of age, we agree with Bobrow that the move away from the early introduction of solids was based on scant evidence as far as food allergy is concerned. Nevertheless, once this concept became entrenched in international infant-feeding guidelines, a state of equipoise existed that required a randomized trial to resolve. We believe that the body of evidence is moving toward the early introduction of allergens to prevent food allergies. Perhaps grandparents know best after all!

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Since publication of their article, the authors report no further potential conflict of interest.

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