

Reply

To the Editor:

We thank Iglesia and Kim¹ for their comments. We did not conclude in the recent Enquiring About Tolerance (EAT) article² that low-risk infants do not benefit from early allergenic food introduction.

Our focus was on the intention-to-treat effect among groups at high risk of developing food allergy. We commented: “Of equal importance was that the early introduction of allergenic foods into the diets of the non-high-risk infants was not associated with any increased risk of food allergy.”² Indeed, subgroup analyses suggest that there is a protective effect in the low-risk populations, although not statistically significant. Specifically, for the 3 outcomes (any food allergy, peanut allergy, egg allergy) within the 3 low-risk subgroups (no enrollment visible eczema [Fig 1], white ethnicity [Fig 2], and no enrollment sensitization [Fig 3]), there was a reduction in the rates of food allergy in the Early Introduction Group in 7 of these 9 analyses.²

We agree with the authors’ insightful comment that the EAT treatment effect would have been larger had we implemented an avoidance strategy similar to the Learning Early About Peanut (LEAP) study³ (ie, complete avoidance of allergenic food through to study completion) because the allergy rate would have increased in the avoidance arm. This may explain the smaller effect size observed in the low-risk groups.

The authors mention type II error as another explanation of “no effect” in the low-risk group. Indeed, prevention studies in low-risk populations require much larger samples sizes.⁴ For example, the 50% reduction in peanut allergy (1.6% to 0.8%) seen in nonsensitized individuals (Fig 3, *B*) requires more than 8000 participants to detect this difference (90% power). This is an inherent problem in studies where meaningful effect sizes, which lack statistical significance, are misinterpreted as evidence of “no benefit.”

The authors correctly conclude that “Even small changes in food allergy incidence in low-risk groups can amount to a large absolute number of food allergy cases prevented on a population level.”¹ Indeed, those without eczema at enrollment into the EAT study, despite having the lowest rate of food allergy, accounted for 38% of the food allergy burden because this low-risk group comprises the majority (76%) of the population.⁵

The authors mention the low adherence as an explanation for the lack of a statistically significant reduction in food allergy in the intention-to-treat analysis. Per-protocol analyses are

particularly relevant when adherence is low.⁶ The analysis of the EAT study’s per-protocol population⁵ showed a 67% reduction in food allergy ($P = .01$). Although per-protocol analyses can be prone to bias, an instrumental variable analysis (which corrects for bias) performed in the EAT study population showed similar results to the per-protocol effect.⁴

In summary we agree with the authors’ comments that it is not justified to conclude no benefit in the low-risk populations; indeed, the early introduction of allergenic foods in the EAT study shows evidence of benefit in the low-risk, high-risk, and general populations.

We thank the Davis Foundation.

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The main components of the EAT study were jointly funded by the UK Food Standards Agency (FSA; contract code T07051) and the Medical Research Council (grant no. MC_G1001205). The skin-related aspects of the EAT study were supported by the UK National Institute for Health Research (NIHR). The analyses presented in this article were supported by a subsequent grant from the FSA (contract code FS101178) and the European Union (Integrated Approaches to Food Allergen and Allergy Risk Management (grant agreement no. 312147).

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

REFERENCES

1. Iglesia EGA, Kim EH. Low-risk infants may still benefit from allergenic food consumption. *J Allergy Clin Immunol* 2020;145 XXX-XXX.
2. Perkin MR, Logan K, Bahnson HT, Marrs T, Radulovic S, Craven J, et al. Efficacy of the Enquiring About Tolerance (EAT) study among infants at high risk of developing food allergy. *J Allergy Clin Immunol* 2019;144: 1606-14.e2.
3. Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med* 2015;372:803-13.
4. Bahnson HT, du Toit G, Lack G. Statistical considerations of food allergy prevention studies. *J Allergy Clin Immunol Pract* 2017;5:274-82.
5. Perkin MR, Logan K, Tseng A, Raji B, Ayis S, Peacock J, et al. Randomized trial of introduction of allergenic foods in breast-fed infants. *N Engl J Med* 2016;374: 1733-43.
6. Hernan MA, Robins JM. Per-protocol analyses of pragmatic trials. *N Engl J Med* 2017;377:1391-8.

<https://doi.org/10.1016/j.jaci.2020.01.015>