EDITORIAL

Can Peanut Allergy Prevention Be Translated to the Pediatric Population?

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The potential to prevent food allergy has been a topic of increasing interest over the past 40 to 50 years. Studies on this topic date back to at least 1936,[1] and a series of studies in the 1980s and 1990s produced inconsistent, but often compelling, data on the potential benefits of breastfeeding, specialized infant formulas, or delaying introduction of allergenic foods. Based on this body of evidence, as well as substantial expert opinion, a guideline by the American Academy of Pediatrics published in 2000 recommended the use of hydrolyzed formulas and delayed introduction of allergenic foods, including peanut, until the age of 3 years.[2] However, expert opinion turned out to be wrong and some of the most persuasive studies were subsequently retracted as fraudulent.[3] As new data emerged and the prevalence of food allergy continued to increase,[4] the 2000 guidelines were replaced by updated recommendations in 2008 that essentially left these decisions "to personal and family preference," because the available evidence was insufficient to justify any specific guidelines.[5]

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In 2015, the results of the Learning Early About Peanut (LEAP) trial were published.[6] This open-label trial included 640 high-risk infants (with eczema, egg allergy, or both) aged 4 to 11 months who were enrolled at a single site in the UK from December 2006 to May 2009. Participants were randomized to receive early peanut introduction, eating at least 6 g of peanut protein per week until the age of 5 years, or complete peanut avoidance. In this trial, among 640 infants in the intention-to-treat population, early and regular peanut ingestion was highly effective in preventing the development of peanut allergy. At 60 months of age, the prevalence of peanut allergy was 4.7% (25 children) in the early peanut introduction group and 16.8% (91 children) in the peanut avoidance group, and this benefit persisted even after a 12-month period of avoidance.[6,7]

The results of the LEAP study prompted changes in infant feeding guidelines around the world.[8-11] To date, at least 23 separate guidelines have been published regarding the prevention of peanut allergy or food allergy in general.[12] These guidelines vary substantially, even among key features such as optimal age, a focus on high-risk infants vs the general population, and the value of allergy testing. Even with the most straightforward strategies, such as to recommend early peanut introduction for all infants, there are barriers to implementation, and the optimal approaches to clinical application remain largely unknown. Most important, it is unclear whether any of the guidelines have led or will lead to meaningful reductions in the prevalence of peanut allergy.

In this issue of *JAMA*, Soriano et al[13] report results of 2 population-based cross-sectional samples in Australia that were used to evaluate the prevalence of peanut allergy before and after introduction of Australia's new infant feeding guidelines.[11] These guidelines took the most straightforward approach by simply recommending that peanut be introduced to all infants before 12 months of age, which is in sharp contrast to the initial US guidelines that focused on peanut introduction for high-risk infants.[8] The authors used this extraordinary opportunity for their study because they had previously conducted detailed studies on peanut allergy prevalence at a time when infants were usually not fed peanut in the first year of life.[14]

In this study, the investigators recruited infants in 2018-2019 (n = 1933; median age, 12.5 months) using the same sampling methods that had been used in their 2007-2011 study (n = 5276; median age, 12.4 months). Data were collected on demographic characteristics, food allergy risk factors, peanut introduction, and reactions. In addition, infants had skin prick testing for peanut allergy at 12 months of age and, if results were positive, underwent an oral food challenge. Peanut was introduced in the first year far more often in the 2018-2019 sample than in 2007-2011 sample (85.6% vs 21.6%). However, there was no significant difference in the prevalence of peanut allergy in the later vs earlier cohort (2.6% vs 3.1%). In both samples, there was no significant association overall between the age of peanut introduction and the development of peanut allergy; however, among children of Australian ancestry (but not East Asian ancestry) in the 2018-2019 sample, peanut introduction in early infancy was associated with lower risk of peanut allergy than introduction at 12 months or older.

These results present a fascinating conundrum. Despite guidelines based on clinical trial evidence, the findings from the observational study by Soriano et al[13] failed to demonstrate generalizability in the population-based setting. One possibility is that results from the LEAP trial are really not applicable to the general population, either because the benefits of early introduction are specific to high-risk infants or because the benefit requires consistent ingestion of high doses of peanut. Another possibility involves several important caveats about the study population and ecologic design that need to be considered. First, there were significant demographic changes in the study populations being compared. Although both samples were recruited from Melbourne using similar methodologies, the 2018-2019 group included a higher percentage of participants with a family history of food allergy, parent-reported eczema, and East Asian ancestry, all of which have been associated with an increased risk of food allergy. Second, given the significant difference in the prevalence of peanut allergy among children of Australian ancestry in the 2018-2019 cohort when comparing those with and without early peanut introduction, it is possible that the widespread practice of early introduction

substantially attenuated what might have otherwise been a continued increase in peanut allergy over time.

Studies such as the investigation by Soriano et al are difficult to accomplish, and, to our knowledge, these data represent the only evaluation of early peanut introduction in a population-based setting. Other clinical trials have been conducted, but when it comes to widespread implementation of a novel guideline, other studies have not had the capacity to study prevalence, but have rather utilized surveys to assess guideline awareness and implementation. For example, in 2018, Johnson et al[15] administered a cross-sectional survey to 825 allergists in the US to assess their awareness and implementation of the 2017 National Institute of Allergy and Infectious Diseases (NIAID) Addendum Guidelines for the Prevention of Peanut Allergy. The survey found that nearly all allergists (97.1%) were aware of the guidelines and 64.5% reported full and 34.4% reported partial implementation. Reported barriers to implementation included physician and parent concern about allergic reactions, parent lack of interest in early feeding, lack of referrals, and lack of clinic time. Two other studies or surveys administered to nonallergist physicians in the US (total sample sizes of 50 and 1781 participants) found an overall high rate of awareness, but very low rates of implementation.[16,17] Both studies found that parental concern or acceptance was a common barrier to implementation and physicians reported a need for further training. However, this field is still evolving. For example, although the 2017 NIAID guidelines[8] that focused on high-risk infants remain in place, the 3 major North American allergy societies have published very different recommendations in an attempt to encourage more widespread early introduction.[10]

The findings of the study on early peanut introduction reported by Soriano et al in this issue of *JAMA* provide several important insights. First, population-level changes in infant feeding practice are possible. Whether this can be replicated elsewhere is unknown, but the results in Australia clearly demonstrate that feeding practice change is a feasible goal. Second, a general recommendation for early introduction of peanut, even if widely adopted, may not lead to a change in the prevalence of peanut allergy. This suggests that other environmental factors might need to be modified to influence the prevalence of peanut allergy. Further research is needed to determine whether other approaches, such as introducing peanut in doses and frequency similar to those used in the LEAP trial, could reduce peanut allergy. However, in the interim, given the potential for benefit and the low risk of harm, the results of this important study should not dissuade clinicians from following current consensus guidance[10] that recommends early peanut introduction for infants.

ARTICLE INFORMATION

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REFERENCES

1. Grulee CG, Sanford HN. The influence of breast and artificial feeding on infantile eczema. *J Pediatr*. 1936;9:223-225. doi:10.1016/S0022-3476(36)80058-4

2. Kleinman RE. American Academy of Pediatrics recommendations for complementary feeding. *Pediatrics*. 2000;106(5)(suppl 4):1274. doi:10.1542/peds.106.S4.1274a

3. Smith R, Godlee F. A major failure of scientific governance. *BMJ*. 2015;351:h5694. doi:10.1136/bmj.h5694

4. Sicherer SH, Muñoz-Furlong A, Sampson HA. Prevalence of peanut and tree nut allergy in the United States determined by means of a random digit dial telephone survey: a 5-year follow-up study. *J Allergy Clin Immunol*. 2003;112(6):1203-1207. doi:10.1016/S0091-6749(03)02026-8

5. Greer FR, Sicherer SH, Burks AW; COMMITTEE ON NUTRITION; SECTION ON ALLERGY AND IMMUNOLOGY. The effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, hydrolyzed formulas, and timing of introduction of allergenic complementary foods. *Pediatrics*. 2019;143(4):e20190281. doi:10.1542/peds.2019-0281

6. Du Toit G, Roberts G, Sayre PH, et al; LEAP Study Team. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med*. 2015;372(9):803-813. doi:10.1056/NEJMoa1414850

7. Du Toit G, Sayre PH, Roberts G, et al; Immune Tolerance Network LEAP-On Study Team. Effect of avoidance on peanut allergy after early peanut consumption. *N Engl J Med*. 2016;374(15):1435-1443. doi:10.1056/NEJMoa1514209

8. Togias A, Cooper SF, Acebal ML, et al. Addendum Guidelines for the Prevention of Peanut Allergy in the United States: report of the National Institute of Allergy and Infectious Diseases-sponsored expert panel. *J Allergy Clin Immunol*. 2017;139(1):29-44. doi:10.1016/j.jaci.2016.10.010

9. Halken S, Muraro A, de Silva D, et al; European Academy of Allergy and Clinical Immunology Food Allergy and Anaphylaxis Guidelines Group. EAACI guideline: preventing the development of food allergy in infants and young children (2020 update). *Pediatr Allergy Immunol*. 2021;32(5):843-858. doi:10.1111/pai.13496

10. Fleischer DM, Chan ES, Venter C, et al. A consensus approach to the primary prevention of food allergy through nutrition: guidance from the American Academy of Allergy, Asthma, and Immunology; American College of Allergy, Asthma, and Immunology; and the Canadian Society for Allergy and Clinical Immunology. *J Allergy Clin Immunol Pract*. 2021;9(1):22-43.e4. doi:10.1016/j.jaip.2020.11.002

11. *ASCIA Guidelines: Infant Feeding and Allergy Prevention*. Australasian Society of Clinical Immunology and Allergy; 2020. Accessed June 8, 2022. https://www.allergy.org.au/hp/papers/infant-feeding-and-allergy-prevention

12. Sampath V, Abrams EM, Adlou B, et al. Food allergy across the globe. *J Allergy Clin Immunol*. 2021;148(6):1347-1364. doi:10.1016/j.jaci.2021.10.018

13. Soriano VX, Peters RL, Moreno-Betancur M, et al. Association between earlier introduction of peanut and prevalence of peanut allergy in infants in Australia. *JAMA*. Published July 5, 2022. doi:10.1001/jama.2022.9224

14. Osborne NJ, Koplin JJ, Martin PE, et al; HealthNuts Investigators. Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants. *J Allergy Clin Immunol*. 2011;127(3):668-76.e1, 2. doi:10.1016/j.jaci.2011.01.039

15. Johnson JL, Gupta RS, Bilaver LA, et al. Implementation of the Addendum Guidelines for Peanut Allergy Prevention by US allergists, a survey conducted by the NIAID, in collaboration with the AAAAI. *J Allergy Clin Immunol*. 2020;146(4):875-883. doi:10.1016/j.jaci.2020.07.020

16. Lai M, Sicherer SH. Pediatricians underestimate parent receptiveness to early peanut introduction. *Ann Allergy Asthma Immunol*. 2019;122(6):647-649. doi:10.1016/j.anai.2019.03.034

17. Gupta RS, Bilaver LA, Johnson JL, et al. Assessment of pediatrician awareness and implementation of the addendum guidelines for the prevention of peanut allergy in the United States. *JAMA Netw Open*. 2020;3(7):e2010511. doi:10.1001/jamanetworkopen.2020.10511