



Perspective

Global perspectives on food allergy

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The prevalence of childhood food allergy has increased sharply during the past 2 decades. Up to 8% of children in the United States and 11% of Australian infants are food allergic, and the prevalence of peanut allergy is between 1% and 3% in these countries.¹ Allergy research has shifted its focus in recent years toward measures aimed at the primary prevention of food allergy in children, such as through dietary interventions in early life. The Learning Early About Peanut Allergy (LEAP) randomized clinical trial enrolled 640 high-risk infants between the ages of 4 and 11 months in the United Kingdom who had severe atopic dermatitis (AD) and/or egg allergy and peanut skin prick test (SPT) responses of 1 to >4 mm. They were randomized to consume 6 g of peanut protein at least 3 times a week, to consume 2 g 3 times a week, or to completely avoid peanut products for the first 5 years of life. In the intention-to-treat analysis, 17.2% of children in the peanut avoidance group developed challenge-proven peanut allergy by 5 years of age compared with only 3.2% in the peanut consumption group, translating to a risk reduction of 81.4%.²

These findings paved the way for the release of new infant feeding guidelines recommending early introduction of peanuts in high-risk infants for the prevention of peanut allergy.^{3,4} A joint consensus communication released by several international allergy, pediatric, and dermatological societies in 2015 thus recommended “introducing peanut-containing products into the diets of ‘high-risk’ infants early in life (between 4 and 11 months of age) in

countries where peanut allergy is prevalent, because delaying the introduction of peanut can be associated with an increased risk of peanut allergy.”³ The National Institute of Allergy and Infectious Diseases–sponsored addendum guidelines released in January 2017 further refined the guidelines into a 3-layered recommendation for early peanut introduction in infants in the United States, risk stratified by eczema severity⁴:

1. Infants with severe eczema, egg allergy, or both—to strongly consider evaluation by specific IgE (sIgE) measurement and/or SPT and, if necessary, an oral food challenge. On the basis of test results, introduce peanut-containing foods at 4 to 6 months.
2. Infants with mild to moderate eczema—to introduce peanut-containing foods at approximately 6 months of age.
3. Infants without eczema or food allergy—to introduce peanut-containing foods in an age-appropriate manner and in accordance with family preferences and cultural practices.

There are, however, still many unanswered questions about the appropriateness or necessity of these guidelines in all countries. Positive predictive values of SPT and sIgE for peanut allergy vary among populations,^{5,6} and following the above-mentioned guidelines on screening cutoffs could result in false-positive results and overdiagnosis of peanut allergy in other populations. The benefits of screening and early peanut introduction in resource-limited countries, which would face significant logistic challenges when performing extensive allergy screening before supervised oral food challenges and the feasibility of widespread adherence to early peanut introduction are also debatable.⁷ The guidelines were originally intended for countries such as the United States, the United Kingdom, and Australia, where peanut allergy prevalence is high. It is unclear whether these early peanut introduction guidelines would be applicable in other regions, such as Asia, where the burden

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of peanut allergy is low (0.1%–0.9%)⁸ or whether this intervention would be efficacious in ethnic groups with different genetic makeup and environmental influences from that of the original trial population.

The prevalence of food allergy, particularly peanut allergy, differs considerably among populations. Although peanut is the major allergen in children younger than 5 years in the United States, United Kingdom, and Australia, peanut allergy is less prevalent than cow's milk and egg allergy in South Africa⁹ and the Middle East¹ and is uncommon in East and Southeast Asia apart from Japan.¹ Early dietary introduction of peanut alone does not appear to be a major reason for the low peanut allergy prevalence in Asia because the prevalence of peanut allergy was very low (0.1%–0.3%) in 12- to 48-month-old children in the Growing Up in Singapore Towards Healthy Outcomes (GUSTO) cohort, despite delayed introduction of peanut beyond 10 months of age in most of the study population.¹⁰ The timing of allergenic food introduction might thus be a less important protective factor in nonwesternized populations, and other environmental influences may play a larger role.

Evidence suggests that gene-environment interactions modulate the pathogenesis of allergic disorders, including food allergy, and thus would also likely influence each population's response to interventions for the prevention of food allergy. Migration data indicate that individuals acquire the food allergy risk of their host environment. Children who were born in Australia to ethnic Asian immigrant parents had 3 times higher risk of parental-reported peanut allergy compared with Australian-born white children, whereas birth within Asia and postnatal migration to Australia was conversely protective.¹¹ This finding suggests that perinatal environmental modifications that result from change of geographic locale with low peanut allergy prevalence to one with a higher peanut allergy risk may unmask a higher peanut allergy risk in offspring who would otherwise retain a low peanut allergy risk while living in their native countries.

Familial aggregation, candidate gene, and genome-wide association studies have demonstrated a heritable susceptibility to peanut allergy¹²; however, these studies were mainly in white populations, and the presence of these traits in nonwhite populations is unknown. Genetic polymorphisms that confer differential peanut allergy risks in various populations may contribute to the observed lower peanut allergy prevalence in Asia and modulate their responses to interventions, such as dietary modifications, for food allergy prevention.

Genetic diversity in food allergy and AD mechanisms may also explain the variability in food allergy risk among populations. Candidate gene and genome-wide association studies demonstrate ethnic differences in susceptibility genes for AD, a major risk factor for food allergy development. The carrier frequency of *FLG* loss-of-function mutations, which are associated with AD and food allergy risk, also varies considerably among populations. *FLG* mutations were found in up to 50% of European patients with AD, and only 2 mutations (R501X and 2282del4) accounted for 80% of the whole European *FLG* spectrum. In contrast, the *FLG* mutation carrier rate was only approximately 20% in Asian patients with AD and with a wider spectrum of genotypes, which were distinct from the European population.¹³ Although *FLG* loss-of-function mutations were found to be associated with peanut allergy in English, Dutch, and Irish patients,¹⁴ no associations between *FLG* null mutations and food sensitization or AD were found in a Japanese cohort.¹⁵

Recent studies have also found that epicutaneous sensitization associated with skin barrier defects in AD is an important factor in causing peanut allergy. Interestingly, the skin immune response in Asians is driven by a combination of T_H2 and T_H17 cytokines, whereas AD in European Americans is primarily T_H2 mediated.¹⁶ Race-related differences in AD phenotypes also exist. In Asian patients, AD manifests with well-demarcated, erythematous plaque-like

lesions, whereas white patients typically have ill-defined, flatter erythematous skin lesions.¹⁷ These differences in epithelial immune responses and phenotypes in Asians as opposed to Americans with AD warrant further exploration regarding their effects on epicutaneous peanut sensitization.

Meteorologic factors, such as UV exposure and vitamin D status, have also been postulated to be modifying factors for food allergy risk in some populations. Food allergy prevalence appears to follow a latitude-dependent gradient in Asia, with higher prevalence in the North Asian countries, such as Japan and South Korea, and lower prevalence in Southeast Asia.¹ Because UV radiation exposure, which induces vitamin D synthesis, decreases with distance from the equator, it was hypothesized that vitamin D insufficiency could be the true risk factor for food allergy development. Genetic polymorphisms in the vitamin D-binding protein gene (rs7041 and rs4588) result in reduced vitamin D-binding protein levels, which translate to a relatively higher amount of circulating bioavailable vitamin D in carriers of these polymorphisms. The HealthNuts cohort found that these genetic polymorphisms modulated associations between vitamin D insufficiency and peanut and/or egg allergy by ethnicity. Vitamin D insufficiency (≤ 50 nmol/L) was associated with peanut and/or egg allergy in infants of Australian-born parents but not of parents born overseas, particularly in East Asia. The latter group were more likely to have genotypes predictive of low vitamin D-binding protein levels and thus correspondingly higher circulating vitamin D levels, which could exert a protective effect against vitamin D insufficiency on food allergy risk in this ethnic group.¹⁸

The hygiene hypothesis proposes that a lack of microbial exposure in early life increases one's risk of developing atopic disorders, and studies have found that the high microbial exposures in early life, such as living in a farming environment, are protective against asthma and atopic disorders. Alterations in the gut microbiome have also been associated with food allergy risk, and the roles of dietary and environmental exposures in shaping these associations are gradually being discovered.¹⁹ High house dust mite loads and traditional agricultural practices are common in many developing Asian and Southeast Asian countries, factors that could influence gene-microbial interactions and modulate food allergy risk in these populations. Cross-sensitization between house dust mite and shrimp tropomyosin because of their close structural homology may also account for the observed higher prevalence of shrimp allergy in tropical Southeast Asian countries compared with Western populations.²⁰

Cultural dietary preferences and culinary methods might also partially explain the differences in food allergy prevalence between the East and West. The South Asian diet comprises a large proportion of rice, legumes, grains, vegetables, and spices. Unusual food allergens predominate in India, such as fenugreek, chickpea, mango, eggplant, and grains, which are not commonly reported in other regions, including East Asia.²¹ Peanuts are commonly boiled or fried in Asian cuisine, which are less allergenic compared with roasted peanuts, which are more common in Western diets.²²

The disparate prevalence of peanut allergy among populations in the world is likely attributable to a complex interplay of genetic, immune, and environmental influences rather than any single factor alone. Significant genetic and environmental diversity exist among populations, which influences predisposition to food allergy and AD (Table 1). Interventions aimed at preventing food allergy development must thus be individualized to each racial population based on each population's specific phenotype, and one size cannot fit all. Early allergenic food introduction may in fact not be appropriate or required for all populations, and more research needs to be performed to verify the efficacy of this intervention in other populations. The socioeconomic effects of population-wide screening of high-risk infants, implementation of early peanut introduction, and the likely ensuing increased anxiety in parents and caregivers might

Table 1
Food Allergy–Related Differences Between Asian and White Populations

Factor	Asian	White
Peanut allergy prevalence	Generally low (0.1%–0.9%)	High (1%–3%)
Migration effect	Increased risk of peanut allergy in children of ethnic Asian parents when migrating from a low-risk geographic locale to a high-risk location	–
Heritable traits for peanut allergy	Unknown	Specific HLA haplotypes and single-nucleotide polymorphisms associated with peanut allergy
Atopic dermatitis skin immune responses	T _H 2 and T _H 17 driven	Mainly T _H 2
Vitamin D insufficiency and food allergy	No association observed	Association observed between vitamin D insufficiency and food allergy
Vitamin D–binding protein polymorphisms	Genotypes predictive of low vitamin D–binding protein levels	Genotypes predictive of normal vitamin D–binding protein levels
Environmental exposures		
House dust mite loads	High	Relatively lower
Rural/urban divide (hygiene hypothesis)	Traditional agricultural practices in many developing Asian countries	Mainly developed and urbanized countries
Dietary peanut preparation methods	Boiling (reduced allergenicity)	Roasting (higher allergenicity than boiling)

not be justifiable in a population where peanut allergy rates are already very low. The choice of allergenic food type to be introduced early might differ among populations, depending on the prevalence of the specific food allergy in that population, although a stronger evidence base is required to prove this.

Although early allergenic food introduction advice may appear to contradict the World Health Organization's recommendations for exclusive breastfeeding for at least 6 months,²³ the latter's intent was to reduce infection and malnutrition and not specifically allergy prevention. The 2016 Australian Infant Feeding Summit consensus agreement harmonizes early introduction guidelines with the World Health Organization's breastfeeding guidelines, recommending that “when your infant is ready, at around 6 months, but not before 4 months, start to introduce a variety of solid foods, starting with iron-rich foods, while continuing breastfeeding” and that “all infants should be given allergenic solid foods... in the first year of life.”²⁴

Future research should include larger prospective cohorts to investigate the role of the environmental microbiome and other potential nutritional interventions, such as maternal folate and perinatal probiotic supplementation,²⁵ in the pathogenesis of food allergy and randomized clinical trials on early introduction of other allergenic foods, such as milk, wheat, and shellfish, into the diets of high-risk infants in the populations where these allergies are highly prevalent. Genetic markers should ideally be incorporated into such intervention studies to explore the effects of ethnic-related polymorphisms on treatment response because it is possible that certain interventions may only be efficacious in a subgroup of high-risk patients. There is a need for international consortiums to study different populations collaboratively to elucidate factors that explain the global and genetic diversity in food allergy and AD mechanisms. Recommendations should be tailored to specific food allergy prevention measures for individual populations.

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