



Perspectives

The environment and food allergy

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Introduction

Food allergy (FA) is an immune-mediated adverse reaction to food, which has become an important global public health problem affecting up to 8% of children and up to 5% of adults in the United States, United Kingdom, Canada, and Australia.¹ Peanut allergy alone affects up to 1.4% to 4.5% of infants and young children in these countries, reaching epidemic proportions. The prevalence of food-induced anaphylaxis is presumed to have increased significantly.

What drives this epidemic is unclear. Allergic diseases are likely determined by gene-environment interactions.² Although genetic factors clearly play an important role in a potential predisposition toward FA, epigenetic modifications could have increasing relevance for the recent increase in FA prevalence. Epigenetic modifications refer to changes in nucleotides that do not change the actual nucleotide sequence (the genotype). These alterations (eg, changes in DNA methylation or histone modifications) can be altered by environmental exposures and can be inherited, thus providing plausible means for environmental exposures to lead to changes in gene expression.

Multiple genes likely determine susceptibility to allergy and there are many potential environmental modifiers that can make epigenetic modifications and influence specific gene expression. The mechanism of action of some of these modifiers has been elucidated, whereas others have been identified through epidemiologic association studies, but their mechanism of action is poorly understood. The environmental modifiers affecting genetic susceptibility to allergy can be adaptive (protective, risk decreasing) or maladaptive (risk increasing). Therefore, an increasing FA prevalence can result from the combination of changes in these environmental modifiers. In addition, the level of allergenic exposure affects the

expression of genetic susceptibility, with high-dose exposures generally enhancing the expression of susceptibility and low-dose or absent exposures generally associated with low(er) expression of genetic susceptibility.

Decreased Exposure of Protective Environmental Factors

The hygiene hypothesis suggests decreased early-life exposures to infectious agents (eg, bacteria, parasites) leads to faulty programming of tolerogenic mechanisms, increasing the host's susceptibility to allergic diseases through imbalance of T-helper cell type 1 and 2 immunity.³ This can be attributed to overall improvements in public health and hygiene, such as increased societal exposure to antibiotics for infectious diseases and in food sources and antimicrobial exposure in soaps. Early-life microbial exposures also correlate with the number of children in a family; thus, the decreasing size of modern families is associated with a potential increased susceptibility to allergic diseases. Urban lifestyles, which lack the early-life exposures to microbiota present in rural and farming environments, also have been identified as risk factors for atopic diseases, particularly asthma, although the mechanisms driving this protection are unclear.⁴ One small observational study comparing 30 Amish (0% with asthma and low prevalence of allergic sensitization) with 30 Hutterite (20% with asthma and high prevalence of allergic sensitization) children noted median endotoxin levels in Amish house dust was 6.8 times higher than in Hutterite house dust.⁵ Detailed analyses identified profound differences in the numbers, phenotypes, and functions of innate immune cells between these groups. In a mouse model of allergic asthma, intranasal administration of dust extracts from Amish but not Hutterite homes significantly inhibited airway hyperreactivity and eosinophilia. These protective effects were abrogated in mice deficient in MyD88 and Trif, critical molecules in innate immune signaling. This study suggested that environmental protection might modify the innate immune responses to the allergens and enhance

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the development of allergic sensitization and clinical expression of the allergic disorders.

Selected data suggest cesarean section (C-section) mildly increases the risk of FA (odds ratio [OR] 1.32, 95% confidence interval [CI] 1.12–0.55). C-section is associated with the abnormal bacterial colonization of a newborn's gut in the absence of exposure to the protective bacterial flora in the birth canal. C-section is associated with older maternal age, first-born infants, and male births, all of which can be independent risk factors for atopy. A pilot study suggested that exposure to vaginal fluid at birth in infants delivered by C-section enriched the gut, oral, and skin bacterial communities during the first 30 days of life in vaginal bacteria similarly to vaginally delivered infants.⁶ A large intervention clinical trial is underway.

In gut dysbiosis, early infancy gut microbiota can determine FA outcomes. Of 226 children with milk allergy enrolled at infancy in an observational study, enrichment of *Clostridia* and *Firmicutes* species in the gut microbiome at 3 to 6 months of age was associated with milk allergy resolution by 8 years ($P = .047$).⁷ Bacterial taxa within *Clostridia* and *Firmicutes* species could be studied as probiotic candidates for milk allergy therapy.

Vitamin D supplementation is another potentially FA-modifying factor. Vitamin D plays a critical role as a cofactor in immunoglobulin E production and function. The potential role of vitamin D in FA stemmed from indirect observation in a 2007 study that noted more epinephrine auto-injector prescriptions in northern vs southern areas in the United States, which, after controlling for multiple factors, was believed to have a possible relation to sunlight exposure, a key component of vitamin D production.⁸ Similar findings were reported in Australia concerning hypoallergenic formula and noted in studies of US hospitalizations for children for food-related anaphylaxis in the northeast vs southern United States.⁹ However, data from prospective studies have been conflicting. In a large Australian birth cohort, infants with vitamin D insufficiency from Australia-born parents (vs parents born outside Australia) were more likely to have peanut allergy, egg allergy, and more than 2 FAs at 1 year vs those with normal vitamin D levels (adjusted OR 11.51, CI 2.01–65.79, for peanut; adjusted OR 3.79, CI 1.19–12.08, for egg; adjusted OR 10.48, CI 1.60–68.61, for >2 FAs), findings that have prompted a current ongoing Australian randomized controlled trial of vitamin D supplementation in infants (VITALITY trial).¹⁰ However, a more recent birth cohort, using a case-control design, noted no association between vitamin D levels at birth (adjusted relative risk [RR] 1.25, CI 0.70–2.22) or 6 months (RR 0.93, CI 0.41–2.14) and FA at 1 year of life.¹¹

A recent meta-analysis noted no association between vitamin D levels in children and FA (OR 1.35, CI 0.79–2.29) but was limited by the use of different cutoff levels to assess vitamin D deficiency. Another large meta-analysis exploring the role of vitamin D supplementation in the prevention of FA noted no significant effect for vitamin D supplementation in pregnant women (RR 1.92, CI 0.57–6.5, in 1 randomized controlled trial; OR 1.5, CI 0.78–2.88, in an observational study) and 1 case-control study showed a lower risk of developing FA in the first year of life with vitamin D supplementation in infants (RR 0.48, CI 0.27–0.88). This review concluded that vitamin D supplementation overall had no effect on FA, and that more research is needed to explore this topic.¹² There is an excellent review of the potential association between vitamin D levels and FA, which reached a similar conclusion, and discussed the details of multiple observational and cohort studies in detail.¹³

The Western diet is characterized by the decreased consumption of ω -3 polyunsaturated fatty acids (found in oily fish) and increased consumption of proinflammatory ω -6 polyunsaturated fatty acids (found in margarine and vegetable oils) and has been associated with an increased production of prostaglandin E₂. This presumably results in decreased production of interferon- γ by T cells

and increased production of immunoglobulin E by B cells, amplifying the risk of atopy and asthma.¹⁴

Decreased consumption of soluble dietary fiber has been associated with decreased intestinal generation of short-chain fatty acids. One short-chain fatty acid, butyric acid, was found to bind to the GPR109A receptor on dendritic cells, stimulate release of pro-tolerogenic interleukin-10, and increase intestinal regulatory T cells.¹⁵

The false alarm hypothesis postulates that FA is associated with high dietary advanced glycation end-products derived from cooked meat, oils, and cheese that are abundant in the Western diet.¹⁶ Advanced glycation end-products and proglycating dietary sugars mimic alarmins, in particular high molecular group S (HMBG1), that induce inflammation and oxidative pathways.

For infant feeding practices, timing of exposure to food allergens can be critical for the development of oral tolerance. A review of 13 studies (1 controlled) found a consistent association between eczema and the introduction of solid foods before 4 months of age but not with an increased risk of asthma, FA, allergic rhinitis, or animal allergies.¹⁷ Several reports suggested that early introduction of peanut, cow's milk, egg, and wheat into the infant diet was associated with decreased risk of allergy to these foods. A large randomized clinical trial (LEAP) of early peanut introduction in 4- to 10-month-olds with severe eczema and/or egg allergy reported an absolute risk decrease in peanut allergy of 17% at 5 years of age vs delayed introduction and persisted after an additional year of avoidance.^{18,19} The National Institute of Allergy and Infectious Diseases Food Allergy Guidelines were updated to strongly recommend early introduction of peanut, as early as 4 to 6 months of age, to infants with severe atopic dermatitis and/or egg allergy.²⁰ The EAT trial randomized 1,303 exclusively breast-fed 3-month-old infants to the early introduction of 6 foods (peanut, cooked egg, cow's milk, sesame, whitefish, and wheat) or to exclusive breast-feeding to approximately 6 months of age (standard introduction).²¹ No associations were noted in the intention-to-treat analysis, but a small yet significant risk decrease was noted with earlier egg and peanut introduction, but not for any other foods. A recent meta-analysis concluded that early peanut and early egg introduction was associated with “moderate certainty” of evidence of lowered risk of allergy.²²

Skin barrier impairment and increased transepidermal water loss are risk factors for FA.^{23,24} There is greater frequency of food sensitization and potential FA with increasing severity of atopic dermatitis. The loss-of-function mutations within the flaggrin (*FLG*) gene are associated with the development of atopic dermatitis and have been associated with peanut allergy. Results also indicate that increasing skin moisturizers in newborns can decrease rates of atopic dermatitis^{25,26} and are being studied further in larger ongoing clinical trials.

Increased Exposure to Negative Environmental Factors

The influence of outdoor and indoor air pollutants has been studied in relation to asthma. Increased exposure to respirable particulate matter (<10 μ m), diesel exhaust particles, sulfur dioxide, nitric dioxide, and ozone have been associated with worsening asthma, airway reactivity, and inflammation.²⁷

Diesel exhaust particles skew immune responses toward T-helper cell type 2 responses and immunoglobulin E production. Indoor pollutants include plant-fuel combustion byproducts rich in polyaromatic hydrocarbons that are strongly associated with increased respiratory illnesses. Environmental tobacco smoke is the most significant indoor air pollutant. A meta-analysis of studies through June 2013 concluded that there was a modest association between smoking and allergic diseases at all ages. FA was associated with passive smoke exposure in pediatric cohort studies (RR 1.43, CI 1.12–1.83).²⁸ Environmental tobacco smoke induces epi-

genetic changes, including DNA methylation in the cells from peripheral blood, saliva, fetal lung, and placenta. Importantly, differences in DNA methylation induced by prenatal environmental tobacco smoke exposure persist over several years of life.

Increased Exposure to Allergens Resulting From Global Warming

Evidence of global warming has been associated with and is likely caused by increased greenhouse gasses, carbon dioxide (CO₂), methane, and nitrous oxide.²⁹ There are ways in which climate change could lead to changes in the prevalence of FA. Warmer temperatures and changes in CO₂ lead to changes in production and possibly allergenicity of pollen.³⁰ Ragweed major allergen Amb a 1 concentration and pollen burden increases with increased CO₂ concentrations.³¹ Modeling forecasts have suggested increasing ragweed sensitization burden, predicting that sensitization to ragweed will more than double in Europe, from 33 to 77 million people, by 2041 to 2060.³² It is possible that increasing pollen sensitization rates will be associated with increased sensitization to pollen cross-reacting foods and increased prevalence of pollen-food syndrome.

The second way in which climate change could affect FA prevalence is by changing the foods. Changes in CO₂ levels and temperature can have an effect on various growth characteristics of plant allergens, such as peanut, and potentially on the concentration of food allergens.³³ However, to the authors' knowledge, there are no studies that have specifically examined changes in allergenicity or primary allergen component ratios in plant allergens as a result of CO₂ or temperature changes.

Conclusion

Benjamin Franklin said, "An ounce of prevention is worth a pound of cure." With the recent global increase in non-communicable inflammatory conditions, including atopic disorders and FA specifically, identification of the environmental modifiers of the genetic susceptibility and deciphering their mechanism of action are of utmost importance. This knowledge will enable mitigation of the impact of lifestyle and dietary changes, pollution, and global warming on the expression of genetic susceptibility to atopic disorders.

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