Perspectives

Potential Provoking Effects of Environmental Pollutants on Food Allergy: An Issue That Is Gaining Increasing Attention

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Allergic diseases are widespread globally, affecting over 40% of the population. Food allergy (FA), characterized by an abnormal immune response to harmless proteins in foods, is one of these prevalent conditions. Current estimates suggest that approximately 220 million people worldwide suffer from FA (*1*). In children, over one-third of parents report their children experiencing hypersensitive reactions to food, with FA affecting around 8% of this demographic. In China, 11.5% of individuals report having a physician-diagnosed FA [95% Confidence Interval(*CI*): 9.8%, 13.5%]. Notably, the prevalence of FA has increased significantly within a single generation, as evidenced by studies showing a rise in prevalence from 3.5% to 11.1% between 1999 and 2019 (*2*–*3*). This sharp increase coincides with rapid industrialization and urbanization, elevating FA to a major public health issue. While genetic factors contribute to around 50% of the susceptibility to allergic diseases (*4*), the dramatic rise in FA prevalence cannot solely be attributed to genetic changes alone. Environmental factors, particularly pollutants, are increasingly recognized as significant contributors to the development of FA (*5*). For instance, higher serum levels of perfluoroalkyl and polyfluoroalkyl substances have been associated with increased self-reported FA in adolescents (*6*–*7*). The widespread dispersion of pollutants such as persistent endocrine-disrupting compounds, persistent organic pollutants (POPs), fine particulates (FPs), and emerging contaminants like pharmaceutical and personal care products (PPCPs) follows industrial and urban expansion. These pollutants pose considerable health risks (*8*) and have been linked to the onset of allergic diseases (*9*–*10*). They can modify immune responses, leading to immunotoxic effects. The dual allergen exposure hypothesis suggests that disruptions to epithelial barrier integrity, along with microbial dysbiosis and immune dysregulation, are plausible mechanisms for the development of FA (*6*,*11*). At the molecular level, processes such as the acute inflammatory response, reactive oxygen species (ROS) generation, neutrophil activation, inflammatory cytokine expression, immune cell signaling disruptions, and apoptosis are implicated in the interaction between environmental pollutants and the immune system (*10*). However, the long-term effects of these pollutants on FA prevalence remain poorly understood.

This narrative review offers a comprehensive examination of risk factors for FA, particularly emphasizing the role of environmental pollutants.

THE GENETICS OF FA

The development of FA is influenced by intricate genetic mechanisms. Research into familial heritability has established a genetic foundation for FA (*1*). Both genome-wide association studies and candidate gene studies confirm that FA are inheritable, associating this condition with variances in the Human Leukocyte Antigen DR/DQ region and genes such as Filaggrin, Human Leukocyte Antigen, and Forkhead Box P3. Studies involving twin pairs reveal significantly higher concordance rates for sensitization in monozygotic twins compared to dizygotic twins. Moreover, children with two or more allergic family members face an increased likelihood of developing FA. Specifically, genetic studies on shellfish and peanut allergies suggest that genetic factors contribute to approximately 50% of the heritability of these allergies (*4*).

ASSOCIATIONS BETWEEN ENVIRONMENTAL POLLUTANTS AND FA

Although genetic factors are significant in the development of FA, environmental factors also play a vital role. Recent decades have seen an increase in the prevalence of FA, which has raised concerns regarding environmental pollutants. Numerous pollutants are known to disrupt immune responses and result in immunotoxicity (*6*). The potential causal link between FA and exposure to environmental pollutants remains

under-investigated. Research utilizing data from the 2005–2006 National Health and Nutrition Examination Survey in the US indicated that increased urinary levels of triclosan, a common EDC, were associated with specific FA in males (*12*). Additionally, exposure to bisphenol A diglycidyl ether may enhance food sensitization in early childhood (*13*). In a weaning mouse model for food sensitization, di(2-ethylhexyl) phthalate acted as an immunoadjuvant, augmenting ovalbumin-specific IgE and IgG1 production, and induced an imbalanced humoral immune response. The development of FA involves a complex two-step process of sensitization and the manifestation of clinical symptoms, with sensitization serving as the foundation for allergies and a focus of many studies (*14*). Collectively, these findings suggest that exposure to environmental pollutants may contribute to the development or exacerbation of FA, underscoring the need for further research into the underlying mechanisms.

UNDERLYING MECHANISM OF ENVIRONMENTAL POLLUTANTS TO FA

Immunotoxicity plays a significant role in the onset of allergic diseases, including FA and asthma, via intricate mechanisms (*5*). Increasing evidence is elucidating the pathophysiological pathways and immunotoxicological impacts of human exposure to environmental pollutants (*15*). At present, direct studies examining the connection between environmental pollutants and FA are scarce; however, several potential mechanisms have been proposed.

The mechanisms by which pollutants contribute to the onset of allergic diseases are complex and multifaceted. Current research is deepening our understanding of the interaction between the epithelial barrier and inflammatory responses (*15*). The dual allergen exposure hypothesis posits that disruptions to the epithelial barrier by various factors are associated with numerous immune-related conditions, including allergies. Pollutants compromise epithelial barrier function, initiate inflammatory immune reactions beneath the epithelium, and enhance exposure to allergens and irritants. Moreover, prolonged exposure to environmental toxins can alter the microbial landscapes of the tissues involved. Such disturbances may facilitate the growth of opportunistic pathogens, increasing the risk of inflammation, tissue damage, and chronic conditions. Impairments in the epithelial barrier, along with microbial dysbiosis, induce a Th2-biased immune response that is central to allergic sensitization and disease manifestation (*11*). These interactions indicate that environmental agents can undermine the protective barriers of the skin, airways, and gastrointestinal mucosa, rendering them susceptible to bacterial translocation and dysbiosis, which further contributes to the development of chronic immune-mediated and metabolic disorders.

Chronic exposure to environmental pollutants is known to induce immunotoxicity (*10*). Exposure to air pollution, for example, leads to the generation of ROS and other oxidative stresses in the airways, resulting in cellular damage that compromises epithelial integrity and increases permeability. In epithelial cells, polycyclic aromatic hydrocarbons (PAHs) activate the aryl hydrocarbon receptor and nuclear factor erythroid 2-related factor 2 , which enhances the production of cytokines such as IL-25, IL-33, and thymic stromal lymphopoietin, thereby promoting inflammatory responses (*9*,*11*). Furthermore, PAHs and other compounds stimulate AhR in keratinocytes, increasing the production of IL-33 and other factors that contribute to pruritus and atopic dermatitis (*10*). Exposure to bisphenol A and phthalates has been shown to suppress regulatory T cell (Treg) activities, elevate the expression of interferon-gamma (IFN-γ) and IL-10, and decrease the expression of transforming growth factor-beta (TGF-β), further promoting inflammatory responses. While molecular mechanisms associated with these effects are becoming clearer, significant knowledge gaps persist regarding the immunotoxic effects of environmental pollutants and their relationship with FA. Addressing these gaps requires a more detailed understanding of how specific pollutants contribute to the development of FA. Continued research is critical to fully elucidate these mechanisms.

DISCUSSION AND PERSPECTIVE

FA results from a complex interaction between genetic factors and environmental influences (*3*). Current epidemiological studies focusing on environmental exposure cohorts that comprehensively assess 'environment-gene' interactions are scarce (*12*). Moreover, the rise in allergy diseases has been associated with the adoption of a westernized lifestyle, marked by rapid urbanization and widespread use of cleaning products. Numerous theories have been

suggested to elucidate the growing prevalence of allergic diseases linked to these lifestyle changes (*9*). The widely accepted dual allergen exposure hypothesis integrates the hygiene and biodiversity hypotheses (also known as the Old Friends Hypothesis). This theory links epithelial barrier defects and microbial dysbiosis with varying allergen exposure pathways, explaining how these can guide the immune response towards either tolerance or allergy in current models.

While the associations between environmental factors and allergic diseases has been explored, the complexities of these relationships remain incompletely understood (*9*). There remain substantial knowledge gaps in defining specific pollutants, exposure levels, and the mechanisms by which they trigger and exacerbate allergic reactions. Challenges persist in the accurate identification, detection, and risk assessment of environmental exposures, influenced by various factors including detection methodologies, modeling techniques, and limited data availability, which add uncertainty to these assessments (*8*). Furthermore, uncertainties also exist in the manifestations of FA reactions. For instance, a study found that over 50% of siblings of children with FA exhibited sensitization (as shown by positive skin prick tests or elevated IgE levels) without displaying clinical symptoms (*4*). Given the complex nature of FA symptoms and variable individual sensitivity influenced by factors such as stress, physical activity, and other health conditions, thresholds for FA may vary. Additionally, cross-reactivity among different foods and changes in an individual's allergic status over time — from sensitization to full-blown allergy — are possible. This highlights that the actual prevalence of FA could be underestimated, and suggests that the interplay between environmental factors and genetics could be more intricate than previously considered. Research into the links between sensitized populations and environmental pollutants could be valuable for the early detection and management of health risks associated with environmental pollution. In recent decades, the prevalence of FA in China has surged, aligning now with rates seen in developed western countries (*9*), primarily due to lifestyle shifts and environmental pollution from urbanization (*5*). In light of China's fast-paced economic development, there is a pressing need for enhanced preventive measures, better policy interventions, and improved treatment strategies to curb the rising prevalence and ensure food safety.

The significance of environmental pollutants in the onset of FA diseases is well-recognized, but the identification of specific culpable pollutants and the mechanisms by which they contribute remain poorly delineated. The current focus centers on pollutants known to pose health hazards and environmental risks even at low concentrations, including POPs, FPs, PPCPs, and pesticides. Strategies to mitigate these pollutants primarily involve reinforcing regulatory frameworks, implementing stringent standards, regular monitoring, and enhancing public awareness of environmental and health implications. Although the proactive elimination or control of these pollutants is critically discussed, efficient strategies are still insufficient. It is vital to further investigate the potential mechanisms through which environmental pollutants influence FA. Enhancing our understanding of these mechanisms is crucial for advancing public health and ensuring food safety, in line with the World Health Organization's food safety mandates for the 21st century.

Conflicts of interest No conflicts of interest.

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REFERENCES

1. Feng H, Luo N, Chen F, Li XY, Wen Y, Liu CW, et al. Self-reported food allergy prevalence among elementary school children - Nanchang City, Jiangxi Province, China, 2021. China CDC Wkly 2022;4(34):761 – 5. https://doi.org/10.46234/ccdcw2022.161.
2. Feng H, Luo N, Lu YA, Lu J, Zhou JD, Xiong XJ, et al. Prevalence of parent-reported food allergy among children in China: a population-based cross-sectional survey. Front Immunol 2022;13:982660. https://doi.org/10.3389/fimmu.2022.982660.
3. Feng H, Chen Y, Chen HB, Liu CW, Zhou W, Wang LL, et al. A methodology of epidemiologic study in the general population focusing on food allergy - China, 2020. China CDC Wkly 2022;4(34):749 – 55. https://doi.org/10.46234/ccdcw2022.159.
4. Johansson E, Mersha TB. Genetics of food allergy. Immunol Allergy Clin North Am 2021;41(2):301 – 19. https://doi.org/10.1016/j.iac.2021.01.010.
5. Wu HT, Eckhardt CM, Baccarelli AA. Molecular mechanisms of environmental exposures and human disease. Nat Rev Genet 2023;24(5):332 – 44. https://doi.org/10.1038/s41576-022-00569-3.
6. Peters RL, Mavoa S, Koplin JJ. An overview of environmental risk

factors for food allergy. Int J Environ Res Public Health 2022;19(2):722. https://doi.org/10.3390/ijerph19020722.
7. Buser MC, Scinicariello F. Perfluoroalkyl substances and food allergies in adolescents. Environ Int 2016;88:74 – 9. https://doi.org/10.1016/j.envint.2015.12.020.
8. Yang LL, Cai XM, Li RB. Ferroptosis induced by pollutants: an emerging mechanism in environmental toxicology. Environ Sci Technol 2024;58(5):2166 – 2184. https://doi.org/10.1021/acs.est.3c06127.
9. Alkotob SS, Cannedy C, Harter K, Movassagh H, Paudel B, Prunicki M, et al. Advances and novel developments in environmental influences on the development of atopic diseases. Allergy 2020;75(12):3077 – 86. https://doi.org/10.1111/all.14624.
10. Suzuki T, Hidaka T, Kumagai Y, Yamamoto M. Environmental pollutants and the immune response. Nat Immunol 2020;21(12):1486 – 95. https://doi.org/10.1038/s41590-020-0802-6.
11. Celebi Sozener Z, Ozdel Ozturk B, Cerci P, Turk M, Gorgulu Akin B, Akdis M, et al. Epithelial barrier hypothesis: effect of the external exposome on the microbiome and epithelial barriers in allergic disease. Allergy 2022;77(5):1418 – 49. https://doi.org/10.1111/all.15240.
12. Savage JH, Matsui EC, Wood RA, Keet CA. Urinary levels of triclosan and parabens are associated with aeroallergen and food sensitization. J Allergy Clin Immunol 2012;130(2):453 – 60.e7. https://doi.org/10.1016/j.jaci.2012.05.006.
13. Tsuji M, Koriyama C, Ishihara Y, Vogel CFA, Kawamoto T. Association between bisphenol A diglycidyl ether-specific IgG in serum and food sensitization in young children. Eur J Med Res 2018;23(1):61. https://doi.org/10.1186/s40001-018-0358-1.
14. Taylor SL, Gendel SM, Houben GF, Julien E. The key events dose-response framework: a foundation for examining variability in elicitation thresholds for food allergens. Crit Rev Food Sci Nutr 2009;49(8):729 – 39. https://doi.org/10.1080/10408390903098707.
15. Chen HB, Wu YN. Risk assessment of food allergens. China CDC Wkly 2022;4(34):771 – 4. https://doi.org/10.46234/ccdcw2022.163.