



The External Exposome and Food Allergy

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Abstract

Purpose of Review The recent increase in childhood food allergy prevalence strongly suggests that environmental exposures are contributing to food allergy development. This review summarizes current knowledge about the role of the external exposome in food allergy.

Recent Findings There is growing evidence that environmental exposure to food antigens in house dust through non-oral routes contributes to food sensitization and allergy. Co-exposure to environmental adjuvants in house dust, such as microbial products and fungal allergens, may also facilitate allergic sensitization. While a high-microbe environment is associated with decreased atopy, studies are mixed on whether endotoxin exposure protects against food sensitization. Several chemicals and air pollutants have been associated with food sensitization, but their role in food allergy remains understudied.

Summary Children are exposed to numerous environmental agents that can influence food allergy risk. Further studies are needed to identify the key early-life exposures that promote or inhibit food allergy development.

Keywords Food allergy · Exposome · Environment · Air pollution · Exposure · House dust

Introduction

Food allergy is a potentially life-threatening disease affecting approximately 5.9 million children in the USA [1, 2]. Over the last few decades, industrialized countries have seen a rapid rise in food allergies [3]. According to the US Centers for Disease Control, food allergy prevalence increased from 3.4% in 1997–1999 to 5.1% in 2009–2011 [4]. During this same period, rates of peanut and tree nut allergies tripled from 0.4% in 1997 to 1.4% in 2008 [5]. Like other allergic diseases, food allergies are thought to arise from complex gene-environment interactions [6]. However, genetic changes alone cannot account for the increase in food allergy prevalence over the past few decades, indicating that environmental exposures are likely driving the epidemic [7, 8]. While there has been extensive research as to how the environment impacts other common allergic diseases such as asthma, few studies have addressed the environmental determinants of food

allergy. This review will summarize the current knowledge on how exposure to specific environmental agents may influence food allergy development.

External Exposome

Beginning during the prenatal period and continuing throughout life, individuals are exposed to a wide array of non-genetic factors as a result of their lifestyle, diet, and behaviors. Since atopy usually presents during childhood, prenatal and early-life exposures are thought to be especially important in the development of allergic diseases [8]. The term “exposome” is used to describe the totality of environmental exposures that an individual experiences throughout life [9]. The exposome can be further divided into specific external exposures (e.g., allergens, microbes, diet, pollutants), general external exposures (e.g., climate, socioeconomic factors), and host-dependent internal exposures (e.g., host microbiota, metabolic factors) [10, 11]. This review will focus on the role of specific external exposures in food allergy development, with a particular emphasis on environmental agents encountered within the home.

Environmental Exposure to Food Allergens

An increasing number of studies show that food antigens are ubiquitous within the living environment [12]. Peanut, cow’s

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milk, egg, and fish are present in dust collected from living room, bedrooms, and child playing areas, indicating that food antigens are widely distributed throughout the home [13–17]. Recently, the presence of clinically important peanut allergens in household dust was confirmed by mass spectrometry [18]. Household consumption of peanut generally correlates with peanut protein levels in dust collected from homes [17]. However, peanut allergen can be detected in homes of families that report complete peanut avoidance [19], indicating that environmental peanut exposure can occur even if peanut is excluded from the home. Peanut protein is present in settled dust from school cafeterias and classrooms, suggesting that environmental exposures can also occur outside of the home [16].

There is growing evidence that non-oral exposure to peanut through the skin or respiratory tract can result in allergic sensitization and food allergy. Rodent models show that epicutaneous or inhalational exposure to peanut can result in allergic sensitization and anaphylaxis upon peanut challenge [20–23, 24]. Moreover, Kulis et al. recently reported that cutaneous application of peanut extract to the skin of nonhuman primates induced peanut-specific antibody responses [25]. Several epidemiological studies further suggest that environmental peanut exposure may be a risk factor for peanut sensitization and allergy. Topical application of peanut in the form of arachis oil was associated with increased risk of peanut allergy at age 5 years [26]. Median weekly household consumption of peanut, which correlates with environmental peanut levels in the home, was greater in homes of peanut-allergic children compared to non-allergic children [27]. In a UK birth cohort, Brough et al. found that peanut protein levels in household dust were directly associated with risk of peanut sensitization in children with filaggrin (FLG) loss-of-function mutations, which is a marker of an impaired skin barrier [28]. In a US cohort of 359 highly atopic children (age 3–15 months), Brough also observed an exposure-response relationship between peanut protein levels in living room dust and peanut sensitization and probable allergy [29]. The effect was strongest in children with a history of atopic dermatitis (AD), but there was no association with FLG mutations as previously noted in the UK cohort. In a Swedish birth cohort study (BAMSE), a nested case-control analysis comparing 411 peanut-sensitized and high-risk control subjects found that higher levels of peanut in maternal bed dust during infancy was associated with increased risk of peanut sensitization at ages 4 (OR 1.4, 95% CI 1.1–1.9) and 8 years (OR 2.1, 95% CI 1.4–3.2) [30]. Interestingly, the authors found no significant association between environmental peanut exposure and infantile eczema or FLG mutations. These reports suggest that environmental peanut exposure is a risk factor for peanut sensitization, particularly in children with an impaired skin barrier.

While environmental exposure to food allergens is associated with allergic sensitization, clinical trials suggest that early oral introduction of food antigens mitigates this risk. The

Learning Early about Peanut Allergy (LEAP) clinical trial found that early oral introduction of peanut promoted tolerance to foods [31]. In the Enquiring About Tolerance (EAT) study, while the initial intention-to-treat analysis did not find a statistical significance [32], a secondary analysis showed that early introduction of foods decreased the risk of food allergy in infants with moderate eczema or food allergen sensitization at enrollment [33•]. Moreover, the risk of peanut allergy associated with high household peanut consumption was mitigated in children consuming peanut at a young age [27]. These studies have led researchers to propose the dual-allergen hypothesis as a mechanism by which food allergy develops. This hypothesis posits that early oral exposure to food protein induces tolerance, whereas non-oral exposure results in food sensitization and allergy development [34].

In addition to food antigens, household dust contains a host of agents with immunomodulatory properties, including microbe-derived molecules, fungal components, and protease allergens [35–37]. These agents can act as mucosal adjuvants and induce allergic sensitization to normally innocuous antigens [38–40]. Our group recently investigated whether adjuvants in residential indoor dust could promote airway sensitization to environmental peanut in an animal model [24•]. We found that co-exposure to indoor dust and peanut protein, but neither alone, induced peanut-specific IgE and development of anaphylaxis upon peanut challenge. Additionally, Walker et al. recently reported that exposure to fungal or house dust mite allergens promoted epicutaneous sensitization to peanut in genetically modified mice with skin barrier defects [23]. These studies suggest that in addition to ambient peanut levels in the home, environmental adjuvants in house dust may also be important determinants of peanut allergy development in children (Fig. 1).

There is little data regarding whether environmental exposure to food antigens other than peanut contributes to sensitization and allergy. One study found that household consumption of almond, but not walnut, was significantly associated with sensitization to the nut in young children with AD [41]. Environmental exposure to non-food allergens can also be a risk factor for food allergy development. This is best exemplified in patients with pollen-food allergy syndrome, where exposure to pollen allergens induces cross-reactive IgE to a variety of plant-based foods [42]. Similarly, studies suggest that exposure to tropomyosin proteins from insects, such as cockroach and house dust mite, can induce IgE that cross-reacts with tropomyosins in shellfish. Exposure to cockroach allergen, but not house mite, was positively associated with shrimp sensitization [43]. A recent analysis of sensitization data from 7894 children enrolled in two National Health and Nutrition Examination Survey (NHANES) studies found positive correlations between cockroach and house dust mite sensitization and shrimp sensitization [44]. Furthermore, exposure to the carbohydrate galactose- α -1,3-galactose (α -gal) in tick saliva

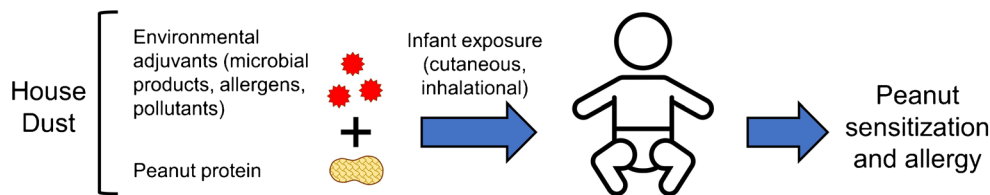


Fig. 1 Co-exposure to environmental peanut and adjuvants in house dust may promote sensitization and peanut allergy development. House dust contains both peanut protein and environmental agents with adjuvant activity, including microbial products (e.g., endotoxin, fungal cell wall

components), protease allergens from house dust mite and fungi, and particulate pollutants. Co-exposure to environmental adjuvants may modify immune responses against peanut protein, resulting in allergic sensitization instead of tolerance

is thought to drive the production of α -gal-specific IgE and hypersensitivity reactions to mammalian meat [45].

Microbial Exposures

Several epidemiological studies have observed that exposure to a microbe-rich environment, particularly on traditional farms, is protective against atopic disease [46–50]. How the farming environment reduces the risk of atopy is unclear, but proposed mechanisms include increased exposure to microbial components that stimulate innate immunity and alterations of the host microbiome [51]. While there is substantial evidence that farm-related exposures reduce the risk of asthma and allergic rhinitis, the impact of the farm environment on food allergy outcomes has seldom been assessed [52]. Recently, Phillips et al. investigated food allergy rates in a cohort of Old Order Mennonites (OOM), who practice traditional single-family farming [53]. OOM children had significantly lower rates of peanut, wheat, fish, and shellfish allergy compared to the general population as determined using NHANES 2007–2010 data. Interestingly, peanut was not introduced into the diet of OOM children until the second year of life, suggesting that early introduction of peanut was not responsible for the decreased rates of peanut allergy in this cohort.

Exposure to higher levels of endotoxin, a cell wall component of Gram-negative bacteria, in farming communities has been associated with protection against allergic respiratory disease in some cohorts [47, 50]. However, studies investigating endotoxin exposure and allergic sensitization are mixed, with some showing an inverse relationship [47, 54, 55], whereas others report either a positive or null association [56, 57]. Regarding food allergies, McGowan et al. investigated the effects of early-life exposures, including endotoxin, on food sensitization and allergy in an inner-city birth cohort of 516 children [58]. Endotoxin levels in household dust collected at 3 months of age were inversely associated with risk of overall food allergy (OR 0.4, 0.2–0.8) and egg allergy (0.2, 0.1–1.6), with a trend for protection against milk and peanut allergy. In contrast, a recent cross-sectional study of NHANES 2005–2006 participants ($n = 6963$) found that household endotoxin levels were positively associated with

sensitization to milk (OR 1.7, 95% CI 1.2–2.1) and egg (OR 1.4, 95% CI 1.0–1.9), but not peanut [59]. Furthermore, another recent study found that exposure to high-endotoxin bedding did not protect against allergic sensitization in an animal model of peanut allergy [60]. These studies suggest that endotoxin exposure alone is not responsible for the protective effects of the farming environment.

Chemical Exposures

Children are exposed to an increasing number of chemical agents with potential to affect immune development and function [7]. A recent literature review identified 355 chemicals of toxicological concern in house dust, including endocrine disrupting chemicals (EDCs), flame retardants, plasticizers, volatile organic compounds (VOCs), pesticides, antimicrobials, and heavy metals [61]. Given their frequent hand-to-mouth activity, crawling behavior, and rapid respiratory rates, infants are particularly at risk for exposure to chemicals in house dust [62].

EDCs comprise a variety of chemicals (e.g., bisphenols, phthalates, parabens, triclosan) that are found in foods, plastics, and personal care products. EDCs can interact with aryl hydrocarbon receptors (AhR) and peroxisome proliferator-activated receptors (PPARs), which are expressed throughout the immune system [63]. As such, EDCs have been reported to impact the differentiation and function of several different immune cells [63]. Both animal and human studies have suggested a possible role of EDCs in food allergy development. The antibacterial agent triclosan promoted epicutaneous sensitization to peanut in a rodent model, indicating it may have adjuvant properties [64]. More recently, triclosan exposure augmented HDM-mediated allergic airway inflammation in mice, which was associated with alterations in the gut microbiome [65]. Analysis of NHANES 2005–2006 data by Savage et al. found that urinary levels of triclosan, but not bisphenol A, were positively associated with food and aeroallergen sensitization in male children (OR 3.9, 1st vs 3rd quartile) [66]. In contrast, no association between triclosan exposure and food allergen sensitization was observed in a cohort of Norwegian children [67]. Moreover, a prospective longitudinal study of 467 mother-child pairs in the USA found

no association between prenatal or early-life triclosan or paraben exposure and food allergen sensitization in children at 3–4 years of age [68]. Regarding phthalates, analysis of NHANES 2005–2006 data found that several phthalate urinary metabolites in adults were associated with shrimp allergy, but not other food allergies [69]. A German prospective study of 629 mother-child pairs reported that exposure to high urinary levels of certain phthalate metabolites during the third trimester was associated with increased risk for food allergen sensitization in the child at 2 years of age [70•]. Elevated maternal levels of phthalate metabolites were also associated with reduced numbers of regulatory T cells in cord blood and peripheral blood of children at age 2 years, which may facilitate allergic sensitization [70•]. More recently, a Polish cohort of 145 mother-child pairs found that higher urinary phthalate metabolite levels (different than those in the German cohort) were associated with increased risk of food allergy in children at 9 years of age (OR 1.8, 95% CI 1.2–2.6) [71]. While some studies suggest a relationship between certain EDCs and food allergy, more prospective studies are needed before definitive conclusions can be made.

Phosphate flame retardants (PFRs) are another category of chemicals that may influence allergic disease development in children [72]. PFRs are found in a variety of building materials and consumer products including cosmetics, baby products, and food packaging. PFRs readily leach out of products and can be found at high levels in indoor dust [73]. Due to increased hand-mouth contact and dermal absorption, young children are at higher risk for PFR exposure relative to other age groups [74]. PFRs induced oxidative stress and cellular activation in murine dendritic cells, indicating that PFRs may influence innate and adaptive immune responses [75]. Few studies have investigated the effects of PFR exposure on allergic disease. PFR levels in indoor dust from 182 single-family dwellings in Japan were positively associated with prevalence of AD, asthma, and allergic rhinitis in home inhabitants [76]. More recently, a cross-sectional study of 128 Japanese children found a significant association between PFR metabolites in indoor dust and eczema (OR 1.4, 95% CI 1.1–1.8) [77]. While no studies have investigated a role of PFRs in food allergy, the increased incidence of AD due to PFR exposure could facilitate epicutaneous sensitization to environmental food antigens. Given the high levels of childhood exposure to PFRs, further studies of how PFRs impact allergic disease are warranted.

Air Pollutant Exposure

There is growing evidence that exposure to traffic-related air pollutants (TRAP), including particulate matter (PM), nitrogen oxides, and ozone, increases the risk of allergic disease [78]. Diesel exhaust particles (DEP), PM, and ozone can act as mucosal adjuvants and promote allergic

sensitization to antigens in the respiratory tract [79–82]. Rodent models also show that exposure to PM can alter intestinal permeability and the gut microbiome, which could modify immune responses to ingested antigens [83, 84]. Furthermore, air pollutants can activate AhR in the skin, leading to inflammation and an AD-like pathology in mice [85]. While several studies indicate a role of TRAP in asthma and AD [78], some birth cohort studies also suggest a relationship between TRAP exposure and food allergen sensitization. In a prospective birth cohort study including roughly 4000 children in the Netherlands (PIAMA), positive associations were found between levels of particulate matter less than 2.5 μm (PM_{2.5}) (OR 1.8, 95% CI 1.2–2.5) or soot (OR 1.6, 95% CI 1.2–2.2) and sensitization to common food allergens [86]. In a Swedish birth cohort study of more than 2500 children (BAMSE), exposure to PM₁₀ and nitrogen oxides was associated with increased risk of food sensitization at 8 years of age (OR 2.3, 95% CI 1.1–4.8) [87]. In a multi-center Canadian birth cohort study involving 2477 children, NO₂ exposure was associated with peanut sensitization (OR 1.07, 95% CI 1.03–1.11) at 1 year of age in a bivariate analysis [88]. More recently, analysis of 996 mother-child pairs in a US birth cohort (Project Viva) found that prenatal exposure to black carbon (OR 1.4, 95% CI 1.1–1.7) or PM_{2.5} (OR 1.3, 95% CI 1.1–1.7) increased the risk of sensitization to food and aeroallergens [89]. Additionally, a meta-analysis of 11 birth cohort studies, including the BAMSE and PIAMA cohorts, found that increasing exposure to PM_{2.5} during early childhood was associated with sensitization to food allergens at 4 and 8 years of life [90].

Because young children spend the majority of their time inside, exposure to indoor air pollutants is of significant concern. Sources of indoor air pollution include environmental tobacco smoke (ETS), cooking stoves, VOCs, and ambient outdoor air pollutants that have penetrated the building envelope [91]. Of these pollutants, ETS has been most strongly implicated with food allergy development. Early studies of European birth cohorts reported that postnatal ETS exposure was a risk factor for food allergen sensitization during the first 3 years of life [92, 93]. More recently, analysis of 3316 children from the BAMSE cohort found that ETS exposure during infancy was associated with increased risk for food allergen sensitization at 4 years of age (OR 1.47, 95% CI 1.1–2.0) and persistent sensitization at 16 years of age (OR 2.2, 95% CI 1.3–3.6) [94]. A systematic review of five birth cohort studies found an overall positive association between ETS exposure and food allergy (OR 1.4, 95% CI 1.1–1.8) in children and adolescents [95]. The mechanisms by which ETS promotes food allergy are unclear, although a recent study found that chemical components of tobacco smoke can augment allergic inflammation by stimulating $\alpha 7$ nicotinic acetylcholine receptors in mast cells [96].

Table 1 Recent clinical studies of select environmental exposures and food allergy outcomes

Exposure	Study	Study population	Findings
Environmental food allergens	Brough et al. (2014) [28]	UK birth cohort of 623 children	• Positive association between peanut dust levels and peanut sensitization and allergy in children with filaggrin loss-of-function mutations
	Brough et al. (2015) [29]	US cohort of 359 atopic children	• Exposure-response relationship between peanut levels in dust and peanut sensitization and allergy at • Strongest association found in children with eczema
	Brough et al. (2018) [30]	Swedish birth cohort of 1878 children	• Maternal bed dust peanut levels associated with peanut sensitization in in nested case-control analysis of 411 high-risk subjects • No association when whole cohort was assessed
Endotoxin	McGowan et al. (2015) [58]	US inner city birth cohort of 516 children	• Endotoxin levels in bedroom dust were inversely associated with overall food allergy and egg allergy
	Tsuang et al. (2020) [59•]	Cohort of 6963 children and adults from NHANES 2005–2006	• Household endotoxin levels positively associated with sensitization to milk and egg, but not peanut
Chemicals	Savage et al. (2012) [66]	Cohort of 860 children from NHANES 2005–2006	• Urinary triclosan levels positively associated with food sensitization in males • No association of parabens or bisphenol A with food sensitization
	Lee-Sarwar et al. (2018) [68]	US cohort of 467 mother-child pairs	• No association between maternal or child urinary levels of triclosan or parabens and food sensitization
	Herberth et al. (2017) [70•]	German cohort of 629 mother-child pairs	• Exposure to phthalate metabolites (MEP and MnBP) during pregnancy was associated with an increased risk for food sensitization in the child
	Podlecka et al. (2020) [71]	Polish cohort of 145 mother-child pairs	• Exposure to the phthalate metabolite 5oxo-MEHP during pregnancy was associated with increased risk of food allergy in the child
Air pollutants	Gruzdeva et al. (2012) [87]	Swedish birth cohort of 2545 children	• Exposure to NO₂ and particulate matter (PM) was associated with increased risk for food sensitization at 8 years of age
	Sbihi et al. (2015) [88]	Canadian birth cohort of 2477 children	• Bivariate analysis showed NO₂ exposure after birth was associated with increased risk of peanut sensitization at 1 year of age
	Sordillo et al. (2019) [89]	US cohort of 996 mother-child pairs	• Black carbon and PM_{2.5} exposure were associated with increased risk of sensitization to food and aeroallergens combined
	Thachere et al. (2016) [94]	Swedish birth cohort of 3316 children	• Environmental tobacco smoke exposure during infancy was associated with increased risk of food sensitization at 4 years of age

Conclusion

In addition to genetic susceptibility, the external exposome likely plays a critical role in food allergy development. Recent clinical studies show that exposure to specific environmental agents may modify food allergy risk (Table 1). There is compelling evidence that non-oral exposure to environmental peanut promotes sensitization rather than tolerance. Animal models also suggest that adjuvants in household dust may facilitate sensitization to environmental food antigens. Early-life exposure to a microbe-rich environment may protect against food allergy development, but the mechanisms involved remain unclear. Childhood exposure to chemicals and air pollutants may alter immune responses to food antigens, but further studies are needed to determine whether

these exposures impact food allergy development. Other components of the exposome, including the host microbiome and diet, are also likely to influence food allergy risk. Identifying the key environmental determinants of food sensitization will be essential for the development of effective interventions aimed at mitigating food allergy risk in children.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of major importance

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