



Review article

It's not just the food you eat: Environmental factors in the development of food allergies

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ABSTRACT

The dramatic rise in the prevalence of food allergy and food allergy-associated anaphylaxis in the past few decades has fueled investigative interest into understanding this puzzling trend. Here, we review the question as to whether important external environmental determinants beyond dietary habits and exposure to food allergens are involved. This review will summarize our current understanding of these environment determinants, derived from the latest experimental and epidemiological research. Specifically, we will review the role of exposures that affect skin barrier function, development of a diverse microbiome, and food processing. Additional exposures of concern are insufficient sunlight, endocrine disrupting chemicals and pesticides, and use of specific pharmaceutical agents that may drive or modify the risk for food allergy. Despite limitations in the quantity and quality of research to date, many new epidemiological associations and experimental data in support of this paradigm have emerged.

1. Introduction

The dramatic rise in the prevalence of food allergy and food allergy-associated anaphylaxis in the past few decades has fueled investigative interest into understanding this puzzling trend (Nwaru et al., 2014; Dyer et al., 2015; Venter et al., 2016; Lee et al., 2017; Motosue et al., 2017; Sicherer and Sampson, 2017). Many (Du Toit et al., 2018), but not all (Elbert et al., 2017), studies implicate a loss of oral tolerance related to the timing and variation of dietary exposures. This may be more pronounced for groups considered at high risk due to genetic predispositions or comorbid diseases. Notably, this rise in food allergies has appeared concurrently with the worldwide increase in other atopic diseases such as asthma, allergic rhinitis, and atopic dermatitis (AD) (D'Amato et al., 2015). This observation also raises the question as to whether important external environmental determinants beyond dietary habits and exposure to food allergens are involved. While these

external non-alimentary factors may not directly disrupt the development of oral tolerance, they may indirectly promote its breakdown along the pathway to clinical food allergy. However, the exact underlying causal mechanisms remain poorly understood (McGowan et al., 2016). This review will summarize our current understanding of these environment determinants, derived from the latest experimental and epidemiological research. Specifically, we will review the role of exposures that affect skin barrier function, development of a diverse microbiome, and food processing. Additional exposures of concern are insufficient sunlight, endocrine disrupting chemicals and pesticides, and use of specific pharmaceutical agents that may drive or modify the risk for food allergy. Of note, while some of these exposures occur through the oral route and therefore are “eaten” (eg pesticides coating foods), they are distinct from the food allergens themselves. Further, emerging research that implicates the importance of a critical prenatal time window of susceptibility to toxicants in food allergy will be

Abbreviations: AD, atopic dermatitis; BEEP, Barrier Enhancement for Eczema Prevention; BPA, bisphenol A; CDC, Center for Disease Control and Prevention; DBP, vitamin D binding protein; IL, interleukin; Ig, immunoglobulin; FLG, filaggrin; FDA, Food and Drug Administration; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; MBP, monobutyl phthalate; MBzP, monobenzyl phthalate; MEP, monoethyl phthalate; MEHP, mono-(2-ethylhexyl) phthalate; MnBO, mono-n-butyl phthalate; PEBBLES, Prevention of Eczema By a Barrier Lipid Equilibrium Strategy; PPIs, proton pump inhibitors; TEWL, trans-epidermal water loss; Th2, T helper 2; Treg, T regulatory; TSLP, thymic stromal lymphopoietin

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included (Stelmach et al., 2015; Jahreis et al., 2017). We conclude with a discussion of research gaps and opportunities for further investigation.

1.1. Skin barrier dysfunction

While oral exposure to food allergens is considered tolerance-inducing, exposure to food allergen through the skin may induce allergic sensitization, potentially leading to allergic symptoms (Panel et al., 2010; du Toit et al., 2016). Both the integrity of the skin barrier and the environmental exposure to allergens are considered to play a role in these mechanisms (Lack, 2008). Therefore, the presence of a defective skin barrier that may alter the usual entry of the food allergen through direct skin contact could facilitate the risk for sensitization to food allergens.

The importance of dermatologic exposure to allergens, further magnified by a dysfunctional skin barrier, in the development of food allergy has been well-demonstrated in murine models (Vaali et al., 2006; Bartnikas et al., 2013). In one model, wildtype mice exposed epicutaneously, but not orally, to ovalbumin produced increased serum levels of the proallergic cytokine interleukin (IL)–4, intestinal mast cell expansion, and signs of immunoglobulin (Ig)E-mediated anaphylaxis to oral ovalbumin challenge. Vaali et al. also demonstrated that mucosal mast cell protease-1, IgE, and IgG₁ were elevated in mice following epicutaneous sensitization and then oral challenge to ovalbumin (Vaali et al., 2006). In another study, sensitization to ovalbumin and peanut through AD-like skin led to the expansion of thymic stromal lymphopoietin (TSLP)-stimulated basophils and promoted proallergic T helper (Th)2 cytokine responses, increased IgE, and increased mast cells in the intestine, all of which are biomarkers of food allergies in mice (Noti et al., 2014). Combined, these murine studies support the concept of a breakdown in tolerance with epicutaneous sensitization to food, and in some cases, physical signs of allergy and anaphylaxis.

Human epidemiological studies largely have focused on patients with AD, which is characterized by a defective skin barrier and is a well-documented risk factor for the subsequent development of food allergies (Panel et al., 2010; Gupta et al., 2016), especially peanut allergy (Brown et al., 2011). For example, a population study by Martin et al. showed that 20% of all infants with AD had a food allergy. In particular, approximately 50% of infants with early-onset of AD before 3 months requiring medical therapy developed a food allergy (Martin et al., 2015). In adults, hand AD was associated with higher rates of self-reported food sensitization in certain high risk workers such as occupational kitchen workers (Minami et al., 2017). Environmental, particularly household, exposure to peanut protein through the contact route has been associated strongly with peanut sensitization and peanut allergy with marked effects in subjects with filaggrin (FLG) mutations or severe AD (Fox et al., 2009; Tordesillas et al., 2014; Anagnostou et al., 2015; Brough et al., 2018).

Mutations in FLG, a protein contributing to skin integrity, have been shown to be strong risk factors for AD (Irvine et al., 2011; Kelleher et al., 2016). In those children with FLG mutations as opposed to those without, house dust peanut exposure correlated with increased peanut sensitization and peanut allergy, supporting this concept of cutaneous sensitization through an impaired barrier (Brough et al., 2014; Leung and Guttman-Yassky, 2014; Brough et al., 2015). However, only approximately 15% of mild-moderate eczema cases, and 50% of moderate-severe eczema cases, may be attributed at least in part to FLG mutations (Brown and McLean, 2009; Mohiuddin et al., 2013). These observations suggest that additional pathogenetic mechanisms in AD besides the loss of FLG expression may contribute to their food allergy (Irvine et al., 2011; Garrett et al., 2013; McAleer and Irvine, 2013). These may include relationships among impaired skin function and antibacterial immunity, staphylococcal colonization (Leung and Guttman-Yassky, 2014), and resulting Th2 responses that further damage the skin (Jones et al., 2016). Children with methicillin-resistant

Staphylococcus aureus (MRSA), which produces more toxins than methicillin-sensitive *Staphylococcus aureus* (MSSA), also had higher peanut-specific IgE levels according to a review of the National Jewish Health Research Database (Jones et al., 2016). A cross-sectional study by Ong and colleagues also reported a correlation between IgE sensitization to staphylococcal superantigens and IgE sensitization to egg among children 4 years and older (Ong, 2014).

Finally, a study by Kelleher and colleagues demonstrated that trans-epidermal water loss (TEWL), a proxy for barrier dysfunction independent of AD, in neonates correlated highly with the development of food allergy at age 2 years (Kelleher et al., 2016). Because a dry, impaired skin barrier may increase the risk for food allergies, a few studies have examined whether treatment of this skin condition may help decrease food allergy risk (Schlievert et al., 2010; Irvine et al., 2011; Brough et al., 2014; Ziyab et al., 2017), just as consistent routine application of emollients have been shown to prevent AD (Horimukai et al., 2014; Simpson et al., 2014; Venkataraman et al., 2014; Lowe et al., 2018). The Prevention of Eczema By a Barrier Lipid Equilibrium Strategy (PEBBLES) trial by Lowe et al. showed some reduction in food sensitization (Lowe et al., 2018); however, there have been very few trials that examined the specific association between routine skin emollient use and the risk for food allergy. The ongoing Barrier Enhancement for Eczema Prevention (BEEP) trial is assessing currently whether daily emollient application will prevent AD in high-risk children and, as a secondary outcome, the development of food allergy and other atopic diseases (Chalmers et al., 2017).

1.2. Altered microbiome

Alterations in the internal microbial environment that may affect host immunity appear important to the development of allergic sensitization (Kuo et al., 2013). Several animal models support this paradigm, including a mouse model in which innate intestinal microbiota containing *Clostridia* inhibited sensitization to food allergens (Stefka et al., 2014). Surrogates for susceptibility to such internal microbial changes have been studied in humans, such as urbanization, milk pasteurization, and delivery by C-section. Several have demonstrated specific associations with the risk of developing allergies to food, as described below.

As an example, living on a farm and in close proximity to animals has been observed to decrease the risk of allergic disease as compared to living in nonfarming areas (eg. U.S. Amish emigrated from Switzerland versus Swiss farm children vs Swiss nonfarm children with asthma rates: 5.2% vs 6.8% vs 11.2%; allergic rhinitis rates: 0.6% vs 3.1% vs 11.6%, respectively) (Liu, 2015). While evidence for decreased clinical food allergy associated with farm living specifically is lacking, the rates of food allergic sensitization are lower for children living on farms (Alfven et al., 2006). Furthermore, the prevalence of milk allergy is lower among those who ingest raw, unpasteurized farm milk compared to commercially available milk products (Braun-Fahrlander and von Mutius, 2011), although causality has not been clearly established (Lucey, 2015; Verhoeckx et al., 2015). There is small but inconsistent evidence that levels of endotoxin may be reduced after pasteurization, addressing the theory that enteral exposure to endotoxin may contribute to the protective effect of raw milk (Perkin, 2007; Braun-Fahrlander and von Mutius, 2011; Stein et al., 2016). Of note, ingestion of raw milk is ill-advised given the risk of serious bacterial disease, with both the Food and Drug Administration (FDA) and Center for Disease Control (CDC) issuing warnings against it and highlighting the potential dangers.

The increased rate of C-sections also parallels the increased rate of allergies over the past few decades (Betrán et al., 2016). Delivery via C-section is thought to increase an infant's risk of allergic disease secondary to bypassing vaginal microbial exposure, thus altering gut microbial flora and predisposing to a proallergic Th2 phenotype (Dominguez-Bello et al., 2016). One study reported a fourfold increased

risk of confirmed egg allergy among those born via C-section who already had an allergic genetic predisposition (i.e. maternal history of allergies) (Eggesbo et al., 2003). In the Pollution and Asthma Risk: an Infant Study (PARIS) birth cohort of 1860 infants, only a nonsignificant trend (adjusted odds ratio 1.45; 95% confidence intervals 0.97–2.19) was found between C-section and food allergen sensitization at age 18 months (Gabet et al., 2016).

1.3. Food processing

Because the rising abundance of processed food in our environment today also parallels the rising prevalence of food allergies, this observation yields the question as to whether the processing of foods impacts its allergenicity. Some processing techniques, like extensively heated (baked) egg or milk products can decrease allergenicity (Robinson and Lanser, 2018). But there is some suggestion for enhanced allergenicity and the development of neoallergens following certain processing techniques as well (Mills et al., 2009). For example, increased IgE binding after roasting peanuts has been observed (Maleki, 2004). In addition, roasting peanuts may permit secondary complexes to form that are less digestible (Maleki, 2004; Kim et al., 2013). In contrast, boiling peanuts is thought to decrease the IgE binding capacity of peanut proteins by denaturing the allergenic proteins or by transferring proteins into cooking water (Robinson and Lanser, 2018). Although boiled peanuts are not hypoallergenic, they may be less sensitizing secondary to decreased allergenic protein, specifically Ara h 2 (Comstock et al., 2016). These observations have been implicated as a cause for the higher prevalence of peanut allergy in the West where peanuts are often consumed roasted as compared to Asia where peanuts are often consumed boiled (1.62% vs. 0.47%) (Robinson and Lanser, 2018). Paradoxically, roasting hazelnuts may make them less allergenic (Maleki, 2004). Ultimately, the effect of processing on a food's allergenicity likely is unique to the food's specific protein components and its thermostability (Mills et al., 2009). While there are limited direct data pinpointing the effects of more hygienic food handling, refrigeration and other processing on microbial load and food allergy, pasteurization of milk through heating between 50 and 90 °C may increase antigenicity by enhancing IgE binding of the milk protein lactalbumin to rabbit serum (Bu et al., 2009).

1.4. Vitamin D and sunlight

The impact of vitamin D in the development and modulation of the immune system, including innate and adaptive immunity, modulation of the Th1/Th2 cell profile, and effects on the integrity of the intestinal epithelium and modification of the intestinal microbiome, has been examined in numerous studies (Mullins and Camargo, 2011). Because vitamin D can induce immunologic tolerance (Mullins and Camargo, 2011), several groups have investigated the association between vitamin D deficiency and the development of asthma and other allergic conditions (Keet et al., 2014b; Aryan et al., 2017). However, the evidence supporting the role of vitamin D specifically in the prevention or development of food allergy is quite limited, and at times, conflicting. Epidemiological studies only have evaluated indirectly the relationship between vitamin D and food allergy using prescriptions for epinephrine autoinjectors for anaphylaxis, and season of birth and latitude, as well as markers for food allergy and vitamin D deficiency, respectively.

In one report, latitude inversely correlated with the development of food sensitization (Matsui et al., 2015); elsewhere, higher rates of anaphylaxis and epinephrine autoinjector use were observed in more northern latitudes and with birth during the fall/winter months (Mullins and Camargo, 2012; Pyrhonen et al., 2012). Additionally, a higher prevalence of food allergy has been observed in Blacks and Hispanics (Ginde et al., 2009; Mansbach et al., 2009; Wegienka et al., 2018), in whom there is a documented higher prevalence of vitamin D deficiency (Mansbach et al., 2009). One study showed that the offspring

of mothers with vitamin D deficiency were more likely to develop food sensitization, implicating the importance of the prenatal window of exposure with later risk for allergy (Tuokkola et al., 2016). However, the caveats of this particular study are that it did not consider the role of genetic predisposition and the far more common prevalence of vitamin D insufficiency compared to food allergy, especially in countries with poor nutrition. The Healthnuts study, an Australian-based prospective population-based cohort study, also showed that lower vitamin D levels were associated with increased risk for peanut and egg allergy (Allen et al., 2013). Moreover, in the same Healthnuts population, Koplin et al. showed that vitamin D deficiency due to specific polymorphic genotypes producing less vitamin D binding protein (DBP) was associated with a higher prevalence of egg and peanut allergy in 1 and 2 year old infants (Koplin et al., 2016). Altogether, these reports suggest an association, albeit weak, between increased food allergy risk with lower vitamin D levels.

On the other hand, a case control study by Molloy et al. failed to show that vitamin D insufficiency and UV exposure in infancy correlated with food allergy, especially egg allergy before one year of age (Molloy et al., 2017). Liu and colleagues reported a similar lack of correlation between cord blood vitamin D and food allergy (Liu et al., 2011), and a number of meta-analyses and systemic reviews also did not find an association between vitamin D and allergic diseases, including food allergy (Willits et al., 2017; Yepes-Nunez et al., 2018). In fact, one study from New Zealand found that children with higher vitamin D levels actually experienced higher rates of food allergy (Hypponen et al., 2009). Additionally, other reports describe a bimodal (U-shaped) association where both the deficiency and excess of vitamin D were associated with the increased odds of developing food allergies (Hypponen et al., 2009; Wjst, 2009).

1.5. Chemicals

Environmental exposure to a number of chemicals has been implicated in the promotion of allergic immune responses. Most prominently, these include phthalates and bisphenol A (BPA), often classified as endocrine disrupting chemicals. Phthalates are found in vinyl floors, carpet backings, polyvinyl chloride (PVC) plastics, cosmetics, house dust and high fat foods (Kwak et al., 2009; Ait Bamai et al., 2016; Benjamin et al., 2017). BPA is used in lacquers to coat food cans, in the manufacturer of polycarbonate plastics, and as an antioxidant, fungicide and antimicrobial in cosmetics (reviewed in (Kwak et al., 2009)). Exposure to both groups of environmental chemicals and allergic sensitization date back many years (Kwak et al., 2009; Robinson and Miller, 2015; Hwang et al., 2017; Zhou et al., 2017), although the supporting evidence remains mixed (Gascon et al., 2015). For example in one epidemiologic study, urinary metabolites of monoethyl phthalate (MEP), monobutyl phthalate (MBP), monobenzyl phthalate (MBzP), and mono-(2-ethylhexyl) phthalate (MEHP) were measured during the 3rd trimester of pregnancy and at ages 2 and 5 years. Only MEHP levels positively correlated with serum IgE levels, and this association was limited to males; in contrast, MBzP levels had a significant association with AD at age two years (Wang et al., 2014).

The association of exposure to these chemicals with the development of specifically food allergy is more limited, and mostly focuses on links with the established risk factor of AD (Brough et al., 2015; Tsakok et al., 2016). For example, higher urinary concentrations of MBP were associated with AD in a Danish cohort of 4–9 year olds (Overgaard et al., 2017). Time series analyses in a Seoul cohort showed that both previous day and same day higher levels of mono-n-butyl phthalate (MnBP) and BPA were associated with aggravation of AD symptoms (Kim et al., 2017). Similar associations have not been replicated in all cohort studies (Smit et al., 2015). Although, one relatively small study from the Polish Mother and Child Cohort reported an association between prenatal urinary measures of MBzP and higher odds of food allergy by age 2 years (Stelmach et al., 2015). In the 2005–2006 National

Health and Nutrition Examination Survey, higher urinary levels of the endocrine disrupting chemical triclosan was associated with a greater odds of developing sensitization to food among males (Savage et al., 2012). Two experimental studies reported that exposure to BPA interrupted the development of oral tolerance in mice (Ohshima et al., 2007; Nygaard et al., 2015), but were unable to detect effects of BPA on the experimental induction of anaphylaxis or elevated IgE levels (Nygaard et al., 2015). Additional mechanistic studies have observed reductions in Treg activity (and in the latter case, T helper CD4 + CD25 + cell populations) after exposure to phthalates and BPA (Menard et al., 2014a, 2014b; Herberth et al., 2017). Moreover, when BPA-treated ovalbumin-tolerized rats were orally challenged with ovalbumin, colonic inflammation developed, with infiltration that was mixed with increased IFN γ , IL-10, and decreased TGF β (Menard et al., 2014a, 2014b).

Similarly, herbicides and pesticides have been implicated in allergic diseases, including food allergy in limited, albeit conflicting, studies. Chlorophenols are relatively common in the soil and water of westernized societies as byproducts during the manufacturing of several chlorinated chemicals used to make preservatives, antiseptics, and disinfectants and pesticides; levels are measured in the indoor air in homes where moth balls and deodorizers are used. (1996,2006) The US National Health and Nutrition Examination Survey for 2005–2006 associated childhood exposure to dechlorophenol-containing pesticides with sensitization to one or more food allergens, and not aeroallergens (Jerschow et al., 2012). Food allergy sensitivity also was associated with the use of home pesticides and urban living, measured by questionnaire (Jerschow et al., 2012). However, a large Danish cohort did not replicate an association between prenatal exposure to persistent organic pollutants and allergic sensitization (i.e. elevated serum-specific IgE) in young adults (Hansen et al., 2015).

1.6. Drugs and other agents

Administration of various therapeutic drugs, including antibiotics, proton pump inhibitors (PPIs), and vaccines, has been implicated in the development of food allergy. Although only a few studies have specifically examined the association between antibiotics and food allergies, increased antibiotic use in early life has been associated with an increased risk for atopic disease (Kuo et al., 2013; Sun et al., 2015; Yamamoto-Hanada et al., 2017; Ahmadizar et al., in press). An analysis of the national registry in Finland showed an association between maternal and child use of antibiotics and risk for cow's milk allergy (Metsala et al., 2013). A case-controlled study using electronic medical record data by Hirsch and colleagues also observed higher odds of developing a milk or other food allergy if a child was prescribed three or more courses of antibiotics, especially penicillins (Hirsch et al., 2017). Similarly, a case controlled study by Love and colleagues correlated the number of antibiotic prescriptions, especially five or more in two years, with a higher odds ratio of developing a food allergy (Love et al., 2016). Moreover, the administration of cephalosporins and sulfonamides was strongly related to a higher rate of food allergy (Love et al., 2016). As described above, antibiotic use may be linked to food allergy through the modification of the intestinal microbiome (Huang et al., 2017). Although epidemiological support for this hypothesis has been limited or absent (Eggesbo et al., 2003), the aforementioned Clostridia mouse model did suggest that antibiotic use and its inhibition of bacterial growth was responsible for the elevated risk for developing allergic sensitization (Stefka et al., 2014).

PPIs that block gastric acid production are thought to interfere with the appropriate processing of food allergens, thus decreasing exposure and potentially increasing sensitization (Astwood et al., 1996). Scholl et al. reported that PPI use increased sensitization to hazelnut allergens in mice and humans (Scholl et al., 2005). Another animal model found an association with IgE sensitivity and low dose ovalbumin feeding following acid suppression by a PPI (Diesner et al., 2008). In contrast,

other studies have reported no association between the presence of H. Pylori and food allergy (Baccioglu et al., 2008; Ma et al., 2016). Given these few contradictory studies, it appears that gastric acid suppression does not have a clear association with food allergies at this time.

Finally, the HealthNuts study from Australia examined the timing of vaccinations with regards to food allergies. While the children who received a delayed first DTaP had lower rates of AD, the authors found no correlation between the timing of vaccine administration and food allergy (Kiraly et al., 2016).

2. Conclusion

While this review focused on the main environmental determinants, meta-analyses of five cohort studies suggest that food allergy was associated with exposure to second hand smoke (relative risk 1.43 [95% confidence interval 1.12–1.83]), although not with maternal prenatal active smoking (Saulyte et al., 2014). Food allergy also has been associated with excessive exposure to advanced glycation end-products derived from dietary sugars, cooked meats, oils and cheese (Smith et al., 2017). Further, disparities in food allergy according to race and ethnicity may not only implicate a link to vitamin D exposure (Keet et al., 2014a), but an impact of acculturation and genetic predisposition that has been difficult to specify and quantify with current approaches.

In summary, mounting evidence suggests that environmental exposures beyond food allergens may affect the risk for food sensitization, and thus the risk of developing food allergy and anaphylaxis. Some of these exposures may occur in association with influences characteristic of more modern Westernized lifestyles that may drive immune dysregulation in the absence of strong infectious stimuli, as has been posited for the rise in other allergic diseases. In addition to the aforementioned observations among the US Amish populations (Liu, 2015), this paradigm may be reflected in the environmentally-associated evolving patterns in allergy incidences as measured in epidemiological studies of former East and West Germany (Ring et al., 1999). Further illustration may be the differences in allergic disease and skin and nasal microbiota that persist in the adjacent but socioeconomically contrasting children from Finnish and Russian Karelia (Haahtela et al., 2015; Ruokolainen et al., 2017).

Study limitations, including results based on small numbers of subjects, varying study methodologies, unmeasured confounding, and lack of validating food challenges, considered the gold standard for a food allergy diagnosis, hamper sound interpretation of the reported findings (Gabet et al., 2016). A number of these studies rely on electronic medical records, which could result in misreporting (Love et al., 2016). Moreover, many of these human and mouse studies appear to report allergic sensitization as their outcome rather than clinical allergy, which is far less prevalent but may be a more clinically relevant endpoint (Ortolani et al., 1998; Valcour et al., 2017). Still, many new epidemiological associations and experimental data have emerged as summarized. Hopefully future studies will correct these methodological limitations. Intervention studies, including rigorous large scale randomized placebo-controlled study designs, that address some of these specific environmental determinants and examine rigorously defined food allergy outcomes, may further elucidate the causes of food allergy and its remediation.

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Conflict of Interests

The authors declare no conflict of interests.

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Further reading

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