

## Review



# Origin of Allergy From *In Utero* Exposures to the Postnatal Environment

Jessica Hui-Beckman , Byung Eui Kim , Donald YM Leung

Department of Pediatrics, National Jewish Health, Denver, CO, USA

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### Correspondence to

Donald YM Leung, MD, PhD

Department of Pediatrics, National Jewish Health, 1400 Jackson Street, Denver, CO 80206, USA.

Tel: +1-303-398-1379

Fax: +1-303-270-2182

Email: leungd@njhealth.org

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### ORCID iDs

Jessica Hui-Beckman

<https://orcid.org/0000-0001-8579-9568>

Byung Eui Kim

<https://orcid.org/0000-0003-4923-1814>

Donald YM Leung

<https://orcid.org/0000-0002-0177-3844>

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## ABSTRACT

As the incidence of atopic conditions continues to increase, emphasis has been placed on understanding the origin of allergy with hope that prevention measures can be achieved. The perinatal environment is important for this understanding, given that both the immune system and microbiome start forming prenatally. Maternal exposure can greatly impact on fetal health. Additionally, the dysfunctional epithelial barrier is influential in allowing allergens and irritants to penetrate the skin or mucosa, leading to the release of proinflammatory cytokines and mediators to drive type 2 tissue inflammation and the onset of allergy. There are numerous factors related to skin, airway, and gut epithelial barriers dysfunction, and genetic predispositions are also present. Comprehensive birth cohort studies and further mechanistic studies will be keys to understanding the origin of allergy.

**Keywords:** Allergy; dermatitis, atopic; food allergy; asthma; immune system; microbiome; allergens; cytokines; etiology

## INTRODUCTION

Since Clemens von Pirquet coined the term “allergy” in 1906 and David Strachan introduced the hygiene hypothesis concept in 1989, the incidence of allergic conditions has markedly increased.<sup>1,2</sup> Studies of allergy and the hygiene hypothesis have been extensively pursued with the industrialization accompanying Westernization as a point of focus. Numerous studies have been published demonstrating the protective effect of increased number of siblings, pets, living on a farm, and day care attendance in attenuating the development of allergic conditions.<sup>3-6</sup> The microbiome is thought to have the link between the external environment and the host immune response.

When discussing the origin of allergic conditions, the focus is on atopic dermatitis (AD), food allergy (FA), asthma, and allergic rhinitis (AR); this progression of diseases encompasses the atopic march. The epithelia of the skin, airway, and gut are important barriers that become disrupted in allergy pathogenesis. In this review, we highlight several factors that promote epithelial dysfunction. It is important to note that the prenatal environment is a major factor, as *in utero* exposure is already shaping the infant's microbiome and immune system.<sup>7</sup> Postnatal

environmental factors also play a role in epithelial dysfunction and allergy development. We then summarize the studies demonstrating that the season of birth impacts on future allergy. Finally, allergy prevention and treatment are discussed.

## SKIN AS THE SITE OF EPICUTANEOUS ALLERGEN SENSITIZATION

The skin, airway, and gut play an integral role in homeostasis with the external environment. The skin is the largest organ and the first line of defense to allergens and pathogens on a structural and functional basis.<sup>8</sup> The skin is an important part of the innate immune system, and adaptive immunity becomes involved when the skin barrier integrity is disturbed. Therefore, it has been considered that skin barrier dysfunction is an initial step to the development of allergic diseases such as AD, FA, asthma, and AR.<sup>9,11</sup> The stratum corneum is the outermost portion of the epidermis and thus is an important barrier to external agents. It is composed primarily of proteins and lipids which form a tight protective barrier to environmental agents and also maintain a low pH barrier to prevent activation of injurious proteases. Tight junctions (TJs) are referred to as the gatekeepers and located below the stratum corneum in the stratum granulosum, as they prevent the penetration of foreign substances through the skin barrier and reduce transepidermal water loss. The claudin family of proteins is an example of TJ proteins, and reduced claudin expression is seen in AD patients.<sup>8</sup> Keratinocytes are the primary cell type in the epidermis, and there are numerous proteins involved in differentiation and cornification of keratinocytes.<sup>8,12</sup> The epidermal differentiation complex contains genes encoding proteins such as filaggrin (FLG), loricrin, and involucrin.

*FLG* has been extensively studied, and *FLG* mutations are associated with earlier onset of AD, disease persistence, and increased risk of asthma and FA.<sup>13,15</sup> While loss-of-function mutations of *FLG* are commonly described in Northern Europe, it is important to note that there are other variants seen in ethnicities such as Asian and African American individuals.<sup>16</sup> The skin of children with both AD and FA has a greater decrease in *FLG* breakdown products compared to children who have AD without FA.<sup>17</sup> The non-lesional skin of children with both AD and FA is also abnormal, which demonstrates that their entire skin surface is susceptible to allergen penetration. Proinflammatory mediators, such as interleukin (IL)-4, have also been shown to decrease the expression of *FLG*.<sup>17</sup> Individuals with AD also have abnormal lipid metabolism in the skin, as an increase in type 2 cytokines leads to a decrease in long-chain sphingolipids.<sup>13,17,18</sup> In AD, the skin becomes permeable and allows the entry of irritants, allergens, and pathogens. The epithelial cells are able to detect external insults through pattern recognition receptors, such as toll-like receptors (TLRs) and nucleotide-binding and oligomerization domain (NOD)-like receptors.<sup>19</sup> This concept is called the “outside-inside” view of pathogenesis, as the penetration through the epithelium leads to a systemic allergic immune response through the release of alarmins such as IL-33 and thymic stromal lymphopoietin (TSLP).<sup>8</sup> There is also the “inside-outside” model which suggests that as the immune response is enhanced, the skin barrier becomes more vulnerable to epithelial dysfunction.<sup>20</sup>

*Staphylococcus aureus* has been identified as a major player in AD and FA, as this contributes to microbial dysbiosis.<sup>17,21-23</sup> Over the last few decades, the presence of *S. aureus* colonization and *S. aureus*-specific immunoglobulin E (IgE) has increased in patients with allergy.<sup>21</sup> *S. aureus* is an opportunistic pathogen that colonizes damaged tissues and is able to further increase

disease severity. It has evolved properties that enable adherence to the skin to promote Th2 and Th17 inflammatory pathways involved in AD, thus hindering the microbiome.<sup>24</sup> It has been shown that during AD flares, the skin has a greater abundance of *Staphylococcus* and that more severe AD patients have a decreased microbiome diversity with increased pathogenic bacteria. Children with *S. aureus* colonization are more likely to be sensitized to childhood-onset allergic foods with a more enhanced production of IgE.<sup>22</sup> They also have more persistent FA that is not influenced by AD severity. Additionally, the lesional and non-lesional skin of children with AD and FA have an increased abundance of *S. aureus*, which makes them unique from AD patients without FA.<sup>17</sup>

## GUT FUNCTION AS A TOLERIZING ORGAN

Increased emphasis has been placed on early oral exposure to allergen-specific foods as a method of inducing tolerance.<sup>23,25,26</sup> This has led to the dual-allergen exposure hypothesis, which has gained attraction in recent years.<sup>13,23</sup> As mentioned above, allergen exposure can occur through the skin epithelium, while early oral exposure to foods leads to tolerance. With this dual-allergen exposure concept, epicutaneous allergen sensitization leads to elevated Th2 immune responses. When the naïve T-cell differentiates into a Th2 cell, it is able to stimulate B cells to make IgE against this allergen. When there is allergen reexposure, activated mast cells release mediators of anaphylaxis that cause the systemic symptoms of FA. Conversely, introduction of foods via the gut leads to induction of regulatory T-cells (Tregs) and tolerance to potential food allergens.<sup>27-29</sup> It is well known that Tregs are important in the immune system for maintaining tolerance. Cord blood studies have demonstrated that even at birth, the infants who eventually develop FA had lower Tregs and higher inflammatory cytokines.<sup>30</sup>

## SKIN AND GUT CROSSTALK

Leyva-Castillo *et al.*<sup>31</sup> demonstrated the crosstalk between the skin and the gut and suggested that scratching can initiate anaphylaxis in AD. Epicutaneous sensitization can occur through scratching, which is a common occurrence in AD. In food-sensitized mice, skin tape stripping serves as a surrogate for scratching. After oral ingestion of the food allergen, there is expansion of intestinal mast cells with intestinal permeability. Thus, it is thought that scratching promotes not only epicutaneous allergen sensitization but also anaphylaxis. Leung *et al.*<sup>17</sup> also demonstrated that the skin of patients with AD and FA compared to that with AD and no FA have a greater itch-scratch response that increases skin damage with release of type 2 cytokine mediators. This intensifies the itch response and further the skin barrier dysfunction. Keet *et al.*<sup>32</sup> recently published findings that infants with increased AD severity and older ages have a higher risk of developing peanut allergy; this further enforces the relationship between the skin and the gut.

It has also been shown that the intestinal immune system and gut epithelial dysregulation play a role in AD flares.<sup>33</sup> Dysbiosis of *Faecalibacterium prausnitzii*, which is a major gut species, is involved in a feedback loop which causes further skin damage in AD. Additionally, it has been suggested that gut epithelial dysfunction induces the passage of toxins and microbes into systemic circulation.<sup>33</sup> This leads to Th2 type immune responses in the skin, promoting the proinflammatory skin damage. These studies all highlight the important connection between the skin and the gut in allergy.

## AIRWAY EPITHELIAL BARRIER DISRUPTION AND ASTHMA

Although the skin and the gut are the major players in allergy development, the respiratory epithelium also has protective mechanisms to maintain the barrier and prevent entry of foreign irritants. The bronchial epithelium is pseudostratified, which provides structural protection.<sup>34</sup> There is a mucociliary apparatus with mucus secretion containing protective molecules and cilia to clear debris. The airway epithelial cells can also detect foreign agents through pattern recognition receptors and NOD-like receptors, similar to the skin. This allows for recruitment of cells involved in host defense, with the goal of limiting host tissue injury while simultaneously responding to the external challenge.<sup>34</sup> Asthma is characterized as a lower airway chronic disease with airway hyperresponsiveness, mucus overproduction, and airway remodeling.<sup>8</sup> These lead to episodic symptoms, commonly coughing, wheezing, and shortness of breath. It is a combination of environmental exposures and genetic susceptibility that promotes asthma. Similar to the skin, the airway epithelium can become disrupted and lead to abnormal inflammatory immune responses that drive airway remodeling. Respiratory infections, such as rhinovirus, can further damage the airway and are common triggers of asthma exacerbations. With the heterogeneous nature of asthma, understanding asthma endotypes is the preferred way to characterize the mechanistic pathways involved.<sup>34</sup> Identifying pathophysiology related to asthma endotypes allows introduction of biologics which target polarized immune pathways. With the increase in availability of biologic therapy, the endotype approach is especially useful.

Some individuals have genetic susceptibility to asthma, and there have been genome-wide association studies that identified these at-risk alleles.<sup>34</sup> For example, the *ORMDL3* locus is associated with early-onset asthma and thought to contribute to decreased epithelial barrier defenses. It has also been shown that 17q21 variants have an association with asthma in children who had wheezing related to rhinovirus.<sup>35</sup> Other susceptibility genes impact on immune dysregulation and abnormal barrier repair. For example, *IL33* and *TSLP* polymorphisms confer susceptibility to disease through dysregulated immune responses. *TGF- $\beta$*  variants are associated with abnormal epithelial barrier repair, and *PCDH1* variants entail risk for asthma when there is smoke exposure.<sup>34</sup>

## PERINATAL FACTORS CONTRIBUTING TO THE DEVELOPMENT OF ALLERGY

As we have addressed the manner in which skin, gut, and airway barrier dysfunctions contribute to allergy, it is important to note various factors influencing allergy development. Birth cohort studies have shown the importance of the *in utero* and the immediate postpartum environment (**Figure**).<sup>3,36</sup> There is maternal exposure during pregnancy that is thought to impact on immune dysregulation and epigenetic changes in the fetus. Cigarette smoke exposure influences the immune system and airway development in the fetus, predisposing to asthma.<sup>37</sup> Mechanistic studies have shown alterations in gene expression with epigenetic modifications through microRNAs and DNA methylation.<sup>38,39</sup> The oxidative stress from pollutants leads to these changes and increased risk of allergy. Infants who were exposed to pollutants *in utero* and developed AD by 1-year old were found to have lower cord blood Tregs at birth.<sup>40</sup> Recently, it has been suggested that particulate matter (PM) exposure during the first trimester of pregnancy is associated with early-onset persistent AD.<sup>41</sup> The maternal diet and use of oral antibiotics also play a role in immune programming. It is thought that

**Maternal exposures:**

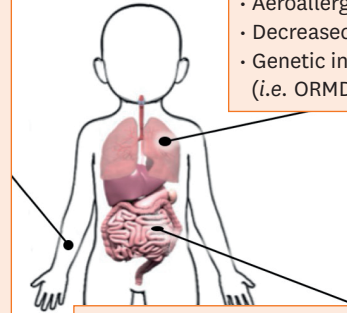
- Outdoor and indoor pollutants
- Cigarette smoke
- Soaps and detergents
- Microplastics
- Increased antibiotic use

**Skin epithelial****dysfunction → AD + FA:**

- Outdoor and indoor pollutants
- Smoke exposure
- *S. aureus* colonization
- Food allergen and aeroallergen penetration
- Vitamin D deficiency
- Soaps and detergents
- Decreased microbial diversity
- Genetic influence (i.e. Filaggrin mutation)

**Airway epithelial****dysfunction → Asthma:**

- Outdoor and indoor pollutants
- Smoke exposure
- Viral and bacterial respiratory pathogens
- Aeroallergen penetration
- Decreased microbial diversity
- Genetic influence (i.e. ORMDL3)

**Gut epithelial dysfunction → FA:**

- Formula feeding
- Increased antibiotic use
- Food allergen and aeroallergen penetration
- Processed foods
- Vitamin D deficiency
- Microplastics
- Decreased microbial diversity
- Genetic influence

**Figure.** Perinatal factors contributing to the development of atopy. Left: the prenatal maternal-fetal environment can cause fetal epigenetic changes and immune dysregulation with maternal exposure. Right: the birth delivery route and post-natal infant exposure are contributing factors to the dysfunctional epithelium of the skin, airway, and gut. Please note that the collectively listed factors affect multiple organ systems, as the factors listed under one category can modulate the immune system leading to systemic consequences. Figure adapted with permission from Hui and Leung.<sup>7</sup> AD, atopic dermatitis; FA, food allergy.

this detrimental exposure leads to lower Treg levels and elevated Th2 immune responses, shifting the neonatal immune system towards type 2 inflammation. Some researchers have proposed that lower maternal vitamin D levels are players in driving allergy.<sup>42</sup> However, there is no definitive data that maternal supplementation with vitamin D during pregnancy play a protective role.<sup>43</sup> These studies emphasize that allergy prevention must begin *in utero*, as this environment is already shaping the immune system of the developing fetus.

The metabolites produced by intestinal microbes influence the immune system, as these metabolites affect T-cell differentiation. Microbiome studies have demonstrated the importance of the perinatal environment, as the infant's gut microbiome is impacted by the mode of delivery and feeding patterns.<sup>36</sup> The gut microbiome of vaginally delivered infants are more reflective of their mother's vaginal microbiota, with organisms such as *Lactobacillus*, *Prevotella*, and *Sneathia*.<sup>44</sup> There is also a richness of microbiome diversity found in vaginally delivered infants. On the other hand, infants born via cesarean section have gut microbiota reflective of those found on the skin surface, such as *Staphylococcus*, *Corynebacterium*, and *Propionibacterium*. It is thought that vaginal births confer a protective and diverse microbiome to the infant. However, the literature has conflicting findings, as past studies have shown that cesarean section deliveries are associated with allergy development,<sup>45</sup> while others have not demonstrated this association.<sup>46</sup> This emphasizes the need for large-scale prospective birth cohort studies, as it will be important to capture the underlying maternal and fetal reasons why cesarean section is performed versus a vaginal delivery. It has also been shown

that there is gut microbiota dysbiosis in the infants whose mothers receive antibiotics during labor and delivery, regardless of method of delivery.<sup>44</sup> Other factors affecting the infant microbiome are gestational age at delivery and the infant's diet. Breast-feeding has several benefits, including passive transfer of maternal antibodies and enhancing immune tolerance to decrease the development of allergy.<sup>47</sup> All of these factors play a role in the child's future health, as the microbiota in early-life is important for the maintenance of homeostasis and the development of a healthy immune system.

## POSTNATAL FACTORS LEADING TO EPITHELIAL BARRIER DYSFUNCTION

As the skin, airway, and gut epithelia are central for maintaining homeostasis, epithelial barrier dysfunction can lead to sensitization and allergy. There are numerous factors that cause epithelial dysfunction, especially with the onset of Westernization.

Commercial detergents and surfactants have been shown to cause damage to the stratum corneum and TJs.<sup>48</sup> With societal practice leading to increased use of cleansing agents for personal and community hygiene, this contributes to the alteration in the proteins and lipids in the skin, leading to dryness and an impaired skin barrier.

There has also been an increased interest in microplastics, which are fragments of plastic smaller than 5 mm that are insoluble in water, and there is concern that microplastics are damaging to our ecosystems.<sup>49-51</sup> The route of human exposure occurs through drinking water, as plastics and microplastics are present in bodies of water used for drinking water. Plastic production has increased remarkably with greater demand, and it has been shown that microplastics are able to be absorbed through the gut epithelium and cause barrier dysfunction.<sup>49</sup> In mouse studies, microplastics accumulate in the gut and cause dysbiosis of gut microbiota in addition to barrier dysfunction.

Indoor and outdoor pollution are other factors that alter the epithelial barrier, as they also have detrimental effects on population health.<sup>52,53</sup> Air pollution plays a significant role in asthma and airway conditions, and according to the World Health Organization, over 90% of the world's population resides where air quality levels are suboptimal.<sup>52</sup> Traffic-related air pollution (TRAP) is a term to include markers such as PM, carbon monoxide, and nitrogen oxides; people in urban locations have greater exposure to TRAP. PM refers to a hazardous pollutant that comes from burning fuel or are formed from gaseous pollutants; a common source is from vehicles.<sup>53</sup> PM<sub>10</sub>, which is PM with a diameter of 10 micrometers or smaller, is associated with asthma exacerbations in developed countries<sup>53</sup> PM<sub>2.5</sub>, which refers to PM that has a diameter of 2.5 micrometers or smaller, has been shown to directly cause airway inflammation. More specifically, it has been shown that PM<sub>2.5</sub> exposure causes decreased expression of TJ proteins in the upper airway.<sup>54</sup> Recently, it has also been reported that PM<sub>2.5</sub>-induced Tumor necrosis factor- $\alpha$  causes FLG deficiency and skin barrier dysfunction through aryl hydrocarbon receptor.<sup>55</sup> Another common outdoor pollutant is ozone, which comes from vehicle exhaust, industrial plants, and chemical solvents.<sup>53</sup> Higher ozone levels have been associated with respiratory morbidity and mortality by causing a decrease in forced expiratory volume in 1 second and forced vital capacity values as well as an increase in neutrophil inflammation. Elevated ozone levels are prominent in the summer months when the weather is warmer, whereas PM is higher in the winter months.

Environmental tobacco smoke is a common cause of indoor air pollution, and it is associated with wheezing and asthma exacerbations in the pediatric population.<sup>56</sup> It has been well described that tobacco smoke exposure plays a role in the development of both asthma and allergy.<sup>57</sup> The mechanism in which PM, ozone, and tobacco smoke affect the innate immune system is through TLR signaling. These pollutants activate TLR signaling directly and through the production of damage-associated molecular patterns, resulting in proinflammatory cytokine responses in the epithelium.<sup>58</sup>

Inflammation secondary to infection is another player in airway epithelial barrier dysfunction.<sup>8,13</sup> Respiratory viruses are common asthma exacerbation triggers, namely rhinovirus and respiratory syncytial virus.<sup>59</sup> Microbiome studies of the airway in children have also shown that colonization of certain bacteria associated with illness (*Streptococcus*, *Haemophilus*, and *Moraxella*), along with allergic sensitization, has greater risk of persistent wheezing. Viral and bacterial infections directly cause injury to the bronchial epithelium. Combined with early allergy sensitization, this leads to chronic obstruction and asthma symptoms secondary to airway remodeling.

It has been reported that epithelial barrier defects lead to microbial dysbiosis and the translocation of bacteria to subepithelial tissues, subsequently inducing tissue inflammation.<sup>21,60</sup> Moreover, it has been suggested that epithelial barrier defects are associated with not only allergy but also chronic autoimmune and neurodegenerative diseases including diabetes and Alzheimer diseases.<sup>21</sup>

## SEASON OF BIRTH IMPACTS ON FUTURE ALLERGY

There have been multiple studies demonstrating that fall (September–December) and winter (January–March) births are associated with increased risk of allergy, especially AD and FA.<sup>42,61–66</sup> A systematic review of studies performed in the Northern Hemisphere demonstrated a significant association of fall and winter births with the development of AD.<sup>66</sup> Based on data from the United States National Health and Nutrition Examination Survey, the odds of FA is 1.91 times greater in children born in the fall.<sup>42</sup> In an Australian study, 57% of FA children were born in the autumn/winter versus 43% who were born in the spring/summer.<sup>64</sup> In Korea, children born during the fall had an 8.3% prevalence of FA compared to 3.0% of those born in the spring.<sup>63</sup> In another study in the United States, both childhood-onset FA and AD had a higher fall birth proportion of 28.6%.<sup>61</sup> It was also described that the entire atopic march of AD + FA + asthma + AR had higher fall birth proportion of 30.3%. Notably, when examining the children with AD + no FA + asthma + AR, there was no seasonal birth predisposition. This suggests the importance of FA as the link between allergy and the season of birth.

The causative factors related to fall birth and allergy are not known. While parental history of allergy does confer risk in offspring, genetic predisposition is not the only cause.<sup>63</sup> Skin barrier dysfunction is a major factor, as AD is the first condition seen in the atopic march. The dysfunctional skin barrier allows allergens and microbes to penetrate the skin and amplify type 2 inflammation through the release of alarmins such as TSLP and IL-33. It has also been shown that children with *S. aureus* skin colonization are more likely to be born in the fall, with an even greater incidence of fall birth in children with AD, FA, and *S. aureus* skin colonization.<sup>61</sup> This suggests that *S. aureus* play a role in atopic march progression. Additionally, it is thought that there are environmental factors contributing to the epithelial

barrier differences in children born in the fall and winter. Future mechanistic studies will better elucidate the pathophysiology connecting season of birth to allergy risk.

## ALLERGY PREVENTION AND TREATMENT

The Learning Early About Peanuts study was a randomized control one of 640 infants with moderate-to-severe AD and/or egg allergy, thus placing them at high risk of peanut allergy.<sup>26</sup> The infants were randomized to introduction of peanuts or avoidance of peanuts. In those who consumed peanuts early, the frequency of peanut allergy was significantly decreased. This landmark study changed clinical practice from food avoidance to emphasizing early introduction of allergenic foods and supports the dual-allergen exposure hypothesis. However, it is important to note that early consumption of one food does not protect against sensitization of other foods.<sup>25</sup> For example, early peanut consumption does not prevent egg allergy, and vice versa.

There is also an emphasis on breast-feeding for the first 3 to 4 months of life. Exclusive breast-feeding during this timeframe in early life has been shown to decrease the incidence of AD and also protect against wheezing.<sup>47</sup> It is thought that human breastmilk contains factors, such as IgA and oligosaccharides, that confer protection, although the composition varies between mothers.<sup>67</sup> Based on current evidence, there is no recommendation for the maternal diet to be restricted during pregnancy or while breast-feeding. Finally, focusing on maintenance of a healthy skin barrier will allow the epithelium to remain intact and prevent penetration of allergens or irritants. It is interesting to note that clinical studies assessing emollients for the prevention of AD in infancy are inconsistent, and it is even postulated that emollients themselves may play a role in increasing exposure to allergens.<sup>68</sup> However, in infants who have skin dryness and who are at risk for AD, we hypothesize that proper skin care with appropriate emollients and introduction of anti-inflammatory agents with onset of AD will prove to be beneficial.

Probiotics have been under investigation as a way of allergy prevention, as it is thought that probiotic supplementation can assist in establishing a healthy microbiome and immune balance.<sup>69</sup> Of the allergic conditions, the most positive data have been for AD prevention, with supplementation of probiotics during pregnancy or during the infant's first week of life.<sup>70</sup> Upon review of 17 studies, Zuccotti *et al.*<sup>70</sup> found that those receiving probiotics were at lower risk of developing AD (relative risk, 0.78; 95% CI, 0.69–0.89;  $P = 0.0003$ ). Another systematic review of 29 probiotic studies examining maternal probiotic use during the third trimester of pregnancy as well as studies of maternal probiotic use while breast-feeding showed that infants of women who received probiotics during pregnancy were at reduced risk of AD.<sup>71</sup> However, not all studies have demonstrated consistent findings, and a major limitation lies in the fact that different probiotic strains have been used. Regarding probiotic use for the treatment of AD, a randomized controlled trial of various probiotics and placebo groups showed that the probiotic and placebo groups significantly improved AD; there was no significant difference between using probiotics versus placebo.<sup>72</sup>

Biologics have played a large role in advancing disease treatment in recent years. Dupilumab is a human monoclonal antibody that targets IL-4 receptor alpha and blocks IL-4 and IL-13 signaling, which are cytokines involved in type 2 inflammation.<sup>13</sup> It is used to treat AD and asthma. Omalizumab is a humanized monoclonal antibody that prevents IgE from binding

**Table.** Allergy prevention strategies**Allergy prevention strategies**

## Recommended interventions for allergy prevention

Early introduction of peanut and egg<sup>25,26</sup>Exclusive breastfeeding for the first 3–4 months of the infant's life<sup>37</sup>

## Interventions currently being studied or inconclusive evidence

Emollient use to maintain an intact skin barrier<sup>68</sup>Probiotic supplementation<sup>69–72</sup>Vitamin D supplementation<sup>42,43</sup>Vaginal delivery<sup>36,44–46</sup>

## Practical strategies

Limiting indoor and outdoor pollution<sup>41,52–56</sup>Limiting cigarette smoke exposure<sup>56,57</sup>Limiting antibiotic use when able<sup>44</sup>Limiting exposures to microplastics and damaging detergents<sup>48–51</sup>

While the exact understanding of allergy development and prevention is not yet elucidated, listed here are recommendations for allergy prevention based on the current understanding of allergy origin. Additionally, interventions currently being studied as well as practical strategies to prevent allergy are listed.

to its receptor on mast cells and basophils. It is also used to treat asthma as well as chronic urticaria and other conditions. Oral immunotherapy (OIT) is being studied for FA, and peanut OIT (Palforzia, AR101) has been shown to be beneficial to children who were allergic to peanut.<sup>73</sup> A combination of biologics and OIT is another area of interest with ongoing clinical trials.

Ultimately, as more is understood about the origin of allergy, different prevention methods will be emphasized. We anticipate that birth cohort studies will further demonstrate the importance of maintaining a healthy skin barrier from birth. Guidance on probiotic and vitamin D supplementation needs to await randomized placebo-controlled trials before the broader allergy community can confidently provide recommendations. For a summary on current recommendations, as well as practical considerations, please refer to **Table**.

## CONCLUSION

There are several organ systems involved in allergy development, as dysfunctional skin, gut, and airway epithelia allow for proinflammatory type 2 responses to occur. Genetics play a role in predisposing to disease, with well-known mutations such as *FLG* causing increased severity of AD, *S. aureus* colonization, and sensitization to FA. With Westernization and increased industrialization, the environment contains indoor and outdoor pollutants that have been shown to damage the epithelial barrier. A significant amount of research has been done in understanding the origin of allergy, but the incidence of allergic conditions continues to rise. Thus, we rely on current and future birth cohort studies to further grasp mechanistic, preventative, and treatment measures to be done.

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