




Advances and novel developments in environmental influences on the development of atopic diseases

Shifaa Suhayl Alkotob¹ | Cade Cannedy¹ | Katharina Harter²  | Hesam Movassagh¹ | Bibek Paudel¹ | Mary Prunicki¹  | Vanitha Sampath¹ | Tamara Schikowski³ | Eric Smith¹ | Qi Zhao³ | Claudia Traidl-Hoffmann^{2,4}  | Kari C. Nadeau¹ 

¹Sean N. Parker Center for Allergy and Asthma Research at Stanford University and Division of Pulmonary and Critical Care Medicine, Department of Medicine, Stanford University, Stanford, CA, USA

²Chair and Institute of Environmental Medicine, UNIKA-T, Technical University of Munich and Helmholtz Zentrum München, Augsburg, Germany

³IUF-Leibniz Institute for Environmental Medicine, Duesseldorf, Germany

⁴CK-CARE, Christine Kühne Center for Allergy Research and Education, Davos, Switzerland

Correspondence

Kari C. Nadeau, Sean N. Parker Center for Allergy and Asthma Research at Stanford University, Biomedical Innovations Building (BMI) - 240 Pasteur Dr, BMI 1755, Palo Alto, CA 94304, USA.
Email: knadeau@stanford.edu

Funding information

Sean N. Parker Center for Allergy and Asthma Research at Stanford University.

Abstract

Although genetic factors play a role in the etiology of atopic disease, the rapid increases in the prevalence of these diseases over the last few decades suggest that environmental, rather than genetic factors are the driving force behind the increasing prevalence. In modern societies, there is increased time spent indoors, use of antibiotics, and consumption of processed foods and decreased contact with farm animals and pets, which limit exposure to environmental allergens, infectious parasitic worms, and microbes. The lack of exposure to these factors is thought to prevent proper education and training of the immune system. Increased industrialization and urbanization have brought about increases in organic and inorganic pollutants. In addition, Caesarian birth, birth order, increased use of soaps and detergents, tobacco smoke exposure and psychosomatic factors are other factors that have been associated with increased rate of allergic diseases. Here, we review current knowledge on the environmental factors that have been shown to affect the development of allergic diseases and the recent developments in the field.

KEYWORDS

allergy, atopic disease, environment, exposome, pollution

1 | INTRODUCTION

Both genes and the environment shape human health and disease. Although IgE-mediated allergic diseases (atopic diseases) have a genetic component and are more prevalent in individuals with a family history of allergic disease, the observed rapid increases in allergic diseases suggest that environmental factors are the predominant driving forces behind these increases rather than genetic alterations.^{1,2} Common atopic diseases include atopic dermatitis, food allergy, allergic rhinitis, and allergic asthma. Human diets and lifestyle have undergone major alterations. The exposome, which is the sum

total of all the exposures of an individual in a lifetime, has undergone major shifts in the last few decades, affecting human health and disease.

A number of environmental factors have been implicated in the increased prevalence of allergic diseases. Predominant among them are increased exposure to pollutants and decreased exposure to microbes and parasitic infections. Air pollution has increased significantly in the last few decades. The hygiene hypothesis suggests that increased hygiene and lack of exposure to microbes and parasitic infections at an early age prevents the necessary stimulus to train the immune system to develop tolerogenic responses. Lifestyle factors,

such as increased time spent indoors, use of antibiotics, and consumption of processed foods and decreased exposure to farm animals and pets, limit exposure to environmental allergens, infectious parasitic worms, and microbes. The lack of exposure to these factors is thought to prevent proper education and training of the immune system. Continuous training through adulthood also appears to play a role in maintaining immune function. A study of healthy men in long-term isolation (1 year) in Antarctica found an imbalance of immune function toward a sensitizing of inflammatory pathways.³ Urbanization has led to reduced biodiversity of plants and animals, which has been associated with increased allergic disease. The biodiversity hypothesis states that contact with natural environments enriches the human microbiome, promotes immune balance and protects from allergy and inflammatory disorders.⁴ Other factors that are also associated with increased risk of allergic diseases are Caesarian birth, birth order, tobacco smoke exposure and psychosomatic factors (Figure 1).

Many of the factors that have been implicated in allergic diseases are affected by climate change.⁵ It is a risk multiplier that aggravates stressors. It is associated with greater variability in temperature, forest fires, heat waves, thunderstorms, droughts, and floods.⁶ Climate change has also been linked to increased concentrations and distribution of air pollutants such as CO₂, ozone, nitric oxide and other volatile organic chemicals. CO₂ has been shown to accelerate plant growth and the onset of pollen season, and increase pollen production, dispersion, allergen potency, and length and duration of the pollen season.^{7,8} Climate change has also brought about new pollen species not endemic to the area.⁹ Thunderstorms are increasing

in frequency and intensity and have been linked during the pollen season with increased asthma exacerbations and emergency room visits.^{10,11} Similarly, dust storms and wildfires have been shown to increase inflammatory responses and asthma exacerbations.¹²⁻¹⁴ Increases in the level and frequency of house dust mite exposure, sensitization, and asthma symptoms have been observed and is thought to be caused, in part, by global increases in temperature and humidity.¹⁵

Air pollutants appear to weaken the immune system and make one more susceptible to infections. COVID-19 appears to worsen in those people suffering from air pollution exposure, smoking, and vaping. In addition, global climate change makes access to health care worse (like in an extreme hurricane) and that will affect the marginalized and the elderly who have COVID-19. A nationwide, cross-sectional study in the United States found that a small increase in long-term exposure to PM_{2.5} leads to a large increase in the COVID-19 death rate.¹⁶

A number of recent high-throughput "omic" technologies are accelerating our understanding of allergic diseases and have revolutionized research and offer the promise of personalized medicine (Figure 2). The use of the term "omics" suggests a comprehensive high-throughput and systematic investigation of biological parameters. Examples of omic technologies include genomics, epigenomics, transcriptomics, proteomics, metabolomics, microbiomics, and exposomics.¹⁷ These technologies generate exponentially growing data sets requiring sophisticated bioinformatics and computational techniques that can integrate, analyze and interpret the data to generate hypothesis, which can

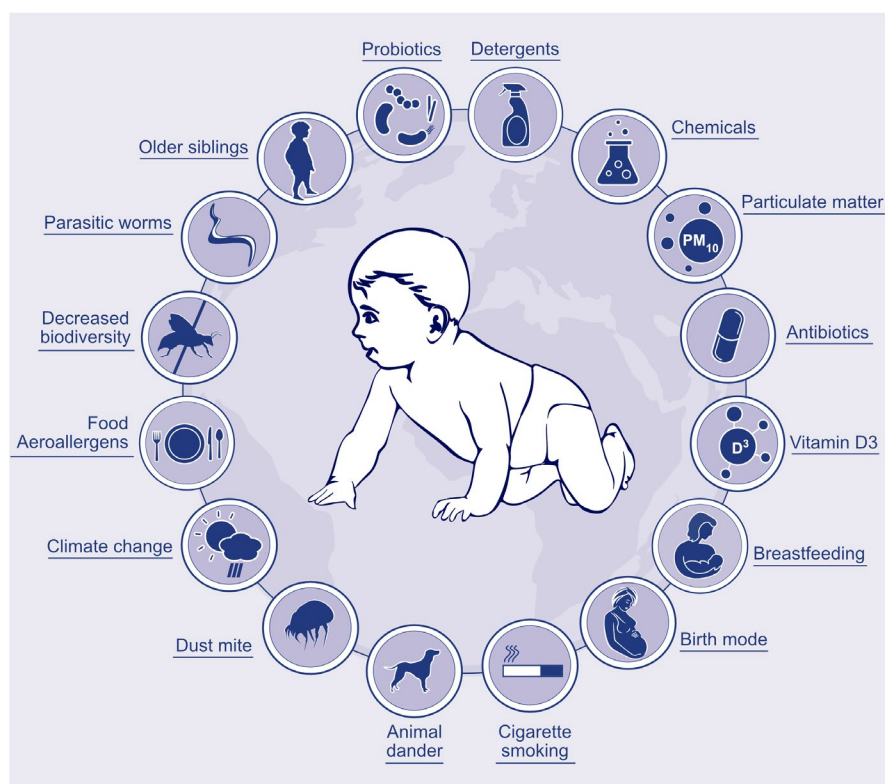


FIGURE 1 A number of environmental factors affect the development of allergy and tolerance in infants. The hygiene hypothesis suggests that increased hygiene and lack of exposure to microbes and parasitic infections at an early age prevents the necessary stimulus to train the developing immune system to develop tolerogenic responses. In modern societies, there is increased time spent indoors, use of antibiotics, and decreased contact with farm animals and pets, which limit exposure to environmental allergens, infectious parasitic worms, and microbes

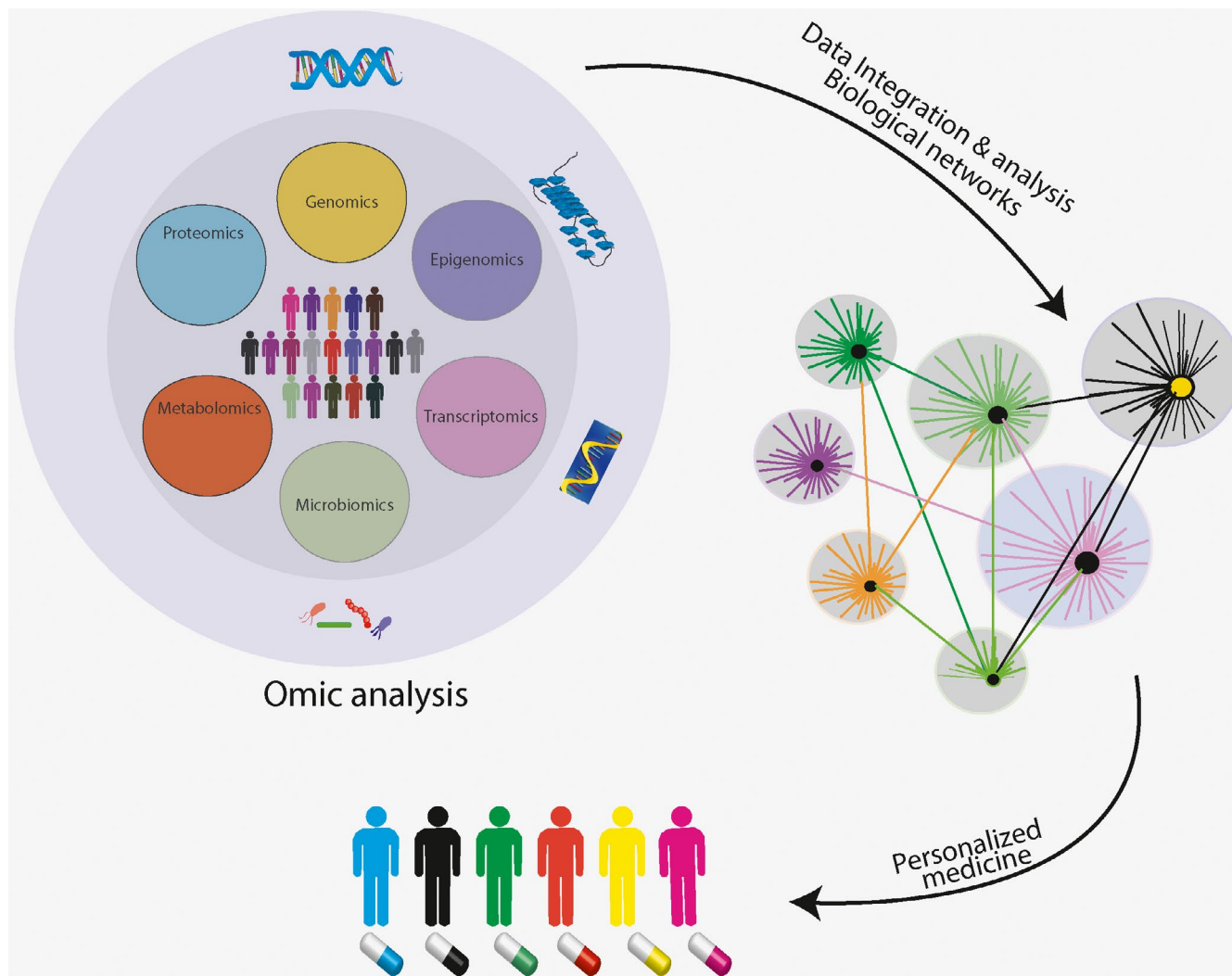


FIGURE 2 High-throughput omics technologies enable generation of large amounts of data that are analyzed and interpreted by sophisticated bioinformatics and computational tools to give us mechanistic information on immune pathways at the DNA, RNA, and protein level. This can allow for personalized medicine

then be further tested. Of these, epigenomics has been key in giving us insight to gene-environment interactions. It has provided us a greater understanding of the mechanisms by which environmental factors modulate epigenetic modifications and expression of genes involved in inflammatory responses and allergy. Technologies such as bisulfite sequencing, ATAC seq and cytometry by Time-Of-Flight (EpiTOF) have made it possible to study DNA methylation and histone modifications, and chromatin accessibility across the whole genome and at a single cell level.¹⁸⁻²¹ Here, we review current knowledge on the environmental factors that have been shown to affect the development of allergic diseases and the recent developments in the field. Research on the exposome can improve our understanding of the connections between environmental exposures and health to help mitigate adverse health outcomes and can provide a risk profile instead of single predictors and thus is particularly applicable to allergic diseases and asthma.²²

2 | FACTORS MODULATING ALLERGIC DISEASE

2.1 | Air pollution

2.1.1 | Direct effects

Air pollutants considered major risk factors for the development of allergic diseases are ground-level ozone, particulate matter (PM), carbon monoxide (CO), sulfur dioxide (SO₂), and nitrogen dioxide (NO₂).^{23,24} CO, SO₂, and NO₂ are released from combustion of fossil fuels. Ground-level ozone is a secondary pollutant that is produced when nitrogen oxides and volatile organic compounds released from industrial sources react in the presence of sunlight.

Particulate matter with diameters $\leq 10 \mu\text{m}$ or smaller (eg, PM₁₀ and PM_{2.5}) can carry organic and inorganic components such as heavy

metals and penetrate deeply into the respiratory tract and skin barrier. In a prospective birth cohort study of over 5000 children during the first 6 years of life, strong positive associations were found between the distance to the nearest main road and asthmatic bronchitis, hay fever, eczema, and sensitization.²⁵ An association between eczema and traffic-related pollutants was also found in children from small towns, where exposure to these traffic-related pollutants was much lower than in urban areas.²⁶ Some studies speculate that ultrafine particles (UFPs) with diameter ≤ 100 nm may have greater effects due to their increased capacity to penetrate the lung alveoli and cardiovascular system.²⁷ A recent meta-analysis estimated that increases in UFPs per 10 000 particles/cm³ were associated with 7%, 11%, and 5% increase in exacerbations, emergency department visits, and hospital admissions for asthma, respectively.²⁸

A recent study estimated that exposure to ambient NO₂ may cause 4 million new cases of pediatric asthma per year, with over 60% occurring in urban areas.²⁹ Norbäck et al observed robust relationships between lifetime exposure to NO₂ and allergic diseases including asthma, eczema, wheeze and rhinitis for children ages 3–6 years in China.³⁰ Similar associations have been observed with SO₂ and CO. A study by Penard-Morand et al found that SO₂ exposure significantly increases the prevalence of asthma in children.³¹ Similarly, Samoli et al³² found an association between SO₂ and PM₁₀ exposure and the number of pediatric asthma hospital admissions among children aged 0 to 14 years in Athens, Greece. Several time-series studies in China reported positive associations between exposure to CO within a few days and the risk of hospital admission/mortality from asthma.³³ Another Korean study found that for children aged 6–7 years, the odds ratio (OR) for lifetime allergic rhinitis was 1.10 per 100 ppb increase in CO concentration during the first year of life. In addition, the OR for current atopic dermatitis was 8.11 for every 1 ppb increase in the average CO concentration during the preceding 12 months.³⁴ In the US, the risk for emergency department visits was estimated to increase by 0.8% for asthma or wheeze and 3.7% for bronchitis per interquartile range (IQR) increase in the preceding 3-day average concentration of CO.³⁵

Ozone in the stratosphere is protective as it shields living things from ultraviolet radiation from the sun. However, ground-level ozone, which forms just above the earth's surface has been associated with adverse health effects. A birth cohort study in Canada reported that ozone exposure at birth was associated with the onset of asthma and allergic rhinitis during a follow-up at age 17.³⁶ In France, a higher annual outdoor concentration of ozone was associated with increased total IgE levels.³⁷ A study estimated that 7-day exposure to ozone was associated with significant increase in physician visits for atopic dermatitis, contact dermatitis and urticaria.³⁸

Volatile organic compounds (VOCs) have been associated with increased risk of allergic disease. A study found that indoor total VOC exposure at 6 months in children was correlated with atopic dermatitis at 3 years.³⁹ Diisononyl phthalate (DINP) is used as a plasticizer and is contained in many consumer products. Children are more likely to have exposure to phthalates than adults through ingestion of dietary sources or inhalation of dust from phthalate containing products. A study in first-grade elementary school children

found correlations between urinary phthalate metabolite concentrations and nasal patency and lower small airway dysfunction.⁴⁰

The pathophysiological mechanisms by which air pollution mediates allergic disease are poorly understood; however, oxidative stress, enhanced sensitization to allergens, inflammatory and immunological responses, and epigenetic modifications have been suggested as possible mechanisms.^{41–43} Exposure of human nasal epithelium cells to PM_{2.5} was found to decrease loss of barrier function, as determined by measures of transepithelial resistance, permeability, decreased expression of tight junction proteins, and production of proinflammatory cytokines, such as thymic stromal lymphopoietin (TSLP).⁴⁴ A genome-wide DNA methylation study found that long-term ambient air pollution exposure impacts DNA methylation of a number of genes, some of which play a role in inflammatory responses.⁴⁵ Short-term and long-term exposures to high levels of CO, NO₂, and PM_{2.5} were associated with alterations in differentially methylated regions of Foxp3.⁴⁶

2.1.2 | Indirect effect on plants and ecosystems

The effects of air pollution reported above on the increase in allergies directly affect the immune system or barrier function in humans. However, there is also an indirect effect: air pollution as well as other effects of climate change affect pollen, plants and biodiversity per se. Air pollution (and climate change) affect not only plant growth, pollen and flower production, and duration of the whole pollen season but can also display more indirect health effects by increasing the amount of allergenic encoding transcripts and proteins of the pollen.^{47,48} When ragweed plants were grown in climate chambers under controlled conditions and fumigated with enhanced levels of NO₂, transcript levels of Amb a 1, a major ragweed allergen, were up-regulated, indicating potentially higher allergenicity due to NO₂.⁴⁷ On exposure of ragweed to varying NO₂ levels during the growing season, a significantly higher allergenicity for Amb a 1 was observed.⁴⁸ Elevated CO₂ levels and drought stress were also found to increase Amb a 1.⁴⁹

Therefore, under global change scenarios, the allergenic potential of pollen is also expected to change. A study found that grass pollen exposure in the first months of life was associated with lower lung function later in childhood and adolescence.⁵⁰ Epidemiologic studies have demonstrated that urbanization, high levels of vehicle emissions, and westernized lifestyle are correlated to an increase in the frequency of pollen-induced respiratory allergy prevalent in people who live in urban areas compared to those who live in rural areas – this can in part be due to the effects of pollution on the pollen and plants themselves and therefore indirectly impacting human health.⁵¹

2.2 | Tobacco smoke and e-cigarettes

Epidemiological studies and meta-analyses indicate that pre- or post-natal maternal smoking increases the risk of wheezing and asthma

in children ≤ 2 years⁵² and that secondhand smoke during infancy without prior exposure in utero leads to an enhanced risk of food sensitization and eczema.⁵³ Tobacco smoke and e-cigarettes may mediate their effects via a number of inflammatory mechanisms. For instance, tobacco smoke provokes oxidative stress⁵⁴ which leads to upregulation of TSLP⁵⁵ and IL-33⁵⁶ suggestive of a pro type-2 inflammation in the lungs. In addition, phagocytic activity of alveolar macrophages from smokers is reduced compared to non-smokers.⁵⁷ Repetitive exposure to cigarette smoke in normal human airway epithelial cells was found to impact the adhesive intercellular junctions and disrupt monolayer integrity. Cortical tension of epithelial cells was observed due to increased actin polymer levels, which further destabilized cell adhesion.⁵⁸ Tobacco smoke may also mediate its effect through microbiome dysbiosis. A study found that sensitization to *Staphylococcus aureus* enterotoxins is increased in smokers with asthma, and it may be a marker of eosinophilic inflammation and severe asthma.⁵⁷ E-cigarettes were also found to be associated with inflammation. A study found that e-cigarette vapors and cigarette smoke altered virulence of key lung pathogens (*Haemophilus influenzae*, *Streptococcus pneumoniae*, *S aureus* and *Pseudomonas aeruginosa*), which may increase bacterial persistence and inflammatory potential.⁵⁹

2.3 | Microbiome

The microbiome has been shown to play a key role in the development of the immune system with microbiome dysbiosis mediating immune deviation.⁶⁰ Characterizing the constituents of the human gastrointestinal, skin, and airway microbiota as well as microbial peptides and metabolites that influence host immunity and immune response to allergens in food allergy, atopic dermatitis, and asthma is the focus of ongoing research.^{60,61} Composition of the microbiome has been found to vary even within an organ system, such as the skin, with variations in the microbiome observed between the scalp, arm, and axilla.⁶² Advances in our understanding of host-microbe interactions have been made possible by 16S rRNA sequencing, which permits precise identification and quantification of bacteria. 16S ribosomal RNA gene is a highly conserved locus in the bacteria genome, yet different in sequences among different bacterial species. Another approach is to sequence the total DNA present in one ecosystem using whole genome shotgun techniques, and subsequently map the genes related to microbes, including viruses and fungi.⁶³ These techniques have enabled us to make inroads in identifying the species found in a healthy microbiota and those that cause dysbiosis. In atopic dermatitis, *S aureus* has been shown to be clearly correlated with severity and to decrease during treatment and to rebound after the end of treatment indicating its use as a potential diagnostic and prognostic biomarker.⁶⁴ It is now recognized that early infancy offers a "critical window" of colonization during which microbial communities shape immune maturation.⁶⁵ In humans, this critical period appears to be within the first 100 days of life.⁶⁶ A number of ecological factors influence development of an infant microbiota and

understanding these factors is critical for developing preventative strategies.^{67,68} A study found that supplementing infants with a probiotic mixture together with at least partial breastfeeding corrected undesired changes in microbiota composition and function caused by antibiotic treatments or caesarean birth.⁶⁹

Studies in mice and humans have shown associations between intestinal bacteria and allergic response to food. In a murine model, germ-free mice were colonized with feces from healthy or cow's milk allergic (CMA) infants. The healthy and CMA mice showed different transcriptome signatures in ileal epithelium, and the healthy mice were protected against anaphylactic responses to cow's milk allergen. The study identified a clostridial species that protected against the allergic response.⁷⁰ In another study, microbiota from infants with a low bifidobacteria/Lachnospiraceae ratio orients the murine immune system toward a Th2 atopic profile with clinical symptoms of allergy.⁷¹ *Bifidobacterium breve* is a species commonly isolated from the intestines of healthy breastfed infants and from human milk and is thought to have a significant impact on the development of immune tolerance.⁷² In a longitudinal study of a Canadian child cohort, it was found that infants at risk of asthma showed gut microbial changes during the first 100 days of life. Four bacteria taxa were reduced in high-risk children and this was accompanied by reduced deregulation of enterohepatic metabolites. To understand causality, the same study also found that inoculating the four taxa of bacteria (*Lachnospira*, *Veillonella*, *Faecalibacterium*, and *Rothia*) in germ-free mice decreased airway inflammation.⁷³ A prospective study from infants through school age found that the gut microbiota of the allergic children were enriched in *Bifidobacterium* and depleted of *Lactobacillus*, *Enterococcus*, and *Lachnospira*.⁷⁴ Individuals with atopic dermatitis have reduced skin lipids and increases in *S aureus*.⁷⁵ A study found a correlation between *Staphylococcus* species-dominated dysbiosis in the skin microbiome and dysregulation of the skin barrier transcriptome in patients with AD, but whether the microbiome dysbiosis is the cause for or result of the skin barrier defect is unclear.⁷⁶ *Staphylococcus aureus* has also been directly correlated with increased expression of inflammatory cytokines, IL-4, IL-13, IL-22, and TSLP and with decreased expression of cathelicidin.⁷⁷ *C difficile* colonization during infancy was associated with a higher risk of developing allergic diseases during early childhood.⁷⁸

A number of factors affect the composition of either the skin or gut microbiome. Vaginal delivery, breast feeding, presence of older siblings and exposure to a variety of microorganisms promote healthy microbiota in infants. In contrast, Caesarean section, formula milk, and exposure to antibiotics have a negative impact.⁷⁹ Dietary factors also play a role in microbiome health. Some of these factors are discussed below.

2.3.1 | Diet

In addition to prebiotics and probiotics, other dietary factors that have been shown to play a role are vitamin D and omega-3 and omega-6 polyunsaturated fatty acids (PUFAs). A study found that

higher second trimester n-6 PUFAs were associated with atopic dermatitis in children of women with atopy.⁸⁰ A meta-analysis found that intake of ω -3 PUFA started during pregnancy may reduce the risk of sensitization to egg and peanut.⁸¹ Levels of ω -3 and ω -6 were measured in the second trimester and found that higher ω -6 PUFAs were associated with a higher risk of all respiratory outcomes among children if the mother has asthma, but that male children born to women with asthma and a higher PUFA ratio had the highest risk for asthma.⁸² A meta-analysis of ω -3 consumption suggests that introduction of fish at 6-9 months and routine consumption once a week reduces asthma and wheeze in children up to 4.5 years old.⁸³ The association between vitamin D insufficiency and increased risk of food allergies have been shown by multiple studies. While controlling for regional and population characteristics, places in northern latitudes were found to have more epinephrine autoinjector prescriptions than those in southern latitudes in both USA and Australia.^{84,85} In another study, food allergies were found to be more likely in infants with low vitamin D.⁸⁶ In children with asthma, vitamin D deficiency was associated with asthma severity and increased serum IgE levels.⁸⁷

2.3.2 | Farming environment and pet ownership

Childhood environments have been shown to play an important role in the protection against allergies. Individuals living at short distances from farms had a lower risk of atopy, as measured by IgE, compared with those living further away. This decrease in atopy risk was even greater for those who grew up on a farm.⁸⁸ Children in rural South African communities with higher exposure to pets and farm animals than children from urban communities were found to be at lower risk of allergic disease.⁸⁹ Marrs et al⁹⁰ reported an association between dog ownership at three months of age and protection against food allergies. However, urban children with pet exposure in the South African cohort had an increased rate of any allergy compared to urban children without pets so conflicting data exist regarding pet ownership in relation to allergies.⁸⁹

2.3.3 | Antibiotics

Antibiotic usage has been documented to perturb the gut flora of individuals, which places them at an increased risk for the development of allergies and asthma. In mice models of atopic dermatitis, antibiotic use was associated with significantly aggravated phenotypes, including clinical score, transepidermal water loss, and histopathology, compared to those treated with healthy feces or probiotics.⁹¹ Timing, dose, and frequency of antibiotics in prenatal and infant populations have also been associated with the development of childhood allergies and asthma.^{92,93} Short chain fatty acids (SCFAs) which are fermentation end products of insoluble fibers by intestinal microorganisms have been implicated in the maintenance

of epithelial integrity and IgA production.⁹⁴ Antibiotics-induced dysbiosis of intestinal microbiota has been shown to increase severity of atopic dermatitis in mice through alterations in SCFA's and decreases in the number of Foxp3⁺ T regulatory cells.⁹¹

2.3.4 | Vaginal vs caesarean section births

The composition of gut flora in children born by caesarean section (C-section) vs vaginal delivery is different and this difference in gut microbiota colonization may impact the development of the immune system.⁹⁵ A vaginal mode of birth exposes the baby to maternal vaginal and fecal flora.⁹⁶ Studies indicate that babies born via C-section have a higher incidence of allergy, atopy, and asthma, increased susceptibility to infectious wheezing⁹⁷ and decreased gut microbiome diversity.⁹⁸ In addition, long-term studies show greater incidence of childhood asthma up to the age of 12 years.⁹⁹

2.4 | Detergents

Soaps and detergents are now frequently used in households to maintain hygiene. As mentioned earlier, increased hygiene can prevent proper development of immune tolerance. Another drawback is that on contact with skin, they can lead to scaling, dryness, and swelling and commonly trigger AD flares.¹⁰⁰ Traditional alkaline soap increased transepidermal water loss and skin erythema, which are signs of prolonged damage to the skin barrier.¹⁰¹ Regular washing with soaps has been shown to decrease the thickness of the stratum corneum in atopic individuals making it detrimental to the skin barrier.¹⁰²

2.5 | Other factors

In addition to environmental and lifestyle factors, household composition has also been shown to affect the risk of allergic diseases. A study that followed 17 414 British children for 23 years found a strong association between the birth order of a child and the risk of hay fever.¹⁰³ Specifically, contact with older siblings was hypothesized to increase immunological protection due to an increase in infections in early childhood through unhygienic contacts with siblings. A study on 10 834 children enrolled in the Chicago Family Cohort Food Allergy study found that younger siblings of kids with food allergies had significantly less prevalence of food sensitization and clinical food allergy.¹⁰⁴

Current research shows that psychosocial stress and poor mental health in mothers increase the risk of allergic diseases in their children.¹⁰⁵⁻¹¹¹ Stressful life events in childhood, for example parental divorce, have also been shown to increase the risk for development of atopic eczema later in life.¹¹² Psychosocial stress might trigger or worsen allergic symptoms, while the interaction with protective or health-promoting factors is still poorly understood.^{113,114} Also, in

adults with allergies, psychoneuroimmunologic mechanisms might play an important role.¹¹⁵ An association of anxiety and depression with allergies was reported in many studies.^{116,117}

3 | SUMMARY AND FUTURE DIRECTIONS

There have been exciting new developments in understanding the role of the environment in mediating allergic diseases. Epigenetics, in particular, has provided us with better insight into how pollution and other environmental factors alter gene expression. Novel high-throughput technologies have enabled characterization of a healthy microbiota and the imbalance that is created with microbial dysbiosis.

Epidemiological studies have shown a natural history for the progression of atopic diseases, termed the atopic march, which starts with atopic dermatitis in early infancy subsequently progressing to food allergy, allergic rhinitis, and allergic asthma. It is now clear that these atopic diseases have a common underlying mechanism.

With allergic diseases increasing globally, there has been much interest in research to prevent, treat, or cure these diseases (Box 1). These are also increased interest in sensitive and specific biomarkers for diagnosis and for evaluation of disease severity and prognosis with therapy. With the understanding of the natural progression of the atopic diseases, studies are now in progress to determine whether by preventing skin sensitization and atopic dermatitis, we can prevent the subsequent manifestation of other atopic diseases, such as food allergy.¹¹⁸ Some of the basic cellular and humoral factors involved in Th2-mediated allergic diseases are well understood and have led to the development of biologics and other novel therapeutics, which are in various stages of development. Further research and a clearer understanding the role that genes, epigenetics, and the environment play in shaping our immune health at the DNA,

RNA, and protein level can further assist with the development of targeted therapies for treating allergic diseases.

CONFLICT OF INTEREST

Shifaa Alkotob, Vanitha Sampath, Cade Cannedy, Katharina Harter, Hesam Movassagh, Qi Zhao, Bibek Paudel, Mary Prunicki, Eric Smith, and Tamara Schikowski declare no conflict of interest. Claudia Traidl-Hoffmann reports grants for research and development of CK-CARE, Sebapharma, Töpfer, Traidl-Hoffmann is involved in Clinical trials with Assana; Data and Safety Monitoring Board member at Novartis Personal fees from Novartis, Töpfer, Sebapharma; Consultant and Advisory Board Member at Novartis, Sanofi, Lilly Pharma; Dr Nadeau reports grants from National Institute of Allergy and Infectious Diseases (NIAID), National Heart, Lung, and Blood Institute (NHLBI), and National Institute of Environmental Health Sciences (NIEHS); Food Allergy Research & Education (FARE), Director of World Allergy Organization (WAO) Center of Excellence at Stanford; Advisor at Cour Pharma; Co-founder of Before Brands, Alladapt, Latitude, and IgGenix; National Scientific Committee member at Immune Tolerance Network (ITN) and National Institutes of Health (NIH) clinical research centers; DSMB member for NHLBI, US patents for basophil testing, multifood immunotherapy and prevention, monoclonal antibody from plasmoblasts, and device for diagnostics.

ORCID

Katharina Harter  <https://orcid.org/0000-0001-7329-2532>

Mary Prunicki  <https://orcid.org/0000-0002-5511-8896>

Claudia Traidl-Hoffmann  <https://orcid.org/0000-0001-5085-5179>

[org/0000-0001-5085-5179](https://orcid.org/0000-0001-5085-5179)

Kari C. Nadeau  <https://orcid.org/0000-0002-2146-2955>

REFERENCES

1. Doll RJ, Joseph NI, McGarry D, Jhaveri D, Sher T, Robert H. Epidemiology of allergic diseases. In: Mahmoudi M, eds. *Allergy and asthma*. Cham: Springer; 2019.
2. Gilles S, Akdis C, Lauener R, et al. The role of environmental factors in allergy: a critical reappraisal. *Exp Dermatol*. 2018;27:1193-1200.
3. Feurecker M, Crucian BE, Quintens R, et al. Immune sensitization during 1 year in the Antarctic high-altitude concordia environment. *Allergy*. 2019;74:64-77.
4. Haahtela T. A biodiversity hypothesis. *Allergy*. 2019;74:1445-1456.
5. Fairweather V, Hertig E, Traidl-Hoffmann C. A brief introduction to climate change and health. *Allergy*. 2020;75:2352-2354.
6. Intergovernmental panel on climate change. Climate Change 2013: The Physical Science Basis. In; 2013.
7. Picornell A, Buters J, Rojo J, et al. Predicting the start, peak and end of the Betula pollen season in Bavaria, Germany. *Sci Total Environ*. 2019;690:1299-1309.
8. Beck I, Jochner S, Gilles S, et al. High environmental ozone levels lead to enhanced allergenicity of birch pollen. *PLoS One*. 2013;8:e80147.
9. D'Amato G, Chong-Neto HJ, Monge Ortega OP, et al. The effects of climate change on respiratory allergy and asthma induced by pollen and mold allergens. *Allergy*. 2020;75:2219-2228.
10. Harun NS, Lachapelle P, Douglass J. Thunderstorm-triggered asthma: what we know so far. *J Asthma Allergy*. 2019;12:101-108.

Box 1 Future directions

- Characterization of microbes in healthy and allergic individuals.
- Identifying type and optimal timing of introduction of probiotics and prebiotics for tolerance induction
- Identifying epigenetic alterations and changes in gene expression on exposure to pollutants
- Evaluating emollients as treatment for prevention of atopic dermatitis and other atopic disorders.
- Targeted therapy for precision medicine
- Identification of sensitive and specific biomarkers for diagnosis, evaluation of disease severity, and prognosis with therapy.
- Identification of molecular mechanisms of tolerance induction.

11. Woodhead M. Hospitals overwhelmed with patients after "thunderstorm asthma" hits Melbourne. *BMJ*. 2016;355:i6391.
12. James KA, Strand M, Hamer MK, Cicutto L. Health services utilization in asthma exacerbations and PM10 levels in rural Colorado. *Ann Am Thorac Soc*. 2018;15:947-954.
13. Reid CE, Jerrett M, Tager IB, Petersen ML, Mann JK, Balmes JR. Differential respiratory health effects from the 2008 northern California wildfires: a spatiotemporal approach. *Environ Res*. 2016;150:227-235.
14. Prunicki MM, Dant CC, Cao S, et al. Immunologic effects of forest fire exposure show increases in IL-1beta and CRP. *Allergy*. 2020;75(9):2356-2358.
15. Acevedo N, Zakzuk J, Caraballo L. house dust mite allergy under changing environments. *Allergy Asthma Immunol Res*. 2019;11:450-469.
16. Wu X, Nethery RC, Sabath BM, Braun D, Dominici F. Exposure to air pollution and COVID-19 mortality in the United States: a nationwide cross-sectional study. *medRxiv*. 2020.
17. Donovan BM, Bastarache L, Turi KN, Zutter MM, Hartert TV. The current state of omics technologies in the clinical management of asthma and allergic diseases. *Ann Allergy Asthma Immunol*. 2019;123:550-557.
18. Buenrostro JD, Wu B, Chang HY, Greenleaf WJ. ATAC-seq: a method for assaying chromatin accessibility genome-wide. *Curr Protoc Mol Biol*. 2015;109:212921-212929.
19. Schwartzman O, Tanay A. Single-cell epigenomics: techniques and emerging applications. *Nat Rev Genet*. 2015;16:716-726.
20. Cheung P, Vallania F, Warsinske HC, et al. Single-cell chromatin modification profiling reveals increased epigenetic variations with aging. *Cell*. 2018;173:1385.
21. Forno E, Wang T, Qi C, et al. DNA methylation in nasal epithelium, atopy, and atopic asthma in children: a genome-wide study. *Lancet Respir Med*. 2019;7:336-346.
22. Agache I, Miller R, Gern JE, et al. Emerging concepts and challenges in implementing the exposome paradigm in allergic diseases and asthma: a Practall document. *Allergy*. 2019;74:449-463.
23. United States Environmental Protection Agency. Criteria air pollutants. 2017. <https://www.epa.gov/criteria-air-pollutants#self>. Accessed May 15, 2020.
24. World Health Organization. Ambient air pollution: pollutants. 2020 <https://www.who.int/airpollution/ambient/pollutants/en/>. Accessed May 15, 2020.
25. Morgenstern V, Zutavern A, Cyrys J, et al. Atopic diseases, allergic sensitization, and exposure to traffic-related air pollution in children. *Am J Respir Crit Care Med*. 2008;177:1331-1337.
26. Kramer U, Sugiri D, Ranft U, et al. Eczema, respiratory allergies, and traffic-related air pollution in birth cohorts from small-town areas. *J Dermatol Sci*. 2009;56:99-105.
27. Ohlwein S, Kappeler R, Kutlar Joss M, Kunzli N, Hoffmann B. Health effects of ultrafine particles: a systematic literature review update of epidemiological evidence. *Int J Public Health*. 2019;64:547-559.
28. Li Q, Yi Q, Tang L, et al. Influence of ultrafine particles exposure on asthma exacerbation in children: a meta-analysis. *Curr Drug Targets*. 2019;20:412-420.
29. Anenberg SC. Global, national, and urban burdens of paediatric asthma incidence attributable to ambient NO2 pollution: estimates from global datasets. *Lancet Planet Health*. 2019;3:e166-e178.
30. Norbäck D, Lu C, Zhang Y, et al. Sources of indoor particulate matter (PM) and outdoor air pollution in China in relation to asthma, wheeze, rhinitis and eczema among pre-school children: synergistic effects between antibiotics use and PM10 and second hand smoke. *Environ Int*. 2019;125:252-260.
31. Penard-Morand C, Raherison C, Charpin D, et al. Long-term exposure to close-proximity air pollution and asthma and allergies in urban children. *Eur Respir J*. 2010;36:33-40.
32. Samoli E, Nastos PT, Paliatatos AG, Katsouyanni K, Priftis KN. Acute effects of air pollution on pediatric asthma exacerbation: evidence of association and effect modification. *Environ Res*. 2011;111:418-424.
33. Zhao Y, Hu J, Tan Z, et al. Ambient carbon monoxide and increased risk of daily hospital outpatient visits for respiratory diseases in Dongguan, China. *Sci Total Environ*. 2019;668:254-260.
34. Kim J, Han Y, Seo SC, et al. Association of carbon monoxide levels with allergic diseases in children. *Allergy Asthma Proc*. 2016;37:e1-e7.
35. Xiao Q, Liu Y, Mulholland JA, et al. Pediatric emergency department visits and ambient Air pollution in the U.S. State of Georgia: a case-crossover study. *Environ Health*. 2016;15:115.
36. To T, Zhu J, Stieb D, et al. Early life exposure to air pollution and incidence of childhood asthma, allergic rhinitis and eczema. *Eur Respir J*. 2020;55:1900913.
37. Rage E, Jacquemin B, Nadif R, et al. Total serum IgE levels are associated with ambient ozone concentration in asthmatic adults. *Allergy*. 2009;64:40-46.
38. Valacchi G, Fortino V, Bocci V. The dual action of ozone on the skin. *Br J Dermatol*. 2005;153:1096-1100.
39. Kwon JH, Kim E, Chang MH, et al. Indoor total volatile organic compounds exposure at 6 months followed by atopic dermatitis at 3 years in children. *Pediatr Allergy Immunol*. 2015;26:352-358.
40. Kim MA, Yon DK, Jee HM, et al. Association of phthalates with nasal patency and small airway dysfunction in first-grade elementary school children. *Allergy*. 2020;75:2967-2969. <https://doi.org/10.1111/all.14423>
41. Brandt EB, Biagini Myers JM, Acciani TH, et al. Exposure to allergen and diesel exhaust particles potentiates secondary allergen-specific memory responses, promoting asthma susceptibility. *J Allergy Clin Immunol*. 2015;136:295.
42. Munoz X, Barreiro E, Bustamante V, Lopez-Campos JL, Gonzalez-Barcala FJ, Cruz MJ. Diesel exhausts particles: Their role in increasing the incidence of asthma. Reviewing the evidence of a causal link. *Sci Total Environ*. 2019;652:1129-1138.
43. Naclerio R, Ansotegui IJ, Bousquet J, et al. International expert consensus on the management of allergic rhinitis (AR) aggravated by air pollutants: impact of air pollution on patients with AR: current knowledge and future strategies. *World Allergy Organ J*. 2020;13:100106.
44. Xian M, Ma S, Wang K, et al. Particulate matter 2.5 causes deficiency in barrier integrity in human nasal epithelial cells. *Allergy Asthma Immunol Res*. 2020;12:56-71.
45. Lee MK, Xu CJ, Carnes MU, et al. Genome-wide DNA methylation and long-term ambient air pollution exposure in Korean adults. *Clin Epigenetics*. 2019;11:37.
46. Prunicki M, Stell L, Dinakarparandian D, et al. Exposure to NO2, CO, and PM2.5 is linked to regional DNA methylation differences in asthma. *Clin Epigenetics*. 2018;10:2.
47. Zhao F, Durner J, Winkler JB, et al. Pollen of common ragweed (*Ambrosia artemisiifolia* L.): Illumina-based de novo sequencing and differential transcript expression upon elevated NO(2)/O(3). *Environ Pollut*. 2017;224:503-514.
48. Zhao F, Elkelish A, Durner J, et al. Common ragweed (*Ambrosia artemisiifolia* L.): allergenicity and molecular characterization of pollen after plant exposure to elevated NO2. *Plant Cell Environ*. 2016;39:147-164.
49. El Kelish A, Zhao F, Heller W, et al. Ragweed (*Ambrosia artemisiifolia*) pollen allergenicity: superSAGE transcriptomic analysis upon elevated CO2 and drought stress. *BMC Plant Biol*. 2014;14:176.
50. Lambert KA, Lodge C, Lowe AJ, et al. Pollen exposure at birth and adolescent lung function, and modification by residential greenness. *Allergy*. 2019;74:1977-1984.
51. Deng SZ, Jalaludin BB, Anto JM, Hess JJ, Huang CR. Climate change, air pollution, and allergic respiratory diseases: a call to action for health professionals. *Chin Med J (Engl)*. 2020;133:1552-1560.

52. Burke H, Leonardi-Bee J, Hashim A, et al. Prenatal and passive smoke exposure and incidence of asthma and wheeze: systematic review and meta-analysis. *Pediatrics*. 2012;129:735-744.
53. Thacher JD, Gruzdeva O, Pershagen G, et al. Parental smoking and development of allergic sensitization from birth to adolescence. *Allergy*. 2016;71:239-248.
54. Chao MR, Cooke MS, Kuo CY, et al. Children are particularly vulnerable to environmental tobacco smoke exposure: evidence from biomarkers of tobacco-specific nitrosamines, and oxidative stress. *Environ Int*. 2018;120:238-245.
55. Nakamura Y, Miyata M, Ohba T, et al. Cigarette smoke extract induces thymic stromal lymphopoietin expression, leading to T(H)2-type immune responses and airway inflammation. *J Allergy Clin Immunol*. 2008;122:1208-1214.
56. Kearley J, Silver JS, Sanden C, et al. Cigarette smoke silences innate lymphoid cell function and facilitates an exacerbated type I interleukin-33-dependent response to infection. *Immunity*. 2015;42:566-579.
57. Strzelak A, Ratajczak A, Adamiec A, Feleszko W. Tobacco smoke induces and alters immune responses in the lung triggering inflammation, allergy, asthma and other lung diseases: a mechanistic review. *Int J Environ Res Public Health*. 2018;15:1033.
58. Nishida K, Brune KA, Putcha N, et al. Cigarette smoke disrupts monolayer integrity by altering epithelial cell-cell adhesion and cortical tension. *Am J Physiol Lung Cell Mol Physiol*. 2017;313:L581-L591.
59. Gilpin DF, McGown KA, Gallagher K, et al. Electronic cigarette vapour increases virulence and inflammatory potential of respiratory pathogens. *Respir Res*. 2019;20:267.
60. Peroni DG, Nuzzi G, Trambusti I, Di Cicco ME, Comberiati P. Microbiome composition and its impact on the development of allergic diseases. *Front Immunol*. 2020;11:700.
61. Borbet TC, Zhang X, Muller A, Blaser MJ. The role of the changing human microbiome in the asthma pandemic. *J Allergy Clin Immunol*. 2019;144:1457-1466.
62. Perez Perez GI, Gao Z, Jourdain R, et al. Body site is a more determinant factor than human population diversity in the healthy skin microbiome. *PLoS One*. 2016;11:e0151990.
63. Ranjan R, Rani A, Metwally A, McGee HS, Perkins DL. Analysis of the microbiome: advantages of whole genome shotgun versus 16S amplicon sequencing. *Biochem Biophys Res Commun*. 2016;469:967-977.
64. Reiger M, Traidl-Hoffmann C, Neumann AU. The skin microbiome as a clinical biomarker in atopic eczema: promises, navigation, and pitfalls. *J Allergy Clin Immunol*. 2020;145:93-96.
65. Ver Heul A, Planer J, Kau AL. The human microbiota and asthma. *Clin Rev Allergy Immunol*. 2019;57:350-363.
66. Stiemsma LT, Turvey SE. Asthma and the microbiome: defining the critical window in early life. *Allergy Asthma Clin Immunol*. 2017;13:3.
67. Walter J, O'Mahony L. The importance of social networks-An ecological and evolutionary framework to explain the role of microbes in the aetiology of allergy and asthma. *Allergy*. 2019;74:2248-2251.
68. Sbihi H, Boutin RC, Cutler C, Suen M, Finlay BB, Turvey SE. Thinking bigger: how early-life environmental exposures shape the gut microbiome and influence the development of asthma and allergic disease. *Allergy*. 2019;74:2103-2115.
69. Korpela K, Salonen A, Vepsäläinen O, et al. Probiotic supplementation restores normal microbiota composition and function in antibiotic-treated and in caesarean-born infants. *Microbiome*. 2018;6:182.
70. Feehley T, Plunkett CH, Bao R, et al. Healthy infants harbor intestinal bacteria that protect against food allergy. *Nat Med*. 2019;25:448-453.
71. Maura A, Wopereis H, Yeop I, et al. Gut microbiota from infant with cow's milk allergy promotes clinical and immune features of atopy in a murine model. *Allergy*. 2019;74:1790-1793.
72. Cukrowska B, Bierla JB, Zakrzewska M, Klukowski M, Maciorkowska E. The Relationship between the infant gut microbiota and allergy. The Role of bifidobacterium breve and prebiotic oligosaccharides in the activation of anti-allergic mechanisms in early life. *Nutrients* 2020;12:946.
73. Arrieta MC, Stiemsma LT, Dimitriu PA, et al. Early infancy microbial and metabolic alterations affect risk of childhood asthma. *Sci Transl Med* 2015;7:307ra152.
74. Simonytė Sjödin K, Hammarström ML, Rydén P, et al. Temporal and long-term gut microbiota variation in allergic disease: a prospective study from infancy to school age. *Allergy*. 2019;74:176-185.
75. Lipsky ZW, Marques CNH, German GK. Lipid depletion enables permeation of *Staphylococcus aureus* bacteria through human stratum corneum. *Tissue Barriers*. 2020;8:1754706.
76. Altunbulakli C, Reiger M, Neumann AU, et al. Relations between epidermal barrier dysregulation and *Staphylococcus* species-dominated microbiome dysbiosis in patients with atopic dermatitis. *J Allergy Clin Immunol*. 2018;142:1643.
77. Nakatsuji T, Chen TH, Two AM, et al. *Staphylococcus aureus* exploits epidermal barrier defects in atopic dermatitis to trigger cytokine expression. *J Invest Dermatol*. 2016;136:2192-2200.
78. Lee SH, Gong YN, Ryoo E. Clostridium difficile colonization and/or infection during infancy and the risk of childhood allergic diseases. *Korean J Pediatr*. 2017;60:145-150.
79. Mohajeri MH, Brummer RJM, Rastall RA, et al. The role of the microbiome for human health: from basic science to clinical applications. *Eur J Nutr*. 2018;57:1-14.
80. Gardner KG, Gebretsadik T, Hartman TJ, et al. Prenatal omega-3 and omega-6 polyunsaturated fatty acids and childhood atopic dermatitis. *J Allergy Clin Immunol Pract*. 2020;8:937-944.
81. Vahdaninia M, Mackenzie H, Dean T, Helps S. omega-3 LCPUFA supplementation during pregnancy and risk of allergic outcomes or sensitization in offspring: a systematic review and meta-analysis. *Ann Allergy Asthma Immunol*. 2019;122:302.
82. Rosa MJ, Hartman TJ, Adgent M, et al. Prenatal polyunsaturated fatty acids and child asthma: effect modification by maternal asthma and child sex. *J Allergy Clin Immunol*. 2020;145:804.
83. Papamichael MM, Shrestha SK, Itsiopoulos C, Erbas B. The role of fish intake on asthma in children: a meta-analysis of observational studies. *Pediatr Allergy Immunol*. 2018;29:350-360.
84. Camargo CA Jr, Clark S, Kaplan MS, Lieberman P, Wood RA. Regional differences in EpiPen prescriptions in the United States: the potential role of vitamin D. *J Allergy Clin Immunol*. 2007;120:131-136.
85. Mullins RJ, Clark S, Camargo CA Jr. Regional variation in epinephrine autoinjector prescriptions in Australia: more evidence for the vitamin D-anaphylaxis hypothesis. *Ann Allergy Asthma Immunol*. 2009;103:488-495.
86. Allen KJ, Koplin JJ, Ponsonby AL, et al. Vitamin D insufficiency is associated with challenge-proven food allergy in infants. *J Allergy Clin Immunol*. 2013;131:1109-1116.
87. Mohammadzadeh I, Darvish S, Qujeq D, Hajiahmadi M, Vaghari-Tabari M. Association of serum 25-OH vitamin D(3) with serum IgE and the pediatric asthma severity score in patients with pediatric asthma. *Allergy Asthma Proc*. 2020;41:126-133.
88. Borlee F, Yzermans CJ, Krop EJM, et al. Residential proximity to livestock farms is associated with a lower prevalence of atopy. *Occup Environ Med*. 2018;75:453-460.
89. Levin ME, Botha M, Basera W, et al. Environmental factors associated with allergy in urban and rural children from the South African food allergy (SAFFA) cohort. *J Allergy Clin Immunol*. 2020;145:415-426.

90. Marrs T, Logan K, Craven J, et al. Dog ownership at three months of age is associated with protection against food allergy. *Allergy*. 2019;74:2212-2219.
91. Kim HJ, Lee SH, Hong SJ. Antibiotics-induced dysbiosis of intestinal microbiota aggravates atopic dermatitis in mice by altered short-chain fatty acids. *Allergy Asthma Immunol Res*. 2020;12:137-148.
92. Zven SE, Susi A, Mitre E, Nylund CM. Association between use of multiple classes of antibiotic in infancy and allergic disease in childhood. *JAMA Pediatr*. 2019;174(2):199-200.
93. Mitre E, Susi A, Kropp LE, Schwartz DJ, Gorman GH, Nylund CM. Association between use of acid-suppressive medications and antibiotics during infancy and allergic diseases in early childhood. *JAMA Pediatr*. 2018;172.
94. O'Mahony L. Short chain fatty acids modulate mast cell activation. *Allergy*. 2020;75(8):1848-1849.
95. Dominguez-Bello MG, Costello EK, Contreras M, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proc Natl Acad Sci USA*. 2010;107:11971-11975.
96. Stokholm J, Thorsen J, Chawes BL, et al. Cesarean section changes neonatal gut colonization. *J Allergy Clin Immunol*. 2016;138:881.
97. Higgins D, Karmaus W, Jiang Y, Banerjee P, Sulaiman IM, Arshad HS. Infant wheezing and prenatal antibiotic exposure and mode of delivery: a prospective birth cohort study. *J Asthma*. 2020;1:12.
98. Sandall J, Tribe RM, Avery L, et al. Short-term and long-term effects of caesarean section on the health of women and children. *Lancet*. 2018;392:1349-1357.
99. Keag OE, Norman JE, Stock SJ. Long-term risks and benefits associated with cesarean delivery for mother, baby, and subsequent pregnancies: systematic review and meta-analysis. *PLoS Medicine*. 2018;15:e1002494.
100. Ortiz de Frutos FJ, Torrel A, de Lucas R, et al. Patient perspectives on triggers, adherence to medical recommendations, and disease control in atopic dermatitis: the DATOP study. *Actas Dermosifiliogr*. 2014;105:487-496.
101. Khosrowpour Z, Ahmad Nasrollahi S, Ayatollahi A, Samadi A, Firooz A. Effects of four soaps on skin trans-epidermal water loss and erythema index. *J Cosmet Dermatol*. 2019;18:857-861.
102. White MI, Jenkinson DM, Lloyd DH. The effect of washing on the thickness of the stratum corneum in normal and atopic individuals. *Br J Dermatol*. 1987;116:525-530.
103. Strachan DP. Hay fever, hygiene, and household size. *BMJ*. 1989;299:1259-1260.
104. Gupta RS, Walkner MM, Greenhawt M, et al. Food allergy sensitization and presentation in siblings of food allergic children. *J Allergy Clin Immunol Pract*. 2016;4:956-962.
105. Brew BK, Lundholm C, Viktorin A, Lichtenstein P, Larsson H, Almqvist C. Longitudinal depression or anxiety in mothers and offspring asthma: a Swedish population-based study. *Int J Epidemiol*. 2018;47:166-174.
106. Smejda K, Polanska K, Merecz-Kot D, et al. Maternal stress during pregnancy and allergic diseases in children during the first year of life. *Respir Care*. 2018;63:70-76.
107. Magnus MC, Wright RJ, Roysamb E, et al. Association of maternal psychosocial stress with increased risk of asthma development in offspring. *Am J Epidemiol*. 2018;187:1199-1209.
108. Flanigan C, Sheikh A, DunnGalvin A, Brew BK, Almqvist C, Nwaru BI. Prenatal maternal psychosocial stress and offspring's asthma and allergic disease: a systematic review and meta-analysis. *Clin Exp Allergy*. 2018;48:403-414.
109. Rosa MJ, Lee AG, Wright RJ. Evidence establishing a link between prenatal and early-life stress and asthma development. *Curr Opin Allergy Clin Immunol*. 2018;18:148-158.
110. Chan CWH, Law BMH, Liu YH, et al. The association between maternal stress and childhood eczema: a systematic review. *Int J Environ Res Public Health*. 2018;15:395.
111. Braig S, Weiss JM, Stalder T, Kirschbaum C, Rothenbacher D, Genueneit J. Maternal prenatal stress and child atopic dermatitis up to age 2 years: the Ulm SPATZ health study. *Pediatr Allergy Immunol*. 2017;28:144-151.
112. Herberth G, Roder S, Bockelbrink A, et al. Stressful life events in childhood and allergic sensitization. *Allergol Select*. 2018;2:1-9.
113. Patterson AM, Yildiz VO, Klatt MD, Malarkey WB. Perceived stress predicts allergy flares. *Ann Allergy Asthma Immunol*. 2014;112:317-321.
114. Harter K, Hammel G, Kirchberger I, Traidl-Hoffmann C. Social and psychosocial effects on atopic eczema symptom severity - a scoping review of observational studies published from 1989-2019. *J Eur Acad Dermatol Venereol*. 2020.
115. Marshall GD, Tull MT. Stress, mindfulness, and the allergic patient. *Expert Rev Clin Immunol*. 2018;14:1065-1079.
116. Harter K, Hammel G, Krabiell L, et al. Different psychosocial factors are associated with seasonal and perennial allergies in adults: cross-sectional results of the KORA FF4 study. *Int Arch Allergy Immunol*. 2019;179:262-272.
117. Ronnstad ATM, Halling-Overgaard AS, Hamann CR, Skov L, Egeberg A, Thyssen JP. Association of atopic dermatitis with depression, anxiety, and suicidal ideation in children and adults: a systematic review and meta-analysis. *J Am Acad Dermatol*. 2018;79:448.
118. Brough HA, Nadeau KC, Sindher SB, et al. Epicutaneous sensitization in the development of food allergy: What is the evidence and how can this be prevented? *Allergy*. 2020;75:2185-2205.

How to cite this article: Alkotob SS, Cannedy C, Harter K, et al. Advances and novel developments in environmental influences on the development of atopic diseases. *Allergy*. 2020;75:3077-3086. <https://doi.org/10.1111/all.14624>