Clinical reviews in allergy and immunology

Environmental determinants of allergy and asthma in early life

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1. To describe the effect of microbial exposure and childhood infections on the risk of allergic disease.
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3. To determine the effect of environmental exposure from tobacco smoke and air pollution on allergic disease.

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Allergic disease prevalence has increased significantly in recent decades. Primary prevention efforts are being guided by study of the exposome (or collective environmental exposures beginning during the prenatal period) to identify modifiable factors that affect allergic disease risk. In this review we explore the evidence supporting a relationship between key components of the external exposome in the prenatal and early-life periods and their effect on atopy development focused on microbial, allergen, and air pollution exposures. The abundance and diversity of microbial exposures during the first months and years of life have been linked with risk of allergic sensitization and disease. Indoor environmental allergen exposure during early life can also affect disease development, depending on the allergen type, dose, and timing of exposure. Recent evidence supports the role of ambient air pollution in allergic disease inception. The lack of clarity in the literature surrounding the relationship between environment and atopy reflects the complex interplay between cumulative environmental factors and genetic susceptibility, such that no one factor dictates disease development in all subjects. Understanding the effect of the summation of environmental exposures throughout a child's development is needed to identify cost-effective interventions that reduce atopy risk in children. (J Allergy Clin Immunol 2017;140:1-12.)

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Like many chronic health conditions, allergic disease likely results from complex gene-environment interactions. Mapping of the human genome has advanced our understanding of genetic risk factors for allergic diseases. However, the increase in the

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prevalence of allergic disease over the past few decades has occurred too rapidly to be accounted for by changes in the genome alone and is more likely to be the result of changes in environmental factors that are in some cases accompanied by epigenetic changes. These observations have led to increasing interest in understanding the effect of the exposome on the development of atopic disease. In 2005, Christopher Wild framed our understanding of the exposome concept to include 3 types of exposures: (1) the general external environment, including factors such as urban-rural residence, climate, air pollution, social capital, and education; (2) one's specific external environment, including diet, physical activity, tobacco exposure, infection, and occupation; and (3) the internal environment, which includes the biological and metabolic/toxicological manifestations of these exposures in the body.[1] In this review we explore the effect of a variety of environmental exposures in early life that have been found to influence the development of allergic disease, with particular focus on exposures to microbes, allergens, and ambient air pollutants.

MICROBIAL EXPOSURE

The increase in the prevalence of allergic disease, particularly in the Western world, has coincided with significant environmental changes that have reduced microbial exposure in early life, such as improved sanitation and increased rates of immunization. Many have proposed that among genetically susceptible subjects, these changes in environmental conditions might alter normal development of the immune system and thus affect susceptibility to allergic disease, the basis of the hygiene hypothesis.[2] In this section we will discuss key findings from studies examining both endogenous and exogenous microbial exposures.

The host microbiome

The human microbiome consists of all microbial communities within the body, including the gut, airways, skin, and others. Alteration of the host microbiome is suspected to play a role in susceptibility to allergic disease, particularly during early life, coinciding with maturation of the immune system. Establishment of the microbiome begins *in utero* and is likely the result of maternal transmission.[3-5] During infancy, differences in the gut microbial environment between those who go on to have atopy and those who do not are apparent in the first few months of life. Reduced diversity of stool flora at age 1 month was predictive of atopic eczema at age 2 years and allergic sensitization and allergic rhinitis at age 6 years.[6]

Similarly, diversity of microbial species in the infant gut was shown to be inversely related to risk of atopic sensitization, allergic rhinitis, and eosinophilia.[7] Atopic children showed reduced early life colonization with *Lactobacillus* species,[8] *Bifidobacterium* species,[8,9] and *Bacteroides* species and increased colonization with *Clostridia* species[8] and yeasts.[9] A greater abundance of *Bacteroides* and *Lactobacillus* species has been associated with protection against allergy, whereas abundance of *Clostridia* species has been associated with wheezing, allergic sensitization, and atopic eczema.[10,11]

Microbial colonization of the airways also begins early in life. Colonization with *Streptococcus* species at age 2 months was associated with increased risk for earlier first lower respiratory tract illness, which has been linked to later asthma development.[12] Similarly, in a study from the Copenhagen Prospective Studies on Asthma in Childhood birth cohort, asymptomatic 1-month-old neonates colonized with *Streptococcus pneumoniae*, *Moraxella catarrhalis*, or *Haemophilus influenzae* through hypopharyngeal aspirate were at greater risk of a first wheezing episode, persistent wheeze, severe exacerbation of wheeze, and hospitalization for wheeze.[13] Lower airway colonization with these organisms was also associated with higher blood eosinophil counts and total IgE levels but not specific IgE levels at 4 years and with bronchodilator reversibility and development of asthma at age 5 years. In a study of children younger than 3 years hospitalized for virus-induced wheezing, 60% demonstrated nasopharyngeal colonization with *Streptococcus pneumoniae*, *Moraxella catarrhalis*, or *Haemophilus influenzae*, and this was associated with increased risk of recurrent wheezing episodes during the following year.[14] Importantly, antibiotic use might select for these organisms.[12]

Many factors can affect microbial colonization in infants and young children, including prenatal and postnatal antibiotic exposure, mode of delivery, and early diet. Wu et al[15] identified dose-dependent relationships between risk of childhood asthma and maternal urinary tract infections during pregnancy or infant antibiotic use during the first year of life. The increase in risk is presumably due to changes in the abundance and diversity of the host's commensal microbes, as demonstrated by Penders et al,[16] who reported that antibiotic use in infancy was associated with decreased abundance of *Bifidobacterium* and *Bacteroides* species.

Mode of delivery is also an important determinant of the infant microbiome,[17] although the effect of vaginal versus caesarean delivery on development of allergic disease is debated. Vaginally delivered infants tended to be colonized with vaginal (*Lactobacillus* species) and fecal (*Prevotella* species) flora, whereas infants born by means of caesarean section tended to be colonized by skin flora (*Staphylococcus* and *Corynebacterium* species),[17] with increased abundance of *Clostridium difficile* and reduced *Bifidobacterium* and *Bacteroides* species.[16] Meta-analyses of studies examining the association between delivery mode and allergic disease in Western countries found an increased risk of childhood asthma,[18,19] allergic rhinitis,[18] and food allergy[18] in children born by means of caesarean section compared with vaginal births. However, studies from outside the United States and Europe have not consistently shown these effects.[20-22]

Diet during early life can also be important for establishing the infant's microbiome. Breast-feeding was associated with greater microbial diversity compared with formula feeding,[23] and a recent study reported that breast-feeding was associated with a trend toward increased *Bifidobacterium* and reduced *Clostridia* species at 3 to 6 months of age.[24]

Despite this evidence, it remains unclear whether these differences in the infant microbiome promote development of allergy or merely serve as a marker of immune dysregulation early in life that leads to allergic disease.

The external microbial environment

Exposure to abundant and diverse microbes in the environment appears to augment the risk of allergic disease. The "biodiversity hypothesis" suggests that reduced exposure during childhood to the rich environmental microbiome inherent within natural green spaces impedes cultivation of a robust host microbial community, leading to immune dysregulation, although the exact mechanisms of this interplay are unknown.[25] To this effect, Ruokolainen et al[26] demonstrated that children living in homes surrounded by forests and agricultural land had lower rates of aeroallergen sensitization compared with their counterparts in industrialized environments.

In addition to environmental biodiversity, specific microbial products have been identified as key players in immune tolerance. Endotoxin, a component of gram-negative bacterial cell walls and a marker of microbial exposure, was among the first microbial products implicated in protection against atopic asthma and other allergic diseases.[27-30] The Allergy and Endotoxin cross-sectional survey found that higher levels of endotoxin in child mattresses were associated with reduced risk of allergic sensitization, hay fever symptoms, and atopic asthma.[27] The precise mechanism for this effect is not known. One theory suggests that increased exposure to environmental endotoxin leads to downregulation of inflammatory responses.[27] Others have suggested the protective effect is the result of polymorphisms within the *CD14* gene, which encodes a coreceptor for Toll-like receptor 4 with high specificity for LPS, and in fact, a recent systematic review found a significant gene-environment interaction between *CD14* polymorphisms and microbial exposure.[31] The timing of endotoxin exposure also appears to be important, with more significant protective effects seen with early-life exposure.[28,32]

The microbial environment within the home is dictated by its human and nonhuman occupants. For instance, homes with dogs contain richer and more diverse bacterial communities compared with homes without pets.[33] Differences in microbial exposure are seen with increasing family size,[15] as well as with certain activities of the occupants, particularly farming. It has long been recognized that the prevalence of allergic disease among the children of farmers is lower than in nonfarming families.[28,34-36] A number of studies have been conducted to identify farm-specific factors, such as consumption of raw milk[37-40] and exposure to high amounts of endotoxin in animal stables, that influence inception of allergic disease.

A recently published study compared the incidence of allergic disease in children from an Amish traditional farming community with those from a Hutterite community that, although genetically similar to the Amish, practices modern industrial farming. The authors reported a significantly lower prevalence of allergic disease in Amish children. Amish homes were found to contain higher levels of endotoxin in airborne house dust, and comparisons of bacteria isolated from mattress dust showed distinct microbial profiles between Amish and Hutterite households. To further examine the effects of the Amish environment on allergy, the authors administered Amish house dust intranasally to ovalbumin (OVA)–sensitized mice and demonstrated reduced airway hyperresponsiveness and bronchoalveolar lavage eosinophilia in response to OVA challenge. Conversely, intranasal administration of Hutterite house dust led to exacerbation of OVA-induced airway hyperresponsiveness and eosinophilia. Although the precise components responsible for this protective effect are unknown, the inhibitory effects of Amish house dust for OVA-mediated inflammation were reduced in mice deficient in myeloid differentiation response gene–88 and TIR-domain-containing adapter-inducing interferon-β (TRIF), suggesting the protective effects were primarily mediated by the innate immune response.[41]

Role of childhood respiratory tract infections

For asthma development in particular, there is abundant literature suggesting a critical role for viral respiratory tract infection in early life. Respiratory syncytial virus (RSV) and human rhinovirus (HRV) are most frequently associated with wheezing episodes in young children.[42-44] In the prospective cohort RSV Bronchiolitis in Early Life study, approximately 50% of the 206 infants with lower respiratory tract illness caused by RSV during the first 12 months of life subsequently had persistent asthma up to age 7 years.[45] Similarly, in a case-control study of infants hospitalized with RSV versus healthy control subjects followed to age 18 years, a significantly higher prevalence of current asthma was seen in the RSV group compared with the control group; RSV was the major risk factor in subsequent asthma development (odds ratio, 7.2; 95% CI, 2.1-23.9).[43]

Others have found that HRV infection might be equally or more important for development of asthma than RSV. Asthma development by school age was 4 times greater in wheezing infants with HRV infection compared with the incidence in infants with other viruses in one study.[44] In the Childhood Origins of Asthma (COAST) birth cohort, a group at high risk for development of asthma, HRV-induced wheezing in infancy was the strongest predictor of persistent wheezing at age 3 years and diagnosis of asthma at age 6 years.[46,47]

Prevention of viral infection in early life has been proposed as a strategy for primary prevention of asthma, but thus far, this has not been possible given the difficulties with synthesizing an effective vaccine against HRV. A few trials have been conducted with palivizumab, or RSV-specific IgG. Simoes et al[48] reported a lower incidence of recurrent wheezing in premature infants treated with palivizumab compared with untreated control subjects. In a randomized controlled trial Blanken et al[49] found that premature infants receiving palivizumab had fewer wheezing days during the first year of life. Whether these effects would translate into reduced incidence of asthma remains unknown.

INDOOR ALLERGEN EXPOSURE

The indoor environmental allergen milieu is of particular interest in the study of the determinants of allergic disease because of constant exposure during early childhood and the potential for intervention. In samples taken from 831 homes across the United States, at least 6 detectable allergens were found in more than 50% of homes.[50] Allergens from house dust mite (HDM), furred pets (cats and dogs), mice, cockroaches, and fungi comprise the most common indoor allergens implicated in patients with atopic disease.[51-53] The strong relationship between allergic sensitization and development of allergic rhinitis and asthma has been well documented.[53-57] Recently, Rubner et al[54] demonstrated that aeroallergen sensitization before the age of 5 years significantly increased the risk of asthma with persistence into adolescence. Although the role of allergen sensitization in the pathogenesis of allergic rhinitis and asthma is clear, the causal relationship between individual allergen exposure and the development of these conditions has been more difficult to delineate, likely because of the complexity of interactions between various environmental factors, the timing and dose of exposure, and genetic predisposition. Similarly, the direct effect of indoor allergens on the development of atopic dermatitis (AD) has not been clearly established, although the correlation between indoor allergen sensitization and disease activity is better understood.[58-60] In turn, AD enhances the development of allergic rhinitis and asthma by providing an epicutaneous route of sensitization to aeroallergens through transepidermal water loss and epidermal barrier dysfunction.[61] In this section we briefly discuss some of the existing literature surrounding each of the indoor allergens and their role in allergic disease.

HDM exposure

HDM allergen has long been implicated as an important determinant of atopic disorders. An early prospective study by Sporik et al[62] followed 65 children from birth to age 11 years and demonstrated increased risk of allergic sensitization and asthma in children exposed to high levels of HDM during the first year of life. Subsequently, similar studies have provided evidence for a causal relationship between HDM sensitization early in life and allergic rhinitis, persistent wheeze, and asthma.[63-67] Although sensitization has a positive correlation with asthma development, studies from European birth cohorts have established that exposure to HDM alone is not sufficient to incur an increased risk of asthma,[68,69] indicating that IgE sensitization is the bridge between allergen exposure and asthma development; however, innate immune responses triggered by HDM have also been implicated in allergic disease pathogenesis.[70] Tovey et al[71] suggest a nonlinear dose-response relationship between HDM exposure and development of allergic disease, with exposure to both very low and very high levels of allergen correlating with decreased risk of sensitization and asthma and exposure to intermediate levels of allergen correlating with increased risk. Whether host or concomitant environmental factors alter the otherwise positive association between HDM exposure and atopy at these critically low and high levels remains unknown. Exposure to intermediate concentrations of HDM allergen has also been linked to atopic disease severity.[72,73] More recent studies have focused on differing routes of early HDM exposure, such as placental and breast milk transfer, as additional potential risk factors for development of allergic respiratory disease.[74,75]

Household pest exposure

In addition to HDM, exposure to mouse and cockroach allergens has been linked to allergic disease prevalence and severity, particularly in urban settings.[76-86] In a prospective birth cohort of 505 infants of atopic parents from the metropolitan Boston area, Gold et al[79] found that exposure to cockroach allergen levels in the family room of greater than 0.05 U/g of dust was an independent predictor for early wheeze. Evidence for cockroach exposure as a risk factor for persistent wheeze and asthma was provided by an evaluation of 222 siblings of the above infants, with those exposed to higher concentrations of allergen having the greatest risk.[80] Data from the same Boston cohort also illustrated an association between early mouse allergen exposure and early wheeze[82] and a nonstatistically significant trend toward predicting asthma, allergic rhinitis, and AD at 7 years of age.[87] In a similar prospective study of infants followed for 3 years, Donohue et al[78] not only found a significant effect of mouse and cockroach sensitization on the prevalence of AD, allergic rhinitis, and asthma but also demonstrated a dose-response relationship between higher cockroach or mouse-specific IgE levels and increased prevalence of allergic disease. Thus the evidence for mouse and cockroach allergen exposure predicting the development of atopic disorders, especially in inner-city children, is compelling.

Furred pet exposure

In contrast, a plethora of contradictory associations exists between furred pet exposure and development of atopy. Studies examining the link between pet ownership and risk of atopic disease have generally focused on the most common household pets, cats and dogs, or examined pet keeping in general. The ubiquitous nature of cat and dog allergens[88-90] makes epidemiologic studies assessing the risk of "exposure" quite difficult. To this effect, Liccardi et al[91] questioned whether surveys regarding the presence of pets in the home or home allergen measurements are sufficient to accurately convey a subject's exposure.

A number of systematic reviews examining the effect of pet exposure on allergic disease have been conducted, a few of which will be highlighted here. Takkouche et al[92] reviewed cohort studies from 1996-2007 that assessed pet allergen exposure. Although dog exposure had no significant effect on asthma, exposure to cat allergen yielded a relative risk for asthma of 0.72 (95% CI, 0.55-0.93); exposure to either pet was found to be slightly protective for allergic rhinitis (relative risk, 0.79; 95% CI, 0.68-0.93). No associations between asthma and early exposures to cat and dog allergens were found in 17 and 13 birth cohorts included in a systematic review, respectively.[93] Finally, pooled analysis of data from 11 European birth cohorts found no effect of early pet ownership on asthma development or allergic rhinitis when examining mutually exclusive pet ownership categories (cat only, dog only, cat and dog only, bird only, or rodent only).[94] Overall, the cumulative evidence suggests no increase in risk of allergic disease from pet allergen exposure, with a possible decreased risk of asthma associated with cat allergen exposure in one study. More recent studies focus on subgroup analyses, which might explain some of the variability in results of existing data.[95]

Indoor fungal exposure

Similar to pet allergens, fungi are ubiquitous in both indoor and outdoor environments, and both predictive and protective associations of indoor fungal exposure on atopic disorders have been discovered. Qualitative assessments of fungal exposure in the form of mildew odor or visible mold have been linked to increased risk of allergic rhinitis and asthma.[96-98] This finding is corroborated by studies using quantitative fungal measures, such as DNA-based analyses[99] and β-1,3-glucan measurements.[100,101] In a longitudinal birth cohort of high-risk infants, Iossifova et al[97,100] demonstrated an increased risk of asthma with exposure to low levels of β-1,3-glucan but a protective effect on exposure to levels of β-1,3-glucan greater than 60 μg per gram of dust, suggesting a possible nonlinear dose-response relationship similar to that observed for HDM allergen. However, although increased levels of β-1,3-glucan might indicate greater fungal concentrations, it could also represent a more diverse fungal population. In fact, exposure to greater fungal diversity offered protection against sensitization to aeroallergens and early childhood wheeze in a German longitudinal birth cohort, mirroring the protective effects of microbial diversity in the human microbiome.[102] Importantly, the predictive effect of fungal exposure on asthma development seems to occur independently of fungal sensitization. Zhang et al[103] demonstrated that nonallergenic components of fungi promote T_H17 responses through direct activation of innate immune receptors. Fungal components also potentiate allergen-induced T_H2 responses through non–IgE-mediated pathways. The mechanism by which greater fungal diversity confers protection against allergic disease remains unclear.

Overall, convincing data exist for the role of environmental indoor allergens in the pathogenesis of allergic disorders. The positive effect of multifaceted environmental interventions on disease prevalence and morbidity[104,105] highlights this point. Further studies are needed that examine the complex interplay of environment and genetics to determine the most effective intervention strategies for reducing the risk of allergic disease.

AMBIENT AIR POLLUTION EXPOSURE

Great strides have been made in understanding the effects of environmental air pollutants on population health, which has affected environmental health policy and consequently improved public health. However, despite overall improvements in air quality, indoor and outdoor air pollutants continue to cause adverse health effects and have been shown recently to promote the onset of atopic disease.

The World Health Organization reported in 2016 that 92% of the world's population lives in places where air quality levels exceed the World Health Organization's ambient air quality guidelines for annual mean particulate matter (PM) with a diameter of less than 2.5 μm ($PM_{2.5}$).[106] Those thought to be especially susceptible to the effects of air pollution include the very young and those of lower socioeconomic status because of increased exposure to pollutants in poor housing conditions. The respiratory tract is particularly susceptible to air pollution because of continuous exposure to the ambient environment. In this section we will discuss the effects of 2 key sources of environmental air pollution, traffic-related air pollution (TRAP) and environmental tobacco smoke (ETS), on the development of allergic airway disease. Markers of TRAP include (but are not limited to) carbon monoxide, nitrogen oxides, black carbon, PM, benzene, and ultrafine particles.

Effects of TRAP on lung development and asthma risk

Numerous studies throughout the world have shown that TRAP (particularly $PM_{2.5}$) negatively affects lung development[107-109] with potential consequences for the development of asthma and chronic obstructive pulmonary disease. The effects of early-life exposure, both prenatal and postnatal, are of particular interest in efforts to prevent detrimental effects on lung development.

The Spanish Infancia y Medio Ambiente cohort examined the association of TRAP exposure during specific trimesters of pregnancy on lung function in children aged 4.5 years.[110] Exposure to higher levels of benzene and nitrogen dioxide (NO_2) during the second trimester of pregnancy was associated with increased risk of clinically significant low lung function (FEV_1 <80% of predicted value). These studies collectively demonstrate that exposure to air pollution has systemic implications, with significant consequences for fetal lung development. Efforts to promote prevention focus on examination of prenatal exposures on asthma development. The Asthma Coalition on Community, Environment and Social Stress project, an urban pregnancy cohort, found that prenatal exposures to black carbon and PM were associated with a significant risk of wheezing by age 2 years.[111] Moreover, exposure to increased $PM_{2.5}$ levels during the second trimester of pregnancy was significantly associated with asthma at age 6 years, particularly in boys.[112]

Postnatal exposure to TRAP, particularly during the first years of life, is also an important determinant of lung function and asthma development. A birth cohort from the Boston metropolitan area recruited between 1999 and 2002 demonstrated that TRAP was associated with reduced lung development in elementary school–aged children, as measured by means of spirometry.[113] Despite improvements in $PM_{2.5}$ levels (less than current US Environmental Protection Agency standards) for most of the cohort during the study, lifetime and prior year exposure to TRAP was associated with a reduction in forced vital capacity, and exposure to $PM_{2.5}$ was specifically associated with higher odds of clinically significant airway obstruction. A Swedish birth cohort examined the effect of TRAP during the first year of life on lung function in later childhood.[114,115] At age 8 years, exposure to PM measuring between 2.5 and 10 μm in diameter during the first year of life had a bigger effect on reduced FEV_1 in children sensitized to food and aeroallergens, with less effect on lung function if exposure occurred later in childhood. Additionally, high exposure to NO_2 during the first year of life was associated with increased odds of having significantly decreased FEV_1 and forced vital capacity values.

Although many studies have demonstrated an association between early-life exposure to pollutants and asthma or persistent wheezing,[116-123] conflicting evidence recently emerged from a cross-sectional examination of 5 European birth cohorts in which no associations were found between air pollutant exposure and asthma prevalence.[124] To further examine these discrepancies, a recent longitudinal examination using birth cohort data from more than 14,000 children from The Netherlands, Germany, and Sweden evaluated the relationship of annual air pollution concentrations (from birth through age 14-16 years) with asthma and rhinoconjunctivitis incidence and prevalence.[125] This study, using both meta-analyses and pooled analyses, found that increasing exposure to NO_2 and $PM_{2.5}$ at the birth address was associated with increased asthma incidence through adolescence. There was no effect of air pollutants on rhinoconjunctivitis. Other European and North American cohorts have shown that increased

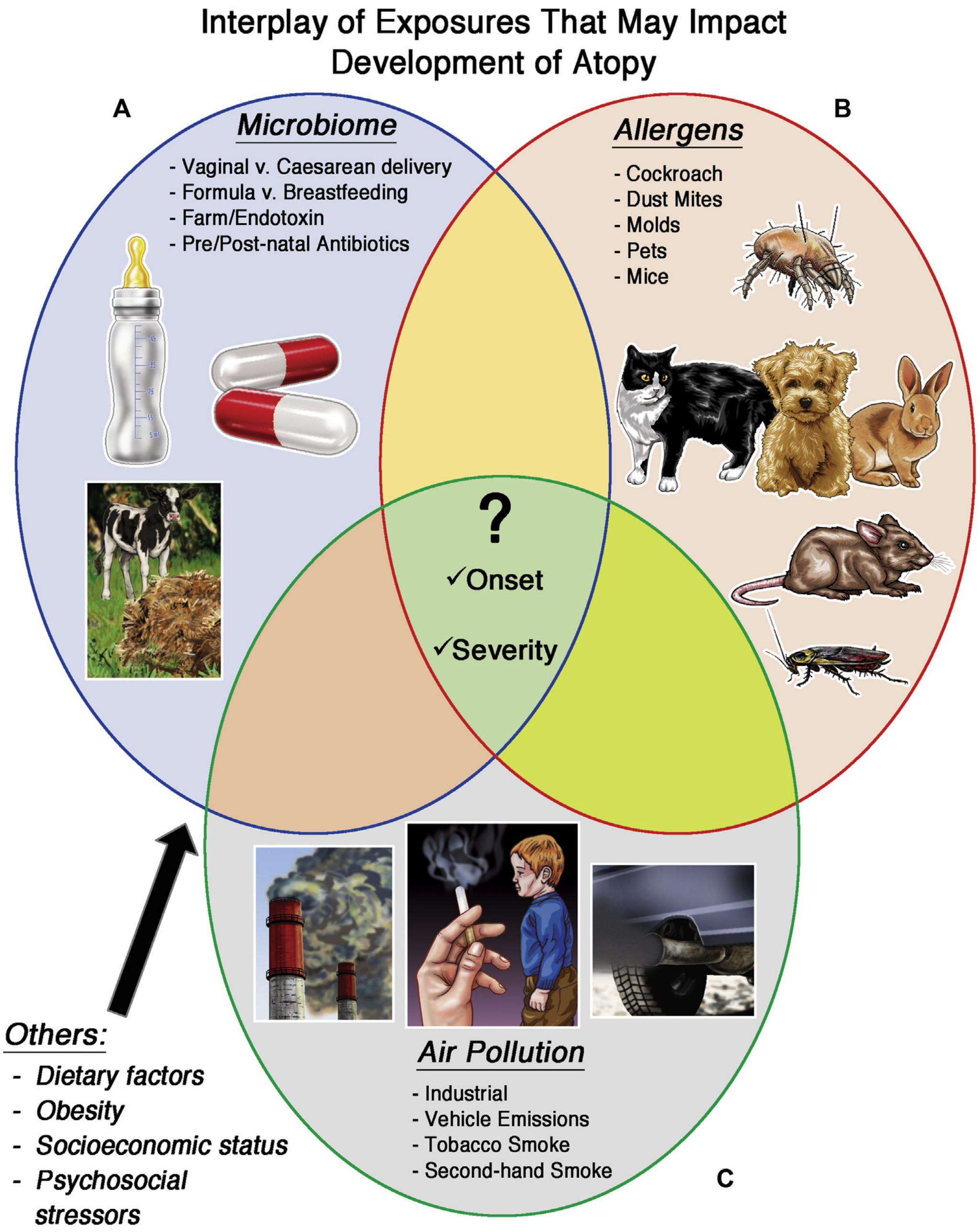

FIG 1. Interplay of early-life exposures that affect allergic disease development. Allergic disease development is influenced by many different factors. This figure displays several of the identified environmental triggers that increase susceptibility to allergic disease. **A,** Common behaviors and determinants that influence a subject's microbiome and external microbial environment, thereby influencing susceptibility to allergic disease. **B,** Allergens that have been linked to development of atopy. **C,** Air pollution exposures that not only influence lung function but also contribute to the immune response. Collectively, this Venn diagram demonstrates the overlapping contributions of each exposure. The center of the figure shows the questions that have yet to be elucidated, including how any of the numerous combinations of these common exposures influence the onset of disease or affect disease severity.

childhood exposure to $PM_{2.5}$ and black carbon was associated with increased risk of asthma at age 12 years.[126]

Effects of ETS on asthma and allergy risk

However, the most profound prenatal and early-life influences of air pollution emerge from ETS. Despite great improvements in reducing the rate of smoking and second-hand smoke (SHS) exposure in the US population, approximately 25% of nonsmokers in the United States (58 million people) were still exposed to SHS in 2011-2012.[127] Of these, 15 million were children aged 3 to 11 years. ETS exposure has been identified as a major risk factor for asthma[128,129] and allergic sensitization,[130] especially with *in utero* or

TABLE I. Early-life exposures affecting allergic disease development

Protective against allergic disease	References	Promoting allergic disease	References
Vaginal birth	16-19	Prenatal/postnatal antibiotics	15,16
Increased microbial/fungal diversity	6-11, 23-26, 102	Viral lower respiratory tract infection (RSV, HRV)	42-47
Increased no. of siblings; later birth order	15	HDM, cockroach, mouse, and fungal exposure	62-67, 71-86, 96-101
Farm exposure	28, 34-40	Prenatal/postnatal exposure to air pollution	110-123, 125,126, 133-136
Endotoxin exposure	27-33	Prenatal/postnatal tobacco smoke exposure	131, 132, 138-140

early-life exposures. The health effects of maternal exposure to SHS have more recently been elucidated. Pooled analyses from 15 European birth cohorts found that children whose mothers were exposed to SHS during pregnancy were more likely to wheeze at age 2 years; this risk was further increased by postnatal SHS exposure and further increased in children of atopic families.[131] SHS exposure during pregnancy alone (in nonsmoking mothers) was recently found to be associated with physician-diagnosed asthma at age 7 years.[132] With the increasing popularity of e-cigarettes throughout the world, it will be imperative to examine the effects of vaporized nicotine, vehicles (eg, propylene glycol), and an endless variety of flavoring agents on the development of asthma and airway disease.

Pollutants and allergen sensitization

A Swedish birth cohort[133] found that high exposure to NO_2 during the first year of life was associated with increased risk of sensitization to pollens (assessed by means of blood IgE measurement) at age 4 years and food sensitization at age 8 years. In North American cohorts diesel exhaust particle exposure in the first year of life was associated with greater aeroallergen sensitization in early childhood than in children with low exposure.[134,135] Children who were aeroallergen sensitized and had high exposure to TRAP during the first year of life had an almost 3-fold higher risk of asthma development compared with children who were not sensitized to allergens,[135] nor did sensitization alone increase the risk of asthma in children exposed to low levels of TRAP, suggesting that the combination of early-life pollutant exposure and allergic sensitization contributes to asthma development.

Exposure to increased levels of TRAP during infancy has also been associated with atopy to foods and perennial aeroallergens at age 1 year.[136] These effects might extend to the prenatal period. The EDEN birth cohort study found that increased maternal exposure to PM measuring between 2.5 and 10 μm in diameter was associated with reduced numbers of infant regulatory T (Treg) cells and increased $CD8^+$ T-cell numbers at birth,[137] with potential to increase the risk of atopy development and/or affecting responses to viral infection in these infants.

The strongest links between pollutant exposure and allergic sensitization relate to ETS exposure. In the absence of maternal smoking, exposure to SHS in infancy was associated with an increased risk of food sensitization at age 4, 8, and 16 years[138] and an increased risk of eczema with allergic sensitization. The German Lifestyle and Environmental Factors and their Influence on Newborns Allergy risk birth cohort found that increased exposure to products of ETS during pregnancy was associated with increased eosinophil/basophil progenitor cell counts in cord blood and that cord blood IL-4 and IL-13 levels were associated with the development of these progenitor cells.[139] This group later described that maternal smoking or ETS exposure during pregnancy was associated with reduced numbers of infant Treg cells at birth and that these infants with reduced numbers of Treg cells had increased risk of allergic sensitization in the first year of life.[140]

Potential mechanisms for effects of air pollution on development of atopic disease

Recent mechanistic studies investigating the effect of pollutant exposure on the development of allergic disease have been guided by key findings from birth cohorts, including the role of oxidative stress on promoting epigenetic modifications that regulate gene expression of Treg cells through microRNAs (miRNAs) and DNA methylation.[129,141] miRNAs are small noncoding RNAs that repress target protein expression through numerous mechanisms, including destabilizing mRNA and translational silencing.[142] ETS exposure during pregnancy was associated with increased maternal and cord blood expression of miRNA-223,[143] an miRNA previously linked with Treg cell development and function.[144-146] Increased miRNA-223 expression was associated with reduced Treg cell numbers in maternal and cord blood; in turn, these reduced Treg cell numbers at birth were associated with increased risk of AD during the first 3 years of life.

Among the most common mechanisms for epigenetic modifications is DNA methylation, in which increased methylation at the promoter and the 3′ end silences a gene, negatively correlating with gene expression. Increased forkhead box P3 methylation from salivary DNA was associated with increased pollutant exposure during childhood, affecting both increased risk of asthma diagnosis at age 7 years[147] and asthma severity.[148] Although pollutant-induced epigenetic modifications are not restricted to Treg cell development and function, their dysregulation has potential to affect the development of allergic disease over the lifespan.[149]

CONCLUSIONS AND FUTURE DIRECTIONS

The effect of microbial, allergen, and air pollutant exposures has been artificially subdivided in this review; in reality, these exposures and many others interact simultaneously with

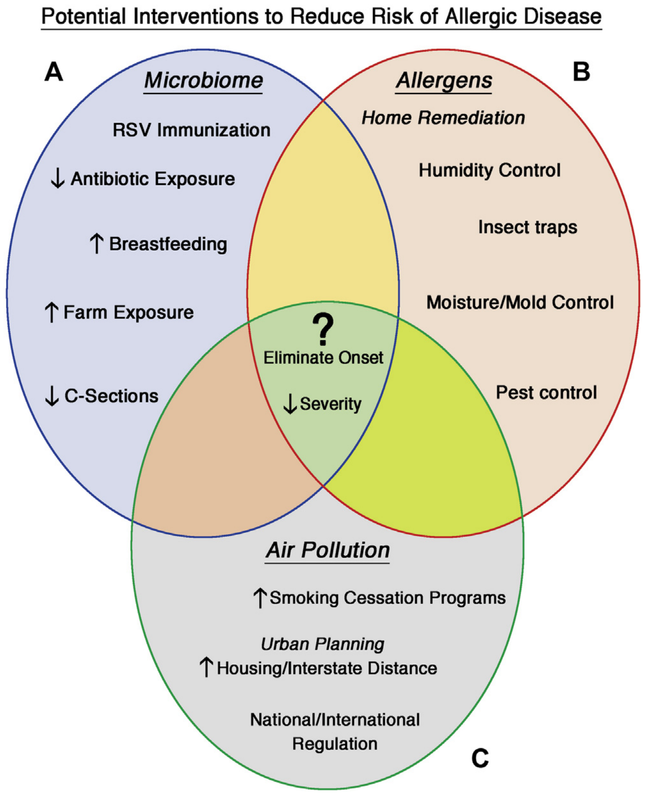

FIG 2. Potential interventions reducing the risk of allergic disease development. **A,** Certain modifications can positively influence a subject's microbiome or select for a protective external microbial environment. **B,** Reducing the quantity of allergen exposure might reduce development of allergic disease. **C,** Although the highest pollutant exposures occur from exposure to ETS, mitigating industrial and TRAP exposures will have to come from national and local regulatory agencies throughout the world. The center of the figure highlights the questions that have yet to be elucidated. Could these interventions affect the incidence of allergic disease, and if so, which are the most pragmatic and cost-effective and have the highest potential effect in different societies? *C-section*, Caesarian section.

each other to promote or prevent allergic disease (Fig 1). For example, air pollution and climate change can promote oxidative stress in pollen-producing plants, increasing both the amounts and allergenicity of pollen grains.[150] Individual factors identified in this review as protective for or promoting the development of atopy are summarized in Table I.* The types of exposures explored here are in no way exhaustive because many other exposures in early life have been linked to allergy and asthma development, including diet, obesity, pharmaceuticals, lifestyle factors, and maternal psychological stress in the prenatal and postnatal period. For example, vitamin D deficiency in the first decade of life was recently associated with increased susceptibility to sensitization and AD by age 3 years and increased risk of persistent asthma by age 10 years.[151] Additionally, the effect of maternal psychological stress on atopic disease development is being pursued by the South Korean Cohort for Childhood Origin of Asthma and Allergic Diseases, who recently demonstrated that increased prenatal maternal depression or anxiety was associated with increased risk of infant AD by age 6 months.[152]

Because human subjects do not develop in exposure silos, future studies should focus on identifying the effect of the summation of these exposures with different degrees of interaction among them in addition to the epigenetic effects of these exposures. This approach can more effectively identify the interventions that will have the greatest effect, both at the legislative and individual levels, on the development and sequelae of atopic disease. Examples of proposed interventions to date are provided in Fig 2. Several research initiatives focused on the exposome are being pursued in Europe (EXPOsOMICS, HELIX, and Heals) and the United States (Hercules) to simultaneously assess a large set of exposures while linking these exposures with the body's response through -omics approaches. These investments might identify atopy risk factors that are underestimated or perhaps yet undiscovered. Use of environment-wide association study approaches to identify associations with adverse health effects will bring their own challenges, highlighted by recent publications noting that some exposures might be highly correlated among each other and some might be synergistic to promote adverse health effects.[153] Additionally, it will be challenging to identify the effect of an early-life exposure on the sensitivity to future exposures over the lifespan. Exposome-focused projects are inherently expensive at this time given the large sample sizes required to assess numerous exposures in addition to the use of numerous tools required to assess both external and internal exposome components, including use of environmental monitoring technology (by using both geographic information system-based pollutant models and personal sensors) and -omics technologies. The cost and efficiency of applying an exposome-focused approach to human disease will have to be improved to make discoveries with the highest effect.

In the interim, integrating data from numerous birth cohort studies throughout the world will aide in more clearly defining the environmental determinants driving atopy and perhaps elucidate the optimal time to implement interventions. The Mechanisms of the Development of Allergy study incorporated data from more than 44,000 European children participating in birth cohort studies, and the Environmental Influences on Child Health Outcomes program in the United States includes more than 50,000 children. Large-scale birth cohort studies with harmonized exposure and outcome assessments throughout the world will need to be pursued as we define the peak susceptibility periods to a variety of exposures during the prenatal and postnatal periods and which exposures relevant to specific geographic areas should be the primary targets for interventions. An important example of harmonized outcome assessments is clearly delineating between allergic versus nonallergic asthma when assessing the effect of various exposures on this outcome. Once key exposures and potential interventions are identified, an integrative approach among clinicians, children and their caregivers, health care organizations, insurance providers, government agencies, and urban planners must be undertaken to establish cost-effective primary and secondary prevention strategies to reduce these risks and promote wellness.

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*References 6-11, 15-19, 23-40, 42-47, 62-67, 71-86, 96-102, 110-123, 125, 126, 131-136, and 138-140.

What do we know?

- **The microbiome differs between atopic and nonatopic subjects, and these differences are seen in the first few months of life.**
- **Children exposed to farms and biodiversity in green spaces during early life are at reduced risk of allergic disease, whereas early-life exposure to HDM, cockroach, mice, and fungi promotes development of allergic disease.**
- **Wheezing episodes associated with RSV and HRV infection increase the risk of asthma in later childhood.**
- **There is no clear evidence that cat or dog exposure promotes or prevents atopy development.**
- **Prenatal and early-life exposure to both indoor and outdoor air pollutants negatively affects lung development and increases the risk of wheezing and asthma.**
- **Maternal smoking or exposure to SHS increases the risk of asthma, allergic sensitization, and AD.**

What is still unknown?

- **Does alteration of the diversity and abundance of commensal microbes in early life directly affect the development of allergic disease, or are these differences merely markers of immune dysregulation?**
- **What are the mechanisms by which early-life farm exposure imparts protection against allergic disease?**
- **Can asthma development be prevented by RSV and/or HRV immunization?**
- **What air quality standards are sufficient to prevent detrimental effects on lung development and atopic disease in children?**
- **When are children most susceptible to the effects of air pollution (prenatal, first year of life, or cumulative lifetime exposure), and what personalized interventions can be developed to reduce the risks associated with pollution exposure?**
- **What are the most cost-effective environmental intervention strategies to prevent allergic disease, and how do these strategies vary geographically?**

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