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Environmental exposures and mechanisms in allergy and asthma development

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Environmental exposures interplay with human host factors to promote the development and progression of allergic diseases. The worldwide prevalence of allergic disease is rising as a result of complex gene-environment interactions that shape the immune system and host response. Research shows an association between the rise of allergic diseases and increasingly modern Westernized lifestyles, which are characterized by increased urbanization, time spent indoors, and antibiotic usage. These environmental changes result in increased exposure to air and traffic pollution, fungi, infectious agents, tobacco smoke, and other early-life and lifelong risk factors for the development and exacerbation of asthma and allergic diseases. It is increasingly recognized that the timing, load, and route of allergen exposure affect allergic disease phenotypes and development. Still, our ability to prevent allergic diseases is hindered by gaps in understanding of the underlying mechanisms and interaction of environmental, viral, and allergen exposures with immune pathways that impact disease development. This Review highlights epidemiologic and mechanistic evidence linking environmental exposures to the development and exacerbation of allergic airway responses.

Background

Environmental exposures can dramatically influence the phenotype of allergic diseases, including atopic eczema, food allergy, asthma, and allergic rhinitis (1–4). These diseases now affect approximately 20% of the population worldwide (4, 5); yet the prevalence has increased too rapidly in recent decades to be explained by genetic changes alone (1, 6). The International Study of Asthma and Allergies in Childhood has demonstrated that the prevalence of these diseases can be very high in settings with low socioeconomic conditions and can vary greatly between regions, countries, and centers within a city or country, indicating the role of local environmental characteristics (7, 8). Global trends of increasing urbanization and rapid population growth contribute to changes in lifestyle (diet, time indoors, physical activity) and environmental exposures (air pollution, smoking, mold, infections) that affect atopic allergic mechanisms and rising disease prevalence worldwide (1, 2, 9–11). Many of these changes are associated with early-life and lifelong risk factors for the development and exacerbation of asthma and atopic allergic diseases.

The terms "allergy" and "atopy" are often used to describe IgE-mediated diseases wherein persons with atopy are predisposed to produce IgE antibodies against common environmental allergens and have one or more atopic allergic diseases (i.e., atopic eczema, food allergy, asthma, and allergic rhinitis), though some nonatopic allergic diseases (e.g., nonatopic asthma, contact dermatitis) develop through IgE-independent mechanisms (4). The interplay of genetic predispositions and environmental exposures is instrumental in shaping the immune system, especially in early life when neonates go from limited environmental exposure in utero to having their skin, lungs, and intestinal tract colonized by fungus and bacteria to form their microbiome. It is increasingly recognized that the timing and route of exposure affect allergic disease development (1, 6). An impaired skin barrier represents an important route of entry for allergens, bacteria, viruses, air pollutants, and environmental chemicals leading to epicutaneous sensitization, atopic dermatitis, and/or asthma in susceptible children (12–16).

In this context, it is useful to consider three types of exposures: (a) the external outdoor environment; (b) the indoor environment; and (c) host environmental factors. Many early-life exposures and physiological mechanisms not included in this Review have been linked to allergic disease development, including lifestyle factors, obesity, pre- and postnatal maternal psychological stress, pharmaceuticals, occupational exposures, chemical pollutants, and more. In addition to varying by host response, geographic regions, and socioeconomic status, these exposures likely interact simultaneously to affect allergic mechanisms such that no one factor dictates disease development in all subjects. This Review summarizes the epidemiologic and mechanistic evidence linking environmental exposures to the development and exacerbation of atopic asthma and allergic responses.

Microbial exposures

Adoption of a Western lifestyle corresponds to environmental, behavioral, and dietary changes characterized by increased time spent indoors, antibiotic usage, obesity prevalence, and decreased physical activity and siblings per family. The hygiene hypothesis theorizes that increased exposures to early-life infections and larger family size lead to decreased risk of allergic disease development (17). Alternatively, the "old friends" hypothesis proposes that increases in allergic diseases are due to the loss of symbiotic relationships with parasites and bacteria that were once beneficial

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Table 1. Consistently observed environmental effects associated with allergic diseases in epidemiologic studies[A]

Exposure or risk factor	Clinical phenotype	Study type	No. of studies	Age group	Consistent findings
Environmental microbial exposures	Microbiome diversity, atopy, asthma	Review; cross-sectional	2	6–13 years	Decrease in environmental symbiosis with parasites/bacteria and microbiome diversity influences immunoregulation, increases allergy and asthma prevalence (18) Exposure to diverse microbes inversely related to risk of asthma (PARSIFAL, OR 0.62, 0.44–0.89; GABRIELA, 0.86, 0.75–0.99) (21)
Dogs and cats (dog and cat exposure and ownership)	Asthma, sensitization	NHANES cross-sectional; cohort	1; 1	1–69 years	Dog and cat allergen exposure and sensitization associated with risk and protective effects for developing allergic disease (37, 39) Early-life dog or cat ownership reduced sensitization to ≥1 aeroallergen (dog, OR 0.65, 0.45–0.95; cat, OR 0.87, 0.73–1.04) and decreased asthma risk in children (dog, OR 0.87, 0.81–0.93) (37) Increased asthma attack prevalence attributable to dog allergen among dog-sensitive (44.2%) and cat allergen among cat-sensitive (30.3%) (39)
Mold (mold odor and visibility, dampness damage)	Asthma, allergic rhinitis	Meta-analyses; birth cohort	27; 2	Birth–44 years	Exposure to *Cladosporium*, *Alternaria*, *Aspergillus*, and *Penicillium* species increased asthma symptom exacerbation 36%–48% (43) Mold or dampness indicator exposure during infancy increased risk of allergic asthma (OR 1.31, 1.08–1.59) and rhinitis (OR 1.29, 1.03–1.62), and nonallergic asthma (OR 1.80, 1.27–2.55) and rhinitis (OR 1.41, 1.03–1.93), up to 16 years of age (45)
Viral infections (HRV, RSV)	Wheezing and asthma	Meta-analyses	15	Birth–18 years	HRV-induced wheezing is more robust marker of asthma risk than RSV/other infection–induced wheezing (67) HRV wheezing illness in first 3, <10, and ≥10 years increased asthma risk in later life (≤3 yr, RR 2.00, 1.62–2.49; <10 yr, RR 2.02, 1.70–2.39; ≥10 yr, RR 1.92, 1.36–2.72) (69)
TRAP (BC, NO_2, $PM_{2.5}$, PM_{10})	Allergy, sensitization, eczema, allergic rhinitis, asthma	Meta-analyses	5–15	Birth–18 years	Childhood TRAP exposure increases risk for development or exacerbation of atopy, sensitization, eczema, and asthma (91, 109, 111) Increased risk of asthma development associated with BC (OR 1.08, 1.03–1.14), NO_2 (OR 1.05, 1.02–1.07), $PM_{2.5}$ (OR 1.03, 1.01–1.05), and PM_{10} (OR 1.05, 1.02–1.08) (111) Living within 50–200 m of major road associated with increased risk of eczema, allergic rhinitis, atopy and asthma (109)
Tobacco smoke (secondhand smoke, pre- or postnatal, household)	Wheeze, asthma, sensitization, eczema	Meta-analyses; birth cohort	71; 1	Birth–18 years	Pre- or postnatal maternal smoking increased risk of incident wheezing (OR 1.70, 1.24–2.35) and incident asthma (OR 1.85, 1.35–2.53) in children ≤2 years (158) Secondhand smoke in infancy without prior exposure in utero increased risk of food sensitization (OR 1.47, 1.08–2.00); risk of eczema with sensitization (OR 1.62, 1.20–2.18) (45)

[A]Odds ratios and risk ratios are reported as (OR, 95% confidence interval) and (RR, 95% confidence interval). BC, black carbon; HRV, human rhinovirus; NHANES, US National Health and Nutrition Examination Survey; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter 2.5 μg/m^3; PM_{10}, particulate matter 10 μg/m^3; RSV, respiratory syncytial virus; TRAP, traffic-related air pollution.

to our evolution (18, 19). Reduced environmental microbial exposures and reduced microbiome diversity may influence host allergic responses by affecting epithelial and immune cells (1, 18, 20).

The outdoor microbial environment. Environmental exposure to diverse microorganisms has repeatedly demonstrated an inverse association with the manifestation of atopic allergic diseases (6, 18, 20–22). European children from the PARSIFAL and GABRIELA studies raised on rural farms had lower prevalence of atopy and asthma and increased microbial exposure than unexposed children in nonrural environments (Table 1 and refs. 21, 23). Studies comparing populations from wealthier, more Westernized Finland versus more rural Russian Karelia have demonstrated significantly greater allergic disease prevalence in Finland and corresponding differences in skin and nasal microbiota despite similar ancestry and geographic location (24, 25). Rural children in China exposed to farming and higher endotoxin levels had decreased asthma risk compared with urban children (26). Amish children living on small traditional US farms had lower asthma prevalence than Hutterite children living on large modern communal farms (5% vs. 23%, respectively) and bacterial home exposure that differed in both quantity and quality (27). Taken together, these findings support a protective role for early bacterial exposure. A clinical trial is under way to test whether oral bacterial extract (ORBEX) administered to high-risk infants can increase the time to occurrence of the first episode of wheezing-related illness after therapy (https://clinicaltrials.gov/ct2/show/NCT02148796).

The origin and nature of bacterial exposure is critical to altering allergic responses. In mice exposed every other day to either Amish or Hutterite house dust extract while being sensitized and challenged with OVA, only Amish dust–exposed mice showed ablated airway resistance and eosinophilia (27). This was dependent on MyD88 and TRIF, which are downstream of TLR4, a pattern recognition receptor that binds endotoxin and the house dust mite (HDM) allergen Derp2 (Figure 1 and ref. 28). In HDM-exposed mice, TLR4 signaling on airway epithelial cells induces Th2 allergic responses (29), but its contribution to allergic responses is

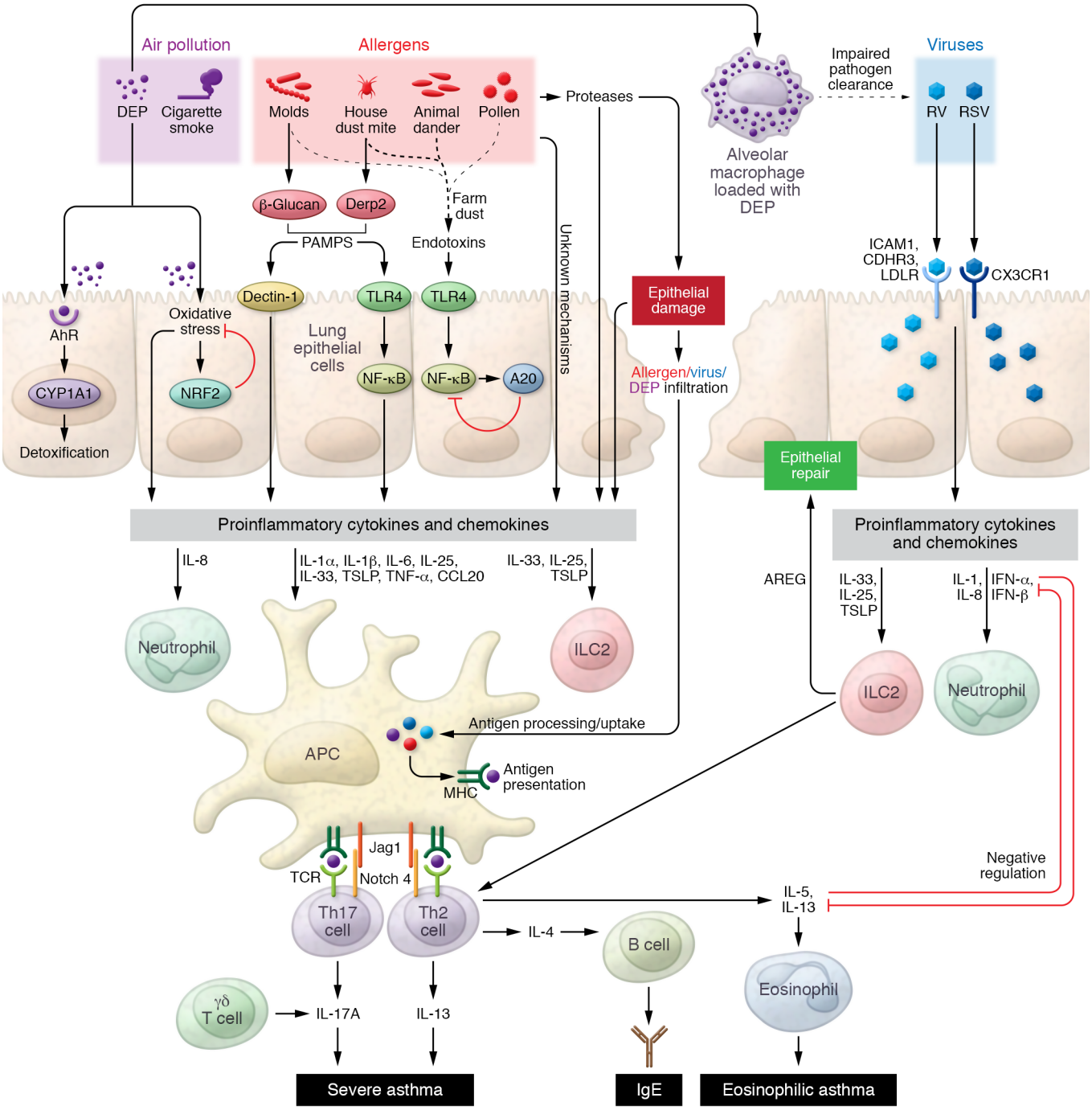

Figure 1. Epithelial pathways impacted by environmental exposures promote asthma pathogenesis. Exposure to air pollutants induces oxidative stress. AhR recognizes polycyclic aromatic hydrocarbons on diesel exhaust particles (DEPs), promoting cytochrome P450 family 1 A1–mediated (CYP1A1-mediated) detoxification. Oxidative stress induces Nrf2 translocation to the nucleus, leading to antioxidant transcription. Failure to detoxify results in release of the neutrophil chemokine IL-8, the antigen-presenting cell (APC) chemokine CCL20, and proinflammatory cytokines (including IL-1, IL-6, and TNF-α) that in the absence of allergen promote naive T cell differentiation into IL-17A–producing Th17 cells. Similarly, exposure to mold-derived β-glucans, which signal through dectin-1, induces recruitment of IL-17A–secreting Th17 and γδT cells and neutrophils. Mold and other complex allergens also stimulate epithelial cells through pathogen-associated molecular pattern (PAMP) receptors like TLRs. TLR4 recognizes the house dust mite allergen Derp2 and endotoxins, which can modulate NF-κB activation of proinflammatory cytokines via the ubiquitin-modifying enzyme A20. Notch4-Jagged1 interaction between T cells and APCs, respectively, can induce Th2 cell generation when APCs are exposed to allergens and epithelial cell–derived IL-25, IL-33, and/or TSLP. These cytokines can be released following viral infection of epithelial cells and cellular damage resulting from exposure to pollutants and/or proteolytic allergens. They can induce innate lymphoid cells (ILC2s) to release IL-13, which drives mucus production and AHR, and IL-5, which is central to eosinophil biology. In addition to interacting with APCs and Th2 cells to potentiate allergic responses and IgE generation, ILC2s also release amphiregulin (AREG) to promote tissue repair. HRV and RSV infections in asthmatics can exacerbate Th2 responses and inhibit type 1 IFN responses, enhancing viral replication and promoting more severe disease.

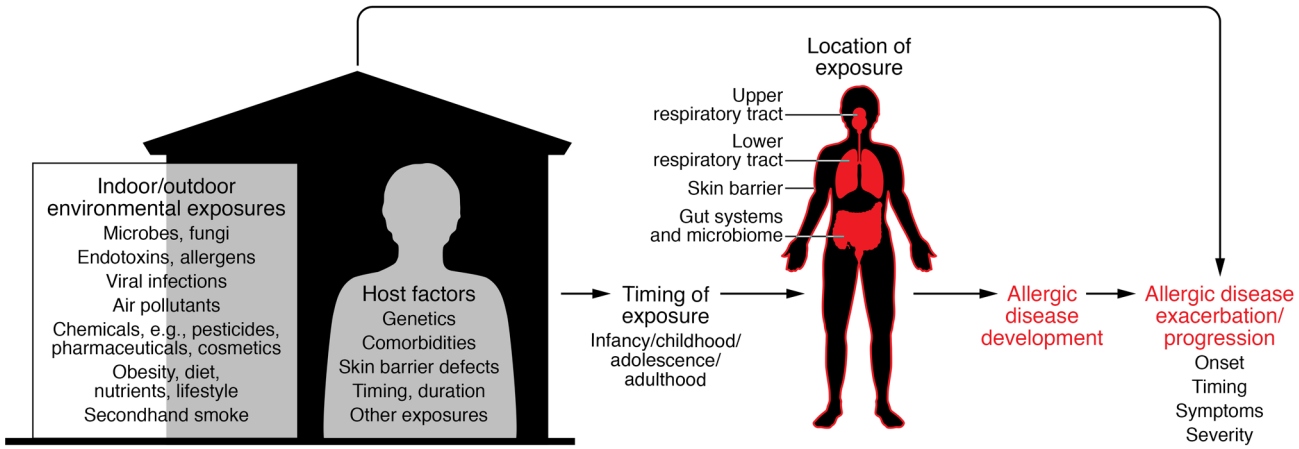

Figure 2. Interplay of indoor and outdoor environmental exposures and host factors that affect lifelong allergic disease development and progression. Allergic disease development is influenced by many environmental exposures that may interact with host factors and trigger a host response. These exposures may be part of the outdoor, indoor, or host environment. The timing of environmental exposures is important in the development and progression of allergic disease. Common factors within the external, internal, and host environments contribute to disease development, exacerbation, and lifelong progression. The host response to different exposures varies depending on host genetics and epigenetics in addition to other host factors that influence the timing and onset of allergic disease symptoms and severity.

likely influenced by load, cell type, and timing of exposure (30). Chronic low-dose LPS or farm dust exposure in mice can prevent development of HDM-induced allergic immune response by a mechanism involving A20, a ubiquitin-modifying enzyme that partially inhibits NF-κB signaling in lung epithelial cells, supporting a protective role for bacterial exposure (31). It remains to be seen which bacteria confer this protective effect and how these findings may differ in urban areas.

Indoor microbe and allergen exposure. The indoor microbial environment is determined by a dwelling's inhabitants. Dog ownership increases house dust diversity by introducing additional bacterial taxa compared with homes with cats or without pets (32). Exposure to dog and/or cat has been implicated as both a risk and a protective factor for developing allergic symptoms, allergic sensitization, or asthma (33, 34). Dog ownership may act as a surrogate marker for particular microbial exposures that enhance the protective effect of pet ownership against allergic disease (32). The protective effect on allergic disease risk may depend on pet exposure during the first year of life, which correlates with the timing of endotoxin exposure that confers the most significant protective effects (Figure 2 and refs. 1, 35, 36). In a Swedish birth cohort, dog exposure during the first year of life conveyed a reduced risk of asthma at age 6 independent of parental asthma (37). The cumulative evidence suggests no increased risk of allergic disease from pet exposure (1, 33, 34). However, the Institute of Medicine recently found sufficient evidence of association between dog and cat allergen exposure and asthma exacerbation, but only in individuals sensitized to those particular allergens (2). Increased levels of IgE to furry-animal allergens are associated with allergy-related symptoms, but polysensitization (IgE-specific for three or more cat or dog allergens) during early childhood may predict cat and dog allergy better than IgE to cat or dog extract (38). In the United States, where pet ownership is common (36.5% of households own a dog and 30.4% a cat), an estimated excess of 1,700,000 asthma attacks and 700,000 asthma emergency care visits each year are associated with elevated levels of pet allergen in bedrooms of sensitized patients (39).

Indoor fungal exposure and asthma. Indoor fungal exposure, defined by the presence of visible fungi/mold, visible dampness, and/or mold odor, is present in 18% to 50% of household dwellings worldwide (40–43). Old houses (≥90 years) and those with damp indoor environments are at increased risk of higher concentrations of *Penicillium* and *Aspergillus* species (43, 44). Indoor fungal profiles vary by geographic location, season, air exchange rates, and interaction with outdoor sources of fungi, such as *Cladosporium* and *Alternaria* species (43). The Institute of Medicine found sufficient evidence of a causal association between dampness or dampness-related agents and asthma exacerbation in children (2). Numerous epidemiologic studies have determined indoor fungal exposure to be associated with asthma, wheeze, allergic rhinitis, and eczema in both atopic and nonatopic individuals (41, 42, 44, 45). Fungal exposure has consistently been associated with the highest excess risk for development and exacerbation of asthma (43, 44) and rhinitis (45, 46). Exposure to an increased number of mold or dampness indicators in infancy has been associated with a greater risk of allergic (47) and nonallergic asthma (44, 45). However, there is evidence that mold exposure can be protective. Exposure to higher fungal diversity shortly after birth has been associated with decreased risk of wheezing and aeroallergen sensitization later in childhood (48, 49) similar to the aforementioned protective role of endotoxins.

Environmental fungal exposure promotes allergic disease through immune responses to both fungal-specific pathogen-associated molecular patterns (PAMPs) and proteolytic allergens (50). Fungal spores and conidia are protected by a rigid outer wall of β-glucans with an outer mannan layer and an inner chitin layer that enables signaling through C-type lectin receptors (ref. 51 and Figure 1). The immune system recognizes β-glucans using the dectin-1 receptor, while mannans bind a range of C-type lectins

(50, 51). In mice, fungal-derived chitin exposure induced IL-25, IL-33, and thymic stromal lymphopoietin (TSLP), activated type 2 innate lymphoid cells (ILC2s), and drove Th2 allergic inflammation, whereas inhibition of this pathway increased activation of IL-17A–producing γδT cells and prolonged neutrophilia (52, 53). In a mouse asthma model, exposure to HDM allergen and curdlan, a linear β-glucan that induces a robust IL-17A response, enhanced airway hyperresponsiveness (AHR) and airway inflammation in the absence of fungal sensitization, demonstrating that the impact of fungal exposure may be more dependent on the direct immunomodulatory functions of fungal components rather than its ability to act as a sensitizing agent (54).

Mold species are capable of inducing distinct inflammatory lung phenotypes based on the mold's available surface PAMPs. *Cladosporium cladosporioides* has high β-glucan content, but limited surface availability (55); *Aspergillus versicolor* has lower β-glucan content, but higher surface availability of β-glucans. In mice, inhalation of *C. cladosporioides* spores induced robust AHR and eosinophilia, whereas *A. versicolor* induced a strong dectin-1–mediated Th17 response and neutrophilic inflammation, but mild AHR (55). Mice exposed to heat-killed *C. cladosporioides* spores with more exposed β-glucans on their surface exhibited dectin-1–mediated Th17 and neutrophilic inflammation (56). In the absence of dectin-1, heat-killed spores induced a predominantly Th2 response similar to that induced by live spores, indicating that the immune response is dependent on surface availability of β-glucans (56). In mice, β-glucans also exacerbated allergen-induced allergic responses in a dectin-1–dependent manner (54, 57). These findings highlight several innate pathways triggered by mold exposure and resulting in a mixed Th2/Th17 response associated with more severe asthma.

Airway smooth muscle cells can respond directly to inhaled fungi to generate AHR. A major allergen of *Aspergillus fumigatus* (Asp f13) is a serine protease (alkaline protease 1; Alp1) that has been detected in the lungs of severe asthmatics and inversely correlated with forced expiratory volume in one second (FEV1) (58). Alp1 promotes calcium flux and contraction of smooth muscle cells (58). Mice repeatedly exposed to *Aspergillus* lacking Asp f13 had significantly lower pulmonary inflammation and signs of remodeling, supporting a role for the endogenous protease activity; however, AHR was unchanged, demonstrating the complexity of fungal actions (59). Fungal proteases can also cleave protease-activated receptor-2 (PAR2), triggering innate immune responses. Following *Alternaria alternata* exposure, PAR2-mediated serine protease–induced activation has been shown to induce the release of IL-33 from human bronchial epithelial cells (60). Similarly, in mice, *Alternaria* exposure induced IL-33, Th2 cytokines, IgE, and AHR (61, 62). These Th2 responses were attenuated in ST2-deficient mice lacking a functional IL-33 receptor, suggesting a role for IL-33 in severe asthma with fungal sensitization (62). However, the mechanisms by which fungal exposure contributes to allergic disease are not fully delineated.

Viral infections in wheezing and asthma development. Early-life acute respiratory tract infections (ARIs) are strongly associated with wheeze in infants and asthma inception and exacerbation in children; however, it is still debated whether they are causative in the pathogenesis of asthma or whether they unmask asthma susceptibility (63–65). ARIs caused by human rhinovirus (HRV), respiratory syncytial virus (RSV), parainfluenza viruses, and other pathogens are common in early childhood (10%–30% bronchiolitis prevalence in the first 2 years) (64). ARIs provoke wheezing in individuals with and without asthma. Up to 50% of children will have acute ARI-associated wheezing before school age, and 30% to 40% of these will have recurrent wheeze (66).

HRV-associated bronchiolitis and wheezing illnesses are a more robust marker of asthma risk than those caused by RSV or other viruses (66, 67). Upon infection with HRV, patients with asthma have more severe airway symptoms than nonasthmatic controls (68). HRVs are single positive-stranded RNA enteroviruses classified into three species (HRV-A, HRV-B, and HRV-C) and over 160 distinct genotypes (67). HRVs utilize three major types of cellular membrane glycoproteins to enter respiratory epithelial cells: intercellular adhesion molecule 1 (ICAM-1) (HRV-A and HRV-B), low-density lipoprotein receptor (LDLR) family members (HRV-A), and cadherin-related family member 3 (CDHR3) (HRV-C) (67). HRV-associated wheezing in the first 3 years of life doubled the risk of subsequent asthma development (69). Among neonates with high familial risk for asthma, having at least one HRV-associated wheezing episode during the first 3 years of life increased the likelihood of wheezing in the third year (OR 10.0) more than having at least one RSV-associated wheezing episode (OR 3.0) (70). Prospective studies have shown that RSV-induced bronchiolitis is associated with subsequent asthma development (67, 71, 72) and with recurrent wheeze (63, 73), but this may reflect an underlying predisposition to asthma and not a causal mechanism.

The interaction between early-life ARI and allergic sensitization increases the risk of subsequent asthma (63, 66). Children followed prospectively from birth to age 13 years with HRV-induced wheeze and aeroallergen sensitization by age 3 years had the highest incidence of subsequent asthma development compared with sensitization or HRV-wheezing alone (74). Among children in the Cincinnati Childhood Allergy and Air Pollution Study (CCAAPS), having at least 6 ARIs in the first year of life and early sensitization to mold increased asthma risk at age 7 years 12-fold compared with children with fewer than 6 ARIs who were not sensitized (75). This suggests that the load and timing of viral exposure may be important in progression to asthma. The strength of association between early-life ARI and childhood asthma is large in comparison with other environmental risk factors, but determining causality in children is not possible for ethical reasons (76). However, Beigelman et al. suggest that at least seven of nine Hill's criteria for causality are met for respiratory viruses (76). Evidence from a randomized, double-blind, placebo-controlled trial showing significant reductions in recurrent wheeze among healthy preterm infants who received palivizumab to prevent RSV infections supports the concept of a causal relationship (76, 77).

Mechanisms of viral-induced wheezing. Transcriptomic analysis comparing asthmatics with nonasthmatic controls following infection with HRV demonstrated increased magnitude and persistence of epithelial gene dysregulation throughout the course of infection (78). Distinct differences in the quality of the response following HRV infection were observed in asthmatics, including increased expression of genes involved in inflammation, decreased expression of viral replication inhibitors, and impaired induction of the

serine protease inhibitor *SPINK5*, which has been implicated in epithelial maintenance and repair (78). Patients with asthma also displayed increased upper and lower respiratory symptoms, markedly higher viral load, and higher nasal Th2 cytokine levels (68). Accordingly, supernatants from HRV-infected primary bronchial epithelial cells induced IL-5 and IL-13 production from isolated CRTH2$^+$ ILC2s and promoted Th2 differentiation in vitro in an IL-33–dependent manner, suggesting a link between infection and asthma exacerbation (68). In a sister study, bronchial epithelial cells from asthmatic individuals released significantly more IL-25 upon infection with HRV-1B than control cells (79). In neonatal mice, HRV infection increased IL-25, IL-33, and TSLP expression (80), and neutralizing antibody against IL-25 abolished ILC2 expansion, mucous metaplasia, and AHR in HRV-infected neonatal mice (81). These findings suggest that early-life viral infection may contribute to asthma development and exacerbation by provoking type 2 immune responses.

In humans, these viral-induced type 2 innate responses likely favor allergic Th2 responses upon exposure to common aeroallergens. This type 2 environment has been shown to inhibit type 1 interferon antiviral responses in infected cells from asthmatic patients, further exacerbating disease (65, 82–84). RSV-infected human neonatal regulatory B cells upregulated CX3CR1 to promote infection and release of IL-10 that inhibited antiviral responses and exacerbated disease in a manner favoring microbial pathogenesis (85). In mice, pathogenic clinical isolates of RSV induced accumulation of ILC2s via a TSLP-dependent mechanism (86) and increased susceptibility to atopic asthma through impairment of regulatory T cells and promotion of a Th2 response (87). Thus, impaired antiviral responses in early life result in increased disease and the development of asthma (65, 67, 88, 89). Treatment strategies limiting type 2 responses may alleviate viral-induced asthma exacerbations partly by restoring antiviral responses (65).

A missense variant in *CDHR3* (receptor for HRV-C) has also been associated with childhood asthma exacerbations (90). Overall, this evidence highlights the complex interplay of environmental microbial exposures and host factors that influence the timing and the development of allergic disease.

Impact of air pollution on allergic disease

Air pollutants can cause adverse health effects worldwide (14, 91–94). Outdoor air pollution frequently occurs as a mixture of natural pollutants (e.g., from wildfires, volcanoes, biological decay, dust storms) and human-made pollutants (e.g., from motor vehicles, biomass burning, power plants, industrial facilities, waste incinerators, pesticides) (Figure 2 and refs. 9, 91, 95). Sulfur dioxide, nitrogen oxides (NO_x), carbon monoxide (CO), and particulate matter (PM) are typical outdoor air pollutants from fuel combustion or motor vehicle emissions.

Concern is increasing over indoor air pollution since some societies spend up to 90% of time inside exposed to pollutants from tobacco smoke, solid fuels, stoves, construction materials, ambient PM, and biological materials (mold spores, viruses and bacteria, animal dander, and HDMs) (91, 96). Indoor air pollution is determined partly by outdoor air quality depending on ventilation systems and cleaning practices. Additional environmental chemical exposures associated with atopic disease include pharmaceuticals, cosmetic products, flame retardants, and others (97–100). Volatile organic compounds (VOCs) are also worrisome as Westernized societal exposure shifts from transport-related VOCs to VOCs from coatings, adhesives, and consumer products that alter urban air quality (101). Additionally, VOCs react with NO_2 in the presence of sunlight to form ozone. Overall, the risk of air pollution is a function of the hazard of the pollutant, the combination of pollutants and their interactions, and the extent of exposure (96). Here, we focus on the impact of traffic-related air pollution (TRAP) and tobacco smoke in allergic disease and asthma.

TRAP exposures. An expert panel for the Health Effects Institute found sufficient evidence that exposure to TRAP causes asthma exacerbation in children (102). TRAP produced by motor vehicles is made up of a complex mixture of PM, reported as black carbon (BC), PM_{10}, and/or $PM_{2.5}$; and gaseous emissions including NO_x, CO, ozone, and other air pollutants (9, 91, 103). Diesel exhaust particles (DEPs) are of particular concern and contributed to more than 90% of the PM derived from traffic sources in European and American cities (103). This exposure is significant in cities where up to 45% of the population resides in zones most impacted by TRAP (102, 104, 105). Despite falling sales, diesel-powered cars still represent a major portion of cars on the road in Europe and India. Air quality and engine exhaust control policies implemented in 2005 to 2010 have not produced rapid changes in TRAP levels (106).

Evidence suggests that TRAP is associated with reduced lung growth, lower lung function, and development and exacerbation of asthma (107–110). Meta-analyses estimated significantly increased risk estimates for BC, NO_2, $PM_{2.5}$, and PM_{10} exposures and subsequent development of childhood asthma (Table 1 and ref. 111). Near-roadway exposure is associated with increased asthma prevalence, chronic lower respiratory symptoms, phlegm production, bronchitis, wheeze, and medication use (112), and decreased lung function, lifetime diagnoses and symptoms of allergic rhinitis, and allergic sensitization among school-aged children (113). Exposure to pollutants from roads with high vehicle traffic contributed to an estimated 14% of incident childhood asthma and 15% of childhood asthma exacerbation (104). In CCAAPS, a child's risk for persistent wheeze and asthma development varied depending on the timing, duration, and level of TRAP exposure (114–117). Accordingly, meta-analysis data suggest that TRAP exposure may have ongoing effects with a 3-year lag time (108). TRAP exposure in infancy resulted in a 40% to 83% increased risk of aeroallergen sensitization by age 4 (118, 119) and increased risk of food allergy by age 8 years (118). TRAP and other air pollutants also act as risk factors for eczema development and/or aggravation of eczema symptoms (91).

Collectively, there is mounting evidence supporting the contribution of TRAP to allergic diseases, although some meta-analyses have reported conflicting associations (108, 120). Meta-analyses of American and European cohorts observed substantial heterogeneity across studies that limited the ability to draw conclusions related to diverse definitions in exposure (land-use regression/dispersion models and roadway proximity) and outcomes (asthma, wheeze, allergic sensitization), and unmeasured confounding of other factors (environmental pollens, fungal spores, climate; socioeconomic) and their complex interactions that drive allergic disease and modify the effects of TRAP exposure (103, 108).

Several mechanisms contribute to TRAP-induced allergic disease development and exacerbation, including oxidative stress, altered barrier integrity, and induction of inflammation (14, 95, 121). Interpretations from mouse studies of TRAP depend on the nature of the traffic pollutant studied. DEPs are coated with heavy metals and organic compounds (e.g., polycyclic aromatic hydrocarbons), but can also carry pollen and airborne PAMPs depending on the local environment (122). Thus, DEPs collected from diesel engine vehicle exhaust will not necessarily recapitulate immune responses to ambient PM collected in urban cities (123). Nevertheless, inhaled ambient PM (and DEPs) adversely affects the bronchial epithelium by promoting oxidative stress, which has been implicated in key pathophysiological features of asthma (124). Briefly, exposure to DEPs induces a cascade of events including translocation of the transcription factor NF-E2–related factor 2 (Nrf2) to the nucleus and induction of antioxidants (e.g., heme oxygenase-1) to detoxify the cell and limit oxidative injury (Figure 1 and refs. 125, 126). PM exposure has also been shown to disrupt epithelial tight junctions in a dose-dependent manner, and alleviating oxidative stress restored normal epithelial barrier function (127–129). Thus, PM-induced oxidative stress could damage the integrity of epithelial barriers, allowing aeroallergens to gain entry into pulmonary tissues, facilitating uptake by antigen-presenting cells (APCs), and promoting allergic sensitization. Numerous studies have demonstrated increased allergen-specific IgE levels following coexposure to allergen and DEPs (108, 118, 119, 130).

Particulate matter–induced inflammation. The nature of PM-induced inflammation is context dependent. In cultured human epithelial cells, DEP exposure leads to NF-κB activation and transcription of proinflammatory cytokines (IL-1β, IL-6, TNF-α) and neutrophil chemokines such as IL-8 (121, 128). Accordingly, acute exposure to DEPs generated an inflammatory response dominated by neutrophils in healthy adults but no changes in lung function (131, 132). In contrast, decreased lung function has been shown in DEP-exposed asthmatics (133). Primary bronchial epithelial cells obtained from asthmatic patients and exposed to DEPs have increased mRNA and protein levels of IL-25, IL-33, and TSLP, and this induction is dependent on the aryl hydrocarbon receptor (AhR) (134). These epithelial-derived cytokines promote dendritic cell maturation and shape APC responses to allergen exposures (135, 136).

In T cells, Notch signaling is essential for allergic inflammation (137). Exposure to fine particles and ultrafine particles (UFPs; <0.2 μm) upregulated Jagged-1 (Jag1), the Notch signaling ligand on APCs (138). In mice, exposure to UFPs enhanced allergen-induced AHR, IgE production, and Th2/Th17 inflammation resulting from AhR-dependent induction of Jag1 expression in alveolar macrophages (AMs) (138). AMs are the major pulmonary cell type involved in phagocytosis of UFPs. Jag1-expressing AMs interacted with Notch4-bearing naive allergen-specific T cells to promote Th2 and Th17 differentiation (138), albeit only in AMs harboring a constitutively active IL-4 receptor (138, 139). This is consistent with a more severe asthma phenotype observed in patients with this IL4RA^{R576} polymorphism (139, 140).

DEP exposure is associated with increased IL-17A levels in human and murine asthma (141). In mice, IL-17A blockade prevented DEP-induced exacerbation of allergic asthma (141). This increase in DEP-mediated disease severity is associated with an impaired response to steroid treatment and increased IL-17A (141, 142), which can directly induce smooth muscle contraction (143). In mice, coexposure to HDMs and DEPs induced pulmonary accumulation of T cells that coproduce Th2 and Th17 cytokines (130, 141). In asthmatic patients, the presence of these dual Th2/Th17 cells, which are more resistant to steroids in vitro, is associated with more severe disease (144). After transfer into naive mice, Th2/Th17 cells have been shown to promote more severe disease than classic Th2 cells (145). Additionally, simultaneous exposures to IL-13 and IL-17A can exacerbate IL-13–induced AHR by enhancing IL-13/STAT6 signaling (146), which suggests that cells cosecreting IL-13 and IL-17A would be ideally poised to generate a stronger STAT6 response in epithelial and smooth muscle cells, a pathway critically involved in allergic AHR (147). DEP exposure promoted increased numbers and persistence of allergen-specific memory T cells in adult and neonatal murine lungs (130). Accordingly, coexposure to high TRAP in the first year of life was associated with earlier allergen sensitization and increased prevalence of asthma at age 7 in allergen-sensitized children (130).

TRAP exposure may alter the immune system even before birth. DEPs can cross the placenta and induce oxidative stress pathways in the fetus; thus maternal exposure has the potential for negative health effects to the fetus (148). Offspring of female mice exposed to DEPs in utero and sensitized to OVA postnatally were primed for enhanced allergen-induced bronchoalveolar lavage fluid inflammation, increased Th2 and Th17 cytokines, and elevated AHR compared with unexposed offspring (149–151). The associated increase in lung levels of genes induced by direct DEP exposures suggests that some DEPs likely crossed the placental barrier and resulted in a primed state and asthma susceptibility in offspring.

Tobacco smoke exposures. In 2015, one-quarter of men and 5.4% of women worldwide smoked daily (152), exposing up to 40% of nonsmokers to secondhand smoke (SHS) (153). An estimated 36,950 asthma deaths in adults and children were attributable to SHS exposure in 2004 according to comprehensive disease data from WHO (153). SHS exposure is also a risk factor for allergic sensitization, allergic rhinitis, and allergic dermatitis among children (154–156). Further, smoking among asthmatics promotes emphysema and decline in lung function, resulting in chronic obstructive pulmonary disease over time.

There is convincing evidence suggesting a causal relationship between SHS exposure and asthma incidence in children (2, 153, 157–159). Prenatal or postnatal maternal smoking was associated with significantly increased risks of incident wheezing (28%–70%) and incident asthma (20%–85%) up to age 18 years (158). Even in the absence of maternal smoking, SHS exposure in infancy increased the risk of food sensitization and the risk of eczema with allergic sensitization up to age 16 years (156, 160). In the Greater Cincinnati Pediatric Clinic Repository cohort, 33% of the asthmatic children aged 5 to 18 years lived with a smoker; of these, 66% of mothers reported smoking in the household (3). Children in lower-income families were almost 3 times more likely to be exposed to SHS than those in higher-income families (161). Strong evidence of an SHS exposure-response relationship and induction of asthma in children, adolescents, and adults makes prevention efforts critical (162–165). Further, thirdhand smoke (THS; residual smoke contamination remaining after the source

of tobacco smoke has been extinguished) can accumulate on surfaces, becoming progressively more toxic, and can contribute to overall tobacco smoke exposure (166–168). New research demonstrated that components of THS can exacerbate a mouse asthma model through mast cells, resulting in airway inflammation and remodeling (168).

E-cigarette use has substantially increased over the past 5 years worldwide (169–171). Levels of toxicants in e-cigarette vapor are lower than those in smoke from combustible cigarettes (172), but safety data regarding their usage are limited. Evidence indicates that e-cigarette vapor can produce oxidative stress and inflammation in airways and may exacerbate or induce rhinitis, asthma, eczema, and allergic symptoms (173). Epidemiologic investigations found increased e-cigarette use among asthmatics (174, 175) and associations between e-cigarette use and increased asthma (176) and asthma attack (175) prevalence. Exposure to nicotine-containing e-liquid in "asthmatic" mice increased airway eosinophils, Th2 cytokines, and AHR (172, 177). The toxicity of components unique to e-cigarettes likely induces unique respiratory and possibly allergic effects and warrants further investigation (172, 174).

Exposure to cigarette smoke alters immune mechanisms involved in allergic disease. As with traffic-related diesel pollution, AMs from smokers displayed reduced phagocytic abilities impairing both pathogen clearance from the lungs and removal of dead cells (178, 179). Exposure to cigarette smoke increased production of IFN-γ and IL-17A by T cells in murine lungs, and recruitment of AMs, neutrophils, and γδT cells, a major source of IL-17A (180). Smoke-exposed γδT cell–deficient mice failed to mount an effective immune response to influenza A (181). Cigarette smoke also induced oxidative stress, which can increase TSLP and IL-33 expression in the lungs (182–184). Smoke exposure induced IL-33 accumulation in epithelial cells, but viral infection or proteolytic allergen exposure is likely needed to release and activate IL-33 (183, 185).

Offspring from mice that are coexposed to allergen and tobacco smoke have increased asthma susceptibility (186, 187). Accordingly, nasopharyngeal aspirates from SHS-exposed asthmatic children revealed higher concentrations of IL-13 compared with SHS-unexposed asthmatic and control subjects (188). In utero exposure to cigarette smoke also affected lung development in murine offspring, and this negative impact extended to the next generation, suggesting epigenetic changes (187, 189). This is supported by recent findings demonstrating durable methylation changes in mice exposed to tobacco smoke in utero (190). Further research is needed to understand how interactions between smoke, viral, and allergen exposures in early life impact allergic disease development.

Conclusion

The effects of environmental exposures early in life contribute to the development of allergic disease and asthma later in life. The influence of these environmental factors on allergic mechanisms likely differs based on host genetics, host immunologic milieu, timing, and other exposures. The inconsistencies in current research regarding the relationship between the environment and atopy reflect these complexities and the need for improved exposure assessment and rigorous study design (1, 2). A comprehensive and integrated approach to allergic diseases that remain a significant public health problem, especially among children, will (a) establish basic molecular profiles to develop novel molecular insights into disease etiology and clinical severity, (b) produce environmental and biological signatures to create a roadmap for primary and secondary prevention of allergic disease, and (c) provide the rationale and targets for disease intervention (191). An improved understanding of the complex interactions between modifiable environmental factors and the dynamic biological processes that govern allergic mechanisms will advance our ability to prevent allergic diseases.

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