

Advances in environmental and occupational disorders in 2016



William J. Sheehan, MD,^{a,b,d} Jonathan M. Gaffin, MD, MMSc,^{b,c} David B. Peden, MD, MSc,^e Robert K. Bush, MD,^f and Wanda Phipatanakul, MD, MS^{a,b} Boston, Mass, Washington, DC, Chapel Hill, NC, and Madison, Wis

In this review we highlight recent studies that advance the knowledge and understanding of the effects of various environmental factors and associated immune responses in patients with allergic diseases. This review will focus on new literature regarding allergic and immune responses to a variety of environmental factors, including aeroallergens, stinging insects, fungi, pollutants, viral respiratory tract infections, climate change, and microbial exposures. (J Allergy Clin Immunol 2017;140:1683-92.)

Key words: Aeroallergens, fungi, air pollutants, viral respiratory tract infections, climate change, occupational asthma

Environmental factors play a major role in the development of allergic sensitization and the persistence of symptomatic allergic diseases. Extensive knowledge has been gained from important birth cohorts¹ and other recent studies. In this selective review we highlight articles published primarily in 2016 that advance our knowledge of the effect of environmental factors on allergic diseases. We focus on allergens, viral infections, and air pollution, which alone or in combination affect allergic diseases, particularly asthma. Major contributions (Table I)²⁻¹⁴ addressed include the following: (1) the importance of climate change and its potential to increase the risk of allergic respiratory diseases in the future; (2) the fact that sensitization to Fel d 1 and Can f 1, especially polysensitization, in childhood (age ≤4 years) is significantly associated with allergic symptoms to these pets in

Abbreviations used

ABPA: Allergic bronchopulmonary aspergillosis
APIC: Asthma Phenotypes in the Inner City
BALF: Bronchoalveolar lavage fluid
BAT: Basophil activation test
CF: Cystic fibrosis
DEP: Diesel exhaust particle
ECAT: Elemental carbon attributable to traffic
HDM: House dust mite
HP: Hypersensitivity pneumonitis
HRV: Human rhinovirus
ILC2: Type 2 innate lymphoid cell
PM: Particulate matter
RSV: Respiratory syncytial virus
SLIT: Sublingual immunotherapy
TET1: Ten-eleven translocation 1 gene
TLR: Toll-like receptor

adolescence (age 16 years); (3) the ability of viral infections to induce fibroblast proliferation; (4) the multiplicity of effects of air pollution on lung function, epigenetics, airway inflammation, and preterm birth in pregnant women with asthma; and (5) the role of school-specific allergenic exposures in asthma morbidity. Emphasis is also directed at severe asthma in residents of inner cities, where allergen exposure and sensitization are significant players in defining asthma phenotypes and are associated with difficult to control asthma. In addition to allergens, environmental tobacco smoke exposure also contributes to the pathogenesis of severe asthma in these populations. Understanding the contribution of environmental factors in the inception and progression of allergic diseases, as discussed in this review, will hopefully lead to improved treatments for these conditions.

IgE RESPONSES TO ENVIRONMENTAL FACTORS

IgE plays a central role in the pathogenesis of allergic diseases. A host of environmental factors influence IgE production. Among these factors, allergens are classically recognized, but viral infections, air pollution, and tobacco smoke can also contribute.¹⁵ Another factor leading to increased plasma IgE levels is high alcohol consumption (ingestion of ≥28 drinks containing 12 g of ETOH/week).¹⁶ However, there was no correlation between these findings and the presence of allergic diseases. Additional studies will be needed to determine the clinical significance of these findings.

Aging can affect allergen-specific and total IgE levels in adults. A large study of adults in the European Community Respiratory Health Survey examined the effects of aging on specific IgE levels

From the Divisions of ^aAllergy and Immunology and ^cRespiratory Diseases, Boston Children's Hospital; ^bHarvard Medical School, Boston; ^dthe Division of Allergy and Immunology, Children's National Health System, Washington, DC; ^ethe Center for Environmental Medicine, Asthma and Lung Biology, Division of Allergy and Immunology, University of North Carolina School of Medicine, Chapel Hill; and ^fthe Department of Medicine, Division of Allergy, Immunology, Pulmonary, Critical Care, and Sleep Medicine, University of Wisconsin School of Medicine and Public Health, Madison.

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Corresponding author: Wanda Phipatanakul, MD, MS, Division of Allergy and Immunology, Boston Children's Hospital, 300 Longwood Ave, Boston, MA 02115. E-mail: wanda.phipatanakul@childrens.harvard.edu.

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TABLE I. Key advances

Advances	References
Proximity of IgE epitopes on an allergen affects its allergenic activity.	Gieras et al ²
Early-life sensitization to Fel d 1 and Can f 1 or polysensitization to cat and dog allergens can predict development of allergic symptoms in adolescence.	Asaranoj et al ³
Sensitivity and specificity of Hymenoptera allergen components depend on the diagnostic assay.	Schrautzer et al ⁴
Chitinases might represent a novel biomarker for CF-associated fungal disease.	Hector et al ⁵
Early-life HRV-triggered wheezing episodes continue to be important in the development of asthma because they can result in airway remodeling and have been associated with persistence of asthma into adolescence.	Rubner et al ⁶
Air pollution exposure early in life in conjunction with allergen exposure might promote a stronger inflammatory response compared with allergen exposure alone.	Shelfoon et al ⁷
Climate change has increased the burden of asthma and allergies in a variety of ways.	Brandt et al ⁸
Exposure to traditional farming environments can be protective against development of asthma by activating innate immune responses.	Brandt et al ⁹
Exposure to mouse allergen in inner-city schools was associated with increased asthma symptom days in students with asthma, irrespective of sensitization status.	Annesi-Maesano ¹⁰
Results of randomized home allergen reduction intervention trials can be affected by motivations in the control groups.	Stein et al ¹¹
	Sheehan et al ¹²
	DiMango et al ¹³
	Matsui et al ¹⁴

to common aeroallergens and on total IgE levels over a 20-year period.¹⁷ Aging was associated with lower levels of sensitization to house dust mite (HDM) and cat allergen and a significant decrease in total IgE levels. The kinetics of IgE sensitization decreased differently for different allergens (ie, grass pollen was less likely to decrease). A better understanding of the mechanisms involved might clarify the cause and treatment of allergic diseases.

Studies of amino acid sequences (peptide epitopes) on allergens indicate that those that acquire enhanced ability to cross-link IgE by means of oligomerization, aggregation, or expression of repetitive epitopes can gain allergenic potency. It has been proposed that repetitive epitopes represent allergen-associated molecular patterns by Pali-Scholl and Jensen-Jarolim.¹⁸ In support of this concept, Gieras et al² found that the proximity of IgE-binding sites on an artificial allergen construct enhanced the magnitude of effector cell activation, basophil activation test (BAT) assays, and *in vivo* inflammation and systemic anaphylaxis in a mouse model. Further investigations into this mechanism, which might regulate allergic inflammation, will be of interest.

Component-resolved diagnostic testing for IgE sensitization to individual allergens has increased steadily in the past several years. An excellent review of the subject has appeared recently.¹⁹ These tests were used to show that sensitization to specific pet allergens correlates with allergic diseases, such as Can f 1 with persistent rhinitis, Can f 2 with asthma, and Fel d 2 with an asthma diagnosis.²⁰ Further evidence from the Barn/Children Allergy/Asthma Milieu Stockholm Epidemiologic/Mechanisms for the Development of Allergy (BAMSE/MeDALL) study³ indicates that early childhood sensitization to Can f 1, Fel d 1, or polysensitization was significantly better than IgE assays using cat or dog extracts in predicting longitudinal development of allergic symptoms. These studies support the benefits of a molecular diagnosis of IgE sensitization and mechanisms of allergic disease.

HDMs are a significant factor in the allergic march from sensitization to asthma. A recent report suggests that inclusion of the HDM allergen Der p 23 in IgE serologic testing is of value when conventional diagnostics fail.²¹ The introduction of HDM sublingual immunotherapy (SLIT) tablets can lead to improved treatment of allergic rhinitis in adults and children.²² In a randomized, double-blind, placebo-controlled phase III trial,

standardized HDM SLIT reduced allergic rhinitis symptoms and medication scores and improved quality of life compared with placebo in adults with moderate-to-severe allergic rhinitis. Furthermore, Roux et al²³ demonstrated that an environmental exposure chamber was beneficial in establishing the dose-dependent safety and efficacy of HDM tablet SLIT. Such studies can lead to improved diagnostic and therapeutic approaches to HDM sensitivity.

Stinging insect reactions can be potentially fatal, and thus accurate diagnosis is critical. Skin tests, BATs, and *in vitro* IgE assays have been investigated extensively to identify patients at risk for serious reactions to stings. Component-resolved diagnostics are being used increasingly to identify high-risk patients, especially those with underlying mast cell disorders.²⁴ Frick et al²⁵ demonstrated that sensitization to Api m 10 was a risk factor for treatment failures with honeybee venom because some preparations lack this allergen. The presence of cross-reactive carbohydrate antibodies in the sera complicates diagnosis. Schrautzer et al⁴ reported that the sensitivity and specificity of Hymenoptera allergen component-resolved testing depends on the assay used. One assay (Immulate; Siemens, Tarrytown, NY) was superior for detecting IgE to the honeybee allergy Api m 1, whereas another (CAP; Thermo Fisher Scientific, Waltham, Mass) was superior for the vespine allergen Ves v 5. Confirmation of these results will be helpful for diagnosis in individual patients and for epidemiologic studies.

Allergic reactions to medications are not uncommon. Investigations of alpha-gal have led to new insights into the mechanisms of drug reactions. Two reports in the *Journal*^{26,27} describe severe immediate-type allergic reactions to pegnivacogin, a PEGylation RNA aptamer investigation agent being evaluated for the treatment of acute coronary artery syndromes. Preformed IgG antibodies to polyethylene glycol were detected in the sera of subjects who experienced reactions. The events were associated with evidence of complement activation (decreased CH50, increased C3a, and increased Factor B levels in sera) and increased tryptase levels (Fig 1).²⁷ The results suggest an IgG-mediated anaphylactic reaction because of antigen-IgG antibody complexes interacting with Fcγ receptors as the mechanism. With a growing interest in genetic factors in patients with drug hypersensitivity reactions,²⁸ it will be of interest to determine whether genetics play a role in these reactions as well.

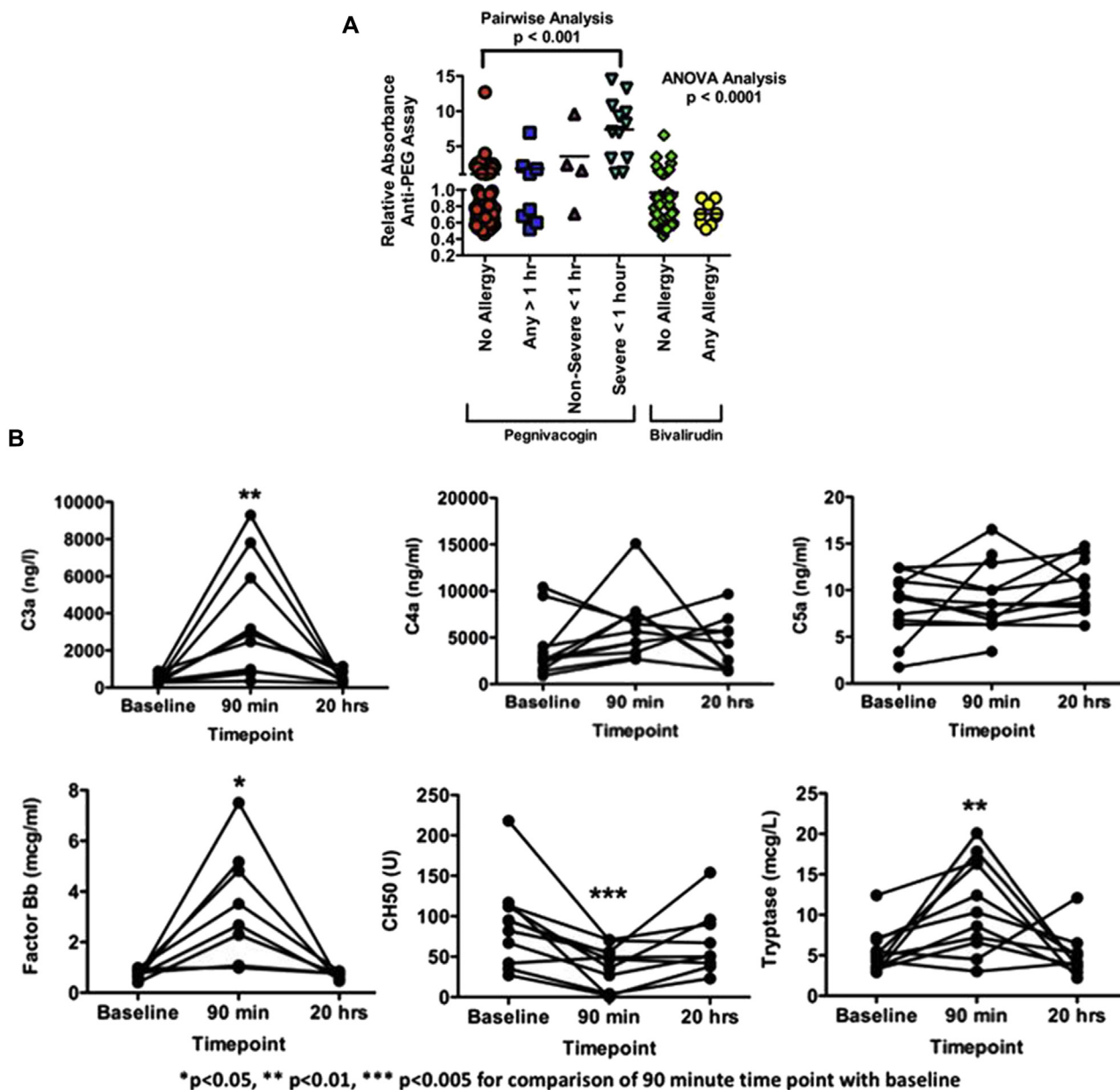


FIG 1. A, Relative levels of anti-PEG antibodies by allergy. B, Changes in individual complement components and tryptase levels in patients with severe immediate acute reactions to pegnivacogin.²⁷

RESPONSES TO ENVIRONMENTAL FUNGI

Fungal exposure has been implicated in the development, persistence, and severity of asthma. Interestingly, exposure to a higher fungal diversity in early life might impart a protective effect in asthma development.²⁹ Our companion journal, the *Journal of Allergy and Clinical Immunology: In Practice*, published a series of articles that update newer information on fungal allergy that range from current taxonomy of fungi,³⁰ innate and adaptive immune responses to fungal allergens and products,³¹ and health effects on human subjects,³² as well as the evaluation and management of patients with suspected fungal sensitivity.³³ Developments in fungal taxonomy indicate substantial IgE cross-reactivity among fungal species that can aid in the selection of representatives from each taxon for diagnostic testing.³⁰ Clearly, both innate and adaptive immune

responses contribute to the pathogenesis of airway diseases because of fungal exposure. A better understanding of these processes can improve treatment.³¹ A symptom questionnaire limited to a skin test panel might assist clinicians in diagnosing fungal allergy; however, there are limitations of fungal immune therapy. These articles will be of particular interest to practicing clinicians.

Studies on the mechanisms of fungal allergy continue. Fungi, particularly *Alternaria* species, have been shown to activate epithelial cells to produce IL-33 and skew type 2 innate lymphoid cells (ILC2s) to produce T_H2 cytokines in animal models. In addition, IL-33 has been shown to mediate eosinophilopoiesis in response to *Alternaria* species and enhance IL-5 expression by ILC2s in the lungs.³⁴ This study, along with a report by Takeda,³⁵ which demonstrated that human platelets are a source

of IL-33, indicate the importance of this cytokine in airway inflammation, which can occur in response to environmental allergen exposure. Additionally, the interaction of genetics and fungal exposures has been investigated. Loser et al³⁶ used murine models to demonstrate that an asthma susceptibility gene, *ORMDL3*, contributed to key pathways promoting airway inflammation induced by *Alternaria* species.

Patients with cystic fibrosis (CF) are prone to colonization of the airways with *Aspergillus fumigatus* and subsequent development of allergic bronchopulmonary aspergillosis (ABPA). Diagnostic tests to identify these events were investigated by Gernez et al³⁷ using BATs. Their report suggests that CD203c upregulation alone was equivalent to a combination of CD63 and CD203c in the BAT for predicting *A fumigatus* colonization with or without ABPA in patients with CF. These investigations have also demonstrated that combining a BAT with the CD203c marker and testing for total and specific *A fumigatus* IgE levels allows for classification of patients with CF into 3 groups: those who are nonsensitized, those with *A fumigatus* sensitization without ABPA, and those with ABPA.³⁸ Thus a BAT with CD203c as a biomarker might be helpful in the management of patients with CF.

Previous studies have shown that chitinase activity is increased in the sera and bronchoalveolar lavage fluid (BALF) of patients with asthma, chronic obstructive pulmonary disease, and patients with CF lung disease. Hector et al⁵ found that chitinase activity is increased in patients with CF compared with healthy control subjects and that *Candida albicans* airway colonization in patients with CF was associated with genetic chitinase deficiency. Interestingly, colonization with *A fumigatus* was not associated with increased chitinase activity. This is another potential biomarker and therapeutic target for CF-associated fungal disease.

In addition to biomarkers, management of ABPA in patients with CF has been investigated. Antifungal agents have been used to treat ABPA; however, a Cochrane review³⁹ suggested that because of the lack of properly controlled trials, no conclusions could be made. Further studies will be needed to establish the role of antifungals for CF-ABPA.

Exposure to fungi and bacterial products can result in hypersensitivity pneumonitis (HP) in susceptible subjects. Unfortunately, diagnostic tests for HP have significant limitations. Millon et al⁴⁰ reported the existence of common peptide epitopes on an antigen (dehydrolipoyl dehydrogenase) from *Mycobacterium immunogenum* and *Lichtheimia corymbifera*. This group⁴¹ also showed that these peptides could induce IFN- γ -specific immune responses after stimulation of PBMCs from healthy blood donors. These data suggest that cross-reactivity among HP etiologic agents can lead to improved diagnosis, classification, and preventive measures for HP.

The above reports indicate that significant advances have occurred in the areas of fungal allergy, ABPA in patients with CF, innate immune responses to fungi, and HP.

RESPONSES TO OCCUPATIONAL EXPOSURES

Occupational exposures have a significant effect on asthma and rhinitis morbidity. In a cross-sectional population-based study, Schyllert et al⁴² found that occupational exposure to chemicals substantially increased the risk for rhinitis and asthma in workers exposed to various vapors, gases, and fumes.

A survey of US adults with current asthma indicated that up to 48% might have work-related symptoms.⁴³ It was estimated that up to 2.7 million persons in the United States might have asthma caused by or exacerbated by workplace conditions. In this survey the prevalence of asthma varied from state to state and by occupation. Identification of high-risk occupations could lead to improved asthma morbidity.

In addition to workplace exposures, genetic factors also play a significant role in the development of occupational asthma. Rava et al⁴⁴ found that patients with occupational asthma caused by low-molecular-weight agents and irritants had single nucleotide polymorphisms in genes of the nuclear factor κ B pathway of inflammation. Such studies can result in new therapeutic approaches.

The diagnosis of occupational asthma is often difficult. Pralong et al⁴⁵ reported that in patients suspected of having occupational asthma, a negative methacholine challenge result while the patient is still exposed to the causative agent virtually excludes the diagnosis. This relatively simple test could reduce the need and expense of additional testing. Lastly, fraction of exhaled nitric oxide might have some benefit in the diagnosis of occupational asthma because it can aid specifically in “ruling-in” the diagnosis rather than excluding the diagnosis because of a lack of sensitivity.⁴⁶

RESPONSES TO VIRAL INFECTIONS

Recent research has focused on evaluating the physiologic pathways that help to further understand the well-known link between viral infections and respiratory disease. Human rhinovirus (HRV) infection is a common trigger for asthma and wheezing in children. It has been known that virus-triggered wheezing episodes in early life are associated with an increased risk of asthma at early school age; however, new research has demonstrated that early-life HRV-triggered wheezing episodes are associated with the persistence of asthma out to age 13 years.⁶ This finding highlights the possible effect of HRV infection on airway remodeling, which was investigated by Shelfoon et al.⁷ In doing so, they discovered that HRV-infected human bronchial epithelial cells produced CXCL10 and CXCL8, which are chemotactic for fibroblasts (Fig 2).⁷ This leads to the speculation that repeated HRV infections in childhood result in fibroblast deposition in the airways, resulting in airway remodeling. Han et al⁴⁷ found that Toll-like receptor (TLR) 2 is necessary for rhinovirus-induced airway inflammation in both naive and allergen-sensitized mice. This was demonstrated by mice lacking TLR2 having decreased airway inflammation in response to rhinovirus infection. Furthermore, transfer of TLR2⁺ macrophages was sufficient to produce airway inflammation in TLR2 knockout mice. The identification of the importance of TLR2 provides a possible future therapeutic target for virus-induced asthma.

Early-life infections with respiratory syncytial virus (RSV) also play an important role in the development of wheezing and possible asthma in later life. Despite almost universal infection in children in the first few years of life, it is highly uncommon for newborns to be infected with RSV in the first few weeks of life. Jacobino et al⁴⁸ evaluated a panel of amniotic fluid samples and discovered that all the samples contained RSV-specific IgG with RSV-neutralizing activity. Thus early-life protection from viral respiratory tract infections can be explained by this *in utero*

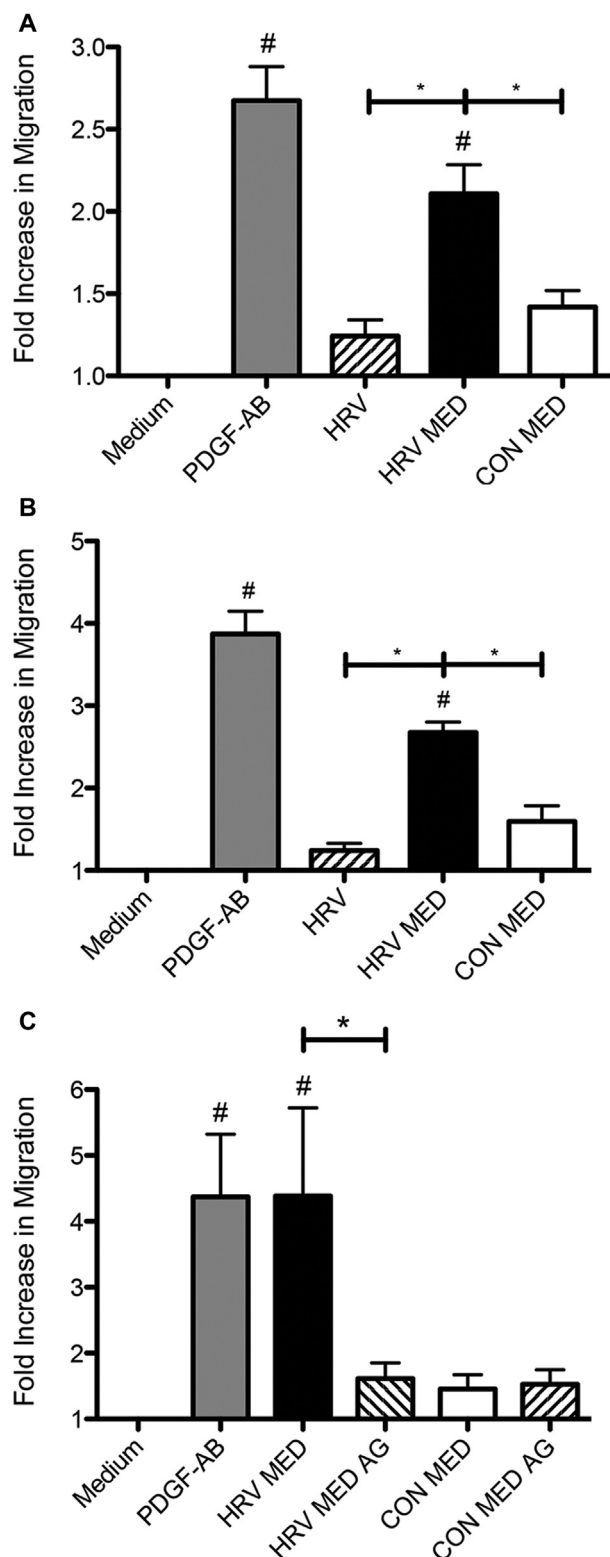


FIG 2. Conditioned medium from epithelial cells infected with HRV (HRV MED) is chemotactic for fibroblasts. **A** and **B**, HRV MED significantly increased migration of human bronchial fibroblasts relative to medium alone, conditioned medium from uninfected cells (CON MED), or HRV alone in the Boyden chamber ($n = 4$; Fig 2, A) or the xCELLigence system ($n = 5$; Fig 2, B). **C**, Abolition of the chemotactic gradient abrogated migration to HRV MED. [#] $P < .05$ versus medium alone. * $P < .05$ versus other treatments. AG, Conditions with abolished gradient.⁷

transfer of amniotic fluid antibodies, which are in direct contact with the fetal respiratory tract. Reducing the risk of asthma development after RSV infection has proved difficult. Carroll et al⁴⁹ conducted a retrospective cohort investigation and found that higher adherence to RSV immunoprophylaxis during infancy was not associated with decreased rates of asthma in later childhood. The authors recommended larger prospective cohorts to better evaluate the potential asthma-preventative benefits of RSV immunoprophylaxis.

Sokolowska et al⁵⁰ found that patients with severe asthma had decreases in antiviral gene and protein expression in response to low-molecular-weight hyaluronan, which is generated during tissue inflammation. This provides insight regarding impaired antiviral response in patients with severe asthma.

In recent years, there has been increasing research regarding the interplay between viral infections and allergen exposures on respiratory disease. For example, Mehta et al⁵¹ demonstrated that infection with rhinovirus inhibits the respiratory epithelium's ability to induce tolerance to inhaled allergens making the lungs more susceptible to inflammation. This interaction might explain why atopy was found to be an important risk factor in not only nonviral asthma exacerbations but also viral exacerbations in children.⁵²

Similarly, trials with omalizumab have noted that blocking IgE-mediated inflammation prevents seasonal peaks in asthma exacerbations related to viral infections.^{53,54} Recent research has focused on the mechanism of this viral and allergic interaction. Toussaint et al⁵⁵ used a mouse model to demonstrate that rhinovirus infections triggered the formation of neutrophil extracellular traps and that blocking this NETosis protects mice from type 2 immunopathology. Future research will likely focus on continued efforts to disrupt the virus and allergen connection with a goal of improving asthma outcomes.

RESPONSES TO AIR POLLUTANTS

Recent studies have both expanded on the epidemiologic risk of exposure to ambient pollutants and further elaborated our understanding of associated immune mechanisms and potential therapeutic targets for patients with asthma. Importantly, because the effect of pollution is rarely experienced in isolation, several coexposure studies have described potentially important interactions to better characterize the combination of threats to respiratory health experienced by subjects, exposures that might be heightened in the context of climate change and the developing industrial world.

Exposure to pollutants can disrupt human biology at each phase of life. Mendola et al⁵⁶ reviewed medical records for 223,502 deliveries in the United States and matched ambient pollution exposure during the course of gestation. Women with asthma and high levels of carbon monoxide and nitrogen oxide exposure either during preconception months or early pregnancy had higher rates of preterm birth than asthmatic women with low levels of these exposures. Particulate matter (PM) exposure was also a risk for early preterm birth (<34 weeks' gestation) in pregnant women with asthma. This demonstrates the important maternal-fetal health implications of high pollution exposure in particular vulnerable populations.

Exposure to pollution in infancy and subsequent risk of asthma was determined in the Genes-Environments and Admixture in Latino Americans II study, the largest US gene-environment

case-control study of asthma in minority children.⁵⁷ Gaseous and particulate exposures in the first year of life were not associated significantly with atopy in this subgroup of children with asthma in the school-age and adolescent cohort; however, there was a significant association between ozone exposure in infancy and the development of nonatopic asthma. This reflects a potential nonallergic mechanism of asthma development in minority children. In fact, in healthy subjects alveolar macrophages are known to have an increased expression of TLR4, TNF- α , and CD14 after ozone inhalation at ambient concentrations, both constitutively and in response to LPS.⁵⁸ In an unselected birth cohort of children from Stockholm, Sweden, enrolled in the BAMSE study, ambient pollutant exposure estimated by road traffic emissions at participant's residential, school, and day care locations were significantly associated with airway obstruction.⁵⁹ This study confirms prior findings from this group demonstrating that exposure to nitrogen oxide and PM₁₀ in infancy significantly decreased spirometric results in adolescence.⁶⁰ In the recent study impulse oscillometry was used to assess peripheral airways obstruction and consistently demonstrated that nitrogen oxide exposure in early life was associated with increased airway resistance in all children, especially those with a diagnosis of asthma at age 16 years. Work by Ierodioakou et al⁶¹ found similar relationships between ambient carbon monoxide, nitrogen dioxide, and reduced lung function. They also report the interesting finding that inhaled corticosteroid use led to an augmented negative response to methacholine in subjects with higher carbon monoxide exposure, suggesting controller medications might not be beneficial for patients with asthma exposed to certain pollutants.

In sum, these studies continue to demonstrate that early-life exposure to pollutants can be an early determinant of the asthmatic disease process and can alter airways function throughout childhood. Because childhood lung function is known to influence trends throughout life,⁶² it is important to identify these potentially modifiable risk factors and targets for therapy. Moreover, although air pollution influences later lung function, concurrent exposure to increased levels of pollutants in adolescence is also directly associated with changes in spirometry.

In the Children's Health Study exposure to nitrogen oxide, nitrogen dioxide, nitric oxide, and PM_{2.5} each were associated with decreases in FEV₁ during the exposure period in adolescent subjects. FEV₁ was found to be even lower in patients who had the absence of a father in the home, a marker for psychosocial stress.⁶³ Annual mean nitrogen dioxide₂ levels and close proximity to a major roadway were found to be associated with asthma symptoms, atopy, and decreased lung function in the middle-aged adult cohort in the Tasmanian Longitudinal Health Study.⁶⁴ Genetic susceptibility to the adverse effects of pollutant exposure was found for the null genotype of the glutathione S-transferase Theta 1 gene (*GSTT1*), an antioxidant gene that plays an important role in modulating the inflammatory response modulated by reactive oxygen species.

A closer approximation to natural exposures in human subjects, several animal and human studies have examined the effect of interaction of ambient pollutants with other environmental triggers for the development and exacerbation of asthma. Animal models in which mice are exposed to diesel exhaust particles (DEPs) and allergens demonstrate that the

degree of inflammatory cellular response, including eosinophils, neutrophils, T_H2 cells, and IL-13⁺IL-17A⁺ cells in BALF and airway hyperresponsiveness, is significantly greater than allergen exposure in the absence of DEPs.⁸ Interestingly, this response was only partially mitigated by steroid treatment but further reduced when anti-IL-17A antibodies were added to the treatment algorithm; this suggests that increased levels of IL-17A might confer an element of steroid resistance, as well as increasing IL-17A levels as a potential therapeutic target in patients with steroid-refractory asthma.⁸

Furthermore, coexposure of DEPs with HDM but not HDM alone promotes persistence of increased lung effector and memory T_H2 cells and, in response to HDM challenge 7 weeks later, demonstrate increased BALF T_H2 cytokine levels and increased airway hyperreactivity. De Grove et al⁶⁵ demonstrated in another mouse model that dual exposure with HDM and DEPs had effects on the epithelial ILC2s and adaptive T_H2 cells; however, only the adaptive T_H2 cells were necessary and sufficient to induce the allergic inflammatory airway response. The clinical correlate to these dual exposure laboratory studies was found by Brandt et al⁹ in the Cincinnati Childhood Allergy and Air Pollution Study birth cohort, in which early-life exposure to traffic related air pollution, measured as elemental carbon attributable to traffic (ECAT), was associated with earlier sensitization. Children who had high exposure to ECAT at birth and sensitization to HDM or any allergen by age 4 years had almost double the prevalence of asthma at age 7 years than those coexposed with low levels of ECAT.⁹

Taken together, these data suggest that pollution exposure early in life in conjunction with allergen exposure might promote a more vigorous inflammatory response during the exposure and a more potent atopic phenotype compared with allergen exposure and sensitization alone. Despite these associations with the development of asthma, Rider et al⁶⁶ found that selective allergen exposure to bronchi of asthmatic adults who had breathed diesel exhaust or purified air in a crossover design study had increased expression of microRNAs and genes associated with bronchial immune responses in bronchial brushing samples; however, there was no augmentation of response by the addition of pollutant exposure. The real-world relationships between pollution and allergen exposure are important to recognize because the increased greenhouse gas accumulation and climate change are anticipated to increase the production, allergenicity, and dispersion of pollen and spores, leading to greater aeroallergen effect on susceptible populations.^{67,68}

The role of epigenetic modification leading to transgenerational disease susceptibility and environmental exposures was investigated by Somnineni et al.⁶⁹ Hypomethylation of the ten-eleven translocation 1 gene (*TET1*) was found to be significantly associated with childhood asthma in both a primary and replication cohort. However, traffic-related air pollution exposure and DEP exposure in tissue culture were found to be associated with increased levels of methylation of *TET1*. Therefore *TET1* gene expression, which is noted to be influenced by pollution exposure, might have an important role in asthma pathogenesis and be a potential target for therapy.⁶⁹ In a randomized crossover clinical trial in adults, Clifford et al⁷⁰ found that the changes in bronchial epithelial cell DNA methylation were marginal at 48 hours after controlled DEP inhalation, isolated bronchial allergen challenge, or both. However, when exposure to allergens and DEPs was separated by 4 weeks,

a much more robust differential methylation pattern emerged. These patterns differed depending on which exposure occurred first. These data suggest that a priming effect by exposure to either pollution or allergen can instruct the airway response to subsequent exposures. More investigation into these relationships will be needed to reconcile the environment-methylation-gene-asthma relationship.

Particulate pollution also impairs mechanical function of the epithelial cell barrier of the respiratory tract, which can promote further insult by infection or allergen. Human sinonasal epithelial cells exposed to PM₁₀ have a dose-dependent destabilization of the epithelial membrane through perturbation of intercellular tight junctions.⁷¹ This destabilization is reversed by activation of nuclear erythroid 2-related factor 2, a known regulator of oxidative and environmental stress.⁷¹ Ecologic data relating airborne dust and heat in the semiarid Sahel region of Africa, where bacterial meningitis is common, found that density of dust (measured as low visibility) during hot weather was significantly associated with meningitis rates over an 8-year period.⁷² Animal models to further investigate the mechanism found that increased dust exposure in mice with asymptomatic pneumococcal nasopharyngeal carriage increased bacterial burden in the nasopharynx and spread to the lungs and brain of the animal. Inflammatory cell response was elicited, but the effectiveness of the response was limited. When increased temperature was added to the animal model, there was a synergistic effect on animal death. The combination of epithelial disruption and increased temperatures creates an environment conducive to disrupting symbiotic microbial colonization in favor of tissue invasion in a manner that might be taking place in the sub-Saharan meningitis belt.

ASTHMA AND THE ENVIRONMENT

On a global level, a perspective on the 2015 United Nations Climate Change Conferences appeared in the *Journal*.¹⁰ This report included an important summary on various ways that climate change has increased the burden of asthma and allergies. Examples include but are not limited to elongation and intensification of the pollen season, increased humidity and mold production, and decreased air quality (Table II). Additionally, there was a recent review describing the phenomenon and increased frequency of thunderstorm-related asthma attacks, including a projection of a further increase in these extreme weather events in future decades caused by climate change.⁶⁷ Annesi-Maesano¹⁰ expressed regret that an agreement from the 2015 international meetings was too weak and did not address health effects from climate change; however, the author shared optimism that future international meetings will be better able to address these topics, including asthma and allergies.

On a more local level, there continues to be new and interesting research on the relationship between environmental exposures and asthma morbidity. This interplay has been well documented in lessons learned from the Inner-City Asthma Consortium. This group has focused research on children with asthma living in low-income urban areas, where asthma burden is high. Their recent study, Asthma Phenotypes in the Inner City (APIC), has expanded the asthma literature by identifying asthma phenotypes, distinguishing characteristics of difficult-to-control asthma, and describing pathways explaining asthma severity in this population. In one of the primary objectives of the APIC study,

TABLE II. Effects of climate change on triggers for allergic and respiratory diseases

- Earlier onset of the pollen season
- Elongation of the pollen season
- Increased plant growth
- Increased pollen allergen produced by each plant
- Increased humidity and increased mold allergen production
- Decreased air quality and increased air pollution
- Changing habitats for stinging insects
- More extreme weather events (ie, heat waves and thunderstorm asthma)

Zoratti et al⁷³ performed a cluster analysis and identified 4 clusters in which more severe asthma often coclustered with increased allergic inflammation. These findings suggest that environmental allergen avoidance, allergen desensitization, and anti-T_H2 therapies are appropriate interventions for most inner-city children with asthma. In contrast, there was 1 previously unreported phenotype that was identified and characterized by frequent asthma symptoms despite only minimal allergic inflammation. These children might benefit from evaluation of uncontrolled comorbidities or unrecognized nonallergic triggers, such as environmental tobacco exposure. Additionally, it was found that approximately 40% of the children in the cohort had difficult-to-control asthma despite good adherence with controller therapies.⁷⁴ In agreement with the findings of the cluster analysis, the children with difficult-to-control asthma were able to be identified early in the course of treatment by using pulmonary physiology measures and allergic markers, such as rhinitis scores, total serum IgE levels, and allergen sensitization. Thus recognition of the amount of allergic inflammation in an inner-city child might not only assist in guiding allergen avoidance strategies but might also predict children in need of closer monitoring because of difficult-to-control asthma.

Finally, Liu et al⁷⁵ investigated pathways through which asthma risk factors contribute to asthma severity in these inner-city children. In this analysis it was discovered that the allergy pathway and tobacco smoke exposure pathway exerted the predominant effects on asthma severity. These findings further underscore the importance of environmental exposures in inner-city asthma.

In addition to allergic triggers, there are other environmental influences that continue to be identified as important factors in asthma development and control. Stein et al¹¹ found that children raised in an Amish environment with traditional farming were exposed to a rich environment of microbes and had low rates of asthma. In an experimental model these researchers showed that the protective effect of that specific environment was due to activation of the innate immune response. Conversely, this suggests that development of asthma might be enhanced when innate immune stimulation is absent or weak. In the APIC study environmental tobacco smoke was associated with worsening pulmonary physiology and increased asthma severity.⁷⁵ Horner et al⁷⁶ reported that increased child-reported stress during the day was associated with an increased likelihood of awakening that night from asthma but not awakening for a reason other than asthma. Finally, a study of inner-city schools discovered that increased exposures to mouse allergen in the schools was associated with increased asthma symptom days and decreased

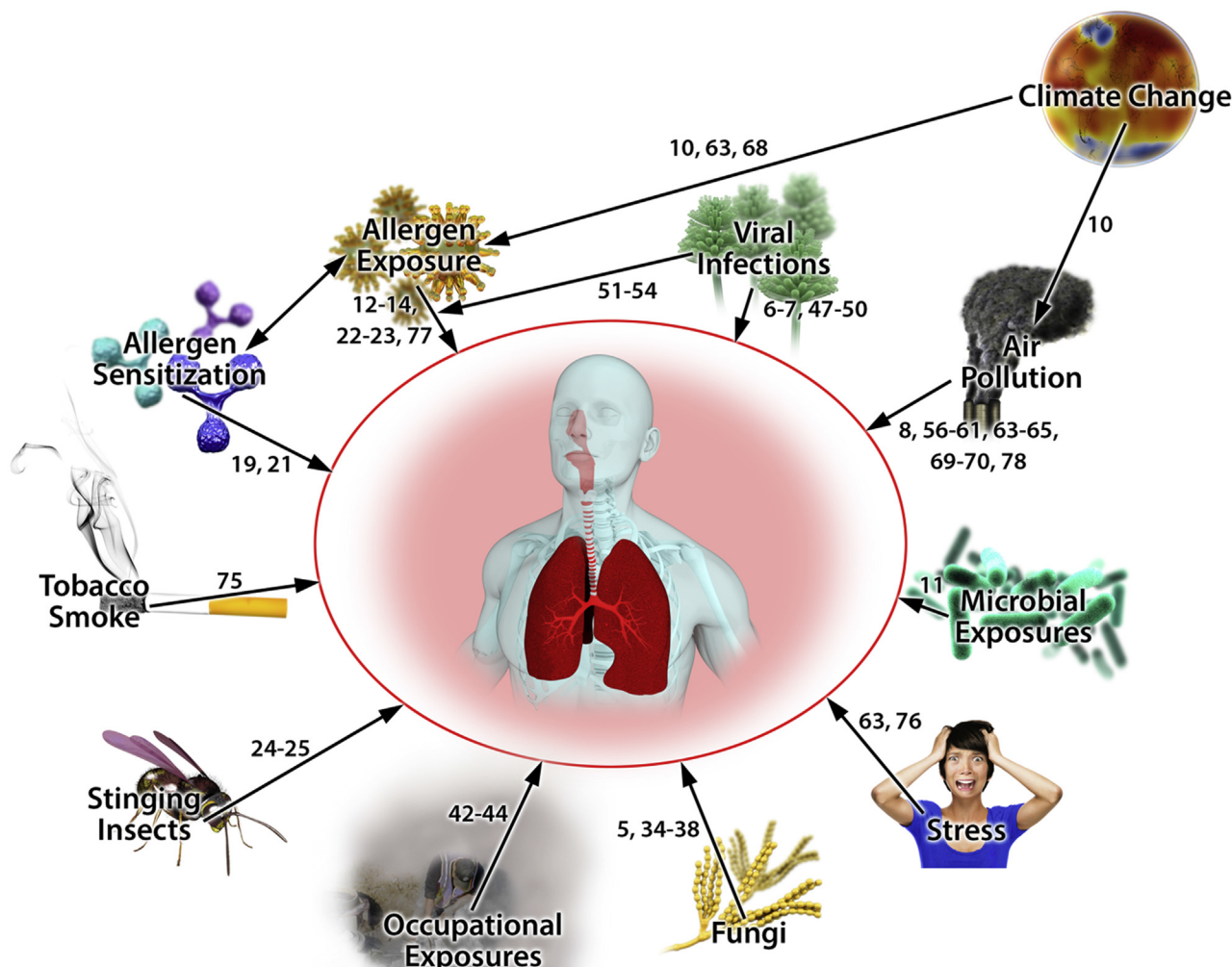


FIG 3. Summary of some of the areas of recent advancement in this field. Numbers indicate reference numbers in this article. Certainly, there are other influences on allergic and respiratory diseases that have not been reviewed in this article.

lung function.¹² A surprising finding of this study was that the association of mouse allergen exposure and asthma outcomes was significant, irrespective of sensitization status. This indicates that high levels of mouse allergen exposure might be a direct irritant or result in nonallergic-mediated inflammation, even in nonsensitized subjects.

Research continues on environmental interventions to reduce harmful exposures and improve asthma outcomes. Rabito et al⁷⁷ evaluated a single intervention, insecticidal bait, to reduce cockroach exposure and improve asthma outcomes in children. When compared with control homes, intervention homes had significantly fewer cockroaches at follow-up, and this was associated with improved asthma outcomes.⁷⁷

In contrast, other recent randomized, controlled, environmental allergen intervention trials have not seen significant differences between intervention and control homes. For example, DiMango et al¹³ demonstrated that targeted household allergen reduction strategies effectively reduced levels of all measured allergens (cockroach, mouse, dust mites, cat, and dog) but did not result in a further reduction in asthma controller therapy when

compared with the control group. Similarly, Matsui et al¹⁴ implemented a randomized home intervention trial targeted for mouse allergen reduction and discovered that professional integrated pest management did not result in a significant difference in maximal asthma symptom days when compared with participants given education alone. Many participants in both groups experienced significant reductions in household mouse allergen exposure, and this reduction was associated with improved asthma outcomes; however, there were not significant differences between the intervention and education groups.

The results of these 2 studies not finding a significant difference highlights a difficulty with home environment intervention trials, namely that both groups (intervention and control) often improve. The reason for this is likely one of 2 factors: (1) control groups also experience a significant reduction in certain household allergen levels, possibly as a result of subject-initiated preparation in anticipation of household inspections, and/or (2) both groups experience improvements in asthma measures, possibly because of enrollment in a study with regular follow-ups and

encouragement of good adherence to freely provided medications. Future household intervention studies will need to continue to develop strategies to overcome these possible hurdles to isolate and examine the specific effect of environmental interventions.

Finally, there is opportunity for environmental intervention studies outside of the home. Jhun et al⁷⁸ demonstrated that classroom-based air cleaners led to significant reductions in PM_{2.5} and black carbon when compared with control classrooms. This highlights the school as a location for future environmental intervention studies aimed at improving asthma symptoms in children.

SUMMARY

In this review we examined recent literature focused on environmental exposures and the links to allergic and respiratory diseases. There were important findings regarding IgE responses to environmental stimuli, mechanisms of fungal allergy, inflammatory responses to viral respiratory tract infections, respiratory effects of air pollution exposures, and the effect of early-life exposures on asthma development. We have highlighted and summarized some of these findings in Fig 3. The understanding of the association of environmental exposure and clinical outcomes has led to new strategies for treatment and intervention. It is expected that future research will continue to expand on these strategies to improve respiratory health for all.

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