



Environmental exposures: evolving evidence for their roles in adult allergic disorders

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Purpose of review

Allergic disorders are the result of complex interactions between genetic predisposition and environmental exposures. Elucidating how specific environmental exposures contribute to allergic diseases in adults is crucial, especially as the world population ages in a rapidly changing environment.

Recent findings

The effects of environmental exposures on allergic diseases remain understudied in adults. Although epidemiological studies suggest various environmental exposures are associated with the development and exacerbation of allergic diseases, further longitudinal studies are needed across various age groups in adults to pinpoint the exposures of concerns and the time windows of susceptibility. Mechanistic studies in adults are few. A multicomponent strategy targeting several allergens has been conditionally recommended for asthma, but recent findings on mitigation strategies remain limited.

Summary

Further research on how environmental exposures cause and exacerbate allergic disorders is needed in adults, particularly across disease phenotypes. The effects of mitigation strategies against environmentally induced adult allergic diseases remain large research gaps. A better understanding of how and which environmental exposures contribute to allergic disorders is necessary to identify patients who are at higher risk and would benefit from specific interventions.

Keywords

air pollution, chemicals, environmental exposure, exposome

INTRODUCTION

The concept of the exposome, defined as the entire exposure from external and internal environments, has created a framework for considering how the totality of the environment contributes to the development and exacerbation of allergic disorders [1]. Studies in monozygotic twins have shown that genetic inheritance alone is an insufficient cause of many chronic diseases, including asthma [2]. Elsewhere, established genetic risk factors such as filaggrin mutations and effects of ancestry have been unable to explain the burden of atopic dermatitis past childhood [3,4]. These findings emphasize the importance of understanding how environmental exposures and other changing conditions interact with inherited genetic predisposition. Although great progress has been made on the importance of the prenatal and early childhood environment risk factors in childhood allergic disorders, the impact of environmental exposures remains understudied in adults. Evolving evidence will remain the focus of this review.

EPIDEMIOLOGIC ASSOCIATIONS

Aeroallergens

Despite the importance of allergen exposure to multiple allergic diseases, recent research among adults has focused mostly on asthma. For example, one retrospective study evaluated short-term effects of aeroallergens gathered from 3 pollen-collecting stations in Seoul on asthma exacerbation visits to emergency rooms (ERs) in 2008–2012. Among cases, 8,639 (29.97%) were adults aged 18–59 years, and 6,675 (23.16%) were in elderly adults aged 60 years or older. Tree, but not grass or weed,

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KEY POINTS

- Many environmental exposures, including aeroallergens, air pollution, chemicals, endotoxin, and the microbiome, appear associated with the development and/or exacerbation of allergic diseases in adults.
- Air pollution appears to be more strongly associated with nonatopic phenotypes of eczema and rhinitis.
- Further studies are required on environmental causes of allergic diseases in adults and mitigation strategies for patients who are at higher risk of exposure.

allergen was associated with asthma exacerbations in adults aged 18–59 years only [5]. These results suggest that specific allergic triggers of ER visits for asthma may vary across aeroallergens.

Roberts *et al.* elucidated the relationship between allergic sensitization and current allergy symptoms by assessing component-resolved diagnostics that detect immunoglobulin (Ig) E for individual allergens. Machine learning was used to study interactions across over 100 allergenic components, and network analyses were applied to determine whether connectivity differed by asthma severity, including among the 509 (65.26%) in their cohort that were adults. There was no relationship between an elevated IgE level to any single allergen and asthma severity. But in severe asthma, there was weak connectivity among IgE levels to proteins that were structurally unrelated, whereas in mild or moderate asthma, there were fewer but stronger connections between structurally similar proteins [6[¶]]. The number, structural similarity, and strength of connectivity patterns among allergenic components may be useful biomarkers of disease severity in patients with allergic asthma.

Air pollution

Despite conflicting evidence [7], an American Thoracic Society workshop published a report in 2020 writing that there was inconclusive evidence regarding outdoor air pollution exposure and new onset asthma in adults [8]. Findings regarding air pollution and eczema are inconsistent and may reflect differences by asthma phenotype, particularly atopic versus nonatopic eczema. The Study on the influence of Air pollution on Lung function, Inflammation and Aging (SALIA) reported on a cohort of adult women in Germany who was followed for 19 years. Traffic-related air pollution (TRAP) exposure was estimated from residential addresses using land-use regression models based on 3 two weeks'

measurements of nitrogen oxides (NO_x), NO₂, and particulate matter (PM). TRAP exposure at baseline was estimated using back-extrapolation algorithm. The incidence of patient-reported eczema after age 55 years was associated with NO₂, NO_x, PM_{2.5} (PM diameter ≤ 2.5 μm), and PM₁₀ (PM diameter ≤ 10 μm) [9]. A subsequent study was done in this cohort of older women using three increasingly strict definitions to exclude atopy: participants who never had hay fever, participants who never had hay fever and did not have IgE levels greater than 100 IU/mL at baseline, and participants who never had hay fever and did not have IgE levels greater than 100 IU/mL at baseline and follow-up. When these stricter definitions were applied, the previously described association between air pollutants (NO₂, NO_x, PM_{2.5}, PM₁₀) at baseline and eczema incidence after age 55 years grew stronger. Thus, TRAP may influence the development of nonatopic eczema more than atopic eczema in older women [10]. However, these findings were not replicated by Lopez *et al.* when they conducted a prospective study on air pollution and eczema in Tasmania, Australia. The participants were 43 years old at baseline, and eczema were evaluated 10 years later. Air pollution exposure at residential address was measured using distance from a major road and NO₂ and PM_{2.5} levels from satellite-based land-use regression models. Atopic eczema was defined as having at least one positive skin prick testing to common aeroallergens. NO₂ exposure was associated with increased odds of prevalent eczema and for atopic eczema specifically at follow-up in males, but not females. Similarly, NO₂ and PM_{2.5} were associated with increased odds of persistent atopic eczema in males only. Unlike the findings from SALIA, no significant association was observed between ambient air pollution and incident eczema [11[¶]].

The association between air pollution and rhinitis may depend on phenotype. A cross-sectional study of two European cohorts after twenty years of follow-up found that higher exposures to PM₁₀ and PM_{2.5} were associated with higher levels of rhinitis severity. When participants were stratified by allergic sensitization, the effects of pollutants strengthened for participants with nonallergic rhinitis. Increasing levels of NO₂, PM₁₀, PM_{2.5}, PM_{coarse} and traffic intensity on the nearest road were associated with increased severity score of rhinitis in nonallergic participants, whereas only PM_{2.5} was associated with severity in participants with allergic sensitization. A similar pattern was observed when participants were stratified by asthma status; increases in NO₂, PM₁₀, PM_{2.5}, and traffic load and intensity were associated with increased severity score of rhinitis only among the nonasthmatics

[12[¶]]. Overall, it appears that air pollution may contribute more to rhinitis severity in individuals with nonatopic phenotypes.

Chemicals

The National Health and Nutritional Examination Survey (NHANES) has yielded abundant cross-sectional findings on chemical exposures from a diverse and large sample across the United States. Overall, the association between chemical exposures and asthma appears to vary by age and sex. For example, one study measured spot urine phthalate metabolite concentrations and found no significant associations between phthalate levels and self-reported asthma in adults overall. However, in stratified analyses, mono-ethyl phthalate (MEP) was associated with current asthma in adult males. In contrast, mono-(3-carboxylpropyl) phthalate (MCPP) and mono-(carboxynonyl) phthalate (MCNP) were negatively associated with current asthma in adult females [13]. Mendy and colleagues found that spot urine levels of bisphenol (BP) F, but not BPA, was associated with higher odds of current asthma. This association was strongest in adults aged 18–59 years compared to younger and older age groups. When stratified by sex, higher BPS levels were associated with increased odds of asthma in males, but not females [14[¶]].

Among the same cohort of patients, Mendy *et al.* found that higher urinary BPF levels were associated with self-reported symptoms of allergic rhinitis after adjustment by age [14[¶]]. Another study evaluating allergic symptoms in relation to urinary nitrate, thiocyanate, and perchlorate levels found that urinary thiocyanate was positively associated with the prevalence of sneeze regardless of age and sex [15].

Endotoxins

Recent research generated from NHANES also suggested that exposure to endotoxin may synergize with other environmental toxicants to cause allergies [16,17]. Mendy and colleagues investigated the contributions of endotoxin measured from bedroom dust with air pollution exposure predominantly (75.8%) among adults participating in NHANES. Annual average exposures to PM_{2.5}, ozone (O₃) and NO₂ at participants' addresses were estimated using air quality modeling systems from the Environmental Protection Agency. PM_{2.5}, O₃, and NO₂ were associated with higher ER visits for asthma in the past 12 months. Interestingly, co-exposure to elevated concentrations of residential endotoxin and ambient PM_{2.5} increased the odds of ER visits for asthma in the past 12 months by fivefold. This association was stronger than the sum of endotoxin

alone and PM_{2.5} alone, suggesting that these environmental exposures interacted synergistically [18].

Microbiome

The influence of the microbiome, part of our internal exposome, on the development of allergic diseases continues to be delineated. A cross-sectional study of adult farmers and their spouses from North Carolina and Iowa found that bedroom dust bacterial diversity was lower in participants with seroatopy or allergic rhinitis, but not asthma. The bacterial composition differed as well, with the genera *Bacteroides*, *Porphyromonas*, and *Fusobacterium* more abundant in homes of participants with asthma and allergic rhinitis [19[¶]].

A cross-sectional study of the adult nasopharyngeal microbiome found that the composition of the microbiome, but not its diversity, differed by asthma diagnosis. Additionally, different patterns were observed by age group. In young adults aged 18–45 years, phylum *Proteobacteria* was more abundant in asthmatics, whereas genera *Corynebacteriales* was higher in nonasthmatics. In the elderly group aged 65 years or older, genera *Moraxella* was more common in nonasthmatics. The relative abundance of genes whose functions related to N-glycan biosynthesis, peroxisome proliferator-activated receptor gamma signaling and degradation of toxins were lower in asthmatics. In contrast, genes whose functions related to pentose phosphate pathway, lipopolysaccharide biosynthesis, flagellar assembly, and bacterial chemotaxis were higher in asthmatics [20]. These findings suggest that bacterial composition, not diversity, may play a functional role in asthma.

MECHANISMS AND BIOMARKERS

Much of the recent mechanistic work addressing which inflammatory pathways are elevated following environmental exposures have focused on determining relevant biomarkers, such as determinants of altered epigenetic regulation. For example, Li and colleagues conducted a randomized, double-blind crossover study to investigate changes in DNA methylation following diesel and allergen exposure among 11 allergen-sensitized adults. Endobronchial biopsies, bronchoalveolar lavages (BAL), and spirometry were obtained 48 h following exposure to filtered air, allergen, and allergen and diesel. Levels of DNA methyltransferases (DNMTs) and ten-eleven translocation (TET) methylcytosine dioxygenases, that mediate hydroxymethylation, were analyzed from endobronchial biopsies. Among all participants, there was a positive correlation between

DNMT and TET levels and lung function. Participants were then categorized by baseline levels of biomarkers of DNA methylation. Those with high TET2 had higher baseline levels of IL-8 in BAL, and allergen exposure was associated with decreased IL-8, implying that TET2 downregulates IL-8 [21[■]].

Another novel experiment evaluated the role of ceramide, a key metabolite in the sphingolipid pathway, in allergen-induced airway inflammation and apoptosis. Mice were sensitized with either dust mite or the fungal allergen *Alternaria alternata* over 2 weeks and then underwent allergen challenge. Analysis of lung tissue demonstrated apoptosis of airway epithelial cells, increased reactive oxygen species and ceramide levels, and activation of the apoptosis precursor caspase 3. Intraperitoneal treatment with myriocin prior to allergen challenge reduced ceramide levels, allergen-induced apoptosis, oxidative stress, and neutrophilia. In comparison, dietary supplementation with antioxidative α -tocopherol reduced reactive oxygen species but not ceramide levels nor apoptosis, suggesting that oxidative stress is not the cause of allergen-induced ceramide generation or apoptosis. To examine whether ceramide may be used as a biomarker in asthmatic patients, the investigators then measured ceramide levels from BAL fluids in 10 severe asthmatics, 5 nonsevere asthmatics, and 5 healthy controls. Ceramide levels were higher in adults with severe asthma, but not mild asthma, compared to healthy controls. Among all of the participants, ceramide levels correlated with airway obstruction on spirometry and neutrophil infiltration in BAL [22[■]]. Combined, these results suggested that allergic airway inflammation may be characterized by ceramide generation and apoptosis.

INTERVENTION STUDIES

Controlled intervention studies for allergic diseases have met many challenges. The recent National Asthma Education and Prevention Program (NAEPP) Coordinating Committee Expert Panel guidelines on asthma management included a systematic review of indoor allergen mitigation strategies on asthma outcomes and reported a low certainty of evidence favoring allergic asthma treatment with mitigation strategies that targeted indoor allergens. A multicomponent mitigation strategy aimed at multiple allergens was recommended over single-component interventions such as high-efficiency particulate air (HEPA) vacuum cleaners, pest removal, and carpet removal. Pest management for asthmatic patients with cockroach and mice sensitivity was the only intervention that was recommended either as a single-component or part of a multicomponent strategy.

There was insufficient evidence regarding pet removal as part of a multicomponent strategy [23[■]]. Notably, the studies cited to make these recommendations were published several years ago, highlighting the need for more recent studies evaluating mitigation strategies on specific asthma outcomes.

The World Allergy Organization published an expert consensus on allergic rhinitis aggravated by air pollutants in 2020 that recommended ventilation either through modern heating, ventilation, and air conditioning systems with HEPA filter or periodically opening windows [24]. A randomized, double-blind, and placebo-controlled study in South Korea evaluated the effect of air purifiers placed in participants' bedroom and living room with HEPA filters on allergic rhinitis among adults with dust mite hypersensitivity. Both PM_{2.5} and PM₁₀ and use of allergic rhinitis medications decreased in the homes with air purifiers. However, symptom and quality of life scores did not appear to improve [25].

A randomized controlled study investigated the effects of higher altitudes on asthma by enrolling patients in a hospital rehabilitation program at either a high-altitude (3100 m) or low-altitude (760 m) center in Kyrgyzstan. Both groups spent 3 weeks at the center and participated in activities such as patient education, endurance training, and breathing exercises. When fractional exhaled nitric oxide (FeNO) was obtained before and at the end of the rehabilitation program, participants in the high-altitude group had a significant reduction in FeNO compared to those in the low-altitude group [26[■]].

Dietary probiotics have been studied as an intervention given their hypothesized effects on restoring homeostasis within the host microbiome. Zwicker *et al.* studied the effects of intranasal treatment with *Escherichia coli* A0 34/86 (*E. coli* O83) during sensitization and airway challenge with ovalbumin in mice. Treatment with *E. coli* O83 reduced airway hyperreactivity and airway levels of eosinophils and Th2 cytokines (IL-5, IL13), with additional experiments supporting a mechanistic role of toll like receptor 4 signaling [27]. The authors interpreted these findings to indicate that local administration of probiotic to mucosal airway surfaces may be an effective therapy for allergic airway inflammation.

FUTURE DIRECTIONS

Current research on environmental causes of allergic diseases has favored studies in children more than the adult population. Further research is needed in adults, including causes for adult disease onset, persistence, and remission. Longitudinal studies are needed to assess the effects of dose and timing and windows of susceptibility to environmental

exposures through adulthood. Future research on mitigation strategies is essential as evidence in this area is limited, as noted in the recent NAEPP guidelines. Additional insight into biomarkers such as connectivity patterns between allergens and molecular signatures such as DNA methylation changes may help identify patients who are more susceptible to environmental exposures and would benefit from customized recommendations.

CONCLUSION

Allergic disorders result from complex interactions between genetics and a continuously changing environment. Recent findings have identified associations between a wide range of environmental exposures and allergic disease in adults. A better understanding of how environmental factors influence allergic disorders in adults is crucial.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
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