

The Effects of the Environment on Asthma Disease Activity



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KEYWORDS

• Asthma • Environment • Allergens • Pollutants • Disparities • Asthma morbidity
• Microbiome • Endotoxin

KEY POINTS

- There are influential factors in the biological, physical, and psychosocial environments of children with asthma. They can be protective or a risk factor for developing asthma depending on the timing of exposure, or they can be a trigger for current asthma.
- Allergen exposure is a significant asthma trigger, and remediation is an important component of asthma management. However, there is a lack of high-quality evidence for single-component interventions.
- Coarse particulate matter has been recently found to be associated with prevalent asthma and asthma health care utilization.
- Social factors are associated with asthma outcomes and should be addressed with law and policy reform.
- More innovative, patient-oriented, and health services research approaches should be considered to further evaluate the environment's role in asthma.

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INTRODUCTION

Asthma is one of the most common chronic conditions in children with, the highest prevalence rates among Puerto Ricans and blacks and minority communities.^{1,2} It is associated with significant morbidity, health care utilization, and productivity loss.^{1,3,4} Despite advances in asthma therapies and health insurance expansion,⁵ the biologic, physical, and psychosocial environment can still impact asthma disease activity.⁶

Understanding influential factors in the biologic, physical, and psychosocial environments of children with asthma is integral to managing asthma. This article highlights current evidence and advances regarding the role of environmental elements affecting asthma activity, through a determinants of health lens.⁷

BIOLOGICAL, PHYSICAL, AND PSYCHOSOCIAL ENVIRONMENTS

The determinants of health framework approach to the role of the environment in asthma, can be thought of in 3 categories: biologic, physical and psychosocial environments.^{8,9}

BIOLOGIC ENVIRONMENT

Over the past 2 decades, there has been increased attention to the role of the indoor environment (eg, work, home, or school) in asthma management. Exposure to multiple indoor allergens in US homes is common. In a cross-sectional study, more than half of surveyed homes had detectable levels of all allergens (dust mite, dog, cat, cockroach, mouse, and *Alternaria alternata*), and most homes had at least 3 allergens at increased levels.¹⁰ Multiple studies have shown that indoor allergens, biologic matter, and pollutants including mouse, cockroach, pets, dust mite, mold, endotoxin, and nitrogen dioxide are important asthma symptom risk factors in homes and schools.¹¹ Simons and colleagues¹² demonstrated in a study of 120 inner-city homes of children with asthma that the high airborne pollutant levels and inner-city home characteristics predisposed them to greater asthma morbidity. In addition to home, children with asthma will have exposures in other environments where they spend time (eg, school).^{11,13} The indoor school environment is a reservoir of allergens, molds, pollutants, and endotoxins, and recent studies suggest a significant relationship between school allergen exposure and pediatric asthma morbidity.^{14,15} Additionally, there is a paucity of high-quality evidence regarding single-component interventions and indoor allergen exposure reduction and asthma outcomes.¹⁶

Allergens

Dust mites

Dust mites are one of the most prevalent sources of indoor allergens and the most studied allergen in asthma development.¹⁷ The most common dust mite species are Der f 1 (*Dermatophagoides farinae*) and Der p 2 (*Dermatophagoides pteronyssinus*). Dust mite allergens activate the adaptive and innate immune systems,¹⁸ and Der f 1 induces inflammatory cell death in bronchial epithelial cells.¹⁹ Almost 85% of allergic asthmatic children are sensitized to either or both dust mite species.²⁰ In children who are sensitized to dust mite, dust mite exposure is associated with increased bronchial hyper-responsiveness, impaired respiratory function, and increased inflammation.²¹

Strategies to reduce dust mite include: frequent washing of all bed linens in hot water, use of allergen-impermeable mattresses and pillow encasements, and measures targeting other dust mite reservoirs such as vacuuming and removal of carpet and

stuffed toys. Of note, there is no recent evidence suggesting modern carpets do not serve as a dust mite allergen reservoir.²² Dust mite acaricides can reduce dust mite allergen burden but are not associated with improvement in pulmonary physiology or asthma symptoms, when compared with placebo or when part of multicomponent interventions.¹⁶ Maintaining indoor humidity at 35% to 50% can reduce dust mite proliferation and survival but can be difficult to sustain. Moreover, high-efficiency particulate air (HEPA) filtration has not been shown to have a great effect on lessening dust mite exposure.²¹

Rodents (mouse)

The major mouse allergen, Mus m 1, is excreted in mouse urine and found in dander and hair follicles. Mus m 1 is carried on small particles, and remains airborne for prolonged periods of time. It is found in house dust particles and is high in kitchens, but also found in bedrooms.²³ Mus m 1 was previously thought to be a significant occupational exposure but is now known to have a role in asthma morbidity.²⁴ Recent studies demonstrate a high prevalence of mouse allergen in domestic households, where urban homes have higher mouse allergen levels compared with suburban and rural homes. Patient report of rodent infestation has a high positive predictive value for high home mouse allergen levels,²⁵ but a negative report is not reliable for ruling out exposure.²⁶

Although dust mite is the most common allergen sensitization in children with asthma, new literature suggests mouse allergen is the most relevant urban allergen, more than cockroach allergen.²⁷ Mouse allergen had the highest rate of detection in homes and schools but was significantly higher in schools in the School Inner-City Asthma Study. Mouse allergen exposure, independent of sensitization and home allergen exposure, was significantly associated with more asthma symptoms days and decreased forced expiratory volume in 1 second percentage (FEV₁%) predicted, suggesting the school environment's importance in urban asthma. An ongoing school-specific environmental intervention is being conducted, targeting exposures including mouse (NCT02291302).^{15,28}

The Mouse Allergen and Asthma Intervention Trial investigated if professionally delivered integrated pest management and education compared with education alone was associated with improved asthma morbidity. No difference was found, and there was no statistically significant difference in the proportion of subjects with large decreases of mouse allergen (except for 1 airborne measure) between groups. Results were limited, as both arms had significant reductions in exposure, limiting the ability to detect a difference and inability to double blind the environmental intervention.²⁹

Cockroach

Cockroach allergy has been established as an important cause of asthma exacerbations for the past few decades. The German cockroach (*Blattella germanica*) and American cockroach (*Periplaneta americana*) are the most medically important species. Cockroach allergens Bla g 1 and Bla g 2 are mostly evaluated in exposure assessment studies.³⁰

Recent evidence based on skin prick testing, found that 60% to 80% of inner-city children with asthma are sensitized to cockroach. A study in 61 homes of low-income Chicago children also found that cockroach allergen exposure in bedrooms was associated with increased asthma symptoms.³¹ Although less investigated, cockroach allergen is also detectable in suburban and rural homes, albeit at lower concentrations.

Two components to cockroach allergen remediation are suppression of cockroach populations and removal of the residual cockroach allergen.³² The New Orleans Roach Elimination Study was a randomized trial examining the effect of cockroach insecticidal bait on asthma symptom days. Interestingly, the intervention effect was associated with cockroach sensitization. Cockroach sensitized children in the control group had a significantly higher number of missed school days, symptom days, and health care utilization.³³ Notably cockroach numbers significantly reduced and stayed low for 6 to 12 months, but symptoms gradually improved over 6 to 12 months. This lag in symptom improvement has been attributed to the cockroach allergen in cracks, crevices and walls, suggesting professional cleaning and abatement are critical to comprehensive cockroach management.^{34,35}

Cat and dog

Cat and dog are the most common indoor furry pets, and sensitization is known to be associated with severe asthma in childhood.³⁶ Allergic sensitization to cat and dog is quite common; approximately 12% of the general population and 25% to 65% of children with persistent asthma are sensitized to cat or dog allergens.³⁷ Fel d 1 and Can f 1 are the major allergens for cat and dog, respectively, and are present in saliva, hair follicles, and skin. Pet allergens are predominantly carried on small particles (<10–20 μ m), allowing them to remain airborne for long periods of time and adhere to clothing and surfaces. Therefore, pet allergens are carried long distances, and are passively transferred to environments where no pets are present, leading to indirect exposure^{35–39} Children in classes with greater than 18% cat owners had a ninefold increased risk of exacerbated asthma after school started compared with children in classes with no more than 18% cat owners.⁴⁰

The ideal approach furry pet allergen exposure reduction is to remove the pet from the home. The only study examining pet removal demonstrated that by 20 to 24 weeks after cat removal, most homes with pet cats had cat allergen levels similar to control homes without cats.⁴¹ Control of cat allergen exposure is accomplished by: pet removal from the home/bedroom; regular cleaning allergen reservoirs (upholstered furniture, walls, and carpet), encase the mattress and pillows with bed encasing (pore diameter <6 μ m), regular pet washing and HEPA filtration.^{35,42}

Mold

There is a wide variety of indoor and outdoor molds, and their allergenic proteins vary by mold species. The most common species to which children are sensitized and exposed are *Alternaria* and *Cladosporium* (outdoor), *Aspergillus*, and *Penicillium* (indoor).⁴³ The prevalence of mold sensitization in children with persistent asthma is variable in the literature, ranging from 12% to 66%.^{44,45} Qualitative assessments of fungal exposure in the form of mildew odor or visible mold have been linked to increased risk of allergic rhinitis and asthma.⁴⁶ Furthermore, a recent study by Baxi and colleagues⁴⁷ demonstrated that the school/classroom environment can be a source of mold exposure, both in quantity of spores and variety of mold types, and the presence of visible mold may be a predictor of high mold spore counts.

Mold exposure can contribute to severe asthma and to asthma development. Mold-sensitized children have significantly lower lung function and increased airway hyper-responsiveness compared with children not sensitized to mold.^{43,44,48,49} Birth cohorts have demonstrated a relationship between mold sensitization and recurrent wheezing and asthma and a recent birth cohort study in Boston revealed a significant relationship between indoor dust-borne *Alternaria* at the age of 2 to 3 months and the

frequency of wheeze by 1 year old, even after adjustment for outdoor airborne *Alternaria* concentrations.^{50–52}

There are no solitary or randomized controlled trials of mold remediation. Mold remediation has only been included in multicomponent strategies (eg, interventions also targeting dust mites or furry pet allergens), which have all shown improved asthma symptoms.¹⁶ Mold remediation includes: mold removal from surfaces (using cleaner and fungicide), repair of leaky water sources, dehumidification, and ventilator system installation. Mold remediation can be costly and burdensome. Chew and colleagues⁵³ proposed a 2-part interview to guide clinicians on how to decide which patients would warrant in-home assessments for mold exposure with an indoor environment professional (IEP). Presently, the literature insufficiently explains which children would be at risk for developing asthma from mold exposure or if there is a dose threshold of mold exposure that will exacerbate asthma.

Endotoxin

Endotoxin is part of the gram-negative bacteria's outer membrane and is shed after bacteria die.⁵⁴ Endotoxin induces airway inflammation via Toll-like receptor (TLR) 4 and is an established asthma risk factor. Higher domestic endotoxin levels are linked to increased asthma prevalence, severity, and exacerbations.

Endotoxin in homes has been demonstrated to increase wheeze⁵⁵ and can potentiate the airway response to allergens in people with asthma.⁵⁶ A cross-sectional study found: poverty, Mexican ethnicity, younger age, carpeting, furry pet, cockroaches, and/or a household smoker predicted higher endotoxin levels.⁵⁷ Endotoxin in other indoor areas such as the school also has an impact on asthma morbidity. Sheehan and colleagues⁵⁸ identified higher settled-dust endotoxin levels in inner-city schools compared with students' homes. In this same cohort, classroom-specific airborne endotoxin levels were found to be independently associated with increased asthma symptoms in children with nonatopic asthma, after adjusting for home exposures.⁵⁹

Conversely, there is also literature supporting the contrary, that early endotoxin exposure is protective of childhood asthma.^{60–62} Endotoxin's protective qualities were recently highlighted by Stein and colleagues⁶⁰ in their investigations of environmental exposures, ancestry, and immune profiles of Amish and Hutterite children. None of the Amish children and 20% of the Hutterite children had asthma. The Amish homes had significantly higher median levels of endotoxin in airborne dust compared with the Hutterite homes, respectively. Endotoxin's protective and exacerbative roles in asthma underscore that the timing of exposures plays a critical role in asthma.

Microbiome

The microbiome is the combination of all microbes colonizing skin and mucosal surfaces, their genomic elements, and interactions.⁶³ Many factors play a role in influencing the development, evolution, and stability of the microbiome, such as the innate immune response, genetic factors and environmental factors (eg, dietary factors, antibiotics, and infections).⁶⁴ Any disruption in this stability can increase risk of allergic diseases later in life.

Several studies have linked early life dysbiosis or microbial imbalance in the gut microbiota with an altered risk of asthma later in life.⁶⁵ Arrieta and colleagues,⁶⁶ reported that the first 100 days may be a critical window for the impact of microbial dysbiosis and the risk of atopic wheezing in early childhood. This linkage has been attributed to the gut-lung axis due to cross-talk between gut and lung microbiota.⁶⁷ More specifically, the gut microbiota can influence the lung immune response by

production of bacterial ligands, bacterial metabolites (eg, short-chain fatty acids, histamine), and immune cells.

Similar to the gut microbiome, the lung microbiota can affect innate and adaptive immune responses in the lung, by its interaction with airway epithelium and immune cells. The upper and lower airway microbiome is a complex niche of diverse microbes that play a role in asthma.⁶³ Some specific phylum have been shown to be more prevalent in asthmatic patients. For example, patients with uncontrolled asthma showed a greater microbiota diversity compared with control subjects; this diversity correlated positively with bronchial hyperresponsiveness.⁶⁸ Teo and colleagues demonstrated that nasopharyngeal aspirates, collected by 7 weeks of age and younger, with greater than 20% *Streptococcus* colonization, were associated with a 4 times increased odds of chronic wheeze at 5 years old. A 2018 observational study concluded several important points relating microbiome and asthma.⁶⁹ First, gut microbiome maturation during the first year of life is important. Second, there is a potential beneficial effect of specific microbial supplementation in the first year of life in children at high risk of developing asthma. Third, gut microbiome immaturity in the first year of life is a critical determinant for increased asthma risk.

Despite the current evidence, it is unclear whether the changes in the microbiome are a result of having asthma or are causative of asthma.

Recent data from Lai and colleagues⁷⁰ suggest that external microbiomes matter also. This study found that the composition of the home and school microbiomes significantly differed, and the classroom microbial diversity was associated with a significantly increased odds of asthma symptom days. Additionally, integrated pest management and not HEPA filtration changed classroom microbial community structure.

Genetics

Genetic variants and epigenetic changes are likely contributors to the origins of asthma, source of phenotypic variability, and response to therapy.^{71–73} There is evidence that complex gene–environment interactions as seen in the increased risk of asthma in offspring of mothers who smoked during pregnancy and 17q21 variants are strongly associated with childhood asthma.⁷⁴ Despite the progress in genetic research, understanding is still limited, as these genetic factors explain a small proportion of total phenotypic variability, and the functional relationships between epigenetic processes, environmental stimuli, and developmental programs.⁷⁵ Farzan and colleagues⁷⁶ examined the association of the rs7216389 (17q21 single SNP) with health care utilization and oral steroid bursts from the Pharmacogenetics in Childhood Asthma consortium. The rs7216389 SNP was significantly associated with asthma emergency room visits and admissions and use of oral steroid bursts. Nevertheless, current studies of human allergy and asthma epigenetics have primarily focused on concurrent disease,⁷¹ showing DNA methylation marks in specific gene loci are associated with asthma and epigenetic changes might play a role in establishing the asthma phenotype.⁷⁷

DNA methylation changes in genes with direct relevance to Th2 immunity and asthma are associated with allergic asthma in African American inner-city children.⁷⁷ The IL4R α -Q576R polymorphism is associated with asthma prevalence and severity. The IL4R α -Q576R genotype was recently found to be an effect modifier of the association between urban classroom endotoxin levels and asthma symptoms days,⁷⁸ demonstrating gene–environment interaction.

Innate immunity genes (CD14, TLR4, and TLR2, the critical mediators of responses to bacteria in the extracellular space) also play a prominent role among gene–environment interaction studies of asthma-related phenotypes.⁷⁹

PHYSICAL ENVIRONMENT

Air Pollution

Air pollution is an ubiquitous combination of pollutants including particulate matter (PM), chemical and biological materials like carbon monoxide (CO), nitrogen dioxide (NO₂), black carbon (CO), and sulfur dioxide (SO₂).⁸⁰ There is a multitude of evidence that ambient air pollution can exacerbate pre-existing asthma. Exposure to high levels of NO₂, PM_{2.5} (aerodynamic diameter of 2.5 microns or less) and CO are associated with increased differentially methylated regions of the Foxp3 gene promoter region, which was shown to be significantly associated with asthma.⁸¹ A 2017 meta-analysis investigated the association between outdoor air pollution and asthma exacerbations, taking into consideration lag times between air pollution increase and asthma exacerbations.⁸² In the subgroup analysis of children, asthma exacerbations were significantly associated with higher concentration of NO₂, SO₂, and PM_{2.5}. Even short-term exposure to ozone, NO₂, or SO₂ can increase children's asthma symptoms.⁸³ Another study revealed a significant association between traffic-related air pollution exposure and higher hospital readmission rates.⁸⁴ Such findings are critical for inner-city schools because of their close proximity to highways, heavy traffic, and industrial buildings. These establishments tend to be located centrally, among condensed traffic, with sites of idling cars increasing air pollution within and around the school.^{83–85}

NO₂ is generated from fossil fuel combustion in homes and outdoors but can be found in other settings. Gaffin and colleagues⁸⁶ showed a nonsignificant temporally distinct association of NO₂ levels measured in inner-city school classrooms with airflow obstruction in children with asthma. This concordance was attributed to NO₂ having adverse effects on health outcomes at levels undetected by the existing standards in a susceptible population.

PM is comprised of airborne particles expressed as either PM_{2.5} or PM_{10-2.5} (aerodynamic diameter more than 2.5 microns to 10 microns). PM_{2.5} is associated with worsening asthma symptoms and increased oxidative stress based on inflammation biomarkers.⁸⁴ Bouazza and colleagues⁸⁷ found an association between PM_{2.5} and pediatric emergency department visits. There are fewer data on the long-term consequences of PM_{10-2.5} because of the lack of monitoring locations for both PM₁₀ and PM_{2.5}. Additionally, PM_{10-2.5} is thought to be less harmful than PM_{2.5}, as its size may limit its lung penetration, but Keet and colleagues⁸⁸ found that PM_{10-2.5} was associated with increased asthma prevalence and health care utilization.

PSYCHOSOCIAL ENVIRONMENT

The psychosocial environment is becoming increasingly recognized⁸⁹ as a significant contributor to asthma morbidity.^{9,90} It includes a person's neighborhood, socioeconomic status, family relationships, and social networks. Kopel and colleagues⁹¹ demonstrated that the primary caregiver's perception of neighborhood safety is associated with childhood asthma morbidity among inner-city schoolchildren with asthma, and caregiver stress is related to asthma morbidity among children.⁸⁹ Census tract-level violent and all-crime rates have also been associated with population-level rates of asthma utilization (emergency department and admissions⁹²).

Chen and colleagues⁹³ investigated whether living in areas high in greenspace would help balance the effects of difficult family relationship for children with asthma. A synergistic effect of positive family relationships across the physical and social domains was seen, and children with asthma benefited the most when they lived in high greenspace areas and had positive family relationships. Discrimination has also been

recently evaluated as a contributor to poor outcomes in medical conditions. Thakur and colleagues⁸⁹ investigated the association between perceived discrimination and asthma status and morbidity in black and Latino youth with asthma. Blacks reporting any severity of discrimination had a 78% increased odds of having asthma and 97% increased odds of poor asthma control.

Structural discrimination can impact asthma as it can manifest as unequal access to high-quality medical resources, substandard housing,⁹⁴ lack of homeownership, and living in neighborhoods with higher levels of pollution (eg, closer proximity to highways, pollutant-producing factories⁹⁵).

The 2011 American Housing Survey was analyzed by Hughes and colleagues, who found that poor housing quality was significantly associated with asthma diagnosis and emergency department visits. Home ownership was associated with lower odds of asthma emergency department visits.

These findings highlight that efforts to improve asthma outcomes should include social support and services and law and policy change.

SUMMARY

Asthma continues to be a significant cause of morbidity in children. The child's environment is integral to asthma development and activity. This review article focused on the most recent evidence supporting the role of environment in asthma disease activity from biologic, physical, and psychosocial perspectives. The evidence supports that some environmental exposures can be protective or a risk factor for asthma depending on exposure timing. Regarding future directions, it is important to investigate the critical exposure windows in pregnancy, childhood, and adulthood through cohort studies and randomized trials. Consideration of pragmatic study designs may allow increased recruitment. There is also a need to improve evidence for single-component allergen remediation interventions and to understand which multifaceted intervention combinations have the best synergistic effects. Law and policy reform are also crucial to reduce pollutant exposures, and to address social factors contributing to poor outcomes. Health services research should be utilized to form the evidence base policymakers seek for their decisions. Lastly, more innovative and patient-oriented interventions are needed to evaluate the environment's role.

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