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The Effects of the Environment on Asthma Disease Activity

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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, healthcare 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 biological, 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,].

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BIOLOGICAL, PHYSICAL AND PSYCHOSOCIAL ENVIRONMENTS

The determinants of health framework approach to the role of the environment in asthma, can be thought of in three categories: biological, physical and psychosocial environments[8,9].

BIOLOGICAL ENVIRONMENT

Over the past two decades, there has been increased attention to the role of the indoor environment (e.g. work, home, school) in asthma management. Exposure to multiple indoor allergens in U.S. 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, biological 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 et al 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[12]. In addition to home, children with asthma will have exposures in other environments where they spend time, e.g. school[11, 13]. The indoor school environment is a reservoir of allergens, molds, pollutants, and endotoxin, 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-hyperresponsiveness, 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, 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 to placebo or when part of multicomponent interventions[16]. Maintaining indoor humidity at 35–50% can reduce dust mite proliferation and survival but can be difficult to sustain. Moreover, 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 to 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 FEV_1 % 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 to 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 60–80% 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 an 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 healthcare 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 is 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 mm), 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[35,36,38,37,39] Children in classes with > 18% cat owners had a 9-fold increased risk of exacerbated asthma after school started compared with children in classes with ≤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 needed 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 μm), regular pet washing and HEPA filtration[42,35].

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 et al., 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[47].

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 to children not sensitized to mold[44,48,49,43,]. 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 – 3 months and the frequency of wheeze, by one year old even after adjustment for outdoor airborne Alternaria concentrations[50,51,52].

There are no solitary or randomized controlled trials of mold remediation. Mold remediation has only been included in multicomponent strategies (e.g. interventions also targeting dust mites or furry pet allergens), which have all showed 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 et al, 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 profession (IEP)[53]. 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 wheeze[55] 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 et al identified higher settled-dust endotoxin levels in inner-city schools compared to students' homes[58]. 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 – early endotoxin exposure is protective of childhood asthma[60,61,62]. Endotoxin's protective qualities were recently highlighted by Stein et al 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 to the Hutterite homes, respectively[60]. Endotoxin's protective and exacerbative roles in asthma underscores 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 (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 et al, reported that the first 100 days[66] 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 (e.g. 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 been shown to be more prevalent in asthmatic patients. For example, patients with uncontrolled asthma showed a greater microbiota diversity compared to control subjects that correlated positively with bronchial hyperresponsiveness[68]. Teo et al, demonstrated that nasopharyngeal aspirates, collected by 7 weeks of age and younger, with >20% Streptococcus colonization were associated with a four times increased odds of chronic wheeze at 5 years old. A 2018 observational study concluded several important point relating microbiome and asthma[69]: 1) Gut microbiome maturation during the first year of life is important; 2) Potential beneficial effect of specific microbial supplementation in the first year of life in children at high risk of developing asthma; 3) 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 is causative of asthma.

Interestingly recent data from Lai et al, suggests that external microbiomes matter as well. In their study they 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[70]. 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[71,72,73]. Evidence of 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, our understanding is still limited as these genetic factors explain small proportion of total phenotypic variability, and the functional relationships between epigenetic processes, environmental stimuli and developmental programs[75]. Farzan et al examined the association of the rs7216389 (17q21 single SNP) with health care utilization and oral steroid bursts - from the Pharmacogenetics in Childhood Asthma consortium[76]. 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 IL4Rα-Q576R polymorphism is associated with asthma prevalence and severity. The IL4Rα-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 (NO_2), black carbon (CO), and sulfur dioxide (SO_2)[80]. There is a multitude of evidence that ambient air pollution can exacerbate pre-existing asthma. Exposure to high levels of NO_2, $PM_{2.5}$ (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 NO_2, SO_2, and $PM_{2.5}$. Even short term exposure to ozone, NO_2, SO_2 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[84, 83,85]

NO_2, is generated from fossil fuel combustion in homes and outdoors but can be found in other settings. Gaffin et al, showed a non-significant temporally distinct association of NO_2 levels measured in inner-city school classrooms with airflow obstruction in children with asthma. This concordance was attributed to NO_2 having adverse effects on health outcomes at levels undetected by the existing standards, in a susceptible population[86].

PM are 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 et al, found an association between $PM_{2.5}$ and ED pediatric visits[87]. There is less data on the long-term consequences of $PM_{10–2.5}$ due to the lack of monitoring locations for both PM_{10} 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 et al found that $PM_{10–2.5}$ was associated with increased asthma prevalence and healthcare utilization[88].

PSYCHOSOCIAL

The psychosocial environment is becoming increasingly recognized[89] as a significant contributor to asthma morbidity[9,90]. It includes a person's neighborhood, socioeconomic

status, family relationships and social networks. Kopel et al. demonstrated that the primary caregiver's perception of neighborhood safety is associated with childhood asthma morbidity among innercity schoolchildren with asthma; and caregiver stress is related to asthma morbidity among children[89,91]. Census tract-level violent and all crime rates have also been associated with population-level rates of asthma utilization (ED and admissions[92]).

Chen et al, 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[93]. Discrimination has also been recently evaluated as a contributor to poor outcomes in medical conditions. Thakur et al, 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[89].

Structural discrimination can impact asthma as it can manifest as unequal access to high-quality medical resources, sub-standard housing[94], lack of homeownership and living in neighborhoods with higher levels of pollution (e.g. closer proximity to highways, pollutant producing factories[95]).

The 2011 American Housing Survey was analyzed by Hughes et al, who found that poor housing quality was significantly associated with asthma diagnosis and ED 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 supports 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 biological, 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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REFERENCES

1. Most Recent Asthma Data. 2017] Available from https://www.cdc.gov/asthma/most_recent_data.htm.
2. Szentpetery SE, Forno E, Canino G, Celedón JC. Asthma in Puerto Ricans: Lessons from a highrisk population. Journal of Allergy and Clinical Immunology 2016; 138:1556–8. [PubMed: 27751794]
3. Akinbami LJ, Simon AE, Rossen LM. Changing Trends in Asthma Prevalence Among Children. Pediatrics 2016; 137.
4. Asthma-related Missed School Days among Children aged 5–17 Years. 2015] Available from https://www.cdc.gov/asthma/asthma_stats/missing_days.htm.
5. Sommers BD, Gawande AA, Baicker K. Health insurance coverage and health—what the recent evidence tells us. Mass Medical Soc, 2017.
6. Gleason M, Cicutto L, Haas-Howard C, Raleigh BM, Szefler SJ. Leveraging partnerships: families, schools, and providers working together to improve asthma management. Current allergy and asthma reports 2016; 16:74. [PubMed: 27709456]
7. People H Healthy people 2010: Office of Disease Prevention and Health Promotion, US Department of Health and Human Services; 2000.
8. Bearer CF. Environmental health hazards: how children are different from adults. Future Child 1995; 5:11–26. [PubMed: 8528683]
9. Chen E, Schreier HM. Does the social environment contribute to asthma? Immunology and Allergy Clinics 2008; 28:649–64.
10. Salo PM, Arbes SJ, Crockett PW, Thorne PS, Cohn RD, Zeldin DC. Exposure to multiple indoor allergens in US homes and its relationship to asthma. Journal of Allergy and Clinical Immunology 2008; 121:678–84. e2. [PubMed: 18255132]
11. Kanchongkittiphon W, Gaffin JM, Phipatanakul W. The indoor environment and inner-city childhood asthma. Asian Pac J Allergy Immunol 2014; 32:103–10. [PubMed: 25003723]
12. Simons E, Curtin-Brosnan J, Buckley T, Breysse P, Eggleston PA. Indoor environmental differences between inner city and suburban homes of children with asthma. J Urban Health 2007; 84:577–90. [PubMed: 17551839]
13. Permaul P, Hoffman E, Fu C, Sheehan W, Baxi S, Gaffin J, et al. Allergens in urban schools and homes of children with asthma. Pediatr Allergy Immunol 2012; 23:543–9. [PubMed: 22672325]
14. Esty B, Phipatanakul W. School exposure and asthma. Ann Allergy Asthma Immunol 2018.
15. Sheehan WJ, Permaul P, Petty CR, Coull BA, Baxi SN, Gaffin JM, et al. Association Between Allergen Exposure in Inner-City Schools and Asthma Morbidity Among Students. JAMA Pediatr 2017; 171:31–8. [PubMed: 27893060]
16. Leas BF, D'Anci KE, Apter AJ, Bryant-Stephens T, Lynch MP, Kaczmarek JL, et al. Effectiveness of indoor allergen reduction in asthma management: A systematic review. J Allergy Clin Immunol 2018; 141:1854–69. [PubMed: 29452202]
17. Gaffin JM, Phipatanakul W. The role of indoor allergens in the development of asthma. Curr Opin Allergy Clin Immunol 2009; 9:128–35. [PubMed: 19326507]
18. Calderon MA, Linneberg A, Kleine-Tebbe J, De Blay F, Hernandez Fernandez de Rojas D, Virchow JC, et al. Respiratory allergy caused by house dust mites: What do we really know? J Allergy Clin Immunol 2015; 136:38–48. [PubMed: 25457152]
19. Tsai YM, Chiang KH, Hung JY, Chang WA, Lin HP, Shieh JM, et al. Der f1 induces pyroptosis in human bronchial epithelia via the NLRP3 inflammasome. Int J Mol Med 2018; 41:757–64. [PubMed: 29207030]
20. Wang JY. The innate immune response in house dust mite-induced allergic inflammation. Allergy Asthma Immunol Res 2013; 5:68–74. [PubMed: 23450108]

21. Portnoy J, Miller JD, Williams PB, Chew GL, Miller JD, Zaitoun F, et al. Environmental assessment and exposure control of dust mites: a practice parameter. Annals of allergy, asthma & immunology: official publication of the American College of Allergy, Asthma, & Immunology 2013; 111:465.
22. Becher R, Ovrevik J, Schwarze PE, Nilsen S, Hongslo JK, Bakke JV. Do Carpets Impair Indoor Air Quality and Cause Adverse Health Outcomes: A Review. Int J Environ Res Public Health 2018; 15.
23. Kopel LS, Phipatanakul W, Gaffin JM. Social disadvantage and asthma control in children. Paediatr Respir Rev 2014; 15:256–62; quiz 62–3. [PubMed: 24928775]
24. Pongracic JA, Visness CM, Gruchalla RS, Evans R, 3rd, Mitchell HE. Effect of mouse allergen and rodent environmental intervention on asthma in inner-city children. Ann Allergy Asthma Immunol 2008; 101:35–41. [PubMed: 18681082]
25. Loo CK, Foty RG, Wheeler AJ, Miller JD, Evans G, Stieb DM, et al. Do questions reflecting indoor air pollutant exposure from a questionnaire predict direct measure of exposure in owneroccupied houses? Int J Environ Res Public Health 2010; 7:3270–97. [PubMed: 20948960]
26. Phipatanakul W, Matsui E, Portnoy J, Williams PB, Barnes C, Kennedy K, et al. Environmental assessment and exposure reduction of rodents: a practice parameter. Ann Allergy Asthma Immunol 2012; 109:375–87. [PubMed: 23176873]
27. Sheehan WJ, Phipatanakul W. Indoor allergen exposure and asthma outcomes. Curr Opin Pediatr 2016; 28:772–7. [PubMed: 27653703]
28. Phipatanakul W, Koutrakis P, Coull BA, Kang CM, Wolfson JM, Ferguson ST, et al. The School Inner-City Asthma Intervention Study: Design, rationale, methods, and lessons learned. Contemp Clin Trials 2017; 60:14–23. [PubMed: 28619649]
29. Matsui EC, Perzanowski M, Peng RD, Wise RA, Balcer-Whaley S, Newman M, et al. Effect of an Integrated Pest Management Intervention on Asthma Symptoms Among Mouse-Sensitized Children and Adolescents With Asthma: A Randomized Clinical Trial. JAMA 2017; 317:1027–36. [PubMed: 28264080]
30. Phipatanakul W Environmental factors and childhood asthma. Pediatr Ann 2006; 35:646–56. [PubMed: 16999298]
31. Turyk M, Curtis L, Scheff P, Contraras A, Coover L, Hernandez E, et al. Environmental allergens and asthma morbidity in low-income children. J Asthma 2006; 43:453–7. [PubMed: 16952864]
32. Coleman AT, Rettiganti M, Bai S, Brown RH, Perry TT. Mouse and cockroach exposure in rural Arkansas Delta region homes. Ann Allergy Asthma Immunol 2014; 112:256–60. [PubMed: 24491312]
33. Rabito FA, Carlson JC, He H, Werthmann D, Schal C. A single intervention for cockroach control reduces cockroach exposure and asthma morbidity in children. J Allergy Clin Immunol 2017; 140:565–70. [PubMed: 28108117]
34. Portnoy J, Chew GL, Phipatanakul W, Williams PB, Grimes C, Kennedy K, et al. Environmental assessment and exposure reduction of cockroaches: a practice parameter. J Allergy Clin Immunol 2013; 132:802–8 e1–25. [PubMed: 23938214]
35. Ahluwalia SK, Matsui EC. Indoor Environmental Interventions for Furry Pet Allergens, Pest Allergens, and Mold: Looking to the Future. J Allergy Clin Immunol Pract 2018; 6:9–19. [PubMed: 29310769]
36. Konradsen JR, Nordlund B, Onell A, Borres MP, Gronlund H, Hedlin G. Severe childhood asthma and allergy to furry animals: refined assessment using molecular-based allergy diagnostics. Pediatr Allergy Immunol 2014; 25:187–92. [PubMed: 24460778]
37. Gergen PJ, Mitchell HE, Calatroni A, Sever ML, Cohn RD, Salo PM, et al. Sensitization and Exposure to Pets: The Effect on Asthma Morbidity in the US Population. J Allergy Clin Immunol Pract 2018; 6:101–7 e2. [PubMed: 28694047]
38. Gruchalla RS, Pongracic J, Plaut M, Evans R 3rd, Visness CM, Walter M, et al. Inner City Asthma Study: relationships among sensitivity, allergen exposure, and asthma morbidity. J Allergy Clin Immunol 2005; 115:478–85. [PubMed: 15753892]
39. Weiss ST, Horner A, Shapiro G, Sternberg AL, Childhood Asthma Management Program Research G. The prevalence of environmental exposure to perceived asthma triggers in children with mildto-

moderate asthma: data from the Childhood Asthma Management Program (CAMP). J Allergy Clin Immunol 2001; 107:634–40. [PubMed: 11295651]

40. Almqvist C, Wickman M, Perfetti L, Berglind N, Renstrom A, Hedren M, et al. Worsening of asthma in children allergic to cats, after indirect exposure to cat at school. American journal of respiratory and critical care medicine 2001; 163:694–8. [PubMed: 11254526]
41. Wood RA, Chapman MD, Adkinson NF Jr., Eggleston PA. The effect of cat removal on allergen content in household-dust samples. J Allergy Clin Immunol 1989; 83:730–4. [PubMed: 2708734]
42. Wilson JM, Platts-Mills TAE. Home Environmental Interventions for House Dust Mite. J Allergy Clin Immunol Pract 2018; 6:1–7. [PubMed: 29310755]
43. Pongracic JA, O'Connor GT, Muilenberg ML, Vaughn B, Gold DR, Kattan M, et al. Differential effects of outdoor versus indoor fungal spores on asthma morbidity in inner-city children. J Allergy Clin Immunol 2010; 125:593–9. [PubMed: 20132971]
44. Byeon JH, Ri S, Amarsaikhan O, Kim E, Ahn SH, Choi IS, et al. Association Between Sensitization to Mold and Impaired Pulmonary Function in Children With Asthma. Allergy, Asthma & Immunology Research 2017; 9:509–16.
45. O'Driscoll BR, Powell G, Chew F, Niven RM, Miles JF, Vyas A, et al. Comparison of skin prick tests with specific serum immunoglobulin E in the diagnosis of fungal sensitization in patients with severe asthma. Clin Exp Allergy 2009; 39:1677–83. [PubMed: 19689458]
46. Fukutomi Y, Taniguchi M. Sensitization to fungal allergens: Resolved and unresolved issues. Allergol Int 2015; 64:321–31. [PubMed: 26433528]
47. Baxi SN, Muilenberg ML, Rogers CA, Sheehan WJ, Gaffin J, Permaul P, et al. Exposures to molds in school classrooms of children with asthma. Pediatric Allergy and Immunology 2013; 24:697703.
48. Vicencio AG, Santiago MT, Tsirilakis K, Stone A, Worgall S, Foley EA, et al. Fungal sensitization in childhood persistent asthma is associated with disease severity. Pediatr Pulmonol 2014; 49:8–14. [PubMed: 23401301]
49. Sharpe RA, Bearman N, Thornton CR, Husk K, Osborne NJ. Indoor fungal diversity and asthma: a meta-analysis and systematic review of risk factors. J Allergy Clin Immunol 2015; 135:110–22. [PubMed: 25159468]
50. Mendell MJ, Mirer AG, Cheung K, Tong M, Douwes J. Respiratory and allergic health effects of dampness, mold, and dampness-related agents: a review of the epidemiologic evidence. Environ Health Perspect 2011; 119:748–56. [PubMed: 21269928]
51. Behbod B, Sordillo JE, Hoffman EB, Datta S, Muilenberg ML, Scott JA, et al. Wheeze in infancy: protection associated with yeasts in house dust contrasts with increased risk associated with yeasts in indoor air and other fungal taxa. Allergy 2013; 68:1410–8. [PubMed: 24118031]
52. Halonen M, Stern DA, Wright AL, Taussig LM, Martinez FD. Alternaria as a major allergen for asthma in children raised in a desert environment. Am J Respir Crit Care Med 1997; 155:1356–61. [PubMed: 9105079]
53. Chew GL, Horner WE, Kennedy K, Grimes C, Barnes CS, Phipatanakul W, et al. Procedures to Assist Health Care Providers to Determine When Home Assessments for Potential Mold Exposure Are Warranted. J Allergy Clin Immunol Pract 2016; 4:417–22 e2. [PubMed: 27021632]
54. Zhu Z, Oh SY, Zheng T, Kim YK. Immunomodulating effects of endotoxin in mouse models of allergic asthma. Clin Exp Allergy 2010; 40:536–46. [PubMed: 20447074]
55. Michel O, Kips J, Duchateau J, Vertongen F, Robert L, Collet H, et al. Severity of asthma is related to endotoxin in house dust. Am J Respir Crit Care Med 1996; 154:1641–6. [PubMed: 8970348]
56. Boehlecke B, Hazucha M, Alexis NE, Jacobs R, Reist P, Bromberg PA, et al. Low-dose airborne endotoxin exposure enhances bronchial responsiveness to inhaled allergen in atopic asthmatics. J Allergy Clin Immunol 2003; 112:1241–3. [PubMed: 14657891]
57. Thorne PS, Mendy A, Metwali N, Salo P, Co C, Jaramillo R, et al. Endotoxin Exposure: Predictors and Prevalence of Associated Asthma Outcomes in the United States. Am J Respir Crit Care Med 2015; 192:1287–97. [PubMed: 26258643]
58. Sheehan WJ, Hoffman EB, Fu C, Baxi SN, Bailey A, King EM, et al. Endotoxin exposure in innercity schools and homes of children with asthma. Ann Allergy Asthma Immunol 2012; 108:418–22. [PubMed: 22626594]

59. Lai PS, Sheehan WJ, Gaffin JM, Petty CR, Coull BA, Gold DR, et al. School Endotoxin Exposure and Asthma Morbidity in Inner-city Children. Chest 2015; 148:1251–8. [PubMed: 26087201]
60. Stein MM, Hrusch CL, Gozdz J, Igartua C, Pivniouk V, Murray SE, et al. Innate Immunity and Asthma Risk in Amish and Hutterite Farm Children. N Engl J Med 2016; 375:411–21. [PubMed: 27518660]
61. Karvonen AM, Hyvarinen A, Gehring U, Korppi M, Doekes G, Riedler J, et al. Exposure to microbial agents in house dust and wheezing, atopic dermatitis and atopic sensitization in early childhood: a birth cohort study in rural areas. Clin Exp Allergy 2012; 42:1246–56. [PubMed: 22805472]
62. O'Connor GT, Lynch SV, Bloomberg GR, Kattan M, Wood RA, Gergen PJ, et al. Early-life home environment and risk of asthma among inner-city children. J Allergy Clin Immunol 2018; 141:1468–75. [PubMed: 28939248]
63. Sokolowska M, Frei R, Lunjani N, Akdis CA, O'Mahony L. Microbiome and asthma. Asthma research and practice 2018; 4:1. [PubMed: 29318023]
64. Chung KF. Airway microbial dysbiosis in asthmatic patients: A target for prevention and treatment? J Allergy Clin Immunol 2017; 139:1071–81. [PubMed: 28390574]
65. Kloepfer KM, Sarsani VK, Poroyko V, Lee WM, Pappas TE, Kang T, et al. Community-acquired rhinovirus infection is associated with changes in the airway microbiome. J Allergy Clin Immunol 2017; 140:312–5 e8. [PubMed: 28327377]
66. Arrieta MC, Stiemsma LT, Dimitriu PA, Thorson L, Russell S, Yurist-Doutsch S, et al. Early infancy microbial and metabolic alterations affect risk of childhood asthma. Sci Transl Med 2015; 7:307ra152.
67. Arrieta MC, Arevalo A, Stiemsma L, Dimitriu P, Chico ME, Loor S, et al. Associations between infant fungal and bacterial dysbiosis and childhood atopic wheeze in a nonindustrialized setting. J Allergy Clin Immunol 2017.
68. Di Cicco M, Pistello M, Jacinto T, Ragazzo V, Piras M, Freer G, et al. Does lung microbiome play a causal or casual role in asthma? Pediatric Pulmonology 2018.
69. Stokholm J, Blaser MJ, Thorsen J, Rasmussen MA, Waage J, Vinding RK, et al. Maturation of the gut microbiome and risk of asthma in childhood. Nature communications 2018; 9:141.
70. Lai PS, Kolde R, Franzosa EA, Gaffin JM, Baxi SN, Sheehan WJ, et al. The classroom microbiome and asthma morbidity in children attending 3 inner-city schools. Journal of Allergy and Clinical Immunology 2018; 141:2311–3. [PubMed: 29518428]
71. Devries A, Vercelli D. Epigenetics of human asthma and allergy: promises to keep. Asian Pac J Allergy Immunol 2013; 31:183–9. [PubMed: 24053700]
72. Arathimos R, Suderman M, Sharp GC, Burrows K, Granell R, Tilling K, et al. Epigenome-wide association study of asthma and wheeze in childhood and adolescence. Clin Epigenetics 2017; 9:112. [PubMed: 29046734]
73. Barton SJ, Ngo S, Costello P, Garratt E, El-Heis S, Antoun E, et al. DNA methylation of Th2 lineage determination genes at birth is associated with allergic outcomes in childhood. Clin Exp Allergy 2017; 47:1599–608. [PubMed: 28756630]
74. Ramadas RA, Sadeghnejad A, Karmaus W, Arshad SH, Matthews S, Huebner M, et al. Interleukin1R antagonist gene and pre-natal smoke exposure are associated with childhood asthma. Eur Respir J 2007; 29:502–8. [PubMed: 17107994]
75. DeVries A, Vercelli D. Early predictors of asthma and allergy in children: the role of epigenetics. Curr Opin Allergy Clin Immunol 2015; 15:435–9. [PubMed: 26258923]
76. Farzan N, Vijverberg SJ, Hernandez-Pacheco N, Bel EH, Berce V, Bønnelykke K, et al. 17q21 variant increases the risk of exacerbations in asthmatic children despite inhaled corticosteroids use. Allergy 2018.
77. Yang IV, Pedersen BS, Liu A, O'Connor GT, Teach SJ, Kattan M, et al. DNA methylation and childhood asthma in the inner city. J Allergy Clin Immunol 2015; 136:69–80. [PubMed: 25769910]
78. Lai PS, Massoud AH, Xia M, Petty CR, Cunningham A, Chatila TA, et al. Gene-environment interaction between an IL4R variant and school endotoxin exposure contributes to asthma

symptoms in inner-city children. Journal of Allergy and Clinical Immunology 2018; 141:794–6. e3. [PubMed: 28943468]

79. Vercelli D Gene-environment interactions in asthma and allergy: the end of the beginning? Curr Opin Allergy Clin Immunol 2010; 10:145–8. [PubMed: 20051845]
80. Mannucci PM, Harari S, Martinelli I, Franchini M. Effects on health of air pollution: a narrative review. Internal and emergency medicine 2015; 10:657–62. [PubMed: 26134027]
81. Prunicki M, Stell L, Dinakarpandian D, de Planell-Saguer M, Lucas RW, Hammond SK, et al. Exposure to NO 2, CO, and PM 2.5 is linked to regional DNA methylation differences in asthma. Clinical epigenetics 2018; 10:2. [PubMed: 29317916]
82. Orellano P, Quaranta N, Reynoso J, Balbi B, Vasquez J. Effect of outdoor air pollution on asthma exacerbations in children and adults: Systematic review and multilevel meta-analysis. PloS one 2017; 12:e0174050. [PubMed: 28319180]
83. Naja A, Phipatanakul W, Permaul P. Taming Asthma in School-Aged Children: A Comprehensive Review. Journal of Allergy and Clinical Immunology 2018.
84. Pollock J, Shi L, Gimbel RW. Outdoor environment and pediatric asthma: an update on the evidence from North America. Canadian respiratory journal 2017; 2017.
85. Yoda Y, Takagi H, Wakamatsu J, Ito T, Nakatsubo R, Horie Y, et al. Acute effects of air pollutants on pulmonary function among students: a panel study in an isolated island. Environmental health and preventive medicine 2017; 22:33. [PubMed: 29165154]
86. Gaffin JM, Hauptman M, Petty CR, Sheehan WJ, Lai PS, Wolfson JM, et al. Nitrogen dioxide exposure in school classrooms of inner-city children with asthma. Journal of Allergy and Clinical Immunology 2017.
87. Bouazza N, Foissac F, Urien S, Guedj R, Carbajal R, Tréluyer J-M, et al. Fine particulate pollution and asthma exacerbations. Archives of Disease in Childhood 2017:archdischild-2017–312826.
88. Keet CA, Keller JP, Peng RD. Long-term coarse particulate matter exposure is associated with asthma among children in Medicaid. American journal of respiratory and critical care medicine 2018; 197:737–46. [PubMed: 29243937]
89. Thakur N, Barcelo NE, Borrell LN, Singh S, Eng C, Davis A, et al. Perceived discrimination associated with asthma and related outcomes in minority youth: the GALA II and SAGE II studies. Chest 2017; 151:804–12. [PubMed: 27916618]
90. Williams DR, Sternthal M, Wright RJ. Social determinants: taking the social context of asthma seriously. Pediatrics 2009; 123:S174–S84. [PubMed: 19221161]
91. Kopel LS, Gaffin JM, Ozonoff A, Rao DR, Sheehan WJ, Friedlander JL, et al. Perceived neighborhood safety and asthma morbidity in the School Inner-City Asthma Study. Pediatric pulmonology 2015; 50:17–24. [PubMed: 24421055]
92. Beck AF, Huang B, Ryan PH, Sandel MT, Chen C, Kahn RS. Areas with high rates of policereported violent crime have higher rates of childhood asthma morbidity. The Journal of pediatrics 2016; 173:175–82. e1. [PubMed: 26960918]
93. Chen E, Miller GE, Shalowitz MU, Story RE, Levine CS, Hayen R, et al. Difficult family relationships, residential greenspace, and childhood asthma. Pediatrics 2017:e20163056. [PubMed: 28280210]
94. Mehta AJ, Dooley DP, Kane J, Reid M, Shah SN. Subsidized Housing and Adult Asthma in Boston, 2010–2015. American journal of public health 2018:e1–e7.
95. Shamasunder B, Collier-Oxandale A, Blickley J, Sadd J, Chan M, Navarro S, et al. Communitybased health and exposure study around urban oil developments in south Los Angeles. International journal of environmental research and public health 2018; 15:138.

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 healthcare 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.

SYNOPSIS

Asthma is highly prevalent and causes significant morbidity in children. The development of asthma depends on complex relationships between genetic predisposition and environmental modifiers of immune function. The biological and physical environmental factors include aeroallergens, microbiome, endotoxin, genetics, and pollutants. The psychosocial environment encompasses stress, neighborhood safety, housing, and discrimination. They all have been speculated to influence asthma control and the risk of developing asthma. Control of the factors that contribute to or aggravate symptoms, interventions to eliminate allergen exposure, guidelines-based pharmacologic therapy and education of children and their caregivers are of paramount importance.