

Pediatric Inner-City Asthma



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KEYWORDS

• Asthma • Inner city • Children • Asthma research networks

KEY POINTS

- Inner-city asthma is often severe and is associated with increased morbidity and mortality.
- Multiple factors contribute significantly to the disease burden, including biological factors, environmental factors, care access, and socioeconomic hardship.
- Risk factors concentrated in these areas such as environmental allergens (cockroach and mouse) and pollutants contribute to increased morbidity.
- Remedial measures focused on reduced exposures to these allergens as well as tobacco smoke, omalizumab, and immunotherapy have been shown to be helpful in control of symptoms in this population.

INTRODUCTION

Inner cities are defined as poor and large urban/metropolitan areas where at least 20% of the households have incomes below the federal poverty level.¹ Several risk factors related to poverty and urban environment independently contribute to increase in asthma morbidity in these children and their daily lifestyle.¹ Although these factors may not be the only causes of asthma development in the children in the inner city, it is certain that many of them contribute to its severity. These risk factors related to poverty and urban environments will be discussed in this article.

PREVALENCE

Asthma is among the most common chronic diseases, affecting over 9.5% of children in the United States.² The prevalence of childhood asthma has increased over the last

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decade and appears to be higher in inner-city children (12.9%) versus noninner-city children (10.6%).³ Ethnic minority children also have much higher prevalence of asthma (African American 17.1%, Puerto Rican 19.8%, and Caucasian 9.6%).³

MORBIDITY AND MORTALITY

In general, pediatric asthma morbidity is measured by asthma symptoms, activity limitation, asthma exacerbations, and the effect of the disease on the caregiver.¹ Although the prevalence of asthma exacerbations decreased from 61.7% in 2001 to 53.7% in 2016,⁴ up to 16.7% of children with asthma still had an asthma exacerbation that required an emergency department (ED) or an urgent care (UC) visit in 2016. In spite of the fact that death related to asthma should be preventable, the mortality rate for children with asthma is at 2.8 cases per million population per year.⁵

It is possible that inner-city children with asthma have more severe disease, needing more medication to control their asthma than noninner-city children. It is hypothesized that decreased responsiveness to corticosteroids can be an underlying cause of this difficult-to-control asthma; however, this hypothesis needs to be further investigated.⁶

Many risk factors related to poverty and urban environment adversely impact asthma severity in inner-city children. These risk factors include increase in certain allergens (mouse and cockroach) sensitization/exposure, environmental tobacco smoke (ETS) exposure, vitamin D insufficiency/deficiency, stress, and obesity. Out of these risk factors, allergen and ETS exposure are noted to be the most important risk factors of severe asthma in the inner-city population.⁷

In the last 15 years, the National Institutes of Allergy and Infectious Diseases (NIAID) funded major research networks to improve asthma care for inner-city children. Three important inner-city asthma networks are the National Cooperative Inner-City Asthma Study (NCICAS), the Inner City Asthma Study (ICAS), and the Inner City Asthma Consortium (ICAC).⁶ The results from the NCICAS confirmed that lack of access to health care, poor adherence to asthma medications, childhood behavioral problems, and allergen sensitization are important risk factors contributing to increased asthma morbidity in inner-city children.^{6,8}

The next section will describe the effects of the individual risk factors on inner-city asthma in detail.

RISK FACTORS FOR INNER-CITY ASTHMA

Allergen Exposure and Sensitization

Exposure to household pests such as cockroach and mice is much higher in inner-city areas, which contributes to poor asthma control. Cockroach (36.8%), house dust mite (34.9%), and cat dander (22.7%) are the main allergens implicated in sensitization for children with inner-city asthma.⁹ Mold is also a factor in poor asthma control. Exposure to these allergens must be curtailed in order to achieve asthma control.

Cockroach

Inner-city areas have high rates of cockroach infestation.^{10–12} Sensitization and exposure to cockroach can contribute to increased asthma morbidity including ED visits and hospitalizations.⁹ Home interventions to reduce exposure to cockroaches, including extermination, resulted in a significant decrease in asthma morbidity.^{13,14}

Mold

Mold exposure has been associated with increased asthma morbidity and mortality,¹⁵ particularly *Alternaria*, which has been associated with increased asthma hospitalizations.¹⁶ Houses with increased dampness and cat and cockroach infestation have high mold levels.¹⁷ Inner-city schools have high levels of *Aspergillus*, *Cladosporium*, and *Penicillium* molds,¹⁸ which can contribute to increased symptoms. Reduction in mold exposure significantly decreased asthma symptoms as well as exacerbations in inner-city children.¹⁹

Dust Mites

Inner-city homes have high levels of dust mite allergens, particularly in the bedrooms.^{20–22} While there is no clear association between dust mite exposure and asthma morbidity, some studies have shown that dust mite sensitization is associated with frequent symptoms and increased use of rescue medications.^{9,16,23,24}

Reduction of house dust mite allergen levels has been shown to have a beneficial effect on asthma control and improved morbidity, specifically, patients experienced fewer hospitalizations and office visits for asthma and fewer days with symptoms.¹⁴

Mouse

Inner-city homes, particularly in northeastern and midwestern US cities, have high levels of mouse allergens, with highest levels in the kitchen.²⁵ Mouse and cockroach infestation are often found to coexist.²⁶ Mouse allergen exposure was associated with wheezing during infancy²⁷ and wheezing and atopy later in childhood.^{28,29} Studies conducted in Baltimore, Maryland, found that mouse allergen exposure was more closely associated with asthma morbidity compared with other indoor allergens.^{30,31}

Inner-city schools have also been shown to have high levels of mouse allergens,^{32,33} which contributes to missed school days caused by asthma.³³

Reduction of mouse allergen levels in ICAS resulted in less sleep disruption, caretaker burden, and missed school but did not reduce asthma symptoms or medical utilization.³⁴

Cat and Dog

High levels of pet allergens are present in homes with a cat or dog.³⁵ Studies have shown variable results regarding the effect of pet allergens on development of asthma or atopic disease. Some studies showed that cat and dog exposure may prevent development of asthma³⁶ and allergen sensitization.^{37,38} Other studies concluded that pet exposure led to higher rates of dog sensitization³⁹ and development of asthma and eczema.⁴⁰ Exposure to high levels of cat allergens in homes of sensitized children resulted in higher asthma severity,⁴¹ frequent wheezing and rescue medication use,⁴² asthma exacerbation,⁴³ and hospitalization.⁴⁴ On the other hand, NCICAS did not show any association between cat allergen exposure and asthma morbidity.⁹

Environmental intervention in a study reduced both cat and dog allergens; however, there was no significant decrease in medication use, asthma symptoms, or exacerbation.⁴⁵ In the ICAS, the environmental interventions significantly decreased cat allergen levels but not dog allergen.¹⁴ The authors did not notice any significant association between cat allergen reduction and asthma morbidity.¹⁴

Infections

Certain infections are noted to be important triggers of asthma. These particular infectious agents include rhinovirus and endotoxin, and their effects on asthma have been studied extensively.

Children younger than 5 years old with rhinovirus-induced acute respiratory illness are more likely to be diagnosed with asthma compared to respiratory illnesses from other viruses.⁴⁶ Rhinovirus is also a well-known trigger for asthma exacerbation. Also, rhinovirus infection in early childhood can increase the risk of asthma development.⁴⁷ The results from the Childhood Origins of Asthma (COAST) study⁴⁷ showed that rhinovirus infection was related to wheezing during the first 3 years of life and the loss of pulmonary function in early school years. This relation was not seen in children who had respiratory syncytial virus (RSV) induced wheezing.

Airborne endotoxin exposure is another risk factor of wheezing and asthma.^{10,48,49} Endotoxin is part of the outer membrane lipopolysaccharide of gram-negative bacteria. Exposure to moisture sources and organic waste, commonly seen in inner-city areas, is associated with endotoxin exposure.⁴⁸ Inner-city schools have been shown to have high endotoxin concentrations,⁴⁹ more so than the inner-city homes. Exposure to high levels of airborne endotoxin at school is associated with increased asthma symptoms in nonatopic asthmatic children.⁵⁰

Seasonal Variations

Inner-city children with asthma typically have more frequent asthma exacerbations during the fall-winter months rather than the summer months.⁵¹ This seasonal variation in asthma exacerbation appears to be related to an allergen-induced immunoglobulin E (IgE)-mediated mechanism. In the Inner City Anti-IgE therapy for Asthma (ICATA) study, asthma exacerbations in inner-city children and young adults during the fall season were almost fully suppressed by the use of anti-IgE monoclonal antibody (omalizumab) therapy in addition to conventional asthma treatment.⁵² Similar findings were reported in the Preventative Omalizumab or Step-up therapy for Fall Exacerbations (PROSE) study, where significant reduction in fall asthma exacerbations were achieved after omalizumab therapy 4 to 6 weeks prior to the return to school.⁵³

Pollution

Air pollution leads to an increase in asthma symptoms and decreased lung function and potentially contributes to asthma development.^{54,55} Inner-city areas are known to be affected by sources of air pollution, particularly traffic and power generation.⁵⁴ Nitrogen dioxide, particulate matter, ozone, sulfur dioxide, carbon monoxide, and lead are common outdoor pollutants.⁵⁶ Indoor air pollution, in the forms of particulate matter, nitrogen dioxide, and ozone, can be further created by the penetration of outdoor pollutants to indoor environment.⁵⁷

Activities like smoking, cooking, and cleaning, and heating/cooling systems can produce indoor air pollutants.^{57,58} As previously mentioned, ETS exposure has been noted to be the single most important risk factors of severe asthma in the inner-city population.^{7,8,57} Besides its adverse effects on asthma, ETS is also a well-known cause of asthma development^{59,60} and a trigger of asthma exacerbation.⁶¹ Prenatal and postnatal passive ETS exposure can increase the risk of wheezing and asthma by 20%.⁵⁹ The risk of asthma at the age of 7 correlates with prenatal ETS exposure.⁶⁰ Furthermore, asthmatic children exposed to ETS have more asthma symptoms and ED visits and are twice as likely to be admitted to the hospital.⁶¹

Thirdhand smoke is residual tobacco-related gases and chemicals that are present on indoor surfaces, including carpets, furniture, blankets, or toys, from which they are released into the air after the secondhand smoke is released in the air.⁶² Although the asthma risks of thirdhand smoke exposure are less well described, evidence has shown that it is likely to adversely affect asthma symptoms as well as the secondhand smoke exposure.⁶²

Poor indoor air quality in inner-city homes may also be related to poor ventilation.^{58,63} In a study by Hansel and colleagues,⁶⁴ use of a gas stove, stove/oven, and space heater caused an increase in indoor nitrogen dioxide levels, which contributed to increased asthma symptoms.

Nonadherence to Medication

Medication adherence, proper inhaler technique, and avoidance of triggers have been identified as key factors for asthma control. A study was conducted to identify the risk factors for poor medication adherence and thus asthma morbidity in inner-city children. These included concerns about medication adverse effects, multiple caregivers, trouble with obtaining appointments, nonavailability of medication in the house when needed, and child refusing to take medication.⁶⁵

The Asthma Control Evaluation (ACE) study further emphasized the importance of medication adherence in control of asthma.⁶⁶ The study showed that in inner-city children, guideline-based asthma care and strict medication adherence can help to achieve asthma control.

A study in Detroit showed that the most severe asthmatics were more likely to miss medications due to running out even when refills are available. The majority of asthmatic children who were hospitalized reported lack of medical supplies and prescription medications in the home.⁶⁷

Family–physician partnership geared at communication, trust, and respect has helped to increase medication adherence in these families.⁶⁸

Stress, Psychological Issues, and Depression

Poor asthma control in inner-city children is associated with caregiver stress. Multiple studies have shown that maternal depression and stress in the initial 3 years of life increase risk of recurrent wheezing at 3 years and asthma at age 7 in children.^{60,69,70} Wing and colleagues⁷¹ conducted a study and found domestic violence to be associated with lifetime asthma in inner-city children.

Vitamin D Deficiency

Vitamin D deficiency has been speculated to play a role in the development of asthma.^{72,73} Prenatal vitamin D supplementation may be protective against recurrent wheezing early in the infant's life.⁷⁴ Liu and colleagues,⁷ however, did not find any significant effect of vitamin D on asthma severity in inner-city children.

Obesity

Obesity has been associated with increased asthma symptoms and exacerbations irrespective of allergic sensitization.^{75–77} Lung function and asthma control improved in obese children after weight loss.⁷⁸ Liu and colleagues,⁷ however, did not notice any significant effect of obesity on asthma severity.

Immune Dysregulation

Immune system dysregulation can increase risk of allergic sensitization and asthma. This can occur prenatally, at birth, or during infancy.^{1,79} Under ICAC (2002), the Urban Environment and Childhood Asthma (URECA, 2004) study was initiated with the aim of determining immunologic causes of asthma in inner-city children.⁸⁰ As part of URECA, a birth cohort of inner-city newborns at risk for asthma has been followed to identify prenatal exposures and maternal factors that can affect development of newborn immune system and cytokine responses.^{81–83} Results from the study so far have identified certain environmental factors such as ethnicity, birth weight/gestational age,

season of birth, and maternal asthma/use of inhaled corticosteroids that can affect newborn immune responses.⁷⁹

Epigenetics

Various genes have been identified as affecting asthma.⁸⁴ Epigenetics is a science that aims to study the effect of environmental exposures in causing functional changes such as methylation of selective genes that are relevant to asthma, particularly for inner-city children. Nasal epithelia in inner-city children with persistent asthma has been shown to have differential methylation patterns (DMRs).⁸⁵ There were significant differences in methylation between asthmatic children and nonasthmatic controls. Of these, 48 DMRs were associated with tobacco smoke.⁸⁵

INTERVENTIONS FOR INNER-CITY ASTHMA

Family-Based Interventions

As multiple risk factors contribute to high asthma morbidity in the inner-city population, asthma management and interventions for this high-risk group are frequently challenging.⁸ As mentioned previously, factors associated with poverty including socioeconomic hardship and lack of knowledge or participation in the health care system contribute to high asthma morbidity in inner-city children. The major NIAID-funded network, NCICAS, focused on family-based interventions. The results from the NCICAS identified that family-based interventions including partnering the family with asthma-trained social workers can reduce asthma-related morbidity by helping families access better medical care.¹³ Furthermore, the results from ACE study (part of the ICAC) also revealed that inner-city asthma children can achieve good asthma control with optimal medication adherence to proper asthma treatment.⁶⁶

Anti-immunoglobulin E Monoclonal Antibody Therapy

As previously discussed, allergen sensitization/exposure is a major risk factor of inner-city asthma that leads to asthma exacerbations despite the use of aggressive inhaled corticosteroid treatment. This fact has been confirmed by both the ICATA⁵² and PROSE⁵³ studies. In both studies, anti-IgE monoclonal antibody (omalizumab) can significantly reduce asthma exacerbations and reduce the dose of inhaled corticosteroid therapy compared with placebo. Omalizumab is able to reduce fall and spring asthma exacerbations, with maximal benefit seen in those who had recent asthma exacerbations.⁵²

Other than reducing seasonal asthma exacerbations, omalizumab appears to be able to alter the immune response to rhinovirus also.^{86,87} Children who received omalizumab demonstrated increased interferon alpha (IFN- α) against rhinovirus.⁸⁷ The results from PROSE study revealed that omalizumab can decrease frequency and duration of rhinovirus infection and also reduce peak rhinovirus shedding.⁸⁶

Immunotherapy

As allergen sensitization and exposure play important roles in inner-city asthma morbidity, allergen immunotherapy (IT) potentially can be beneficial to inner-city asthma patients.⁸ It is known that IT is a disease-modifying therapy with sustained benefits, unlike other pharmacologic treatments for asthma.⁸⁸ As mentioned concerning the risk factors of inner-city asthma, cockroach allergy and exposure are associated with higher asthma morbidity in inner-city children. The ICAC study evaluated the clinical effects of cockroach IT along with biomarkers, such as cockroach IgE or cockroach IgG4 levels, which link to clinical outcome of the IT in inner-city patients with asthma.⁸⁹

The important findings from the ICAC study regarding cockroach IT are that significant but inconsistent changes in serum-specific cockroach IgE levels were identified after German cockroach sublingual immunotherapy (SLIT). In contrast, use of cockroach subcutaneous immunotherapy (SCIT) resulted in significant and substantial immunologic changes in the treatment group. These results conclude that SCIT might be a better option for cockroach IT in inner-city patients with asthma.⁸⁹

Environmental Interventions

Population-level environmental interventions such as prohibiting smoking in public places, vehicle emission regulations, and replacing indoor gas heaters in schools with alternative heating sources have been shown to be beneficial for inner-city children with asthma.⁸

Elimination of indoor allergens and improving home conditions have also shown to improve asthma outcome in inner-city population.^{14,90} In the ICAS, comprehensive environmental control by eliminating home allergens and ETS exposure demonstrated enduring decrease in asthma symptoms and unscheduled asthma visits up to 12 months after cessation of the active intervention.¹⁴ This result emphasizes that environmental allergens and ETS are important factors of asthma control in inner-city children. Improving home conditions, such as home winterization, can decrease mold and moisture exposure and also lead to improved asthma control.⁹⁰

School-Based Interventions

The importance of school-based asthma programs in inner-city asthma care cannot be underestimated, especially in places where transportation to clinics is limited. School-based Asthma Management Program (SAMPRO)⁹¹ contributes asthma education for children, families, clinicians, and school nurses. This program allows multidirectional communications between children and their families, health care providers, and schools. The aim of the program is to encourage better asthma care for children within the school environment by supplying asthma action plans and asthma emergency plans to the school staff.

Other school-based intervention such as Asthma Self-Management for Adolescents (ASMA) provides asthma education for Hispanic and African American adolescents with moderate persistent asthma during the school day. ASMA-enrolled students reported fewer daytime and nighttime asthma symptoms and reduced asthma morbidity and UC usage.⁹²

Technology-Based Interventions

Technology-based interventions (text messaging, computer/Web-based, and interactive voice response) are being used to support inner-city asthma care. Of these, only computer/Web-based programs have been successful in reducing asthma symptoms in inner-city children with asthma. Puff City is a Web-based asthma management program designed to improve asthma control in inner-city adolescent with asthma in Detroit, Michigan. Teenagers enrolled in the program experienced fewer ED visits from asthma.⁹³

SUMMARY

Inner-city asthma is a complex medical problem with multiple risk factors contributing to high morbidity and mortality. Of these risk factors, allergen sensitization/exposure, ETS exposure, and pollutants are considered to have the most impact on inner-city children with asthma. Other distinctive risk factors of inner-city asthmatics involve

poverty and socioeconomic hardship. These factors include poor housing quality, inability to access proper health care, and poor adherence to medications and complicate care for inner-city children with asthma.

Several interventions have shown positive outcome for inner-city children with asthma; however, many of these interventions may not be easily available in real practice settings. These interventions include comprehensive control of home allergens and ETS exposure, the use of anti-IgE monoclonal antibody to prevent seasonal asthma exacerbations, school-based asthma programs, and technology-based initiatives. Future sustainable and expandable interventions in real clinical practice settings are the next targets for inner-city physicians treating children with asthma.

REFERENCES

1. Busse WW, Mitchell H. Addressing issues of asthma in inner-city children. *J Allergy Clin Immunol* 2007;119(1):43–9.
2. Moorman JE, Akinbami LJ, Bailey CM, et al. National surveillance of asthma: United States, 2001–2010. *Vital Health Stat* 3 2012;(35):1–58.
3. Keet CA, McCormack MC, Pollack CE, et al. Neighborhood poverty, urban residence, race/ethnicity, and asthma: rethinking the inner-city asthma epidemic. *J Allergy Clin Immunol* 2015;135(3):655–62.
4. Zahran HS, Bailey CM, Damon SA, et al. Vital signs: asthma in children - United States, 2001–2016. *MMWR Morb Mortal Wkly Rep* 2018;67(5):149–55.
5. Centers for Disease Control and Prevention. National asthma mortality 2016. Most recent asthma data 2018. Available at: https://www.cdc.gov/asthma/most_recent_data.htm. Accessed May 16, 2018.
6. Busse WW. The National Institutes of Allergy and Infectious Diseases networks on asthma in inner-city children: an approach to improved care. *J Allergy Clin Immunol* 2010;125(3):529–37 [quiz: 538–9].
7. Liu AH, Babineau DC, Krouse RZ, et al. Pathways through which asthma risk factors contribute to asthma severity in inner-city children. *J Allergy Clin Immunol* 2016;138(4):1042–50.
8. Poowuttikul P, Saini S, Seth D. Inner-city asthma in children. *Clin Rev Allergy Immunol* 2019;56(2):248–68.
9. Rosenstreich DL, Eggleston P, Kattan M, et al. The role of cockroach allergy and exposure to cockroach allergen in causing morbidity among inner-city children with asthma. *N Engl J Med* 1997;336(19):1356–63.
10. Kanchongkittiphon W, Gaffin JM, Phipatanakul W. The indoor environment and inner-city childhood asthma. *Asian Pac J Allergy Immunol* 2014;32(2):103–10.
11. Sheehan WJ, Rangsithienchai PA, Wood RA, et al. Pest and allergen exposure and abatement in inner-city asthma: a work group report of the American Academy of Allergy, Asthma & Immunology Indoor Allergy/Air Pollution Committee. *J Allergy Clin Immunol* 2010;125(3):575–81.
12. Cohn RD, Arbes SJ, Jaramillo R, et al. National prevalence and exposure risk for cockroach allergen in U.S. households. *Environ Health Perspect* 2006;114(4):522–6.
13. Evans R, Gergen PJ, Mitchell H, et al. A randomized clinical trial to reduce asthma morbidity among inner-city children: results of the National Cooperative Inner-City Asthma Study. *J Pediatr* 1999;135(3):332–8.
14. Morgan WJ, Crain EF, Gruchalla RS, et al. Results of a home-based environmental intervention among urban children with asthma. *N Engl J Med* 2004;351(11):1068–80.

15. Targonski PV, Persky VW, Ramekrishnan V. Effect of environmental molds on risk of death from asthma during the pollen season. *J Allergy Clin Immunol* 1995; 95(5 Pt 1):955–61.
16. Wang J, Visness CM, Calatroni A, et al. Effect of environmental allergen sensitization on asthma morbidity in inner-city asthmatic children. *Clin Exp Allergy* 2009; 39(9):1381–9.
17. O'Connor GT, Walter M, Mitchell H, et al. Airborne fungi in the homes of children with asthma in low-income urban communities: the Inner-City Asthma Study. *J Allergy Clin Immunol* 2004;114(3):599–606.
18. Baxi SN, Muilenberg ML, Rogers CA, et al. Exposures to molds in school classrooms of children with asthma. *Pediatr Allergy Immunol* 2013;24(7):697–703.
19. Kercsmar CM, Dearborn DG, Schluchter M, et al. Reduction in asthma morbidity in children as a result of home remediation aimed at moisture sources. *Environ Health Perspect* 2006;114(10):1574–80.
20. Call RS, Smith TF, Morris E, et al. Risk factors for asthma in inner city children. *J Pediatr* 1992;121(6):862–6.
21. Arlian LG, Bernstein D, Bernstein IL, et al. Prevalence of dust mites in the homes of people with asthma living in eight different geographic areas of the United States. *J Allergy Clin Immunol* 1992;90(3 Pt 1):292–300.
22. Rabito FA, Iqbal S, Holt E, et al. Prevalence of indoor allergen exposures among New Orleans children with asthma. *J Urban Health* 2007;84(6):782–92.
23. Chan-Yeung M, Manfreda J, Dimich-Ward H, et al. Mite and cat allergen levels in homes and severity of asthma. *Am J Respir Crit Care Med* 1995;152(6 Pt 1):1805–11.
24. Turyk M, Curtis L, Scheff P, et al. Environmental allergens and asthma morbidity in low-income children. *J Asthma* 2006;43(6):453–7.
25. Matsui EC. Management of rodent exposure and allergy in the pediatric population. *Curr Allergy Asthma Rep* 2013;13(6):681–6.
26. Phipatanakul W, Eggleston PA, Wright EC, et al. Mouse allergen. I. The prevalence of mouse allergen in inner-city homes: the National Cooperative Inner-City Asthma Study. *J Allergy Clin Immunol* 2000;106(6):1070–4.
27. Phipatanakul W, Celedón JC, Sredl DL, et al. Mouse exposure and wheeze in the first year of life. *Ann Allergy Asthma Immunol* 2005;94(5):593–9.
28. Phipatanakul W, Celedón JC, Hoffman EB, et al. Mouse allergen exposure, wheeze and atopy in the first seven years of life. *Allergy* 2008;63(11):1512–8.
29. Donohue KM, Al-alem U, Perzanowski MS, et al. Anti-cockroach and anti-mouse IgE are associated with early wheeze and atopy in an inner-city birth cohort. *J Allergy Clin Immunol* 2008;122(5):914–20.
30. Ahluwalia SK, Peng RD, Breyse PN, et al. Mouse allergen is the major allergen of public health relevance in Baltimore City. *J Allergy Clin Immunol* 2013;132(4):830–5.e1-2.
31. Matsui EC, Eggleston PA, Buckley TJ, et al. Household mouse allergen exposure and asthma morbidity in inner-city preschool children. *Ann Allergy Asthma Immunol* 2006;97(4):514–20.
32. Sheehan WJ, Permaul P, Petty CR, et al. Association between allergen exposure in inner-city schools and asthma morbidity among students. *JAMA Pediatr* 2017; 171(1):31–8.
33. Sheehan WJ, Rangsithienchai PA, Muilenberg ML, et al. Mouse allergens in urban elementary schools and homes of children with asthma. *Ann Allergy Asthma Immunol* 2009;102(2):125–30.

34. Pongracic JA, Visness CM, Gruchalla RS, et al. Effect of mouse allergen and rodent environmental intervention on asthma in inner-city children. *Ann Allergy Asthma Immunol* 2008;101(1):35–41.
35. Arbes SJ, Cohn RD, Yin M, et al. Dog allergen (Can f 1) and cat allergen (Fel d 1) in US homes: results from the National Survey of Lead and Allergens in Housing. *J Allergy Clin Immunol* 2004;114(1):111–7.
36. Gaffin JM, Spergel JM, Boguniewicz M, et al. Effect of cat and daycare exposures on the risk of asthma in children with atopic dermatitis. *Allergy Asthma Proc* 2012; 33(3):282–8.
37. Kerkhof M, Wijga AH, Brunekreef B, et al. Effects of pets on asthma development up to 8 years of age: the PIAMA study. *Allergy* 2009;64(8):1202–8.
38. Wegienka G, Johnson CC, Havstad S, et al. Indoor pet exposure and the outcomes of total IgE and sensitization at age 18 years. *J Allergy Clin Immunol* 2010;126(2):274–9, 279.e271–275.
39. Wegienka G, Johnson CC, Havstad S, et al. Lifetime dog and cat exposure and dog- and cat-specific sensitization at age 18 years. *Clin Exp Allergy* 2011;41(7): 979–86.
40. McHugh BM, MacGinnitie AJ. Indoor allergen sensitization and the risk of asthma and eczema in children in Pittsburgh. *Allergy Asthma Proc* 2011;32(5):372–6.
41. Gent JF, Belanger K, Triche EW, et al. Association of pediatric asthma severity with exposure to common household dust allergens. *Environ Res* 2009;109(6): 768–74.
42. Gent JF, Kezik JM, Hill ME, et al. Household mold and dust allergens: exposure, sensitization and childhood asthma morbidity. *Environ Res* 2012;118:86–93.
43. Gergen PJ, Mitchell HE, Calatroni A, et al. Sensitization and exposure to pets: the effect on asthma morbidity in the US population. *J Allergy Clin Immunol Pract* 2018;6(1):101–7.e2.
44. Murray CS, Poletti G, Keadze T, et al. Study of modifiable risk factors for asthma exacerbations: virus infection and allergen exposure increase the risk of asthma hospital admissions in children. *Thorax* 2006;61(5):376–82.
45. DiMango E, Serebrisky D, Narula S, et al. Individualized household allergen intervention lowers allergen level but not asthma medication use: a randomized controlled trial. *J Allergy Clin Immunol Pract* 2016;4(4):671–9.e4.
46. Iwane MK, Prill MM, Lu X, et al. Human rhinovirus species associated with hospitalizations for acute respiratory illness in young US children. *J Infect Dis* 2011; 204(11):1702–10.
47. Jackson DJ, Gern JE, Lemanske RF. Lessons learned from birth cohort studies conducted in diverse environments. *J Allergy Clin Immunol* 2017;139(2):379–86.
48. Thorne PS, Kulhánková K, Yin M, et al. Endotoxin exposure is a risk factor for asthma: the national survey of endotoxin in United States housing. *Am J Respir Crit Care Med* 2005;172(11):1371–7.
49. Sheehan WJ, Hoffman EB, Fu C, et al. Endotoxin exposure in inner-city schools and homes of children with asthma. *Ann Allergy Asthma Immunol* 2012;108(6): 418–22.
50. Lai PS, Sheehan WJ, Gaffin JM, et al. School endotoxin exposure and asthma morbidity in inner-city children. *Chest* 2015;148(5):1251–8.
51. Gergen PJ, Teach SJ, Togias A, et al. reducing exacerbations in the inner city: lessons from the inner-city asthma consortium (ICAC). *J Allergy Clin Immunol Pract* 2016;4(1):22–6.
52. Busse WW, Morgan WJ, Gergen PJ, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. *N Engl J Med* 2011;364(11):1005–15.

53. Teach SJ, Gill MA, Togias A, et al. Preseasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations. *J Allergy Clin Immunol* 2015;136(6):1476–85.
54. Guarnieri M, Balmes JR. Outdoor air pollution and asthma. *Lancet* 2014;383(9928):1581–92.
55. Mortimer KM, Neas LM, Dockery DW, et al. The effect of air pollution on inner-city children with asthma. *Eur Respir J* 2002;19(4):699–705.
56. United States Environmental Protection Agency. Criteria air pollutants 2018. Available at: <https://www.epa.gov/criteria-air-pollutants>. Accessed June 25, 2018.
57. Matsui EC, Hansel NN, McCormack MC, et al. Asthma in the inner city and the indoor environment. *Immunol Allergy Clin North Am* 2008;28(3):665–86, x.
58. Permaul P, Phipatanakul W. School environmental intervention programs. *J Allergy Clin Immunol Pract* 2018;6(1):22–9.
59. Burke H, Leonardi-Bee J, Hashim A, et al. Prenatal and passive smoke exposure and incidence of asthma and wheeze: systematic review and meta-analysis. *Pediatrics* 2012;129(4):735–44.
60. O'Connor GT, Lynch SV, Bloomberg GR, et al. Early-life home environment and risk of asthma among inner-city children. *J Allergy Clin Immunol* 2018;141(4):1468–75.
61. Wang Z, May SM, Charoenlap S, et al. Effects of secondhand smoke exposure on asthma morbidity and health care utilization in children: a systematic review and meta-analysis. *Ann Allergy Asthma Immunol* 2015;115(5):396–401.e2.
62. Jacob P 3rd, Benowitz NL, Destailats H, et al. Thirdhand smoke: new evidence, challenges, and future directions. *Chem Res Toxicol* 2017;30(1):270–94.
63. Godwin C, Batterman S. Indoor air quality in Michigan schools. *Indoor Air* 2007;17(2):109–21.
64. Hansel NN, Breyse PN, McCormack MC, et al. A longitudinal study of indoor nitrogen dioxide levels and respiratory symptoms in inner-city children with asthma. *Environ Health Perspect* 2008;116(10):1428–32.
65. Bauman LJ, Wright E, Leickly FE, et al. Relationship of adherence to pediatric asthma morbidity among inner-city children. *Pediatrics* 2002;110(1 Pt 1):e6.
66. Szeffler SJ, Mitchell H, Sorkness CA, et al. Management of asthma based on exhaled nitric oxide in addition to guideline-based treatment for inner-city adolescents and young adults: a randomised controlled trial. *Lancet* 2008;372(9643):1065–72.
67. Poowuttikul P, Hart B, Thomas R, et al. Poor adherence with medication refill and medical supplies maintenance as risk factors for inpatient asthma admission in children. *Glob Pediatr Health* 2017;4. 2333794X17710588.
68. Michalopoulou G, Briller S, Myers-Schim S, et al. Teaching about better family-clinician partnerships in high-risk pediatric asthma care. *J Patient Exp* 2016;3(3):96–9.
69. Dutmer CM, Kim H, Searing DA, et al. Asthma in inner city children: recent insights: United States. *Curr Opin Allergy Clin Immunol* 2018;18(2):139–47.
70. Ramratnam SK, Visness CM, Jaffee KF, et al. Relationships among maternal stress and depression, type 2 responses, and recurrent wheezing at age 3 years in low-income urban families. *Am J Respir Crit Care Med* 2017;195(5):674–81.
71. Wing R, Gjelsvik A, Nocera M, et al. Association between adverse childhood experiences in the home and pediatric asthma. *Ann Allergy Asthma Immunol* 2015;114(5):379–84.
72. Litonjua AA, Weiss ST. Is vitamin D deficiency to blame for the asthma epidemic? *J Allergy Clin Immunol* 2007;120(5):1031–5.

73. Freishtat RJ, Iqbal SF, Pillai DK, et al. High prevalence of vitamin D deficiency among inner-city African American youth with asthma in Washington, DC. *J Pediatr* 2010;156(6):948–52.
74. Vahdaninia M, Mackenzie H, Helps S, et al. Prenatal intake of vitamins and allergic outcomes in the offspring: a systematic review and meta-analysis. *J Allergy Clin Immunol Pract* 2017;5(3):771–8.e5.
75. Gergen PJ, Togias A. Inner city asthma. *Immunol Allergy Clin North Am* 2015; 35(1):101–14.
76. Belamarich PF, Luder E, Kattan M, et al. Do obese inner-city children with asthma have more symptoms than nonobese children with asthma? *Pediatrics* 2000; 106(6):1436–41.
77. Kattan M, Kumar R, Bloomberg GR, et al. Asthma control, adiposity, and adipokines among inner-city adolescents. *J Allergy Clin Immunol* 2010;125(3):584–92.
78. Jensen ME, Gibson PG, Collins CE, et al. Diet-induced weight loss in obese children with asthma: a randomized controlled trial. *Clin Exp Allergy* 2013;43(7): 775–84.
79. Gern JE. The urban environment and childhood asthma study. *J Allergy Clin Immunol* 2010;125(3):545–9.
80. Bousquet J, Gern JE, Martinez FD, et al. Birth cohorts in asthma and allergic diseases: report of a NIAID/NHLBI/MeDALL joint workshop. *J Allergy Clin Immunol* 2014;133(6):1535–46.
81. Rinas U, Horneff G, Wahn V. Interferon-gamma production by cord-blood mononuclear cells is reduced in newborns with a family history of atopic disease and is independent from cord blood IgE-levels. *Pediatr Allergy Immunol* 1993;4(2):60–4.
82. Sullivan Dillie KT, Tisler CJ, Dasilva DF, et al. The influence of processing factors and non-atopy-related maternal and neonate characteristics on yield and cytokine responses of cord blood mononuclear cells. *Clin Exp Allergy* 2008;38(2): 298–304.
83. Pfefferle PI, Büchele G, Blümer N, et al. Cord blood cytokines are modulated by maternal farming activities and consumption of farm dairy products during pregnancy: the PASTURE Study. *J Allergy Clin Immunol* 2010;125(1):108–15.e1-3.
84. Eder W, Ege MJ, von Mutius E. The asthma epidemic. *N Engl J Med* 2006; 355(21):2226–35.
85. Yang IV, Pedersen BS, Liu AH, et al. The nasal methylome and childhood atopic asthma. *J Allergy Clin Immunol* 2017;139(5):1478–88.
86. Esquivel A, Busse WW, Calatroni A, et al. Effects of omalizumab on rhinovirus infections, illnesses, and exacerbations of asthma. *Am J Respir Crit Care Med* 2017;196(8):985–92.
87. Gill MA, Liu AH, Calatroni A, et al. Enhanced plasmacytoid dendritic cell antiviral responses after omalizumab. *J Allergy Clin Immunol* 2018;141(5):1735–43.e9.
88. Durham SR, Till SJ. Immunologic changes associated with allergen immunotherapy. *J Allergy Clin Immunol* 1998;102(2):157–64.
89. Wood RA, Togias A, Wildfire J, et al. Development of cockroach immunotherapy by the inner-city asthma consortium. *J Allergy Clin Immunol* 2014;133(3): 846–52.e6.
90. Breyse J, Dixon S, Gregory J, et al. Effect of weatherization combined with community health worker in-home education on asthma control. *Am J Public Health* 2014;104(1):e57–64.
91. Lemanske RF, Kakumanu S, Shanovich K, et al. Creation and implementation of SAMPRO™: a school-based asthma management program. *J Allergy Clin Immunol* 2016;138(3):711–23.

92. Bruzzese JM, Sheares BJ, Vincent EJ, et al. Effects of a school-based intervention for urban adolescents with asthma. A controlled trial. *Am J Respir Crit Care Med* 2011;183(8):998–1006.
93. Joseph CLM, Mahajan P, Stokes-Buzzelli S, et al. Pilot study of a randomized trial to evaluate a Web-based intervention targeting adolescents presenting to the emergency department with acute asthma. *Pilot Feasibility Stud* 2018;4:5.