Clinical Reviews in Allergy & Immunology (2019) 56:248–268
https://doi.org/10.1007/s12016-019-08728-x

Inner-City Asthma in Children

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Published online: 21 January 2019

Abstract

Asthma in inner-city children is often severe and difficult to control. Residence in poor and urban areas confers increased asthma morbidity even after adjusting for ethnicity, age, and gender. Higher exposure to household pests, such as cockroaches and mice, pollutants and tobacco smoke exposure, poverty, material hardship, poor-quality housing, differences in health care quality, medication compliance, and heath care access also contribute to increased asthma morbidity in this population. Since 1991, the National Institutes of Allergy and Infectious Diseases established research networks: the National Cooperative Inner-City Asthma Study (NCICAS), the Inner-City Asthma Study (ICAS), and the Inner-City Asthma Consortium (ICAC), to improve care for this at risk population. The most striking finding of the NCICAS is the link between asthma morbidity and the high incidence of allergen sensitization and exposure, particularly cockroach. The follow-up ICAS confirmed that reductions in household cockroach and dust mite were associated with reduction in the inner-city asthma morbidity. The ICAC studies have identified that omalizumab lowered fall inner-city asthma exacerbation rate; however, the relationship between inner-city asthma vs immune system dysfunction, respiratory tract infections, prenatal environment, and inner-city environment is still being investigated. Although challenging, certain interventions for inner-city asthma children have shown promising results. These interventions include family-based interventions such as partnering families with asthma-trained social workers, providing guidelines driven asthma care as well as assured access to controller medication, home-based interventions aim at elimination of indoor allergens and tobacco smoke exposure, school-based asthma programs, and computer/web-based asthma programs.

Keywords Asthma · Inner-city · Children · Asthma Research Networks · Asthma risk factors · Severe asthma · Asthma morbidity

Abbreviations

ACE	Asthma Control Evaluation
ACT	Asthma Control Test
APIC	Asthma Phenotypes in the Inner City
ASMA	Asthma Self-Management for Adolescents
CASI	Composite Asthma Severity Index
CDC	Center for Disease Control
COAST	Childhood Origins of Asthma study
CXCL 1	C-X-C motif chemokine ligand 1
DMRs	Differentially methylated regions
ED	Emergency department
ETS	Environmental tobacco smoke
FAB	Facilitated allergen binding
FeNO	Fractional exhaled nitric oxide
ICAC	Inner-City Asthma Consortium
ICAS	Inner-City Asthma Study
ICATA	Inner-City Anti-IgE Therapy for Asthma
IFN	Interferon
Ig	Immunoglobulin
IL	Interleukin
ISAAC	International Study of Asthma and Allergies in Childhood
IT	Immunotherapy
MAIT	Mucosal-associated invariant T cells
NAEPP	National Asthma Education and Prevention Program
NCICAS	National Cooperative Inner-City Asthma Study
NHIS	National Health Interview Survey
NHLBI	National Heart, Lung, and Blood Institute
NIAID	National Institutes of Allergy and Infectious Diseases

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NIH	National Institute of Health
NKT cells	Natural killer T cells
PBMCs	Peripheral blood mononuclear cells
PM	Particulate matter
PROSE	Preventative Omalizumab or Step-Up Therapy for Fall Exacerbations
RSV	Respiratory syncytial virus
SARP	Severe Asthma Research Program
SAMPRO	School-based Asthma Management Program
SICAS	School Inner-City Asthma Study
SCIT	Subcutaneous immunotherapy
SLIT	Sublingual immunotherapy
Th 2	T helper 2
Th 17	T helper 17
URECA	Urban Environment and Childhood Asthma Study
UC	Urgent care
US	United States

Introduction

Inner-city areas can be defined as urban census tracts in large metropolitan areas in which at least 20% of the households have incomes below the federal poverty level [1]. Inner-city areas are both poor and urban, and both of these factors are independent risk factors for asthma morbidity. Risk factors concentrated in poor and urban areas contribute to asthma morbidity, even if they may not necessarily contribute to its development. Numerous factors including biological, environmental, disease management, access, and socioeconomic hardship contribute significantly to the disease burden found in these children and compromise their day-to-day lifestyle [1]. Environmental factors such as allergens, pollutants, and infections are important risk factors for sensitization, development, and possibly the persistence and severity of asthma. Exposures to these allergens (cockroach) and pollutants (nitrogen dioxide) occur in inner-city homes [2] as well as schools [3]. Interventions aimed to reduce exposure to these helps to improve asthma outcomes [4].

Access to quality care is an important factor in asthma control. Accessibility for asthma care is often burdensome for this population due to lack of transport which in turn hinders ongoing care of this chronic illness [5]. Also compliance with controller medications is often poor resulting in frequent use of reliever medications. Among socioeconomic factors, family income and education level, car and house ownership, and marriage status influence asthma admissions [2].

Prevalence

In the United States, the prevalence of asthma increased among children and adolescents (17 years and younger) between 2001 through 2010. The prevalence was estimated to be 9.5% in 2008–2010 [6]. Asthma prevalence varies among racial/ethnic groups. African American children have 1.6 times the current level of asthma when compared to white children [7]. Puerto Rican children have the highest prevalence of asthma among the Hispanic groups in United States (US) which is approximately 2.4 times than white children [7]. These differences in prevalence could reflect differences in disease or disease diagnosis. Poor access to appropriate asthma care is a major problem in low socioeconomic status and has a major effect on asthma control.

In a study by Keet et al., the prevalence of current asthma was 12.9% in inner-city and 10.6% in non-inner-city children. Asthma prevalence was much higher in blacks (17.1%), Puerto Ricans (19.8%) as against in whites (9.6%), and Asians (8.1%). Black race, Puerto Rican ethnicity, and lower household income were identified as independent risk factors for current asthma. Household poverty was noted to increase the risk of asthma among non-Hispanics and Puerto Ricans but not among other Hispanics [8]. Studies in other countries have compared prevalence of asthma between urban and rural areas. The prevalence rates of asthma in rural Chinese children (1.1%) were significantly lower than urban children (6.3%) [9]. In Brazil, the prevalence of asthma-related symptoms were higher among those adolescents living in urban centers in comparison to rural areas. These are attributable to harmful environmental exposures in urban areas such as use of biomass fuel and kerosene for cooking, and exposure to motor vehicles fumes [10].

Morbidity and Mortality

Asthma morbidity can be assessed in terms of the clinical symptoms the child is experiencing, the limitation in daily activities, and the effect it has on the parent or caregiver [1]. According to the Center for Disease Control (CDC), the overall percentage of children who had an asthma attack during the preceding year decreased significantly, from 61.7% in 2001 to 53.7% in 2016. This decline was notable across all ages, gender, and racial/ethnic groups. Yet, nearly half of asthmatic children still had one or more asthma attack in 2016 [11]. As per the 2016 National Health Interview Survey (NHIS), the child's current asthma control was rated as "fair or poor" for 25.6%, and "good" for 15.2% by their caregivers. The asthma control was described as "very good or excellent" in only 6.9% of the children [12].

Another way to assess asthma morbidity is from the utilization of health care services. The 2013 NHIS data reported hospitalization in nearly 4.7% of asthmatic children. In 2016, the NHIS data showed that 16.7% of children with asthma had an emergency room (ED) or urgent care (UC) visit due to asthma attack. Almost half (49%) of school-age children with asthma missed one or more days at school in the last 12 months

due to asthma. As per this data, children 4 years old and younger were less likely to have asthma overall but those with asthma were more likely to have exacerbations (62.4%) and more likely to have health care utilization (31.1% ED/UC visits and 10.4% hospitalizations) compared to asthmatic children aged 12 to 17 year olds [11]. The NHIS data shows that the prevalence of adverse health outcomes decreased between 2003 and 2013, while the prevalence of using an asthma action plan was significantly increased [11].

The CDC national asthma mortality data for 2016 states that the total number of asthma-related deaths in children less than 18 years of age was 209 (128 for boys and 81 for girls). This gives a death rate of 2.8 per million per year for asthmatic children less than 18 years [13].

A review of asthma prevalence showed that African American and Hispanic children residing in low-socioeconomic-status urban environments tend to have higher asthma morbidity and mortality compared to white children [14]. Hispanic children are twofold more likely than white children to use emergency care whereas African American children are 2.6-fold more likely to use emergency room care and threefold more likely to be hospitalized [15].

Residence in poor and urban areas confers increased asthma morbidity as in frequent hospitalizations or ED visits [2] even after adjusting for race/ethnicity, age, and gender. Several risk factors contribute to this increased asthma morbidity. There is higher exposure to common household pests that are more common in poor and urban areas, such as cockroaches [16] and mice [17]. Other factors such as differences in health care quality, medication compliance, and heath care access also contribute to increased morbidity [2].

Other studies have evaluated the impact of poverty, material hardship, and poor-quality housing on asthma control in the U.S. urban children. Material hardship included poor housing quality, housing overcrowding, lack of amenities, and no vehicle access. Poor housing quality was found to be independently associated with increased asthma morbidity. Home ownership was associated with a lower risk of asthma-related ED visits [18]. Beck et al. conducted a study to evaluate factors contributing to asthma readmission rates between African American and white children. African American children are twice more than white children to require readmission. More than half of the asthma readmission risk was related to socioeconomic hardship. Other contributing factors included biologic (age, sex, aeroallergen sensitization), environmental (tobacco smoke, air pollution, in-home exposure to mold/pets), disease management, and health care access (vehicle ownership, medical insurance) [3] .

Air pollution also has been shown to contribute to increased morbidity in poor and urban areas [19]. These areas tend to have higher densities of major roadways and other sources of air pollution, such as power plants. This results in exposure to high levels of pollutants such as particulate matter, nitric oxides, and ozone which are associated with increased asthma morbidity [13].

Other environmental factors such as exposure to secondhand tobacco smoke [20], prematurity [21], and social stress [5] also contribute to asthma morbidity. Smoke-free legislation substantially reduced hospitalizations related to asthma. Preterm birth and childhood asthma are major health problems affecting inner-city children. Preterm children are at a higher risk of asthma [21]. Thus, prevention of preterm birth can help reduce the burden of asthma as well as associated mortality and morbidity. Inner-city living is associated with various behavioral and psychosocial stresses such as violence [5]. In addition, differences in health care quality, lack of medication compliance, and care access patterns have been shown to be contributing to asthma severity in this population [5, 22].

Inner-City Asthma Research Networks

In the United States, asthma has a major effect on the health of inner-city children. For children living in the inner city, asthma tends to be more frequent and severe. The National Institutes of Allergy and Infectious Diseases (NIAID) established research networks to improve care for this at risk population. It is helpful to first define who the asthmatic children in NIAID networks are. These children live in the inner-city neighborhoods which have been identified on the basis of census tracts. The census tracts have been designed to be similar in regard to population demographics, economic status, and living conditions. In general, urban census tracts in which at least 20% of the households have incomes below the federal poverty level were included in the network [1].

Over the past 15 years, the NIAID has funded three distinct inner-city networks: the National Cooperative Inner-City Asthma Study (NCICAS), the Inner-City Asthma Study (ICAS), and the Inner-City Asthma Consortium (ICAC) [23]. National Cooperative Inner-City Asthma Study (NCICAS) aimed to recognize the causes of increased asthma morbidity in inner-city children as well as to develop measures to reduce them. The results from the NCICAS indicate that it is not a single cause or factor that is associated with high asthma morbidity in the inner-city children, but rather many contributing factors were involved. These factors include the access to healthcare, quality of healthcare, inadequate treatment, associated psychological issues of the child and/or caregiver, family functioning, and medication adherence. Regardless of many risk factors involved with the disease, the most striking finding is the link between pediatric inner-city asthma morbidity and the high incidence of allergen sensitization and high levels of allergen exposure. Allergic sensitization to cockroach was found to be significantly associated with asthma exacerbations [24].

The ICAS was the second major program and was designed to conduct multicenter intervention trials to reduce allergen and irritant exposures [23]. The study showed that reduction in environmental allergen exposure such as dust mite and cockroach had led to reduction in asthma morbidity and the benefits were noted to be long lasting. In 2002, ICAC was established with the aim to develop immune-based therapies for asthma as well as define the immune-pathogenesis of asthma in inner-city children. Table 1 summarizes the NIAID-funded studies.

School Inner-City Asthma Study: Exposures in School and Asthma Severity

The NIAID sponsored the School Inner-City Asthma Study (SICAS) to evaluate the impact of multiple exposures in public schools on severity of asthma. The SICAS was a prospective cohort study evaluating 284 students aged 4–13 years with asthma who were enrolled from 37 inner-city elementary schools between March 1, 2008 and August 31, 2013. Indoor classroom nitrogen dioxide levels were noted to be associated with increased airflow obstruction in patients with asthma [25].

During this time period, dust samples were collected from students' classroom and home which showed significantly higher levels of mouse allergen in schools. Exposure to higher levels of mouse allergen in school was associated with increased asthma symptoms and decreased lung function. Other common indoor aeroallergens (rat, cockroach, cat, dog, and dust mites) were not found to be associated with worsening asthma outcomes [17].

Children with non-atopic asthma in the SICAS had increased asthma symptoms associated with high levels of airborne endotoxin at school. This resulted in higher daytime wheeze and exercise-related symptoms, but was not associated with nighttime wheeze. Thus, reduction of school-related exposures may represent a strategy to decrease asthma morbidity in this population [26].

Phenotypes of Inner-City Asthma

Numerous environmental factors such as allergens, obesity, nutrition, and stress influence development and severity of asthma. These external factors interplay differently within individual patients and generate an immune inflammatory response which influences the clinical features, or phenotype of asthma. Different inner-city asthma phenotypes such as obesity related, cockroach sensitive, viral respiratory tract infections associated, and cigarette smoke exposed have been identified and determine the patient's response to treatment as well as risk for loss of asthma control.

The NIAID sponsored the ICAC to conduct the Asthma Phenotypes in the Inner-City (APIC) study. The aim of the study was to define asthma phenotypes as well as severity determinants in inner-city children [27]. In the APIC study, 717 children aged 6–17 years (65% black and 28% Hispanic) with asthma living in nine U.S. inner-city communities were enrolled. Children with difficult-to-control asthma had high exacerbation rates, frequent daytime and nocturnal symptoms, and persistent airflow limitation despite ongoing high-dose inhaled corticosteroid controller therapy compared to children with easy-to-control asthma. These children also had large

Table 1 The National Institutes of Allergy and Infectious Diseases (NIAID) funded asthma studies

Study	Years	Key objective	Key findings
NCICAS	1991–1995	Determine the relationship of allergic sensitization and severity of asthma.	Cockroach is the main allergen associated with asthma severity.
ICAS	1996–2001	An environmental avoidance trial to improve asthma control.	Reductions in household cockroach and dust mite were associated with reduction in asthma morbidity.
ICAC	2002–present		
-ACE		Compare the addition of FeNO measurements and the NAEPP guideline care to the NAEPP care alone.	Asthma control of the inner-city children can be achieved by using guideline-based asthma care and adherence to asthma medication alone.
-ICATA		Evaluate the effect of anti-IgE therapy in inner-city asthma.	Omalizumab lowered exacerbation rate and reduced the dose of inhaled corticosteroid treatment compared to placebo. There was also a reduction in seasonal (fall and spring) peak in asthma exacerbations.
-URECA		Identify the effect of perinatal factors and environment exposures on the expression of asthma in inner-city children.	Ongoing.

ACE, Asthma Control Evaluation; FeNO, fractional exhaled nitric oxide; ICATA, Inner-City Anti-IgE Therapy for Asthma; NAEPP, National Asthma Education and Prevention Program; URECA, Urban Environment and Childhood Asthma Study

bronchodilator response to albuterol and poorer scores on an age-appropriate Asthma Control Test (ACT) at the start of the study. Despite good adherence, children with difficult-to-control asthma showed minimal improvement in symptoms, exacerbations, or pulmonary physiology over the year. Thus, children with difficult-to-control asthma can be identified early based on ACT, spirometry, atopy, severity of rhinitis, and response to bronchodilator.

There is significant asthma heterogeneity among inner-city children. In the APIC study, cluster analysis was performed in 616 participants which showed that asthma tend to cluster by the degree of atopy (eczema and rhinitis), and impaired pulmonary physiology. These factors were noted to be worsened in parallel and correlate with more severe disease. Asthma was noted to be more severe and exacerbations prone in those with severe rhinitis and abnormal lung function tests. However, 15% of the study population had few or no allergies but was highly symptomatic for asthma despite high doses of controller medications. Thus, in the inner-city children, there are two discrete severe asthma phenotypes: highly allergic, exacerbation-prone asthma; and highly symptomatic asthma with low/no allergy. The former group should then be managed with focused environmental allergen management and allergen desensitization [28].

The National Heart, Lung, and Blood Institute (NHLBI) sponsored the Severe Asthma Research Program (SARP III) to compare the phenotypic characteristics of children with adults with severe asthma. Severe asthma in adults is characterized by a higher proportion of women, obesity, and greater airflow limitation. These adults also exhibited fewer allergen sensitization and low blood eosinophils suggesting less reliance on Th2 pathways. On the contrary, children with severe asthma had more symptoms and more exacerbations. There was also a higher proportion of male gender and African American ethnicity compared to children with non-severe asthma. There was no difference in baseline features of obesity, airflow obstruction, allergen sensitization, or markers of inflammation in children with severe asthma [29]. Thus, the phenotypic features of asthma differ by severity and with advancing age.

Endotype of Inner-City Asthma

The endotype of difficult-to-control asthma was evaluated in 235 African American children enrolled in the APIC study. These children had higher peripheral blood eosinophil and neutrophil counts. They also had higher IL-5, interferon gamma (IFN-γ), and Th17-associated cytokines (CXCL-1, IL-17A, and IL-8). This suggests a generalized inflammatory state in inner-city African American children with difficult-to-control asthma [30]. In this study, Th2-associated inflammation was associated with easy-to-control asthma. Th2 dominant asthma is generally steroid responsive. On the other hand, difficult-to-control asthma was positively associated with a combination of Th2 and Th17 inflammation. This pattern of inflammation results in steroid-resistant asthma. Authors have suggested that using therapies targeting these two pathways may help achieve control of symptoms in this population [30].

Asthma Severity in Inner-City Children

Generally, asthma severity is gauged by the amount of medication needed to achieve asthma control and by the ease by which control is achieved [31]. Asthma in inner-city children could be inherently more severe [23]. It is unclear if inner-city children with asthma need more medication to attain the same level of control as their non-inner-city peers. Also whether inner-city asthmatic children have decreased responsiveness to corticosteroids needs to be further explored [23]. However the Asthma Control Evaluation (ACE) study results suggest that asthma control in inner-city children can be achieved by strict adherence to medications per asthma care guideline [32].

The APIC study investigated the effect of environmental factors and host factors on severity of asthma in children living in nine U.S. inner-city communities. Liu et al. analyzed several risk factors (stress, obesity, vitamin D, rhinitis severity, allergen sensitization, allergic inflammation, lung physiology, and environmental tobacco smoke (ETS) exposure) that affect asthma severity in the APIC children. Severity of asthma was assessed based on frequency of daytime and nocturnal symptoms, exacerbations, and use of controller. Of these risk factors, allergy and ETS exposure were noted to be the most important factors that contribute to impaired lung physiology and increased rhinitis severity. Thus, asthma severity can be reduced in inner-city children by focusing on these two factors [33].

To determine the severity of asthma, NIH-supported Inner-City Asthma Consortium developed CASI (Composite Asthma Severity Index). CASI was developed during ACE study and the results were extrapolated for validation in the Inner-City Anti-IgE therapy for Asthma (ICATA) trial. This includes five independent domains of asthma: day time symptoms and albuterol use, night time symptoms and albuterol use, current controller medication usage, lung function tests, and asthma exacerbation. CASI thus helps to assess severity of asthma by combining domains of impairment and future risk with the level of treatment by incorporating symptoms, exacerbations, lung function, and treatment requirements into a single index [34].

Risk Factors of Inner-City Asthma

Allergen Exposure and Sensitization

Allergen exposure and sensitization play an important role in asthma among inner-city children. The NCICAS, funded by

the NIAID in 1991–1997, aimed to identify and intervene in the factors responsible for increase in asthma among inner-city children. The investigators identified a significant influence of allergen exposure and sensitization on asthma symptoms and healthcare utilization [1, 23, 24].

In this large-year-long epidemiologic study, 1528 asthmatic children living in eight major cities (Baltimore, MD; Bronx, NY; Chicago, IL; Cleveland, OH; Detroit, MI; East Harlem, NY; St. Louis, MO and Washington, D.C.) were recruited. All participants lived in the areas where 30% of the households had incomes below the 1990 poverty level and more than 60% had a household income of less than $15,000 annually. The majority of the children were black or Hispanic and the mean age was 6.2 years. The comprehensive evaluations of allergen sensitization, the presence, distribution and exposure of allergens, clinical picture of asthma, activities of daily life, access to healthcare, medication adherence, family/psychosocial problems, effect on the parents/caregiver, home environment, and cigarette smoke exposure were studied [24]. The results from the NCICAS indicate that many contributing factors were involved in high asthma morbidity in the inner-city children. However, the most striking finding is the link between pediatric inner-city asthma morbidity and the high incidence of allergen sensitization and high levels of allergen exposure [24].

Prior to the NCICAS, many studies had reported that exposing to environmental allergens led to sensitization and potentially the development of persistent and severe asthma [35]. The allergens reported include dusts [36], pets [37], molds [38], and cockroaches [39]. In the NCICAS findings, the main allergens identified to cause sensitization the children with inner-city asthma include cockroach (36.8%), house dust mite (34.9%), and cat dander (22.7%) [24]. However, comparing to other allergens, the sensitization and exposure to cockroach were associated with increased morbidity related to asthma including increased rate of admissions, unscheduled healthcare visits, wheezing, increased asthma symptom days, missing school days, and caregiver loss of sleep [24]. Interestingly, the effects of sensitization and exposure to dusts and pets were not associated with asthma morbidity [24].

The second phase of the NCICAS then aimed to intervene in these risk factors of inner-city asthma morbidity. In 1033 studied families, the investigators found that a-year-long guidance by asthma counselors on reducing allergen exposures, including the extermination of cockroaches, resulted in a significant reduction in asthma morbidity [40].

The second NIAID-funded network, the Inner-City Asthma Study (ICAS), was conducted in 1994–2001. This multicenter intervention study is designed to decrease pediatric inner-city asthma morbidity by means of allergens and environmental risk factor reduction. About half of the recruited 937 inner-city asthma children were assigned to an intervention that reduce the exposure of cockroaches, house dust mites, cats, dogs, rodents, molds, and passive smoking, depended on their sensitizations and environmental risk factors [4]. The study patients aged from 5 to 11 years were diagnosed for moderate to severe asthma, and had at least one hospitalization or two ED visits for asthma in the past 6 months at the initial enrollment. The child's caregiver was instructed, with knowledge skills, motivation, equipment, and supplies, to the methods of environmental modification. The investigators conducted a detailed evaluation of the child's home by obtaining samples for allergen detection every 6 months. The key findings in the ICAS were that the intervention was effective in reducing indoor allergens and it had lasting effects for at least 12 months after the active intervention has stopped. The asthma control was improved with significant reductions in maximal number of days with asthma symptoms and unscheduled healthcare visits for asthma [4]. However, there was no change in the lung functions. This result may be due to an absence of severe airflow obstruction in the patients enrolled or because the development of the asthma symptoms was primarily from airway allergen sensitization [1, 4]. The results from the ICAS confirmed that a reduction of the environmental allergens is an important element to achieve asthma control. The findings also suggested that some components of asthma control, such as symptoms and exacerbations, are likely be reached by effective allergen avoidance; however, other part of asthma control, such as lung functions, may not be achieved [4, 23].

Individual Allergens and Inner-City Asthma

Cockroach

Low-income families living in the inner-city, crowded, urban environment are known to have high rates of cockroach infestation [41–43]. Various studies across the U.S., including the NCICAS, reported in-home high levels of cockroach allergens up to 56–98% of the home studied [24, 44, 45]. Many studies also reported that inner-city schools (Baltimore, MD; Birmingham, AL; Detroit, MI; Houston, TX and Manchester U.K.) had high levels of cockroach allergen, some of which were greater than the proposed sensitization thresholds for asthma [46–49]. On the contrary, the SICAS reported the levels of cockroach allergen were very low to undetectable from both schools and homes in the northeastern U.S. [17]. These findings suggest that geographic, socioeconomic, climatic, and cultural differences may influence the prevalence of cockroach allergen [50]. Regardless of the differences, it is important to emphasize that the sensitization and exposure to cockroach are linked to higher asthma morbidities, including hospitalizations, ED visits, and asthma symptoms [24, 51]. Reducing cockroach allergen exposures by effective home interventions, including the extermination of cockroaches, resulted in a significant reduction in asthma morbidity [4, 40].

Molds

Higher mold allergens in indoor air were related to homes with increased dampness, cat, and cockroach infestation [52]. Exposure to environmental molds played a role in asthma-related mortality [38]; moreover, sensitization to *Alternaria* was linked to increased asthma admissions in inner-city children [53]. Although mold exposure and sensitization were not reported in the NCICAS to be associated with asthma morbidity, other studies reported that high indoor levels of *Penicillium* exposure were related to frequent asthma symptoms and unscheduled asthma visits [51, 54]. The presence of molds or mold odor in home, including self-reported, was also associated with asthma symptoms, admissions, and poor asthma control in children [55, 56]. Other than homes, inner-city schools were also found to have high levels of molds, including *Aspergillus*, *Cladosporium*, and *Penicillium* [57], which may affect asthma morbidity further.

Although respiratory symptoms are common from mold exposure, many patients present with multiple deliberate symptoms, including fatigue, neurocognitive symptoms, pain syndromes, anxiety, depression, insomnia, dizziness, and movement disorders [58–60]. These neurocognitive symptoms are known to be caused by several mycotoxins which are neurotoxic [61] and neuroinflammation based on brain studies assessing levels of proinflammatory cytokines [62]. Many studies also reported that children exposed to indoor molds showed significant IQ deficit [63] and lower scores on cognitive testing [64–66].

Mold remediation aimed at the cause of moisture sources significantly reduced symptom days and asthma exacerbations in a randomized, controlled, single-site study of the inner-city children who live in homes with a documented mold problem [67]. Unfortunately, the commonly used methods for cleaning water-damaged materials such as bleach, ammonium-chloride or sodium-hypochlorite-based chemicals, ultraviolet (UV) light, heating, and ozone were not found to completely remove mold and mycotoxins from water-damaged building materials [68]. With this reason, patients who experienced non-respiratory symptoms from mold exposure are recommended to strictly avoid further exposure to water-damaged environments and items contaminated by those environments [58]. Air spore counts are frequently done but have significant limitations as they typically collect over a short (5-min) period and can easily result in false negative results [58]. The use of various antioxidants and sequestering agents in treating patients with non-respiratory symptoms from mold exposure shown various results [58] and details is beyond the scope of this review.

Dust Mite

Very high levels of dust mite allergens were found in the inner-city homes, especially in the bedrooms, in various large-scale studies across the U.S., including Atlanta, GA; Cincinnati, OH; Delray Beach, FL; Galveston, TX; Greenville, NC; Los Angeles, CA; Memphis, TN; New Orleans, LA; and San Diego, CA [69–71].

However, because dust mite allergen levels are strongly associated with level of humidity, although dust mite allergens were detectable, very low levels of dust mite allergens were reported in other studies from Chicago, IL [51] and the northeastern U.S. (the SICAS from both homes and schools) [17]. Surprisingly, the levels of dust mite allergens in the inner-city homes were also reported to be low in the NCICAS, despite up to 34.9% of the studied children were sensitized to dust mites [24]. The investigators concluded that these results may reflect the timing of the dust sample collection that did not occur at the time that the dust mite allergens are the highest [24].

In a large cohort of British children, the investigators found that exposure in early childhood to dust mite allergens is an important determinant of the subsequent development of asthma [36]. A birth cohort from Boston, MA, also revealed that early exposure to high levels of dust mite allergens was associated with increased risks of asthma at age of 7 [72]. Various studies confirmed a dose-response relation between dust mite exposure and sensitization when different geographic regions are compared [73–76].

Relationship between dust mite allergens and asthma morbidity is varied and less clear. A study from New York, NY, reported that dust mite sensitization was correlated with asthma morbidity, including unscheduled asthma visits, hospitalizations and medication use, independent of exposure [53]. Another study from Vancouver, BC, reported that dust mite-sensitized children had higher mean daily asthma symptoms and lower daily mean peak expiratory flow rate [77]. Another study from France also found that dust mite-sensitized adults with more severe asthma were found to be exposed to higher levels of dust mite allergen than those with milder asthma [76].

On the contrary, a study from Sydney, Australia, reported that in their dust mite-sensitized children, the symptoms of asthma and airway hyperresponsiveness did not correlate with higher levels of dust mite allergens in their home [78]. Another study from Chicago, IL, also reported that higher levels of dust mite allergens in home were not associated with number or frequency of asthma symptoms [51]. Lastly the results from the NCICAS showed no significant associations between asthma morbidity and high bedroom levels of dust mite allergen even among allergic children [24].

Despite of the variable relationship between dust mite allergens and asthma morbidity, effective home interventions to

reduce dust mite allergen levels were reported to have a good outcome on asthma. The results from the ICAS showed that reduction in exposure to dust mite allergens improved asthma morbidity by decreasing the maximal number of days with symptoms, the number of hospitalizations, and the number of unscheduled visits for asthma [4]. Another study from Egypt also reported that physical interventions to reduce dust mite allergens at home decreased asthma admissions and improved lung function [79].

Mouse

Most homes in the U.S. have detectable mouse allergen, but the allergen levels are much higher in the inner-city homes, especially in the Northeastern and Midwestern U.S. cities [80, 81]. The results from the NCICAS revealed that mouse allergen was detected in 95% of the studied inner-city homes with the highest allergen levels in the kitchen, and that cockroach infestation was associated with high mouse allergen levels [82]. Significantly higher mouse allergen levels were reported in the inner-city schools vs homes in the Northeastern U.S. from the SCICAS and other studies [17, 83, 84].

Mouse allergen exposure in home is associated with sensitization to mouse [80, 82], even at low levels of exposure [81]. The rate of sensitization to mouse allergen was also higher in the inner-city vs suburban and rural asthmatic children [80, 85]. Exposure to mouse allergen was associated with wheezing in the first year of life [86] and wheezing and atopy later in childhood [87, 88].

Although the relationship between mouse allergen exposure/sensitization and asthma morbidity was not significant in the NCICAS [82], other study reported that mouse sensitization and exposure were associated with asthma severity [89]. Dose-response relationships between mouse allergen exposure and asthma morbidity among inner-city asthmatic children were also reported [80, 90]. Higher mouse allergen levels in bed were associated with asthma-related health care utilization, ED visit, and unscheduled asthma visit in sensitized asthmatic children [80, 90]. More studies from Baltimore, MD, also reported that mouse allergen was the major contributor to asthma morbidity vs other indoor allergens in that city, even cockroach [91, 92]. These asthma morbidities include more asthma symptom days, more rescue medication use, increased asthma-related health care utilization, ED visits, and hospital admissions [91, 92]. The results from the ICAS also confirmed that mouse allergen is an independent risk factor for asthma morbidity [81]. In the SICAS, exposure to mouse allergen in schools was associated with increased asthma symptoms and decreased lung function [17].

The effect of reducing mouse allergen levels by environmental interventions on asthma morbidity is less studied. In the ICAS, reducing mouse allergen levels was associated with less missed school, sleep disruption, and caretaker burden but not asthma symptoms or medical utilization [81]. Further investigation on evaluating the role of a school-based mouse allergen reduction and asthma morbidity are underway in the SICAS study [93].

Cat and Dog

Cat or dog ownership is associated with high pet allergens in home [94]. Because pet ownership increases with higher income, pet allergens are less common in poor urban inner-city homes [94]. However, cat and dog allergens are still detectable in many public areas [48], including schools [17, 84]. In the NCICAS, only 10% of the inner-city homes studied had resident cats, as compared with 20–30% nationally [24]. However, up to 62.6% of the bedrooms studied still had detectable levels of cat allergen, while 12.6% had high levels of cat allergen [24]. Still, as many as 22.7% of the inner-city asthmatic children in the NCICAS were sensitized to cat.

The relationship between pet allergens and the development of asthma or atopic diseases is more complex. Some studies reported that cat and dog exposure maybe protective to the development of asthma [95] and allergen sensitization [96, 97]. However, other studies reported that pet exposure was associated with higher rate of dog sensitization [98] and the diagnosis of asthma and eczema [99].

Regarding asthma morbidity and pet exposure, the NCICAS found no association between high levels of cat allergen exposure and asthma morbidity even among cat allergic children [24], in contrast to cockroach allergen. However, due to the fact that so few studied children had high levels of bedroom cat allergen, the NCICAS investigators concluded that the relation between cat exposure and asthma morbidity is difficult to access accurately [24]. In the SCICAS, cat and dog allergen exposures in schools were not significantly associated with increased asthma symptoms [17]. Nevertheless, other studies reported that in sensitized children, higher levels of cat or dog allergens in home were associated with greater asthma severity [100], increased risk of wheeze and rescue medication use [101], asthma attack [102], and hospitalization from asthma [103].

In the ICAS, the environmental intervention effectively reduced the levels of cat allergen in home, but not for dog allergen [4]. The investigators found no significant association between cat allergen reduction and asthma morbidity in inner-city children [4]. In another randomized controlled trial from New York, the environmental intervention effectively reduced both cat and dog allergens but no significant reduction of asthma medication use; asthma symptoms or exacerbation was identified [104].

Other Environmental Risk Factors and Inner-City Asthma

One of the studies of the ICAC (2002), known as the Urban Environment and Childhood Asthma (URECA, 2004), is designed to determine the immunologic causes of asthma in inner-city children by following a birth cohort of inner-city newborns at risk for asthma [105]. The relationship between immune system dysfunction, lower respiratory tract infections, prenatal environment, and inner-city environment including stress, diet, pollutants, and obesity is being evaluated [105, 106].

Immune Dysregulation

Dysregulation of innate immune response, either prenatally, at birth, or during the infancy, may increase the risk of allergen sensitization and asthma [1, 106]. Birth cohort studies identified that immune hyporesponsiveness enhanced Th2-like cytokines and reduced IFN-γ responses at birth and during infancy are associated with the increased risk of lower respiratory tract infections, wheezing illnesses, allergen sensitization, and the development of atopic diseases and asthma [105–108]. These changes to the immune response apply to both inner-city and non-inner-city children. The immune dysregulations identified in the URECA study targeted inner-city children with asthma are discussed below; however, the present data is insufficient to conclude which immune dysregulations are more prominent in the inner-city population.

Certain prenatal exposures and maternal characteristics can affect the development of newborn immune system and cytokine responses [109–112]. It is hypothesized that many of these unique exposures and characteristics are more notable in the inner-city populations (e.g., indoor allergen sensitization, pollutions, obesity, stress, low birth weight, lifestyle, and nutrition) and potentially interact with certain genetic factors [92], however, head-to-head studies comparing these factors between inner-city and non-inner-city children with asthma remain insufficient at present time.

The preliminary data from the URECA study identified that the environmental predictors affecting the newborn innate immune responses included season of birth, ethnicity, birth weight/gestational age, and maternal asthma/use of inhaled corticosteroids [106]. It was also noted that IFN-γ responses, levels of innate immune cells, IL-5, type 17-related immune mediators, and activated T cells were increased in infants who were born during the winter months [113] and that the innate immune cytokine responses varied in newborns of black and Hispanic background [106]. Nevertheless, a survey study did not identify significant relationship between birth season and asthma or allergy in inner-city children [114].

Preterm birth and low birth weight are one of the significant findings seen in inner-city population, comparing to non-inner-city population [21, 115, 116]. Birth weight was inversely related with IFN-γ responses to respiratory syncytial virus (RSV) but positively correlated with IL-8 responses to many innate stimuli [106]. Previous data has also shown that preterm birth and low birth weight increased risk of asthma from ages 7–43 [117].

Children of asthmatic mothers also had lower RSV-induced cytokine responses, which may lead to impaired antiviral responses and may increase the risk of wheezing from viral infections [106]. Lower cytokine responses were also observed in infants born to atopic parents, in particular IL-12p40 and IL-8 responses [106].

Deficiencies in CD4+ T regulatory cell responses at birth were associated with allergen sensitization and wheezing [118]. An early finding from one of the URECA sites was that the inner-city newborns showed similar expression of Foxp3 on their CD4+ T cell compared to their mothers, but the cells from newborns had lower suppressive function [119].

Recent findings from one of the URECA birth cohort studies identified the possible role of mucosal-associated invariant T (MAIT) cells in inner-city asthma. The number of MAIT cells was associated with increased IFN-γ production and higher MAIT cells at 1 year of age was associated with a decreased risk of asthma by age 7 in the inner-city children [120]. The investigators also found that invariant NKT cell antigenic activity, which is a marker for increased microbial exposures, was related with higher endotoxin level and with reduced risk of asthma [120].

Epigenetics

Asthma is a heritable condition. Multiple genes have been identified in asthma [121]. Studies have shown that risk of inheriting asthma and atopic conditions in the offspring is four times higher from affected mother compared to affected father [122]. Thus, epigenetic changes can account for parent-of-origin patterns of inheritance.

Epigenetics aims to explore the role of environmental exposures (smoke exposure as well as exposure to allergens) in causing functional changes, such as methylation, of selective genes. These changes can result in rapid and persistent changes in gene expression [123]. For example, in utero exposure to tobacco smoke is linked to childhood asthma and this can modify gene expression through DNA methylation [124]. DNA methylation can alter the function of genes that is relevant to development of Th2 immunity and allergic airway result in altered function of genes that is relevant to development of Th2 immunity and allergic airway disease including asthma, particularly for inner-city children. In ICAC sponsored studies, Yang et al. showed differential methylation patterns in peripheral blood mononuclear cells (PBMCs) [125] as

well as from nasal epithelia [126] in inner-city children with persistent asthma. The methylation differences between atopic, persistent asthmatic children vs non-atopic, non-asthmatic controls were substantial. In the same study, the investigators looked into the influence of environmental factors on the epigenome and identified 48 unique differentially methylated regions (DMRs) in the nasal epithelium epigenome associated with tobacco smoke [104].

Exposure to environmental allergens can also cause epigenetic changes. Another study examined methylation of T regulatory gene (forkhead box P3, FOXP3) in buccal mucosal cells of inner-city children with asthma who were exposed to mouse allergens. The authors demonstrated that a decrease in household mouse allergen exposure (measured in dust) resulted in decreased levels of methylation at FOXP3 enhancer and promoter sites [105]. However cockroach and dust mite allergen did not affect methylation. Thus, allergen interventions can modify the natural course of disease among susceptible children through epigenetic mechanisms.

Exposure to air pollutants such as diesel exhaust particles also has been shown to cause DNA methylation in bronchial epithelium which may contribute to increased risk of allergic sensitization and asthma [127].

Rhinovirus

Rhinovirus is a known trigger for asthma exacerbations. Iwane et al. reported that children less than 5 years of age who were admitted for acute respiratory illness and tested positive for human rhinovirus on PCR analysis were more likely to have asthma diagnosis or have a history of wheezing when compared with children infected with other viruses [128]. Another study reported by Papadopoulos et al. showed that 72% of their infants with bronchiolitis were tested positive to RSV. Fewer infants in the study (29%) tested positive for rhinovirus. Interestingly in this cohort, rhinovirus infection was associated with more severe disease than RSV infection as reflected in higher clinical severity score based on severity of wheezing, oxygen saturation, heart rate, respiratory rate, presence of cyanosis, and feeding difficulty. Also infants who tested positive for rhinovirus required hospitalization earlier in the course of illness [129]. A large birth cohort by Belakian et al. showed an increased risk of asthma by 27.6% in children with severe bronchiolitis. When controlled for other asthma risk factors, severe bronchiolitis was associated with a 2.6-fold increased risk for asthma at 3–5 years of age in this cohort [130, 131].

In the Childhood Origins of Asthma (COAST) study, the investigators identified that wheezing during the first 3 years of life was associated with rhinovirus infection and the loss of lung function in early school-age children. This association was not seen in children who had wheezing from RSV. The study supports that rhinovirus infection in early childhood increases the risk for future asthma illness [132].

Rhinovirus infection stimulates the release of cytokines (IL-4, IL-13, eotaxin) which cause influx of inflammatory cells including eosinophils and macrophages into the airways. Other inflammatory proteins such as vascular endothelial growth factor, transforming growth factor, and fibroblast growth factor are also released which causes airway remodeling. These findings further support that rhinovirus infection can be an asthmagenic infection [133].

Endotoxin

Endotoxin is the outer membrane lipopolysaccharide of gram-negative bacteria. It is more commonly associated with exposure to animals including pets, moisture sources, and organic waste [134, 135]. Exposure to airborne endotoxin is a risk factor for wheezing and asthma [41, 135, 136].

Sheehan et al. studied the concentrations of endotoxin in both home and urban elementary school environments of inner-city asthmatic children. The authors concluded that the concentrations of endotoxins were higher in schools as compared to homes [136].

Lai et al. studied the SICAS cohort and concluded that inner-city children are exposed to high levels of airborne endotoxin at school which results in increased asthma symptoms in children with non-atopic asthma [26]. The authors also investigated the genetic variation of the IL-4 receptor alpha chain, in particular glutamine to arginine substitution at position 576 (Q576R), in relation to endotoxin exposure and asthma symptoms [137]. They concluded that higher endotoxin levels were associated with fewer asthma symptoms in Q/Q genotype (more common in white ethnicity) in contrast to increased asthma symptoms for R/R genotype (more common in black ethnicity) [137, 138].

In a nationwide study of endotoxin levels [139] that utilized samples collected from National Survey of Lead and Allergens in Housing (NSLAH) over 800 housing units were selected to represent U.S. demographics. The study sample represented the different geographic regions of the U.S.; urban, suburban, and rural areas; different ethnic groups; wealthy and poor demographic groups; apartment units and single family homes; children and adults; households with and without pets, with and without allergy or asthma. The study identified major predictors of increased endotoxin levels to be poverty, increasing number of household occupants, presence of children, cockroach infestation, food debris, and cigarette smoking in the home. These risk factors are known to be prominent in inner-city populations. On the contrary, this study reported dog ownership was also a predictor of increased endotoxin levels which is not representing inner-city population as mentioned previously.

Seasonal Variations

The ICAC results suggest that asthma exacerbations among inner-city children are more frequent during fall-winter months (September–December) and less frequent during summer months (June–August) [22].

Participants of the NCICAS were followed by Gergen et al. [140] for about 4 years to determine if outdoor/indoor allergic sensitization (determined by skin testing), exposure to ETS, or air pollution contributed to the seasonal pattern of asthma. The authors concluded that there was no significant relationship between sensitization to allergens, ETS exposure or most air pollutants and asthma seasonal pattern [140].

To a large extent, seasonal variation seems to be activated by IgE-mediated mechanisms as supported by the Inner-City Anti-IgE therapy for Asthma (ICATA) and Preventative Omalizumab or Step-up therapy for Fall Exacerbations (PROSE) studies. The ICATA study was a multicenter study by Busse et al. [141] in which 419 inner-city children and young adults who were 6–20 years of age with persistent asthma were given anti-IgE (omalizumab) in addition to guideline-based therapy. The results from the ICATA study showed that it was possible to control asthma symptoms in patients receiving anti-IgE to the extent of nearly eliminating the pattern of peaks of asthma exacerbation and seasonal variation in spring and fall. Similarly, the PROSE study showed a substantial decrease in fall exacerbations in participants who were treated with omalizumab 4 to 6 weeks prior to return to school [142]. It is worth mentioning that other than IgE-mediated mechanisms, there are other less understood pathways which may contribute to asthma seasonal variation and frequency of asthma exacerbations. These are demonstrated by asthma exacerbations that occurred despite being on omalizumab therapy [22].

Pollution

Traffic and power generation are the main sources of urban air pollution [143]. Proximity to a major road predisposes children in inner-city homes to more traffic pollution when compared to non-inner-city homes which are more likely to be away from heavy traffic [144, 145]. Ambient air pollution adversely affects asthma and likely contributes to the development of new onset asthma [143, 146–148]. Motrimer et al. [146] utilized data from the NCICAS and followed a cohort of 846 asthma children residing in eight U.S. urban areas for effects of ambient air pollution. The authors concluded that air pollution was significantly related to asthma symptoms and decreased pulmonary function. Traffic-related air pollution was reported to be associated with new onset of asthma in the Southern California Children's Health Study when participants were followed over 8 years and other confounding factors were controlled [147].

The 6 common outdoor air pollutants include nitrogen dioxide, particulate matter, ozone, sulfur dioxide, carbon monoxide, and lead [149]. Outdoor pollutants can penetrate indoors and contribute to indoor pollution in the form of particulate matter, nitrogen dioxide, and ozone [150]. Air pollution can also be generated indoors as by-products of activities like smoking, cooking, cleaning, and from heating/cooling systems [50, 150]. Tobacco smoke is a major indoor air pollutant that adversely affects inner-city asthma [150]. As noted by Simons et al., inner-city homes are more likely to have cigarette smokers which further contribute to increased asthma morbidity [144]. Tobacco smoke exposure is well established in causation of asthma [151, 152] as well as a trigger for asthma exacerbations [153]. A meta-analysis by Burke et al. suggested that both antenatal and postnatal passive smoke exposure increased the risk of wheezing and asthma by 20% at the very least [151] Prenatal tobacco smoke exposure (confirmed by cord blood cotinine) was recently studied by O'Connor et al. in 442 children and was associated with increased risk of asthma at 7 years of age [152] . Wang et al. concluded from meta-analysis of 25 studies that children with asthma and passive smoke exposure were more symptomatic, had more emergency room/urgent care visits and were twice more likely to be hospitalized than their unexposed counterparts [153]. While deleterious effects of secondhand smoke exposure are widely recognized, the health risks of thirdhand smoking are less well understood but are thought to be concerning based on gathered evidence so far [154].

Other factors that can contribute to poor indoor air quality are poor ventilation [50, 155]. Hansel et al. studied the effects of indoor nitrogen dioxide concentrations on 150 inner-city children with asthma who were 2 to 6 years old and concluded that higher nitrogen dioxide levels were associated with increased asthma symptoms. They also noted that the use of a gas stove, stove/oven, and space heater was independently associated with higher indoor nitrogen dioxide levels [156]. More recently Gaffin et al. have reported increased airflow obstruction with increased nitrogen dioxide levels in classrooms of the SICAS cohort participants [25]. The deleterious effects of increased concentrations of indoor particulate matter on asthma morbidity have also been observed in atopic as well as non-atopic children [157].

Non-adherence to Medication

Successful management of asthma relies to a large extent on medication adherence, proper inhaler technique, and avoidance of triggers that bring about exacerbations. Studies to investigate the relationship of medication adherence and asthma morbidity in inner-city children were undertaken [158] [24]. The investigators found that being at risk for medication non-adherence and admitting non-adherence independently and jointly were associated with increased asthma morbidity.

The risk factors for medication non-adherence in this study included more than 1 prescribed medication, patients who take more than 1 medication per day, caregivers concerned about medication side effects, caregivers who perceived that the child was getting too much medication or not enough medication, caregivers who perceived that medications are only somewhat useful, multiple asthma caregivers, trouble with getting appointments, problems with giving medications, not having medication in the house when needed, and child refusing to take medication [158]. The importance of medication adherence is further highlighted by the ACE study [32] according to which asthma control of the inner-city children can be achieved by using guideline-based asthma care and strict adherence to asthma medication. The details about the ACE study are mentioned in the interventions for the inner-city asthma in this article.

Stress, Psychological Issues, and Depression

Caregiver stress is associated with poor asthma control and increased risk of recurrent wheezing. In the URECA study, maternal stress and depression during the first 3 years of life were associated with recurrent wheezing at 3 years of age and asthma at age 7 in children [138, 152, 159]. It is known that inner-city children are at risk for violence exposure [160, 161]. Exposure to violence is also reported to contribute to inner-city asthma morbidity [161, 162]. Furthermore, adverse childhood experiences like witnessing domestic violence were found to be strongly associated with reported lifetime asthma in a study done on inner-city asthma children by Wing et al. [163]. This study showed that exposure to even one adverse childhood event increased the risk of reported lifetime asthma to 28% when compared to children without exposure to such adverse events supporting that psychosocial factors could contribute to pediatric asthma.

Vitamin D Deficiency

Studies done in children with asthma have long speculated the role of vitamin D deficiency in the development of asthma [164, 165]. Other studies have also reported a higher prevalence of vitamin D deficiency in inner-city children with asthma comparing to non-inner-city children [165, 166]. Prenatal vitamin D supplementation may be beneficial in reducing recurrent wheezing in early years of life [130, 167]. Although in the APIC study, Liu et al. concluded that the total effect of vitamin D on asthma severity was insignificant in inner-city population [33].

Obesity

Many studies suggest that obesity is associated with increased asthma prevalence, symptoms, and exacerbations without difference in allergic sensitization [5, 168, 169]. The prevalence of obesity in inner-city children is also higher than the national average in many studies [170–172]. A randomized controlled trial reported that weight loss among obese asthmatics resulted in an improvement in static lung function and asthma control without changes in inflammation [173]. On the contrary, Liu et al. found that obesity was not directly associated with asthma severity in the APIC study cohort [33].

Interventions for Inner-City Asthma

Interventions for the inner-city children with asthma are often challenging due to multiple factors that contribute to the high burden of asthma in this population. These include family's lack of knowledge/participation in the medical care system and other socioeconomic hardships. The NIAID-funded NCICAS revealed that family-based interventions such as partnering families with asthma-trained social workers allowed families to obtain better medical care and reduced asthma-related morbidity [40].

It is now evident that inner-city asthmatics can be well controlled with proper treatment. The NIAID-funded ACE study concluded that asthma symptoms can be reduced by providing NAEPP guidelines driven asthma care as well as assured access to controller medication. The study was a randomized, double-blind trial which included 780 inner-city asthma patients, aged 12–20 years. The aim of the study was to assess whether measurement of fractional exhaled nitric oxide (FeNO), a biomarker of airway inflammation, used as an adjunct to guideline-based asthma care could increase the effectiveness of asthma treatment. At the initial study visit, each subject was assessed for ongoing symptoms, pulmonary function, and the overall level of asthma control. The recruited subjects were then randomly assigned to 46 weeks of either standard treatment based on NAEPP guidelines or standard treatment modified on the basis of FeNO levels. A six-step escalating algorithm was used to achieve asthma control; the treatment began with fluticasone, 100 mcg/day, and ranged up to fluticasone 500 mcg/Salmeterol 50 mcg, twice a day, along with either low-dose theophylline or montelukast. The primary outcome was the number of days with asthma symptoms. Most participants exhibited good control of symptoms as well as fewer exacerbations with conventional asthma management. Approximately one-third of the children experienced an exacerbation despite using high-dose inhaled steroids. Thus, asthma control can be achieved in inner-city asthma patients using guideline-based asthma care and medication adherence. However, the ACE study did not include patients with severe asthma; furthermore, the study included patients who were known to the study centers and those who were interested in participating [32].

Based on the NCICAS observation that allergic sensitization is a major factor predicting asthma exacerbations and that exacerbations occur despite aggressive inhaled steroid therapy, the Inner-City Anti-IgE Therapy for Asthma (ICATA) trial was initiated. This trial aimed to evaluate whether IgE monoclonal antibody (omalizumab) when used as an adjunct to Expert panel Report (EPR-3)-based asthma therapy would reduce exacerbations. Omalizumab significantly lowered the exacerbation rate (38% reduction) as well as reduced the dose of inhaled corticosteroid treatment compared to placebo. There was also a reduction in seasonal (fall and spring) peak in exacerbations. The ICATA study concluded that allergic sensitization plays a significant role in the seasonal variation in asthma exacerbations especially during fall season [141] .

The Preventative Omalizumab or Step-up Therapy for Severe Fall Exacerbations (PROSE) was developed by the ICAC team in view of the seasonal nature of exacerbations (highest rates in fall season). Two approaches were evaluated, the short-term use of omalizumab (based on the results of the ICATA study) or the increased dose of inhaled corticosteroid above the dose needed to control symptoms (based on ACE study). There was a significant reduction in fall exacerbations with pre-seasonal treatment with omalizumab, whereas little to no reduction of asthma exacerbations was seen in the group receiving steroid boost [142]. Maximal benefit was seen in the participants who had a recent exacerbation.

As previously mentioned, rhinovirus infection is a common trigger of asthma exacerbations. The PROSE investigators also found that children receiving omalizumab had decreased frequency and duration of rhinovirus infection as well as reduced peak rhinovirus shedding [174]. The omalizumab treatment group demonstrated increased production of interferon alpha (IFN-α) to rhinovirus. Thus omalizumab can also alter the immune response to rhinovirus [175].

Immunotherapy for Inner-City Asthma

The ICAC 2 investigators aimed to develop clinical interventional protocols to evaluate immune-based therapies such as immunotherapy (IT) to control asthma in inner-city children. Studies have shown that IT can be disease modifying and has sustained benefit, unlike other current pharmacological therapies for asthma [176]. These trials also aim to identify biomarkers (e.g., change in antigen-specific IgE or increase in IgG4 levels) which may correlate to clinical outcomes of the IT in inner-city asthmatics. Under the ICAC, four pilot studies were conducted to evaluate immunotherapy for cockroach allergy since cockroach exposure has been shown to be associated with higher asthma morbidity in the inner-city population. These involved a total of 190 children and adults: (1) an open-label 2-week study to assess the safety of cockroach SLIT in adults and children; (2) a randomized, double-blind 6-month study of cockroach SLIT versus placebo in adults; (3) a randomized, double-blind 3-month study of two doses of cockroach SLIT versus placebo in children; and (4) an open-label 6-month safety study of cockroach subcutaneous immunotherapy (SCIT) in adults. The authors concluded that German cockroach sublingual immunotherapy (SLIT) induces significant but inconsistent changes in serum specific IgE levels. On the other hand, cockroach subcutaneous immunotherapy (SCIT) induces significant and substantial immunologic changes, especially in IgG4 and facilitated allergen binding (FAB) inhibition. Thus, SCIT might be a better option for cockroach immunotherapy in the inner-city population [177].

Other Interventions

Environmental interventions at a population level have also been shown to have beneficial effect in urban children with asthma. These include prohibiting smoking in public places, vehicle emission regulations, and replacing indoor gas heaters in schools with alternative heating sources.

Home-based interventions aim at elimination of indoor allergens as well as improving housing conditions. The NIAID-funded ICAS completed a comprehensive environmental clean-up trial which included control of home allergens and exposure to tobacco smoke. The participants exhibited long-lasting decrease in asthma symptoms and unscheduled health care visits for at least 12 months after the active intervention has stopped [4]. Although the improvement of lung function was not achieved, the results from the ICAS still highlighted that environmental allergens and ETS are important elements of asthma control in inner-city children [4]. Other interventions have focused on improving housing conditions. A study reported that programs designed to weatherize homes have resulted in decreased mold and moisture exposure and led to the improvement in asthma control [178].

School-based asthma programs have also been recently recognized for their importance in childhood asthma management. School-based Asthma Management Program (SAMPRO™) provides asthma education for children, families, clinicians, and school nurses. The program aims to enhance multidirectional communication to promote better asthma care for children within the school environment. This includes provision of asthma action plan and asthma emergency plan to the school personnel as well as educating school personnel regarding care of children with asthma at school. School-based asthma triggers are assessed and remediation measures are provided such as application of pesticides [179]. Other interventions such as providing asthma education to students during school day have also been successful. Asthma Self-Management for Adolescents (ASMA) is a school-based intervention for Hispanic and African

American adolescents with moderate persistent asthma wherein student completed bimonthly assessments. ASMA enrolled students reported fewer symptoms (daytime and nocturnal) as well reduced asthma morbidity and urgent care usage [180].

The School-based Asthma Therapy was implemented with the aim to decrease morbidity in inner-city children with asthma by improving adherence to medications as well reduction of environmental tobacco smoke exposure at home. Under the program, school nurse directly observed use of asthma preventive medications. The program resulted in a significant reduction in asthma exacerbations, urgent care visits, and missed school days over the study period [181].

Step-Up Asthma Program is a school-centered asthma management program which employs asthma counselors to provide evidence-based asthma education to children with asthma in school. The program improved asthma control resulting in fewer asthma exacerbations, urgent care visits, and missed school days [182]. Other interventions such as the use of classroom-based air cleaners in schools have resulted in significant reduction in classroom fine particulate matter (PM2.5) and black carbon, which also shown to decrease asthma morbidity [183].

Technology-based initiatives are also being used to aid in inner-city asthma management. These include text messaging, computer/web-based, video games, and interactive voice response. Of these methods, only computer/web-based programs have been successful in reducing asthma symptoms. Puff City is a web-based asthma management program which has been developed to help African American adolescents to achieve better control of their asthma. A pilot study utilized the Puff City program in urban teens (13–19 years) with asthma in Detroit, MI. The authors concluded that the treatment group experienced fewer ED visits [184].

Summary

Inner-city asthma is a complex medical problem with several risk factors contributing to the high morbidity and mortality of the disease. Some of these risks factors, e.g., allergens, tobacco smoke exposure, and pollutants, are known to be important triggers for asthma in general, but many studies have shown their impact on inner-city children vary to a great extent. Other unique risk factors include social inequities, poor housing quality, inability to access proper medical care, and poor adherence to medications complicate inner-city asthma further. Although they may not be easily available in real practice settings, several interventions have shown promising outcome for inner-city asthmatic children. These interventions include comprehensive control of home allergens and exposure to tobacco smoke, the use of omalizumab to prevent seasonal asthma exacerbations, school-based asthma program, and technology-based initiatives. Future sustainable and scalable interventions in real-world settings are still required.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval and Informed Consent This article does not contain any studies with human participants or animals performed by any of the authors. Informed consent is not applicable.

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References

1. Busse WW, Mitchell H (2007) Addressing issues of asthma in inner-city children. J Allergy Clin Immunol 119(1):43–49. https://doi.org/10.1016/j.jaci.2006.10.021
2. Keet CA, Matsui EC, McCormack MC, Peng RD (2017) Urban residence, neighborhood poverty, race/ethnicity, and asthma morbidity among children on Medicaid. J Allergy Clin Immunol 140(3):822–827. https://doi.org/10.1016/j.jaci.2017.01.036
3. Beck AF, Huang B, Auger KA, Ryan PH, Chen C, Kahn RS (2016) Explaining racial disparities in child asthma readmission using a causal inference approach. JAMA Pediatr 170(7):695–703. https://doi.org/10.1001/jamapediatrics.2016.0269
4. Morgan WJ, Crain EF, Gruchalla RS, O'Connor GT, Kattan M, Evans R, Stout J, Malindzak G, Smartt E, Plaut M, Walter M, Vaughn B, Mitchell H, Group I-CAS (2004) Results of a home-based environmental intervention among urban children with asthma. N Engl J Med 351(11):1068–1080. https://doi.org/10.1056/NEJMoa032097
5. Gergen PJ, Togias A (2015) Inner city asthma. Immunol Allergy Clin N Am 35(1):101–114. https://doi.org/10.1016/j.iac.2014.09.006
6. Moorman JE, Akinbami LJ, Bailey CM, Zahran HS, King ME, Johnson CA, Liu X (2012) National surveillance of asthma: United States, 2001-2010. Vital Health Stat 3(35):1–58
7. Akinbami LJ, Moorman JE, Garbe PL, Sondik EJ (2009) Status of childhood asthma in the United States, 1980-2007. Pediatrics 123(Suppl 3):S131–S145. https://doi.org/10.1542/peds.2008-2233C
8. Keet CA, McCormack MC, Pollack CE, Peng RD, McGowan E, Matsui EC (2015) Neighborhood poverty, urban residence, race/ethnicity, and asthma: rethinking the inner-city asthma epidemic. J Allergy Clin Immunol 135(3):655–662. https://doi.org/10.1016/j.jaci.2014.11.022
9. Ma Y, Zhao J, Han ZR, Chen Y, Leung TF, Wong GW (2009) Very low prevalence of asthma and allergies in schoolchildren from rural Beijing, China. Pediatr Pulmonol 44(8):793–799. https://doi.org/10.1002/ppul.21061
10. Sole D, Camelo-Nunes IC, Wandalsen GF, Mallozi MC (2014) Asthma in children and adolescents in Brazil: contribution of the International Study of Asthma and Allergies in Childhood (ISAAC). Rev Paul Pediatr 32(1):114–125
11. Zahran HS, Bailey CM, Damon SA, Garbe PL, Breysse PN (2018) Vital signs: asthma in children—United States, 2001-2016. MMWR Morb Mortal Wkly Rep 67(5):149–155. https://doi.org/10.15585/mmwr.mm6705e1

12. Black L, Benson V (2018) Tables of summary health statistics for U.S. children: 2016 National Health Interview Survey. https://www.cdc.gov/nchs/nhis/SHS/tables.htm
13. Center for Disease Control and Prevention (2018) National Asthma Mortality 2016. https://www.cdc.gov/asthma/most_recent_data.htm. Accessed May 16, 2018
14. Bryant-Stephens T (2009) Asthma disparities in urban environments. J Allergy Clin Immunol 123(6):1199–1206; quiz 1207-1198. https://doi.org/10.1016/j.jaci.2009.04.030
15. Akinbami LJ, Moorman JE, Simon AE, Schoendorf KC (2014) Trends in racial disparities for asthma outcomes among children 0 to 17 years, 2001-2010. J Allergy Clin Immunol 134(3):547–553 e545. https://doi.org/10.1016/j.jaci.2014.05.037
16. Gruchalla RS, Pongracic J, Plaut M, Evans R, Visness CM, Walter M, Crain EF, Kattan M, Morgan WJ, Steinbach S, Stout J, Malindzak G, Smartt E, Mitchell H (2005) Inner City Asthma Study: relationships among sensitivity, allergen exposure, and asthma morbidity. J Allergy Clin Immunol 115(3):478–485. https://doi.org/10.1016/j.jaci.2004.12.006
17. Sheehan WJ, Permaul P, Petty CR, Coull BA, Baxi SN, Gaffin JM, Lai PS, Gold DR, Phipatanakul W (2017) Association between allergen exposure in inner-city schools and asthma morbidity among students. JAMA Pediatr 171(1):31–38. https://doi.org/10.1001/jamapediatrics.2016.2543
18. Hughes HK, Matsui EC, Tschudy MM, Pollack CE, Keet CA (2017) Pediatric asthma health disparities: race, hardship, housing, and asthma in a national survey. Acad Pediatr 17(2):127–134. https://doi.org/10.1016/j.acap.2016.11.011
19. Ierodiakonou D, Zanobetti A, Coull BA, Melly S, Postma DS, Boezen HM, Vonk JM, Williams PV, Shapiro GG, EF MK, Hallstrand TS, Koenig JQ, Schildcrout JS, Lumley T, Fuhlbrigge AN, Koutrakis P, Schwartz J, Weiss ST, Gold DR, Group CAMPR (2016) Ambient air pollution, lung function, and airway responsiveness in asthmatic children. J Allergy Clin Immunol 137(2):390–399. https://doi.org/10.1016/j.jaci.2015.05.028
20. Been JV, Nurmatov UB, Cox B, Nawrot TS, van Schayck CP, Sheikh A (2015) Effect of smoke-free legislation on perinatal and child health: a systematic review and meta-analysis. Eur J Paediatr Dent 16(3):210–211
21. He H, Butz A, Keet CA, Minkovitz CS, Hong X, Caruso DM, Pearson C, Cohen RT, Wills-Karp M, Zuckerman BS, Hughes ME, Wang X (2015) Preterm birth with childhood asthma: the role of degree of prematurity and asthma definitions. Am J Respir Crit Care Med 192(4):520–523. https://doi.org/10.1164/rccm.201503-0522LE
22. Gergen PJ, Teach SJ, Togias A, Busse WW (2016) Reducing exacerbations in the inner city: lessons from the Inner-City Asthma Consortium (ICAC). J Allergy Clin Immunol Pract 4(1):22–26. https://doi.org/10.1016/j.jaip.2015.07.024
23. Busse WW (2010) The National Institutes of Allergy and Infectious Diseases networks on asthma in inner-city children: an approach to improved care. J Allergy Clin Immunol 125(3):529–537; quiz 538-529. https://doi.org/10.1016/j.jaci.2010.01.036
24. Rosenstreich DL, Eggleston P, Kattan M, Baker D, Slavin RG, Gergen P, Mitchell H, McNiff-Mortimer K, Lynn H, Ownby D, Malveaux F (1997) The role of cockroach allergy and exposure to cockroach allergen in causing morbidity among inner-city children with asthma. N Engl J Med 336(19):1356–1363. https://doi.org/10.1056/NEJM199705083361904
25. Gaffin JM, Hauptman M, Petty CR, Sheehan WJ, Lai PS, Wolfson JM, Gold DR, Coull BA, Koutrakis P, Phipatanakul W (2018) Nitrogen dioxide exposure in school classrooms of inner-city children with asthma. J Allergy Clin Immunol 141(6):2249–2255.e2242. https://doi.org/10.1016/j.jaci.2017.08.028
26. Lai PS, Sheehan WJ, Gaffin JM, Petty CR, Coull BA, Gold DR, Phipatanakul W (2015) School endotoxin exposure and asthma morbidity in inner-city children. Chest 148(5):1251–1258. https://doi.org/10.1378/chest.15-0098
27. Pongracic JA, Krouse RZ, Babineau DC, Zoratti EM, Cohen RT, Wood RA, Khurana Hershey GK, Kercsmar CM, Gruchalla RS, Kattan M, Teach SJ, Johnson CC, Bacharier LB, Gern JE, Sigelman SM, Gergen PJ, Togias A, Visness CM, Busse WW, Liu AH (2016) Distinguishing characteristics of difficult-to-control asthma in inner-city children and adolescents. J Allergy Clin Immunol 138(4):1030–1041. https://doi.org/10.1016/j.jaci.2016.06.059
28. Zoratti EM, Krouse RZ, Babineau DC, Pongracic JA, O'Connor GT, Wood RA, Khurana Hershey GK, Kercsmar CM, Gruchalla RS, Kattan M, Teach SJ, Sigelman SM, Gergen PJ, Togias A, Visness CM, Busse WW, Liu AH (2016) Asthma phenotypes in inner-city children. J Allergy Clin Immunol 138(4):1016–1029. https://doi.org/10.1016/j.jaci.2016.06.061
29. Teague WG, Phillips BR, Fahy JV, Wenzel SE, Fitzpatrick AM, Moore WC, Hastie AT, Bleecker ER, Meyers DA, Peters SP, Castro M, Coverstone AM, Bacharier LB, Ly NP, Peters MC, Denlinger LC, Ramratnam S, Sorkness RL, Gaston BM, Erzurum SC, Comhair SAA, Myers RE, Zein J, DeBoer MD, Irani AM, Israel E, Levy B, Cardet JC, Phipatanakul W, Gaffin JM, Holguin F, Fajt ML, Aujla SJ, Mauger DT, Jarjour NN (2018) Baseline features of the severe asthma research program (SARP III) cohort: differences with age. J Allergy Clin Immunol Pract 6(2):545–554.e544. https://doi.org/10.1016/j.jaip.2017.05.032
30. Brown KR, Krouse RZ, Calatroni A, Visness CM, Sivaprasad U, Kercsmar CM, Matsui EC, West JB, Makhija MM, Gill MA, Kim H, Kattan M, Pillai D, Gern JE, Busse WW, Togias A, Liu AH, Khurana Hershey GK (2017) Endotypes of difficult-to-control asthma in inner-city African American children. PLoS One 12(7):e0180778. https://doi.org/10.1371/journal.pone.0180778
31. Szefler SJ, Gergen PJ, Mitchell H, Morgan W (2010) Achieving asthma control in the inner city: do the National Institutes of Health Asthma Guidelines really work? J Allergy Clin Immunol 125(3):521–526; quiz 527-528. https://doi.org/10.1016/j.jaci.2010.01.025
32. Szefler SJ, Mitchell H, Sorkness CA, Gergen PJ, O'Connor GT, Morgan WJ, Kattan M, Pongracic JA, Teach SJ, Bloomberg GR, Eggleston PA, Gruchalla RS, Kercsmar CM, Liu AH, Wildfire JJ, Curry MD, Busse WW (2008) 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 372(9643):1065–1072. https://doi.org/10.1016/S0140-6736(08)61448-8
33. Liu AH, Babineau DC, Krouse RZ, Zoratti EM, Pongracic JA, O'Connor GT, Wood RA, Khurana Hershey GK, Kercsmar CM, Gruchalla RS, Kattan M, Teach SJ, Makhija M, Pillai D, Lamm CI, Gern JE, Sigelman SM, Gergen PJ, Togias A, Visness CM, Busse WW (2016) Pathways through which asthma risk factors contribute to asthma severity in inner-city children. J Allergy Clin Immunol 138(4):1042–1050. https://doi.org/10.1016/j.jaci.2016.06.060
34. Wildfire JJ, Gergen PJ, Sorkness CA, Mitchell HE, Calatroni A, Kattan M, Szefler SJ, Teach SJ, Bloomberg GR, Wood RA, Liu AH, Pongracic JA, Chmiel JF, Conroy K, Rivera-Sanchez Y, Busse WW, Morgan WJ (2012) Development and validation of the Composite Asthma Severity Index—an outcome measure for use in children and adolescents. J Allergy Clin Immunol 129(3):694–701. https://doi.org/10.1016/j.jaci.2011.12.962
35. Etzel RA (2003) How environmental exposures influence the development and exacerbation of asthma. Pediatrics 112(1 Pt 2):233–239

36. Sporik R, Holgate ST, Platts-Mills TA, Cogswell JJ (1990) Exposure to house-dust mite allergen (Der p I) and the development of asthma in childhood. A prospective study. N Engl J Med 323(8):502–507. https://doi.org/10.1056/NEJM199008233230802
37. Ingram JM, Sporik R, Rose G, Honsinger R, Chapman MD, Platts-Mills TA (1995) Quantitative assessment of exposure to dog (Can f 1) and cat (Fel d 1) allergens: relation to sensitization and asthma among children living in Los Alamos, New Mexico. J Allergy Clin Immunol 96(4):449–456
38. Targonski PV, Persky VW, Ramekrishnan V (1995) Effect of environmental molds on risk of death from asthma during the pollen season. J Allergy Clin Immunol 95 (5 Pt 1):955–961
39. Kang B (1976) Study on cockroach antigen as a probable causative agent in bronchial asthma. J Allergy Clin Immunol 58(3):357–365
40. Evans R, Gergen PJ, Mitchell H, Kattan M, Kercsmar C, Crain E, Anderson J, Eggleston P, Malveaux FJ, Wedner HJ (1999) A randomized clinical trial to reduce asthma morbidity among inner-city children: results of the National Cooperative Inner-City Asthma Study. J Pediatr 135(3):332–338
41. Kanchongkittiphon W, Gaffin JM, Phipatanakul W (2014) The indoor environment and inner-city childhood asthma. Asian Pac J Allergy Immunol 32(2):103–110
42. Sheehan WJ, Rangsithienchai PA, Wood RA, Rivard D, Chinratanapisit S, Perzanowski MS, Chew GL, Seltzer JM, Matsui EC, Phipatanakul W (2010) 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 125(3):575–581. https://doi.org/10.1016/j.jaci.2010.01.023
43. Cohn RD, Arbes SJ, Jaramillo R, Reid LH, Zeldin DC (2006) National prevalence and exposure risk for cockroach allergen in U.S. households. Environ Health Perspect 114(4):522–526
44. Wang C, Abou El-Nour MM, Bennett GW (2008) Survey of pest infestation, asthma, and allergy in low-income housing. J Community Health 33(1):31–39. https://doi.org/10.1007/s10900-007-9064-6
45. Chew GL, Carlton EJ, Kass D, Hernandez M, Clarke B, Tiven J, Garfinkel R, Nagle S, Evans D (2006) Determinants of cockroach and mouse exposure and associations with asthma in families and elderly individuals living in New York City public housing. Ann Allergy Asthma Immunol 97(4):502–513. https://doi.org/10.1016/S1081-1206(10)60942-8
46. Abramson SL, Turner-Henson A, Anderson L, Hemstreet MP, Bartholomew LK, Joseph CL, Tang S, Tyrrell S, Clark NM, Ownby D (2006) Allergens in school settings: results of environmental assessments in 3 city school systems. J Sch Health 76(6):246–249. https://doi.org/10.1111/j.1746-1561.2006.00105.x
47. Tortolero SR, Bartholomew LK, Tyrrell S, Abramson SL, Sockrider MM, Markham CM, Whitehead LW, Parcel GS (2002) Environmental allergens and irritants in schools: a focus on asthma. J Sch Health 72(1):33–38
48. Custovic A, Green R, Taggart SC, Smith A, Pickering CA, Chapman MD, Woodcock A (1996) Domestic allergens in public places. II: dog (Can f1) and cockroach (Bla g 2) allergens in dust and mite, cat, dog and cockroach allergens in the air in public buildings. Clin Exp Allergy 26(11):1246–1252
49. Amr S, Bollinger ME, Myers M, Hamilton RG, Weiss SR, Rossman M, Osborne L, Timmins S, Kimes DS, Levine ER, Blaisdell CJ (2003) Environmental allergens and asthma in urban elementary schools. Ann Allergy Asthma Immunol 90(1):34–40. https://doi.org/10.1016/S1081-1206(10)63611-3
50. Permaul P, Phipatanakul W (2018) School environmental intervention programs. J Allergy Clin Immunol Pract 6(1):22–29. https://doi.org/10.1016/j.jaip.2017.10.002
51. Turyk M, Curtis L, Scheff P, Contraras A, Coover L, Hernandez E, Freels S, Persky V (2006) Environmental allergens and asthma morbidity in low-income children. J Asthma 43(6):453–457. https://doi.org/10.1080/02770900600758333
52. O'connor GT, Walter M, Mitchell H, Kattan M, Morgan WJ, Gruchalla RS, Pongracic JA, Smartt E, Stout JW, Evans R, Crain EF, Burge HA (2004) Airborne fungi in the homes of children with asthma in low-income urban communities: the Inner-City Asthma Study. J Allergy Clin Immunol 114(3):599–606. https://doi.org/10.1016/j.jaci.2004.05.064
53. Wang J, Visness CM, Calatroni A, Gergen PJ, Mitchell HE, Sampson HA (2009) Effect of environmental allergen sensitization on asthma morbidity in inner-city asthmatic children. Clin Exp Allergy 39(9):1381–1389. https://doi.org/10.1111/j.1365-2222.2009.03225.x
54. Pongracic JA (2010) Asthma in adolescents living in the inner city. Adolesc Med State Art Rev 21(1):34–43 **viii**
55. Bonner S, Matte TD, Fagan J, Andreopoulos E, Evans D (2006) Self-reported moisture or mildew in the homes of Head Start children with asthma is associated with greater asthma morbidity. J Urban Health 83(1):129–137. https://doi.org/10.1007/s11524-005-9012-7
56. Değer L, Plante C, Goudreau S, Smargiassi A, Perron S, Thivierge RL, Jacques L (2010) Home environmental factors associated with poor asthma control in Montreal children: a population-based study. J Asthma 47(5):513–520. https://doi.org/10.3109/02770901003615778
57. Baxi SN, Muilenberg ML, Rogers CA, Sheehan WJ, Gaffin J, Permaul P, Kopel LS, Lai PS, Lane JP, Bailey A, Petty CR, Fu C, Gold DR, Phipatanakul W (2013) Exposures to molds in school classrooms of children with asthma. Pediatr Allergy Immunol 24(7):697–703. https://doi.org/10.1111/pai.12127
58. Hope J (2013) A review of the mechanism of injury and treatment approaches for illness resulting from exposure to water-damaged buildings, mold, and mycotoxins. ScientificWorldJournal 2013:767482. https://doi.org/10.1155/2013/767482
59. Lieberman A, Rea W, Curtis L (2006) Adverse health effects of indoor mold exposure. J Allergy Clin Immunol 118(3):763; author reply 767-768. https://doi.org/10.1016/j.jaci.2006.06.037
60. Rea WJ, Didriksen N, Simon TR, Pan Y, Fenyves EJ, Griffiths B (2003) Effects of toxic exposure to molds and mycotoxins in building-related illnesses. Arch Environ Health 58(7):399–405
61. Doi K, Uetsuka K (2011) Mechanisms of mycotoxin-induced neurotoxicity through oxidative stress-associated pathways. Int J Mol Sci 12(8):5213–5237. https://doi.org/10.3390/ijms12085213
62. Calderon-Garciduenas L, Mora-Tiscareno A, Ontiveros E, Gomez-Garza G, Barragan-Mejia G, Broadway J, Chapman S, Valencia-Salazar G, Jewells V, Maronpot RR, Henriquez-Roldan C, Perez-Guille B, Torres-Jardon R, Herrit L, Brooks D, Osnaya-Brizuela N, Monroy ME, Gonzalez-Maciel A, Reynoso-Robles R, Villarreal-Calderon R, Solt AC, Engle RW (2008) Air pollution, cognitive deficits and brain abnormalities: a pilot study with children and dogs. Brain Cogn 68(2):117–127. https://doi.org/10.1016/j.bandc.2008.04.008
63. Jedrychowski W, Maugeri U, Perera F, Stigter L, Jankowski J, Butscher M, Mroz E, Flak E, Skarupa A, Sowa A (2011) Cognitive function of 6-year old children exposed to mold-contaminated homes in early postnatal period. Prospective birth cohort study in Poland. Physiol Behav 104(5):989–995. https://doi.org/10.1016/j.physbeh.2011.06.019
64. Gordon WA, Cantor JB, Johanning E, Charatz HJ, Ashman TA, Breeze JL, Haddad L, Abramowitz S (2004) Cognitive impairment associated with toxigenic fungal exposure: a replication and extension of previous findings. Appl Neuropsychol 11(2):65–74. https://doi.org/10.1207/s15324826an1102_1

65. Baldo JV, Ahmad L, Ruff R (2002) Neuropsychological performance of patients following mold exposure. Appl Neuropsychol 9(4):193–202. https://doi.org/10.1207/S15324826AN0904_1
66. Crago BR, Gray MR, Nelson LA, Davis M, Arnold L, Thrasher JD (2003) Psychological, neuropsychological, and electrocortical effects of mixed mold exposure. Arch Environ Health 58(8):452–463. https://doi.org/10.3200/AEOH.58.8.452-463
67. Kercsmar CM, Dearborn DG, Schluchter M, Xue L, Kirchner HL, Sobolewski J, Greenberg SJ, Vesper SJ, Allan T (2006) Reduction in asthma morbidity in children as a result of home remediation aimed at moisture sources. Environ Health Perspect 114(10): 1574–1580
68. Peitzsch M, Bloom E, Haase R, Must A, Larsson L (2012) Remediation of mould damaged building materials—efficiency of a broad spectrum of treatments. J Environ Monit 14(3):908–915. https://doi.org/10.1039/c2em10806b
69. Call RS, Smith TF, Morris E, Chapman MD, Platts-Mills TA (1992) Risk factors for asthma in inner city children. J Pediatr 121(6):862–866
70. Arlian LG, Bernstein D, Bernstein IL, Friedman S, Grant A, Lieberman P, Lopez M, Metzger J, Platts-Mills T, Schatz M (1992) 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 90(3 Pt 1):292–300
71. Rabito FA, Iqbal S, Holt E, Grimsley LF, Islam TM, Scott SK (2007) Prevalence of indoor allergen exposures among New Orleans children with asthma. J Urban Health 84(6):782–792. https://doi.org/10.1007/s11524-007-9216-0
72. Celedón JC, Milton DK, Ramsey CD, Litonjua AA, Ryan L, Platts-Mills TA, Gold DR (2007) Exposure to dust mite allergen and endotoxin in early life and asthma and atopy in childhood. J Allergy Clin Immunol 120(1):144–149. https://doi.org/10.1016/j.jaci.2007.03.037
73. Platts-Mills TA, Sporik RB, Wheatley LM, Heymann PW (1995) Is there a dose-response relationship between exposure to indoor allergens and symptoms of asthma? J Allergy Clin Immunol 96(4):435–440
74. Platts-Mills TA, Thomas WR, Aalberse RC, Vervloet D, Champman MD (1992) Dust mite allergens and asthma: report of a second international workshop. J Allergy Clin Immunol 89(5):1046–1060
75. Peat JK, Tovey E, Toelle BG, Haby MM, Gray EJ, Mahmic A, Woolcock AJ (1996) House dust mite allergens. A major risk factor for childhood asthma in Australia. Am J Respir Crit Care Med 153(1):141–146. https://doi.org/10.1164/ajrccm.153.1.8542107
76. Vervloet D, Penaud A, Razzouk H, Senft M, Arnaud A, Boutin C, Charpin J (1982) Altitude and house dust mites. J Allergy Clin Immunol 69(3):290–296
77. Chan-Yeung M, Manfreda J, Dimich-Ward H, Lam J, Ferguson A, Warren P, Simons E, Broder I, Chapman M, Platts-Mills T (1995) Mite and cat allergen levels in homes and severity of asthma. Am J Respir Crit Care Med 152 (6 Pt 1):1805–1811. https://doi.org/10.1164/ajrccm.152.6.8520740
78. Marks GB, Tovey ER, Toelle BG, Wachinger S, Peat JK, Woolcock AJ (1995) Mite allergen (Der p 1) concentration in houses and its relation to the presence and severity of asthma in a population of Sydney schoolchildren. J Allergy Clin Immunol 96(4):441–448
79. El-Ghitany EM, Abd El-Salam MM (2012) Environmental intervention for house dust mite control in childhood bronchial asthma. Environ Health Prev Med 17(5):377–384. https://doi.org/10.1007/s12199-011-0263-5
80. Matsui EC (2013) Management of rodent exposure and allergy in the pediatric population. Curr Allergy Asthma Rep 13(6):681–686. https://doi.org/10.1007/s11882-013-0378-4
81. Pongracic JA, Visness CM, Gruchalla RS, Evans R, Mitchell HE (2008) Effect of mouse allergen and rodent environmental intervention on asthma in inner-city children. Ann Allergy Asthma Immunol 101(1):35–41. https://doi.org/10.1016/S1081-1206(10)60832-0
82. Phipatanakul W, Eggleston PA, Wright EC, Wood RA, Study NCI-CA (2000) Mouse allergen. II. The relationship of mouse allergen exposure to mouse sensitization and asthma morbidity in inner-city children with asthma. J Allergy Clin Immunol 106(6):1075–1080. https://doi.org/10.1067/mai.2000.110795
83. Sheehan WJ, Rangsithienchai PA, Muilenberg ML, Rogers CA, Lane JP, Ghaemghami J, Rivard DV, Otsu K, Hoffman EB, Israel E, Gold DR, Phipatanakul W (2009) Mouse allergens in urban elementary schools and homes of children with asthma. Ann Allergy Asthma Immunol 102(2):125–130. https://doi.org/10.1016/S1081-1206(10)60242-6
84. Permaul P, Hoffman E, Fu C, Sheehan W, Baxi S, Gaffin J, Lane J, Bailey A, King E, Chapman M, Gold D, Phipatanakul W (2012) Allergens in urban schools and homes of children with asthma. Pediatr Allergy Immunol 23(6):543–549. https://doi.org/10.1111/j.1399-3038.2012.01327.x
85. Kailasnath VP, Raj S, Sublett JL (2013) Mouse allergen skin sensitization in asthmatic children of suburban, rural, and inner-city populations. Allergy Asthma Proc 34(2):176–178. https://doi.org/10.2500/aap.2013.34.3633
86. Phipatanakul W, Celedón JC, Sredl DL, Weiss ST, Gold DR (2005) Mouse exposure and wheeze in the first year of life. Ann Allergy Asthma Immunol 94(5):593–599. https://doi.org/10.1016/S1081-1206(10)61139-8
87. Phipatanakul W, Celedón JC, Hoffman EB, Abdulkerim H, Ryan LM, Gold DR (2008) Mouse allergen exposure, wheeze and atopy in the first seven years of life. Allergy 63(11):1512–1518. https://doi.org/10.1111/j.1398-9995.2008.01679.x
88. Donohue KM, Al-alem U, Perzanowski MS, Chew GL, Johnson A, Divjan A, Kelvin EA, Hoepner LA, Perera FP, Miller RL (2008) Anti-cockroach and anti-mouse IgE are associated with early wheeze and atopy in an inner-city birth cohort. J Allergy Clin Immunol 122(5):914–920. https://doi.org/10.1016/j.jaci.2008.08.034
89. Grant T, Aloe C, Perzanowski M, Phipatanakul W, Bollinger ME, Miller R, Matsui EC (2017) Mouse sensitization and exposure are associated with asthma severity in urban children. J Allergy Clin Immunol Pract 5(4):1008–1014.e1001. https://doi.org/10.1016/j.jaip.2016.10.020
90. Torjusen EN, Diette GB, Breysse PN, Curtin-Brosnan J, Aloe C, Matsui EC (2013) Dose-response relationships between mouse allergen exposure and asthma morbidity among urban children and adolescents. Indoor Air 23(4):268–274. https://doi.org/10.1111/ina.12009
91. Ahluwalia SK, Peng RD, Breysse PN, Diette GB, Curtin-Brosnan J, Aloe C, Matsui EC (2013) Mouse allergen is the major allergen of public health relevance in Baltimore City. J Allergy Clin Immunol 132(4):830–835.e831–832. https://doi.org/10.1016/j.jaci.2013.05.005
92. Matsui EC, Eggleston PA, Buckley TJ, Krishnan JA, Breysse PN, Rand CS, Diette GB (2006) Household mouse allergen exposure and asthma morbidity in inner-city preschool children. Ann Allergy Asthma Immunol 97(4):514–520. https://doi.org/10.1016/S1081-1206(10)60943-X
93. Phipatanakul W, Koutrakis P, Coull BA, Kang CM, Wolfson JM, Ferguson ST, Petty CR, Samnaliev M, Cunningham A, Sheehan WJ, Gaffin JM, Baxi SN, Lai PS, Permaul P, Liang L, Thorne PS, Adamkiewicz G, Brennan KJ, Baccarelli AA, Gold DR (2017) The school inner-city asthma intervention study: design, rationale, methods, and lessons learned. Contemp Clin Trials 60:14–23. https://doi.org/10.1016/j.cct.2017.06.008

94. Arbes SJ, Cohn RD, Yin M, Muilenberg ML, Friedman W, Zeldin DC (2004) 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 114(1):111–117. https://doi.org/10.1016/j.jaci.2004.04.036
95. Gaffin JM, Spergel JM, Boguniewicz M, Eichenfield LF, Paller AS, Fowler JF, Dinulos JG, Tilles SA, Schneider LC, Phipatanakul W (2012) Effect of cat and daycare exposures on the risk of asthma in children with atopic dermatitis. Allergy Asthma Proc 33(3):282–288. https://doi.org/10.2500/aap.2012.33.3572
96. Kerkhof M, Wijga AH, Brunekreef B, Smit HA, de Jongste JC, Aalberse RC, Hoekstra MO, Gerritsen J, Postma DS (2009) Effects of pets on asthma development up to 8 years of age: the PIAMA study. Allergy 64(8):1202–1208. https://doi.org/10.1111/j.1398-9995.2009.02016.x
97. Wegienka G, Johnson CC, Havstad S, Ownby DR, Zoratti EM (2010) Indoor pet exposure and the outcomes of total IgE and sensitization at age 18 years. J Allergy Clin Immunol 126(2):274–279, 279.e271–275. https://doi.org/10.1016/j.jaci.2010.05.001
98. Wegienka G, Johnson CC, Havstad S, Ownby DR, Nicholas C, Zoratti EM (2011) Lifetime dog and cat exposure and dog- and cat-specific sensitization at age 18 years. Clin Exp Allergy 41(7):979–986. https://doi.org/10.1111/j.1365-2222.2011.03747.x
99. McHugh BM, MacGinnitie AJ (2011) Indoor allergen sensitization and the risk of asthma and eczema in children in Pittsburgh. Allergy Asthma Proc 32(5):372–376. https://doi.org/10.2500/aap.2011.32.3456
100. Gent JF, Belanger K, Triche EW, Bracken MB, Beckett WS, Leaderer BP (2009) Association of pediatric asthma severity with exposure to common household dust allergens. Environ Res 109(6):768–774. https://doi.org/10.1016/j.envres.2009.04.010
101. Gent JF, Kezik JM, Hill ME, Tsai E, Li DW, Leaderer BP (2012) Household mold and dust allergens: exposure, sensitization and childhood asthma morbidity. Environ Res 118:86–93. https://doi.org/10.1016/j.envres.2012.07.005
102. Gergen PJ, Mitchell HE, Calatroni A, Sever ML, Cohn RD, Salo PM, Thorne PS, Zeldin DC (2018) Sensitization and exposure to pets: the effect on asthma morbidity in the US population. J Allergy Clin Immunol Pract 6(1):101–107.e102. https://doi.org/10.1016/j.jaip.2017.05.019
103. Murray CS, Poletti G, Kebadze T, Morris J, Woodcock A, Johnston SL, Custovic A (2006) Study of modifiable risk factors for asthma exacerbations: virus infection and allergen exposure increase the risk of asthma hospital admissions in children. Thorax 61(5):376–382. https://doi.org/10.1136/thx.2005.042523
104. DiMango E, Serebrisky D, Narula S, Shim C, Keating C, Sheares B, Perzanowski M, Miller R, DiMango A, Andrews H, Merle D, Liu X, Calatroni A, Kattan M (2016) Individualized household allergen intervention lowers allergen level but not asthma medication use: a randomized controlled trial. J Allergy Clin Immunol Pract 4(4):671–679.e674. https://doi.org/10.1016/j.jaip.2016.01.016
105. Bousquet J, Gern JE, Martinez FD, Anto JM, Johnson CC, Holt PG, Lemanske RF, Le Souëf PN, Tepper RS, von Mutius ER, Arshad SH, Bacharier LB, Becker A, Belanger K, Bergström A, Bernstein DI, Cabana MD, Carroll KN, Castro M, Cooper PJ, Gillman MW, Gold DR, Henderson J, Heinrich J, Hong SJ, Jackson DJ, Keil T, Kozyrskyj AL, Lødrup Carlsen KC, Miller RL, Momas I, Morgan WJ, Noel P, Ownby DR, Pinart M, Ryan PH, Schwaninger JM, Sears MR, Simpson A, Smit HA, Stern DA, Subbarao P, Valenta R, Wang X, Weiss ST, Wood R, Wright AL, Wright RJ, Togias A, Gergen PJ (2014) Birth cohorts in asthma and allergic diseases: report of a NIAID/NHLBI/MeDALL joint workshop. J Allergy Clin Immunol 133(6):1535–1546. https://doi.org/10.1016/j.jaci.2014.01.018
106. Gern JE (2010) The urban environment and childhood asthma study. J Allergy Clin Immunol 125(3):545–549. https://doi.org/10.1016/j.jaci.2010.01.037
107. Gern JE, Brooks GD, Meyer P, Chang A, Shen K, Evans MD, Tisler C, Dasilva D, Roberg KA, Mikus LD, Rosenthal LA, Kirk CJ, Shult PA, Bhattacharya A, Li Z, Gangnon R, Lemanske RF (2006) Bidirectional interactions between viral respiratory illnesses and cytokine responses in the first year of life. J Allergy Clin Immunol 117(1):72–78. https://doi.org/10.1016/j.jaci.2005.10.002
108. Heaton T, Rowe J, Turner S, Aalberse RC, de Klerk N, Suriyaarachchi D, Serralha M, Holt BJ, Hollams E, Yerkovich S, Holt K, Sly PD, Goldblatt J, Le Souef P, Holt PG (2005) An immunoepidemiological approach to asthma: identification of in-vitro T-cell response patterns associated with different wheezing phenotypes in children. Lancet 365(9454):142–149. https://doi.org/10.1016/S0140-6736(05)17704-6
109. Rinas U, Horneff G, Wahn V (1993) 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 4(2):60–64
110. Sullivan Dillie KT, Tisler CJ, Dasilva DF, Pappas TE, Roberg KA, Carlson-Dakes KT, Evans MD, Rosenthal LA, Gangnon RE, Gern JE, Lemanske RF (2008) 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 38(2):298–304. https://doi.org/10.1111/j.1365-2222.2007.02891.x
111. Pfefferle PI, Büchele G, Blümer N, Roponen M, Ege MJ, Krauss-Etschmann S, Genuneit J, Hyvärinen A, Hirvonen MR, Lauener R, Pekkanen J, Riedler J, Dalphin JC, Brunekeef B, Braun-Fahrländer C, von Mutius E, Renz H, Group PS (2010) Cord blood cytokines are modulated by maternal farming activities and consumption of farm dairy products during pregnancy: the PASTURE Study. J Allergy Clin Immunol 125(1):108–115.e101-103. https://doi.org/10.1016/j.jaci.2009.09.019
112. Gold DR, Bloomberg GR, Cruikshank WW, Visness CM, Schwarz J, Kattan M, O'Connor GT, Wood RA, Burger MS, Wright RJ, Witter F, Lee-Parritz A, Sperling R, Sadovsky Y, Togias A, Gern JE (2009) Parental characteristics, somatic fetal growth, and season of birth influence innate and adaptive cord blood cytokine responses. J Allergy Clin Immunol 124(5):1078–1087. https://doi.org/10.1016/j.jaci.2009.08.021
113. Thysen AH, Rasmussen MA, Kreiner-Moller E, Larsen JM, Folsgaard NV, Bonnelykke K, Stokholm J, Bisgaard H, Brix S (2016) Season of birth shapes neonatal immune function. J Allergy Clin Immunol 137(4):1238–1246 e1213. https://doi.org/10.1016/j.jaci.2015.08.041
114. Clark NM, Baptist AP, Ko YA, Leo HL, Song PX (2012) The relationship of season of birth to asthma and allergy in urban African American children from 10 to 13 years of age. J Asthma 49(10):1037–1043. https://doi.org/10.3109/02770903.2012.739239
115. Orr ST, James SA, Miller CA, Barakat B, Daikoku N, Pupkin M, Engstrom K, Huggins G (1996) Psychosocial stressors and low birthweight in an urban population. Am J Prev Med 12(6):459–466
116. Binsacca DB, Ellis J, Martin DG, Petitti DB (1987) Factors associated with low birthweight in an inner-city population: the role of financial problems. Am J Public Health 77(4):505–506
117. Matheson MC, AL DO, Burgess JA, Giles GG, Hopper JL, Johns DP, Abramson MJ, Walters EH, Dharmage SC (2017) Preterm birth and low birth weight continue to increase the risk of asthma

from age 7 to 43. J Asthma 54(6):616–623. https://doi.org/10.1080/02770903.2016.1249284

118. Holt PG (2015) The mechanism or mechanisms driving atopic asthma initiation: the infant respiratory microbiome moves to center stage. J Allergy Clin Immunol 136(1):15–22. https://doi.org/10.1016/j.jaci.2015.05.011
119. Ly NP, Ruiz-Perez B, McLoughlin RM, Visness CM, Wallace PK, Cruikshank WW, Tzianabos AO, O'Connor GT, Gold DR, Gern JE (2009) Characterization of regulatory T cells in urban newborns. Clin Mol Allergy 7:8. https://doi.org/10.1186/1476-7961-7-8
120. Chandra S, Wingender G, Greenbaum JA, Khurana A, Gholami AM, Ganesan AP, Rosenbach M, Jaffee K, Gern JE, Wood R, O'Connor G, Sandel M, Kattan M, Bacharier L, Togias A, Horner AA, Kronenberg M (2018) Development of asthma in inner-city children: possible roles of MAIT cells and variation in the home environment. J Immunol 200(6):1995–2003. https://doi.org/10.4049/jimmunol.1701525
121. Eder W, Ege MJ, von Mutius E (2006) The asthma epidemic. N Engl J Med 355(21):2226–2235. https://doi.org/10.1056/NEJMra054308
122. Moffatt MF, Cookson WO (1998) The genetics of asthma. Maternal effects in atopic disease Clin Exp Allergy 28(Suppl 1): 56–61 discussion 65-56
123. Anway MD, Cupp AS, Uzumcu M, Skinner MK (2005) Epigenetic transgenerational actions of endocrine disruptors and male fertility. Science 308(5727):1466–1469. https://doi.org/10.1126/science.1108190
124. Breton CV, Byun HM, Wenten M, Pan F, Yang A, Gilliland FD (2009) Prenatal tobacco smoke exposure affects global and gene-specific DNA methylation. Am J Respir Crit Care Med 180(5): 462–467. https://doi.org/10.1164/rccm.200901-0135OC
125. Yang IV, Pedersen BS, Liu A, O'Connor GT, Teach SJ, Kattan M, Misiak RT, Gruchalla R, Steinbach SF, Szefler SJ, Gill MA, Calatroni A, David G, Hennessy CE, Davidson EJ, Zhang W, Gergen P, Togias A, Busse WW, Schwartz DA (2015) DNA methylation and childhood asthma in the inner city. J Allergy Clin Immunol 136(1):69–80. https://doi.org/10.1016/j.jaci.2015.01.025
126. Yang IV, Pedersen BS, Liu AH, O'Connor GT, Pillai D, Kattan M, Misiak RT, Gruchalla R, Szefler SJ, Khurana Hershey GK, Kercsmar C, Richards A, Stevens AD, Kolakowski CA, Makhija M, Sorkness CA, Krouse RZ, Visness C, Davidson EJ, Hennessy CE, Martin RJ, Togias A, Busse WW, Schwartz DA (2017) The nasal methylome and childhood atopic asthma. J Allergy Clin Immunol 139(5):1478–1488. https://doi.org/10.1016/j.jaci.2016.07.036
127. Clifford RL, Jones MJ, MacIsaac JL, McEwen LM, Goodman SJ, Mostafavi S, Kobor MS, Carlsten C (2017) Inhalation of diesel exhaust and allergen alters human bronchial epithelium DNA methylation. J Allergy Clin Immunol 139(1):112–121. https://doi.org/10.1016/j.jaci.2016.03.046
128. Iwane MK, Prill MM, Lu X, Miller EK, Edwards KM, Hall CB, Griffin MR, Staat MA, Anderson LJ, Williams JV, Weinberg GA, Ali A, Szilagyi PG, Zhu Y, Erdman DD (2011) Human rhinovirus species associated with hospitalizations for acute respiratory illness in young US children. J Infect Dis 204(11):1702–1710. https://doi.org/10.1093/infdis/jir634
129. Papadopoulos NG, Moustaki M, Tsolia M, Bossios A, Astra E, Prezerakou A, Gourgiotis D, Kafetzis D (2002) Association of rhinovirus infection with increased disease severity in acute bronchiolitis. Am J Respir Crit Care Med 165(9):1285–1289. https://doi.org/10.1164/rccm.200112-118BC
130. Schatz M, Sicherer SH, Zeiger RS (2018) The journal of allergy and clinical immunology: in practice 2017 year in review. J Allergy Clin Immunol Pract 6(2):328–352. https://doi.org/10.1016/j.jaip.2017.12.016
131. Balekian DS, Linnemann RW, Hasegawa K, Thadhani R, Camargo CA (2017) Cohort study of severe bronchiolitis during infancy and risk of asthma by age 5 years. J Allergy Clin Immunol Pract 5(1):92–96. https://doi.org/10.1016/j.jaip.2016.07.004
132. Jackson DJ, Gern JE, Lemanske RF (2017) Lessons learned from birth cohort studies conducted in diverse environments. J Allergy Clin Immunol 139(2):379–386. https://doi.org/10.1016/j.jaci.2016.12.941
133. Stone CA, Miller EK (2016) Understanding the association of human rhinovirus with asthma. Clin Vaccine Immunol 23(1):6–10. https://doi.org/10.1128/CVI.00414-15
134. Park JH, Spiegelman DL, Gold DR, Burge HA, Milton DK (2001) Predictors of airborne endotoxin in the home. Environ Health Perspect 109(8):859–864
135. Thorne PS, Kulhánková K, Yin M, Cohn R, Arbes SJ, Zeldin DC (2005) Endotoxin exposure is a risk factor for asthma: the national survey of endotoxin in United States housing. Am J Respir Crit Care Med 172(11):1371–1377. https://doi.org/10.1164/rccm.200505-758OC
136. Sheehan WJ, Hoffman EB, Fu C, Baxi SN, Bailey A, King EM, Chapman MD, Lane JP, Gaffin JM, Permaul P, Gold DR, Phipatanakul W (2012) Endotoxin exposure in inner-city schools and homes of children with asthma. Ann Allergy Asthma Immunol 108(6):418–422. https://doi.org/10.1016/j.anai.2012.04.003
137. Lai PS, Massoud AH, Xia M, Petty CR, Cunningham A, Chatila TA, Phipatanakul W (2018) Gene-environment interaction between an IL4R variant and school endotoxin exposure contributes to asthma symptoms in inner-city children. J Allergy Clin Immunol 141 (2):794–796.e793. https://doi.org/10.1016/j.jaci.2017.08.023
138. Dutmer CM, Kim H, Searing DA, Zoratti EM, Liu AH (2018) Asthma in inner city children: recent insights: United States. Curr Opin Allergy Clin Immunol 18(2):139–147. https://doi.org/10.1097/ACI.0000000000000423
139. Thorne PS, Mendy A, Metwali N, Salo P, Co C, Jaramillo R, Rose KM, Zeldin DC (2015) Endotoxin exposure: predictors and prevalence of associated asthma outcomes in the United States. Am J Respir Crit Care Med 192(11):1287–1297. https://doi.org/10.1164/rccm.201502-0251OC
140. Gergen PJ, Mitchell H, Lynn H (2002) Understanding the seasonal pattern of childhood asthma: results from the National Cooperative Inner-City Asthma Study (NCICAS). J Pediatr 141(5):631–636
141. Busse WW, Morgan WJ, Gergen PJ, Mitchell HE, Gern JE, Liu AH, Gruchalla RS, Kattan M, Teach SJ, Pongracic JA, Chmiel JF, Steinbach SF, Calatroni A, Togias A, Thompson KM, Szefler SJ, Sorkness CA (2011) Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. N Engl J Med 364(11):1005–1015. https://doi.org/10.1056/NEJMoa1009705
142. Teach SJ, Gill MA, Togias A, Sorkness CA, Arbes SJ, Calatroni A, Wildfire JJ, Gergen PJ, Cohen RT, Pongracic JA, Kercsmar CM, Khurana Hershey GK, Gruchalla RS, Liu AH, Zoratti EM, Kattan M, Grindle KA, Gern JE, Busse WW, Szefler SJ (2015) Preseasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations. J Allergy Clin Immunol 136(6):1476–1485. https://doi.org/10.1016/j.jaci.2015.09.008
143. Guarnieri M, Balmes JR (2014) Outdoor air pollution and asthma. Lancet 383(9928):1581–1592. https://doi.org/10.1016/S0140-6736(14)60617-6
144. Simons E, Curtin-Brosnan J, Buckley T, Breysse P, Eggleston PA (2007) Indoor environmental differences between inner city and

suburban homes of children with asthma. J Urban Health 84(4): 577–590. https://doi.org/10.1007/s11524-007-9205-3
145. Rice MB, Rifas-Shiman SL, Litonjua AA, Gillman MW, Liebman N, Kloog I, Luttmann-Gibson H, Coull BA, Schwartz J, Koutrakis P, Oken E, Mittleman MA, Gold DR (2018) Lifetime air pollution exposure and asthma in a pediatric birth cohort. J Allergy Clin Immunol 141(5):1932–1934 e1937. https://doi.org/10.1016/j.jaci.2017.11.062
146. Mortimer KM, Neas LM, Dockery DW, Redline S, Tager IB (2002) The effect of air pollution on inner-city children with asthma. Eur Respir J 19(4):699–705
147. Jerrett M, Shankardass K, Berhane K, Gauderman WJ, Künzli N, Avol E, Gilliland F, Lurmann F, Molitor JN, Molitor JT, Thomas DC, Peters J, McConnell R (2008) Traffic-related air pollution and asthma onset in children: a prospective cohort study with individual exposure measurement. Environ Health Perspect 116(10): 1433–1438. https://doi.org/10.1289/ehp.10968
148. United States Environmental Protection Agency (2018) Outdoor pollution. Indoor pollution. https://www.epa.gov/clean-air-act-overview/air-pollution-current-and-future-challenges. Accessed June 25th, 2018
149. United States Environmental Protection Agency (2018) Criteria air pollutants. https://www.epa.gov/criteria-air-pollutants. Accessed June 25th 2018
150. Matsui EC, Hansel NN, McCormack MC, Rusher R, Breysse PN, Diette GB (2008) Asthma in the inner city and the indoor environment. Immunol Allergy Clin N Am 28 (3):665–686, x. https://doi.org/10.1016/j.iac.2008.03.004
151. Burke H, Leonardi-Bee J, Hashim A, Pine-Abata H, Chen Y, Cook DG, Britton JR, McKeever TM (2012) Prenatal and passive smoke exposure and incidence of asthma and wheeze: systematic review and meta-analysis. Pediatrics 129(4):735–744. https://doi.org/10.1542/peds.2011-2196
152. O'Connor GT, Lynch SV, Bloomberg GR, Kattan M, Wood RA, Gergen PJ, Jaffee KF, Calatroni A, Bacharier LB, Beigelman A, Sandel MT, Johnson CC, Faruqi A, Santee C, Fujimura KE, Fadrosh D, Boushey H, Visness CM, Gern JE (2018) Early-life home environment and risk of asthma among inner-city children. J Allergy Clin Immunol 141(4):1468–1475. https://doi.org/10.1016/j.jaci.2017.06.040
153. Wang Z, May SM, Charoenlap S, Pyle R, Ott NL, Mohammed K, Joshi AY (2015) Effects of secondhand smoke exposure on asthma morbidity and health care utilization in children: a systematic review and meta-analysis. Ann Allergy Asthma Immunol 115(5): 396–401 e392. https://doi.org/10.1016/j.anai.2015.08.005
154. Jacob P 3rd, Benowitz NL, Destaillats H, Gundel L, Hang B, Martins-Green M, Matt GE, Quintana PJ, Samet JM, Schick SF, Talbot P, Aquilina NJ, Hovell MF, Mao JH, Whitehead TP (2017) Thirdhand smoke: new evidence, challenges, and future directions. Chem Res Toxicol 30(1):270–294. https://doi.org/10.1021/acs.chemrestox.6b00343
155. Godwin C, Batterman S (2007) Indoor air quality in Michigan schools. Indoor Air 17(2):109–121. https://doi.org/10.1111/j.1600-0668.2006.00459.x
156. Hansel NN, Breysse PN, McCormack MC, Matsui EC, Curtin-Brosnan J, Williams DL, Moore JL, Cuhran JL, Diette GB (2008) A longitudinal study of indoor nitrogen dioxide levels and respiratory symptoms in inner-city children with asthma. Environ Health Perspect 116(10):1428–1432. https://doi.org/10.1289/ehp.11349
157. McCormack MC, Breysse PN, Matsui EC, Hansel NN, Peng RD, Curtin-Brosnan J, Williams DL, Wills-Karp M, Diette GB, Environment CCAU (2011) Indoor particulate matter increases asthma morbidity in children with non-atopic and atopic asthma. Ann Allergy Asthma Immunol 106(4):308–315. https://doi.org/10.1016/j.anai.2011.01.015
158. Bauman LJ, Wright E, Leickly FE, Crain E, Kruszon-Moran D, Wade SL, Visness CM (2002) Relationship of adherence to pediatric asthma morbidity among inner-city children. Pediatrics 110 (1 Pt 1):e6
159. Ramratnam SK, Visness CM, Jaffee KF, Bloomberg GR, Kattan M, Sandel MT, Wood RA, Gern JE, Wright RJ (2017) 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 195(5):674–681. https://doi.org/10.1164/rccm.201602-0272OC
160. Finkelhor D, Dziuba-Leatherman J (1994) Children as victims of violence: a national survey. Pediatrics 94(4 Pt 1):413–420
161. Wright RJ, Mitchell H, Visness CM, Cohen S, Stout J, Evans R, Gold DR (2004) Community violence and asthma morbidity: the Inner-City Asthma Study. Am J Public Health 94(4):625–632
162. Wright RJ, Steinbach SF (2001) Violence: an unrecognized environmental exposure that may contribute to greater asthma morbidity in high risk inner-city populations. Environ Health Perspect 109(10):1085–1089. https://doi.org/10.1289/ehp.011091085
163. Wing R, Gjelsvik A, Nocera M, McQuaid EL (2015) Association between adverse childhood experiences in the home and pediatric asthma. Ann Allergy Asthma Immunol 114(5):379–384. https://doi.org/10.1016/j.anai.2015.02.019
164. Litonjua AA, Weiss ST (2007) Is vitamin D deficiency to blame for the asthma epidemic? J Allergy Clin Immunol 120(5):1031–1035. https://doi.org/10.1016/j.jaci.2007.08.028
165. Freishtat RJ, Iqbal SF, Pillai DK, Klein CJ, Ryan LM, Benton AS, Teach SJ (2010) High prevalence of vitamin D deficiency among inner-city African American youth with asthma in Washington, DC. J Pediatr 156(6):948–952. https://doi.org/10.1016/j.jpeds.2009.12.033
166. Bose S, Breysse PN, MC MC, Hansel NN, Rusher RR, Matsui E, Peng R, Curtin-Brosnan J, Diette GB, Center for Childhood Asthma in the Urban E (2013) Outdoor exposure and vitamin D levels in urban children with asthma. Nutr J 12:81. https://doi.org/10.1186/1475-2891-12-81
167. Vahdaninia M, Mackenzie H, Helps S, Dean T (2017) Prenatal intake of vitamins and allergic outcomes in the offspring: a systematic review and meta-analysis. J Allergy Clin Immunol Pract 5(3):771–778.e775. https://doi.org/10.1016/j.jaip.2016.09.024
168. Belamarich PF, Luder E, Kattan M, Mitchell H, Islam S, Lynn H, Crain EF (2000) Do obese inner-city children with asthma have more symptoms than nonobese children with asthma? Pediatrics 106(6):1436–1441
169. Kattan M, Kumar R, Bloomberg GR, Mitchell HE, Calatroni A, Gergen PJ, Kercsmar CM, Visness CM, Matsui EC, Steinbach SF, Szefler SJ, Sorkness CA, Morgan WJ, Teach SJ, Gan VN (2010) Asthma control, adiposity, and adipokines among inner-city adolescents. J Allergy Clin Immunol 125(3):584–592. https://doi.org/10.1016/j.jaci.2010.01.053
170. Hales CM, Carroll MD, Fryar CD, Ogden CL (2017) Prevalence of obesity among adults and youth: United States, 2015–2016. NCHS data brief, no 280. Hyattsville, MD. National Center of Health Statistics. https://www.cdc.gov/obesity/data/childhood.html
171. Robbins JM, Benson BJ, Esangbedo IC, Ward RL, Haden RN (2016) Childhood obesity in an inner-city primary care population: a longitudinal study. J Natl Med Assoc 108(3):158–163. https://doi.org/10.1016/j.jnma.2016.05.006
172. Isasi CR, Whiffen A, Campbell E, Florez Y, Freeman K, Wylie-Rosett J (2011) High prevalence of obesity among inner-city adolescent boys in the Bronx, New York: forgetting our boys. Prev Chronic Dis 8(1):A23
173. Jensen ME, Gibson PG, Collins CE, Hilton JM, Wood LG (2013) Diet-induced weight loss in obese children with asthma: a

randomized controlled trial. Clin Exp Allergy 43(7):775–784. https://doi.org/10.1111/cea.12115

174. Esquivel A, Busse WW, Calatroni A, Togias AG, Grindle KG, Bochkov YA, Gruchalla RS, Kattan M, Kercsmar CM, Khurana Hershey G, Kim H, Lebeau P, Liu AH, Szefler SJ, Teach SJ, West JB, Wildfire J, Pongracic JA, Gern JE (2017) Effects of omalizumab on rhinovirus infections, illnesses, and exacerbations of asthma. Am J Respir Crit Care Med 196(8):985–992. https://doi.org/10.1164/rccm.201701-0120OC
175. Gill MA, Liu AH, Calatroni A, Krouse RZ, Shao B, Schiltz A, Gern JE, Togias A, Busse WW (2018) Enhanced plasmacytoid dendritic cell antiviral responses after omalizumab. J Allergy Clin Immunol 141 (5):1735–1743.e1739. https://doi.org/10.1016/j.jaci.2017.07.035
176. Durham SR, Till SJ (1998) Immunologic changes associated with allergen immunotherapy. J Allergy Clin Immunol 102(2):157–164
177. Wood RA, Togias A, Wildfire J, Visness CM, Matsui EC, Gruchalla R, Hershey G, Liu AH, O'Connor GT, Pongracic JA, Zoratti E, Little F, Granada M, Kennedy S, Durham SR, Shamji MH, Busse WW (2014) Development of cockroach immunotherapy by the Inner-City asthma consortium. J Allergy Clin Immunol 133(3):846–852 e846. https://doi.org/10.1016/j.jaci.2013.08.047
178. Breysse J, Dixon S, Gregory J, Philby M, Jacobs DE, Krieger J (2014) Effect of weatherization combined with community health worker in-home education on asthma control. Am J Public Health 104(1):e57–e64. https://doi.org/10.2105/AJPH.2013.301402
179. Lemanske RF, Kakumanu S, Shanovich K, Antos N, Cloutier MM, Mazyck D, Phipatanakul W, Schantz S, Szefler S, Vandlik R, Williams P (2016) Creation and implementation of SAMPRO™: a school-based asthma management program. J Allergy Clin Immunol 138(3):711–723. https://doi.org/10.1016/j.jaci.2016.06.015
180. Bruzzese JM, Sheares BJ, Vincent EJ, Du Y, Sadeghi H, Levison MJ, Mellins RB, Evans D (2011) Effects of a school-based intervention for urban adolescents with asthma. A controlled trial. Am J Respir Crit Care Med 183(8):998–1006. https://doi.org/10.1164/rccm.201003-0429OC
181. Halterman JS, Szilagyi PG, Fisher SG, Fagnano M, Tremblay P, Conn KM, Wang H, Borrelli B (2011) Randomized controlled trial to improve care for urban children with asthma: results of the school-based asthma therapy trial. Arch Pediatr Adolesc Med 165(3):262–268. https://doi.org/10.1001/archpediatrics.2011.1
182. Liptzin DR, Gleason MC, Cicutto LC, Cleveland CL, Shocks DJ, White MK, Faino AV, Szefler SJ (2016) Developing, implementing, and evaluating a school-centered asthma program: step-up asthma program. J Allergy Clin Immunol Pract 4(5):972–979 e971. https://doi.org/10.1016/j.jaip.2016.04.016
183. Jhun I, Gaffin JM, Coull BA, Huffaker MF, Petty CR, Sheehan WJ, Baxi SN, Lai PS, Kang CM, Wolfson JM, Gold DR, Koutrakis P, Phipatanakul W (2017) School environmental intervention to reduce particulate pollutant exposures for children with asthma. J Allergy Clin Immunol Pract 5(1):154–159.e153. https://doi.org/10.1016/j.jaip.2016.07.018
184. Joseph CLM, Mahajan P, Stokes-Buzzelli S, Johnson DA, Duffy E, Williams R, Zhang T, Ownby DR, Considine S, Lu M (2018) 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 4:5. https://doi.org/10.1186/s40814-017-0147-6