



Asthma in inner city children: recent insights: United States

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Purpose of review

Children living in US inner cities experience disparate burdens of asthma, especially in severity, impairment, exacerbations, and morbidity. Investigations seeking to better understand the factors and mechanisms underlying asthma prevalence, severity, and exacerbation in children living in these communities can lead to interventions that can narrow asthma disparities and potentially benefit all children with asthma. This update will focus on recent (i.e. late 2016–2017) advances in the understanding of asthma in US inner city children.

Recent findings

Studies published in the past year expand understanding of asthma prevalence, severity, exacerbation, and the outcomes of guidelines-based management of these at-risk children, including: asthma phenotypes in US inner city children that are severe and difficult-to-control; key environmental determinants and mechanisms underlying asthma severity and exacerbations (e.g. allergy-mediated exacerbation susceptibility to rhinovirus); the importance of schools as a place for provocative exposures (e.g. mouse allergen, nitrogen dioxide) as well as a place where asthma care and outcomes can be improved; and the development and validation of clinically useful indices for gauging asthma severity and predicting exacerbations.

Summary

These recent studies provide a trove of actionable findings that can improve asthma care and outcomes for these at-risk children.

Keywords

asthma, children, exacerbation, inner city, phenotype

INTRODUCTION: ASTHMA PHENOTYPES AND SEVERITY DETERMINANTS IN US INNER CITY CHILDREN

Children living in poor urban communities experience a high burden of severe asthma and exacerbations despite guidelines-directed care. A strong understanding of asthma phenotypes and severity determinants can improve asthma characterization and advance asthma management via phenotype-directed care, especially in children experiencing severe, exacerbation-prone asthma [1[¶]]. In the National Heart, Lung, and Blood Institute (NHLBI)-sponsored Severe Asthma Research Program (SARP III), a recent comparison of severe versus nonsevere asthma in children versus adults determined that adults with severe asthma had higher proportions of women, obesity, greater airflow obstruction, higher blood eosinophils, and less allergen sensitization than nonsevere adults [2[¶]]. In comparison, children with severe versus nonsevere asthma had a

higher proportion of men and African Americans, and were not distinguished by their baseline features of obesity, airflow obstruction, allergen sensitization, or markers of inflammation that distinguished severe adults. This dissimilarity in distinguishing features seen in children with severe asthma whenever compared with adults indicates the importance of understanding asthma phenotypes specifically in children to improve childhood asthma management via phenotype-directed care, and to understand the

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KEY POINTS

- Characterizing asthma phenotypes in US inner city children is an important step towards improving care. Difficult-to-control asthma is characterized by high exacerbation rates, greater daytime and nocturnal symptoms, and compromised lung function despite ongoing high-dose controller therapies. There are also two discrete severe asthma phenotypes in US inner city children: highly allergic, exacerbation-prone asthma, with a high number of aeroallergen sensitizations; and highly symptomatic asthma with low/no allergy.
- As allergy and tobacco smoke account for more than 50% of asthma severity in US inner city children, prioritizing these two asthma severity pathways can substantially improve asthma in inner city children.
- Allergic (i.e. IgE-mediated) mechanisms impair innate immune responses to rhinovirus that underlie most asthma exacerbations in children.
- School environments can have respirable irritants and inflammogens (e.g. mouse allergen, nitrogen dioxide) that worsen asthma severity in their students with asthma. Schools can also be an effective place for identifying children in need of asthma education and care coordination, and providing these resources.
- Two useful indices have been developed and validated for gauging asthma severity (Composite Asthma Severity Index, <http://www.asthmaseverity.org>) and predicting asthma exacerbations (Seasonal Asthma Exacerbation Predictive Index).

processes leading children to develop severe asthma as adults.

ASTHMA PHENOTYPES IN THE INNER CITY STUDY

To define asthma phenotypes and severity determinants of difficult-to-control asthma in inner city children in the context of guidelines-based care, the National Institutes of Health (National Institute of Allergic and Infectious Diseases) sponsored the Inner-City Asthma Consortium (ICAC) to conduct the Asthma Phenotypes in the Inner City (APIC) study [3^{***}]. This epidemiologic, multicenter, longitudinal study enrolled 717 children aged 6–17 years (65% black and 28% Hispanic) living in nine US urban communities. Study participants received evaluation and management visits every 2 months over an entire year during which standardized algorithms were used to optimize asthma management based upon National Asthma Education and Prevention Program (NAEPP) Guidelines as well as to evaluate and manage rhinitis based upon Allergic Rhinitis and Its Impact on Asthma (ARIA)

Guidelines. Three different analytic approaches were used to characterize asthma severity and identify its main determinants and phenotypic features in these children.

Characteristics and endotype of difficult-to-control asthma

Pongracic *et al.* [3^{***}] reported the characteristics that differentiate difficult-to-control from easy-to-control asthma in US inner-city children. Difficult-to-control and easy-to-control asthma were defined a priori as daily therapy on at least four of six visits requiring at least 500 µg of fluticasone with or without a long-acting beta-agonist versus 100 mcg or less of fluticasone, respectively. Among 619 participants, 40.9% had difficult-to-control asthma and 37.5% had easy-to-control asthma. Adherence to controller treatment was similar among the three groups. The phenotypes of difficult-to-control and easy-to-control asthma were distinctly evident from the start of the study and maintained clear distinctions over the study year. Difficult-to-control asthma was characterized by high exacerbation rates, especially in the spring and fall; greater daytime and nocturnal symptoms, especially in the fall and winter; and compromised pulmonary physiology despite ongoing high-dose controller therapy (Fig. 1). At baseline, spirometric (forced expiratory volume at 1 second) bronchodilator responsiveness was the most important characteristic that distinguished difficult-to-control asthma from easy-to-control asthma. In addition to pulmonary physiology, other major discriminating features were Asthma Control Test score, rhinitis severity, and atopy.

The authors concluded that despite good adherence, difficult-to-control asthma showed little improvement in symptoms, exacerbations or pulmonary physiology over the year. In addition, clinical characteristics, specifically bronchodilator responsiveness, Asthma Control Test, spirometry, rhinitis severity, and atopy represent potential assessments that can be employed early in the course of evaluation and treatment to identify children with difficult-to-control asthma.

Brown *et al.* [4^{***}] evaluated the endotype of difficult-to-control asthma in an African American subset of 235 APIC children via peripheral blood cytokine and inflammatory cell profiles. People with difficult-to-control asthma (versus easy-to-control) had higher peripheral blood eosinophil and neutrophil counts and higher IL-5, IFN-γ (interferon gamma), and TH17-associated cytokines (CXCL-1, IL-17A, IL-8). Cytokines improved a best fit multivariate model for difficult-to-control asthma such that including selected cytokines with

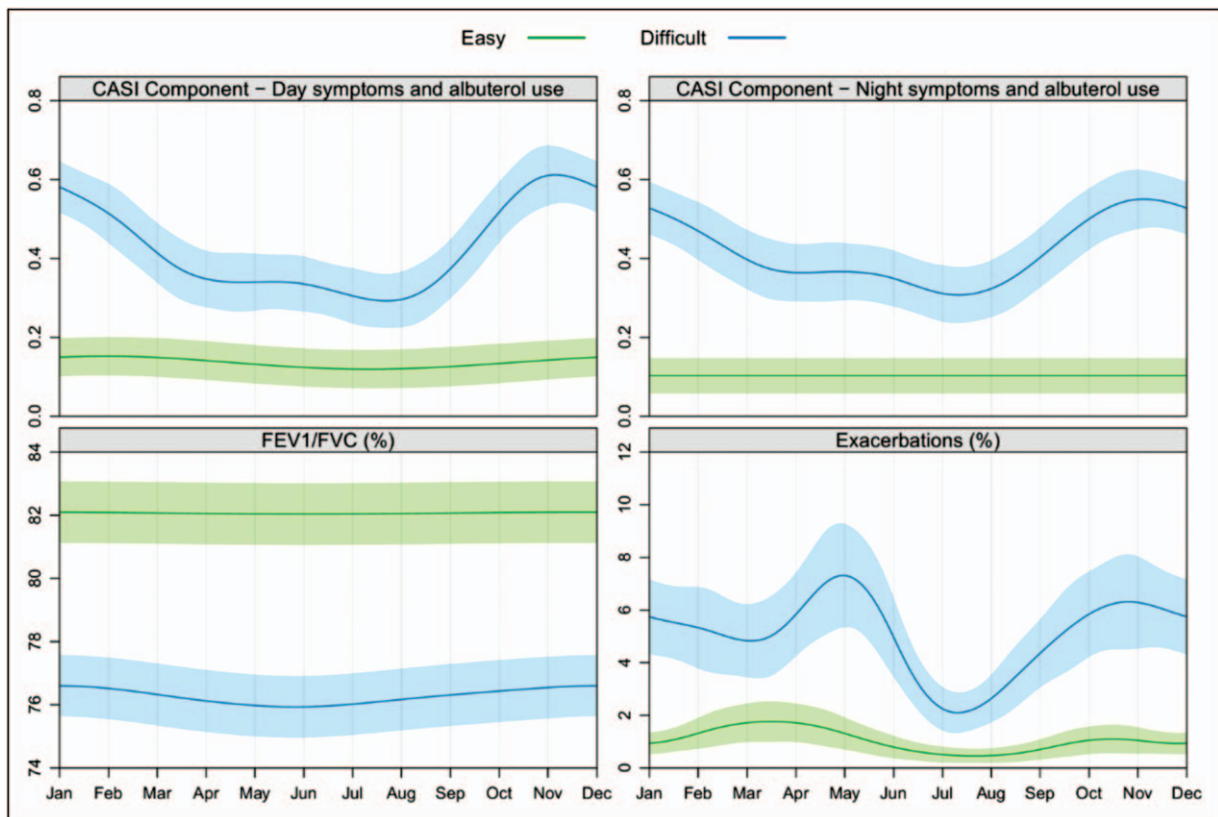


FIGURE 1. Difficult-to-control asthma in US inner city children: Asthma Phenotypes in the Inner City (APIC) study. US inner-city children with difficult-to-control asthma received guidelines-based asthma management and high-dose controller therapy (i.e. at least fluticasone 500 µg/day with LABA) over the course of a year, yet demonstrated seasonally varying day and night symptoms and exacerbations as well as persistent airflow limitation that was significantly worse than inner city children whose asthma was easy-to-control. Blue and green lines (shaded areas) indicate means or probabilities (95% CIs) of clinical severity measures for the difficult-to-control and easy-to-control groups, respectively. Clinical severity measures are the Composite Asthma Severity Index (CASI [33]) component measuring day symptoms and albuterol use in the last 2 weeks (0–3 points), the CASI component measuring nighttime symptoms and albuterol use in the last 2 weeks (0–3 points), the FEV1/FVC ratio (%), and the monthly incidence of exacerbations, as defined by prednisone use. FEV1, forced expiratory volume at 1 second; FVC, forced vital capacity. Adapted from [3**].

demographics and inflammatory counts achieved an area under the curve (AUC) 0.75 ($P < 0.001$) versus 0.62 ($P = 0.006$) without the inclusion of cytokines. This study indicates that the peripheral endotype of difficult-to-control asthma in inner city African American children may be a generalized inflammatory state with Type 1, Type 2, and TH17 features.

Asthma phenotypes in inner city children

Using a computer ‘clustering’ program, Zoratti *et al.* [5**] categorized APIC children into different asthma groups based on whether they had similar or different characteristics. Five separate groups of children were identified by the clustering program and the characteristics that most distinguished the groups included the severity of asthma, the presence and degree of allergy, nasal symptoms, and lung function tests (Fig. 2). The greatest levels of asthma severity (representing 15% of the study population)

were in a highly allergen-sensitized group with severe rhinitis and abnormal lung function tests. However, another group (representing 15% of the study population), had few to no allergies, but was highly symptomatic for asthma despite high doses of controller medications. Similarly, there were two groups with relatively mild asthma that were distinguished by allergy versus low/no allergy.

The authors concluded that allergy and its associated inflammation are important features of severe childhood asthma that provide a basis for many asthma management strategies. However, some children have a type of highly symptomatic asthma where allergy is less important and alternative management strategies may be necessary.

Asthma severity pathways

Although key factors underlying asthma severity have been identified, an integrated understanding

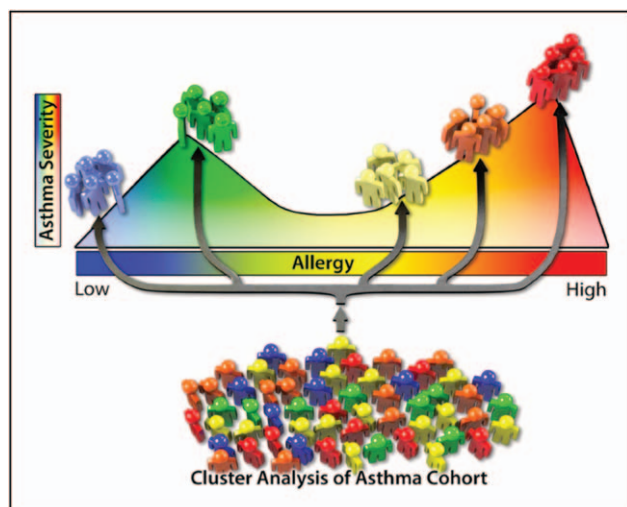


FIGURE 2. Asthma phenotypes in APIC children: asthma in APIC children was further characterized by cluster phenotyping into five groups that were strongly distinguished by asthma severity and allergy. Two clusters with relatively severe asthma were strongly differed by being highly allergic [red: highest total serum IgE level (median, 733 kU/l) and allergen sensitizations (15 of 22 tested)] or low/nonallergic (green: serum IgE level (71 kU/l) and allergen sensitizations (2 of 22 tested)). There were also two clusters of mild asthma distinguished by allergy (yellow) versus low/no allergy (blue). APIC, Asthma Phenotypes in the Inner City study, Adapted from [5^{***}].

of how these factors are linked and contribute to severe asthma is lacking. Liu *et al.* [6^{***}] used medical evidence in the published literature to develop and test a conceptual diagram of how eight key factors are linked to asthma severity in APIC children: allergen sensitization, allergic inflammation, pulmonary physiology, stress, obesity, vitamin D, environmental tobacco smoke (ETS) exposure, and rhinitis severity. Asthma severity was characterized by a 1-year composite assessment of day and night symptoms, exacerbations, and controller usage. The researchers found their conceptual diagram explained 53.4% of the asthma severity observed in these children. Two pathways were the main contributors to asthma severity: an allergy pathway and an ETS exposure pathway. These pathways affected asthma mostly through their effects on lung function and the nose, such that pulmonary physiology and rhinitis severity had the largest effects on asthma severity, followed by ETS exposure and allergic inflammation (Fig. 3).

The authors concluded that in US inner city children receiving guidelines-directed asthma and rhinitis care, the main factors affecting asthma severity are allergy and ETS exposure that exert their effects on lung function and the nose. This diagrammatic understanding of the key factors underlying

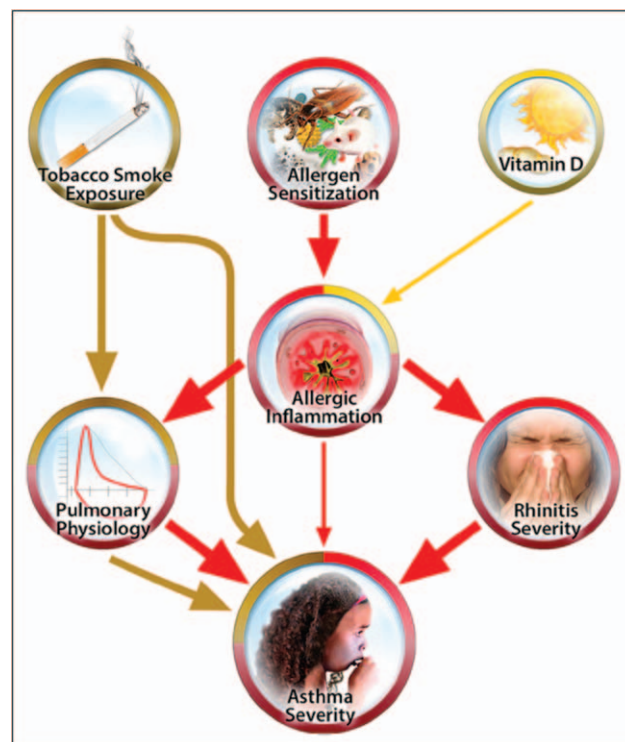


FIGURE 3. Main pathways to asthma severity in APIC children: in testing a literature-based model of personal and environmental pathways affecting asthma severity in APIC children, allergy and tobacco smoke exposure accounted for 53% of the variance in asthma severity, and exerted their influence through impairment in pulmonary physiology and increased rhinitis severity. Vitamin D had modest and relatively insignificant effects on asthma severity. APIC, Asthma Phenotypes in the Inner City study. Adapted from [6^{***}].

asthma severity and their relative contributions can be used as a roadmap for prioritizing interventions to reduce disease severity and personalize asthma management, and for targeting interventional studies to improve guidelines-directed care.

RHINOVIRUS INFECTIONS AND MECHANISMS OF ASTHMA EXACERBATIONS IN US INNER CITY CHILDREN: PREVENTIVE OMALIZUMAB OR STEP-UP THERAPY FOR SEVERE FALL EXACERBATIONS STUDY

Rhinovirus infection is a well known and extensively characterized trigger of asthma exacerbations [7], yet mechanisms by which such infections elicit pathophysiologic changes observed in people with asthma remain elusive. As skillfully reviewed by Bochkov and Gern [8], much has been learned about the pathobiology of rhinoviruses, including infection inception, and propagation; however, gaps in

linking rhinovirus infection with allergic (or type-2) inflammation remain.

With the advent of biologic agents, previously designed immunologically based treatment regimens have also acted as a probe to investigate impaired (or dysregulated) immune responses to rhinovirus. As the first biologic agent approved for the treatment of asthma, omalizumab – a humanized, antiimmunoglobulin E (IgE) monoclonal antibody – has provided key insights. Through the NIAID-sponsored PROSE (Preventive Omalizumab or Step-up Therapy for Severe Fall Exacerbations) study, effects of omalizumab on rhinovirus infection were studied in nearly 500 children with allergic asthma from low-income census tracts in whom the burden of asthma exacerbations is high [9]. Although the primary study objectives of this randomized, double-blind, double placebo-controlled, multicenter clinical trial were to compare the effectiveness of omalizumab to placebo and omalizumab to a boost in inhaled corticosteroid in preventing fall exacerbations among participants receiving ongoing guidelines-based asthma care, the study population and season during which participants were followed provided a unique opportunity to assess the interactions between IgE-blockade, rhinovirus infection, and aeroallergen exposure. Compared with placebo, children receiving omalizumab had decreased duration of rhinovirus infection, reduced peak rhinovirus shedding, and decreased frequency of rhinovirus illnesses [10^{***}]. Investigating mechanisms through which omalizumab may alter immune responses to rhinovirus infection, Gill *et al.* [11^{***}] performed ex-vivo assays on blood drawn from a subset of PROSE participants. Analyses of both peripheral blood mononuclear cells and purified plasmacytoid dendritic cells revealed that generation of IFN- α to rhinovirus in the presence of IgE cross-linking was significantly increased in the postomalizumab treatment group. Therefore, by interrogating effects of IgE cross-linking, a plausible explanation surfaced that could explain not only the clinical effectiveness of omalizumab but also alterations in the immune response to rhinovirus. As illustrated by these select examples of clinical translational studies in exacerbation-prone inner city children with asthma, the influence of rhinovirus infection on asthma exacerbations continues to be an active area of investigation.

EXPOSURES IN PUBLIC SCHOOLS AND ASTHMA SEVERITY IN US INNER CITY CHILDREN: SCHOOL INNERCITY ASTHMA STUDY

Phipatanakul and colleagues have conducted the NIAID-sponsored School Inner-City Asthma Study

(SICAS), an invaluable epidemiologic, prospective study that demonstrates the impact of multiple exposures in public schools on asthma severity in US urban elementary school children with asthma. Important SICAS findings were published in the past year: indoor classroom nitrogen dioxide levels were associated with increased airflow obstruction [12]; and higher levels of mouse allergen in school was associated with increased odds of having an asthma symptom day and lower predicted airflow [13^{***}]. These investigators previously reported that high levels of airborne endotoxin at school are associated with increased asthma symptoms in SICAS children with nonatopic asthma [14]. Lai *et al.* [15] further examined the genetic regulation of school endotoxin exposure's effects on SICAS participants with asthma by studying the interaction between an IL-4 receptor alpha (IL4R α)-chain gene variant associated with asthma inception and severity (glutamine to arginine substitution at amino acid residue 576, or IL4R α -Q576R polymorphism), school endotoxin exposure, and asthma symptoms. IL4R α -Q576R genotypes had paradoxical interactions with classroom endotoxin levels such that higher classroom endotoxin levels were associated with fewer asthma symptoms for children with the Q/Q genotype [odds ratio (OR) 0.76; (95% confidence interval; CI 0.55–1.04)], and increased asthma symptoms for the R/R genotype [OR 1.34 (95% CI 0.85–2.13)]. Notably, the frequency of the R allele was highest in children of black or mixed race. This investigation further reveals how genetic variation contributes to endotoxin exposure's paradoxical effects on asthma severity because of genetic variation away from the endotoxin receptor complex.

Phipatanakul and colleagues are naturally following SICAS findings with a NIAID-sponsored randomized, blinded, sham-controlled school environmental intervention trial, School Inner-City Asthma Intervention Study, to determine if a multilevel school exposure mitigation can reduce asthma severity in school children [16]. A pilot trial of classroom-based air cleaners was conducted by these investigators and demonstrated significant reductions in classroom fine particulate matter (PM_{2.5}) and black carbon, supporting the use of this intervention in their ongoing school intervention trial [17].

DEMOGRAPHIC RISK FACTORS ASSOCIATED WITH ASTHMA MORBIDITY IN US INNER CITY CHILDREN: UPDATE

The extent to which higher asthma prevalence and higher asthma morbidity among children can be specifically attributed to 'inner city' residence has

been debated. To better understand asthma risk associated with inner-city living or its associated characteristics such as poverty, race, and the urban environment, Keet *et al.* [18²²] used claims data from a large 2009–2010 Medicaid database of children and adolescents ages 5–19 years. They determined that, while inner city residence was not related to higher asthma prevalence, urban residence, living in poor neighborhoods, and non-Hispanic black ethnicity were all independently related to higher asthma morbidity (i.e. higher risk of asthma-related emergency department visits and hospitalizations).

This interplay between urban residence, race/ethnicity, and socioeconomic in childhood asthma was further investigated in two additional reports. Data on 6–17-year-old children from the 2011 American Housing Survey was analyzed to untangle the relationships of race/ethnicity and material hardship (crowded and poor quality housing, and lack of amenities and vehicle access) on asthma diagnosis and emergency department visits [19]. Compared with households headed by non-Hispanic whites, non-Hispanic blacks were more likely (odds ratio 1.72) to have a child with asthma in their home and ~3-fold more likely to have had a child visit the emergency department for asthma. These disparities were reduced, but not eliminated whenever adjusting for material hardship and home ownership. Furthermore, poor housing quality was independently associated with both asthma diagnosis and emergency department visits whereas home ownership was associated with a lower likelihood of asthma emergency department visits. Key factors thought to potentially explain differential asthma readmission rates between African American and white children were analyzed in the population-based Greater Cincinnati Asthma Risks Study cohort [20²³]. Using a causal inference analytic approach, the investigators evaluated biological, environmental, disease management, access, and socioeconomic hardship variables. Whenever compared with white children, African American children were 2.26 times more likely to be readmitted for asthma, but also differed with respects to most of the assessed variables. Socioeconomic hardship explained more than half of the asthma readmission risk, and all variables explained 80% of the observed disparity in readmissions. Notably, after accounting for all variables, the differential readmission rates were no longer statistically significant. These recent studies substantiate the impact of poverty, material hardship, and poor-quality housing on severe exacerbation risk in US urban children.

ENVIRONMENTAL DETERMINANTS OF ASTHMA IN US INNER CITY CHILDREN

As US inner city children have a high burden of problematic asthma, there has long been interest in how they develop asthma. NIAID sponsored ICAC investigators to conduct a longitudinal birth cohort of 560 urban families from neighborhoods with high rates of poverty and at increased risk of developing asthma, the Urban Environment and Childhood Asthma (URECA) study. Using a rigorous multifactorial definition of current asthma at age 7 years, URECA investigators reported a notable association of higher additive exposure to house-dust, cockroach, cat, and mouse allergens in the first 3 years of life to a lower risk of current asthma at age 7 [21²⁴]. This unexpected finding was potentially attributed to a substantial number of microbial taxa that were significantly more or less abundant in the house-dust samples containing high allergen levels and also differentially related to the likelihood of asthma. Gern *et al.* [22] reported how innate immune responses to common exposures (i.e. allergens, microbial exposures, respiratory viruses) develop over the first 3 years of life. Early life exposure to cockroach, mouse, and dust mite was associated with enhanced IFN- α and IL-10 responses to various stimuli at age 3 years, whereas reduced lipopolysaccharide (LPS)-induced IL-10 responses at birth were associated with recurrent wheeze. How environmental exposures early in life may alter immune responses to various stimuli (including rhinovirus) is integral to our understanding of asthma onset and morbidity, and is therefore, another field of ongoing research.

Epigenetic dysregulation in asthma

In ICAC-sponsored studies, Yang *et al.* [23] previously demonstrated differential methylation patterns in peripheral blood mononuclear cells (PBMCs) in inner city children with persistent asthma. As the respiratory epithelia is the first to interact with the environment, it may represent an important mediator of airways allergy and asthma. Yang *et al.* [24²⁵] analyzed DNA methylation patterns from nasal epithelia brushings of atopic persistent asthmatic children versus nonatopic, nonasthmatic children and found 186 genes that had significant differentially methylated regions (DMRs), including genes known to have established roles in asthma and atopy. The methylation differences between asthmatics and controls were substantial (median 9.5%) and similar in magnitude to those observed in other diseases (e.g. cancer). Also, as predicted, hypomethylated and hypermethylated genes were associated with increased and decreased

epithelial gene expression, respectively. To begin to explore the influence of environmental exposures on the nasal epithelial epigenome, the investigators identified 48 unique DMRs associated with tobacco smoke. These findings are amongst the first to link epigenetic regulatory mechanisms in the airway epithelium to asthma.

Mouse allergen is a concerning asthma-related exposure in inner city homes [25] and schools [13²²]; in mouse-sensitized inner city children with asthma, household exposure is associated with higher hospitalization rates, symptom days, and nights of lost sleep [26]. Miller *et al.* [27] examined methylation levels in buccal mucosal cells of children who were exposed and sensitized to mice. Targeted asthma candidate genes were those associated with regulating allergy (T regulatory gene forkhead box P3 gene (*FOXP3*), and allergy suppressive gene interferon (*IFN γ*). The authors demonstrated that decreasing household mouse allergen exposure (measured in dust) correlated with decreased levels of methylation at *FOXP3* enhancer and promoter sites. The differing rates of methylation were not related to cockroach or dust mite allergens. This is another example linking common exposures in inner city asthmatic children with epigenetic dysregulation.

PSYCHOSOCIAL STRESS AND ASTHMA IN US INNER CITIES

The psychosocial stress associated with inner city living has been increasingly linked to childhood asthma morbidity. In the SICAS Study, an analysis of four-item Perceived Stress Scores (PSS-4) among 351 caregivers of school-age children confirmed higher degrees of stress in lower income and unemployed caregivers [28]. In addition, asthmatic children of caregivers reporting high-stress scores had greater activity limitation, and those with 'very high stress' had more asthma-symptom days and greater dyspnea scores. Although poverty, hardship, lack of social support, and safety concerns are common stressors for urban mothers, the stressful impact of having a child with severe asthma has been poorly studied in this context. A recent report indicates that, in low-income, minority inner city mothers of children with severe asthma, home and community hardships were more consistently associated with maternal daily stress scores than asthma-related factors [29]. However, among factors reflecting asthma severity and control, the high utilization of emergency services for their child's asthma contributed most to daily stress.

Maternal stress and depression in early life also appears to be an important contributor to the

development of asthma. In the ICAC URECA study, maternal perceived stress and depression prior to age 3 years were associated with recurrent wheeze at age 3 [30], and asthma at age 7 [21²²]. Although neither depression nor stress were related to allergen sensitization, caregiver depression in the first year of the child's life was inversely associated with the child's peripheral blood type 2 cytokine responses at age 3 years.

An additional potential contributor to the high-stress levels in inner city families is the perception of racial/ethnic discrimination. In the GALA II and SAGE II studies, perceived discrimination was independently associated with asthma probability and poorer asthma control among African Americans [31]. Thus, greater caregiver stress associated with inner city living is linked to poverty, perceived discrimination, and depression, and impact not only asthma control in their children but also the risk of developing recurrent wheeze and asthma.

CONCLUSIONS: TRANSLATING RECENT RESEARCH TO IMPROVE ASTHMA CARE AND OUTCOMES FOR US INNER CITY CHILDREN

This has been a remarkably productive year for insights to improve asthma care and outcomes for US inner city children. As described above and summarized in 'Key Points', rigorous clinical investigations have provided meaningful insights to the nature and distinguishing characteristics of difficult-to-control asthma as well as two discrete severe asthma phenotypes in children (highly atopic and low/no atopy). Environmental determinants of problematic asthma (e.g. allergy, tobacco smoke, rhinovirus, stress, school environments) as well as the development of recurrent wheeze and asthma (allergens, microbiome, stress) were identified in US inner city children and linked to immune (e.g. IgE-mediated impairment of innate immunity to rhinovirus) and epigenetic regulatory mechanisms. A recently published chapter synthesizes the current evidence into approaches to improve care by 'Predicting and Preventing Asthma Exacerbations' [32²³]. Two validated tools developed by ICAC with immediate clinical utility are the Composite Asthma Severity Index (online calculator at <http://www.asthmaseverity.org>) [33,34²⁴] and a Seasonal Asthma Exacerbation Predictive Index [35²⁵,36²⁶].

In closing, we highlight some implementation studies that provide insights to improve asthma care for US inner city children. School-based asthma programs have been recently recognized for their importance in childhood asthma management [37]. The prototypical school-centered Step-Up asthma

program, based on the National Cooperative Inner City Asthma Study model of asthma advisers, [38] is an outreach program with asthma counselors bridging between subspecialty asthma care, primary care providers, school nurses, and children with asthma to provide evidence-based asthma education and case management [39]. Followed over 2 years, program participants had significant improvements in asthma knowledge and inhaler technique, and significant reductions in asthma exacerbations, urgent care visits, and missed school days. Technology-based initiatives to aid in asthma management are widely used, but in inner city adolescents, it is unknown if these tools are effective [40]. Out of various methods for interacting with minorities specifically (MP3 messages, text messaging, computer/web-based, video games, interactive voice response), only computer/web-based programs were successful in reducing healthcare utilization. Puff City is a web-based asthma management program for urban adolescents that has been evaluated in Detroit Public High Schools. In a pilot study, Joseph *et al.* [41] utilized the program in urban teens (13–19 years) presenting with asthma exacerbations and determined that the treatment group showed a nonsignificant trend towards fewer emergency department visits (33.8 versus 46.4%). These studies exemplify many efforts by healthcare providers and systems nationwide to improve asthma care and reduce disparate outcomes experienced by US inner city children.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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Excellent overview conveying the importance of understanding asthma phenotypes to advance asthma management, especially for people with severe asthma, with management models for precision medicine and phenotype-directed care.

2. Teague WG, Phillips BR, Fahy JV, *et al.* Baseline features of the Severe ■ Asthma Research Program (SARP III) Cohort: differences with age. *J Allergy Clin Immunol Pract* 2017. [Epub ahead of print]

This report contrasts the phenotypic characteristics of children versus adults with severe asthma. Comparatively, severe asthma in adults is characterized by a higher proportion of women, higher rates of obesity and greater airflow limitation. Adult severe asthma was also associated with lower blood eosinophils and allergen sensitization suggesting less reliance on Th2 pathways.

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This is the first of a trilogy of articles from the NIH/NIAID-sponsored Asthma Phenotypes in the Inner City (APIC) study conducted by the US Inner City Asthma Consortium. In APIC, 717 children with asthma living in nine US inner city communities were enrolled in this study and received evaluation and management visits every 2 months over an entire year. This manuscript described the characteristics of children with difficult-to-control asthma with high exacerbation rates, greater daytime and nocturnal symptoms, and compromised pulmonary physiology despite ongoing high-dose controller therapy. Other distinguishing features of difficult-to-control asthma at the start of the study included their large bronchodilator response to albuterol and poorer scores on an age-appropriate Asthma Control Test.

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11. Gill MA, Liu AH, Calatroni A, *et al.* Enhanced plasmacytoid dendritic cell ■ antiviral responses after omalizumab. *J Allergy Clin Immunol* 2017. [Epub ahead of print]

In analyses from a subset of participants in the PROSE study, peripheral blood mononuclear cells and purified plasmacytoid dendritic cells revealed that generation of IFN- α to rhinovirus in the presence of IgE cross-linking was significantly increased in the postomalizumab treatment group, elucidating a potential mechanism to explain the dampened effects of rhinovirus infection in those treated with omalizumab.

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