Allergic sensitization and clinical outcomes in urban children with asthma, 2013–2016

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ABSTRACT

Background: The aim of this study was to examine if food and/or aeroallergen sensitization was associated with worse asthma, pulmonary function tests (PFT), and laboratory markers.

Methods: At our institution, 386 children with asthma were divided into allergic and nonallergic groups based on allergen-specific immunoglobulin E (IgE) testing classes 1–6 versus 0. Asthma severity and/or control, IgE level, eosinophil counts and/or percentages, forced vital capacity (FVC), forced expiratory volume in the first second of expiration (FEV₁), and FEV₁/FVC, were compared by using bivariate, regression, and subgroup analyses for children who were highly allergic (≥ 4 allergens).

Results: A total of 291 subjects with asthma were allergic, significantly older, and had higher mean IgE levels and eosinophil counts and percentages (all $p < 0.001$). A total of 203 subjects who were highly allergic had worse obstruction on PFTs. Increasing age predicted allergen sensitization after confounder adjustment, odds ratio (OR) 1.54 (95% confidence interval [CI], 1.18–2.02). Similarly, PFT obstruction was associated with multiple allergen sensitization (OR 0.97 [95% CI, 0.93–1.02]).

Conclusion: Increasing age predicted allergic sensitization and multiple allergen sensitization. Worse obstruction on PFT also predicted multiple allergen sensitization. Continued surveillance of aeroallergen sensitization and PFT results may be beneficial in asthma management, particularly in older urban children.

(Allergy Asthma Proc 39:281–288, 2018; doi: 10.2500/aap.2018.39.4147)

Worldwide, since the 1960s, the prevalence of allergic disease, particularly asthma and allergic rhinitis, has continued to increase steadily in both middle- and high-income countries.¹ For instance, allergic sensitization (measured by the presence of allergen-specific immunoglobulin E [IgE] antibodies) to foreign proteins in the environment is present in 40% of the population in industrialized nations.^{2,3} Traditionally, this sensitization has been measured by biomarkers, such as IgE and eosinophil counts, high levels of which may contribute to atopy,⁴ a genetic predilection to produce IgE after exposure to allergens.

There was recent evidence that established the synergistic relationship between atopy and/or allergic sensitization and asthma. Allergic processes mediated by IgE and eosinophils play a role in the development and persistence of lower airway inflammation in sub-

jects with allergic asthma. IgE antibodies bind to mast cells and interact with allergens and release inflammatory mediators, which causes airway inflammation, bronchial hyperresponsiveness, and asthma exacerbations or worsening of asthma control. Environmental and food allergies are thus important determinants in asthma development and exacerbation.

A growing body of work has focused on using new therapies that target allergic sensitization to optimize clinical outcomes in patients with asthma. Epidemiologic studies have harnessed the immunologic basis of allergic responses in the prognosis of asthma.⁵ Immunotherapy in patients with asthma is still relatively new, however, and warrants further research to promote the development of novel allergen-based vaccines and/or monoclonal antibody-based immunotherapies.⁶

There are limited studies that examined the associations between pediatric allergic sensitization and clinical markers of asthma severity and control, particularly in an urban setting. Previously examined associations between allergy and clinical asthma have been limited by a lack of concurrently measured atopy and asthma, and an undue reliance on self-reported symptoms. There is little quantitative literature that investigated the association between allergic sensitization and multiple indicators of asthma severity and

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No external funding sources reported

The authors have no conflicts of interest to declare pertaining to this article

Supplemental data available at www.IngentaConnect.com

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control in pediatric populations. Perhaps more importantly, there is a paucity of evidence that describes these associations in inner-city populations.

We examined the relationships of several demographic variables, biomarkers of allergy, and clinical markers of severity of asthma between patients with allergic and patients with nonallergic asthma at a large inner-city asthma clinic at our university hospital. We hypothesized that individuals with allergy would demonstrate elevated atopic biomarkers, have more severe asthma, and have worse asthma control. Furthermore, we examined if these associations differed by age, gender, ethnicity, and multiple-allergen sensitizations in our study population.

METHODS

Study Design and Study Population

A retrospective review of medical records was carried out for 386 children with asthma, ages 0–20 years, who attended the pediatric pulmonology clinic at the State University of New York Downstate Medical Center, Brooklyn, New York, over 3 years, from 2013 to 2016. These children were routinely evaluated for allergic sensitization to common allergens by allergen-specific IgE tests in addition to complete blood cell (CBC) count, IgE values, and pulmonary function test (PFT). Patient demographic data included age, gender, ethnicity, and body mass index. Institutional review board approval was obtained for the study from the State University of New York Downstate Medical Center (1001465–2). Individual patient data were de-identified to protect private health information in keeping with hospital policy and institutional review board requirements.

Inclusion Criteria

To warrant inclusion in this study, all the patients had to have been 0–21 years of age at the time of this study, have a diagnosis of asthma by a physician of any category of severity and/or control, information on laboratory biomarkers of allergen sensitization (eosinophil counts from complete blood cell counts with differentials and total IgE and allergen-specific IgE tests). Although we received many referrals for patients with wheezing and/or reactive airway disease from primary care providers in the community and from continuity clinics at our institution, these patients were not included in the study if they did not meet the following criteria: a history of cough, recurrent wheezing, recurrent difficulty breathing, recurrent chest tightness, with worsening at night or with exercise; viral infection; exposure to allergens and/or irritants; or other environmental triggers such as weather changes, or behavioral triggers such as vigorous laughing, crying or emotional stress. These criteria were

based on the Expert Panel Report on the diagnosis and management of asthma by the National Asthma Education and Prevention Program.⁷

Exclusion Criteria

Pregnant patients and patients who were current smokers were not included for the purposes of this study because both were deemed proinflammatory states.

Testing of Allergic Sensitization

All new patients who presented to our clinic underwent the ImmunoCAP (ImmunoCAP TM, Pharmacia Diagnostics AB, Uppsala, Sweden) test to determine allergic sensitization to commonly encountered airborne and food allergens. The standard food and aeroallergen inhalant panel at our institution was used to measure allergen-specific IgEs, including the following foods: egg white, milk, wheat, oats, peanuts, soybean, shrimp, egg yolk, and casein. Inhalants included Bermuda, orchard, timothy, and June grasses; common and giant ragweeds; English plantains; and box elder, birch, beech, oak, elm, and sycamore trees. The dust panel, composed of *Dermatophagoides pteronyssinus* and *Dermatophagoides farina* as well as house dust (Greer Labs Inc., Lenoir, NC). We also tested for animals: cat, mouse, and rat epithelium, and horse and dog danders. Cockroach (German) was also measured. Also, mold-specific IgE to *Penicillium notatum*, *Cladosporium* species, *Aspergillus fumigatus*, *Candida* species, and *Alternaria*.

This test was carried out by using the standardized technique to determine allergic sensitization status to specific allergens in our patient population. Allergen-specific IgE testing was chosen for its easy accessibility, high reliability (reproducibility), validity indices across the full measuring range, and high specificity in binding to allergen-specific IgE and a moderate-to-high degree of sensitivity compared with the other standard, skin-prick test.⁸

Skin-prick testing to similar allergens (aero-allergen, plant-allergen, and dust) has previously been described in the literature. We chose blood tests because they were superior to skin-prick tests in our population because of the objective nature of the *in vitro* test and the lack of the need to discontinue antihistamines if our patients were taking antihistamines. A high prevalence of eczema (in our population: allergic group versus nonallergic group, 46% versus 27%) is known to interfere with skin-prick testing.⁹ The patients were deemed allergic when their level of allergen-specific IgE, as measured by ImmunoCAP, was >0.35 kU/L (class 1–6); <0.35 kU/L of allergen-specific IgE (class 0) was deemed nonallergic. Complete blood cell counts were

analyzed for absolute eosinophil counts and percentages.

Clinical Tests

On accrual into the study, further questions regarding severity (day- and nighttime symptoms, emergency department [ED] visits, hospitalizations, and steroid use) as well as questions on asthma control were asked, and this information was recorded in our data bases. Information on other clinical variables of interest were abstracted from the electronic medical record of our patients, including information on concurrent eczema; allergies to plant, food, dust, and animal; and inhalant allergies as defined by the Expert Panel Report 3 of the National Asthma Education and Prevention Program.⁷

Statistical Analysis

Demographic variables included age, gender, ethnicity, and body mass index [BMI] at different levels of allergen-specific IgE classes, 0 versus 1–6. Similar categorical distributions were examined for classification of asthma severity and control, with albuterol use as an adjunct, proxy indicator of asthma control. The prevalence of these characteristics were compared at levels of allergen-specific IgE tests by using the Pearson χ^2 test. Unless otherwise specified, all continuous variables are presented as means $\pm$ standard deviations, and all categorical variables are presented as frequencies.

Summary statistics of all continuous variables were also carried out to examine their distribution. Although they demonstrated mildly non-normal distributions, no significant degree of skewness was determined for IgE, Absolute Eosinophil Count (AEC) and eosinophil percentage, both from the CBC. Therefore, these variables were analyzed without logarithmic or geometric transformations. Nonparametric testing was used to handle comparisons for these variables. Unweighted univariate analyses of variance of the mean serum IgE, AEC, and eosinophil percentage values across allergen-specific IgE test levels were carried out. The mean values for these continuous variables were compared by using parametric and non-parametric testing with the Student *t*-test or Mann-Whitney *U*-test as appropriate. Similar analyses were carried out on PFTs, *viz.*, for prebronchodilator forced vital capacity (FVC), forced expiratory volume in the first second of expiration (FEV₁) and FEV₁/FVC values. PFTs were described as medians with interquartile ranges.

In addition, *post hoc* stratified analyses of all demographic, laboratory biomarkers of allergy and PFTs were carried out for patients with multiple allergies of four or more compared with those with fewer allergies. We also examined logistic regression models of allergen sensitization after controlling for confounders

identified from the literature, including age, gender, and medication use, and by examining three predictors: asthma severity, asthma control and PFT (FEV₁: FVC). We examined these predictors for the development of multiple allergies as well. All statistical analyses were conducted with R version 3.2.2, and the statistical significance level was 0.05, unless otherwise specified. No weight variables were included or analyzed for the purposes of this study.

RESULTS

Among our 386 patients with asthma, a greater proportion of children and adolescents were allergic than were nonallergic based on allergen-specific IgE tests. Food allergies were more prevalent in our younger patients, in contrast to environmental allergies in our older patients. A total of 291 patients (75%) were allergic and 95 patients (25%) were nonallergic. House dust, mouse, dog, and cockroach were the four most prevalent allergies detected on allergen-specific IgE tests in children >4 years of age. In the 0–4 year old patients, however, food allergies to milk, egg white, peanuts, and wheat were the most common, followed by house dust, mouse, and dog.

The patients with allergic asthma were, on average, 4.6 years older than the nonallergic group, 7.5 versus 2.9 years ($p < 0.001$). Of these, 62% were boys, 92% were African American, 4% were Hispanic, and the remainder were Asian and white. The nonallergic group was 59% boys, 91% African American, and 6% Hispanic, and the remainder were Asian and white. Overall, there were no significant differences in gender and ethnicity between the patients with allergic asthma and the patients with nonallergic asthma (Table 1). With regard to clinical outcomes, asthma severity was mostly mild persistent or moderate persistent. Asthma control was similar in the two groups (Table 1). Overall comparisons across all categories of severity and control did not reveal significant differences. Clinically, a greater proportion of the patients with allergic asthma reported a history of eczema (46% with eczema vs. 27% without eczema).

However, laboratory biomarkers of allergy demonstrated significant differences at all levels of allergen-specific IgE tests (Table 2), *i.e.*, IgE levels, eosinophil percentages, and AEC were all significantly higher in the patients with allergic asthma compared with the patients with nonallergic asthma. In the patients with allergic versus nonallergic asthma, the mean IgE levels were 337 μ /mL versus 14.4 μ /mL ($p < 0.001$), the mean AEC was 400 cells/ μ L versus 200 cells/ μ L ($p < 0.001$), and the mean eosinophil percentage was 5.8% versus 2.5% ($p < 0.001$). The differences were even more remarkable when these results were compared for multiple allergen-specific IgE positivity (≥ 4 allergens versus < 4 allergens).

Table 1 Demographic characteristics among subjects with allergic vs subjects with nonallergic asthma (N = 386)

Characteristic	Subjects with Allergic Asthma (n = 291)	Subjects with Nonallergic Asthma (n = 95)	p
Age, mean $\pm$ SD, y	7.5 $\pm$ 4.8	2.9 $\pm$ 2.3	<0.001*
Gender, no. (%)			0.7#
Boys	180 (61.9)	56 (58.9)	
Girls	111 (38.1)	39 (41.1)	
Ethnicity, no. (%)			0.29#
African American	269 (92)	86 (91)	
Hispanic	11 (4)	6 (6)	
Asian, white, other	11 (4)	3 (3)	
Asthma severity, no. (%)			0.52#
Intermittent	63 (21.6)	17 (17.9)	
Mild persistent	106 (36.4)	54 (56.8)	
Moderate persistent	100 (34.4)	20 (21.1)	
Severe persistent	22 (7.6)	4 (4.2)	
Asthma control, no. (%)			0.58#
Well controlled	148 (50.9)	52 (54.7)	
Not well controlled	115 (39.5)	37 (38.9)	
Very poorly controlled	28 (9.6)	6 (6.3)	

SD = Standard deviation.

Bolded values indicate a significant p-value.

*The Student t-test shows significant differences in the mean levels of this continuous variable.

#Pearson χ^2 test, comparing proportions of frequencies for categorical variables.

Table 2 Laboratory biomarkers for subjects with allergic asthma versus subjects with nonallergic asthma (N = 386)

Test	Subjects with Allergic Asthma, median (IQR) (n = 291)	Subjects with Nonallergic Asthma, median (IQR) (n = 95)	p*
Immunoglobulin E value	337 (130.5–808)	14.40 (6.2–35.5)	<0.001
Absolute eosinophil count	0.4 (0.2–0.6)	0.2 (0.1–0.3)	<0.001
Eosinophil, %	5.8 (2.35–8.2)	2.5 (1.65–4.45)	<0.001

IQR = Interquartile range.

Bolded p-values were represent significant at the $\alpha = 0.05$ level.

*Mann-Whitney U-test, compared medians (IQR) of laboratory biomarkers in the subjects with asthma.

PFTs were also compared (Table 3) for the patients with allergic asthma versus the patients with nonallergic asthma. We did not find any differences in PFTs overall. However, the patients with highly allergic asthma (≥ 4 allergens) had significantly lower FEV₁/FVC, than the group with < 4 allergens, 83% (76–90%) versus 87% (83–96%) ($p < 0.001$; Fig. 1), but FEV₁ and FVC were not significantly different; FEV₁ was 89% (78–99%) versus 92% (78–97%), and FVC was 94% (81–107%) versus 89% (77–99%) (Table 4).

The results of the logistic regression models are represented in Table 5. After controlling for age, gender, medication use, and FEV₁/FVC, we found, in multivariate regression models, that, for younger children (ages < 5

years), increasing age seemed to be an important risk factor for allergen sensitization. (odds ratio [OR] 1.54 [95% confidence interval {CI}, 1.18–2.02]), whereas gender, asthma severity, control, and medication use (albuterol, montelukast, and Inhaled corticosteroid [ICS]) were not significant predictors in the fully adjusted model. Similar subgroup regression analyses for predicting multiple allergen sensitization in older children (ages ≥ 5 years for whom PFT data were available), also showed increased odds of allergen sensitization with increasing age (OR 1.26 [95% CI, 1.07–1.55]). Furthermore, worsening obstruction on PFT, as measured by FEV₁/FVC was significantly associated with increased allergen sensitization (OR 0.96 [95% CI, 0.89–1.03]).

Table 3 Pulmonary function test results (N = 386)

Test	Subjects with Allergic Asthma, median (IQR) (n = 291)	Subjects with Nonallergic Asthma, median (IQR) (n = 95)	p*
FVC, %	93 (79.5–105)	96.5 (77.8–110.2)	0.85
FEV ₁ , %	91 (81–100)	90 (83.3–103.5)	0.77
FEV ₁ /FVC	85 (77.5–90.5)	89 (78–95.25)	0.18

IQR = Interquartile range; FVC = forced vital capacity; FEV₁ = forced expiratory volume in the first second of expiration.

*Mann-Whitney U-test, comparing pulmonary function test in the subjects with asthma.

Figure 1. Pulmonary function tests (PFT) with ≥ 4 allergens versus < 4 allergens. Obstruction on PFT in the subjects with highly allergic asthma with ≥ 4 allergens. The p values are from the Mann-Whitney U-test.

DISCUSSION

In this study, the four most common allergies in inner-city children and adolescents with asthma were house dust, mouse, dog, and cockroach. As expected, the patients with asthma and with allergies had increased total IgE levels, AEC, eosinophil percentages compared with the patients with asthma and with no allergies. Interestingly, allergen-specific IgE test positivity was not associated with increased asthma severity or poorer control of asthma. Overall, patients with asthma and with allergies did not demonstrate greater reduction in FEV₁ compared with the patients with nonallergic asthma. However, the patients with highly allergic asthma (*i.e.*, allergen-specific IgE tests positivities of ≥ 4 allergens) had significantly lower FEV₁:FVC than those with < 4 allergens.

We also demonstrated that age was a significant risk factor in predicting any allergen sensitization for young children and multiple allergen sensitization in older children, despite confounder adjustment. Older children also demonstrated worsening obstruction on PFT as measured by FEV₁:FVC (4% reduction) with increasing allergies (*i.e.*, multiple allergen sensitization). Overall, these results supported the notion that multiple allergic sensitizations portend worse airflow obstruction later in life for children and adolescents

with asthma, and that increasing age could significantly influence a subject's likelihood of allergen sensitization.¹⁰

The findings of our study were consistent with limited published literature from other domestic and international urban populations. Turner *et al.*¹¹ showed that urban children demonstrated a higher incidence of skin-test reactivity to dust mite, mold, and dog dander than did rural children, with urban children at a higher risk of asthma. In a seminal study by Gelber *et al.*¹², IgE antibodies to dust mite, cat, and cockroach were each significantly associated with asthma, with a stronger association in urban participants without medical insurance and African Americans. More recently, Zoratti *et al.*¹³ showed that severe asthma often co-clustered in children with multiple allergen sensitivities, when children with different asthma phenotypes were analyzed. A multicenter study showed that New York City children with asthma had the highest pest-allergen sensitization and more asthma exacerbations, with Puerto Rican and other Latino youth more likely to be hospitalized.¹⁴

There are other possible venues to explore the issue of sensitization to multiple allergens and worsening asthma control in inner-city children. One obvious measure to consider is to avoid exposure to allergen at home by routine home allergen remediation programs.¹⁵ Alternatively, allergen desensitization therapy, such as subcutaneous immunotherapy, for allergens found in bedding and in the home environment, or sublingual immunotherapy (SLIT) may be considered.

Our study added to the body of literature that corroborates the need for allergic sensitization testing in the management of childhood and adolescent asthma. A Cochrane review showed, with 52 studies, reduced asthma symptoms and corticosteroid dosage and/or use in patients who had undergone SLIT.¹⁶ In conjunction with this, a meta-analysis demonstrated the effectiveness of subcutaneous immunotherapy versus SLIT for the treatment of allergic rhinoconjunctivitis and asthma.¹⁷ In another study, SLIT offered clinical responses in patients with Radio Allergo-Sorbent test (RAST) positive with concurrent improvements in the skin-prick tests.¹⁸ Also, in a review on SLIT in asthma

Table 4 Demographics, medications, biomarkers, and PFT in ≥ 4 allergens vs < 4 allergens (N = 291)

Characteristic	Subjects with Highly Allergic Asthma (≥ 4 allergens)	Subjects with Allergic Asthma (< 4 allergens)	<i>p</i> *§
Patients, no. (%)	203 (70)	88 (30)	—
Age, mean $\pm$ SD, y	8.6 $\pm$ 4.7	4.8 $\pm$ 3.8	<0.001
Eczema, no. (%)	111 (54.7)	23 (26.1)	<0.001
ICS, no. (%)	133 (65.5)	57 (64.8)	0.9
Montelukast, no (%)	89 (43.8)	21 (23.9)	<0.001
IgE value, μ /mL	547 (277–1226)	102 (35.95–76.5)	<0.001
AEC, cells/ μ L	0.4 (0.2–0.6)	0.3 (0.1–0.4)	<0.001
EOS, %	5.9 (2.8–9.2)	3.15 (1.9–5.6)	<0.001
FVC, %	94 (80.5–107)	89 (76.5–99.2)	0.85
FEV ₁ , %	89 (78–98.5)	91.5 (77.8–96.5)	0.77
FEV ₁ /FVC	83 (76–90)	87 (83–96)	<0.001

PFT = Pulmonary function test; SD = standard deviation; ICS = inhaled corticosteroid; IgE = immunoglobulin E; AEC = absolute eosinophil count; EOS = eosinophil percentage; FVC = forced vital capacity; FEV₁ = forced expiratory volume in the first second of expiration.

Values in bold are significant at the $\alpha = 0.05$ level.

IgE, AEC, Eosinophil%, FVC%, FEV₁%, FEV₁/FVC ratio are all medians with IQR.

Eczema, ICS and Montelukast use were compared with a χ^2 test.

Mann-Whitney U-test compared median differences of continuous variable.

The Pearson χ^2 test compared proportions of frequencies for categorical variables.

*The variable age was compared with a *t*-test.

Student's *t*-test compared mean differences of continuous variable.

§All the other tests from IgE to FEV₁/FVC are Mann-Whitney U-tests.

Table 5 Regression models for the subjects with allergic asthma vs the subjects with nonallergic asthma, and subjects with asthma and with ≥ 4 allergens vs < 4 allergens

Independent Variable	Subjects < 5 -y old, with Allergic Asthma vs Subjects with Nonallergic Asthma, overall OR (95% CI) (<i>n</i> = 113)*	Subjects ≥ 5 -y old, with ≥ 4 Allergens vs Subjects with < 4 Allergens, OR (95% CI) (<i>n</i> = 185)#
Asthma severity: persistent vs intermittent	0.65 (0.30–1.37)	242 (0.53–11.32)
Asthma control: poorly and not well controlled vs controlled	1.32 (0.74–2.70)	0.90 (0.25–3.21)
Age§	1.54 (1.18–2.02)¶	1.26 (1.07–1.55)¶
Gender: boys vs girls	1.05 (0.58–1.91)	4.69 (1.46–16.55)¶
Medication use: albuterol, montelukast, and ICS use	1.33 (0.65–2.77)	2.54 (0.62–12.59)
FEV ₁ /FVC§	—	00.97 (0.93–1.02)¶

OR = Odds ratio; CI = confidence interval; ICS = inhaled corticosteroid; FEV₁ = forced expiratory volume in the first second of expiration; FVC = forced vital capacity.

*Regression model that demonstrates ORs for overall allergen sensitization in the subjects (< 4 y of age) with allergic asthma vs with nonallergic asthma.

#Also represented are ORs for the subjects with highly allergic asthma vs the subjects with less allergic asthma in older children (age ≥ 5 y).

§Continuous variable.

¶Significant at the $\alpha = 0.05$ levels.

||Only available for older children (*n* = 185).

and allergic rhinoconjunctivitis published in *JAMA* in 2013, strong evidence from 63 studies supported that SLIT improved asthma symptoms (>40% improvement) and medication use for asthma and allergies decreased (>40% improvement).¹⁹ In this context, reducing allergen sensitization seems to be a valid way of synergistically ameliorating the body's natural immunologic mechanisms in allergic asthma.⁶

There is increasing evidence to indicate that asthma-promoting mechanisms operate *via* a dose-response relationship to various environmental factors.¹⁵ Several reports have postulated the pathophysiology that underlies the causation of asthma in patients who are atopic.²⁰ The Urban Environment and Childhood Asthma study examined a birth cohort at high risk for asthma in New York, Boston, Baltimore, and St Louis. Cumulative allergen exposure in the first 3 years was associated with allergic sensitization at age 3 years and recurrent wheezing.²¹ The highest exposure to specific allergens and bacteria during the first year was least associated with recurrent wheeze and allergic sensitization.²¹ The immunologic environment and age of exposure are thus critical in determining the prognostic milieu in subjects with allergic sensitization to increasing allergens.²²

Understanding the unique pathology of specific clinical presentations of allergic sensitization is also helpful in identifying potential sources of therapy. It is now well established that subjects with asthma have airway hyperreactivity to various triggers, including allergens, usually measured by PFT. We found that children who were highly allergic had significantly higher atopic biomarkers, eczema, and more obstruction on PFT compared with those subjects with three or fewer allergies. For patients with highly allergic asthma (≥ 4 allergens), FEV₁/FVC was significantly lower than the group with <4 allergens; 83% versus 87% ($p < 0.001$). One study found that allergic rhinitis was a significant factor that affected recovery from an obstruction on PFT during an asthma exacerbation and may impact asthma management.²³ Indeed, it seemed that treatment with anti-IgE antibody, omalizumab, resulted in significant improvements in PFT across all metrics, FVC, FEV₁, FEV₁/FVC and Forced Expiratory Fraction (FEF)_{25–75%} in patients with comorbid rhinosinusitis and allergic asthma.²⁴ (Supplemental Table 1 to 5).

In our study, the mean serum levels of both IgE and eosinophils were higher in the subjects with asthma sensitized to allergens compared with the subjects with nonallergic asthma, and this relationship was even more pronounced in the subjects with highly allergic asthma. The increased levels of IgE in patients sensitized to allergens are thought to stimulate mast cell degranulation, the generation and recruitment of eosinophils and interleukins 4 and 5 to produce inflammation of type I hypersensitivity reactions.²⁵ Increased

degranulation of eosinophil products, eosinophil cationic protein, tumor necrosis factor α , and granzyme β are locally present, all of which are active proinflammatory mediators.²⁶ This cytokine cascade is the hallmark of the allergic response and provides many avenues for pharmaceutical intervention.

One of the limitations of our study was the retrospective nature of the study with the use of self-reported asthma severity and control, which could have led to recall bias and yielded nonsignificant results. A longitudinal and/or prospective design might help alleviate such concerns and help identify causal inferences. Future studies could consider separate analyses of food-allergen and aeroallergen sensitization on asthma outcomes. This study did not include information on other residual confounders that might be clinically related to the association between allergic sensitization and asthma, such as physical activity; the timing and duration of allergen exposure, especially pets at home; the distance of the home from roads with heavy traffic; household smoking or use of gas stoves; early childhood respiratory infections; and antihistamine therapy.

Despite these limitations, to our knowledge, this was the first study that analyzed multiple allergenic determinants and the clinical state of asthma concurrently in an urban pediatric setting. One of the strengths of this analysis was the relatively large sample size ($N = 386$) obtained over a 3-year period, which yielded well-powered estimates. Second, the use of identical methodologies across our population made standardized comparisons among subjects possible. The marked degree of difference in the mean serum levels of allergic biomarkers and PFTs in this study for patients with allergic and patients with nonallergic asthma were not likely to be due to chance or confounding factors alone. Stratification by degree of allergen positivity (four or more versus fewer allergies) lends further credibility to the underlying biologic plausibility of these analyses.

The increasing prevalence of allergies since the early 1980s has a direct negative impact on the quality of life in children with asthma,²⁷ which necessitated frequent surveillance of allergen sensitization, particularly in refractory and/or severe asthma. Allergen immunotherapy and, recently, U.S. Food and Drug Administration approved anti-interleukin 5 therapeutics such as mepolizumab and reslizumab are likely to help patients with allergic asthma in the future.²⁸

CONCLUSION

In New York City, by using a large urban sample of children and adolescents with asthma, we examined several demographic variables, biomarkers of allergy, and clinical indicators of patients with allergic asthma and of patients with nonallergic asthma. Although allergic sensitization was not associated with worsening asthma se-

verity or control, the patients with allergic asthma had increased IgE levels, eosinophil percentages, and AEC values compared with patients with asthma and no allergies. Multiple allergies correlated significantly with more obstruction on PFT. These results highlighted the current and future need for continued surveillance of aeroallergen sensitization in urban patients with allergic asthma. As per the National Heart, Lung, and Blood Institute guidelines²⁹ on asthma, food allergen testing may be useful in younger patients, ages 0–4 years, with four or more episodes of wheezing in the past 12 months, in whom long-term controller therapy is being considered. Future research should consider a longitudinal design in an effort to understand the complex relationship between allergic sensitization status and asthma. Also, randomized trials that use allergen desensitization and immunotherapies or new interleukin-5 antagonists and inhaled corticosteroids, leukotriene antagonists may foster understanding of concurrent atopic sensitization in influencing clinical outcomes in asthma and pave the way for future modalities of management.

REFERENCES

- Mastorilli C, Posa D, Cipriani F, and Caffarelli C. Asthma and allergic rhinitis in childhood: what's new. *Pediatr Allergy Immunol* 2016; 27:795–803.
- Allergy Statistics. American Academy of Allergy, Asthma & Immunology. 2014. Available from: <http://www.aaaai.org/about-the-aaaai/newsroom/allergy-statistics.aspx>. Accessed May 1, 2017.
- Allergies and Hay Fever. National Center for Health Statistics, Centers for Disease Control and Prevention. 2016. Available from <https://www.cdc.gov/nchs/fastats/allergies.htm>. Accessed May 1, 2017.
- Teo PZ, Utz PJ, and Mollick JA. Using the allergic immune system to target cancer: activity of IgE antibodies specific for human CD20 and MUC1. *Cancer Immunol Immunother*. 2012; 61:2295–2309.
- Epstein TG, Calabria C, Cox L, and Dreborg S. Current Evidence on Safety and Practical Considerations for Administration of Sublingual Allergen Immunotherapy (SLIT) in the United States. *J Allergy Clin Immunol Pract*. 2017; 5:34–40.e2.
- Elenius V, and Jartti T. Vaccines: could asthma in young children be a preventable disease? *Pediatr Allergy Immunol*. 2016; 27:682–686.
- Camargo CA Jr, Rachelefsky G, and Schatz M. Managing asthma exacerbations in the emergency department: summary of the National Asthma Education and Prevention Program Expert Panel Report 3 guidelines for the management of asthma exacerbations. *J Allergy Clin Immunol*. 2009; 124(Suppl):S5–S14.
- Hartmann AL, Wuthrich B, Deflorin-Stolz R, Helfenstein U, Hewitt B, and Guerin B. [Atopy screening: prick multitest, total IgE or RAST? On the value of allergologic testing of the staff of an industrial bakery]. *Schweiz Med Wochenschr*. 1985; 115:466–475.
- Onell A, Whiteman A, Nordlund B, et al. Allergy testing in children with persistent asthma: comparison of four diagnostic methods. *Allergy*. 2017; 72:590–597.
- Ownby DR. Measurement of serum IgE concentrations in cancer patients. *Ann Allergy*. 1985; 55:518.
- Turner KJ, Dowse GK, Stewart GA, and Alpers MP. Studies on bronchial hyperreactivity, allergic responsiveness, and asthma in rural and urban children of the highlands of Papua New Guinea. *J Allergy Clin Immunol*. 1986; 77:558–566.
- Gelber LE, Seltzer LH, Bouzoukis JK, Pollart SM, Chapman MD, and Platts-Mills TA. Sensitization and exposure to indoor allergens as risk factors for asthma among patients presenting to hospital. *Am Rev Respir Dis*. 1993; 147:573–578.
- Zoratti EM, Krouse RZ, Babineau DC, et al. Asthma phenotypes in inner-city children. *J Allergy Clin Immunol*. 2016; 138:1016–1029.
- Fishbein AB, Lee TA, Cai M, et al. Sensitization to mouse and cockroach allergens and asthma morbidity in urban minority youth: Genes-environments and Admixture in Latino American (GALA-II) and Study of African-Americans, Asthma, Genes, and Environments (SAGE-II). *Ann Allergy Asthma Immunol*. 2016; 117:43–49.e1.
- Matsui EC, Sampson HA, Bahnson HT, et al. Allergen-specific IgE as a biomarker of exposure plus sensitization in inner-city adolescents with asthma. *Allergy*. 2010; 65:1414–1422.
- Normansell R, Kew KM, and Bridgman AL. Sublingual immunotherapy for asthma. *Cochrane Database Syst Rev*. 2015; (8): CD011293.
- Chelladurai Y, Suarez-Cuervo C, Erekosima N, et al. Effectiveness of subcutaneous versus sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: a systematic review. *J Allergy Clin Immunol Pract*. 2013; 1:361–369.
- Tao L, Shi B, Shi G, and Wan H. Efficacy of sublingual immunotherapy for allergic asthma: retrospective meta-analysis of randomized, double-blind and placebo-controlled trials. *Clin Respir J*. 2014; 8:192–205.
- Lin SY, Erekosima N, Kim JM, et al. Sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: a systematic review. *JAMA*. 2013; 309:1278–1288.
- Borres MP, and Bjorksten B. Peripheral blood eosinophils and IL-4 in infancy in relation to the appearance of allergic disease during the first 6 years of life. *Pediatr Allergy Immunol*. 2004; 15:216–220.
- Lynch SV, Wood RA, Boushey H, et al. Effects of early-life exposure to allergens and bacteria on recurrent wheeze and atopy in urban children. *J Allergy Clin Immunol*. 2014; 134:593–601.e12.
- Turner MC. Epidemiology: allergy history, IgE, and cancer. *Cancer Immunol Immunother*. 2012; 61:1493–1510.
- Yilmaz O, Bakirtas A, Ertoyl Karagol HI, Topal E, and Demirsoy MS. Allergic rhinitis may impact the recovery of pulmonary function tests after moderate/severe asthma exacerbation in children. *Allergy*. 2014; 69:652–657.
- Clavenna MJ, Turner JH, Samuelson M, Tanner SB, Duncavage J, and Chandra RK. Differential effect of omalizumab on pulmonary function in patients with allergic asthma with and without chronic rhinosinusitis. *Allergy Asthma Proc*. 2016; 37:23–26.
- Barata LT, Ying S, Meng Q, et al. IL-4- and IL-5-positive T lymphocytes, eosinophils, and mast cells in allergen-induced late-phase cutaneous reactions in atopic subjects. *J Allergy Clin Immunol*. 1998; 101(Pt 1):222–230.
- Daniels TR, Martinez-Maza O, and Penichet ML. Animal models for IgE-mediated cancer immunotherapy. *Cancer Immunol Immunother* 2012; 61:1535–1546.
- Singh K, Axelrod S, and Bielory L. The epidemiology of ocular and nasal allergy in the United States, 1988–1994. *J Allergy Clin Immunol*. 2010; 126:778–783.e6.
- Liu AH, Anderson WC III, Dutmer CM, Searing DA, and Szefer SJ. Advances in asthma 2015: Across the lifespan. *J Allergy Clin Immunol*. 2016; 138:397–404.
- National Asthma Education and Prevention Program, Third Expert Panel on the Diagnosis and Management of Asthma. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Bethesda (MD): National Heart, Lung, and Blood Institute (US); 2007 Aug. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK7232/>. Accessed May 1, 2018. □