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Exercise-Induced Wheeze, Urgent Medical Visits, and Neighborhood Asthma Prevalence

AUTHORS: Timothy R. Mainardi, MD, MA,[a] Robert B. Mellins, MD,[b] Rachel L. Miller, MD,[a,b,c] Luis M. Acosta, MD,[c] Alexandra Cornell, MD,[d] Lori Hoepner, MPH,[c,e] James W. Quinn, MA,[f] Beizhan Yan, PhD,[g] Steven N. Chillrud, PhD,[g] Omar E. Olmedo, BS,[c] Frederica P. Perera, DrPH,[c] Inge F. Goldstein, DrPH,[h] Andrew G. Rundle, DrPH,[h] Judith S. Jacobson, DrPH,[h] and Matthew S. Perzanowski, PhD[c]

[a]Division of Pulmonary, Allergy, Critical Care Medicine, Department of Medicine, and [b]Department of Pediatrics, Columbia University College of Physicians and Surgeons, New York, New York; [c]Departments of Environmental Health Sciences, [h]Epidemiology, and [e]Data Coordinating Center, Mailman School of Public Health, Columbia University, New York, New York; [f]Institute for Social and Economic Research and Policy, Columbia University, New York, New York; [d]Division of Pediatric Pulmonology, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire; and [g]Lamont-Doherty Earth Observatory, Columbia University, Palisades, New York

KEY WORDS

asthma, allergy, exercise, emergency department, exercise-induced bronchoconstriction

ABBREVIATIONS

BC—black carbon
ED—emergency department
EIB—exercise-induced bronchoconstriction
EIW—exercise-induced wheeze
ETS—environmental tobacco smoke
FeNO—fractional exhaled nitric oxide
FEV_1—forced expiratory volume in 1 second
FVC—forced vital capacity
GEE—generalized estimating equation
GIS—geographic information system
HAPN—higher asthma prevalence neighborhood
IgE—immunoglobulin E
ISAAC—International Study of Asthma and Allergy in Childhood
LAPN—lower asthma prevalence neighborhood
NO—nitric oxide
PR—prevalence ratio
SES—socioeconomic status
UHF—United Hospital Fund

(Continued on last page)

WHAT'S KNOWN ON THIS SUBJECT: The prevalence of asthma and associated urgent medical visits vary dramatically across neighborhoods in New York City. Some, but not all, children with asthma wheeze when they exercise.

WHAT THIS STUDY ADDS: Exercise-induced wheeze was more common for asthmatic children living in neighborhoods with higher versus lower asthma prevalence. Because exercise-induced symptoms indicate a propensity for rapid-onset symptoms, this increased prevalence may contribute to the observed increase in urgent medical visits.

abstract

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OBJECTIVE: Exercise-induced wheeze (EIW) may identify a distinct population among asthmatics and give insight into asthma morbidity etiology. The prevalence of pediatric asthma and associated urgent medical visits varies greatly by neighborhood in New York City and is highest in low-income neighborhoods. Although increased asthma severity might contribute to the disparities in urgent medical visits, when controlling for health insurance coverage, we previously observed no differences in clinical measures of severity between asthmatic children living in neighborhoods with lower (3%–9%) versus higher (11%–19%) asthma prevalence. Among these asthmatics, we hypothesized that EIW would be associated with urgent medical visits and a child's neighborhood asthma prevalence.

METHODS: Families of 7- to 8-year-old children were recruited into a case-control study of asthma through an employer-based health insurance provider. Among the asthmatics (n = 195), prevalence ratios (PRs) for EIW were estimated. Final models included children with valid measures of lung function, seroatopy, and waist circumference (n = 140).

RESULTS: EIW was associated with urgent medical visits for asthma (PR, 2.29; P = .021), independent of frequent wheeze symptoms. In contrast to frequent wheeze, EIW was not associated with seroatopy or exhaled NO, suggesting a distinct mechanism. EIW prevalence among asthmatics increased with increasing neighborhood asthma prevalence (PR, 1.09; P = .012), after adjustment for race, ethnicity, maternal asthma, environmental tobacco smoke, household income, and neighborhood income.

CONCLUSIONS: EIW may contribute to the disparities in urgent medical visits for asthma between high- and low-income neighborhoods. Physicians caring for asthmatics should consider EIW an indicator of risk for urgent medical visits. *Pediatrics* 2013;131:e127–e135

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Patterns of asthma symptoms are important to understanding the etiology and treatment of the disease.[1,2] Exercise-induced bronchoconstriction (EIB) and exercise-induced wheeze (EIW) are common among asthmatics, with estimates that 40% to 90% of asthmatics have symptoms with exercise.[3] With EIB, drying and cooling of the mucosa after brief exercise cause rapid bronchoconstriction through release of inflammatory mediators including histamine and leukotrienes.[4,5] Although different entities, EIB may cause the symptoms that occur with EIW for many asthmatics. Although EIW is often described as a phenotype of asthma,[2,6,7] it may be simply a discrete clinical expression of asthma.[8] EIW among mild asthmatics has been implicated in >40 deaths during sporting activities between 1993 and 2000.[9] Therefore, EIW may represent a clinically relevant asthma phenotype defined by a rapid onset of symptoms.

In New York City, the range in pediatric asthma prevalence (3%–19%) among neighborhoods is striking.[10] The frequency of associated urgent medical visits varies even more dramatically; emergency department (ED) visits for asthma are up to 20 times more common in lower than in higher socioeconomic status (SES) neighborhoods.[10,11] Differences in asthma severity could explain these differences in urgent medical visits. However, after controlling for health insurance coverage among a middle-income population of 7- to 8-year-old asthmatics, we observed no difference in clinical indicators of asthma severity (lung function, exhaled nitric oxide [NO], and frequency of wheeze) between children living in higher versus lower asthma prevalence neighborhoods (LAPNs).[12,13] Although neighborhood SES was associated with urgent medical visits,[13] we considered the possibility that an underlying biological determinant of these differences might also be involved. An asthma phenotype associated with rapid-onset exacerbations, like EIW, might increase a child's risk for an urgent medical visit for asthma. We hypothesized that EIW would be associated with urgent medical visits, independent of clinical indicators of asthma severity, and with the prevalence of asthma in a child's neighborhood. To minimize heterogeneity in potential confounders such as access to health care and household income, we tested this hypothesis among the children described previously,[12–14] a group of middle-income asthmatic children living throughout New York City neighborhoods.

METHODS

The NYC Neighborhood Asthma and Allergy Study is a case-control study of children with and without asthma described previously.[12–14] Parents of 7- to 8-year-old children were recruited through the Health Insurance Plan of New York, a provider used primarily by a middle-income population. Neighborhoods were selected based on United Hospital Fund (UHF) level (several zip codes) asthma prevalence among 5-year-olds as reported by the New York City Department of Health and Mental Hygiene.[10] All LAPNs (3%–9%) and higher asthma prevalence neighborhoods (HAPNs; 11%–19%) in the Bronx, Brooklyn, Queens, and Manhattan were selected for recruitment by mail.

A caregiver completed a detailed questionnaire on the child's health, the family's demographics, and environmental tobacco smoke (ETS) exposure. Parents were questioned about how many hours per week their child exercised or played sports. During the home visit, spirometry, fractional exhaled NO (FeNO) testing, and waist circumference measurements were conducted, serum was collected for total and allergen specific immunoglobulin E (IgE), and settled dust and airborne particulate matter were collected (details, online supplement). Columbia University's Institutional Review Board approved this study.

Asthma Case Definition, Exercise-Induced Wheeze, and Frequent Wheeze

Asthma cases were defined by questionnaire, including the modules from the International Study of Asthma and Allergy in Childhood (ISAAC). Children were classified as asthmatic if their caregiver reported at least 1 of the following for the child in the past 12 months: (1) wheeze, (2) being awakened at night by cough without having a cold, (3) wheeze with exercise, or (4) report of medication use for asthma. Children not meeting the asthma definition were excluded from the current analyses.

The following outcomes also were reported for the previous 12 months. Exercise-induced wheeze (EIW) was defined as an affirmative response to questions about (1) wheezing after running or active play and/or (2) child's chest sounding wheezy during or after exercise. Frequent wheeze was defined as ≥4 episodes of wheeze. Urgent medical visits were defined as a positive response to questions about taking the child either to the doctor in a hurry or to the ED due to breathing difficulties.

Neighborhood Variables

Children's home addresses were geocoded and linked to a geographic information system (GIS) demographic database described previously.[12,15] A child's local neighborhood was assigned the demographic characteristics of households in the 500-m radius surrounding the home. Additional built environment variables related to air pollution sources are described in

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the online supplement. Each child was assigned a neighborhood asthma prevalence based on the UHF level asthma prevalence described earlier.[10]

Statistical Analysis

FeNO and total IgE were log-normally distributed; we used natural log-transformed values in the analyses. GIS variables were not normally distributed and thus were compared by using nonparametric tests. Prevalence ratios (PRs) were calculated by using generalized estimating equation (GEE) models with UHF used as a cluster variable because the neighborhood asthma prevalence was available at the UHF level. Variables conventionally considered as potential confounders were included in the multivariable models including gender, race, Hispanic ethnicity, maternal asthma, ETS, neighborhood income, and material hardship.[16] Sensitivity analyses of the association between neighborhood asthma prevalence and EIW are described in the online supplement. Data were analyzed in SPSS version 17 (SPSS, Inc, Chicago, IL) and visualized in R version 2.14.0.

RESULTS

There were 195 children classified as asthmatic who had a blood sample, 95 and 100 in LAPN and HAPN, respectively (Fig 1). Among those, valid lung function and FeNO were available on 166 (eg, 85%) and 167 (86%) children, respectively. Waist circumference was not measured in the first 25 children and was thus available on 170 (87%) children. A complete set of data for multivariable models including lung function, household income, and waist circumference was available on 140 children.

Asthmatics in the LAPN and HAPN had similar demographics, except for differences in Asian and mixed races, Hispanic ethnicity, report of seeing cockroaches or mice, and the presence of a smoker in their home (Table 1). As reported previously, there were no differences in clinical measures of asthma severity (lung function, FeNO, symptom frequency) or seroatopy (measureable IgE to at least 1 inhalant allergen) between asthmatics in the LAPN versus HAPN (Table 1).[13] The local neighborhoods (500 m surrounding the homes) differed in the proportions of households reporting African-American race and Hispanic ethnicity and median household income.

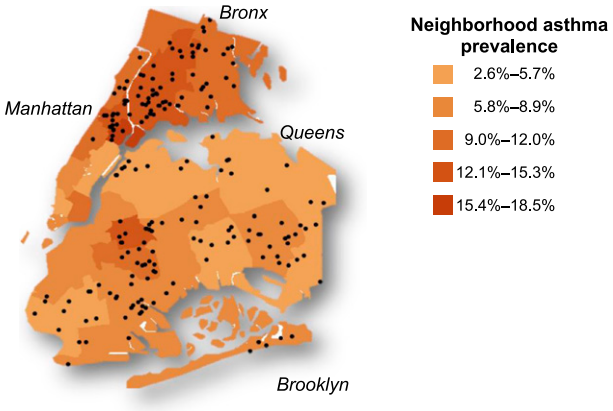

FIGURE 1
Map of New York City depicting study subjects' places of residence overlaying neighborhood asthma prevalence. Neighborhood asthma prevalence was defined for 5-year-old school children as reported by the New York City Department of Health and Mental Hygiene.[10] Participants were recruited from neighborhoods with lower (3%–9%) or higher (11%–18%) neighborhood asthma prevalence.

Wheeze, Urgent Medical Visits, and Medication Use

Among the children classified as asthmatic, 84/195 (43%) had a report of EIW, whereas frequent wheeze was less common (21%). Many but not all of the children with frequent wheeze also had EIW, whereas more than half of those children with EIW did not have frequent wheeze (Fig 2). Urgent medical visits for asthma in the past year were also common (26.7%) with 21.9% and 17.5% reporting taking their child to a doctor in a hurry and to the ED, respectively. In a multivariable model controlling for potential confounders, EIW (PR: 2.29 [1.13–4.63]; P = .021) and frequent wheeze (PR: 2.07 [1.12–3.84]; P = .020) were independently associated (same model) with urgent medical visits. In 2 similar models, EIW was associated with taking their child to the doctor in a hurry (PR: 2.62 [1.19–5.75]; P = .016) and borderline associated with ED visits for asthma (PR: 2.31 [0.95–5.63]; P = .066). Many asthmatics with EIW had used controller medications in the past year (42%) and a majority, but not all, had used short-acting bronchodilators (65%) in the past year. The association between EIW and urgent medical visits remained statistically significant (PR: 2.27 [1.11–4.63]; P = .024) after adjustment for use of preventative medications (1%, 16.5%, and 14.4% had taken long-acting β antagonist, inhaled or oral corticosteroids and leukotriene modifiers in the past year, respectively).

Comparing Clinical Features of EIW and Frequent Wheeze

To validate EIW as distinct from frequent wheeze, we examined the clinical features of these phenomenon, first in bivariate analyses (Fig 3) and then in adjusted models. In multivariable analyses with individual models for each clinical variable, after controlling for gender, race, and Hispanic ethnicity, EIW was associated with forced

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TABLE 1 Characteristics of the Study Participants and Their Neighborhood (n = 195)

	LAPN	HAPN	P
Child's demographics			
Boy (%)	59/95 (62.1)	53/100 (53.0)	.20
African-American race (%)[a]	43/95 (45.3)	55/100 (55.0)	.17
Asian race (%)[a]	16/95 (16.8)	2/100 (2.0)	<.001
White race (%)[a]	17/95 (17.9)	7/100 (7.0)	.021
Other/mixed race (%)[a]	15/95 (15.8)	34/100 (34.0)	.003
Hispanic ethnicity (%)[b]	24/95 (25.3)	45/100 (45.0)	.004
Mother's age (mean years)	38.4	35.3	<.001
Maternal asthma (%)	21/95 (22.1)	27/100 (27.0)	.43
Material hardship reported (%)[c]	26/94 (27.4)	29/100 (29.0)	.80
Mother has college degree (%)	37/94 (39.4)	31/98 (31.6)	.26
Household income (median)[d]	$50–60K	$40–45K	.077
Smoker in the home (%)	14/94 (14.9)	26/99 (26.3)	.051
Cockroach sightings not rare (%)	19/95 (20.0)	34/100 (34.0)	.028
Mouse sightings not rare (%)	6/95 (6.3)	15/100 (15.0)	.051
Clinical features			
Frequent wheeze past 12 mo (%)	18/95 (18.9)	22/100 (22.0)	.60
Controller medication past 12 mo (%)	19/94 (20.2)	31/100 (31.0)	.086
Bronchodilator past 12 mo (%)	52/94 (55.3)	51/100 (51.0)	.55
Seroatopy (%)[e]	58/95 (61.1)	61/100 (61.0)	.99
Total IgE (IU/mL, GM [95% CI])	111 [85.2–146]	98.9 [70.2–139]	.59
FeNO (ppb, GM [95% CI])[f]	10.4 [8.9–12.1]	10.5 [9.0–12.4]	.92
FEV_1/FVC (median [25% to 75%])[g]	0.88	0.87	.60
Waist circumference (cm, mean [95% CI])[h]	63.1 [61–65]	61.9 [60–63]	.32
Neighborhood demographics[i]			
African-Americans, median, %	28.8	45.9	.040
Hispanic, median, %	14.1	42.8	<.001
Households below federal poverty income, median, %	17.3	37.2	<.001
Median household income (median $ in 1000)	40.4	21.3	<.001
Adult population with high school degree, median, %	18.2	10.1	<.001

95% CI, 95% confidence interval; GM, geometric mean.

[a] Race was not reported for 4 (4.2%) and 2 (2.0%) of the children in the LAPN and HAPN, respectively.

[b] Whether the child was of Hispanic ethnicity was not reported for 1 (1.1%) and 5 (5.0%) of the children in the LAPN and HAPN, respectively.

[c] Mother reported that in the past 6 mo she and her family could not afford needed food, rent, clothing or medical care, or that gas/electricity was suspended because of bill nonpayment.[30]

[d] There were 5 families in each group that did not report household income.

[e] Seroatopy defined as serum IgE > 0.35 kIU to at least 1 of the tested allergens.

[f] Missing data for FeNO on 17 (18%) and 15 (15%) children because of high ambient NO in the home at the time of testing.

[g] Missing data for FEV_1/FVC on 18 (19%) and 11 (11%) of children.

[h] Missing data for waist circumference on 15 (16%) and 10 (10%).

i Neighborhood variables are defined for each of the study participant based on 2000 US Census data for the households in the 500 m surrounding the participant's home.

expiratory volume in 1 second/forced vital capacity FEV_1/FVC (as percent) (PR: 0.95 [0.92–0.99]; P = .010), but not with FeNO (PR: 1.21 [0.89–1.65]; P = .25) or total IgE (PR: 1.06 [0.92–1.22]; P = .43). In similar models, frequent wheeze was associated with FEV_1/FVC (PR: 0.94 [0.89–0.99]; P = .025), FeNO (PR: 2.21 [1.40–3.49]; P = .001), and total IgE (PR: 1.61 [1.29–2.00]; P < .001). Seroatopy was associated with frequent wheeze (PR: 3.55 [1.48–8.54]; P = .005) but not EIW (PR: 1.12 [0.76–1.92]; P = .41).

Neighborhood Asthma Prevalence and EIW

The prevalence of EIW increased with increasing neighborhood asthma prevalence in bivariate analyses (Fig 4A) and after adjustment for potential confounders (PR: 1.06 [1.003–1.13]; P = .040) including local neighborhood income. The prevalence of frequent wheeze was not associated with neighborhood asthma prevalence in bivariate analyses (Fig 4B) or in the multivariable model (PR: 0.93 [0.83–1.04]; P = .19). As we have described previously,[13] the prevalence of urgent medical visits modestly increased with increasing asthma prevalence, although this was not statistically significant (Fig 4C). In the multivariable model, local neighborhood income (PR: 0.96 [0.93–0.998]; P = .039) and not neighborhood asthma prevalence (PR: 0.99 [0.90–1.09]; P = .84]) was associated with urgent visits and a similar association was observed with ED visits as the outcome (data not shown).

Stratification by Seroatopy, Sensitivity Analyses, and Report of Exercise

In multivariable models, neither lung function nor neighborhood asthma prevalence was associated with prevalence of EIW among the nonseroatopic asthmatics, although waist circumference trended toward a positive but not statistically significant association (Table 2). Among seroatopic children, both lung function and neighborhood asthma prevalence were independently associated with EIW. The association between neighborhood asthma prevalence and EIW was not altered (<10% change in PR) by stepwise inclusion of previously reported measures and estimations of allergens and combustion byproducts in or around the child's homes (Supplemental Table 3). Median reported time spent exercising or playing sports did not differ significantly (P > .05) between children in HAPN versus LAPN or between children with or without EIW or urgent visits (all medians 4–5 hours per week). Also, the frequency of children with limited exercise or sports (<1 hour per week) did not differ by neighborhood or report of symptoms (data not shown).

DISCUSSION

Among middle-income asthmatic children with the same health insurance provider, the proportion of asthmatics

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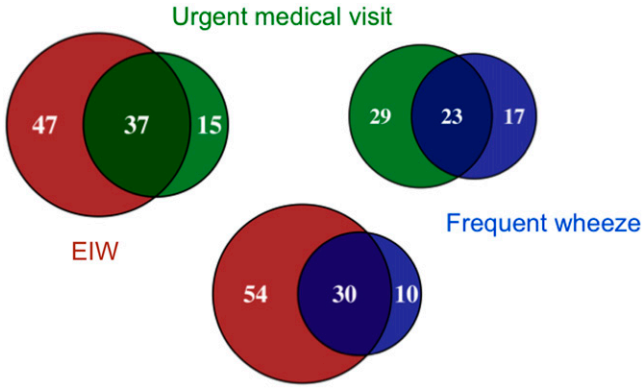

FIGURE 2
Venn diagrams depicting overlap in frequent wheeze, EIW, and urgent medical visits for asthma. There were 89/195 asthmatics who had no report of EIW, frequent wheeze, or urgent medical visits and thus not depicted in this figure.

with a report of EIW increased with increasing asthma prevalence in the child's neighborhood. These findings were robust in models adjusting for potential confounders and indicators of asthma severity. EIW and frequent wheeze symptoms were independently associated with urgent medical visits. These findings are intriguing because (1) EIW is an indicator of rapid-onset exacerbation, (2) there is an excess of urgent medical visits among asthmatics living in neighborhoods with higher asthma prevalence, and (3) urgent medical visits could be triggered by any rapid-onset exacerbation.

These results build on our previously observed associations between neighborhood income and urgent medical visits in this study population that reinforced the established dogma that urgent medical visits (eg, to the ED) for asthma in lower-income neighborhoods have socio-demographic determinants.[13] Our findings also support a novel hypothesis: higher prevalence of an asthma phenotype, defined by rapid-onset symptoms, could provide an underlying biological mechanism for the higher frequency of urgent medical visits in HAPNs.

The authors of other studies have examined the associations of specific triggers with slow- versus rapid-onset asthma exacerbations. Although viral infections are thought to trigger a majority of asthma exacerbations in children,[17] upper respiratory infections have been associated with slower onset exacerbations.[18] In contrast, allergen exposure and exercise have been associated with more rapid onset.[19] An explanation for the rapid onset of symptoms with EIW lies in the mechanism of airway hyperresponsiveness, with release of bronchoconstrictive mediators from inflammatory cells upon rewarming and rehydration of the airway after exercise.[5] A previous study in children demonstrated that an exercise challenge can increase subsequent airway hyperresponsiveness to allergens.[20] Although we did not determine whether exercise was the trigger for the exacerbations leading to the urgent medical visits, our findings combined with those revealing susceptibility to allergen challenge after exercise[20] suggest that a report of EIW may be an indicator of a rapid-onset phenotype that could be aggravated by other extrinsic exposures.

It is likely that the EIW phenotype and socio-demographic determinants could act together and lead to urgent medical visits. Repeat ED visits for asthma have been associated with families lacking confidence in the efficacy of asthma medications and not using criteria in deciding to seek emergency care.[21,22] The proportion of children with EIW in this study who had taken controller medications in the past year (41%) may be consistent with current National Heart, Lung, and Blood Institute guidelines, or even high, given their relatively mild disease.[6] However, one-third of children with an EIW episode in the past year had not used a bronchodilator, which is not in keeping with current guidelines. A rapid-onset exacerbation combined with a parent incorrectly treating their child's symptoms could result in an urgent medical visit. Collectively, these findings suggest that physicians treating even mild asthmatics should consider EIW as a risk for urgent medical visits and provide appropriate education and medication.

The overall goal of the New York City Neighborhood Asthma and Allergy Study is to better understand neighborhood disparities in asthma prevalence and morbidity. Allergens and combustion byproducts are 2 types of exposures that we and others have hypothesized contribute to these disparities.[23] In support of these hypotheses, we demonstrated the relevance of both cockroach allergen and airborne black carbon (BC) to allergy and airway inflammation among the children in this cohort.[12,14] Other studies have revealed that exercise can modify the effect of air pollutants, including BC, on asthma outcomes.[24,25] We examined whether allergen or combustion byproduct exposures partially explained the association between neighborhood and EIW (Supplemental Table 3). Despite testing a comprehensive set of both measured and modeled estimations of exposures, we were unable to show any associations with EIW or that exposures substantially diminished the association between neighborhood asthma prevalence and

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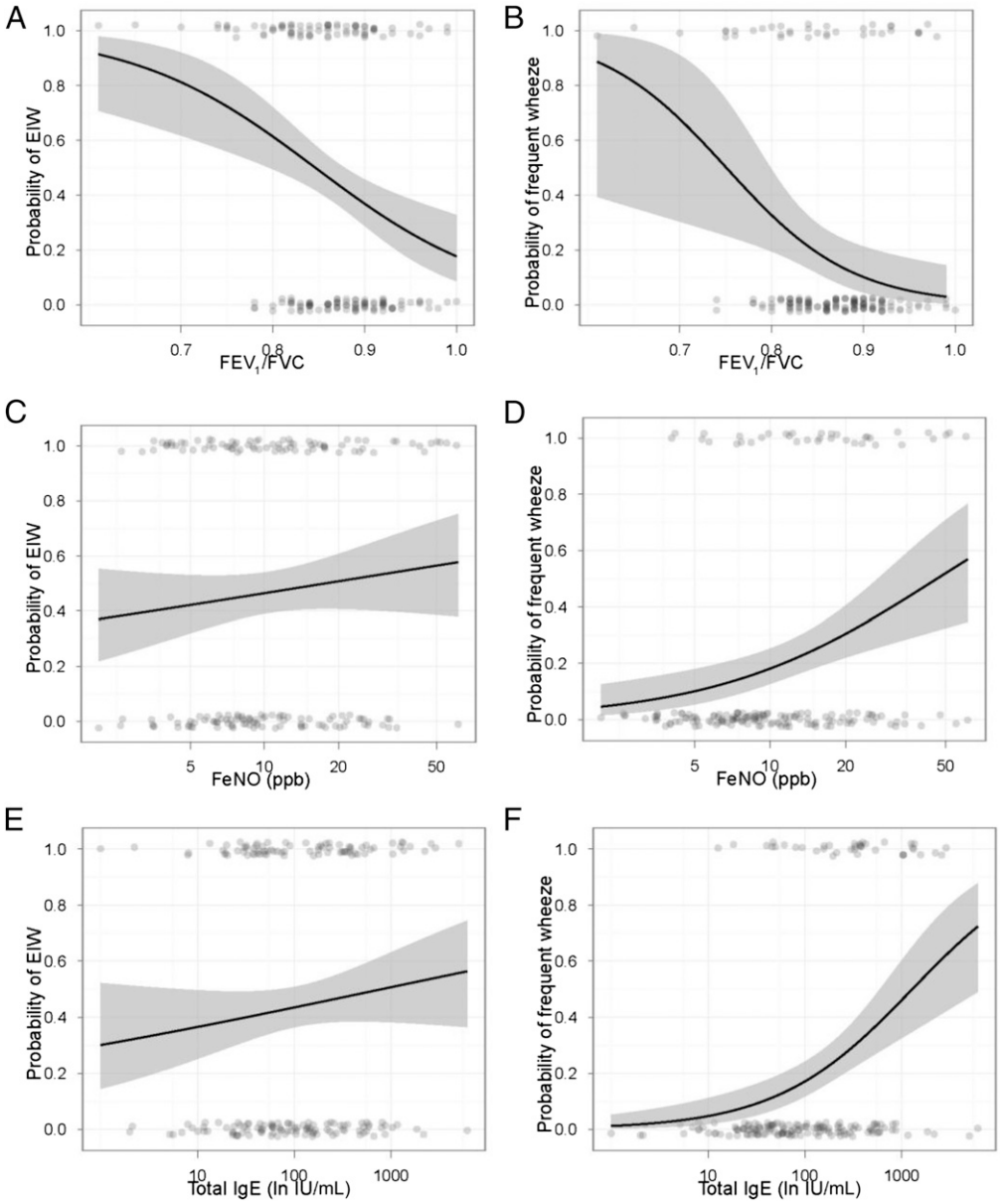

FIGURE 3

Logistic regression lines for univariate analyses are depicted in black with 95% confidence intervals in gray. *P* values are for the univariate logistic regressions. A, EIW with FEV_1/FVC ($P < .001$); B, frequent wheeze with FEV_1/FVC ($P = .018$); C, EIW with FeNO ($P = .21$); D, frequent wheeze with FeNO ($P < .001$); E, EIW with total IgE ($P = .22$); F, frequent wheeze with total IgE ($P = .001$). Probability of EIW (A, C, D) and frequent wheeze (B, E, F) with FEV_1/FVC (A and B), FeNO (C and D), and total IgE (E and F).

EIW. Future studies into the cause of the higher prevalence of EIW in HAPNs (eg, environment, stress) could lead to a better understanding of the etiology of urban asthma.

Despite overlap, EIW appeared to represent a phenotype with clinical outcomes that differed from those of frequent wheeze. Poorer lung function was associated with both outcomes, but FeNO and total IgE concentrations, traditional biomarkers of inflammation and atopy, although associated with frequent wheeze, were not associated with EIW. In our study, FeNO and total IgE were higher among asthma cases in general[12] and among those cases with EIW (data not shown), than among controls, as others have observed.[26] However, unlike frequent wheeze, FeNO and total IgE did not differ among asthmatics with and without EIW.

We did observe modest differences in risk patterns for EIW among children with and without seroatopy. Among the nonseroatopic asthmatics, there was an (statistically nonsignificant) association between EIW and waist circumference but no association with lung function. This lack of association

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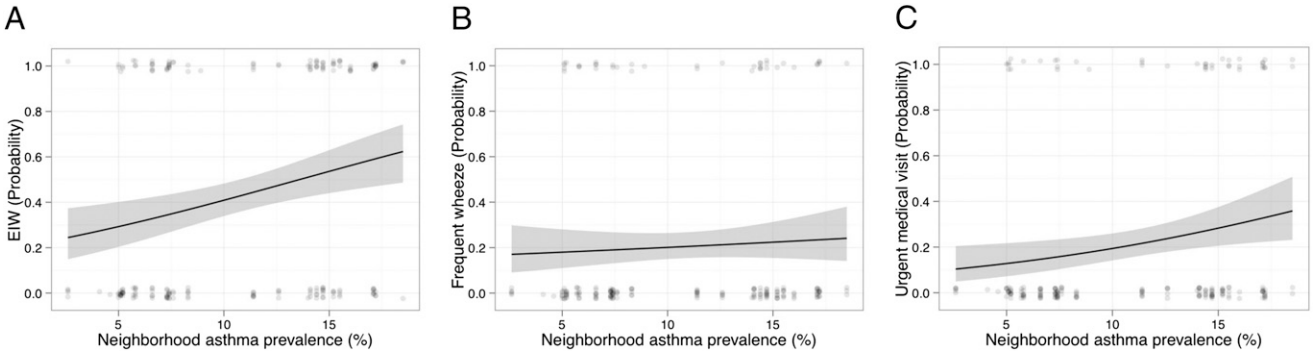

FIGURE 4
Logistic regression lines for the univariate analyses in black with 95% confidence in gray. *P* values are for the univariate logistic regression. A, EIW (*P* = .011); B, frequent wheeze (*P* = .054); C, urgent medical visit (*P* = .098).

TABLE 2 Multivariable PRs for EIW

	Overall[a] (*n* = 140)[b]	Nonatopic (*n* = 52)	Atopic (*n* = 88)
FEV_1/FVC	0.96 (0.92–0.997); *P* = .037	1.02 (0.92–1.13); *P* = .75	0.94 (0.89–0.99); *P* = .022
Abdominal circumference	1.01 (0.98–1.04); *P* = .40	1.05 (0.99–1.12); *P* = .11	1.01 (0.97–1.04); *P* = .67
Neighborhood asthma prevalence	1.09 (1.02–1.16); *P* = .012	1.09 (0.93–1.28); *P* = .27	1.09 (1.01–1.17); *P* = .024

[a] PRs calculated by using a GEE model with community district used as a cluster variable, adjusted for gender, race, Hispanic ethnicity, maternal asthma, ETS, neighborhood income, and material hardship.
[b] Sample size restricted based on complete information from cases.

among this group suggests that deconditioning may explain some of the dyspnea in the nonseroatopic asthmatic children, not EIW, which has been reported previously to be associated with obesity.[27] But a recent study demonstrating associations between EIW and leptin and adiponectin in serum also lends support to the idea that EIW may have multiple etiologies.[28] Neighborhood asthma prevalence was only a statistically significant predictor of EIW among the seroatopic asthmatics; however, whether the risk conferred by living in neighborhoods is really modified by seroatopy or if the relatively small sample size among the nonseroatopics led to type-2 error remains to be determined.

This study has several limitations. First, because the recruitment method was designed to reduce heterogeneity in health care access and household income, our participants are not fully representative of their neighborhoods. However, the health plan through which they were recruited has observed neighborhood differences in physician-diagnosed asthma among its members that are consistent geographically with those observed by the New York City Department of Health. Therefore, these children should be representative of middle-income children with employer-based health insurance. Second, we did not measure EIB. Although an objective measure of bronchoconstriction would have strengthened the findings, the ISAAC question assessing EIW has been shown to be predictive of EIB among 7-year-olds.[27,29] Also, although our question about EIW came from the internationally validated ISAAC questionnaire to allow for comparison with the many other studies that have employed this questionnaire, we did not ask about other symptoms of bronchial hyperreactivity after exercise (eg, cough, chest tightness) that could manifest in the absence of wheeze. Therefore, we may have underestimated the prevalence of exercise-associated asthma symptoms among these children. Third, the cross-sectional design of the study did not allow us to evaluate the temporality of medication usage and urgent medical visits or the impact of previous controller medication use on EIW prevalence. Fourth, this population-based study included primarily asthmatics with only a few exacerbations in the previous year, preventing generalizability to asthmatic populations with more severe asthma. Finally, neighborhood differences in access to physical activity or limitation in physical activity because of previous exacerbations could have confounded our findings. However, we did not observe differences in the report of exercise by neighborhood or EIW symptoms, and the density of parks around the child's home was not associated with EIW.

CONCLUSIONS

In a relatively homogenous, middle-income pediatric asthmatic population, EIW was more commonly reported for children living in New York City neighborhoods with higher versus lower asthma prevalence. EIW was significantly associated with urgent medical visits among these children, independent of measures of asthma

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severity or neighborhood income. Because exercise-induced symptoms indicate a propensity for rapid-onset exacerbation, the increased prevalence of EIW may be contributing to the observed increase in urgent medical visits. Therefore, the presence of EIW may be useful to pediatric practitioners to identify children at risk for urgent medical visits. Practitioners then may apply appropriate interventions, such as a primary care asthma evaluation, comprehensive asthma education, and medical treatment (eg, bronchodilators and leukotriene modifiers used before exercise, and/or other medications to improve asthma control).

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Dr Mainardi contributed to the acquisition, analyses and interpretation of data, and was involved in drafting, revising, and final approval of the article; Dr Mellins contributed to the conception and design of the study, analyses and interpretation of data, and was involved in revising and final approval of the article; Dr Miller contributed to the conception and design of the study, analyses and interpretation of data, and was involved in revising and final approval of the article; Dr Acosta contributed to the acquisition, analyses and interpretation of data, and was involved in drafting, revising, and final approval of the article; Dr Cornell contributed to the interpretation of data and was involved in revising and final approval of the article; Dr Hoepner contributed to the acquisition, analyses and interpretation of data, and was involved in revising and final approval of the article; Dr Perera contributed to the conception and design of the study and was involved in revising and final approval of the article; Mr Quinn contributed to the acquisition, analyses and interpretation of data, and was involved in revising and final approval of the article; Dr Yan contributed to the acquisition, analyses and interpretation of data, and was involved in revising and final approval of the article; Dr Chillrud contributed to the conception and design of the study and was involved in revising and final approval of the article; Mr Olmedo contributed to the acquisition of data and was involved in revising and final approval of the article; Dr Goldstein contributed to the conception and design of the study, analyses and interpretation of data, and was involved in revising and final approval of the article; Dr Rundle contributed to the conception and design of the study, analyses and interpretation of data, and was involved in revising and final approval of the article; Dr Jacobson contributed to the conception and design of the study, analyses and interpretation of data, and was involved in revising and final approval of the article; and Dr Perzanowski contributed to the conception and design of the study, analyses and interpretation of data, and was involved in drafting, revising, and final approval of the article.

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Address correspondence to Matthew S. Perzanowski, PhD, Department of Environmental Health Sciences, 722 W 168th St, 11th Floor, New York, New York 10032. E-mail: mp2217@columbia.edu

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Exercise-Induced Wheeze, Urgent Medical Visits, and Neighborhood Asthma Prevalence

Timothy R. Mainardi, Robert B. Mellins, Rachel L. Miller, Luis M. Acosta, Alexandra Cornell, Lori Hoepner, James W. Quinn, Beizhan Yan, Steven N. Chillrud, Omar E. Olmedo, Frederica P. Perera, Inge F. Goldstein, Andrew G. Rundle, Judith S. Jacobson and Matthew S. Perzanowski

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Supplemental Information

Exercise-Induced Wheeze, Urgent Medical Visits, and Neighborhood Asthma Prevalence

METHODS

Clinical Measurements

IgE antibodies against German cockroach, mouse urine, *Dermatophagoides farinae*, cat dander, dog dander, common ragweed, mixed tree pollen (Tx8), and mixed grass pollen (Gx2) were measured in serum by ImmunoCAP (Phadia, Uppsala, Sweden).[14] Seroatopy was defined as IgE $\geq$ 0.35 IU/mL against any allergen tested.

Pulmonary function tests (PFTs) were conducted by using a spirometer (Koko, nSpire Health, Longmont, CA). PFTs were scored based on acceptability criteria developed by study pulmonologists according to American Thoracic Society guidelines described previously. FEV_1/FVC was selected as the primary outcome.[12]

FeNO and ambient NO measurements were collected by the offline method described previously.[12,31] Breath samples were considered valid only if (1) the child exhaled at a consistent, correct flow and (2) either the child inhaled correctly through the NO sampling device filter or the ambient NO was <20 ppb. Samples collected when the ambient NO exceeded 100 ppb were excluded regardless of proper inhalation.[12]

We identified the child's waist by palpating the iliac crest. The circumference was measured during normal expiration with a flexible, cloth tape

SUPPLEMENTAL TABLE 3 Sensitivity Analyses of the Association Between Neighborhood Asthma Prevalence and EIW (n = 169)

	PRs for EIW[a,b]	
	Exposure Variable	Neighborhood Asthma Prevalence
Without exposure variable	—	1.08 (1.01-1.15)[c]
Bed dust allergens (μg/g)[d]		
Cockroach (Bla g 2)	0.97 (0.79–1.18)	1.08 (1.01–1.15)[c]
Mouse (Mus m 1)	1.03 (0.91–1.15)	1.08 (1.01–1.15)[c]
Dust mite (Der f 1)	0.93 (0.76–1.14)	1.08 (1.02–1.15)[c]
Cat (Fel d 1)	0.90 (0.76–1.07)	1.08 (1.02–1.15)[c]
Dog (Can f 1)	1.00 (0.88–1.15)	1.08 (1.01–1.15)[c]
Indoor airborne particulate matter[e]		
PM2.5 (ng/m^3)	0.99 (0.67–1.44)	1.08 (1.01–1.15)[c]
BC (ng/m^3)	1.19 (0.75–1.88)	1.07 (1.01–1.14)[c]
Community average outdoor air pollution[f]		
PM2.5 (μg/m^3)	1.00 (0.70–1.42)	1.08 (1.01–1.15)[c]
Elemental carbon (abs)	0.96 (0.17–5.4)	1.08 (1.00–1.16)
Nitrogen dioxide (ppb)	0.98 (0.91–1.06)	1.08 (1.01–1.15)[c]
Sulfur dioxide (ppb)	1.01 (0.89–1.16)	1.07 (1.00–1.1)]^c
Ozone (ppb)	0.96 (0.85–1.09)	1.08 (1.01–1.14)[c]
GIS estimated variables for surrounding 500 m[g]		
Truck route density (km/km^2)	1.02 (0.87–1.19)	1.07 (1.01–1.15)[c]
Street density (km/km^2)	1.01 (0.94–1.08)	1.08 (1.01–1.15)[c]
Traffic density	1.00 (1.00–1.00)	1.07 (1.01–1.14)[c]
Distance to major highway (m)[h]	1.00 (0.80–1.27)	1.08 (1.01–1.15)[c]
Residential buildings burning residual oil[i]	1.00 (0.99–1.01)	1.07 (1.01–1.14)[c]
Density of parks[j]	1.52 (0.13–17.5)	1.07 (1.01–1.15)[c]

[a] Sample size was restricted to those study subjects that had a complete set of variables for the exposure variables and potential confounding variables included in the models.
[b] PRs calculated by using a GEE model with community district used as a cluster variable, adjusted for gender, race, Hispanic ethnicity, maternal asthma, ETS, neighborhood income, and material hardship.
[c] $P < .05$.
[d] Allergens were measured in the child's bed dust as described previously.[14]
[e] Fine particulate matter (PM2.5) and BC in the PM2.5 were measured in air samples collected for 7 d after the home visit.[12,32]
[f] Reported by the New York City Community Air Survey at the UHF level (ie, several zip codes).[34]
[g] Geographic information system estimates for densities of traffic related measurements in the 500 m surrounding the child's home as described previously.[12]
[h] Distance in meters to the nearest major highway (A1) rather than a density variable.
[i] Buildings burning residual oil (#4 or #6) as described previously.[12]
[j] Density of parks as percentage land in the 500-m radius of the home.

measure wrapped around midaxillary line.

Bed Dust Allergens

Dust samples were collected during home visits by vacuuming the upper half of the fitted sheet and both sides of the pillows from the child's bed by using a Duststream collector (Indoor Biotechnologies, Charlottesville, NC) for 3 minutes as described previously.[14] Bed dust samples were extracted by using Phosphate buffered saline 0.05% Tween, pH 7.4, at a concentration of 50 mg/mL and stored at −20°C until analysis. Der f 1 Fel d 1, Can f 1, and Mus m 1 were measured by using multiplex bead immunoassays. Bla g 2 was measured by enzyme-linked immunosorbent assay (Indoor Biotechnologies). All results are based on the universal allergen standard curve. For results below the limit of detection (LOD), we used values of 1/2 the LOD. LODs and coefficients of variance for duplicates are described in a previous publication.[14]

Indoor Air Particulate Matter

Fine particulate matter was collected in the child's home by sampling air at 1.5 mL/minute for the 7 days after the home visit during which the clinical measures were assessed as described previously.[12] BC was quantified on filters by using multiwavelength optical absorption technique.[32]

New York City Neighborhood Level Outdoor Pollution

In partnership with Queens College, the New York City Department of Health conducted the New York City Community Air Survey. During 2008 and 2009, 150 outdoor air-monitoring stations were places throughout New York City to measure ozone, nitrogen oxides, elemental carbon, particulate matter, and sulfur dioxide. UHF level (UHF level = several zip codes) annual average concentrations from this data were made publically available by the New York City Department of Health and Mental Hygiene.[33] These average concentrations were linked to the study subject's home address by zip code.

Local Neighborhood Estimated Variables

The subject's residential school addresses were geo-coded by using Geosupport and LION geocoding services GIS as previously described.[12] For those used in this article, variables were created for the 500-m radius surrounding the child's home. Neighborhood variables included average daily traffic variables (number of vehicles per area), truck density as a marker of diesel combustion byproduct exposure (density of truck routes per measured area), use of #4 and #6 heating oil (count of oil burners by oil burner type per measured area), and access to parks or green space (percent of neighborhood definition that is covered by parks or green spaces).

Sensitivity Analyses Models

The purpose of testing the sensitivity analyses models was to determine whether estimations of exposure to allergens or combustion byproducts were associated with EIW or if adjustment for these exposure variables decreased the effect size of the estimated association between neighborhood asthma prevalence and EIW. As described for the main analyses, PRs were calculated by using a GEE model with UHF used as a cluster variable. Variables conventionally considered as potential confounders or covariates were included in the multivariable model, including gender, race, Hispanic ethnicity, maternal asthma, ETS, neighborhood income, and material hardship. Lung function and waist circumference were not included because inclusion of these variables reduced the sample size. The estimated PR for neighborhood asthma prevalence and EIW in the model that included lung function and waist circumference (PR = 1.09 [1.02–1.16], Table 2) was similar to that estimated without those variables (PR = 1.08 [1.01–1.15], Supplemental Table 3).