Obesity may enhance the adverse effects of NO_2 exposure in urban schools on asthma symptoms in children

Perdita Permaul, MD,[a,b] Jonathan M. Gaffin, MD, MMsc,[c,d] Carter R. Petty, MA,[e] Sachin N. Baxi, MD,[f,d] Peggy S. Lai, MD, MPH,[d,g,h] William J. Sheehan, MD,[i,j] Carlos A. Camargo, Jr, MD, DrPH,[d,k] Diane R. Gold, MD, MPH,[g,l] and Wanda Phipatanakul, MD, MS[f,d]

New York, NY, Boston, Mass, and Washington, DC

Background: Sparse data address the effects of nitrogen dioxide (NO_2) exposure in inner-city schools on obese students with asthma.

Objective: We sought to evaluate relationships between classroom NO_2 exposure and asthma symptoms and morbidity by body mass index (BMI) category.

Methods: The School Inner-City Asthma Study enrolled students aged 4 to 13 years with asthma from 37 inner-city schools. Students had baseline determination of BMI percentile. Asthma symptoms, morbidity, pulmonary inflammation, and lung function were monitored throughout the subsequent academic year. Classroom NO_2 data, linked to enrolled students, were collected twice per year. We determined the relationship between classroom NO_2 levels and asthma outcomes by BMI stratification.

Results: A total of 271 predominantly black (35%) or Hispanic students (35%) were included in analyses. Fifty percent were normal weight (5-84th BMI percentile), 15% overweight (≥85-94th BMI percentile), and 35% obese (≥95th BMI percentile). For each 10-parts per billion increase in NO_2, obese students had a significant increase in the odds of having an asthma symptom day (odds ratio [OR], 1.86; 95% CI, 1.15-3.02) and in days caregiver changed plans (OR, 4.24; 95% CI, 2.33-7.70), which was significantly different than normal weight students who exhibited no relationship between NO_2 exposure and symptom days (OR, 0.90; 95% CI, 0.57-1.42; pairwise interaction $P = .03$) and change in caregiver plans (OR, 1.37; 95% CI, 0.67-2.82; pairwise interaction $P = .02$). Relationships between NO_2 levels and lung function and fractional exhaled nitric oxide did not differ by BMI category. If we applied a conservative Holm-Bonferroni correction for 16 comparisons (obese vs normal weight and overweight vs normal weight for 8 outcomes), these findings would not meet statistical significance (all $P > .003$).

Conclusions: Obese BMI status appears to increase susceptibility to classroom NO_2 exposure effects on asthma symptoms in inner-city children. Environmental interventions targeting indoor school NO_2 levels may improve asthma health for obese children. Although our findings would not remain statistically significant after adjustment for multiple comparisons, the large effect sizes warrant future study of the interaction of obesity and pollution in pediatric asthma. (J Allergy Clin Immunol 2020;■■■:■■■-■■■.)

Key words: *Asthma, obesity, body mass index, BMI, inner-city, urban, school, nitrogen dioxide, NO_2, children, environment, exposure, indoor, pollutant, air*

Obesity and asthma are 2 chronic childhood diseases that have shown a striking surge in prevalence over the past 2 decades,[1,2] particularly in inner-city children. Obesity rates are higher among Hispanic children (25.8%) and black children (22%) than among their white (14.1%) and Asian (11.0%) counterparts.[1] Similarly, urban populations suffer a disproportionately higher rate of asthma prevalence and morbidity.[3-5] A number of studies have demonstrated greater asthma severity in inner-city children with asthma, translating into higher amounts of medication to achieve asthma control, poor response to medication, and greater health care use.[6] Epidemiologically, there is a higher incidence and severity of asthma in obese populations, leading many to investigate the link between these 2 conditions.[7]

Several theories have been proposed to explain the connection between obesity and asthma risk. They have included resistance

From [a]the Division of Pediatric Pulmonology, Allergy and Immunology, New York-Presbyterian/Weill Cornell Medicine, New York; [b]Weill Cornell Medical College, New York; [c]the Division of Pulmonary Medicine, Boston Children's Hospital, Boston; [d]Harvard Medical School, Boston; [e]the Clinical Research Center, Boston Children's Hospital, Boston; [f]the Division of Allergy and Immunology, Boston Children's Hospital, Boston; [g]the Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston; [h]the Division of Pulmonary and Critical Care, Massachusetts General Hospital, Boston; [i]the Division of Allergy and Immunology, Children's National Health System, Washington; [j]George Washington University School of Medicine, Washington; [k]the Department of Emergency Medicine, Massachusetts General Hospital, Boston; and [l]Channing Division of Network Medicine, Brigham and Women's Hospital, Boston.

This research is supported by the National Institutes of Health (grant nos. R01 AI 073964, U01 AI 110397, and K24 AI 106822 [PI, W.P.], grant no. K23 AI 123517 [PI, P.P], grant no. R01 ES 030100 [PI, J.M.G.], grant no. R01 AI 144119 [PI, P.S.L.], and grant no. K23 AI 104780 [PI, W.J.S.]). Funding was provided by The Allergy and Asthma Awareness Initiative, Inc. This work was conducted with support from Harvard Catalyst | The Harvard Clinical and Translational Science Center (National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health Award UL1 TR001102) and financial contributions from Harvard University and its affiliated academic health care centers. The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University and its affiliated academic health care centers, or the National Institutes of Health.

Disclosure of potential conflict of interest: W. Phipatanakul is a consultant advisory for Teva, Genentech, Novartis, GlaxoSmithKline, and Regeneron, for asthma-related therapeutics. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication October 7, 2019; revised February 26, 2020; accepted for publication March 9, 2020.

Corresponding author: Wanda Phipatanakul, MD, MS, Division of Allergy and Immunology, Boston Children's Hospital, 300 Longwood Ave, Boston, MA 02115. E-mail: wanda.phipatanakul@childrens.harvard.edu.

0091-6749/$36.00

https://doi.org/10.1016/j.jaci.2020.03.003

Abbreviations used
BMI: Body mass index
FENO: Fraction of exhaled nitric oxide
FVC: Forced vital capacity
NO: Nitric oxide
NO_2: Nitrogen dioxide
OR: Odds ratio
ppb: Parts per billion
SICAS: School Inner-City Asthma Study

to the treatment effects of steroids, chest wall restriction and resulting low lung volumes, obesity-related comorbidities such as gastroesophageal reflux and obstructive sleep apnea, and the effects of obesity-related systemic inflammatory mediators and circulating oxidants.[8] Furthermore, obesity-related systemic inflammation has been hypothesized as a priming agent for the lung, leading to exaggerated responses to environmental triggers and subsequent asthma symptoms.[9-11] In this context, inner-city environmental exposures might play a significant role in asthma symptoms for the obese subset of children with asthma.

A large number of epidemiological studies have convincingly shown that home exposure to indoor air pollutants has a major effect on childhood asthma development,[12] morbidity, and severity,[13-15] particularly in urban settings.[16-19] Concentrations of many pollutants are higher indoors than outdoors,[20] and higher in urban areas as compared with rural settings.[21] This is of significant consequence because exposure to indoor pollutants is independently associated with increased respiratory symptoms and rescue asthma medication usage in urban children with asthma.[22] One of the best studied indoor pollutants is nitrogen dioxide (NO_2), a pollutant gas produced from high-temperature combustion. Indoor combustion sources include gas stoves, heaters, and poorly vented furnaces and fireplaces, which can produce high indoor NO_2 concentrations. Elevated levels are also seen in metropolitan areas secondary to traffic-related combustion. Belanger et al showed that children with asthma exposed to indoor NO_2 levels well below the Environmental Protection Agency outdoor standard (53 parts per billion [ppb])[23] were at risk for increased frequency of wheeze, night symptoms, and use of rescue medication.[24] Indoor air pollutant exposure in locations other than the home have also garnered a great deal of interest because children spend a majority of their day in school and daycare settings.[25] School-based exposure to pollutants has been associated with asthma symptoms.[26-28] We previously showed that indoor classroom NO_2 levels are associated with increased airflow obstruction.[26] Given the prevalence of childhood obesity in urban communities, this study sought to investigate whether obese students with asthma are differentially affected by exposure to NO_2 in inner-city school classrooms.

METHODS

Study population and design

This investigation was conducted in the School Inner-City Asthma Study (SICAS), a single-center 5-year prospective cohort study examining the effect of school classroom environmental exposures on asthma morbidity in urban schoolchildren. The SICAS methods have previously been reported.[29] Children with asthma attending inner-city public elementary schools were recruited between 2008 and 2013 for study participation through validated screening surveys distributed to participating schools in the spring before the start of the academic study year. Each year of the study consisted of a different group of participating schools and students; enrolled students were observed for 1 school year for health outcomes. The study population consisted of children aged 4 to 13 years with physician-diagnosed asthma for at least 1 year and at least 1 of the following: current daily preventive asthma medication use, wheezing in the past year, or an unscheduled health care visit for asthma in the past year. All parents/legal guardians of enrolled students gave written informed consent, and written assent was obtained from participants older than 7 years before study enrollment. This study was approved by the Boston Children's Hospital Institutional Review Board.

Study visit procedures

A baseline clinical evaluation of enrolled students was performed during the summer before the start of the academic year to ascertain sociodemographic and environmental factors, medical history, baseline asthma symptoms, and medication use through use of questionnaires. Aeroallergen skin prick testing (MultiTest device, Lincoln Diagnostics, Decatur, Ill) or serum specific IgE testing (ImmunoCAP, Phadia AB, Uppsala, Sweden) was performed during the baseline visit as well. The allergens tested include cat, dog, cockroach, mouse, rat, dust mites, grass, tree pollens, ragweed, and molds (Greer Laboratories, Lenoir, NC). Sensitization was defined by a wheal size 3 mm or larger than that produced by the negative saline control on skin prick testing or a specific IgE level of 0.35 kU/L or greater. Both spirometry and fractional exhaled nitric oxide (FENO) measurements were performed at baseline with a Koko spirometer (Ferraris Respiratory, Louisville, Colo) and NIOX MINO device (Aerocrine, Solna, Sweden), respectively, according to the American Thoracic Society standards. FENO was measured using standardized methodology. Both spirometric and FENO measurements were performed in the school during the same season (fall or spring) of exposure measurement.

Follow-up surveys were administered to a parent/guardian during telephone interviews at 3, 6, 9, and 12 months to evaluate asthma symptoms, health care use, and effect on the parent/guardian. Follow-up spirometry and FENO were performed twice during the academic year at school, approximately 6 months apart. Fig 1 shows the study schema.

Definition of overweight and obesity

Body mass index (BMI) was calculated using the weight data (kg) and dividing it by height (m) squared (kg/m^2) collected at the baseline clinical research visit. Pediatric age and sex-adjusted BMI percentiles were then calculated using the Centers for Disease Control and Prevention classification category: (underweight, BMI < 5th percentile; normal weight, 5th percentile ≤ BMI < 85th percentile; overweight, 85th percentile ≤ BMI < 95th percentile; obese, BMI ≥ 95th percentile).[30]

Classroom NO_2 exposure assessment

Classrooms of enrolled students were sampled twice during the academic year while school was in session, approximately 6 months apart. Ogawa samplers[31] positioned in classrooms collected NO_2 through passive monitoring for 1-week periods. NO_2 analysis was performed with ion chromatography. Average NO_2 level per assessment period was used for analyses. All enrolled elementary school students remained in their classroom throughout the day. Therefore, classroom NO_2 exposure was linked to enrolled students in that particular classroom.

Outcome measures

The primary outcome was the number of days with asthma symptoms in the past 14 days, as used in other inner-city studies,[32] defined as the greatest quantity of the following: (1) number of days with wheezing, chest tightness, or cough; (2) number of days on which the child had to slow down or discontinue play activities because of wheezing, chest tightness, or cough; or (3) number of nights with wheezing, chest tightness, or cough leading to disturbed sleep. Therefore, possible values range from 0 to 14 days.

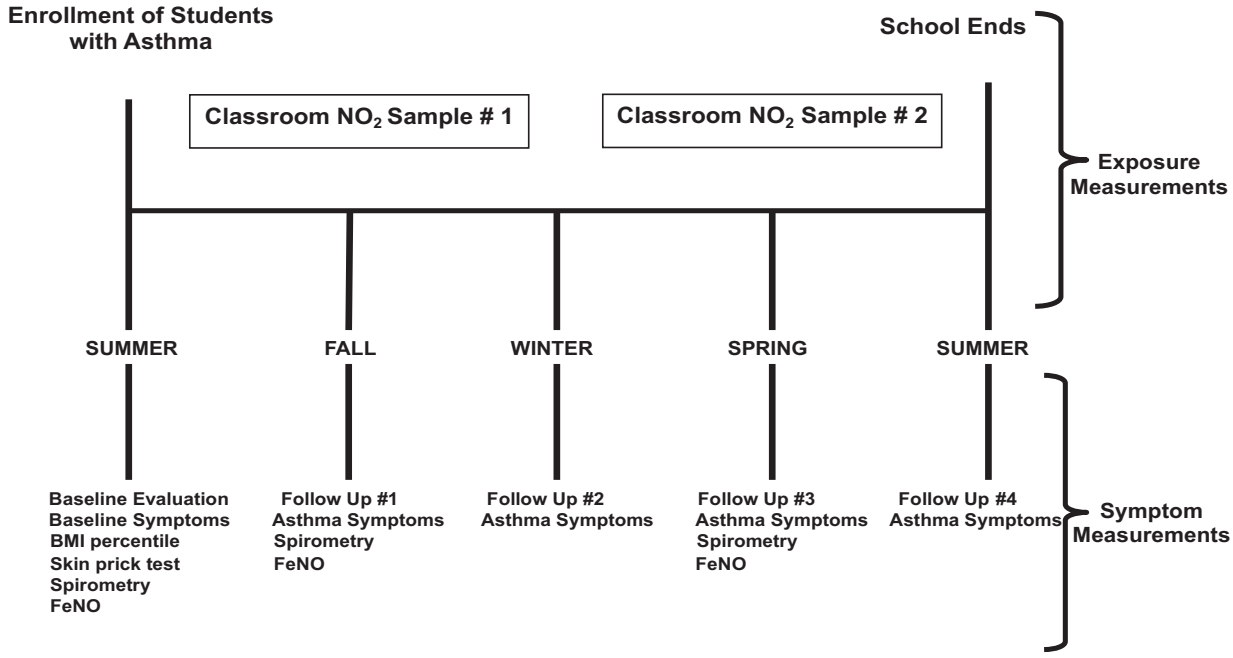

FIG 1. Schematic diagram of SICAS procedures and assessments.

Secondary outcome measures included the following: in the 2 weeks before the survey, number of days the child missed school because of asthma, asthma exacerbations defined as the number of hospitalizations and unscheduled health care visits for asthma, number of days the caregiver changed plans because of the child's asthma, frequency of short-acting β-agonist use in the 4 weeks before the survey; FENO level; and lung function measures such as forced vital capacity (FVC), FEV_1, and forced expiratory flow between the 25th and 75th percentile of FVC. All spirometric measures were assessed for acceptability and repeatability by study physicians per American Thoracic Society guidelines.[33]

Statistical analysis

Descriptive statistics were used to express the characteristics of this cohort. We excluded underweight participants (n = 3) because there were too few to perform meaningful analyses. Only outcome measures obtained during the academic school year were used for the analysis. Symptom outcomes were adjusted for age, race, sex, controller medication use at baseline, season, any sensitization (≥1 sensitization determined by skin prick test responses or specific IgE levels of >0.35 kU/L), and report of environmental tobacco smoke exposure. Differences in baseline spirometry, FENO, and number of positive skin test results among the BMI groups were tested with 1-way ANOVA and Kruskal-Wallis rank test, respectively. All clinical outcomes were linked to the temporally closest measured NO_2 exposure during the academic school year. Relationships between NO_2 levels and asthma outcomes are presented as the effect of a 10-ppb change in NO_2 levels. The exposure-outcome relationship was evaluated using generalized estimating equations with an exchangeable correlation structure, robust variance estimates, and clustered at the participant level. Binomial family generalized estimating equations with a logit link and an overdispersion parameter were used for 2-week outcomes (ie, 2-week outcomes were modeled as the sum of 14 binomial "successes"). Health care utilization and short-acting β-agonist use were modeled with negative binomial family and log link. Spirometry and FENO were modeled using Gaussian family and identity link. We report interaction effects of NO_2 exposure and BMI status as well as stratified effects of classroom NO_2 levels by BMI category calculated by combining the appropriate model terms. Analyses were performed with STATA software, version 15.1 (StataCorp, College Station, Tex). All tests were 2-tailed, and alpha was set at 0.05.

RESULTS

Study population

A total of 271 students, aged 4 to 13 years, with asthma from 37 inner-city public elementary schools in the northeastern United States with complete data for BMI assessment, asthma outcome measures, and NO_2 exposure data were included in this analysis. The baseline characteristics of this study population are detailed in Table I. Participants were predominantly black (35%) or Hispanic (35%), and impoverished, with 49% reporting an annual household income of less than $25,000. Fifty percent of the participants were normal weight, 15% were overweight, and 35% were obese. There was a high prevalence of atopy, with 69% of the population demonstrating at least 1 positive skin test response. On average, baseline lung function was normal and without obstruction. Fifty-five percent of participants reported use of an asthma controller medication.

BMI and baseline asthma characteristics

Obese students with asthma exhibited a lower FVC % predicted and FEV_1 % predicted, but not FEV_1/FVC ratio, greater number of positive aeroallergen skin test results, and lower FENO level when compared with normal weight students (see Table E1 in this article's Online Repository at www.jacionline.org). There was no difference among BMI categories and asthma symptoms (asthma symptom days; cough, wheeze, and chest tightness; limitation in activity; nocturnal symptoms; and short-acting β-agonist use) or morbidity (health care use; missed school days), with the exception of change in caregiver plans in which normal weight children experienced more days of changed plans than overweight children (see Table E2 in this article's Online Repository at www.jacionline.org).

TABLE I. Baseline characteristics of study population (n = 271)

Characteristic	n (%)
Demographic	
Age (y), median (range)	8 (4-13)
Sex: male	141 (52)
Race or ethnic group	
Black	95 (35)
Hispanic	96 (35)
White	13 (5)
Mixed race	48 (18)
Other	19 (7)
Annual household income <$25,000	111 (49)
Clinical	
Allergic sensitization ≥1 allergen*	187 (69)
Skin test sensitivities†	
Cat	101 (37)
Cockroach	58 (21)
Dog	28 (10)
Dust mite	91 (34)
Mouse	84 (31)
FENO (ppb), mean ± SD‡	21.8 ± 23.0
Environmental tobacco smoke exposure	90 (33)
Asthma symptom days, mean ± SD§	2.9 ± 4.1
Controller medication use over previous 12 mo	150 (55)
Pulmonary function testing‖	
FVC % predicted, mean ± SD	101.2 ± 17.7
FEV_1 % predicted, mean ± SD	101.9 ± 18.6
FEV_1/FVC, mean ± SD	0.87 ± 0.07
FEF_{25-75} % predicted, mean ± SD	112.5 ± 48.6
BMI category	
Normal weight (5th-<85th percentile)	133 (49)
Overweight (85th-<95th percentile)	41 (15)
Obese (≥95th percentile)	97 (36)

FEF_{25-75}, Forced expiratory flow between the 25th and 75th percentile of FVC.
*n = 271 (skin prick test and/or specific IgE).
†n = 271.
‡n = 104.
§Asthma symptom days = the greatest result of the following 3 variables in the 2 wk before each follow-up survey: (1) number of days with wheezing, chest tightness, or cough; (2) number of days on which the child had to slow down or discontinue play activities because of wheezing, chest tightness, or cough; and (3) number of nights with wheezing, chest tightness, or cough leading to disturbed sleep.
‖n = 237.

Combined effects of NO_2 exposure, BMI, and asthma outcomes

Relationships between school classroom NO_2 levels and asthma outcomes were stratified by BMI category to determine whether there was an association between NO_2 exposure and BMI status (see Table II). There were no associations between NO_2 levels and any of the asthma symptom outcomes among normal weight and overweight participants. However, NO_2 levels were associated with some asthma outcomes among obese participants. For example, for every 10-fold increase in classroom NO_2 levels, obese participants had a 1.9-fold increased odds of asthma symptom day, 2.4-fold increased odds of health care use for asthma-related symptoms, 3.1-fold increase in the odds of a missed school day due to asthma, and lastly, 4.2-fold increased odds of change in caregiver plans because of child's asthma.

Separate pairwise interaction analyses were performed between BMI categories. For each 10-ppb increase in NO_2, obese students had a significant increase in the odds of having an asthma symptom day (odds ratio [OR], 1.86; 95% CI, 1.15-3.02), which was significantly different than among normal weight students who exhibited no relationship between NO_2 exposure and symptom days (OR, 0.90; 95% CI, 0.57-1.42; pairwise interaction P = .03; see Fig 2). In addition, a 10-ppb increase in NO_2 exposure was associated with a significant increase in the number of days that a caregiver changed plans because of their child's asthma (OR, 4.24; 95% CI, 2.33-7.70), which was significantly different than among normal weight students who exhibited no relationship between NO_2 exposure and change in caregiver plans (OR,1.37; 95% CI, 0.67-2.82; pairwise interaction P = .02; see Fig 3). If we had applied a conservative Holm-Bonferroni correction for 16 comparisons (obese vs normal weight and overweight vs normal weight for 8 outcomes), these findings would not meet statistical significance (all P > .003). There were no differences seen in relationships between NO_2 levels and the other symptom outcomes, lung function, and FENO values across BMI categories. In addition, allergic sensitization did not modify the relationship between NO_2 levels, BMI status, and asthma outcomes.

DISCUSSION

This study sought to examine whether obese students are at risk for the effects of classroom pollutant exposure on asthma symptoms because children in the United States spend most of their day in the school environment. We found that higher concentrations of classroom NO_2 exposure are associated with increased asthma symptoms among obese students, but not among normal weight children. Our results suggest that obese inner-city children with asthma are more vulnerable to the respiratory health effects of indoor NO_2 exposure in school classrooms.

As previously reported, classroom NO_2 levels in our SICAS cohort were relatively low when compared with the US Environmental Protection Agency national ambient air quality standards for NO_2.[26] However, even at these lower levels of exposure, obese students had significantly more asthma symptoms days compared with their normal weight counterparts. Moreover, a child's asthma had a greater effect on caregiver plans if they were both obese and exposed to NO_2. Although it is well established that obesity is a risk factor for the development and worsening of asthma in children,[34] our findings support the idea that the combined effects of school NO_2 exposure and childhood obesity lead to increased asthma morbidity. Although there seemed to be a trend for some outcomes such as missed school days and nocturnal symptoms, overweight BMI status did not confer susceptibility to the pulmonary effects of NO_2 exposure in our enrolled students with asthma as seen in other studies,[35,36] possibly because of a smaller sample size for this subset of children. It is also plausible that overweight individuals possess different biologic underpinnings than the obese, accounting for the differences seen. Even though multiple outcomes were assessed, we did not apply statistical methods to correct for multiple analyses from the inception because they are very conservative, particularly when the multiple outcomes are related to one another.[37] Although our findings would not remain significant with adjustments for multiple comparisons, the large effect sizes observed in the obese group highlight the clinical importance of this study and the need for replication and further research into the interaction of BMI and pollution in children with asthma.

Forno et al[38] demonstrated that overweight/obese children aged 7 to 19 years with asthma have a higher FVC and lower

TABLE II. Association between NO_2 and symptoms stratified by BMI category*

Symptoms	NW†	OV‡	OB§	*P* value,‖ pairwise interaction		
				NW vs OV	NW vs OB	OV vs OB
Primary outcome						
Asthma symptom days	0.90 (0.57-1.42)	0.78 (0.31-1.94)	**1.86 (1.15-3.02)**	.78	**.03**	.10
Secondary outcomes						
Health care use	1.20 (0.58-2.48)	1.91 (0.60-6.11)	**2.44 (1.15-5.14)**	.48	.16	.73
Missed school days	1.10 (0.55-2.21)	2.71 (0.94-7.80)	**3.11 (1.29-7.51)**	.18	.08	.84
Cough, wheeze, or tightness	0.88 (0.57-1.36)	0.60 (0.27-1.36)	1.42 (0.88-2.28)	.41	.14	.07
Limited activity	0.74 (0.41-1.37)	1.41 (0.42-4.77)	1.61 (0.93-2.79)	.34	.06	.13
Change in caregiver plans	1.37 (0.67-2.82)	1.73 (0.72-4.15)	**4.24 (2.33-7.70)**	.67	**.02**	.09
Nocturnal symptoms	1.01 (0.98-1.03)	0.97 (0.93-1.01)	0.98 (0.92-1.04)	.14	.46	.76
SABA use	1.10 (0.80-1.51)	1.25 (0.69-2.27)	1.28 (0.90-1.83)	.70	.51	.94

IRR, Incidence rate ratio; *NW*, normal weight; *OB*, obese; *OV*, overweight; *SABA*, short-acting β-agonist.
Values for NW, OV, and OB are OR/IRR (95% CI).
*Results are from binomial models adjusted for age, race, sex, baseline controller medication use, season, any sensitization, and environmental tobacco smoke exposure.
†NW = 336 observations, 133 normal weight participants.
‡OV = 109 observations, 41 overweight participants.
§OB = 235 observations, 97 participants.
‖The *P* values were generated from models including interaction terms for BMI status and NO_2 exposure, and statistically significant associations are indicated in boldface.

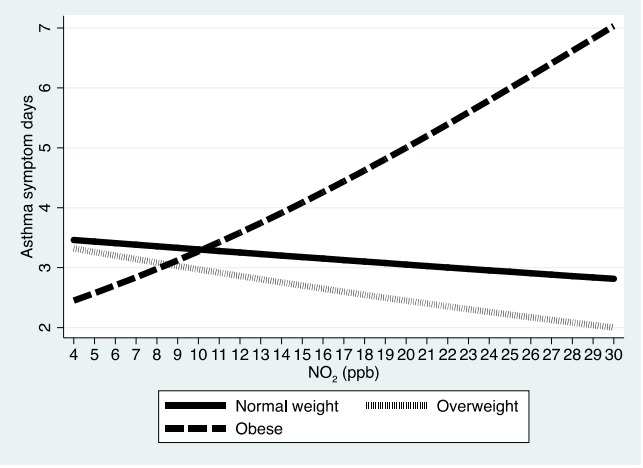

FIG 2. Effect of BMI status on the association of increasing classroom NO_2 exposure and asthma symptom days. The *P* value for pairwise interaction between obese and normal weight BMI effects is .03 (see Table II statistics). All models adjusted for age, race, sex, baseline controller medication use, season, any sensitization, and environmental tobacco smoke exposure.

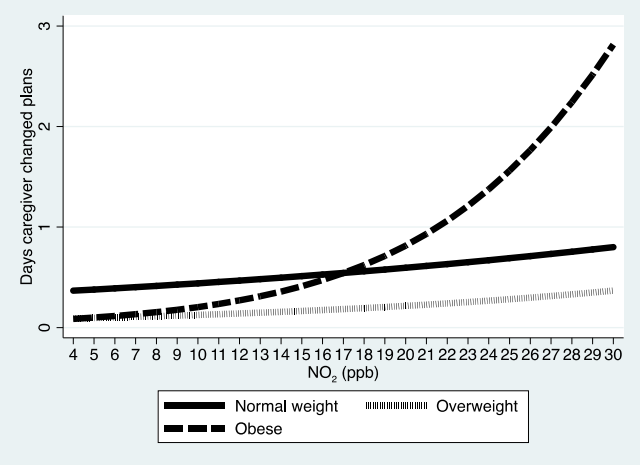

FIG 3. Effect of BMI status on the association of increasing classroom NO_2 exposure and change in caregiver plans. The *P* value for pairwise interaction between obese and normal weight BMI effects is .02. All models adjusted for age, race, sex, baseline controller medication use, season, any sensitization, and environmental tobacco smoke exposure.

FEV_1/FVC compared with normal weight children, suggesting airway dysanaptic growth for this group.[38] We did not appreciate this finding in SICAS, which might be attributed to the younger age range of our cohort at the time of lung function testing. Rather, we found sequential decrease in both FVC and FEV_1 with increased BMI group, suggesting weight-related decrements in vital capacity and, therefore, FEV_1. In this study, all participants exposed to high concentrations of NO_2 maintained an average FEV_1 and FEV_1/FVC ratio in the normal range. The effect of NO_2 exposure on lung function did not result in significant differences among BMI categories. We did, however, identify an increase in maximum asthma symptom days in obese students exposed to higher levels of classroom NO_2 compared with normal weight children. Maximum symptom days, our primary outcome measure, is a validated composite measure of asthma symptomatology[32] and has been used as an outcome measure in a number of inner-city asthma studies.[39-41] Our discrepant finding between lung function testing parameters and clinical asthma symptoms in obese children exposed to NO_2 is consistent with other study findings and highlights the importance of symptom assessment as an outcome measure in pediatric asthma studies.[42] Asthma symptoms are considered the most robust asthma outcomes in inner-city children, specifically with respect to indoor pollutant exposure.[18,22,35,43] In contrast, without the effect of NO_2 exposure, an association between obese BMI and maximum asthma symptom days was not observed. Hence, the interaction between indoor NO_2 exposure and BMI status should be considered particularly for children living in neighborhoods with a high prevalence of both obesity and indoor pollutant exposure given the potential for greater asthma morbidity.

Interestingly, a main effect of obesity on asthma morbidity was seen in relation to lower FENO levels and increased allergen sensitization when compared with normal weight children (see Table E1). As a result, all interaction analyses assessing the

relationship between BMI status, NO_2 exposure, and asthma outcomes were adjusted for allergen sensitization. FENO, a marker of eosinophilic airway inflammation,[44] was significantly lower in the obese subpopulation despite having a higher rate of allergic sensitization diverging from current dogma supported by studies showing a positive, linear dose-response relation between skin test results and FENO levels in children with asthma.[45-48] Our data indicate that in obese children with asthma, allergen sensitization is not predictive of elevated FENO and, consequently, eosinophilic lung inflammation. Studies looking at obese adolescents[49] and adults with asthma have shown similar findings whereby increasing BMI is associated with reduced exhaled nitric oxide (NO).[50,51] Lugogo et al[51] reported lower FENO levels and blood eosinophil counts in obese adults with asthma compared with normal weight adults, concluding that conventional biomarkers of inflammation are poorly predictive of eosinophilic airway inflammation in the obese.[51] In addition, as BMI increased there was a poor correlation between FENO, blood eosinophils, sputum eosinophils, and IgE. One possible explanation for this phenomenon is that lower NO levels in the obese may be related to the presence of underlying oxidative stress and subsequent changes in NO synthase signaling, resulting in an increase in asymmetric dimethylarginine, which is known to reduce NO production.[52] Hence, the unique effects of obesity have the potential to influence surrogate markers of inflammation. When considering the relationship between NO_2 levels and FENO values in the obese subset of students with asthma, a significant interaction was not appreciated. Thus, the respiratory effects caused by obesity and inhalation of NO_2 are likely not mediated by T_H2 inflammatory pathways often linked to pediatric asthma. These findings underscore the importance of considering the different domains of asthma morbidity such as symptoms, exacerbations, lung function, and airway inflammation, when studying diverse asthma endotypes and phenotypes because differences are likely to exist among groups. This approach allows for better insight into asthma pathobiology and the development of personalized targeted therapy for individuals.

Although emerging evidence suggests that the presence of obesity may modify the exposure effects of air pollution on respiratory disease,[35,36,53,54] the mechanism underlying this synergism between pollutant and obesity on asthma morbidity is not entirely clear. Nonetheless, there are a few plausible biological mechanisms by which obesity could lead to greater susceptibility to the respiratory effects of pollutant exposure. First, in our cohort, the obese students exhibited a lower FVC, which suggests an elevated respiratory rate to compensate for slightly lower volumes, thereby enhancing the effect of NO_2 exposure. In support of this, Shore et al[55] reported an increase in airway hyperresponsiveness and inflammation in obese mice exposed to ozone, a common air pollutant and nonallergic asthma trigger, compared with wild-type mice due to higher breathing frequency and greater pulmonary deposition of pollutant particles. Second, obesity is associated with low-grade systemic inflammation and oxidative stress and its role in asthma development and exacerbation is characterized by a complex interplay of proinflammatory and anti-inflammatory adipokines and cytokines.[56] Similarly, through mechanisms of oxidative stress and nonallergic inflammation, NO_2 exerts its direct effects on the respiratory epithelium and smooth muscle, potentially leading to an adverse cumulative effect on a child's asthma. Finally, there is growing interest in the role of diet and alteration in the gut microbiome in the pathophysiology of asthma in obese individuals through direct effects on the airway or indirectly via inflammation.[57] A recent murine study showed that dietary supplementation with fermentable fiber dampened obesity-related increases in the pulmonary response to ozone, by reducing ozone-induced release of IL-17A in obese mice.[58] Tobias et al[59] demonstrated that a diet low in carotenoids and n-3 fatty acid levels correlated with airway obstruction and metabolic dysregulation in obese adolescents with asthma.

Despite existing epidemiological evidence supporting the association between quantitative estimates of indoor NO_2 levels and childhood asthma,[18,23] we know that children are exposed to a mixture of air pollutants with varying composition and correlation based on time and space.[60] Therefore, it is feasible that NO_2 has no direct effect itself but is, instead, only acting as a marker for primary particles or other organic matter carried on these particles to particular locations in the lung. Classroom NO_2 may be an indicator for other unmeasured gaseous, volatile organic, or particulate pollutants produced from the same sources, or for other pollutants chemically related to NO_2, such as ozone or particulate matter. Our single pollutant analysis was limited in the ability to assess the effects of NO_2 apart from other copollutants that might also be present. Although more complex and not as easily attainable, future studies using multipollutant exposure metrics to assess health effects in children are warranted.[61] It is conceivable that there might be other confounding factors associated with obesity driving the interaction between NO_2 and asthma morbidity such as allergen exposure. Studies have shown an additive or synergistic effect of air pollution and allergen coexposure, whereby coexposure increases the release of inflammatory cytokines in human nasal epithelial cells[62] and impairs lung function.[63] We previously reported that mouse allergen (Mus m 1) was the most commonly detected allergen in SICAS classrooms, with a 99.5% detection rate and significantly higher levels than the other measured allergens (90th percentile level, 10.95 μg/g), associated with increased asthma symptom days and lower lung function.[41] Therefore, because mouse allergen was the predominant exposure in SICAS, whereas levels of cockroach, pet, and dust mite allergens were undetectable or very low, we specifically analyzed whether mouse allergen exposure interacts with NO_2 and found no interaction effect ($P = .38$). This does not discount the possibility, however, that other unmeasured allergen exposures could be influencing the interaction between NO_2 and asthma symptoms. In addition, other confounders associated with obesity, such as stress or diet, may have influenced this relationship; however, we were unable to evaluate these factors within this study.

We examined the effects of school NO_2 exposure in an urban cohort primarily consisting of black and Hispanic children with asthma, thereby limiting generalizability to all children but still representative of other large inner-cities in the United States. Another potential confounder to account for the increased vulnerability to classroom NO_2 exposure in obese children is the possibility for more frequent viral upper respiratory tract infections in this group. A limitation of this study is that we did not obtain upper respiratory tract samples to assess for the contribution of viral infections to asthma symptoms. However, previous studies have used season to adjust for covariates that often exhibit seasonal patterns, such as rhinovirus infection.[64] To mitigate this, we adjusted all analyses for environmental tobacco smoke and season to account for seasonal variation in environmental exposures and viral

infection. Although lung function outcomes in children are felt to be less sensitive than other measures of asthma morbidity, perhaps a larger sample size would have provided greater statistical power needed to determine whether overweight or obese BMI status yields similar results for lung function outcomes as maximum asthma symptom days, when exposed to NO_2. Moreover, although we were unable to determine the differential effects that various controller medication regimens may have had on outcomes among all obese children, we found no difference in the effect of NO_2 between obese students using a controller medication (OR, 1.08) and those not using a controller medication (OR, 1.09), $P = .91$.

Our study examined the effects of classroom NO_2 exposure on asthma outcomes in obese schoolchildren in the northeastern United States. Because SICAS is a longitudinal study with children followed over time, we were able to assess the temporal relationship between classroom NO_2 exposure and outcome by BMI category during the academic school year. We demonstrate that higher concentrations of classroom NO_2 exposure are associated with increased asthma symptoms and greater effect on change in caregiver plans among obese students, but not among normal weight children, suggesting that obese inner-city students with asthma might benefit the most from reductions in classroom NO_2 levels. We have a greater ability to modify the indoor environment compared with the outdoor environment. Interventions to alter the outdoor environment such as proximity of major roadways, reduction of pollutant sources, or air pollution standards require considerable regulatory effort and political will, factors that are often outside the control of an individual or even a school system. Therefore, the indoor school environment provides an attractive setting for targeted intervention.[65] Some feasible strategies for reducing indoor NO_2 levels include implementation of appropriate ventilation methods with suitable filters, location planning of new schools to minimize proximity to heavy traffic routes, reduction of traffic idling near schools, diminishing the use of NO_2-releasing indoor sources particularly in schools with cooking stoves, and ventilating indoor NO_2-releasing indoor sources to the outdoors.[66] An intervention strategy of replacing gas stoves with electric stoves in Australian schools resulted in a 40% to 50% reduction in indoor NO_2 levels.[67] Placement of air purifiers with high efficiency particulate air and carbon filters has also been shown to decrease indoor NO_2 levels in urban homes.[68] In addition to the many other important reasons for weight reduction, weight loss in these children who are both obese and have asthma should be encouraged because it may also improve susceptibility to indoor pollutants. Finally, further research is needed to fully understand the biologic mechanisms for why obese children with asthma appear to be more vulnerable to the effects of indoor pollutant exposure.

Clinical implications: Obese urban students with asthma appear to be particularly vulnerable to the effects of classroom indoor pollutant exposures, specifically NO_2. Implementing environmental interventions to reduce classroom NO_2 levels and weight loss strategies may improve asthma symptoms.

REFERENCES

1. Ogden CL, Fryar CD, Hales CM, Carroll MD, Aoki Y, Freedman DS. Differences in obesity prevalence by demographics and urbanization in US children and adolescents, 2013-2016. JAMA 2018;319:2410-8.
2. Akinbami LJ, Simon AE, Rossen LM. Changing trends in asthma prevalence among children. Pediatrics 2016;137.
3. Gergen PJ, Togias A. Inner city asthma. Immunol Allergy Clin North Am 2015;35:101-14.
4. Keet CA, Matsui EC, McCormack MC, Peng RD. Urban residence, neighborhood poverty, race/ethnicity, and asthma morbidity among children on Medicaid. J Allergy Clin Immunol 2017;140:822-7.
5. Gergen PJ, Teach SJ, Togias A, Busse WW. Reducing exacerbations in the inner city: lessons from the Inner-City Asthma Consortium (ICAC). J Allergy Clin Immunol Pract 2016;4:22-6.
6. Dutmer CM, Kim H, Searing DA, Zoratti EM, Liu AH. Asthma in inner city children: recent insights: United States. Curr Opin Allergy Clin Immunol 2018;18:139-47.
7. Peters U, Dixon AE, Forno E. Obesity and asthma. J Allergy Clin Immunol 2018;141:1169-79.
8. Lang JE. Obesity and childhood asthma. Curr Opin Pulm Med 2019;25:34-43.
9. Lang JE, Williams ES, Mizgerd JP, Shore SA. Effect of obesity on pulmonary inflammation induced by acute ozone exposure: role of interleukin-6. Am J Physiol Lung Cell Mol Physiol 2008;294:L1013-20.
10. Shore SA, Schwartzman IN, Mellema MS, Flynt L, Imrich A, Johnston RA. Effect of leptin on allergic airway responses in mice. J Allergy Clin Immunol 2005;115:103-9.
11. Berry MA, Hargadon B, Shelley M, Parker D, Shaw DE, Green RH, et al. Evidence of a role of tumor necrosis factor alpha in refractory asthma. N Engl J Med 2006;354:697-708.
12. Jerrett M, Shankardass K, Berhane K, Gauderman WJ, Künzli N, Avol E, et al. Traffic-related air pollution and asthma onset in children: a prospective cohort study with individual exposure measurement. Environ Health Perspect 2008;116:1433-8.
13. Breysse PN, Diette GB, Matsui EC, Butz AM, Hansel NN, McCormack MC. Indoor air pollution and asthma in children. Proc Am Thorac Soc 2010;7:102-6.
14. Ierodiakonou D, Zanobetti A, Coull BA, Melly S, Postma DS, Boezen HM, et al. Ambient air pollution, lung function, and airway responsiveness in asthmatic children. J Allergy Clin Immunol 2016;137:390-9.
15. Paulin LM, Williams DL, Peng R, Diette GB, McCormack MC, Breysse P, et al. 24-h Nitrogen dioxide concentration is associated with cooking behaviors and an increase in rescue medication use in children with asthma. Environ Res 2017;159:118-23.
16. Mortimer KM, Neas LM, Dockery DW, Redline S, Tager IB. The effect of air pollution on inner-city children with asthma. Eur Respir J 2002;19:699-705.
17. Matsui EC, Hansel NN, McCormack MC, Rusher R, Breysse PN, Diette GB. Asthma in the inner city and the indoor environment. Immunol Allergy Clin North Am 2008;28:665-86, x.
18. Hansel NN, Breysse PN, McCormack MC, Matsui EC, Curtin-Brosnan J, Williams DL, et al. A longitudinal study of indoor nitrogen dioxide levels and respiratory symptoms in inner-city children with asthma. Environ Health Perspect 2008;116:1428-32.
19. O'Connor GT, Neas L, Vaughn B, Kattan M, Mitchell H, Crain EF, et al. Acute respiratory health effects of air pollution on children with asthma in US inner cities. J Allergy Clin Immunol 2008;121:1133-9.e1.
20. Matsui EC. Environmental exposures and asthma morbidity in children living in urban neighborhoods. Allergy 2014;69:553-8.
21. Hulin M, Caillaud D, Annesi-Maesano I. Indoor air pollution and childhood asthma: variations between urban and rural areas. Indoor Air 2010;20:502-14.
22. McCormack MC, Breysse PN, Matsui EC, Hansel NN, Williams D, Curtin-Brosnan J, et al. In-home particle concentrations and childhood asthma morbidity. Environ Health Perspect 2009;117:294-8.
23. Primary National Ambient Air Quality Standards (NAAQS) for nitrogen dioxide. Available from: https://www.epa.gov/no2-pollution/primary-national-ambient-air-quality-standards-naaqs-nitrogen-dioxide. Accessed September 26, 2019.
24. Belanger K, Holford TR, Gent JF, Hill ME, Kezik JM, Leaderer BP. Household levels of nitrogen dioxide and pediatric asthma severity. Epidemiology 2013;24:320-30.
25. Godwin C, Batterman S. Indoor air quality in Michigan schools. Indoor Air 2007;17:109-21.
26. Gaffin JM, Hauptman M, Petty CR, Sheehan WJ, Lai PS, Wolfson JM, et al. Nitrogen dioxide exposure in school classrooms of inner-city children with asthma. J Allergy Clin Immunol 2018;141:2249-55.e2.
27. Sasso F, Izard M, Beneteau T, Rakotozandry T, Ramadour M, Annesi-Maesano I, et al. 18-year evolution of asthma and allergic diseases in French urban schoolchildren in relation to indoor air pollutant levels. Respir Med 2019;148:31-6.
28. Norbäck D, Lu C, Zhang Y, Li B, Zhao Z, Huang C, et al. Sources of indoor particulate matter (PM) and outdoor air pollution in China in relation to asthma,

wheeze, rhinitis and eczema among pre-school children: synergistic effects between antibiotics use and PM. Environ Int 2019;125:252-60.
29. Phipatanakul W, Bailey A, Hoffman EB, Sheehan WJ, Lane JP, Baxi S, et al. The school inner-city asthma study: design, methods, and lessons learned. J Asthma 2011;48:1007-14.
30. Barlow SE. Expert Committee. Expert Committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. Pediatrics 2007;120:S164-92.
31. Ogawa & Co, Inc. NO, NO_2, NO_x and SO_2 sampling protocol using the Ogawa sampler. Pompano Beach, FL: Ogawa & Co, Inc; 2006.
32. Wu TD, Perzanowski M, Peng RD, Wise RA, Balcer-Whaley S, Newman M, et al. Validation of the maximum symptom day among children with asthma. J Allergy Clin Immunol 2019;143:803-5.e10.
33. Beydon N, Davis SD, Lombardi E, Allen JL, Arets HG, Aurora P, et al. An official American Thoracic Society/European Respiratory Society statement: pulmonary function testing in preschool children. Am J Respir Crit Care Med 2007;175:1304-45.
34. Lang JE, Bunnell HT, Hossain MJ, Wysocki T, Lima JJ, Finkel TH, et al. Being overweight or obese and the development of asthma. Pediatrics 2018;142.
35. Lu KD, Breysse PN, Diette GB, Curtin-Brosnan J, Aloe C, Williams DL, et al. Being overweight increases susceptibility to indoor pollutants among urban children with asthma. J Allergy Clin Immunol 2013;131:1017-23, 1023. e1-3.
36. Dong GH, Qian Z, Liu MM, Wang D, Ren WH, Fu Q, et al. Obesity enhanced respiratory health effects of ambient air pollution in Chinese children: the Seven Northeastern Cities study. Int J Obes (Lond) 2013;37:94-100.
37. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc B 1995;57:289-300.
38. Forno E, Weiner DJ, Mullen J, Sawicki G, Kurland G, Han YY, et al. Obesity and airway dysanapsis in children with and without asthma. Am J Respir Crit Care Med 2017;195:314-23.
39. Morgan WJ, Crain EF, Gruchalla RS, O'Connor GT, Kattan M, Evans R, et al. Results of a home-based environmental intervention among urban children with asthma. N Engl J Med 2004;351:1068-80.
40. Matsui EC, Perzanowski M, Peng RD, Wise RA, Balcer-Whaley S, Newman M, et al. Effect of an integrated pest management intervention on asthma symptoms among mouse-sensitized children and adolescents with asthma: a randomized clinical trial. JAMA 2017;317:1027-36.
41. Sheehan WJ, Permaul P, Petty CR, Coull BA, Baxi SN, Gaffin JM, et al. Association between allergen exposure in inner-city schools and asthma morbidity among students. JAMA Pediatr 2017;171:31-8.
42. Bacharier LB, Strunk RC, Mauger D, White D, Lemanske RF, Sorkness CA. Classifying asthma severity in children: mismatch between symptoms, medication use, and lung function. Am J Respir Crit Care Med 2004;170:426-32.
43. Weinmayr G, Romeo E, De Sario M, Weiland SK, Forastiere F. Short-term effects of PM10 and NO_2 on respiratory health among children with asthma or asthma-like symptoms: a systematic review and meta-analysis. Environ Health Perspect 2010;118:449-57.
44. Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. Am J Respir Crit Care Med 2011;184:602-15.
45. Jackson DJ, Virnig CM, Gangnon RE, Evans MD, Roberg KA, Anderson EL, et al. Fractional exhaled nitric oxide measurements are most closely associated with allergic sensitization in school-age children. J Allergy Clin Immunol 2009;124:949-53.
46. Barreto M, Villa MP, Monti F, Bohmerova Z, Martella S, Montesano M, et al. Additive effect of eosinophilia and atopy on exhaled nitric oxide levels in children with or without a history of respiratory symptoms. Pediatr Allergy Immunol 2005;16:52-8.
47. van Amsterdam JG, Janssen NA, de Meer G, Fischer PH, Nierkens S, van Loveren H, et al. The relationship between exhaled nitric oxide and allergic sensitization in a random sample of school children. Clin Exp Allergy 2003;33:187-91.
48. Rao DR, Sordillo JE, Kopel LS, Gaffin JM, Sheehan WJ, Hoffman E, et al. Association between allergic sensitization and exhaled nitric oxide in children in the School Inner-City Asthma Study. Ann Allergy Asthma Immunol 2015;114:256-7.e1.
49. Flashner BM, Rifas-Shiman SL, Oken E, Camargo CA, Platts-Mills TJ, Workman L, et al. Obesity, sedentary lifestyle, and exhaled nitric oxide in an early adolescent cohort. Pediatr Pulmonol 2020;55:503-9.
50. Komakula S, Khatri S, Mermis J, Savill S, Haque S, Rojas M, et al. Body mass index is associated with reduced exhaled nitric oxide and higher exhaled 8-isoprostanes in asthmatics. Respir Res 2007;8:32.
51. Lugogo N, Green CL, Agada N, Zhang S, Meghdadpour S, Zhou R, et al. Obesity's effect on asthma extends to diagnostic criteria. J Allergy Clin Immunol 2018;141:1096-104.
52. Holguin F, Comhair SA, Hazen SL, Powers RW, Khatri SS, Bleecker ER, et al. An association between L-arginine/asymmetric dimethyl arginine balance, obesity, and the age of asthma onset phenotype. Am J Respir Crit Care Med 2013;187:153-9.
53. Choi H, Dostal M, Pastorkova A, Rossner P, Sram RJ, Ho SM. Greater susceptibility of girls to airborne Benzo[a]pyrene for obesity-associated childhood asthma. Environ Int 2018;121:308-16.
54. Wu TD, Brigham EP, Peng R, Koehler K, Rand C, Matsui EC, et al. Overweight/obesity enhances associations between secondhand smoke exposure and asthma morbidity in children. J Allergy Clin Immunol Pract 2018;6:2157-9.e5.
55. Shore SA, Rivera-Sanchez YM, Schwartzman IN, Johnston RA. Responses to ozone are increased in obese mice. J Appl Physiol (1985) 2003;95:938-45.
56. Dixon AE, Holguin F, Sood A, Salome CM, Pratley RE, Beuther DA, et al. An official American Thoracic Society Workshop report: obesity and asthma. Proc Am Thorac Soc 2010;7:325-35.
57. Mohan A, Grace J, Wang BR, Lugogo N. The effects of obesity in asthma. Curr Allergy Asthma Rep 2019;19:49.
58. Tashiro H, Cho Y, Kasahara DI, Brand JD, Bry L, Yeliseyev V, et al. Microbiota contribute to obesity-related increases in the pulmonary response to ozone. Am J Respir Cell Mol Biol 2019;61:702-12.
59. Tobias TAM, Wood LG, Rastogi D. Carotenoids, fatty acids and disease burden in obese minority adolescents with asthma. Clin Exp Allergy 2019;49:838-46.
60. Levy I, Mihele C, Lu G, Narayan J, Brook JR. Evaluating multipollutant exposure and urban air quality: pollutant interrelationships, neighborhood variability, and nitrogen dioxide as a proxy pollutant. Environ Health Perspect 2014;122:65-72.
61. Oakes M, Baxter L, Long TC. Evaluating the application of multipollutant exposure metrics in air pollution health studies. Environ Int 2014;69:90-9.
62. Koehler C, Paulus M, Ginzkey C, Hackenberg S, Scherzad A, Ickrath P, et al. The proinflammatory potential of nitrogen dioxide and its influence on the house dust mite allergen Der p 1. Int Arch Allergy Immunol 2016;171:27-35.
63. Wooding DJ, Ryu MH, Hüls A, Lee AD, Lin DTS, Rider CF, et al. Particle depletion does not remediate acute effects of traffic-related air pollution and allergen: a randomized, double-blind crossover study. Am J Respir Crit Care Med 2019;200:565-74.
64. Busse WW, Morgan WJ, Gergen PJ, Mitchell HE, Gern JE, Liu AH, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. N Engl J Med 2011;364:1005-15.
65. Gold DR, Adamkiewicz G, Arshad SH, Celedón JC, Chapman MD, Chew GL, et al. NIAID, NIEHS, NHLBI, and MCAN Workshop Report: the indoor environment and childhood asthma—implications for home environmental intervention in asthma prevention and management. J Allergy Clin Immunol 2017;140:933-49.
66. Salonen H, Salthammer T, Morawska L. Human exposure to NO. Environ Int 2019;130:104887.
67. Pilotto LS, Nitschke M, Smith BJ, Pisaniello D, Ruffin RE, McElroy HJ, et al. Randomized controlled trial of unflued gas heater replacement on respiratory health of asthmatic schoolchildren. Int J Epidemiol 2004;33:208-14.
68. Paulin LM, Diette GB, Scott M, McCormack MC, Matsui EC, Curtin-Brosnan J, et al. Home interventions are effective at decreasing indoor nitrogen dioxide concentrations. Indoor Air 2014;24:416-24.

TABLE E1. Lung function, FENO, and skin prick test by BMI category

Asthma-related measures	Normal weight	Overweight	Obese	*P* value*
Lung function				
FVC % predicted, mean ± SD	104.1 ± 18.7	100.0 ± 17.6	97.9 ± 15.9	.047
FEV_1 % predicted, mean ± SD	105.0 ± 19.1	100.6 ± 18.2	98.4 ± 17.6	.04
FEV_1/FVC, mean ± SD	0.87 ± 0.07	0.88 ± 0.07	0.86 ± 0.08	.32
FEF_{25-75} % predicted, mean ± SD	114.6 ± 46.4	113.2 ± 53.1	109.5 ± 49.7	.77
FENO (ppb), mean ± SD	28.9 ± 29.8	23.7 ± 30.1	15.1 ± 11.0	.03
No. of positive skin prick test results, median (IQR)	1 (0-2)	0 (0-1)	2 (0-3)	.04

FEF_{25-75}, Forced expiratory flow between the 25th and 75th percentile of FVC; *IQR*, interquartile range.
Values are mean ± SD.
*The *P* values were generated from 1-way ANOVA testing for lung function and FENO and Kruskal-Wallis rank test for no. of positive skin test results, adjusted for age, race, sex, baseline controller medication use, season, any sensitization, and environmental tobacco smoke exposure.

TABLE E2. Days of asthma symptoms by BMI category

Asthma-related symptoms	Normal weight*	Overweight†	Obese‡	*P* value§
Asthma symptom days‖	3.2 ± 4.3	2.8 ± 4.1	3.4 ± 4.2	.48
Health care use	0.2 ± 0.6	0.2 ± 0.7	0.1 ± 0.4	.55
Missed school days	0.4 ± 0.9	0.5 ± 1.0	0.6 ± 1.3	.73
Cough, wheeze, or tightness	2.7 ± 3.9	2.3 ± 3.7	2.7 ± 3.8	.62
Limited activity	1.5 ± 3.2	1.3 ± 3.2	2.2 ± 3.6	.11
Change in caregiver plans¶	0.5 ± 1.3	0.1 ± 0.5	0.3 ± 0.9	.003
Nocturnal symptoms	0.5 ± 0.5	0.7 ± 0.5	0.5 ± 0.5	.08
SABA use	1.1 ± 1.3	1.1 ± 1.4	1.2 ± 1.4	.79

SABA, Short-acting β-agonist.

*Normal weight = 336 observations, 133 normal weight participants.

†Overweight = 109 observations, 41 overweight participants.

‡Obese = 235 observations, 97 participants.

§The *P* values were generated from binomial models adjusted for age, race, sex, baseline controller medication use, season, any sensitization, and environmental tobacco smoke exposure.

‖Asthma symptom days = the greatest result of the following 3 variables in the 2 wk before each follow-up survey: (1) number of days with wheezing, chest tightness, or cough; (2) number of days on which the child had to slow down or discontinue play activities because of wheezing, chest tightness, or cough; and (3) number of nights with wheezing, chest tightness, or cough leading to disturbed sleep.

¶The only statistically significant difference was for change in caregiver plans between normal weight and overweight ($P = .001$).