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Obesity May Enhance the Adverse Effects of NO₂ Exposure in Urban Schools on Asthma Symptoms in Children

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Abstract

Background: Sparse data address the effects of nitrogen dioxide (NO₂) exposure in inner-city schools on obese students with asthma.

Objective: To evaluate relationships between classroom NO₂ exposure and asthma symptoms and morbidity by body mass index (BMI) category.

Methods: The School Inner-City Asthma Study enrolled students aged 4–13 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

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subsequent academic year. Classroom NO₂, linked to enrolled students, was collected twice per year. We determined the relationship between classroom NO₂ 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 ppb increase in NO₂, obese students had a significant increase in the odds of having an asthma symptom day (OR=1.86, 95% confidence interval [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 NO₂ exposure and symptom days (OR=0.90, 95% CI=0.57–1.42, pairwise interaction p=0.03) and change in caregiver plans (OR=1.37, 95% CI=0.67–2.82, pairwise interaction p=0.02). Relationships between NO₂ levels and lung function and F_ENO 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>0.003).

Conclusion: Obese BMI status appears to increase susceptibility to classroom NO₂ exposure effects on asthma symptoms in inner-city children. Environmental interventions targeting indoor school NO₂ 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.

Capsule Summary:

Obese urban students with asthma appear more susceptible to the effects of classroom indoor NO₂ exposure. Obese BMI status and the school environment should be taken into consideration when assessing childhood asthma risk factors.

Keywords

asthma; obesity; body mass index; BMI; inner-city; urban; school; nitrogen dioxide; NO₂; children; environment; exposure; indoor; pollutant; air

INTRODUCTION

Obesity and asthma are two chronic childhood diseases that have shown a striking surge in prevalence over the past two decades(1,2), particularly in inner-city children. Obesity rates are higher among Hispanic children (25.8%) and Black children (22%) than among their Caucasian (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 two conditions.(7)

Several theories have been proposed to explain the connection between obesity and asthma risk. They have included resistance 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) Further, 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 to rural settings.(21)

This is of significant consequence since exposure to indoor pollutants is independently associated with increased respiratory symptoms and rescue asthma medication usage in urban gas stoves, heaters, and poorly vented furnaces and fireplaces which can produce high indoor NO₂ concentrations. Elevated levels are also seen in metropolitan areas secondary to traffic-related combustion. Belanger and colleagues showed that children with asthma exposed to indoor NO₂ levels well below the EPA outdoor standard (53 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 since children spend a majority of their day in school and daycare settings.(25) School based exposure to pollutants have been associated with asthma symptoms.(26–28) We previously showed that indoor classroom NO₂ levels is 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 NO₂ 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 2008–2013 for study participation through validated screening surveys distributed to participating schools in the spring prior to 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 prior to 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 prior to 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, IL) 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 fraction of exhaled nitric oxide ($F_{E}NO$) were performed at baseline with a Koko spirometer (Ferraris Respiratory, Louisville, CO) and NIOX MINO device (Aerocrine, Solna, Sweden), respectively, according to the American Thoracic Society (ATS) standards. $F_{E}NO$ was measured using standardized methodology. Both spirometric and $F_{E}NO$ 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 $F_{E}NO$ were performed twice during the academic year at school, approximately 6 months apart. Figure 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 classification category: (underweight, $BMI < 5^{th}$ percentile; normal weight, $5^{th} \text{ percentile} \leq BMI < 85^{th}$ percentile; overweight, $85^{th} \text{ percentile} \leq BMI < 95^{th}$ percentile; obese, $BMI \geq 95^{th}$ 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 levels 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 due to 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.

Secondary outcome measures included the following: in the 2 weeks prior to survey, number of days the child missed school due to 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 beta agonist (SABA) use in the 4 weeks prior to survey; $F_{E}NO$ level; and lung function measures such as forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and forced expiratory flow between the 25th and 75th percentile of forced vital capacity (FEF_{25-75}). All spirometric measures were assessed for acceptability and repeatability by study physicians per ATS 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 or more sensitizations determined by skin prick test responses or specific IgE levels of greater than 0.35 kU/L), and report of environmental tobacco smoke exposure. Differences in baseline spirometry, $F_{E}NO$ and number of positive skin tests among the BMI groups were tested with one-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 (GEEs) with an exchangeable correlation structure, robust variance estimates, and clustered at the participant level. Binomial family GEEs with a logit link and an overdispersion parameter were used for two-week outcomes (i.e., two-week outcomes were modeled as the sum of 14 binomial "successes"). Healthcare utilization and SABA use were modeled with negative binomial family and log link. Spirometry and $F_{E}NO$ 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, TX). All tests were two-tailed and alpha was set at 0.05.

RESULTS

Study Population

A total of 271 students, aged 4–13 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 NO₂ exposure data were included in this analysis. The baseline characteristics of this study population are detailed in Table 1. 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 FEV₁ % predicted, but not FEV₁/FVC ratio, greater number of positive aeroallergen skin tests, and lower F_ENO level when compared to normal weight students (see Table E1). There was no difference among BMI categories and asthma symptoms (asthma symptom days; cough, wheeze, and chest tightness; limitation in activity; nocturnal symptoms; and SABA use) or morbidity (healthcare 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 (see Table E2).

Combined effects of NO₂ exposure, BMI and asthma outcomes.

Relationships between school classroom NO₂ levels and asthma outcomes were stratified by BMI category to determine whether there was an association between NO₂ exposure and BMI status (see Table 2). There were no associations between NO₂ levels and any of the asthma symptom outcomes among normal-weight and overweight participants. However, NO₂ levels were associated with some asthma outcomes among obese participants. For example, for every 10-fold increase in classroom NO₂ levels, obese participants had a 1.9-fold increased odds of asthma symptom day, 2.4-fold increased odds of healthcare 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 NO₂, obese students had a significant increase in the odds of having an asthma symptom day (OR=1.86, 95% CI=1.15–3.02) which was significantly different than normal weight students who exhibited no relationship between NO₂ exposure and symptom days (OR = 0.90, 95% CI = 0.57–1.42, pairwise interaction $p = 0.03$, see Figure 2). In addition, a 10 ppb increase in NO₂ exposure was associated with a significant increase in the number of days that a caregiver changed plans due to their child's asthma (OR = 4.24, 95% CI = 2.33 – 7.70) which was significantly different than normal weight students who exhibited no relationship between NO₂ exposure and change in caregiver plans (OR =1 .37,

95% CI = 0.67 – 2.82, pairwise interaction $p = 0.02$, see Figure 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 $p > 0.003$). There were no differences seen in relationships between NO₂ levels and the other symptom outcomes, lung function and F_ENO values across BMI categories. Additionally, allergic sensitization did not modify the relationship between NO₂ 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 since children in the U.S. spend the majority of their day in the school environment. We found that higher concentrations of classroom NO₂ exposure is 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 NO₂ exposure in school classrooms.

As previously reported, classroom NO₂ levels in our SICAS cohort were relatively low when compared with the U.S. Environmental Protection Agency national ambient air quality standards for NO₂.⁽²⁶⁾ However, even at these lower levels of exposure, obese students had significantly more asthma symptoms days compared to their normal weight counterparts. Moreover, a child's asthma had a greater effect on caregiver plans if they were both obese and exposed to NO₂. While 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 NO₂ exposure and childhood obesity leads 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 NO₂ exposure in our enrolled students with asthma as seen in other studies,^(35, 36) possibly due to 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 and colleagues demonstrated that overweight/obese children aged 7–19 years with asthma have a higher FVC and lower FEV₁/FVC compared to 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 FEV₁ with increased BMI group, suggesting weight related decrements in vital capacity and, therefore, FEV₁. In this study, all participants exposed to high concentrations of NO₂ maintained an

average FEV₁ and FEV₁/FVC ratio in the normal range. The effect of NO₂ 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 NO₂ compared to 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 NO₂ 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 NO₂ exposure, an association between obese BMI and maximum asthma symptom days was not observed. Hence, the interaction between indoor NO₂ 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 F_ENO levels and increased allergen sensitization when compared to normal weight children (see Table E1). As a result, all interaction analyses assessing the relationship between BMI status, NO₂ exposure, and asthma outcomes were adjusted for allergen sensitization. F_ENO, 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 F_ENO levels in children with asthma.(45–48) Our data indicates that in obese children with asthma, allergen sensitization is not predictive of elevated F_ENO 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. reported lower F_ENO levels and blood eosinophil counts in obese adults with asthma compared to normal weight adults, concluding that conventional biomarkers of inflammation are poorly predictive of eosinophilic airway inflammation in the obese.(51) Additionally, as BMI increased there was a poor correlation between F_ENO, 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 NO₂ levels and F_ENO 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 NO₂ are likely not mediated by Th₂ 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 as 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.

While 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 NO₂ exposure. In support of this, Shore et al. reported an increase in airway hyperresponsiveness (AHR) and inflammation in obese mice exposed to ozone, a common air pollutant and non-allergic asthma trigger, compared to wild-type mice due to higher breathing frequency and greater pulmonary deposition of pollutant particles.(55) 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 pro- and anti-inflammatory adipokines and cytokines.(56) Similarly, through mechanisms of oxidative stress and nonallergic inflammation, NO₂ 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 on 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) Rastogi et al. 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.(59)

Despite existing epidemiological evidence supporting the association between quantitative estimates of indoor NO₂ levels and childhood asthma(18, 24), 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 NO₂ 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 NO₂ 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 NO₂, such as ozone or particulate matter. Our single pollutant analysis was limited in the ability to assess the effects of NO₂ apart from other co-pollutants that might also be present. Although more complex and not as easily attainable, future studies employing 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 NO₂ and asthma morbidity such as allergen exposure. Studies have shown an additive or synergistic effect of air pollution and allergen co-exposure, whereby co-exposure 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 ug/g), associated with

increased asthma symptom days and lower lung function(41). Therefore, since mouse allergen was the predominant exposure in the SICAS study, whereas levels of cockroach, pet, and dust mite allergens were undetectable or very low, we specifically analyzed whether mouse allergen exposure interacts with NO₂ and found no interaction effect (p=0.38). This does not discount the possibility, however, that other unmeasured allergen exposures could be influencing the interaction between NO₂ and asthma symptoms. Additionally, 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 NO₂ 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 U.S. Another potential confounder to account for the increased vulnerability to classroom NO₂ 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 samples to assess for the contribution of viral infections to asthma symptoms. However, prior 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 NO₂. Moreover, while 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 NO₂ between obese students using a controller medication (OR=1.08) and those not using a controller medication (OR=1.09), p=0.91.

Our study examined the effects of classroom NO₂ exposure on asthma outcomes in obese schoolchildren in the northeastern U.S. As SICAS is a longitudinal study with children followed over time, we were able to assess the temporal relationship between classroom NO₂ exposure and outcome by BMI category during the academic school year. We demonstrate that higher concentrations of classroom NO₂ exposure is 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 NO₂ levels. We have a greater ability to modify the indoor environment compared to 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 NO₂ 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 NO₂-releasing indoor sources particularly in schools with cooking stoves, and ventilating indoor NO₂-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 NO₂ levels.(67) Placement of air purifiers with high efficiency particulate air and carbon filters have also been shown to decrease indoor NO₂ 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 as it may also improve susceptibility to indoor pollutants. Lastly, 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

SICAS	School Inner-City Asthma Study
BMI	body mass index
NO₂	nitrogen dioxide
F_ENO	fraction of exhaled nitric oxide
EPA	Environmental Protection Agency
ATS	American Thoracic Society
NW	Normal weight
OV	Overweight
OB	Obese
IgE	immunoglobulin E
SABA	short-acting beta agonist
ppb	parts per billion
SD	standard deviation
FVC	forced vital capacity

FEV₁	forced expiratory volume in 1 second
FEF_{25–75}	forced expiratory flow between the 25 th and 75 th percentile of forced vital capacity
OR	odds ratio
IRR	incidence rate ratio
CI	confidence interval
IQR	interquartile range

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Clinical Implications:

Obese urban students with asthma appear to be particularly vulnerable to the effects of classroom indoor pollutant exposures, specifically NO₂. Implementing environmental interventions to reduce classroom NO₂ levels and weight loss strategies may improve asthma symptoms.

FIGURE 1. Schematic diagram of SICAS procedures and assessments.

FIGURE 2. Effect of BMI Status on the Association of Increasing Classroom NO₂ Exposure and Asthma Symptom Days

The p value for pairwise interaction between obese and normal weight BMI effects is 0.03, see Table 2 statistics. All models adjusted for age, race, sex, baseline controller medication use, season, any sensitization, and environmental tobacco smoke exposure.

FIGURE 3. Effect of BMI Status on the Association of Increasing Classroom NO₂ Exposure and Change in Caregiver Plans

The p value for pairwise interaction between obese and normal weight BMI effects is 0.02.

All models adjusted for age, race, sex, baseline controller medication use, season, any sensitization, and environmental tobacco smoke exposure.

TABLE 1.

Baseline Characteristics of Study Population (n = 271)

Characteristic	No. (%)
Demographics	
Age (yrs), median (range)	8 (4–13)
Male gender	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 characteristics	
Allergic sensitization 1 allergen ¹	187 (69)
Skin test sensitivities²	
Cat	101 (37)
Cockroach	58 (21)
Dog	28 (10)
Dust mite	91 (34)
Mouse	84 (31)
F _E NO (ppb), mean (SD) ³	21.8 (23.0)
Environmental tobacco smoke exposure	90 (33)
Asthma symptom days, mean (SD) [*]	2.9 (4.1)
Controller medication use over prior 12 months	150 (55)
Pulmonary function testing⁴	
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 (5 th – <85 th percentile)	133 (49)
Overweight (85 th – <95 th percentile)	41 (15)
Obese (≥ 95 th percentile)	97 (36)

¹ n = 271 (SPT and/or specific IgE),² n = 271,³ n = 104,⁴ n = 237

Abbreviations: FENO = fraction of exhaled nitric oxide; ppb = parts per billion; SD = standard deviation; FVC = forced vital capacity; FEV₁ = forced expiratory volume in 1 second; FEF_{25–75} = forced expiratory flow between the 25th and 75th percentile of forced vital capacity; BMI = body mass index

* Asthma symptom days = the greatest result of the following 3 variables in the 2 weeks 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.

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TABLE 2.Association between NO₂ and Symptoms Stratified by BMI Category *

Symptoms	¹ NW, OR/IRR (95% CI)	² OV, OR/IRR (95% CI)	³ OB, OR/IRR (95% CI)	** p value, Pairwise Interaction		
				NW vs OV	NW vs OB	OV vs OB
<i>Primary Outcome</i>						
Asthma symptom days	0.90 (0.57–1.42)	0.78 (0.31–1.94)	1.86 (1.15–3.02)	0.78	0.03	0.10
<i>Secondary Outcomes</i>						
Healthcare use	1.20 (0.58–2.48)	1.91 (0.60–6.11)	2.44 (1.15–5.14)	0.48	0.16	0.73
Missed school days	1.10 (0.55–2.21)	2.71 (0.94–7.80)	3.11 (1.29–7.51)	0.18	0.08	0.84
Cough, wheeze, or tightness	0.88 (0.57–1.36)	0.60 (0.27–1.36)	1.42 (0.88–2.28)	0.41	0.14	0.07
Limited activity	0.74 (0.41–1.37)	1.41 (0.42–4.77)	1.61 (0.93–2.79)	0.34	0.06	0.13
Change in caregiver plans	1.37 (0.67–2.82)	1.73 (0.72–4.15)	4.24 (2.33–7.70)	0.67	0.02	0.09
Nocturnal symptoms	1.01 (0.98–1.03)	0.97 (0.93–1.01)	0.98 (0.92–1.04)	0.14	0.46	0.76
SABA use	1.10 (0.80–1.51)	1.25 (0.69–2.27)	1.28 (0.90–1.83)	0.70	0.51	0.94

¹NW = 336 observations, 133 normal weight participants;²OV = 109 observations, 41 overweight participants,³OB = 235 observations, 97 participants.

* Results are from binomial models adjusted for age, race, sex, baseline controller medication use, season, any sensitization, and environmental tobacco smoke exposure.

** The p values were generated from models including interaction terms for BMI status and NO₂ exposure, and statistically significant associations are indicated in boldface.Abbreviations: NO₂ = nitrogen dioxide; BMI = body mass index; OR = odds ratio; IRR=incidence rate ratio; NW = Normal weight; OV = Overweight; OB = Obese; SABA = short-acting beta agonist; vs = versus; CI = confidence interval