HHS Public Access

Author manuscript

J Allergy Clin Immunol. Author manuscript; available in PMC 2019 June 01.

Published in final edited form as:

J Allergy Clin Immunol. 2018 June ; 141(6): 2249–2255.e2. doi:10.1016/j.jaci.2017.08.028.

Nitrogen Dioxide Exposure in School Classrooms of Inner-City Children with Asthma

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Abstract

Background—Ambient and home exposure to nitrogen dioxide (NO_2) causes asthma symptoms and decreased lung function in children with asthma. Little is known about the health effects of school classroom pollution exposure.

Objective—We aimed to determine the effect of indoor classroom NO_2 on lung function and symptoms of inner-city schoolchildren with asthma.

Methods—Children enrolled in the School Inner City Asthma Study were followed for one academic year. Subjects performed spirometry and fractional exhaled nitric oxide (FeNO) twice during the school year, at school. Classroom NO_2 was collected by passive sampling for 1 week periods, twice per year coinciding with lung function testing. Generalized estimating equation models assessed lung function and symptom relationships with the temporally nearest classroom NO_2 level.

Results—NO_2 mean values were 11.1ppb (range 4.3 – 29.7ppb). In total, exposure data was available for 296 subjects; 188 with complete spirometry data. Above a threshold of 8ppb NO_2, and after adjusting for race and season (spirometry standardized by age, height, and gender), NO_2 was highly associated with airflow obstruction such that each 10ppb rise in NO_2 was associated

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with a 5% decline in FEV_1/FVC (β: −0.05, 95% confidence interval (CI) [−0.08, −0.02], p=0.01). FEF_{25-75}% predicted was also inversely associated with higher NO_2 exposure (β: −22.8, 95%CI [−36.0, −9.7], p=0.01). There was no significant association of NO_2 with FEV1% predicted, FeNO or asthma symptoms. Additionally, there was no effect modification of atopy on lung function or symptom outcomes.

Conclusion—In children with asthma, indoor classroom NO_2 may be associated with increased airflow obstruction.

Keywords

Asthma; indoor air pollution; obstructive lung disease; nitrogen dioxide; spirometry; exhaled nitric oxide

Introduction

Exposure to ambient air pollutants has been associated with asthma development, asthma exacerbations, and reduction in lung function[1–8]. Moreover, home-based measurements of nitrogen dioxide (NO_2) and other pollutants with indoor sources have been associated with asthma symptom severity[9] and lower lung function[2, 10, 11] in children, even at modest levels of exposure[10].

NO_2, a gaseous pollutant generated from fossil fuel combustion, has emerged as one of the most notable pollutants associated with health effects. In urban environments NO_2 is generated by traffic related combustion, home heating and cooking with fossil fuels (gas, oil, coal), and tobacco smoke[12, 13]. It is a prevalent indoor pollutant in homes, where heating and cooking are common activities, and during these exposures asthma symptoms worsen [11, 14]. However, little is known about the effect of NO_2 in indoor environments aside from the home.

Urban schools represent a unique and important microenvironment for indoor pollution. In most schools, there is no cooking, tobacco smoke is prohibited, and the centralized furnace system minimizes the combustion exposure to any individual classroom. However, exposure to combustion-related pollutants from outside sources may enter through traditional ventilation and intrusion through doors, windows and structural imperfections of the school building. The school classroom represents the occupational setting for children, the environment in which they spend 6–10 hours per day. Therefore, exposures encountered in this environment may have a substantial health effect.

Several studies have cataloged indoor air quality in schools[15–19] and associations with respiratory[19–21] and neurodevelopmental measures[22]. However, variation in source and type of pollutants varies significantly by geographic region[16] and few studies have focused on US inner city schools[23]. Furthermore, few studies have specifically evaluated lung function in relation to the school based exposure[24]. In this study, we examine the symptomatic effects of NO_2 and objective assessment of lung function in inner city children with asthma.

We hypothesized that exposure to NO_2 in schools would be associated with lung function deficits and higher rates of asthma symptoms in children with asthma.

Methods

Study Population

The School Inner City Asthma Study (SICAS) is a single center epidemiologic study of the effect of school classroom environmental exposures on asthma morbidity in inner city school children with asthma. Methods have been previously published[25]. Briefly, children with asthma were recruited from inner city school classrooms from 2008 – 2013 for participation. Screening surveys were distributed school-wide to participating schools the spring prior to the study year. Children with a physician's diagnosis of asthma or with report of signs and symptoms consistent with persistent asthma, and at least one asthma symptom within the past year were invited to participate. This study was approved by the Boston Children's Hospital institutional review board. Written informed consent was obtained from the subject's guardian and assent was obtained from the subject prior to enrollment.

Study procedures

Figure 1 illustrates the study schema. Baseline characterization of study subjects was performed at a formal research clinic visit during the summer prior to the academic year in which sociodemographic information, medical history and baseline symptom profiles were assessed by questionnaire. Subjects performed spirometry with a Koko spirometer (Ferraris Respiratory, Louisville, CO) using ATS guidelines[26], Fractional exhaled nitric oxide (FeNO) with the Niox Mino device (Aerocrine, Solna, Sweden) and aeroallergen sensitization testing by allergy skin testing (MultiTest device, Lincoln Diagnostics, Decatur, IL) and/or serum specific IgE (ImmunoCAP, Phadia AB, Uppsala, Sweden). Sensitization was defined by a wheal 3 mm or larger than the negative saline control on skin prick testing or a specific-IgE level of 0.35 kU/L or greater. The tested allergens included tree pollen, grass, ragweed, dust mites, cat, dog, mouse, rat, cockroach, and molds (Greer, Lenoir, NC).

Subsequently, questionnaire based symptom assessments were performed up to 4 times throughout the academic school year by telephone interviews at 3,6,9, and 12 months. Spirometry and FeNO was assessed at two in-school visits that coincided with school environmental assessments, approximately 6 months apart. Testing occurred throughout the day with 90% of tests occurring after 10am, and the majority occurring between 10am and 3PM.

Exposure assessment

Classrooms of participating students were sampled twice during the academic yearwhile school was in session, approximately 6 months apart. NO_2 was collected via passive monitoring with Ogawa samplers[27] for 1 week periods. NO_2 analysis was performed using ion chromatography. Average NO_2 levels per assessment period were determined and used for analyses.

Outcome measures

The ratio of forced expiratory volume in 1 second (FEV_1) per forced vital capacity ratio (FEV_1/FVC) was chosen as the primary spirometric outcome of interest because it is the most sensitive marker of airflow obstruction in children with asthma[28, 29]. FEV_1 percent

predicted, FVC percent predicted and the forced expiratory flow rate between the 25th and 75th percent of FVC (FEF_{25-75}), a measure of medium and small caliber airways, were also assessed. All spirometry measures were assessed for acceptability and repeatability by study physicians per ATS guidelines[26, 30]. Reference values were derived from the NHANES III[31] reference equations which account for age, race, and gender. FeNO was measured per standardized methodology. Both spirometry and FeNO measurements were performed in the school during the same season (fall or spring) of exposure measurement.

Symptom outcomes were measured as maximum symptom days, as used in prior urban home-based studies[32, 33] and school studies[34, 35]. To define this outcome, three variables of symptoms in the 2 weeks prior to each survey were evaluated: (a) number of days with wheezing, chest tightness, or cough, (b) number of days on which child had to slow down or discontinue play activities due to wheezing, chest tightness, or cough, or (c) number of nights with wheezing, chest tightness, or cough leading to disturbed sleep. The greatest result of these three variables was used as the asthma symptom days outcome. As such, this outcome was a score from 0–14 days.

Statistical analysis

Characteristics of the cohort are expressed with descriptive statistics. Variability of NO_2 levels between schools and between classrooms within schools was determined with random effects linear regression. All clinical outcomes were linked to the temporally closest measured exposure during the academic school year. Only outcome measures obtained during the academic school year were used for analysis. The relationship between NO_2 and lung function testing was evaluated with locally weighted regression (Lowess) to examine possible non-linear relationships. Based on these smoothers, we then fit a linear spline of NO_2 with a single knot at 8ppb to be used in all subsequent models. Relationships between NO_2 and the lung function outcomes are presented as the effect of a 10ppb change in NO_2 above the threshold of 8ppb. The exposure-outcome relationship was evaluated using generalized estimating equations (GEE) with an exchangeable correlation structure, robust variance estimates, with clustering defined at the participant level. We considered clustering at the school level in addition to the participant level within a multilevel random effects model containing both subject and school random effects, but this was deemed unnecessary because there was little to no between school variability in all outcomes (intra-class correlations between 0.00 and 0.04). All models included linear and quadratic terms for the number of days since school started to address the time variation of asthma activity across the study period. Symptom outcomes were adjusted for age, race, and gender due to *a priori* assumptions that these may be important confounders. Age and gender were part of the NHANES III reference equations and so were not used as further adjustment for spirometry outcomes. 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”). Spirometry and FeNO were modeled using Gaussian family and identity link. Potential confounders that were not included in models due to a lack of association with the NO_2 ($P>0.1$) included vacuumed dust mouse allergen and endotoxin from the classrooms, income, environmental tobacco smoke (ETS) exposure, Body Mass

Index (BMI), time (hour of the day) of lung function testing, and use of asthma controller medication at baseline visit.

A term for "Any Sensitization" was created to indicate subjects with ≥1 sensitization by skin prick test or specific IgE >0.35 kU/L at baseline assessment. Based on prior literature, any sensitization was examined as a potential moderator of the NO_2 effects on asthma morbidity. Post-hoc analysis stratified by sensitization status was performed to further evaluate main effects by group. Statistical computations were performed using STATA software, version 13.1 (StataCorp). All tests were 2-tailed, and $P < .05$ was considered significant.

Results

In total, 296 participants had assessments of classroom NO_2 and were included in the analysis. Subjects were predominantly Black or Hispanic and 49% were from impoverished households (Table 1). Baseline lung function was normal and non-obstructed.

NO_2 was measured in 218 classrooms across 37 schools. Mean NO_2 levels were 11.1ppb, median 10.4ppb, and range 4.3 to 29.7ppb. Figure 2 shows the distribution of NO_2 by school for fall and spring measurements, demonstrating the variability between classrooms within schools and between schools for the spring season. School to school variability accounted for 75% of the variance in NO_2 measures, leaving 25% of the variability attributable to the classroom level.

One hundred eighty eight participants had complete data for NO_2 and acceptable spirometry for analysis. In adjusted analyses, NO_2 exposure above 8ppb was significantly associated with airflow obstruction as measured by FEV_1/FVC ratio and FEF_{25-75}, a measure of small airways dysfunction. For each 10ppb increase in NO_2, there was a 5% decline in FEV_1/FVC ratio with ratios crossing the clinically relevant normal value for FEV_1/FVC ratio of 0.85 [36] at approximately 16ppb of NO_2 (Table 2; unadjusted correlations can be found in supplementary table 1 in the online repository). Figure 3 depicts the relationship between NO_2 level and FEV_1/FVC ratio within the range of our data. Allergic sensitization did not modify the effect of this association (p=0.55 for the interaction). However, in post-hoc stratified analysis, non-atopic children demonstrated a decreased FEV_1% predicted in association with NO_2 exposure whereas atopic subjects did not (see supplementary table 2 in the online repository). There was a 22.8% decline in FEF_{25-75} for each 10ppb increase in NO_2. While FEV_1 and FVC percent predicted were negatively associated with NO_2 exposure, associations were not significant at $P<0.05$. There was no significant association of NO_2 with FeNO, a measure of airway inflammation, which was also measured at the time of exposure assessment.

There was no significant association of NO_2 exposure with maximum symptom days, the main symptom-based outcome (Table 2). Additionally, allergic sensitization did not modify the relationship between NO_2 and asthma symptoms (p=0.59 for the interaction).

Discussion

In this study, we demonstrate a temporally distinct association of school classroom measured NO_2 with airflow obstruction in inner city school children with asthma. As children spend the majority of their day in the school environment, this microenvironment for potential respiratory insults is equivalent to an occupational exposure in adults.

There are several important findings highlighted by these analyses. First, the levels of NO_2 detected in the classrooms were relatively low compared to the US Environmental Protection Agency national ambient air quality standards for NO_2 currently set at a 1 hour maximum level of 100ppb and annual average level of 53ppb[37]. Despite overall low levels, there was a clear signal of lung function impairment and a trend toward more symptoms associated with higher NO_2 exposures in this vulnerable pediatric population. This finding complements work by Belanger et al.[10] who found respiratory health effects at relatively low home levels of NO_2 and Pilotto and colleagues[15] who found health effects of NO_2 in Australian school classrooms with unflued gas heaters, though the exposure in our school classrooms was far less. In sum, this suggests that there is a concentration – response relationship of NO_2 that adversely affects health at levels below existing standards, especially in vulnerable populations. Furthermore, our data indicate a threshold level at which physiologic effects of NO_2 may occur in children with asthma. To our knowledge, this has not been previously demonstrated in other studies, which may be a reflection of our unique study design measuring levels in schools of asthmatic children– where there is no cooking, smoking, or other immediate sources of NO_2 emissions, so that the range of our data was able to elicit this level of detail. Interventional exposure studies typically use high concentrations of NO_2 for short periods of time which may not elicit the same responses as prolonged exposure to lower levels[38]. It may also be due to differences in statistical methodology in used to evaluate non-linear associations between NO_2 and respiratory outcomes[39].

Second, we did not find any interaction between NO_2 exposure and atopy, measured by specific sensitization to a battery of common aeroallergens, in relation to asthma outcomes. Furthermore, there was no association between NO_2 exposure and FeNO, a marker of allergic airway inflammation. While some prior studies have found that air pollution differentially affects allergen sensitized children with asthma[40–43], others have found that non-atopic children are more affected[11]. While our stratified analysis did find a significant association between NO_2 and FEV_1% in non-sensitized subject, this does not reflect a significant difference between the atopic and non-atopic groups in response to the exposure, which is reflected by the lack of significant interaction term. Our finding, that the relationship of NO_2 and airflow obstruction is not modified by allergic sensitization, suggests that it may influence lung function through a direct effect on the respiratory epithelium and smooth muscle by induction of oxidative stress and non-allergic inflammation. Previous literature on the biologic effects of NO_2 support the stimulation of innate immune responses rather than the TH_2 driven inflammation more characteristic of asthma[44, 45]. Human exposure studies demonstrate bronchial washings enriched for IL6, IL8, neutrophilic infiltration and acute phase reactions within 24 hours of NO_2 inhalant exposure[45]. Simultaneously, oxidative stress induction as evidenced by increased HMOX1 gene expression following NO_2 exposure to human bronchial epithelial cells is also likely to

play a significant role[44, 46]. Summation of these study results with the current epidemiologic findings of our study suggest that respiratory effects caused by inhalation of NO_2 are not mediated by the TH_2 inflammatory paradigm that is primarily implicated in pediatric asthma.

Third, we found significant variability in NO_2 levels between schools that were not seasonally dependent. The school microenvironment, particularly the school classroom, is unique in that there are few indoor sources of NO_2. Primary sources of indoor combustion leading to elevated levels of NO_2 in homes include home heating and cooking and cigarette smoking. Among the schools included in this study, there was only one with a kitchen that cooked food for lunches and all prohibited smoking on school property. Similarly, the effect of a central furnace heating multiple classrooms – when the heat is on – is unlikely to account for significant classroom to classroom variation in NO_2 exposure. In this case, differences in NO_2 levels between classrooms and between schools likely represent variable penetration and ventilation of outdoor generated ambient gases through the school classroom envelope along with local differences in traffic related emissions near each school. Similar associations of inner city school measures of NO_2 were reported by Rivas et al. in the BREATHE study of indoor pollutants in Barcelona, Spain[17]. These are potentially modifiable school classroom characteristics that may be amenable to remediation of structural imperfections, ventilation systems, or altering local traffic patterns.

The association of classroom NO_2 level with asthma symptoms was suggestive of a positive relationship but did not reach statistical significance. The lack of precision of the effect estimates may, in part, be due to exposure misclassification. By the nature of the study design, lung function testing was carried out at the time exposure measurement devices were deployed in the schools, twice per year; however, symptom outcomes were collected by phone on a quarterly basis and not necessarily in close temporal relation to the exposure measure. As such, the temporal variability significantly limits the ability to find acute health effects on asthma symptoms related to the exposure. A larger sample size may have elicited a significant long-term relationship between exposure and outcome that was not found here. It is also possible that NO_2 found in classrooms is a marker for other, unmeasured, pollutants produced by the same processes or for other pollutants chemically related to NO_2, such as ozone (O_3) or particulate matter. While this is possible, NO_2 is known to be associated with biologically plausible mechanisms to induce airway inflammation[44], hyper-responsiveness and airflow obstruction[2] in its own right. Our data is limited in the ability to tease apart NO_2 from other co-pollutants that may also be present. Additionally, unmeasured confounding factors, such as viral URIs or specific characteristics influencing susceptibility to the exposure, may have influenced our results. However, we attempted to address any seasonal variation in asthma morbidity, such as viral seasons, by including a variable for time in each analytical model, and known factors related to asthma morbidity, such as low socioeconomic status and environmental tobacco smoke, among others, were evaluated as potential confounders. Notably, time was not significantly associated with lung function or asthma symptoms within our models. Finally, our exposure measure is an average of NO_2 collected over a one-week timeframe, which limits our ability to determine the potential effect of peak levels and our ability to specify the personal exposure during school hours only. As such, this runs the risk of some element of exposure misclassification, which may

have biased our findings toward the null. Despite this, we found compelling evidence linking exposure to decrements in lung function.

Additional evidence to support the association between NO_2 and health effects exists in the form of few interventional studies in schools with high pollution levels due to poor venting of furnaces[20]. In population-based studies, ambient NO_2 has been associated with the development of childhood asthma[47] and asthma exacerbations requiring emergency services[48], as well as abnormal lung function testing in asthmatic cohorts[49]. Modeled assessments of effects and benefits of reducing NO_2 near primary schools in London indicate that a significant improvement in the number of childhood asthma exacerbations, costs to schools, and costs to parents, would be achieved by lowering exposure[50].

In conclusion, we demonstrate that exposure to NO_2 in the school classroom microenvironment is significantly related to airflow limitation in children with asthma, through a pathway that is not dependent on allergy nor production of allergic inflammation. Intervention studies are needed to determine whether reducing inhaled pollutants in the school environment may produce health benefits for vulnerable populations of children.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding source: This study was supported by NIH grants K23AI106945 (PI Gaffin), R01 AI 073964, R01AI 073964-02S1, K24 AI 106822, U01 AI 110397, U10HL098102 (PI: Phipatanakul), NIH-NIEHS K23ES023700 (PI Lai), K23AI104780 (PI Sheehan), P01 ES009825, and P30ES000002 (Gold). This study was also supported by EPA center grants RD-834798 and RD-83587201. 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 healthcare 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 healthcare centers, or the National Institutes of Health. This publication was also made possible by US Environmental Protection Agency (USEPA) grant RD-83479801 and was also funded (in part) by the cooperative agreement award number FAIN: U61TS000237 from the Agency for Toxic Substances and Disease Registry (ATSDR). The USEPA supports the Pediatric Environmental Health Specialty Units by providing partial funding to the ATSDR under Inter-Agency Agreement number DW-75-92301301. Its contents are solely the responsibility of the grantee and do not necessarily represent the official views of the ATSDR or USEPA. Further, USEPA or ATSDR do not endorse the purchase of any commercial products or services mentioned in the publication. Additional acknowledgment to The Allergy and Asthma Awareness Initiative, Inc. We thank the following companies for their generous donations. Lincoln Diagnostics, Inc., Decatur, IL, USA, Multi-Test II devices; Greer, Inc, Lenoir, NC allergenic extracts for skin testing; Thermo Fisher, Inc. ImmunoCAP® testing; Monaghan Medical, Inc aerochambers; Aeorcrine, Inc., NiOx Machines.

We are thankful for the thoughtful guidance provided by Sachin Baxi, Perdita Permaul, and Lisa Bartnikas, and for the study staff, participants and families who contributed to this research.

Abbreviations

NO_2	Nitrogen dioxide
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity

FEF_{25-75}	forced expiratory flow between the 25th and 75th percent of forced vital capacity
FeNO	Fractional exhaled nitric oxide

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Clinical implications

Nitrogen dioxide in the urban school environment is associated with airflow obstruction in children with asthma. Environmental interventions at schools may improve the health of children with asthma.

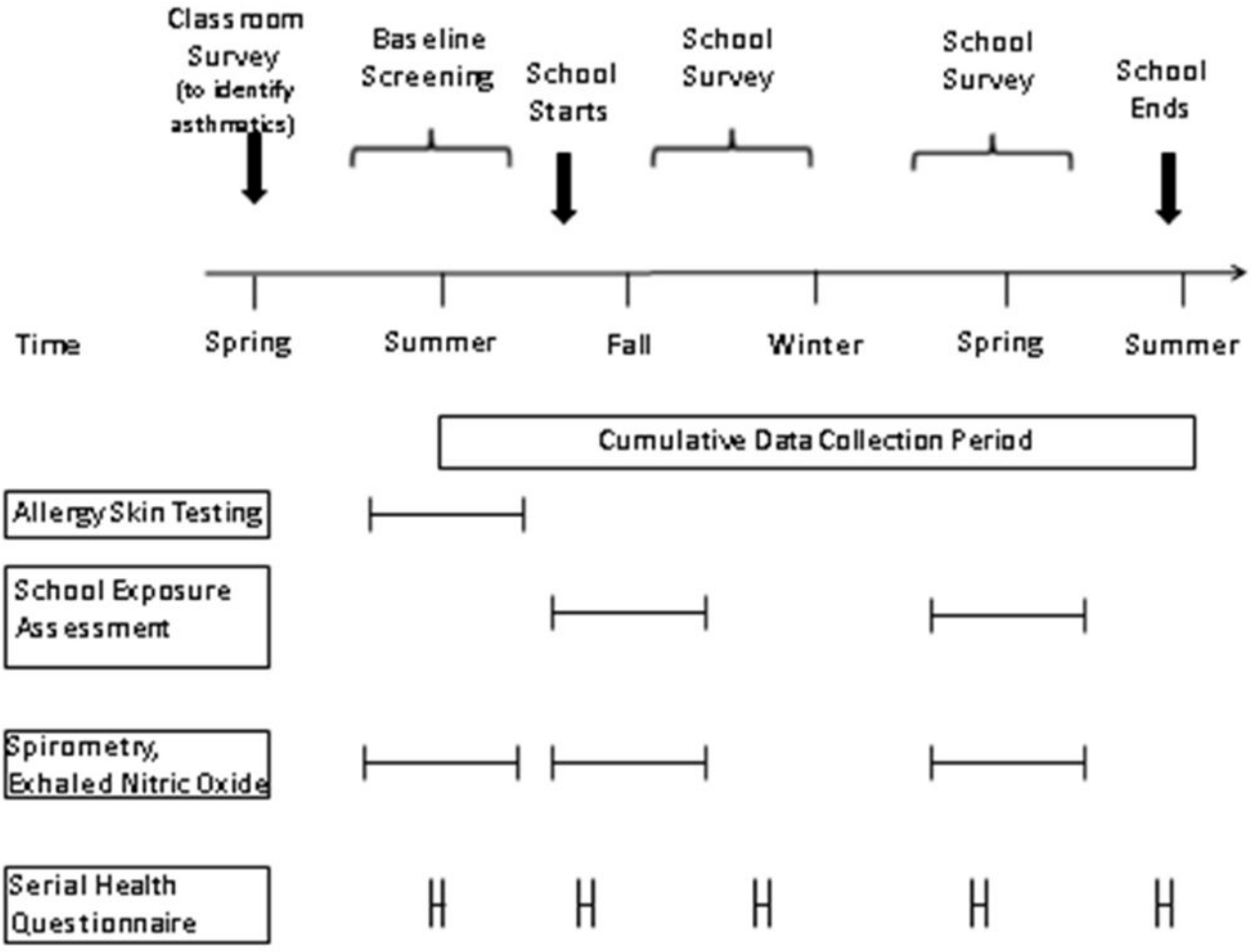

Figure 1.
Schema of Assessments in the School Inner City Asthma Study

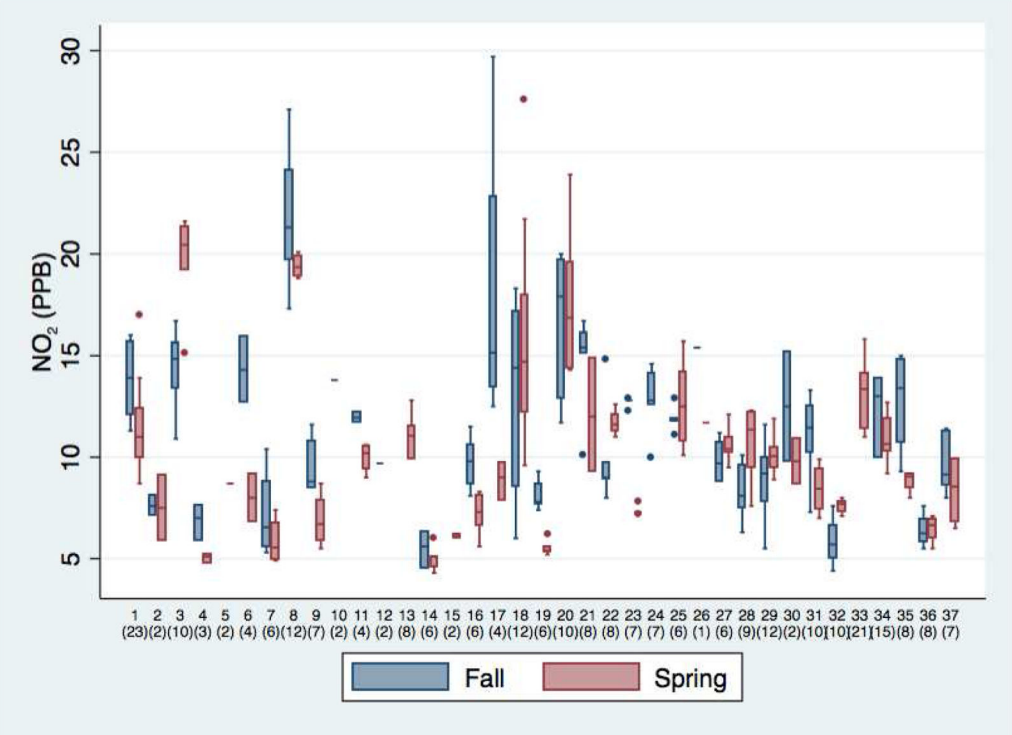

Figure 2.

Distribution of NO_2 concentrations by school, by season. X axis represents each individual school, number of subjects attending each school is in parentheses (). Box and whiskers plots represent the distribution of NO_2 across multiple classrooms within each school. Box parameters are the IQR, hash mark is the median, whiskers extend to 1.5 times the IQR above the 75^{th} and below the 25^{th} percentile.

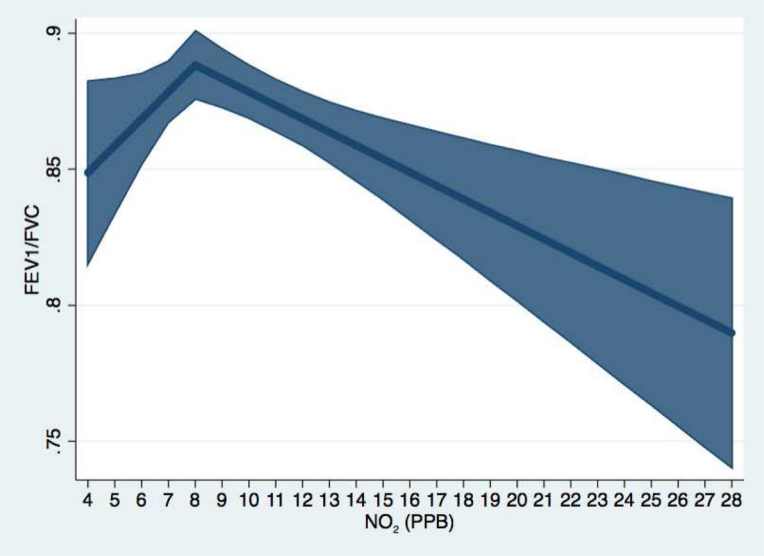

Figure 3.

Effect of classroom NO_2 on FEV_1/FVC. Association of NO_2 and FEV_1/FVC using piecewise linear regression with breakpoint at NO_2 level of 8ppb. Shaded area represents 95% confidence intervals.

Table 1

Characteristics of Study Population.

Characteristic	No. (%)
Demographic	
Age, median (range),	8 (4–13)
Female sex	143 (48)
Race or ethnic group	
White	13 (4)
Black	102 (34)
Hispanic	107 (36)
Mixed race	52 (18)
Other	22 (7)
Annual income<$25,000	120 (49)
Pulmonary Testing[a]	
FVC% predicted, mean (SD)	98 (15.5)
FEV_1% predicted, mean (SD)	100 (17.9)
FEV_1/FVC, mean (SD)	0.87 (0.08)
FEF_{25-75}% predicted, mean (SD)	118 (103.2)
FeNO, ppb, Mean (SD) (n=73)	19.6 (20.9)
Allergy sensitization ≥ 1 allergen	197 (69)
Maximum symptom days[b], mean (sd)	3.0 (4.2)
Controller medication over prior 12 months	167 (56%)
Environmental tobacco smoke exposure	97 (33%)

[a] n=188 for pulmonary testing

[b] Maximum symptom days = the greatest result of the following three variables in the 2 weeks prior to each follow-up survey: 1) number of days with wheezing, chest tightness, or cough 2) number of days on which child had to slow down or discontinue play activities due to wheezing, chest tightness, or cough 3) number of nights with wheezing, chest tightness, or cough leading to disturbed sleep.

FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; FEF_{25-75}: forced expiratory flow between the 25^{th} and 75^{th} percent of FVC; FeNO: fractional exhaled Nitric Oxide.

Table 2

Effect of NO_2 above 8ppb on spirometry and asthma outcomes in school age children with asthma

	Univariate model		Multivariate model[b]	
	Odds ratio	**95% Confidence interval (CI)**	**Odds ratio**	**95% Confidence interval (CI)**
Maximum Symptom Days[a]	1.31	0.90, 1.90	1.15	0.80, 1.64
	Beta	95% CI	Beta	95% CI
FEV_1/FVC	−0.049*	−0.077, −0.021	−0.049*	−0.078, −0.021
$FEV_1\%$	−5.5	−12.0, 0.9	−5.5	−11.7, 0.8
FVC%	−0.7	−5.8, 4.4	−0.5	−5.5, 4.5
$FEF_{25-75}\%$	−22.8*	−36.0, −9.7	−22.8*	−36.0, −9.7
FeNO	3.5	−6.9, 13.9	−0.5	−12.0, 11.0

[a]Maximum symptom days = the greatest result of the following three variables in the 2 weeks prior to each follow-up survey: 1) number of days with wheezing, chest tightness, or cough; 2) number of days on which child had to slow down or discontinue play activities due to wheezing, chest tightness, or cough, and; 3) number of nights with wheezing, chest tightness, or cough leading to disturbed sleep;

[b]Multivariate model: Maximum symptom days adjusted for Age, Race, Gender and season; spirometry and FeNO adjusted for race and time. Results scaled to each 10 ppb increment of NO_2 above 8ppb.

*p-value = 0.001.

FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; FEF_{25-75}: forced expiratory flow between the 25^{th} and 75^{th} percent of FVC; FeNO: fractional exhaled Nitric Oxide.