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Jennifer Zora April 24, 2012

Associations between weekly traffic-related air pollutants and pediatric asthma control in El Paso, Texas

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By

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Bachelor's of Arts (A.B.)
Harvard University
2006

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An abstract of
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Abstract

Associations between weekly traffic-related air pollutants
and pediatric asthma control in El Paso, Texas

By Jennifer E. Zora

Background- Previous studies have demonstrated harmful effects of traffic-related air pollution on lung function and respiratory symptoms among asthmatic children. However, no air pollution studies to date have estimated changes in lung function and symptoms concurrently using a validated, clinically relevant measure of asthma control.

Objective- To determine whether associations exist between traffic-related air pollution and asthma control in children with asthma living in El Paso, Texas, a city known for heavy traffic and high air pollution levels in the Paso del Norte (PdN) region at the United States – Mexico border.

Methods- For 13 consecutive weeks, 36 children between the ages of 6 and 12 from two El Paso area elementary schools underwent weekly pulmonary function testing and reported symptoms medication use per the Asthma Control Questionnaire (ACQ). Preceding 96-hour integrated measurements of air pollutants, including fine and coarse particles, black carbon (BC), nitrogen dioxide (NO_2), benzene, and toluene were measured outdoors at each school. Ozone (O_3), temperature, and relative humidity levels were obtained from a regulatory monitoring site located between the two schools. Linear mixed effects models were used to examine associations between the 96-hour integrated pollutant levels and weekly ACQ scores.

Results- Positive, but not significant, associations were found between weekly ACQ scores and the preceding 96-hour average pollutant levels. Subgroup analysis revealed significant associations between ACQ scores and weekly benzene levels among subjects taking daily inhaled corticosteroids (ICS, $p = 0.01$) and borderline significant associations between scores and toluene levels in this group ($p = 0.05$). Among allergic subjects, levels of BC and NO_2 were also associated with ACQ scores ($p = 0.098$ and $p = 0.057$ respectively).

Conclusion- ACQ scores were associated with weekly traffic-related pollutant concentrations among elementary school children with asthma, especially those in certain subgroups. The ACQ may serve as clinically relevant tool to evaluate acute changes in pediatric asthma related to air pollution, but further studies are needed to validate the utility of this tool in this setting.

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A. Introduction

In 2009, 7.1 million children within the United States (9.6 % of persons 0 – 17 years of age) were estimated to suffer from asthma [1], a chronic inflammatory disease of the airways with the potential for acute worsening of symptoms and lung function in response to environmental exposures. Short-term increases in traffic-related air pollutants such as particulate matter with aerodynamic diameter less than 10 microns (PM_{10}), particulate matter with diameter between 2.5 and 10 µm ($PM_{10-2.5}$, coarse PM), particulate matter with diameter less than 2.5 microns ($PM_{2.5}$, fine PM), nitrogen dioxide (NO_2), black carbon (BC), ozone (O_3), benzene, and toluene have been associated with increased respiratory symptoms [2-7], decreased lung function [8-14], and emergency room (ER) visits and/or hospital admissions [15-21] among children with asthma. In addition, residential proximity to roadways and heavy traffic has been associated with decreased lung function [22, 23] and increased hospital utilization [24, 25] among asthmatic children. Certain factors have previously been also shown to modify the effect of air pollution on asthma, such as socioeconomic status [26-30], atopy [5, 11], and use of inhaled corticosteroids (ICS) [31].

The Paso del Norte (PdN) region at the United States-Mexico border is plagued by high traffic-related pollution, and this places a vulnerable pediatric population at risk for increased asthma-related morbidity. It was estimated that 10 million passenger cars and over 700,000 trucks passed through the portal city of El Paso, Texas in 2010 [32] contributing to combustion- derived air pollutants such as $PM_{2.5}$, BC, volatile organic compounds (VOCs) such as benzene and toluene, and NO_2. Sustained high temperatures as well as temperature inversions, older cars owned by an

impoverished population, and infrequent rainfall also contribute to significant urban air pollution exposures [33-35]. Several cities within this region have repeatedly exceeded National Ambient Air Quality Standards related to particulate matter and ozone, including El Paso [36]. High levels of ground- level ozone in the region may be related to factors such as intense sunlight with limited winds and high levels of ozone-forming precursors such as NO_x and VOCs as shown by the 1996 Paso del Norte ozone study [37].

Previous studies have demonstrated that short-term exposure to various air pollutants adversely affects respiratory status among asthmatic children in the PdN region [38], including studies by our group in 2008 in El Paso and Jaurez, Mexico [39] and in 2010 in El Paso [40]. Among asthmatic children living in El Paso and Ciudad Juarez in 2008, levels of exhaled nitrous oxide (eNO, a biomarker associated with asthma exacerbation and inflammation) were measured as a function of air pollutant levels measured at schools and central sites in a longitudinal study over 16 weeks [39]. Results from that study indicate that interquartile increases in pollutants $PM_{2.5}$, PM_{10}, $PM_{10-2.5}$, NO_2, and BC (including 48- and 96- hour time lags) were significantly associated with increased eNO among the study participants. Analysis of data from our 2010 study of asthmatic children from El Paso area elementary schools demonstrates that levels of several traffic-related outdoor air pollutants are significantly associated with eNO, including particulate BC, benzene, and toluene [40]. This longitudinal study also demonstrated that outdoor benzene levels were significantly linked to a decrease in the lung function measurement of forced expiratory volume in 1 second (FEV_1), and this effect was modified by weight category.

In the current analysis, we use data from our 2010 study to examine the relationship between weekly traffic-related pollutant levels and the responses of elementary school children to a clinical survey tool, the Asthma Control Questionnaire (ACQ). The ACQ is a 7 question survey that was first developed for adults [41] that was later validated for use among children 6 – 16 years of age [42] for use in clinical settings to assess asthma status. ACQ questions score respiratory symptoms (4 questions), activity limitation (1 question), use of short-acting beta agonist (1 question), and the percent predicted FEV_1 for age, race, and height. Higher individual ACQ scores are thought to represent reduced asthma "control" that may warrant the initiation or modulation of asthma medications to decrease risk and impairment from asthma exacerbation [43].

Thus, asthma "control" as approximated by the ACQ may represent a health metric that to our knowledge as not been previously used in air pollution studies either in children or adults. Use of the ACQ allows for a survey of symptoms, medication use, and objective lung function simultaneously instead of separately as has been done previously. Additionally, the ACQ is a clinically relevant tool that allows for consistent quantification of asthma status. In this study, we examine associations between ACQ scores and several traffic-related air pollutants among asthmatic children in El Paso, Texas located at the border between the United States and Mexico.

B. Methods

Study overview

This study was conducted in El Paso, Texas from March to June, 2010 at 2 elementary schools, both of which participated in our 2008 study [39]. School 1 was designated as a "high traffic" location within 300 feet of principal arterial or high-service, capacity-controlled access roadways. School 2 was a "low traffic" location near local streets only. The study consisted of weekly repeated measurements of health outcomes, air pollution, and meteorology over a 13 week study period, which spanned from the spring to early summertime. Baseline data (related to asthma medication use, symptoms, activity limitation, prior emergency room visits and hospital admissions for the participants) was collected from their parents prior to the start of the study. Outdoor pollutant measurements and meteorological data were gathered in 96-hour segments ending on Fridays from March 12, 2010 to June 4, 2010. Weekly health outcomes sampling occurred most Fridays at each school (data not collected during spring break and testing weeks at both schools). The protocol for this study was approved by the International Review Board of Emory University.

Subject recruitment

At each school, children were recruited to participate in the study through school nurses. A legal guardian for each child provided written consent; children greater than or equal to 11 years of age provided written assent, while younger children provided verbal assent. Consent and assent forms were provided in both English and Spanish. Eligibility criteria included age between 6 and

12, a physician diagnosis of asthma, no other lung disease or major illness, a non-smoking household, and residency proximal to school location. A $50 gift card was provided to children who completed the study protocol.

Among the 38 subjects who completed the study protocol, 1 subject from School 1 was excluded from the current analysis due to missing information related to ACQ scoring, and 1 subject from School 2 was excluded due to a lack of current asthma medication use. After these exclusions, 19 children included in the study attended School 1, and 17 children attended School 2. Several children at each school had participated in the previous 2008 study.

Exposure and meteorological measurements

Air pollutants, including size resolved particles, gases, and speciated volatile organic compounds were measured for 96-hours from Monday to Friday outdoors and indoors at each school to approximate weekly traffic-related pollution [40]. Concentrations in the Paso del Norte (PdN) region have been shown to vary by school [44], and outdoor and indoor measurements of these pollutants correlate fairly well with corresponding personal exposures [45, 46]. The current analysis focused only on outdoor measurements of select pollutants, including coarse particles ($PM_{10-2.5}$), fine particles ($PM_{2.5}$), coarse and fine particles (PM_{10}), black carbon (BC), nitrogen dioxide (NO_2), benzene, and toluene. BC, NO_2, benzene and toluene were specifically chosen as more specific indicators of combustion-related traffic emissions. For outdoor measurements, samplers were placed on the roof or in a fenced area next to each school, and monitoring

equipment was placed between 8:30 and 11:30 AM on days when sampling was initiated. Sampling ended on Friday mornings, approximately at the time of health outcome measurement.

Particulate matter (PM)

$PM_{10-2.5}$ and $PM_{2.5}$ were measured using Harvard cascade impactors with isolation of particles by size through separate stages of impaction. $PM_{10-2.5}$ was collected on polyurethane foam (PUF) filters, and $PM_{2.5}$ was collected on polytetrafluoroethylene (PTFE) filters (37-mm diameter, 2 mm pore size; Pall Life Sciences, Ann Arbor, MI). Static interference was reduced using a static neutralizing bar (MEB Shockless Static Neutralizing Bar; SIMCO, Hartfield, PA, USA). MEDO pumps (Model No.VPO125; MEDO USA, Inc., IL) were used to generate air flow through the samplers at a rate of approximately 5 liters per minute. The sampling flow rate was determined after each sampling period using a Buck flow calibrator (Model M-30, 0.1-30 LPM; A.P. Buck, Inc., Orlando, FLA), and the acceptable flow rate range was +/- 5% of the target flow rate. All filters were weighed and conditioned at room temperature (25º +/- 3º Celsius) and humidity (30 +/- 5%) for at least 24 hours before and after sampling and were stored for less than or equal to 30 days.

Mass concentrations were quantified by gravimetric analysis at the University of Texas-El Paso (UTEP) Air Quality Laboratory using a microbalance (CAHN Model C-33; Orion Research, 1997) with an accuracy of 2 µg and an absolute precision of 1 µg. The accuracy of the process was checked using a certified mass prior to each session, and blank filters were weighed prior to sampling. The average of 3 separate weight

measurements was used for analysis, and the acceptable range for each of the measurements was +/- 10 µg (filter was re-weighed if outside the acceptable range). The difference of the average weight measurement and the blank filter represented the collected mass concentration which was measured in micrograms of PM per cubic meter of air (µg/ m^3). $PM_{10-2.5}$ and $PM_{2.5}$ were measured during two 48-hour sampling sessions (Monday – Wednesday and Wednesday – Friday) each week, and the two measurements were integrated to obtain weekly 96-hour averages. PM_{10} values were calculated as the sum of the $PM_{10-2.5}$ and $PM_{2.5}$ measurements.

Black carbon (BC)

A surrogate of elemental carbon [47] that is well-correlated with traffic-related pollutants [48], BC was calculated as a loss of reflectance from $PM_{2.5}$ filters. Digital Smoke Stain Reflectometers (Model EEL, 43D; Diffusion Systems, Ltd., London, UK) were used to calculate reflectance of the sampled filters compared to blank filters which were set to a reflectance of 100%. The overall reflectance measurement was averaged from 5 measurements at 5 separate locations on each filter (5-point method). The percentage of reflectance was transformed onto absorption coefficients using standard ISO-approved methods (ISO 9835, International Organization for Standardization), using the equation:

$$a = \frac{A}{2V} \ln \frac{R_o}{R} \quad (1),$$

where

R = Reflectance of sampled filter;

R_o = Reflectance of the field blank filters;

A = Area of the loaded filter (m^2);

V = Volume of air sampled (m^3); and

a = Absorption coefficient (m^{-1} x 10^{-5}).

The absorption coefficient was multiplied by 10^{-5} for reporting and was used to calculate the mass of BC in µg per unit volume air that passed through the sampler (µg/m^3). Since these measurements were deduced from $PM_{2.5}$ measurements, BC reflected a sampling session from Monday to Friday each week (96-hour integrated average).

Nitrous oxide (NO_2)

NO_2 measurements were obtained using passive badge samplers with a single cellulose filter coated with triethanolamine (Ogawa and Company, Pompano Beach, FLA). Samplers were prepared at the Harvard School of Public Health (Boston, MA) and were placed in the field from Monday through Friday for a 96-hour sampling session. Loaded samplers were stored at -4° Celsius at the UTEP Air Quality Laboratory prior to shipment back to the Harvard School of Public Health analysis. NO_2 was extracted and quantified using ion chromatography analysis [49] in parts per billion (ppb) air particles.

Volatile organic compounds (VOCs, benzene and toluene)

Outdoor VOC concentrations at each school were measured using passive badge samplers (3M 3500 Organic Vapor Monitor, 3M Company, St. Paul, Minnesota). The

samplers were placed in the field for a four day sampling period (96-hours) from Monday to Friday of each week. Samplers were refrigerated and shipped on ice to the University of Texas School of Public Health laboratory in Houston for analysis on a biweekly basis, and samplers were analyzed within 4 -5 days of receipt. Details of the extraction and processing procedures have been described elsewhere [50]. Gas chromatography- mass spectrometry (GC-MS) analysis was performed using a gas chromatograph (HP 6890 series; Hewlett-Packard, Palo Alto, CA) and a mass spectrometry detector ((MSD) Agilent Technologies, Santa Clara, CA). The mass spectrometry was analyzed using appropriate computer software (EnviroQuant; Agilent Technologies, Santa Clara, CA).

The VOC samplers were analyzed in 7 separate batches (22 field blanks and 14 field samplers analyzed) using column-based chromatography (Restek, RTX- 624, 60-m, 0.25 mm ID with a 1.4 mm thickness column; Restek Corporation, Bellefonte, PA). The mean of blank sampler masses was subtracted from individual sampler masses to obtain the concentration of benzene and toluene in parts per billion (ppb). Prior to each batch, a calibration curve was performed for the column. A duplicate analysis was performed after 20 sampling runs (and then every 20^{th} run) followed by a 1.0 µg/mL standard and a solvent wash.

Ozone (O_3) and meteorological data

Ozone (in ppb), temperature (in º Farenheit), and relative humidity (%) were collected from Continuous Air Monitoring Station (CAMS)-41 in El Paso, operated by the Texas Commission on Environmental Quality (TCEQ). Hourly values were aggregated to

produce 96-hour averages from Monday to Fridays. The CAMS-41 site was chosen *a priori* to be used for analysis due to its central location between School 1 and School 2.

Health outcomes measurement

Health outcomes were collected at school sites as has been done in other studies [51, 52] as well as in our 2008 [39] and 2010 studies [40]. Most Fridays during the study (not including spring break and testing weeks), children underwent pulmonary function testing and reported symptoms and use of asthma medications in response to survey questions.

Lung function testing

The percent predicted lung function for each subject was assessed for use for question 7 of the ACQ. Spirometers (EasyOne; NDD Medical Technologies, Andover, MA) were used with disposable spirettes through which the subjects exhaled and inhaled. English-Spanish bilingual coaches were available as needed. Lung function was assessed based on forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), peak expiratory flow (PEF), and forced expiratory flow during the 25^{th} through the 75^{th} percentiles of the time used for exhalation (FEV_{25-75}). The best effort was selected based on maximum FEV_1, and the percent of predicted FEV_1 was determined using age, height, gender, and ethnicity as suggested by analysis of data from the National Health and Nutrition Examination Survey III (NHANES III) [53]. The FEV_1 percent predicted value was used to calculate the score for one ACQ question (see below).

Questionnaires- Asthma control - as determined by ACQ

In addition to lung function measurements, subjects answered questions about symptoms and medications use per the first 6 questions of the ACQ [41, 54]. Subjects also answered other questions about respiratory symptoms that were not included in the current analysis. English-Spanish interpretation was available as needed. On Fridays, ACQ scores for each subject were calculated as the mean of the sum of the individual question scores, which included 5 questions relating to respiratory symptoms secondary to asthma (nighttime awakenings, morning symptoms, activity limitation, shortness of breath, wheezing), 1 question regarding the use of short-acting bronchodilators (SABA), and 1 question concerning the FEV_1 percent predicted value. Individual question scores on the 7 question ACQ are scaled from 0 to 6, and higher numbers on the scale are associated with greater severity. The averaged sum comprises the total ACQ score. Therefore, the minimum overall ACQ score is 0.0, and the maximum score is 6.0 for poorly-controlled asthma.

Statistical analysis

Linear mixed effects models (PROC MIXED, SAS v9.3) were used to examine associations between weekly asthma control scores and corresponding 96-hour average air pollution levels. In the main analyses, pollutants were modeled as fixed effects, and subjects were modeled as random effects. Covariates in the models included 96-hour average relative humidity and temperature as linear terms with school as a categorical variable [6, 55]. Additional control for repeated measures was obtained through the use of a compound symmetry covariance structure.

The distributions of independent and dependent variables were evaluated for unusual trends and general distribution.

To assess for potential effect modification of the air pollution-asthma control associations, analyses were stratified by allergic phenotype (defined as allergic to aeroallergens or food: yes/no), use of government-sponsored insurance status [defined as Medicaid coverage at some point in past year (yes/no)], current daily use of inhaled corticosteroids (yes/no), use of oral corticosteroids during the previous 3 months (yes/no). Analyses stratified by school and by weight status (obese versus non-obese) were also conducted. Two-pollutant models of PM with either NO_2, benzene, toluene, or O_3 were run to assess for potential co-pollutant confounding. To compare the magnitude of effect across different pollutants, effect estimates were scaled to interquartile range (IQR) increases in pollutant concentrations determined from the distribution of all measurements from both schools. Sensitivity analysis was also performed to assess the effects of individual subjects on overall trends using Cook's D statistics (data not shown).

C. Results

Study population

Table 1 presents the baseline characteristics of the study subjects, who ranged from 6 to 11 years of age with an overall mean age of 9.3 [standard deviation (SD) +/- 1.5] years. The mean age of subjects at School 1 [8.8 (+/- 1.6) years] was significantly lower than that at School 2 [9.9 (+/- 1.1) years; p-value = 0.02 for School 1 versus School 2]. Overall, 33.3% of the subjects were female; 66.6% were male. The study population included 22 (61.1%) individuals of self-reported (by parents) Mexican descent, 5 (13.9%) of Hispanic (non-Mexican) descent, 1 (2.8%) of African-American descent, 5 (13.9%) of Caucasian race/ethnicity, and 1 (2.8%) of mixed race (with 2 missing values overall (5.6%)). At School 1, 9 subjects (47.4%) had a healthy weight, 2 (10.5%) were overweight, and 8 (42.1%) were obese per the Centers for Disease Control and Prevention (CDC) weight categories for children and adolescents [56]. At School 2, 13 (76.5%) subjects had a healthy weight, 3 (17.6%) were overweight, and 1 (5.9%) was obese per the CDC guidelines. Overall, the distribution by weight category differed significantly by school, with a greater number of obese children at School 1 (p-value = 0.02 for School 1 versus School 2).

Additional baseline factors related to socioeconomic and asthmatic type/status included government sponsored insurance (during the past year) for 14 subjects (73.7%) at School 1 compared to 4 subjects (23.5%) at School 2 (p-value = 0.003). From School 1, 8 subjects (42.1%) had allergies to either food or aeroallergens, and 9 subjects (52.9%) suffered from allergies from School 2. A marker of more severe asthma, inhaled corticosteroids were used for asthma treatment by 7 (36.8%) from School 1 and by 5 (29.4%) from School 2. Oral

corticosteroids (OCS) were used during the past 3 months by 8 subjects from both School 1 and School 2 (42.1 and 47.2% respectively). From School 1, 7 (36.8%) had gone to the emergency room (ER) for asthma during the past 3 months, while 4 (25.5%) from School 2 had utilized the ER during the same time period.

Air quality data

Air pollution and meteorological data are presented in Table 2 by measurement location and overall (calculated as the average of the two school-based measurements each week, with trends by school graphed in Appendix, Figures 1 - 10). Overall PM_{10} levels ranged between 6.6 and 66.1 $\mu g/m^3$ overall (with interquartile range (IQR) = 19.7); $PM_{10-2.5}$ ranged between 2.6 and 41.2 $\mu g/m^3$ (IQR = 14.8); and $PM_{2.5}$ ranged between 4.0 and 24.9 $\mu g/m^3$ (IQR = 5.7). Levels of BC ranged from 0.0 to 0.9 $\mu g/m^3$ (IQR = 0.4), and measured NO_2 ranged from 1.2 to 16.2 ppb (IQR = 5.5). Benzene levels overall ranged from 0.2 to 2.4 ppb (IQR = 0.8), and toluene levels overall ranged from 0.2 to 8.2 ppb (IQR = 2.4). Levels of ozone ranged from 20.1 to 39.6 ppb with an IQR of 8.7. Temperatures over the course of the study ranged from 49.1 to 82.9 º Fahrenheit with an IQR of 15.9. Relative humidity ranged from 12.3 to 42.7 percent with an IQR of 21.5. PM values were consistently higher at School 1 compared to School 2. Levels of NO_2, benzene, and toluene were also substantially higher at School 1 compared to School 2. This difference in traffic-related pollutant concentrations between the schools was expected given that School 1 is located closer to major highways with higher traffic density, compared to School 1.

Spearman correlations among the school-based monitors for School 1 and School 2 are presented in Table 3. At the School 1, PM_{10} was significantly and positively correlated with both $PM_{10-2.5}$

($r_s = 0.96$) and $PM_{2.5}$ ($r_s = 0.68$). Also at School 1, the outdoor concentrations of traffic-specific BC, NO_2, benzene, and toluene were all significantly and positively inter-correlated ($r_s \geq 0.56$). Patterns of correlation among the pollutants were different at School 2, in that correlations among PM_{10}, $PM_{10-2.5}$, and $PM_{2.5}$ were all high ($r_s \geq 0.87$), and correlations among pollutants BC, NO_2, benzene, and toluene were weaker ($r \leq 0.53$). At both schools, the PM pollutants (PM_{10}, $PM_{10-2.5}$, $PM_{2.5}$) showed weak or negative correlations with the traffic-specific pollutants. Moderate to strong correlations in pollutant concentrations between the schools were found for all particulate pollutants, except for PM_{10-25} ($r_s = 0.09$); strongest correlations were found for $PM_{2.5}$ ($r_s = 0.89$). Strong correlation was also found for NO_2, benzene, and toluene levels between schools ($r_s \geq 0.59$).

ACQ score data

A total of 386 Asthma Control Questionnaires were completed throughout the study, with 7 to 12 repeated measures per subject (average of 10.7 ACQ scores per subject). Table 4 presents ACQ score summary statistics overall and by school. Overall, the mean ACQ score for the study subjects was 0.8 (SD +/- 0.6) with a minimum score of 0.0 and a maximum score of 3.3. For School 1, the mean ACQ score (N = 210; mean ACQ score = 0.9 (+/- 0.7)) was slightly higher than that at School 2 (N = 176; mean ACQ score = 0.6 (+/- 0.5)). Weekly trends for each subject by school are presented in Appendix, Figures 11 and 12, and subject-specific ACQ summary statistics are listed in Table 1 of the Appendix.

Epidemiologic associations

Associations between the ACQ scores and 96-hour pollutant concentrations per interquartile range increase in pollutant level are presented in Table 5. All pollutants showed positive (albeit non-significant) associations with ACQ score. With the exception of NO_2 and O_3, most models indicated an approximate 0.03 unit increase in ACQ score for each IQR increase in pollutant concentration.

The results of two-pollutant models are available in Table 2 of the Appendix as effect estimates that can be compared to Table 5 of the main text. Particularly for the particulate pollutants, results for each pollutant were similar whether examined in a single-pollutant model or a two-pollutant model with another pollutant, suggesting that co-pollutant confounding did not drive the main associations for these pollutants. In contrast, effect estimates were generally less similar in comparisons for NO_2, benzene, toluene, and ozone between one- and two-pollutant models including these pollutants. Associations for the secondary pollutant O_3 changed sign from positive to negative in several two-pollutant models, but the effect estimates remained non-significant.

Associations between ACQ score and selected pollutants were analyzed according to subgroups of allergic (vs. non-allergic), government-sponsored insurance (i.e., Medicaid over the past year versus not) as an indicator of socio-economic status, daily inhaled corticosteroids (ICS vs. not), recent oral steroid (in the past 3 months vs. none) in Table 6. For several pollutants, including PM, BC, and NO_2, associations were stronger in allergic subjects than non-allergic subjects (with marginally-significant associations in allergic subjects observed with BC and NO_2). Patterns of

association by daily ICS use were mixed among the pollutants, but strong associations in ICS users were found for benzene (change in ACQ score = 0.18 per IQR increase, p-value=0.01) and toluene (change in ACQ score = 0.12 per IQR increase, p-value = 0.05). Among subjects having utilized government-sponsored insurance during the previous year, associations were not significant but were consistently stronger than those subjects not having used government sponsored insurance. For all pollutants, subjects without recent oral steroids use showed stronger associations than those with recent oral corticosteroids (OCS), with marginally-significant associations found with PM_{10}, $PM_{10-2.5}$, and $PM_{2.5}$ among those without recent OCS use.

Additional subgroup analyses by school and by weight status are available in Tables 3 and 4 of the Appendix, respectively. Using a model that did not include the fixed effect of school but rather utilized school in subgroup analysis, associations remained non-significant and patterns of association by school were not consistent across the pollutants (Appendix, Table 3). No consistent pattern of effects was observed in these weight category subgroup analyses, though effect estimates demonstrated positive associations with weight category strata of obese and non-obese children except for the model that included the pollutant NO_2 (Appendix, Table 4).

Sensitivity analysis

To examine the sensitivity of our overall results to individual subjects, the four subjects with the highest Cook's D effects by pollutant (data not shown) were individually removed from the analyses and the resulting model estimates are presented in Table 5 of the Appendix. Overall, exclusion of these subjects generally demonstrated the same trend of non-significant positive associations between ACQ score and each pollutant. Two subjects, however, did impact the

magnitude of observed effects. For example, removal of subject 30 from School 2 weakened the effect estimate substantially for $PM_{2.5}$, PM_{10}, $PM_{10-2.5}$, and BC. Removal of subject 9 from School 1 notably strengthened the effect estimate for BC, benzene, and toluene, although results remained non-significant.

D. Discussion (include strengths and limitations)

A measure of asthma "control," the Asthma Control Questionnaire (ACQ) score was created to reflect asthma status as the combination of subjective symptoms and objective lung function [41, 42], and a shortened version of the ACQ has been shown to correlate significantly with changes in eNO in a study of adults with asthma [57]. The ACQ is intended to serve as a clinical tool for individual patients to assess the need for medical treatment (or more intensive treatment), the efficacy of treatment, and/or the response to treatment. Physicians might use the ACQ score or individual questions to initiate medical treatment or to "step-up" or "step-down" current asthma treatment based on the "severity" of asthma symptoms, lung function decrement, and/or perceived activity limitation, which are together represented by the ACQ score. To our knowledge, no study of the effects of air pollution on asthma in children has utilized an asthma control tool to analyze how pollutants might lead to reduced asthma control through worsened asthma symptoms and lower lung function. One of the main aims of the current analysis was to determine if the ACQ is a suitable tool to reflect changes in air quality, in particular traffic-related air pollutants, that have previously been shown to impact asthma among children in the PdN region [38-40].

In this study, we found strongly suggestive, albeit largely non-significant associations between ACQ score and PM_{10}, $PM_{10-2.5}$, $PM_{2.5}$, BC, NO_2, benzene, toluene, and ozone. Based on previous studies that have shown adverse effects of air pollution on respiratory symptoms [2-7] and lung function [8-12, 58], our observation of positive associations when modeling the overall ACQ score was expected given that this score includes measurements of both subjective asthma

symptoms and objective lung function measurement. Previously the minimally clinically important change in ACQ value among children in one study was 0.52 ± 0.45 [42], and IQR increases in pollutants found in our study did not lead to ACQ changes of this magnitude. However higher pollutant levels as have been seen in other studies might lead to clinically significant changes in ACQ scores.

Observation of positive associations largely held in subgroup analyses when considering allergic vs. non-allergic patients, government-based health insurance use during the last year vs. not, daily ICS vs. not, and recent oral steroid use vs. not recent use. Associations were stronger for some subgroups, in particular among subjects taking daily inhaled corticosteroids (ICS). Among those subjects, a significant association was found with benzene ($p = 0.01$), and a borderline significant association was found for toluene ($p = 0.05$). Among those not taking daily ICS, associations with benzene or toluene were negative and non-significant. Other near-significant associations were noted among children without recent oral corticosteroid (OCS) exposure. It is important to note that some associations were negative (although not significant) for some strata using various pollutant models.

The patterns that emerged related to steroid medication use may reflect the immune system response in more severe asthmatics, those who might have comparatively worse asthma "control" and higher ACQ scores at baseline (i.e. prior to optimal medication intervention) and/or after the initiation of asthma treatment medication(s). Since children with more severe asthma are prescribed daily ICS, air pollutants may lead to greater asthma exacerbation for this group. Similar results have been shown previously with generally stronger associations of

fractional exhaled nitric oxide (Fe_{NO}) with particulate pollution for asthmatic children on ICS therapy alone for long-term control [36]. In our study, stronger associations were not seen for the separate subgroup of children with recent OCS exposure as a medication with potent anti-inflammatory effects typically used for more serious exacerbation. It could be that use of daily ICS reflects persons with more severe asthma as does the use of OCS, but that the comparatively reduced potency of daily ICS allows for air pollutant exposures to influence asthma control. It is important to note though that our results contrast with previous studies in which asthmatic children not taking ICS demonstrated comparatively increased eNO [59] and reduced response to bronchodilators [60] with short term exposure to air pollutants including PM.

Other subgroup findings pertain to allergic phenotype and socioeconomic status/access to care as measured by use of government-sponsored insurance during the past year. Associations were not significant for those having used government sponsored insurance during the previous year, although associations were elevated compared to those without government-sponsored insurance. These findings are consistent with previous studies that have found stronger associations between air pollutants and poorer asthma outcomes among those of low socioeconomic status (SES) [26-30]. In our study, non-significant findings for the low SES group may be due to a number of factors including lack of power as well as measurement error since insurance status might not appropriately reflect SES. In those who were not defined as having an allergic phenotype, associations were also negative with BC, NO_2, benzene, and toluene. Previously, subgroups of asthmatic children with allergy have demonstrated stronger associations between air pollution and asthma symptoms and signs [5, 61].

An ACQ score for an individual may reflect a variety of factors both directly and indirectly related to the asthma disease process [62-73]. For example, the ACQ score for a given individual may reflect his/her access or adherence to medications, education related to the disease [69], current medications [66, 68], exposure to illness [72], and/or allergic status [62]. The ACQ may also reflect appropriate prescription of medications based on level of asthma severity [68] and appropriate medication and equipment use [63]. Both short-term and long-term indoor and outdoor environmental exposures and propensity to an allergic response would be expected to influence the ACQ score, and ACQ scores have also been shown to differ among persons based on body mass index [65, 67]. Moreover the ACQ might reflect certain unintended factors, such as socioeconomic status [71], stress exposure [70], mood status [73], or quality of parenting. In the case of using the ACQ score in pediatrics, the score reflects not just the child's approach to managing the disease, but also that of the parent. ACQ scores are also dependent on the individual answering the questions in terms of their understanding of the questions and personal perception of asthma symptom severity, and this perception has been shown to differ by gender [64].

Since a multitude of factors could potentially influence the ACQ score for a given individual, it was important to use a longitudinal study design to assess the impact of short-term changes in air quality. This design allowed for each individual to serve as his/her own control throughout the length of the study, and allowed for the analysis of changes in ACQ scores within each individual in relation to changes in air pollutant levels, rather than a comparison of scores between subjects. If an individual person had reduced access to medications or consistently used improper form when using medications that resulted in little inhaled medication, then this person

may present with more “severe” asthma at baseline and during exacerbation that would reflect poor asthma “control.” This person might therefore start at a higher ACQ score at baseline and then change more with air pollutant exposures or change at the same or different rate as another person with a lower baseline score.

Limitations of this study exist related to the study methods in the current analysis. First, the use of the *a priori* model involving 96-hour measurements of pollutants, relative humidity, and temperature may not accurately reflect the interaction and effects of air pollutants on asthma. In addition, the use of outdoor monitoring at school-based sites is superior to region-based monitoring, but perhaps inferior to more costly personal monitoring. Due to the variability of conversion as well as the lack of correlation with $PM_{2.5}$ measurements, measurement error associated with the use of this microenvironmental exposure metric may undermine risk estimates. Medication use was also not controlled during the study, and changes in medications used either added or discontinued may have led to unaccounted within-subject in response. It is possible that the children who participated in the study did not understand the questions to the ACQ or could have received unbalanced coaching, which might have unfairly strengthened effect estimates for these individuals. It should also be noted that subgroup analysis that appears to reflect one aspect of asthma control status could actually be measuring some other unknown factor that is affecting asthma control in the context of air pollutant exposures. The inclusion of a greater number of subjects in the study could have provided more power to observe significant associations.

Additional limitations relate to the study in the context of sensitivity analysis which suggests certain individuals might have strongly affected the results. This limitation must be considered particularly in the interpretation of the borderline significant effect estimates among children who had not recently used oral steroids and particulate pollutants, since this group contained an influential subject who would have strengthened the effect estimate (Subject 30 from School 2) and also did not contain one that would have weakened the estimate (Subject 9 from School 1). The inclusion of an influential subject in the non-Medicaid group (Subject 30 from School 2) might have also contributed to the lack of significantly increased susceptibility among subjects with Medicaid status over the past year as has been seen in other studies [26-29]. It is possible that Medicaid status also does not appropriately reflect socioeconomic status as a subject characteristic.

E. Conclusion

We believe that these suggestive findings strongly warrant additional studies with larger sample sizes that might be able to detect significant changes in ACQ scores based on pollutant levels that might exist, with stronger results seen in certain subject subgroups. Since asthma exacerbation leads to poor quality of life for children and their families, as well as a high economic burden for society [29, 74, 75], this issue remains paramount. If the ACQ is appropriately used in the context of air pollution studies, it could reflect clinically measurable and relevant changes in lung function and asthma symptoms that result from poor air quality and could increase our understanding of how air pollution influences asthma exacerbation. If the adverse health effect of air pollution can be more precisely quantified, public-health related instructions to avoid certain clinically harmful pollutant for asthmatic children might also be further delineated. Environmental regulations to reduce air pollutant emissions or allowable ambient levels might also be changed and/or improved. This would be especially important in high traffic regions like Paso del Norte and cities like El Paso that contain a vulnerable pediatric population subjected to high air pollution exposures at the United States – Mexico border.

F. Tables

Table 1. Subject demographic and baseline characteristics.[1]

Characteristic	Overall (n = 36)	School 1 (n = 19)	School 2 (n = 17)	p-value
Age (years as a whole number) [2ǂ]	9.33 ± 1.53	8.79 ± 1.65	9.94 ± 1.14	0.022
Height (inches) [2]	55.83 ± 4.29	55.00 ± 4.77	55.76 ± 3.58	0.224
Gender[3]				
Female	12 (33.3)	7 (36.8)	5 (29.4)	
Male	24 (66.7)	12 (63.2)	12 (70.6)	0.637
Race[4]				
Mexican	22 (61.1)	11 (57.9)	11 (64.7)	
Other Hispanic	5 (13.9)	5 (26.3)	0 (0.0)	
African American/Black American	1 (2.8)	0 (0.0)	1 (5.9)	
Caucasian	5 (13.9)	2 (10.5)	3 (17.6)	
Mixed race	1 (2.8)	0 (0.0)	1 (5.9)	
Missing	2 (5.6)	1 (5.3)	1 (5.9)	0.984
Weight category[4, 5 ǂ]				
Healthy weight	22 (61.1)	9 (47.4)	13 (76.5)	
Overweight	5 (13.9)	2 (10.5)	3 (17.6)	
Obese	9 (25.0)	8 (42.1)	1 (5.9)	0.024
Parent with asthma[3]	13 (36.1)	9 (47.4)	4 (23.5)	0.137
Sibling with asthma[4]	10 (27.8)	6 (31.6)	4 (23.5)	0.596
Caretaker (parent or sitter) smoking[4]	5 (13.9)	2 (10.5)	3 (17.7)	0.543
Medicaid coverage (at some point past year)[3ǂ]	18 (50.0)	14 (73.7)	4 (23.5)	0.003
Allergic phenotype (aeroallergens or food)	17 (47.2)	8 (42.1)	9 (52.9)	0.517
Inhaled corticosteroid use (current daily)[3]	12 (33.3)	7 (36.8)	5 (29.4)	0.637
SABA use (for symptoms or daily)[3]	24 (66.7)	14 (73.7)	10 (58.8)	0.345
Asthma control (over past 3 months)				
Asthma symptoms with exercise[3]	22(61.1)	12 (63.2)	10 (58.8)	0.790
Asthma symptoms at night[3]	17 (47.2)	9 (47.4)	8 (47.2)	0.985
Oral steroid use[3]	16 (44.4)	8 (42.1)	8 (47.2)	0.765
Emergency Room visit (for asthma) [3]	11 (30.6)	7 (36.8)	4 (25.5)	0.387

[1] Abbreviations: BMI = body mass index (weight in kilograms/ (height in meters)^2); SABA = short-acting beta-agonist.

[2] Mean ± standard deviation (Pooled T-test for significance).

[3] Test of significance is Pearson chi-square test for specific proportions.

[4] Test of significance is Mantel Haenszel chi-square test for specific proportions.

[5] Weight classifications are determined by Centers for Disease Control and Prevention guidelines for pediatric weights ("Healthy" weight greater than 5th and less than 85th percentile for age, "overweight" is greater than the 85th and less than the 95th percentile age, and the "obese" is greater than or equal to the 95th percentile for age).

ǂ P-value for test of significant difference between School 1 and School 2 is less than 0.05.

Table 2. Air pollution and meteorology summary statistics overall and by measurement location.[1, 2]

Pollutant (Unit)	N	Mean	SD	Minimum	Maximum	IQR
PM_{10} ($\mu g/m^3$)	21	28.2	15.2	6.6	66.1	19.7
School 1	11	35.2	12.1	16.7	66.1	9.6
School 2	10	20.4	14.9	6.6	59.3	11.7
$PM_{10-2.5}$ ($\mu g/m^3$)	21	16.2	10.8	2.6	41.2	14.8
School 1	11	21.4	8.0	9.6	41.2	7.2
School 2	10	10.5	10.9	2.6	40.8	5.0
$PM_{2.5}$ ($\mu g/m^3$)	21	11.9	4.9	4.0	24.9	5.7
School 1	11	13.8	4.4	7.1	24.9	2.0
School 2	10	9.9	4.8	4.0	18.5	6.7
BC ($\mu g/m^3$)	21	0.3	0.3	0.0	0.9	0.4
School 1	11	0.5	0.3	0.2	0.9	0.5
School 2	10	0.2	0.2	0.0	0.7	0.2
NO_2 (ppb)	26	6.4	3.9	1.2	16.2	5.5
School 1	13	9.3	3.2	5.6	16.2	2.1
School 2	13	3.4	1.7	1.2	7.5	1.6
Benzene (ppb)	26	1.0	0.6	0.2	2.4	0.8
School 1	13	1.5	0.5	0.8	2.4	0.7
School 2	13	0.5	0.2	0.2	0.8	0.3
Toluene (ppb)	26	2.6	2.0	0.2	8.2	2.4
School 1	13	4.1	1.8	1.8	8.2	1.9
School 2	13	1.1	0.5	0.2	2.4	0.6
O_3 (ppb)						
CAMS-41	12	31.7	6.0	20.1	39.6	8.7
Temperature (ºC)						
CAMS-41[3]	12	68.0	10.5	49.1	82.6	15.9
Relative humidity (%)						
CAMS-41[3]	12	25.2	11.2	12.3	42.7	21.5

[1] Abbreviations: N = number; SD = standard deviation; IQR = interquartile range; $\mu g/m^3$ = microgram/ (meter)^3; ppb = parts per billion; $PM_{2.5}$ = particulate matter with aerodynamic diameter less than 2.5 µm (fine PM); $PM_{10-2.5}$ = particulate matter with aerodynamic diameter between 2.5 and 10 µm (coarse PM); PM_{10}= particulate matter with aerodynamic diameter less than 10 µm; NO_2 = nitrogen dioxide; BC = black carbon; O_3 = ozone; C = Celcius. CAMS-41 = Continuous Air Monitoring Station # 41.

[2] Pollutant, temperature, and humidity measurements are 96-hr averages from Monday through Friday.

[3] Measured at central monitoring station CAMS-41, operated by the Texas Commission on Environmental Quality (TCEQ).

Table 3. Spearman correlations among school outdoor and ambient environmental concentrations (N = 10 – 13).[1, 2]

		School 1							School 2							CAMS-41		
		PM_{10}	$PM_{10-2.5}$	$PM_{2.5}$	BC	NO_2	Benz	Tol	PM_{10}	$PM_{10-2.5}$	$PM_{2.5}$	BC	NO_2	Benz	Tol	O_3	T	RH
School 1	PM_{10}	1.00																
	$PM_{10-2.5}$	**0.96**	1.00															
	$PM_{2.5}$	**0.68**	0.53	1.00														
	BC	-0.25	-0.2	-0.02	1.00													
	NO_2	-0.12	-0.10	-0.33	**0.56**	1.00												
	Benz	-0.22	-0.19	-0.02	**0.88**	**0.71**	1.00											
	Tol	-0.04	0.01	0.10	**0.87**	**0.71**	**0.91**	1.00										
School 2	PM_{10}	0.47	0.25	**0.84**	-0.10	-0.26	-0.07	0.07	1.00									
	$PM_{10-2.5}$	0.26	0.09	**0.68**	-0.25	-0.50	-0.22	-0.08	**0.92**	1.00								
	$PM_{2.5}$	0.52	0.30	**0.89**	-0.01	-0.20	0.02	0.15	**0.99**	**0.87**	1.00							
	BC	-0.41	-0.55	0.13	0.60	0.26	0.49	0.26	0.09	-0.03	0.15	1.00						
	NO_2	-0.22	-0.18	-0.45	0.29	**0.59**	0.36	0.40	-0.21	-0.26	-0.19	0.02	1.00					
	Benz	-0.11	-0.15	0.07	0.50	0.37	**0.70**	0.53	0.20	0.08	0.25	0.38	0.34	1.00				
	Tol	0.05	0.11	0.20	**0.69**	0.16	**0.64**	**0.77**	0.28	0.21	0.33	0.04	0.20	0.53	1.0			
CAMS-41	O_3	**0.62**	**0.67**	0.47	-0.51	-0.46	-0.36	-0.29	0.31	0.36	0.28	-0.53	-0.58	-0.30	-0.15	1.00		
	T	-0.06	-0.12	0.45	0.20	-0.15	0.17	0.29	0.60	**0.70**	**0.56**	-0.32	-0.42	0.06	0.37	0.20	1.00	
	RH	-0.40	-0.50	-0.30	-0.19	-0.10	-0.25	-0.41	-0.27	-0.32	-0.28	0.14	0.24	-0.05	-0.39	-0.49	**-0.64**	1.00

[1] Abbreviations: $PM_{2.5}$ = particulate matter with aerodynamic diameter less than 2.5 µm (fine PM); $PM_{10-2.5}$ = particulate matter with aerodynamic diameter between 2.5 and 10 µm (coarse PM); PM_{10}= particulate matter with aerodynamic diameter less than 10 µm; NO2 = nitrogen dioxide; BC = black carbon; Benz = benzene; Tol = toluene.

[2] P-value less than 0.05 in bold indicates significant correlation.

Table 4. Overall Asthma Control Questionnaire score summary statistics.[1, 2]

Location	Subgroup		N	Mean[3]	SD	Min	Max
Overall			386	0.8	0.6	0.0	3.3
	Allergic	Yes	184	0.8	0.6	0.0	2.4
		No	202	0.8	0.7	0.0	3.3
	Medicaid[4]	Yes	195	0.7	0.6	0.0	3.3
		No	191	0.8	0.6	0.0	3.0
	Daily ICS	Yes	129	0.6	0.4	0.0	2.1
		No	257	0.9	0.7	0.0	3.3
	Recent oral steroid[5]	Yes	169	0.7	0.7	0.0	3.3
		No	217	0.8	0.6	0.0	3.0
School 1			210	0.9	0.7	0.0	3.3
	Allergic	Yes	86	1.0	0.7	0.0	2.4
		No	124	0.8	0.7	0.0	3.3
	Medicaid[4]	Yes	156	0.8	0.6	0.0	3.3
		No	54	1.2	0.7	0.3	2.6
	Daily ICs	Yes	77	0.6	0.4	0.0	2.1
		No	133	1.1	0.8	0.0	3.3
	Recent oral steroid[5]	Yes	85	0.9	0.8	0.0	3.3
		No	125	0.9	0.6	0.0	2.4
School 2			176	0.6	0.5	0.0	3.0
	Allergic	Yes	98	0.5	0.3	0.1	1.6
		No	78	0.7	0.7	0.0	3.0
	Medicaid[4]	Yes	39	0.5	0.2	0.3	1.1
		No	137	0.6	0.5	0.0	3.0
	Daily ICS	Yes	52	0.5	0.3	0.1	1.6
		No	124	0.7	0.5	0.0	3.0
	Recent oral steroid[5]	Yes	84	0.5	0.4	0.0	2.0
		No	92	0.7	0.6	0.1	3.0

[1] Abbreviations: N = number; SD = standard deviation; Min = minimum; Max = maximum.

[2] Score equals mean of sum of total question score, with higher scores indicating less control.

[3] Mean of ACQ scores.

[4] Medicaid coverage for child was used for some amount of time during the last year.

[5] Signifies one or more oral corticosteroid (OCS) uses during last 3 months.

Table 5. Associations between Asthma Control Questionnaire score and 96-hour integrated pollutant concentrations.[1, 2]

Pollutant used in model	IQR[3]	N	Effect estimate	Δ in ACQ score with IQR increase in pollutant (95% CI)[4]	P-value[5]
PM_{10}	19.7	303	0.0019	0.0365 (-0.0349, 0.1080)	0.315
$PM_{10-2.5}$	14.8	303	0.0024	0.0350 (-0.0414, 0.1115)	0.368
$PM_{2.5}$	5.7	303	0.0062	0.0352 (-0.0268, 0.0972)	0.264
BC	0.4	303	0.0967	0.0387 (-0.0561, 0.1334)	0.422
NO_2	5.5	352	0.0017	0.0096 (-0.1345, 0.1537)	0.896
Benzene	0.8	352	0.0391	0.0313 (-0.0684, 0.1309)	0.538
Toluene	2.4	352	0.0104	0.0249 (-0.0621, 0.1118)	0.574
Ozone (CAMS-41)[6]	8.7	432	0.0007	0.0060 (-0.0887, 0.1007)	0.901

[1] Abbreviations: $PM_{2.5}$ = particulate matter with aerodynamic diameter less than 2.5 μm (fine PM); $PM_{10-2.5}$ = particulate matter with aerodynamic diameter between 2.5 and 10 μm (coarse PM); PM_{10}= particulate matter with aerodynamic diameter less than 10 μm; NO_2 = nitrogen dioxide; BC = black carbon; IQR = interquartile range; N = number of observations used in model for analysis; ACQ = Asthma Control Questionnaire. CAMS-41 = Continuous Air Monitoring Station #41.

[2] Using mixed effects modeling with repeated week and random subject effect, each model controls for 96-hour averaged relative humidity, 96-hour averaged temperature, and school.

[3] IQR in $\mu g/m^3$ for $PM_{2.5}$, PM_{10}, $PM_{10-2.5}$, and BC; IQR in ppb for NO_2, benzene, toluene, and ozone. IQR ($PM_{2.5}$, PM_{10}, $PM_{10-2.5}$, BC, NO_2, benzene, toluene) is average from measurement overall, including School 1 and School 2. The IQR value for O_3 is taken from measurements at CAMS-41 site only.

[4] Δ in ACQ score and 95% CIs derived by multiplication of effect estimate, its lower bound, and its upper bound by the IQR.

[5] P-value from t-test solution for fixed effects.

[6] Measured at central monitoring station CAMS-41, operated by the Texas Commission on Environmental Quality (TCEQ).

Table 6. Associations between Asthma Control Questionnaire score and selected pollutants with subgroup analysis (continued on next page).[1, 2]

Pollutant (IQR)[2]	Subgroup		N	Δ in ACQ score with IQR increase in pollutant (95% CI)[3]	P-value[4]
PM_{10} (19.7)	Allergic	Yes	143	0.0297 (-0.0565, 0.1159)	0.497
		No	160	0.0497 (-0.0630, 0.1624)	0.384
	Medicaid[5]	Yes	158	0.0495 (-0.0504, 0.1496)	0.329
		No	145	0.0163 (-0.0883, 0.1210)	0.758
	Daily ICS	Yes	102	-0.0270 (-0.1353, 0.0815)	0.623
		No	201	0.0694 (-0.0234, 0.1623)	0.142
	Recent oral steroid[6]	Yes	133	-0.0305 (-0.1277, 0.0664)	0.533
		No	170	0.0911 (-0.0114, 0.1937)	**0.081**
$PM_{10-2.5}$ (14.8)	Allergic	Yes	143	0.0233 (-0.0682, 0.1148)	0.616
		No	160	0.0542 (-0.0675, 0.1760)	0.380
	Medicaid[5]	Yes	158	0.0524 (-0.0605, 0.1653)	0.360
		No	145	0.0130 (-0.0944, 0.1204)	0.812
	Daily ICS	Yes	102	-0.0374 (-0.1548, 0.0800)	0.528
		No	201	0.0708 (-0.0280, 0.1696)	0.159
	Recent oral steroid[5]	Yes	133	-0.0351 (-0.1387, 0.0685)	0.503
		No	170	0.0930 (-0.0170, 0.2032)	**0.097**
$PM_{2.5}$ (5.7)	Allergic	Yes	143	0.0379 (-0.0380, 0.1138)	0.324
		No	160	0.0373 (-0.0591, 0.1337)	0.445
	Medicaid[5]	Yes	158	0.0419 (-0.0388, 0.1226)	0.307
		No	145	0.0212 (-0.0763, 0.1187)	0.667
	Daily ICS	Yes	102	-0.0075 (-0.1004, 0.0854)	0.873
		No	201	0.0589 (-0.0224, 0.1397)	0.155
	Recent oral steroid[6]	Yes	133	-0.0198 (-0.1051, 0.0654)	0.645
		No	170	0.0776 (-0.0108, 0.1660)	**0.085**
BC (0.4)	Allergic	Yes	143	0.1160 (-0.0033, 0.2354)	**0.057**
		No	160	-0.0235 (-0.1660, 0.1190)	0.745
	Medicaid[5]	Yes	158	0.0729 (-0.0460, 0.1917)	0.228
		No	145	-0.0391 (-0.1973, 0.1191)	0.626
	Daily ICS	Yes	102	0.0851 (-0.0588, 0.2289)	0.243
		No	201	0.0090 (-0.1140, 0.1320)	0.885
	Recent oral steroid[6]	Yes	133	-0.0529 (-0.1816, 0.0757)	0.417
		No	170	0.1164 (-0.0200, 0.2528)	0.094
NO_2 (5.5)	Allergic	Yes	168	0.1528 (-0.0287, 0.3343)	**0.098**
		No	184	-0.0797 (-0.2948, 0.1354)	0.465
	Medicaid[5]	Yes	179	0.0554 (-0.1114, 0.2224)	0.513
		No	173	-0.1132 (-0.3718, 0.1453)	0.388
	Daily ICS	Yes	117	-0.0470 (-0.2534, 0.1593)	0.652
		No	235	0.0320 (-0.1601, 0.2240)	0.743
	Recent oral steroid[6]	Yes	154	-0.0338 (-0.2380, 0.1703)	0.744
		No	198	0.0405 (-0.1612, 0.2421)	0.692

Table 6 Continued.[1, 2]

Benzene (0.8)	Allergic	Yes	168	0.0780 (-0.0461, 0.2021)	0.216
		No	184	-0.0070 (-0.1578, 0.1438)	0.927
	Medicaid[5]	Yes	179	0.0746 (-0.0387, 0.1880)	0.195
		No	173	-0.0694 (-0.2562, 0.1175)	0.464
	Daily ICS	Yes	117	0.1749 (0.0357, 0.3141)	**0.014**
		No	235	-0.0500 (-0.1826, 0.0826)	0.458
	Recent oral steroid[6]	Yes	154	-0.0232 (-0.1617, 0.1154)	0.741
		No	198	0.0707 (-0.0703, 0.2117)	0.324
Toluene (2.4)	Allergic	Yes	168	0.0767 (-0.0325, 0.1858)	0.167
		No	184	-0.0142 (-0.1448, 0.1164)	0.830
	Medicaid[5]	Yes	179	0.0643 (-0.0322, 0.1609)	0.190
		No	173	-0.0750 (-0.2446, 0.0948)	0.384
	Daily ICS	Yes	117	0.1203 (-0.0008, 0.2414)	**0.052**
		No	235	-0.0321 (-0.1489, 0.0846)	0.588
	Recent oral steroid[6]	Yes	154	-0.0093 (-0.1299, 0.1113)	0.879
		No	198	0.0507 (-0.0727, 0.1742)	0.419

[1] Abbreviations: $PM_{2.5}$ = particulate matter with aerodynamic diameter less than 2.5 µm (fine PM); $PM_{10\text{-}2.5}$ = particulate matter with aerodynamic diameter between 2.5 and 10 µm (coarse PM); PM_{10}= particulate matter with aerodynamic diameter less than 10 µm; NO_2 = nitrogen dioxide; BC = black carbon; IQR = interquartile range; N = number of observations used in analysis; ACQ = Asthma Control Questionnaire.

[2] Using mixed effects modeling with repeated week and random subject effect, each model controls for 96-hour averaged relative humidity, 96-hour averaged temperature, and school.

[3] IQR in $\mu g/m^3$ for $PM_{2.5}$, PM_{10}, $PM_{10\text{-}2.5}$, and BC; IQR in ppb for NO_2, benzene, toluene, and ozone. IQR ($PM_{2.5}$, PM_{10}, $PM_{10\text{-}2.5}$, BC, NO_2, benzene, toluene) is average from measurement overall, including School 1 and School 2.

[4] Δ in ACQ score and 95% CIs are derived by multiplication of the effect estimate, its lower bound, and its upper bound by the IQR.

[5] P-value from t-test solution for fixed effects.

[6] Medicaid coverage for child was used for some amount of time during the last year.

[7] Signifies oral corticosteroid (OCS) use during the last 3 months.

G. Appendix

a. Tables and Figures

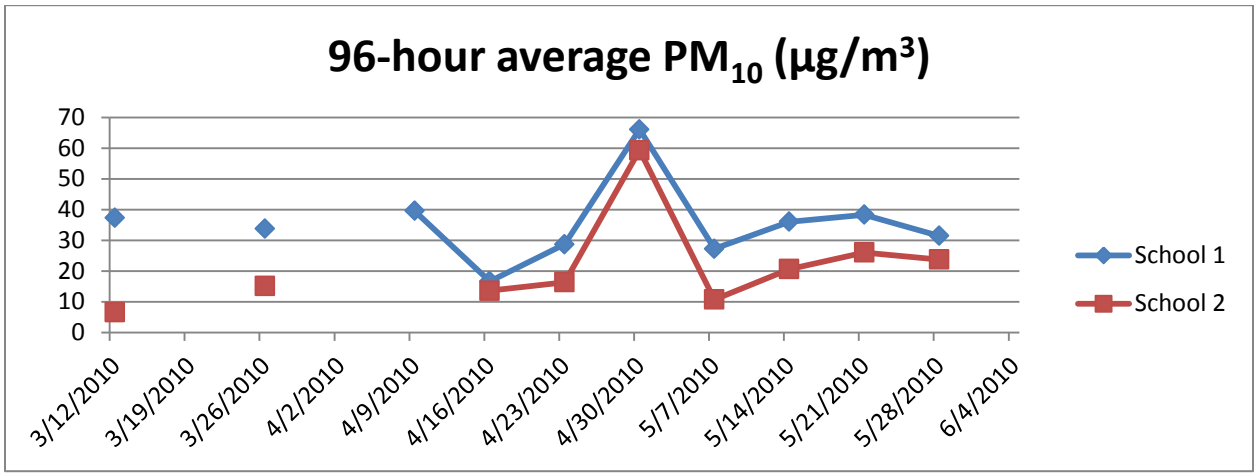

Figure 1. Time series for integrated 96-hour average PM_{10} concentrations at each school.

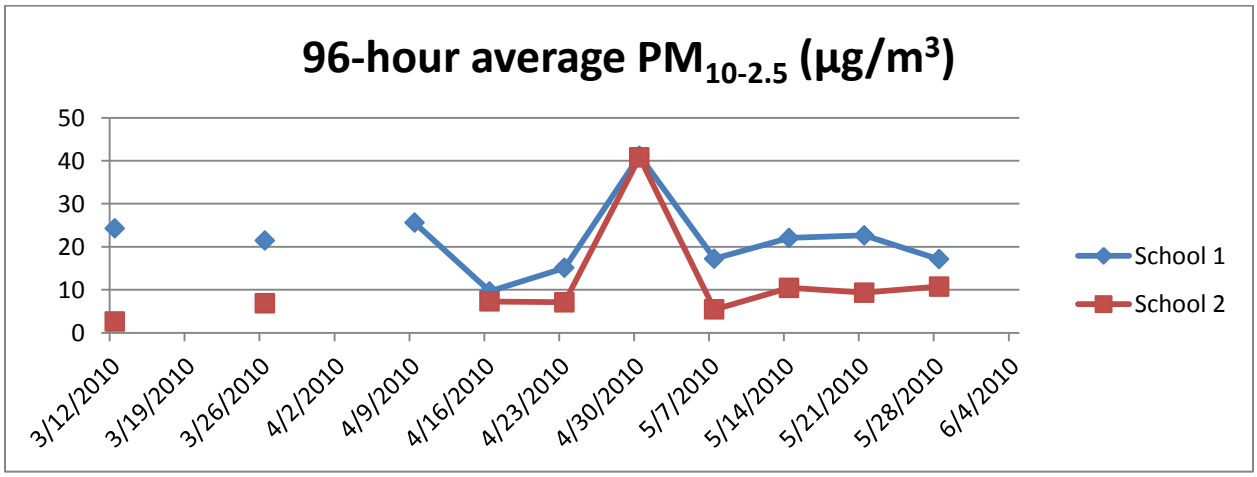

Figure 2. Time series for integrated 96-hour average $PM_{10\text{-}2.5}$ concentrations at each school.

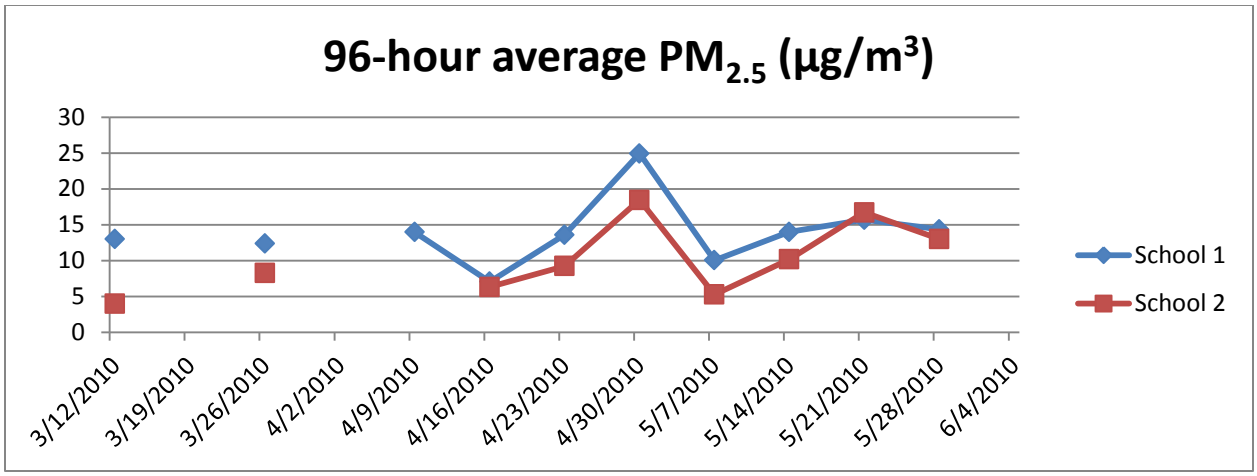

Figure 3. Time series for integrated 96-hour average $PM_{2.5}$ concentrations at each school.

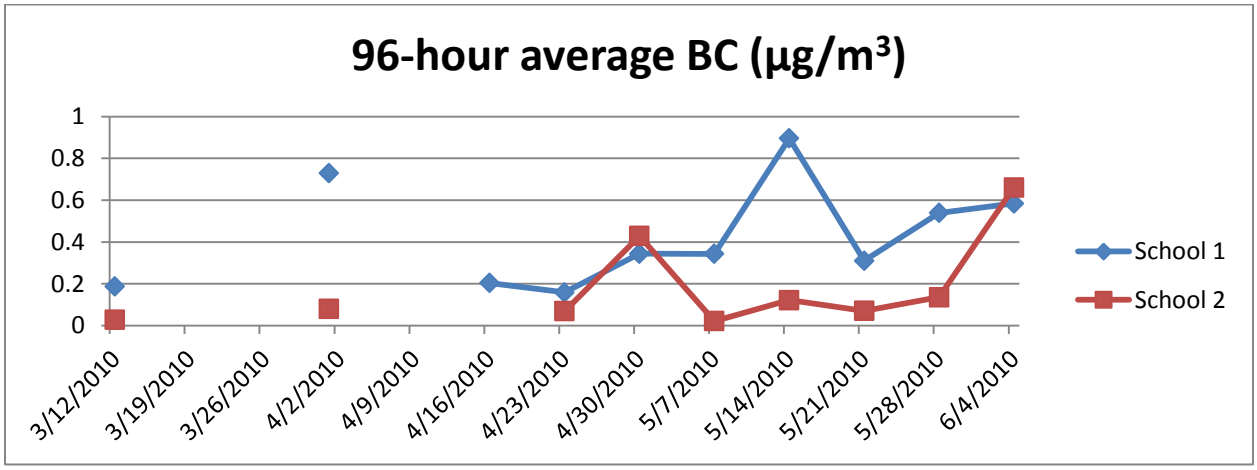

Figure 4. Time series for integrated 96-hour average BC concentrations at each school.

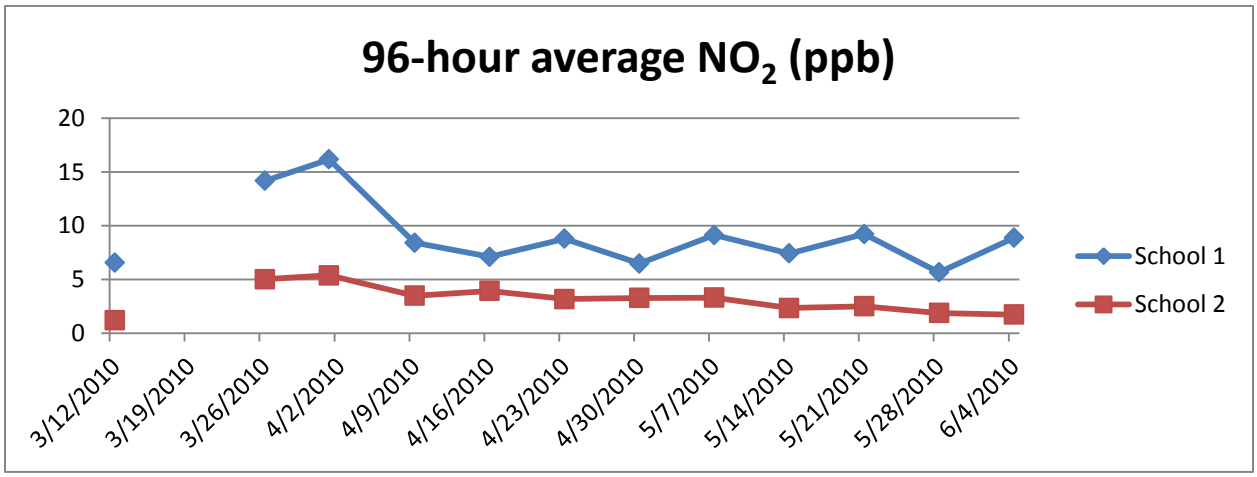

Figure 5. Time series for integrated 96-hour average NO_2 concentrations at each school.

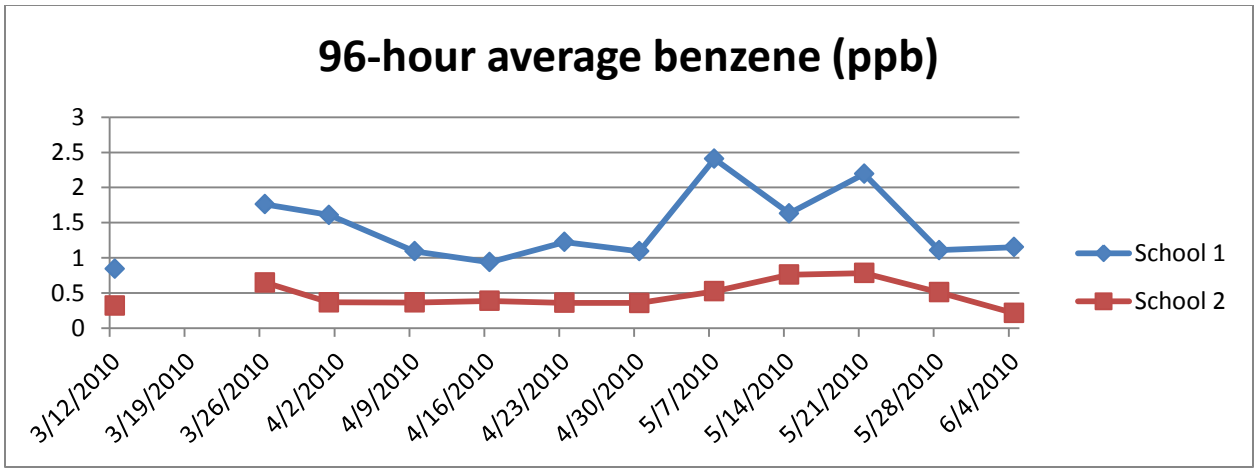

Figure 6. Time series for integrated 96-hour average benzene concentrations at each school.

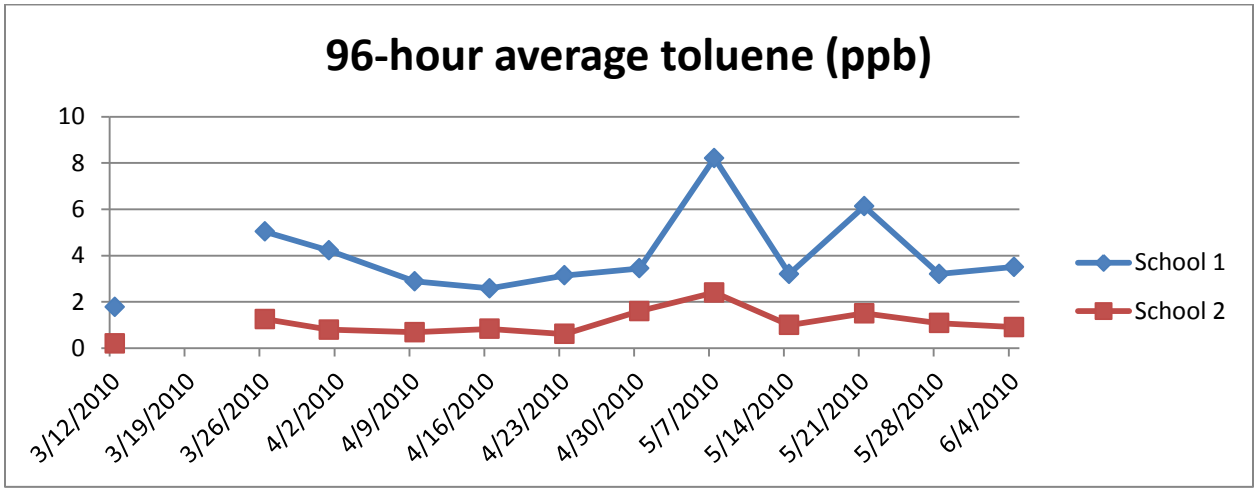

Figure 7. Time series for integrated 96-hour average toluene concentrations at each school.

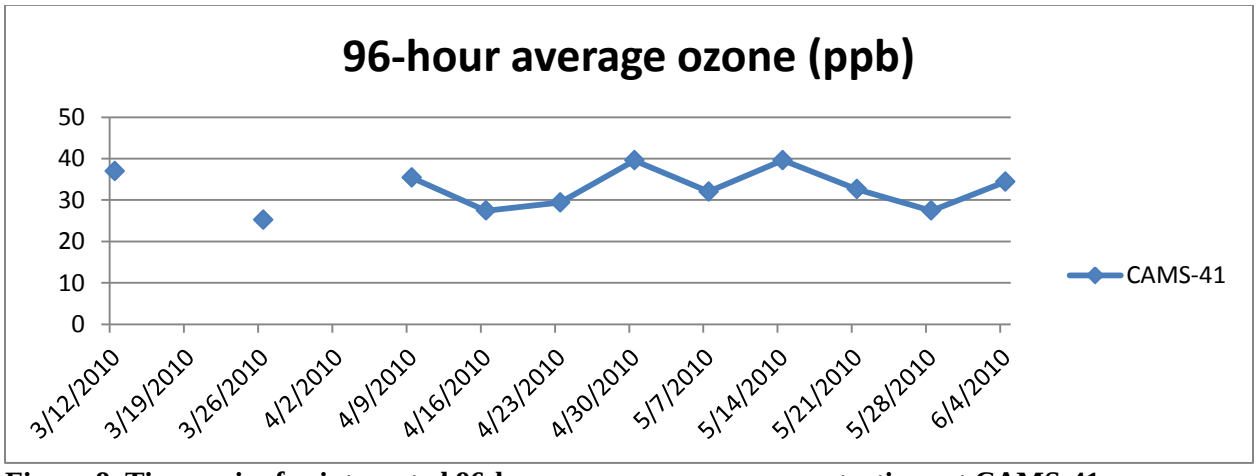

Figure 8. Time series for integrated 96-hour average ozone concentrations at CAMS-41.

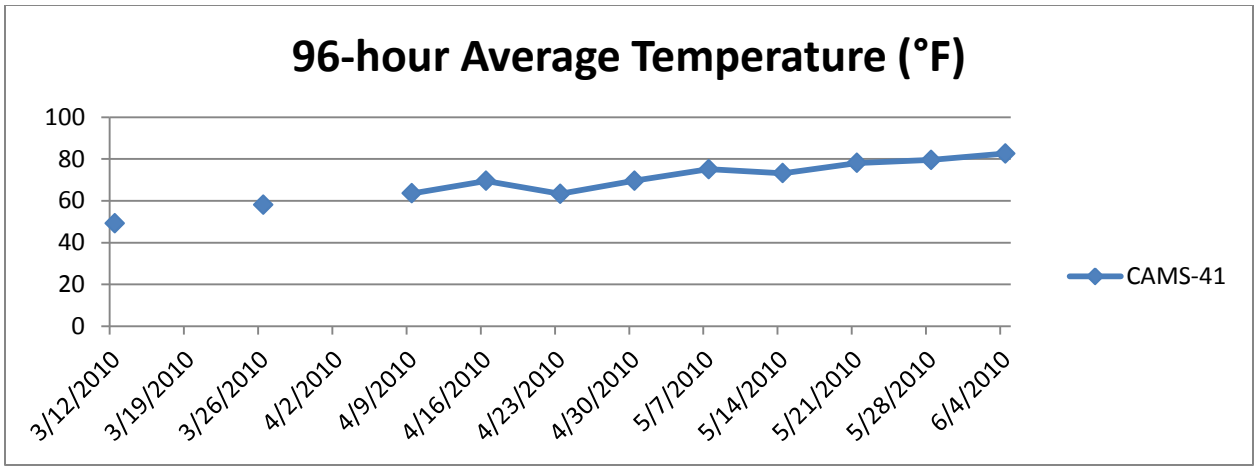

Figure 9. Time series for integrated 96-hour average temperatures (° Farenheit) at CAMS-41.

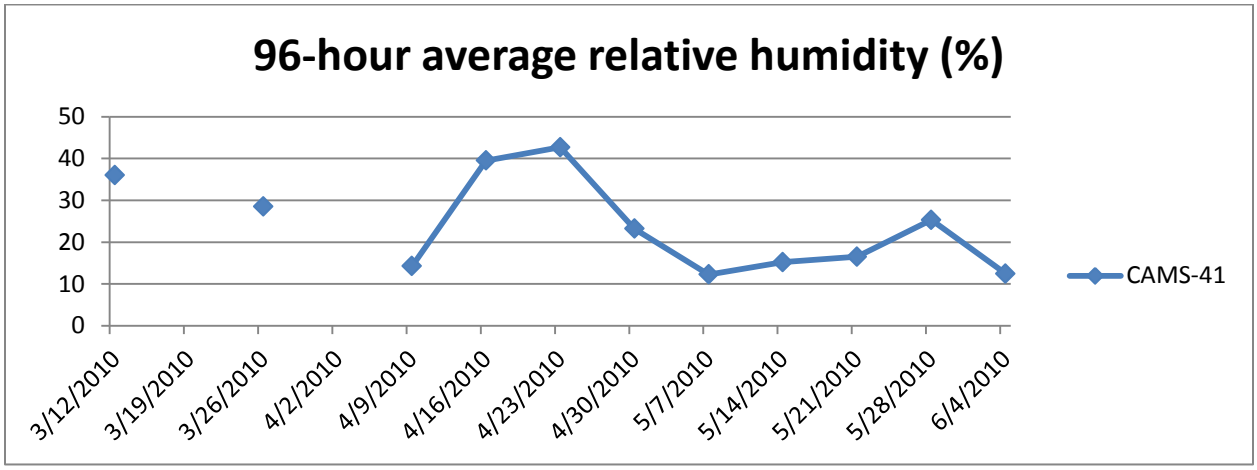

Figure 10. Time series for integrated 96-hour average relative humidity at CAMS-41.

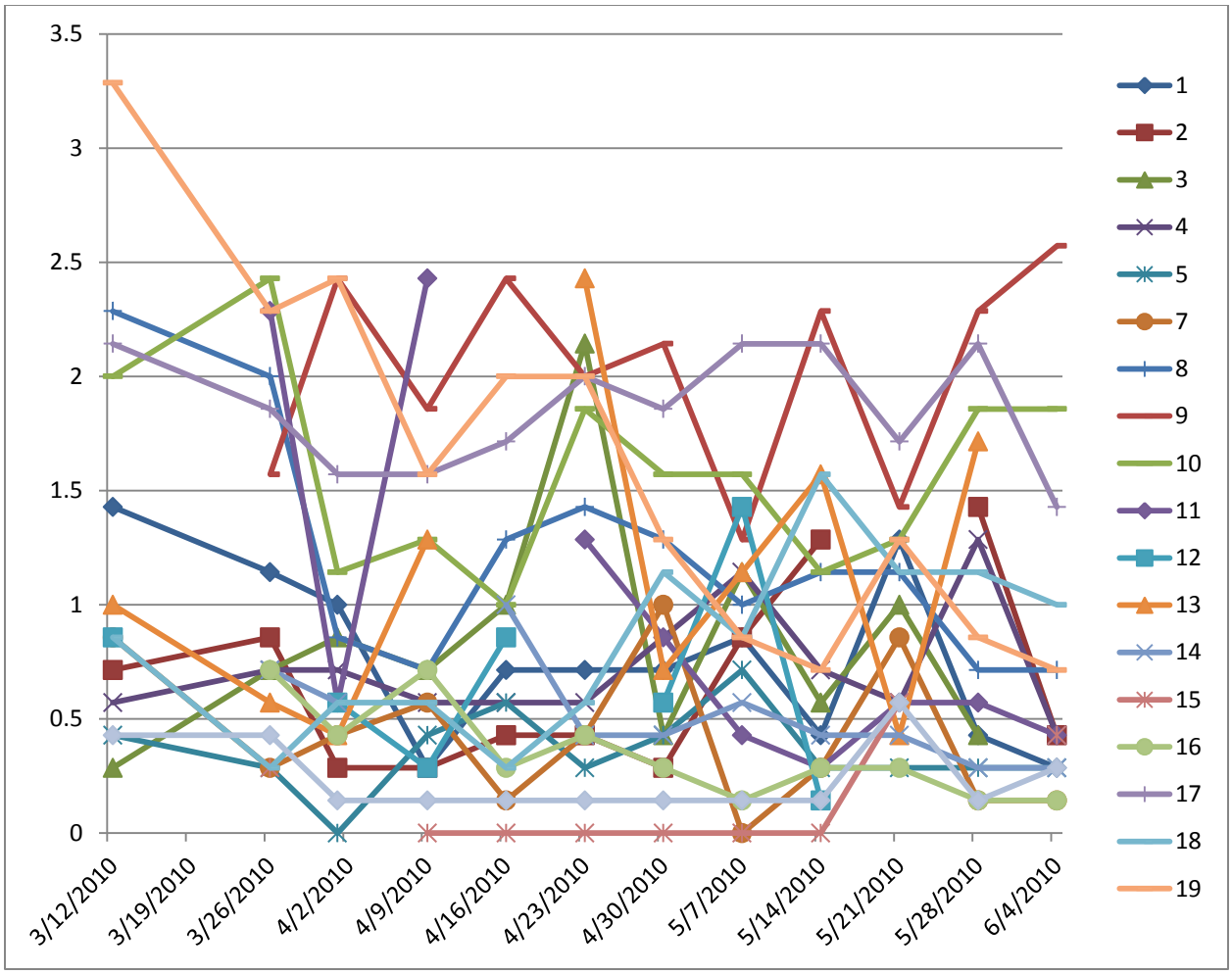

Figure 11. ACQ scores for School 1 by subject.

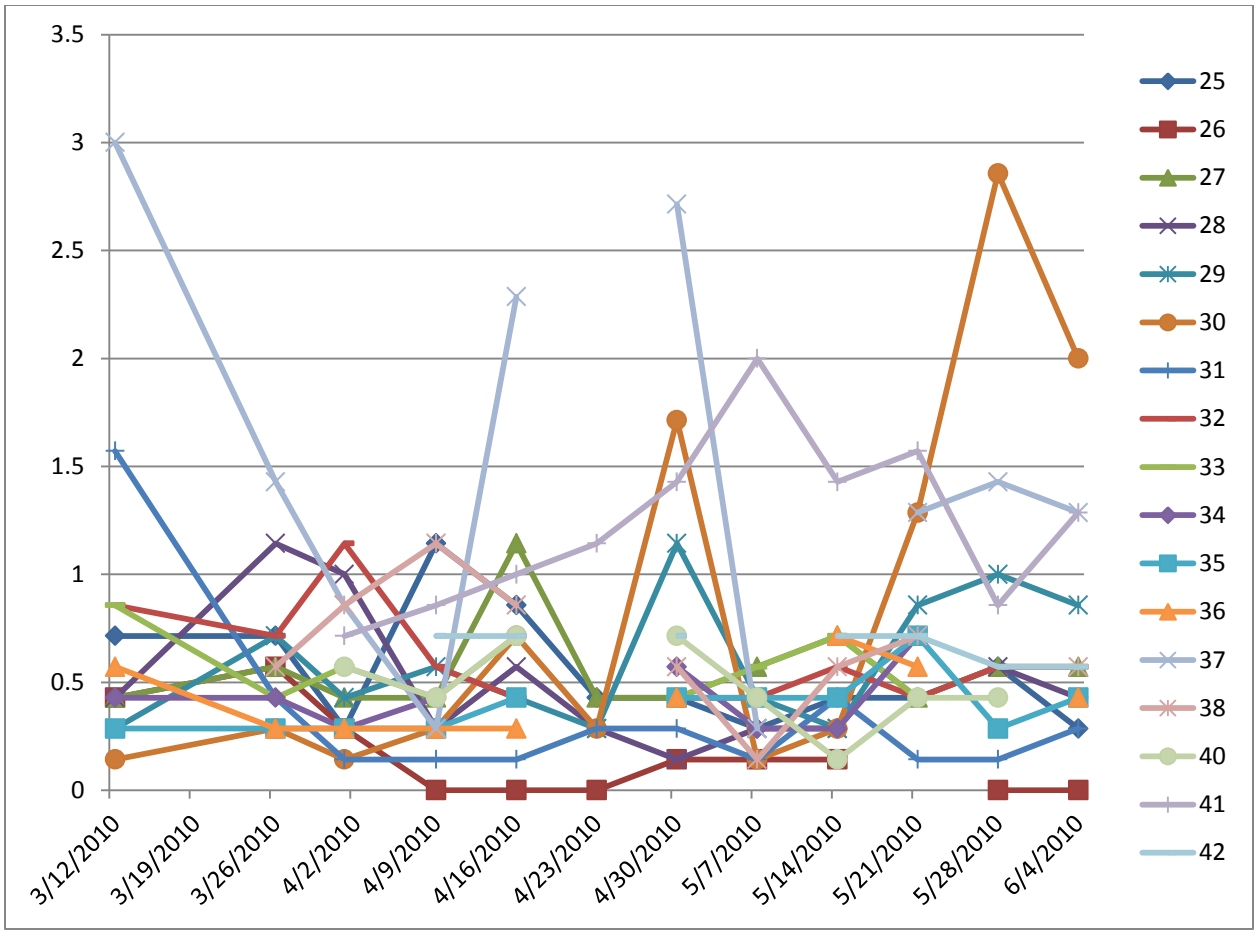

Figure 12. ACQ scores for School 2 by subject.

Table 1. Asthma Control Questionnaire score summary statistics by subject.[1, 2]

Subject	School	N	Mean	SD	Min	Max	IQR
01	1	12	0.8	0.4	0.3	1.4	0.6
02	1	11	0.7	0.4	0.3	1.4	0.6
03	1	11	0.8	0.5	0.3	2.1	0.6
04	1	12	0.7	0.3	0.4	1.3	0.2
05	1	12	0.4	0.2	0.0	0.7	0.1
07	1	12	0.4	0.3	0.0	1.0	0.6
08	1	12	1.2	0.5	0.7	2.3	0.6
09	1	11	2.0	0.4	1.3	2.6	0.9
10	1	12	1.6	0.4	1.0	2.4	0.6
11	1	10	1.0	0.8	0.3	2.4	0.9
12	1	7	0.7	0.4	0.1	1.4	0.6
13	1	10	1.1	0.6	0.4	2.4	1.0
14	1	10	0.5	0.2	0.3	1.0	0.1
15	1	9	0.1	0.2	0.0	0.6	0.3
16	1	11	0.4	0.2	0.1	0.7	0.3
17	1	12	1.9	0.3	1.4	2.1	0.5
18	1	12	0.8	0.4	0.3	1.6	0.6
19	1	12	1.6	0.8	0.7	3.3	1.3
21	1	12	0.2	0.2	0.1	0.6	0.2
25	2	12	0.5	0.3	0.3	1.1	0.4
26	2	11	0.2	0.2	0.0	0.6	0.3
27	2	12	0.6	0.2	0.4	1.1	0.1
28	2	11	0.5	0.3	0.1	1.1	0.3
29	2	12	0.6	0.3	0.3	1.1	0.5
30	2	12	0.8	0.9	0.1	2.9	1.3
31	2	12	0.3	0.4	0.1	1.6	0.2
32	2	11	0.6	0.2	0.4	1.1	0.3
33	2	10	0.6	0.2	0.4	0.9	0.3
34	2	9	0.4	0.1	0.3	0.7	0.1
35	2	11	0.4	0.1	0.3	0.7	0.1
36	2	9	0.4	0.2	0.3	0.7	0.3
37	2	10	1.5	0.9	0.3	3.0	1.4
38	2	9	0.7	0.3	0.1	1.1	0.3
40	2	8	0.5	0.2	0.1	0.7	0.2
41	2	10	1.2	0.4	0.7	2.0	0.6
42	2	7	0.7	0.1	0.6	0.7	0.1

[1] Abbreviations: N = number; SD = standard deviation; Min = minimum; Max = maximum.

[2] Score is mean of sum of total question score.

Table 2. Associations between Asthma Control Questionnaire score and pollutants in 2-pollutant models including particulate and gaseous pollutant.[1, 2]

Pollutants in model	N	Effect estimate	Standard error	P-value
PM_{10}		0.0019	0.0019	0.295
NO_2	303	0.0062	0.0138	0.654
PM_{10}		0.0025	0.0020	0.200
Benzene	303	0.0783	0.0777	0.314
PM_{10}		0.0021	0.0019	0.268
Toluene	303	0.0131	0.0205	0.522
PM_{10}		0.0026	0.0022	0.241
O_3	303	-0.0041	0.0067	0.543
$PM_{10-2.5}$,		0.0025	0.0026	0.351
NO_2	303	0.0057	0.0137	0.680
$PM_{10-2.5}$		0.0033	0.0028	0.243
Benzene	303	0.0750	0.0776	0.335
$PM_{10-2.5}$		0.0026	0.0027	0.331
Toluene	303	0.0116	0.0203	0.567
$PM_{10-2.5}$		0.0033	0.0031	0.293
O_3	303	-0.0037	0.0067	0.584
$PM_{2.5}$		0.0066	0.0056	0.238
NO_2	303	0.0071	0.0138	0.608
$PM_{2.5}$		0.0080	0.0058	0.171
Benzene	303	0.0773	0.0769	0.316
$PM_{2.5}$		0.0074	0.0057	0.201
Toluene	303	0.0156	0.0209	0.445
$PM_{2.5}$		0.0079	0.0063	0.211
O_3	303	-0.0036	0.0064	0.571
BC		0.0997	0.1362	0.465
NO_2	303	-0.0007	0.0155	0.963
BC		0.0828	0.1545	0.592
Benzene	303	0.0135	0.0942	0.886
BC		0.1125	0.1633	0.492
Toluene	303	-0.0039	0.0273	0.886
BC		0.1369	0.1420	0.336
O_3	303	0.0036	0.0067	0.594

[1] Abbreviations: N = number of observations used; $PM_{2.5}$ = particulate matter with aerodynamic diameter less than 2.5 µm (fine PM); $PM_{10-2.5}$ = particulate matter with aerodynamic diameter between 2.5 and 10 µm (coarse PM); PM_{10}= particulate matter with aerodynamic diameter less than 10 µm; NO_2 = nitrogen dioxide; BC = black carbon.

[2] Using mixed effects modeling with repeated week and random subject effect, each model controls for 96-hour averaged relative humidity, 96-hour averaged temperature, and school.

Table 3. Associations between Asthma Control Questionnaire score and 96-hour integrated pollutant concentrations by school.[1, 2]

Pollutant (IQR)[3]	Subgroup	N	Δ in ACQ score with IQR increase in pollutant (95% CI)[4]	P-value[5]
PM_{10} (19.7)	School 1	176	-0.0189 (-1.3081, 0.0928)	0.738
	School 2	127	0.0705 (-0.0256, 0.1666)	0.149
$PM_{10-2.5}$ (14.8)	School 1	176	-0.0275 (-0.1622, 0.1071)	0.687
	School 2	127	0.0612 (-0.0337, 0.1561)	0.204
$PM_{2.5}$ (5.7)	School 1	176	-0.0093 (-0.0939, 0.0752)	0.828
	School 2	127	0.0827 (-0.0144, 0.1797)	0.094
BC (0.4)	School 1	176	0.0799 (-0.0406, 0.2004)	0.192
	School 2	127	-0.0301 (-0.2176, 0.1574)	0.751
NO_2 (5.5)	School 1	192	0.0403 (-0.1245, 0.2052)	0.630
	School 2	160	-0.2466 (-0.5957, 0.1024)	0.165
Benzene (0.8)	School 1	192	0.0628 (-0.0506, 0.1761)	0.276
	School 2	160	-0.0349 (-0.0324, 0.2541)	0.812
Toluene (2.4)	School 1	247	0.0486 (-0.0462, 0.1434)	0.313
	School 2	221	-0.1007 (-0.4274, 0.2261)	0.544

[1] Abbreviations: $PM_{2.5}$ = particulate matter with aerodynamic diameter less than 2.5 µm (fine PM); $PM_{10-2.5}$ = particulate matter with aerodynamic diameter between 2.5 and 10 µm (coarse PM); PM_{10}= particulate matter with aerodynamic diameter less than 10 µm; NO_2 = nitrogen dioxide; BC = black carbon; IQR = interquartile range; N = number of observations used in model for analysis; ACQ = Asthma Control Questionnaire.

[2] Using mixed effects modeling with repeated week and random subject effect, each model controls for 96-hour averaged relative humidity and 96-hour averaged temperature only (school not included in this model).

[3] IQR in $\mu g/m^3$ for $PM_{2.5}$, PM_{10}, $PM_{10-2.5}$. IQR in ppb for BC, NO_2, benzene, and toluene. IQR is an overall average including measurements from School 1 and School 2.

[4] Δ in ACQ score and 95% CIs derived by multiplication of effect estimate, and its lower and upper bound by the IQR for each specific school.

[5] P-value from t-test solution for fixed effects.

Table 4. Associations between Asthma Control Questionnaire score and selected pollutants with subgroup analysis of obese versus non-obese subjects. [1, 2]

Pollutant (IQR)[3]	Subgroup		N	Δ in ACQ score with IQR increase in pollutant (95% CI) [4]	P-value5
PM_{10} (19.7)	Obese	Yes	80	0.0489 (-0.1340, 0.2317)	0.595
		No	223	0.0276 (-0.0447, 0.0999)	0.453
$PM_{10-2.5}$ (14.8)	Obese	Yes	80	0.0734 (-0.1387, 0.2855)	0.492
		No	223	0.0232 (-0.2855, 0.0990)	0.547
$PM_{2.5}$ (5.7)	Obese	Yes	80	0.0171 (-0.1261, 0.1604)	0.812
		No	223	0.0327 (-0.0322, 0.0976)	0.322
BC (0.4)	Obese	Yes	80	0.1115 (-0.0988, 0.3218)	0.294
		No	223	0.0373 (-0.0638, 0.1384)	0.467
NO_2 (5.5)	Obese	Yes	88	-0.0189 (-0.3293, 0.2914)	0.904
		No	264	0.0381 (-0.1176, 0.1938)	0.630
Benzene (0.8)	Obese	Yes	88	0.0369 (-0.1738, 0.2477)	0.728
		No	264	0.0714 (-0.0378, 0.1806)	0.199
Toluene (2.4)	Obese	Yes	80	0.0419 (-0.1354, 0.2191)	0.639
		No	223	0.0474 (-0.0499, 0.1446)	0.338

[1] Abbreviations: $PM_{2.5}$ = particulate matter with aerodynamic diameter less than 2.5 μm (fine PM); $PM_{10-2.5}$ = particulate matter with aerodynamic diameter between 2.5 and 10 μm (coarse PM); PM_{10}= particulate matter with aerodynamic diameter less than 10 μm; NO_2 = nitrogen dioxide; BC = black carbon; IQR = interquartile range; N = number of observations used in analysis; ACQ = Asthma Control Questionnaire.

[2] Using mixed effects modeling with repeated week and random subject effect, each model controls for 96-hour averaged relative humidity, 96-hour averaged temperature, and school.

[3] IQR in $\mu g/m^3$ for $PM_{2.5}$, PM_{10}, $PM_{10-2.5}$. IQR in ppb for BC, NO_2, benzene, and toluene. IQR is an overall average including measurements from School 1 and School 2.

[4] Δ in ACQ score and 95% CI derived by multiplication of effect estimate, and its lower and upper bounds by the IQR.

[5] P-value from t-test solution for fixed effects.

Table 5. Associations between Asthma Control Questionnaire score and pollutants, with selective removal of potentially influential subjects.[1, 2, 3]

Model	Subjects	N	Effect estimate	Standard error	P-value
PM_{10}	**All subjects**	**303**	**0.0019**	**0.0018**	**0.315**
	11 excluded	295	0.0018	0.0018	0.307
	19 excluded	293	0.0018	0.0018	0.323
	30 excluded	294	0.0006	0.0017	0.718
	37 excluded	296	0.0011	0.0018	0.548
PMC	**All subjects**	**303**	**0.0024**	**0.0026**	**0.368**
	11 excluded	295	0.0023	0.0026	0.359
	19 excluded	293	0.0023	0.0026	0.375
	30 excluded	294	0.0007	0.0025	0.776
	37 excluded	296	0.0011	0.0026	0.664
$PM_{2.5}$	**All subjects**	**303**	**0.0062**	**0.0055**	**0.264**
	11 excluded	295	0.0061	0.0054	0.257
	19 excluded	293	0.0059	0.0054	0.275
	30 excluded	294	0.0025	0.0052	0.628
	37 excluded	296	0.0048	0.0054	0.376
NO_2	**All subjects**	**352**	**0.0017**	**0.0133**	**0.896**
	11 excluded	343	-0.0044	0.0131	0.740
	19 excluded	341	0.0018	0.0132	0.889
	30 excluded	341	0.0021	0.0124	0.869
	P37 excluded	343	0.0044	0.0127	0.731
BC	**All subjects**	**303**	**0.0967**	**0.1203**	**0.422**
	09 excluded	294	0.1487	0.1226	0.226
	19 excluded	293	0.1102	0.1183	0.352
	30 excluded	294	0.0532	0.1136	0.640
	37 excluded	296	0.1032	0.1165	0.376
Benzene	**All subjects**	**352**	**0.0391**	**0.0633**	**0.538**
	09 excluded	342	0.0766	0.0645	0.236
	19 excluded	341	0.0534	0.0626	0.394
	30 excluded	341	0.0556	0.0588	0.345
	37 excluded	343	0.0294	0.0604	0.627
Toluene	**All subjects**	**352**	**0.0104**	**0.0184**	**0.574**
	09 excluded	342	0.0220	0.0188	0.243
	19 excluded	341	0.0133	0.0182	0.466
	30 excluded	341	0.0139	0.0171	0.416
	37 excluded	343	0.0080	0.0176	0.651

[1] Abbreviations: N = number of observations used; $PM_{2.5}$ = particulate matter with aerodynamic diameter less than 2.5 μm (fine PM); $PM_{10\text{-}2.5}$ = particulate matter with aerodynamic diameter between 2.5 and 10 μm (coarse PM); PM_{10}= particulate matter with aerodynamic diameter less than 10 μm; NO_2 = nitrogen dioxide; BC = black carbon.

[2] Using mixed effects modeling with repeated week and random subject effect, each model controls for 96-hour averaged relative humidity, 96-hour averaged temperature, and school.

[3] Four subjects with highest Cook's D are removed for each model different than the overall model (with the overall model effect estimate in bold).

b. Literature Review

Introduction

In 2009, 7.1 million children within the United States (9.6% of persons 0 – 17 years of age) were estimated to suffer from asthma [1], a chronic inflammatory disease of the airways with the potential for acute worsening of symptoms and lung function in response to environmental exposures. Short-term increases in traffic-related air pollutants such as particulate matter with aerodynamic diameter less than 10 microns (PM_{10}), particulate matter with diameter between 2.5 and 10 μm ($PM_{10-2.5}$, coarse PM), particulate matter with diameter less than 2.5 microns ($PM_{2.5}$, fine PM), nitrogen dioxide (NO_2), black carbon (BC), ozone (O_3), benzene, and toluene have been associated with increased respiratory symptoms [2-7], decreased lung function [8-14, 58], and Emergency Room visits and/or hospital admissions [15-21] among asthmatic children. In addition, residential proximity to roadways and heavy traffic has been associated with decreased lung function [22, 23] and increased hospital utilization [24, 25] among children with asthma. Certain factors have been shown to modify the effect of air pollution on asthma, such as socioeconomic status [26-30], atopy [5, 61], and use of inhaled corticosteroids (ICS) [31]. Since asthma exacerbation leads to poor quality of life for children and their families as well as high economic cost to society [29, 74, 75], the relationship between pediatric asthma and air pollution is an issue that warrants further understanding and research.

Traffic-related air pollution

Traffic-related air pollutants include particulate matter (PM), nitrogen dioxide ($N0_2$), volatile organic compounds (VOCs), and ozone (O_3) that are produced and propagated by the internal combustion engine of passenger cars that use gasoline and diesel-powered freight trucks. Particulate matter related to traffic emissions include that of particulate size less than 2.5 microns in diameter ($PM_{2.5}$), PM less than 10 microns in diameter (PM_{10}), and PM between 2.5 and 10 microns in diameter ($PM_{10\text{-}2.5}$, coarse PM). $PM_{2.5}$ may be more specifically linked to engine combustion and comprises primarily lead halides, sulfates, and carbonaceous matter [76]. PM less than 10 microns and greater than 2.5 microns in diameter ($PM_{10\text{-}2.5}$) may capture a comparatively larger fraction of gravel and fugitive dust [33]. A component of particulate matter, black carbon may also be measured as a surrogate to traffic emissions [77, 78]. Volatile organic compounds (VOCs) defines all vapor-phase atmosphere organic gases (except for carbon monoxide (CO) and carbon dioxide (CO2), and motor vehicles are the primary contributor to these compounds on the ground in the United States. Primarily resulting from transportation emissions, nitrogen oxides (NO_x) including nitrogen dioxide (NO_2) contribute to the production of secondary pollutants such as ozone. The creation of ozone as a secondary pollutant is propagated by partially combusted hydrocarbon and nitrous elements as reactive oxygen species (ROS) from diesel and gasoline in the setting of high temperatures and bright sunlight [76].

Molecular mechanisms of pediatric asthma and the air pollution response

In children, asthma is a heterogeneous process characterized by airway inflammation, airway hyper-responsiveness, reversible airflow obstruction, and symptoms such as cough, wheeze,

chest tightness, and sputum production. In general, allergic-type asthma is considered to be T helper type 2 (Th2) cell-driven response in the airways. The release of various cytokines and chemokines by Th2 cells, mast cells, and native airway cell leads to the production of immunoglobulin E (IgE) by plasma cells as well as the further recruitment of inflammatory cells, including eosinophils and neutrophils, to the lung [79, 80]. The inflammatory response that takes place in the airways then leads to the signs and symptoms of asthma. The underlying immune cell profile of the asthmatic response may vary based on the influence of specific environmental exposures such as allergens and/or air pollutants [81].

A few studies demonstrate specific elements of the immune system response among children with asthma. In a study that compared asthmatic children in a high-pollution area of Fresno, California to those in who resided in an area with lower pollution in Stanford, California, higher levels of pollutants such as polycyclic aromatic hydrocarbons (PAH), PM_{10}, and O_3 were associated with impaired regulatory T cell (T_{reg}) function and lower asthma symptom scores. Since T_{reg} cells dampen the immune response, T_{reg} cell dysfunction might contribute to the inflammatory asthma response to air pollutants [82]. In addition, decreased expression of the molecular marker CD14 (cellular differentiation 14) on neutrophils has been associated with increased susceptibility to air pollution among asthmatic children [83]. Common polymorphisms in genetic pathways associated with oxidative inflammation are also shown to modulate the effect of short-term exposures to O_3 on lung function in asthmatic children [84, 85].

Biomarkers such as exhaled nitric oxide have been used in studies to examine the effects of air pollution on pediatric asthma. Exhaled nitric oxide (eNO) as a measurable biomarker has been

associated with the production of reactive nitrogen species and subsequent oxidation and nitration of proteins in the lung [86] as well as eosinophilic airway inflammation in children with asthma [87]. High exposure to roadways near to residence has been associated with increased eNO in children [22, 88]. Among a panel of multiple traffic-related pollutants measurements, personal $PM_{2.5,}$ personal particulate elemental carbon (EC) exposure, personal NO_2 exposure were most significantly associated with eNO in children with asthma in southern California. Significant associations with ambient $PM_{2.5}$ and organic carbon (OC, both personal and ambient) were only found among children taking inhaled corticosteroids, suggesting the potential for increased susceptibility to air pollution among children with more persistent asthma [36]. In addition, increased eNO has been significantly associated with 10 microgram/ meter^3 increases in levels of $PM_{2.5}$ using outdoor, indoor, personal, and central monitors at lag day 0. This effect was strengthened among 9 children who did not use inhaled corticosteroids for their asthma treatment (separate from the 10 children who did use inhaled corticosteroids for treatment, with inhaled corticosteroids typically used for more severe asthma) [59]. Previous day levels of PM_{10} and NO and day before levels of NO_2, CO, and NO were also shown to be associated with increased eNO among children in the Netherlands [89].

Air pollution and pediatric asthma symptoms

Several studies demonstrate that an acute increase in traffic-related air pollutant levels exacerbates respiratory symptoms among children with asthma. Among 22 Hispanic children ages 10 – 16 years of age in Los Angeles, same-day interquartile range increases (IRQ) in levels of PM_{10}, NO_2, benzene, EC, organic carbon, ozone are associated with increased symptom scores

as measured in daily diaries over three months [3]. In a study that followed 147 asthmatic children and 50 healthy children over 22 weeks in Mexico City, 1-hour maximum IQR increases in pollutants NO_2 and O_3 were each significantly associated with the odds of cough and wheeze among asthmatics, and this effect strengthened with several preceding days of exposure. In another study, the 24-hour averaged $PM_{2.5}$ level and exposure to diesel vehicles were both independently and significantly associated with wheeze in the asthmatic children [2]. The same-day levels of petroleum-related volatile organic compounds (VOCs), including benzene and toluene, were also significantly associated with the odds of more "bothersome" asthma symptoms as rated by a survey of 21 Hispanic children in Los Angeles. Also significantly associated with more asthma symptoms were 1-hour and 8-hour maximum levels of NO_2 and sulfur dioxide (SO_2) [8] .

The fraction of PM more specific to traffic-related sources, $PM_{2.5}$ has been associated with respiratory symptoms among asthmatic children in several studies. Among 40 fifth-graders with asthma at 4 schools in the Bronx, personal exposure to same day elemental carbon was significantly associated with increased risk of wheeze and shortness of breath during the month-long study period. Overall exposure to $PM_{2.5}$ did not demonstrate the same risk, suggesting the relative importance of the diesel related fraction of particulate pollution [6]. Traffic-derived $PM_{2.5}$ including elemental carbon, zinc, lead, and copper were also associated with asthma symptoms among 149 asthmatic children between 4 and 12 years of age [4]. In a longitudinal study over 13 weeks that enrolled African American children from Los Angeles, levels of $PM_{2.5}$ (12-hour average) and PM_{10} (1-hour maximum, 24-hour averages) were significantly associated with cough [7].

Certain characteristics among children with asthma may worsen their response to air pollution. Among 315 children ages 6 – 11 followed over 5 years in Fresno, California, increases in NO_2 and $PM_{2.5-10}$ with lags of 2 and 3 days respectively were associated with significantly increased wheeze. Among children with atopy, the effect was strengthened [5]. A panel of asthmatic children in southern California demonstrated increased symptoms with exposures to PM_{10} (same day and 5-day lag) and same-day O_3. The largest of the effects for both pollutants was seen among children with less severe asthma not on anti-inflammatory medications, suggesting that these medicines could protect from the pro-inflammatory effects of air pollutants [31]. Using the California Health Interview Study of adults, adolescents, and children, persons in poverty were two times as likely to experience asthma symptoms. In addition, the association between traffic and symptoms was strengthened among those living below the federal poverty level [27].

Air pollution and pediatric lung function

Studies also demonstrate that short-term increases in various pollutants lead to significant lung function impairment as measured in children. Levels of $PM_{2.5}$ averaged over 5 days were inversely associated with forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC, a measure of expelled lung volume) in asthmatic children and with FVC in non-asthmatic children in Mexico City [9]. Similarly in a 2-year longitudinal study of 861 low-income, asthmatic children from various cities across the United States, higher 5-day averages of NO_2, SO_2, and $PM_{2.5}$ were significantly and inversely correlated with FEV_1 [14]. In another study, a significant drop in bedtime FEV_1 was found with IQR increases in previous-day $PM_{2.5}$ in asthmatic elementary school students in Windsor, Ontario, Canada [12].

Studies have shown modification of the relationship between air pollutants and changes in lung function. Hourly maximum and 8-hour maximum personal levels of $PM_{2.5}$ were associated with decreased FEV1 in asthmatic children 9 – 18 years of age in Los Angeles, but this effect was not seen with ambient $PM_{2.5}$ measurements. In this study, both personal and ambient NO_2 levels acutely and inversely correlated with lung function. However, the effect of 1-hour maximum levels of $PM_{2.5}$ and preceding NO_2 measurements was strengthened among those not taking bronchodilator medications [13]. In another study, the inverse effect of personal and indoor $PM_{2.5}$ levels over the preceding days were on FEV_1 was made significant among boys with indoor allergies [11].

Air pollution and pediatric hospital utilization

Acute increases in Emergency Room visits and/or hospital admissions have been associated with high ground-level ozone levels in the city of Atlanta, Georgia. It was found that visits for asthma and reactive airway disease among low-income, African-American children between 1 and 16 years of age were 37% higher after 6 days of ozone levels greater than 0.11 parts per million (ppm) compared to other days [19]. Out of 130,000 pediatric emergency room visits to major centers in Atlanta during the summers 1993 - 1995, the risk of asthma-related visits was highest for children residing within zip codes with highest maximum 8-hour ozone and PM_{10} levels [20]. During the summer Olympic Games in Atlanta in 1996, levels of ozone dropped significantly as commuters were encouraged to seek alternate forms of transportation to reduce traffic levels in the city. This drop in ozone was associated with a significant reduction in pediatric asthma-related acute care events and hospitalizations as recorded in the Atlanta Medicaid database [18].

Other studies demonstrate increased hospital utilization for traffic-related pollutants in addition to ozone as well as in locations outside of Atlanta. In Helsinki, Finland, $PM_{2.5}$ measured at urban stations with 3 - 5 day lagged ozone measurements were associated with a significant increase in asthma-related emergency room visits for children less than 15 years of age between 1998 and 2004 [15]. In a study of children 5 – 17 years of age, emergency room visits for asthma and wheezing were found to be most significantly correlated with same-day concentrations of ozone and other traffic-related pollutants (including NO_2, and PM) among 91,386 recorded visits to 41 Atlanta- area hospitals [17]. Previous day high versus low levels of zinc particulate matter in Baltimore, Maryland was associated with significantly higher risk of emergency department visits and asthma exacerbations in children 0 to 17 years of age [21].

It has also been found that hospital admissions are increased among children from backgrounds of lower socioeconomic status [26-30]. Among children less than 18 years of age, it was found that asthma hospitalization rates were increased among those with lower socioeconomic status using discharge data from hospitals in Maine, New Hampshire, Vermont, and New York. This risk was increased among Black, non-Hispanics and Hispanics compared to White, non-Hispanics [28]. In a subsequent study, children in poverty regardless of race were at increased risk of hospitalization for asthma based on data from the 1993 California Hospital Discharge File [30]. In a more recent study, exposure to carbon monoxide (CO) led to a significant increase in hospital admissions for asthma in children, and this risk was increased for those with lower socioeconomic status [26].

Asthma control as health outcome

The 2007 National Asthma Education and Prevention Program Expert Summary Report for the Guidelines of Diagnosis and Management of Asthma defines asthma "severity" versus "control" and sets goals of care related to asthma control [43]. Asthma "severity" relates to the intrinsic severity of the disease process among those not receiving long-term control medications. Asthma "control" involves the reduction of impairment and risk through the appropriate use and escalation of medications as well as avoidance of environmental irritants. Impairment due to asthma is marked by chronic symptoms, the need for frequent use of short-acting bronchodilator medications, poor pulmonary function as measured by spirometry, and an inability to engage in age-appropriate activity and exercise. Attempts to reduce asthma risk involve efforts to increase control through the prevention of recurrent exacerbations, the need for Emergency Room visits and hospital admissions, and irreversible loss of lung function through the use of short-term and long-term medications.

Surveys have been developed to assess asthma control in adults as a potential guide for the adjustment (if needed) of medical treatment [41, 90]. The Asthma Control Questionnaire (ACQ) was developed in 1999 by Juniper et al. as a 7-question tool found to significantly predict changes in asthma control based on the limitation of activity by asthma, quantification of asthma symptoms, use of short-acting bronchodilator medications, and percent predicted FEV_1 over the preceding week. The ACQ score is calculated as the mean of the sum of the series of 7 questions based on a scale of 0 – 6, with more poorly controlled asthma represented by a higher numbers on the scale and therefore a higher mean score [41]. The mimimu score is therefore 0.0, and the

maximum score is 6.0. A subsequent study by Juniper el al. [54] among 1323 adults determined that “well-controlled” asthma comprised scores below 0.75 and that “poorly controlled” asthma reflected scores greater than 1.50 with various levels of control defined by the Global Initiative for Asthma [91] and National Institutes of Health guidelines [43]. In a study of asthmatic adults, it was found that scores from the first 5 questions of the ACQ (ACQ-5) significantly correlated with changes in eNO values after 3 months of high dose ICS treatment [57], thus pointing to the clinical utility of the tool. However, other studies refute the correlation of eNO with the ACQ among adults [92].

The ACQ has also been validated in children 6 – 16 years of age [42]. The questions were completed by children as was possible, except that for children ages 6 – 10, a trained interviewer was available to assist with the questions using secondary phrasing as needed as had been done previously [93]. It was found that in children, the questionnaire was able to accurately reflect significant changes in asthma control among children between weekly visits over 4 weeks. It was also possible to differentiate children whose asthma remained stable compared to those whose asthma control varied over the study period. Using the Global Rating of Change Method (n = 11), it was determined that the smallest clinically relevant change in ACQ score (related to symptoms, medication change, and activity limitation) was 0.52 +/- 0.45 [42]. However, this tool has been criticized more recently for use in children since its validation aggregated data from both written and oral versions in a study with a very small sample size [94]. Moreover, the association of ACQ scores with eNO among children has been questioned [95]. The ACQ also did not reflect clinically significant changes in FEV_1 found in a study of asthmatic children using inhaled nasal steroids for allergic rhinitis [96].

El Paso del Norte region and air pollution

The Paso del Norte (PdN) region at the United States-Mexico border includes the cities of El Paso, Texas; Ciudad Jaurez, Chichahua, Mexico; and Sunland Park, New Mexico and is plagued by high traffic-related pollution. Cities within this region have repeatedly exceeded National Ambient Air Quality Standards related to particulate matter and ozone [97]. Approximately 10 million passenger cars and over 700,000 trucks passed through the portal city of El Paso, Texas between the United States and Mexico in 2010 [32]. In this region, heavy traffic in addition to high temperatures, temperature inversions, older cars owned by an impoverished population, and infrequent rainfall lead to significant urban air pollution exposures [33-35].

Studies have quantified various traffic related pollutant levels in the PdN region in an effort to better understand how heavy traffic affects air quality in the region. In the cities of El Paso, Texas and Ciudad Juarez, 1/2 to 2/3 of aerosolized, non-methane hydrocarbons were demonstrated to come from on-road vehicle emissions [98]. Volatile organic compounds including benzene and toluene are linked to traffic emissions in the region [99]. The 1996 Paso del Norte ozone study concluded that high levels of ozone in the region may be related to factors such as intense sunlight with limited winds, and high levels of ozone-forming precursors such as NO_x and VOCs [37].

Previous investigations in the PdN region have demonstrated that short-term exposure to air various air pollutants adversely affects pediatric lung function [38, 55]. Biochemical mechanisms implicated in the asthmatic response were investigated in the PdN region using in vitro studies, and these studies point to the activation of oxidative [100] and inflammatory pathways in the

pulmonary response to particulate matter [101]. In the former of these studies, Lauer et al. demonstrated that oxidative changes in human bronchial epithelial cell culture were greatest in areas of the PdN region with higher traffic levels [100]. Levels of pollutants have been shown to vary within the community of El Paso, Texas and to differ at schools in high versus low traffic areas, thus putting certain children at a relative higher risk of exposure [44].

Preliminary findings in asthmatic children living in the region of El Paso – Ciudad Juarez

An initial study was performed in 2008 by our study group to investigate traffic-related pollutants and asthma among children in the first binational study of air pollution effects [40, 44, 55] in response to the US-Mexico Border 2012 program to fund air quality studies to promote sustainable development in the region [102]. In a cohort of 58 asthmatic children ages 6 – 12 living in El Paso in the United States and Ciudad Juarez across the border in Mexico, levels of eNO were measured as a function of air pollutant levels [55]. Indoor and outdoor levels of $PM_{2.5}$, PM_{10}, $PM_{10-2.5}$, NO_2, and BC were recorded over a period of 16 weeks using school-based and central monitors. The children filled out questionnaires related to asthma symptoms and medication use on a weekly basis, and levels of eNO were measured on a weekly basis. Results from that study indicate that interquartile increases in $PM_{2.5}$, PM_{10}, $PM_{10-2.5}$, NO_2, and BC (including 48- and 96- hour time lags) were significantly associated with increased eNO for the children included in the study. In these two cities, it was also found that exposures differed based on school location in high- or low- traffic zones [44].

The Mickey Leland National Urban Air Toxics Research Center (NUATRC) was established in 1991 as a public-private partnership to support scientific research to reduce health disparities for

the urban poor of Texas, in honor of the late United States Congressman George Thomas "Mickey" Leland of Texas. This organization was authorized under the Clean Air Act Amendments (CAAA) of 1990 and largely funded by the United States Environmental Protection Agency (EPA). In addition, this organization was supported in part by a 2009 special appropriation of the Texas Legislature through the Texas Commission on Environmental Quality (TCEQ). The following study was made possible through the Request of Proposal (RFP) 02-2009 "Evaluation of exposures (including measurement of air quality and potential harmful health effects) with a focus on vulnerable and underserved populations (including schools and school children in the Texas/Mexico border region)." The objective of this study was to characterize traffic-related pollutants in high- and low- exposure school zones and to measure respiratory health outcomes among children at these schools [40].

Data from this project contributed to our study, and separate findings from this project have been published in the 2011 NUATRC Research Report by Li et al., "Characterization of Traffic Related Air Pollution in Elementary Schools and its Impact on Asthmatic Children in El Paso, Texas" [40]. Among 38 asthmatic children from 2 El Paso area elementary schools over a 14 week study period, levels of eNO were significantly related to traffic-related pollutants, including particulate BC, benzene, and toluene [40]. This study also demonstrated that outdoor benzene levels were significantly linked to a decreased in forced expiratory volume in 1 second (FEV_1). However this effect was modified by weight category (per Centers for Disease Control (CDC) guidelines), with obese subjects showing a statistically stronger association.

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