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Increased ultrafine particles and carbon monoxide concentrations are associated with asthma exacerbation among urban children

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Abstract

Objectives—Increased air pollutant concentrations have been linked to several asthma-related outcomes in children, including respiratory symptoms, medication use, and hospital visits. However, few studies have examined effects of ultrafine particles in a pediatric population. Our primary objective was to examine the effects of ambient concentrations of ultrafine particles on asthma exacerbation among urban children and determine whether consistent treatment with inhaled corticosteroids could attenuate these effects. We also explored the relationship between asthma exacerbation and ambient concentrations of accumulation mode particles, fine particles (≤ 2.5 micrograms [μm]; $PM_{2.5}$), carbon monoxide, sulfur dioxide, and ozone. We hypothesized that increased 1 to 7 day concentrations of ultrafine particles and other pollutants would be associated with increases in the relative odds of an asthma exacerbation, but that this increase in risk would be attenuated among children receiving school-based corticosteroid therapy.

Methods—We conducted a pilot study using data from 3–10 year-old children participating in the School-Based Asthma Therapy trial. Using a time-stratified case-crossover design and conditional logistic regression, we estimated the relative odds of a pediatric asthma visit treated with prednisone (n=96 visits among 74 children) associated with increased pollutant concentrations in the previous 7 days. We re-ran these analyses separately for children receiving medications through the school-based intervention and children in a usual care control group.

Results—Interquartile range increases in ultrafine particles and carbon monoxide concentrations in the previous 7 days were associated with increases in the relative odds of a pediatric asthma

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visit, with the largest increases observed for 4-day mean ultrafine particles (interquartile range=2088 p/cm^3; OR=1.27; 95% CI=0.90–1.79) and 7-day mean carbon monoxide (interquartile range=0.17 ppm; OR=1.63; 95% CI=1.03–2.59). Relative odds estimates were larger among children receiving school-based inhaled corticosteroid treatment. We observed no such associations with accumulation mode particles, black carbon, fine particles (≤ 2.5 μm), or sulfur dioxide. Ozone concentrations were inversely associated with the relative odds of a pediatric asthma visit.

Conclusions—These findings suggest a response to markers of traffic pollution among urban asthmatic children. Effects were strongest among children receiving preventive medications through school, suggesting that this group of children was particularly sensitive to environmental triggers. Medication adherence alone may be insufficient to protect the most vulnerable from environmental asthma triggers. However, further research is necessary to confirm this finding.

Keywords

ultrafine particles; asthma; children; corticosteroids; intervention

1. INTRODUCTION

The United States Environmental Protection Agency recently concluded that the current literature supports a causal association between ambient particulate pollution and respiratory morbidity, with effect estimates ranging from 1% to 4% increases in respiratory hospital admissions associated with each 10 μg/m^3 increase in fine particle (particulate matter ≤2.5 μm diameter) concentration on the same and previous day (National Center for Environmental Assessment, 2009). Studies in children have reported decreases in pulmonary function and increases in respiratory symptoms and medication use associated with increased particulate pollutant concentrations (Weinmayr et al., 2010, Sacks et al., 2011, and Yeh et al., 2011). However, only a few studies have examined respiratory effects of ultrafine particles (< 0.1 μm diameter) (Pekkanen et al., 1997, Tiitanen et al., 1999, Penttinen et al., 2001, Ibald-Mulli et al., 2002, de Hartog et al., 2003, and Belleudi et al., 2010), and even fewer have examined ultrafine particle effects on respiratory function or asthma symptoms in children (Pekkanen et al., 1997 Tiitanen et al., 1999, and Andersen et al., 2008). Given that pollution exposure during childhood has been associated with impaired lung function (Jedrychowski et al., 2005) and asthma onset even at high levels of lung function (Islam et al., 2007), interventions that can reduce or mute respiratory effects of pollution during childhood may help to preserve respiratory health later in life.

Ultrafine particles may be particularly important with regard to respiratory effects because their higher surface area, compared to fine particles, allows them to evade respiratory clearance mechanisms, thus increasing the burden of reactive oxygen species and airway inflammation (Chalupa et al., 2004). Therefore, further studies are needed of the acute respiratory effects of ultrafine particles as well as evaluation of ways to protect against their impact. To examine the acute effects of ultrafine particles and other ambient pollutants on pediatric asthma exacerbation, we conducted a pilot study, taking advantage of a completed asthma therapy trial and an ongoing ambient pollutant monitoring program in Rochester, NY.

In light of evidence of poor adherence to preventive asthma treatment regimens among children, particularly among low-income and minority groups (Halterman et al., 2000 and Desai et al., 2011), the School-Based Asthma Therapy trial (Halterman et al., 2011) was designed to investigate whether consistent administration of inhaled corticosteroids by school nurses resulted in more symptom-free days in asthmatic 3–10 year-old children living in urban Rochester, NY. Given that particulate matter and other pollutants have been

associated with airway inflammation in children (Mar et al., 2005; Delfino et al., 2006; Lin et al., 2011) and that daily use of inhaled corticosteroids is commonly prescribed to prevent asthma exacerbations by reducing airway inflammation (National Heart, Lung and Blood Institute, 2007), we also sought to determine whether the association between pollutant concentrations and asthma exacerbation is modified by adherence to preventive medications. Thus, we hypothesized that the relative odds of an acute asthma exacerbation would increase as mean 1 to 7 day ultrafine particle and other pollutant concentrations increased. We also hypothesized that this increased risk would be attenuated in the children receiving the school-based corticosteroid intervention.

2. METHODS

2.1 Study population

The source population for the School-Based Asthma Therapy trial consisted of 3–10 year-old children attending over 60 preschools and elementary schools in the Rochester City School District whose caregiver indicated on school screening forms that the child had asthma. To be deemed eligible for the trial, verification of each child's asthma diagnosis and need for preventive medication was required from their primary care physician. Additionally, children were required to meet National Heart, Lung, and Blood Institute Expert Panel guidelines for persistent asthma symptoms (National Heart, Lung, and Blood Institute, 2002 & 2007), and they were excluded if they had any health condition that would complicate the assessment of asthma outcomes or if their caregiver did not speak English. Out of 713 eligible children, 530 (74%) were randomized to either a group receiving daily preventive asthma medications administered by school nurses (n=265) or a usual care group in which caregivers were responsible for medication administration (n=265). There were 112 refusals to participate from parents (97), physicians (14), and children (1), and no baseline assessments were obtained for 71 children. Randomization occurred at the beginning of either the 2006, 2007, or 2008 school year (August-November) and each child was followed through the end of the respective school year (June). Nearly all (91%) of the randomized children were non-white, with 63% being black. More than one quarter (28%) were of Hispanic ethnicity (any race). This was also a predominantly low-income population, with 85% of the 530 randomized children being covered by Medicaid or New York State's Children's Health Insurance Program (Halterman et al., 2011).

Children enrolled in the School-Based Asthma Therapy trial whose caregivers reported any asthma-related doctor's office or emergency department visit at which their child received prednisone during the follow-up period comprised the study population for this analysis. Both the School-Based Asthma Therapy trial and this study were approved by the Research Subjects Review Board at the University of Rochester, and informed consent and assent were obtained from caregivers and children, respectively. The School-Based Asthma Therapy trial was conducted in accordance with the World Medical Association's code of ethics for experiments involving human subjects.

2.2 Outcomes and other covariates

The outcomes for this study, including pediatric asthma visits, were ascertained via monthly telephone interviews with children's caregivers during the School-Based Asthma Therapy trial. Each month, caregivers reported the number and dates of asthma-related medical visits that their child experienced that month. We defined an acute pediatric asthma visit as any doctor's office or emergency department visit where prednisone was prescribed. Multiple visits for a single child that occurred 7 or more days apart were considered as separate events. These visits were then used as outcomes in the statistical analyses described below.

We also retained data on each subject's age, sex, race/ethnicity, baseline measures of pulmonary function, certain child and family member diagnoses, baseline asthma symptom frequency, baseline salivary cotinine (a biomarker of tobacco smoke exposure), insurance status, and baseline use of preventive asthma medications. Information on caregiver characteristics including age, education, and marital status were also obtained from the School-Based Asthma Therapy trial data.

2.3 Air pollution, meteorology, and individual exposure assessment

We utilized a program of continuous pollutant monitoring at the New York State Department of Environmental Conservation site in Rochester, NY to quantify the exposures for this study. Particle counts 0.01–0.50 μm in diameter were measured using a Scanning Mobility Particle Sizer (TSI, Inc., Shoreview, MN), and were categorized into ultrafine particles (< 0.1 μm) and accumulation mode particles (0.10–0.50 μm) (Wang et al., 2011). Concentrations of fine particles (≤ 2.5 μm) were measured using a Tempered Elemental Oscillating Microbalance (ThermoFisher, Franklin, MA), while concentrations of black carbon were measured with an aethelometer (Magee Scientific, Berkeley, CA) (Wang et al., 2011 and Wang et al., 2012). Continuous carbon monoxide, sulfur dioxide, ozone, and hourly weather data were also measured at this site and used in our analyses. Pollutant concentrations and weather variables were determined for the day of each asthma visit and the 7 preceding days to determine each child's ambient concentrations of ultrafine particles, accumulation mode particles, fine particles, carbon monoxide, sulfur dioxide, and ozone during their case and control time periods. Our analyses were limited to the pollutants that are currently measured at the Rochester monitoring site, which precluded us from analyzing the effects of other potentially relevant pollutants such as nitrogen dioxide. Although monitors for nitric oxide, nitrogen dioxide, and other nitrogen compounds were added to the monitoring site in 2011 and will be available for future studies, these subject data are from 2006–2009 and so those pollutant measurements were not available for our analyses. Additionally, pollutant data were not available on certain days during the study period (i.e. monitor not operating on that day), thus resulting in an inability to calculate 1 to 7-day moving averages for some pollutants for some subjects' case and/or control periods. Thus, the number of events available for each pollutant moving average analysis may not be the same (See Tables 3 and 4, and Supplemental Table 1). The monitoring site is about 1500 meters from the intersection of two interstate highways, and ranges from less than 1.6 kilometers (km; ~1 mile) to greater than 11 km (~7 miles) away from study subjects' schools. Given that children generally must live within the city limits in order to attend one of the participating schools, we estimate the maximum distance from the monitor to a given child's home to be approximately 14.5 km (~9 miles).

2.4 Study design

We conducted a pilot study using a time-stratified case-crossover study design (Maclure, 1991 and Levy et al., 2001) in which children's pollutant exposures on the day of and in the days preceding their asthma visit were contrasted with pollutant concentrations during times when such a visit did not occur. This design is analogous to a matched case-control study. However, instead of contrasting air pollutant concentrations between a child experiencing a doctor's visit for asthma (case) and a child who did not (control), it contrasts pollutant concentrations on the day of the asthma doctor's visit (case period) to other periods when the child did not have an asthma visit (3–4 control periods per case depending on the number of days in the calendar month). For example, if a child experienced an exacerbation on Monday, March 10, 2008, then the case period for that exacerbation would be March 10, and the control periods would be Mondays March 3, 17, 24, and 31. This control selection matches the case and control periods by calendar year, month, and weekday. The daily air pollution concentrations on and before these case and control period dates are then

contrasted. Since the case and control periods are within the follow-up time of the same child, non-time varying confounders such as health history are controlled by design. Factors that vary between case and control time periods (e.g. weather variables), however, are possible confounders that should be included in statistical models. Pollutant concentrations corresponding to these case and control periods are then contrasted in the statistical analyses described below.

2.5 Statistical analyses

2.5.1 Main analyses—We used conditional logistic regression models, stratified on each case-control matched set, to regress case–control status against the mean concentrations of ultrafine particles and other pollutants (accumulation mode particles, fine particles (≤ 2.5 μm), carbon monoxide, ozone, and sulfur dioxide) on the day of the asthma visit, as well as the mean pollutant levels across 1 to 7 days prior to each visit. From these single-pollutant models, we estimated the relative odds (and 95% confidence intervals) of an asthma visit associated with interquartile range increases in the 1 to 7 day mean pollutant concentrations.

By design, a case-crossover study controls for potential confounders that do not vary over time (e.g. race, sex, smoking history, health history), though variables that may be related to both air pollution levels and pediatric asthma visits that vary over short time periods (e.g. weather conditions such as temperature and relative humidity) are possible confounders that must be included in analytic models. We did not consider age as a time-varying confounder, since age only varied by, at most, one month within each matched set (1 case period and 3–4 control periods). To determine which time lags of weather variables (e.g. lag day 0 [day of visit], mean of lag days 0 and 1…mean of lag days 0 through 7) should be included in our models, we first ran separate conditional regression models using 1-day mean to 7-day mean temperature and relative humidity (1–3 degrees of freedom). From this group of models, we chose the time lags and degrees of freedom of temperature and humidity that best estimated the relative odds of an asthma visit, as indicated by Akaike's Information Criterion, and we used these weather variables in our pollutant models.

We then conducted stratified analyses to examine whether the relative odds of a pediatric asthma visit associated with increased pollutant concentrations was different for children randomized to the school-based intervention versus those randomized to usual care. We separately estimated the relative odds of an asthma visit associated with an increase in pollutant concentration among those randomized to the school-based corticosteroid delivery intervention, and those randomized to the usual care group. We also examined whether there were seasonal variations in the effect of pollutants on our outcome by running separate models within case-control matched sets occurring during the colder months (November through April) and those occurring during the warmer months (May through October).

2.5.2 Sensitivity analyses—To evaluate whether our relative odds estimates were robust to changes in how we modeled temperature and relative humidity, we re-ran the conditional logistic regression models described above using the mean temperature and relative humidity for the same averaging time as the pollutant variable in all models. Next, we examined whether our findings were limited to the subset of acute asthma-related visits at which a child received prednisone by re-running the analyses described above using all asthma-related doctor's office, emergency department, and hospital visits (with or without prednisone treatment) during the follow-up period. We also conducted stratified analyses by treatment group among this larger set of asthma events. Finally, we also ran analyses using only those children who had a single pediatric asthma visit during follow-up to determine whether it was necessary to account for potential non-independence of multiple events within subjects with more than 1 asthma visit.

3. RESULTS

During the School-Based Asthma Therapy trial follow-up period, 74 children (mean age: 6.7 ± 2.0 yrs) experienced a total of 96 pediatric asthma visits. Among the children who experienced multiple visits (n=12; 16%), there was an average of 74.5 (± 55.1) days between events. The 74 children with an asthma visit were predominantly male (64%) and black (65%), nearly a third were Hispanic (32%), and most were covered by Medicaid insurance (78%). At baseline, 80% of caregivers reported having a preventive asthma medication prescription for their child. Caregivers reported their children had an average of 6.7 (±5.0) symptom-free days in the past 2 weeks, and 50% of children had at least one smoker living in their home. Children's caregivers (mean age=33.6 ± 9.3 yrs) were most often their mother (87%), mostly single (64%), and 41% had at least some college education.

The characteristics of all 530 children in the School-Based Asthma Therapy trial, by treatment group, and the subgroup who experienced an asthma visit requiring prednisone administration are shown in Table 1. The 74 children who experienced an asthma visit did not differ substantially from all 530 children enrolled in the School-Based Asthma Therapy trial with regards to age, gender, race/ethnicity (93% vs. 91% non-white), insurance status (84% vs. 86% low-income insurance), or the presence of smokers in the home. Our sample was also racially and socioeconomically comparable (93% non-white; 84% low income) to the overall population of children attending Rochester city elementary schools (89% non-white; 87.5% low-income; Brown 2012). However, the children in our sample were more likely to report use of preventive medications at baseline (80% vs. 69%), and had lower baseline peak expiratory flow (126.3 ± 51.6 vs. 146.1 ± 59.3 L/min), lower baseline forced expiratory volume in one second (0.96 ± 0.39 vs. 1.10 ± 0.42 L), and fewer symptom-free days in the past 2 weeks (6.7 ± 5.0 vs. 8.0 ± 4.8) compared to the entire School-Based Asthma Therapy trial cohort. The children in the school-based intervention group who had an asthma visit requiring prednisone (n=31) were younger, more likely to be male, had higher mean salivary cotinine levels, and exhibited various signs of greater asthma severity at baseline, compared to the whole treatment group.

The mean 24-hour pollutant concentrations and weather conditions over the School-Based Asthma Therapy trial period are shown in Table 2. Pearson coefficients (r) showed moderate correlations between some pairs of pollutants throughout the study period (accumulation mode and fine particles: r=0.64; ultrafine and accumulation mode particles: r=0.46; carbon monoxide and ozone: r= −0.48), and some correlation coefficients were larger in the either the colder months (November through April; ultrafine and accumulation mode particles: r=0.62; accumulation mode and fine particles: r=0.74; ozone and carbon monoxide: r= −0.62) or the warmer months (May through October; ozone and accumulation mode particles: r=0.51; ozone and fine particles: r=0.57) Temperature was moderately correlated with accumulation mode particles (r=0.49) and fine particles (r=0.53) in the warmer months only.

Each interquartile range increase in the 2 to 7 day mean ultrafine particle concentration was associated with an increase in the relative odds of an asthma visit, though many effect estimates lacked precision as indicated by relatively wide 95% confidence intervals (Table 3). The greatest increase in the relative odds was observed for 4-day mean ultrafine particles (interquartile range=2088 p/cm^3; OR=1.27, 95% CI=0.90 – 1.79) A similar pattern of association was observed with interquartile range increases in the 1 to 7 day mean black carbon concentrations (e.g. 4-day interquartile range=0.36 μg/m^3, OR=1.20, 95% CI=0.85 – 1.70). There was also a consistent increase in the odds of an asthma visit associated with increasing 1 to 7 day mean carbon monoxide levels, with significant and increasing effect

estimates across the 4 to 7 day mean carbon monoxide concentrations. Each 0.17 parts per million (ppm) increase in the 7-day mean carbon monoxide concentration was associated with a 63% (95% CI = 3% – 159%) increase in the odds of a pediatric asthma visit. No such pattern of response was observed for accumulation mode particles, fine particles (≤ 2.5 μm), sulfur dioxide, or ozone. Interquartile range increases in the mean 1 to 7 day ozone concentrations were generally associated with a decrease in the relative odds of a pediatric asthma visit, with a significant decrease associated with each interquartile range increase in the 5-day mean ozone concentration (interquartile range=12.6 parts per billion (ppb), OR=0.41, 95% CI=0.18 – 0.92). However, only 6 (6%) of these events occurred during the peak ozone season (i.e. June 1 through August 31; mean temperature = 22.0 ± 14.5°C, mean ozone concentration = 31.8 ± 10.3 ppb), of which none were in July or August. Eighty-four (88%) of these events occurred during colder, low ozone months (mean temperature = 5.5 ± 9.2°C; mean ozone concentration = 23.7 ± 9.1 ppb).

Stratified analyses by treatment group showed larger relative odds of a pediatric asthma visit associated with interquartile range increases in 1 to 7 day ultrafine particle and carbon monoxide concentrations among children who received the school-based intervention, compared to the usual care group (Table 4). In the treatment group, the largest relative odds estimates were associated with interquartile range increases in the 4-day mean ultrafine particle concentration (interquartile range=2088 p/cm^3, OR=1.42, 95% CI=0.89 – 2.27) and the 7-day mean carbon monoxide concentration (interquartile range=0.17 ppm, OR=2.05, 95% CI=1.03 – 4.11). Stratified analyses by season showed a substantially larger relative odds of a pediatric asthma visit associated with each interquartile range increase in the 4-day mean ultrafine particle concentration during the warmer months of the year (May through October: OR=2.81, 95% CI=1.09 – 7.19), compared to the colder months (November through April: OR=1.06, 95% CI=0.71 – 1.58). No seasonal effect modification was observed for 1 to 7 day mean carbon monoxide or ozone concentrations (data not shown).

The relative odds estimates associated with interquartile range increases in 4 to 7 day mean carbon monoxide concentrations were smaller in our sensitivity analyses that controlled for the average temperature and humidity at the same time lag as the pollutant (7-day OR=1.34, 95% CI=0.88 – 2.05), whereas larger relative odds estimates were observed for each interquartile range increase in the mean 4-day ultrafine particle concentration (OR = 1.39, 95% CI = 1.01–1.93). Further, the relative odds of an asthma visit associated with each interquartile range increase in the 5-day mean ozone concentration was closer to 1.00 and no longer statistically significant (OR = 0.54, 95% CI = 0.26 – 1.14). The relative odds of an asthma visit associated with interquartile range increases in 1 to 7 day mean ultrafine particle and carbon monoxide concentrations seen in our main and stratified analyses were substantially decreased and the odds associated with increases in ozone were closer to 1.0 and non-significant when we expanded our outcome definition to include all 293 asthma-related doctors' office, emergency department, and hospital visits among 186 children (4-day ultrafine particle OR = 0.94, 95% CI = 0.77 – 1.15; 7-day carbon monoxide OR = 1.10, 95% CI = 0.85 – 1.42; 5-day ozone OR = 0.79, 95% CI = 0.50 – 1.25).

We also ran two-pollutant models using the pollutants shown to be associated with asthma exacerbation (ultrafine particles, carbon monoxide, and ozone). The effect estimates in these models did not differ substantially from those in the single-pollutant models (data not shown).

Finally, our analyses excluding those children who experienced multiple events during follow-up showed similar odds ratios associated with each 2088 p/cm^3 increase in the 4-day mean UFP concentration (OR=1.33; 95% CI = 0.85 – 2.10) and each 0.17 ppm increase in the 7-day mean CO concentration (2.01; 95% CI = 1.17 – 3.42). In fact, compared to our

main analysis (Table 3), we observed similar patterns, but larger odds ratios and confidence intervals, for these pollutants across most averaging times (i.e. 1 to 7 day average UFP and CO concentrations), when only children with a single event were included (data not shown).

4. DISCUSSION

This pilot study coupled ambient pollutant data with data on caregiver-reported pediatric asthma visits requiring prednisone administration from a randomized intervention trial and suggested associations between ultrafine particle and carbon monoxide concentrations in the past 7 days and increased relative odds of an asthma visit among 3–10 year-old urban children. We observed increased relative odds of a pediatric asthma visit associated with increases in 2 to 7-day mean ultrafine particle and 1 to 7-day mean carbon monoxide concentrations, with the largest percent increases in the relative odds associated with 4-day mean ultrafine particles (27%) and 7-day carbon monoxide (63%). However, inconsistent with our hypothesis, these increases in the relative odds of an asthma visit were considerably larger among children randomized to receive school-based administration of inhaled corticosteroids, compared to those receiving usual care.

Our findings regarding carbon monoxide and pediatric asthma events are consistent with previous research showing increases in the risk of emergency department visits and hospital admissions for asthma in children (≤ 18 years) associated with increased ambient carbon monoxide concentrations (Delfino et al., 2009 and Li et al., 2011). However, we did not observe an increased risk of a pediatric asthma visit associated with acute increases in fine particles (≤2.5 μm) or sulfur dioxide, which have also been reported previously (Segala et al., 1998, Ko et al., 2007, Andersen et al., 2008, Li et al., 2011 and Iskandar et al., 2012). Although two previous studies were suggestive of an association of increased ultrafine particle concentration with decreases in children's peak expiratory flow, the associations with ultrafine particles were not statistically significant and larger particles (0.1 to 10 um) were found to be more strongly associated with the outcomes in those analyses (Pekkanen et al., 1997 and Tiitanen et al., 1999). Discrepancies between this and previous studies may be due to differences in study populations, designs, and methods, including differences in sample size, the age group(s) of children studied, outcome definitions and data sources (e.g. International Classification of Diseases, 9^{th} revision diagnostic codes vs. parental reports of asthma attacks) and subjects' medication regimens (e.g. known daily inhaled steroids and/or β_2 agonists vs. no daily preventive medication).

The observation of decreased odds of an asthma visit associated with increasing ozone concentrations, occurring almost exclusively during colder months with low ozone concentrations, is likely a result of the negative correlation of ozone with nitrogen dioxide, another marker of traffic pollution which was not measured at the Rochester site. Similar spurious protective effects of ozone have been observed in previous studies of pollutant effects on asthma, as well as cardiovascular biomarkers (Anderson et al., 1998, Hajat et al., 1999 and Rich et al., 2012).

We found larger relative odds of a pediatric asthma visit associated with increased ambient pollution among children who were consistently taking inhaled corticosteroids as part of the School-Based Asthma Therapy trial, with up to a 105% increase in the relative odds of an asthma visit associated with each 0.17 ppm increase in ambient carbon monoxide levels in the school-based treatment group. Several, though not all, previous studies have also observed greater detrimental effects of pollutants on children taking preventive medications. Delfino et al. (2003) observed greater asthma symptom severity associated with increased 8-hour ozone, coarse particles (< 10 um), organic carbon, nitrogen dioxide, and sulfur dioxide concentrations, as well as larger increases in exhaled nitric oxide associated with increasing

2-day mean fine particles, coarse particles, elemental and organic carbon, and nitrogen dioxide concentrations among children and adolescents taking anti-inflammatory medications (Delfino et al., 2006). Greater decreases in peak expiratory flow with increasing 24-hour mean nitrogen dioxide and 24 to 72 hour mean sulfur dioxide levels have also been found among subjects taking inhaled long-acting beta agonists and inhaled corticosteroids, respectively (Qian et al., 2009), and 2 to 5 day lagged fine and coarse particles and ozone have been associated with lower forced expiratory volume in one second among children taking preventive treatments (Lewis et al., 2005). Additionally, Gent et al. (2003) observed increased asthma symptoms and rescue medication use associated with increases in 1-hour ozone levels among children using maintenance medications (corticosteroids, cromolyn, leukotriene inhibitors), but no association among children not taking these medications.

Some studies, however, have not observed the same effect modification by corticosteroid treatment of the association between pollutants and lung function as is suggested by our study and other previous work. Hernandez-Cadena et al. (2000), for example, observed a significant pollutant-related decrease in airway reactivity (as measured by changes in forced expiratory volume) in response to use of a short-acting beta agonist only among asthmatic children who were not taking an inhaled corticosteroid. Zora et al. (2012) saw worsening of asthma control, albeit it non-significant, associated with increased weekly particulate concentrations (PM_{10}, $PM_{10–2.5}$, $PM_{2.5}$) only among children not receiving regular corticosteroid treatment. However, they also reported significant worsening of asthma control associated with increased benzene and toluene concentrations among those receiving corticosteroids. Differences among previous studies in the observed relationships of asthma symptoms and lung function with pollutant concentrations are likely due, in part, to between-study differences in subjects' medication types (e.g. inhaled corticosteroids [Delfino et al., 2006] vs. beta agonists [Qian et al., 2009]). Similar to our study, some others specifically looked at differences between those using and not using inhaled corticosteroids (Delfino et al., 2003; Hernandez-Cadena et al., 2000; Zora et al., 2012), while others simply stratified subjects according to whether they were or were not taking any preventive medication (Gent et al., 2003). Also, the criteria for defining a "user" of a particular medication differed among studies (e.g. self-reported daily use [Delfino et al., 2006] vs. recording of medication use in ≥50% of symptom diary entries during study [Lewis et al., 2005]), and was often not reported. Patient adherence to medication regimens was also not generally reported.

It is not clear why this and previous studies have found greater effects of pollutants on asthmatics consistently taking preventive medications. However, it is possible that this subgroup of asthmatic children suffers a greater degree of underlying disease severity and thus may be more sensitive to environmental exposures. Lewis et al. (2005) suggested that subclinical airway inflammation or remodeling in children with more severe asthma may contribute to their greater sensitivity to pollutants despite their use of corticosteroids. Indeed, the children in the school-based corticosteroid treatment group who had an exacerbation requiring prednisone administration had lower peak expiratory flow and forced expiratory volume in 1 second at baseline compared to the usual care group, indicating poorer lung function. These children, therefore, may have been expected to have less of a response to consistent inhaled corticosteroid treatment through the school-based intervention. This suggests the need for more targeted interventions to reduce environmental exposures for this group. In addition, specialist asthma care may be warranted in order to optimize therapy among these children for whom consistent corticosteroid treatment appears to be insufficient.

Ultrafine particles and carbon monoxide are products of combustion reactions such as those that occur in motor vehicles, which suggests that the observed associations with these

pollutants likely reflect the amount of vehicular traffic to which these children are regularly exposed. Black carbon is an additional marker of traffic pollution which followed a pattern of association with pediatric asthma visits similar to that of ultrafine particles, further supporting a relationship between traffic pollutants and pediatric asthma. This relationship is also supported by the lack of a substantial change in any of the effect estimates when multiple pollutants were included in the same model. The children included in the School-Based Asthma Therapy study lived and attended preschool or elementary school within the city limits of Rochester, NY. Rochester is the third most populous city in New York State and is comprised of a densely settled (>2100 people/km^2) urban core surrounded by four major highways. Previous work at our institution has determined that concentrations of these pollutants within Rochester are largely attributable to local traffic patterns (Oberdörster et al., 2009). Our finding of increased relative odds of a pediatric asthma visit requiring prednisone administration associated with increased ultrafine particles in the summer, but not the winter, may be due to varying degrees of exposure misclassification and downward bias due to more open windows and more time outside in the summer versus winter. However, despite the relatively large odds ratio associated with 4-day ultrafine particle concentrations (OR=2.81), the 95% confidence interval (1.09–7.19) indicates a lack of precision in this effect estimate and is likely a result of the small number of events (25) that occurred during the warmer months. Additionally, data were not available regarding children's activities immediately prior to an asthma exacerbation, so we were unable to assess whether outdoor versus indoor activities modified the relationship of pollutant concentrations to pediatric asthma visits. However, the seasonal differences also may reflect different compositions of ultrafine particles in the summer and winter in Rochester (i.e. more secondary organic aerosol with reactive oxygen species in the summer versus winter (Venkatachari et al., 2005 and Venkatachari et al., 2007)). More work is needed to assess health effects of different ultrafine particle compositions.

There were several limitations of this study that should be considered when making inference. First, only 74 of the 530 School-Based Asthma Therapy subjects experienced an acute asthma visit at least once over the study period, resulting in a relatively small sample size and reduced statistical power. The direction of the observed associations, however, was generally consistent with our hypothesis, particularly for ultrafine particles and carbon monoxide. Second, our reliance on caregiver reports of asthma visits introduced the potential for outcome misclassification. However, this outcome error was minimized by specifying our outcome as a doctor's office or emergency department visit where the child received prednisone, an anti-inflammatory steroid used specifically to treat asthma exacerbations. Further, the smaller effect estimates observed in our sensitivity analyses using an expanded outcome definition (any asthma-related visit) suggests a greater degree of exposure misclassification using that definition and supports the validity of our narrower outcome classification. Third, the children in the School-Based Asthma Therapy trial attended over 60 preschools and elementary schools in the Rochester City School District. Therefore variability in the distance of children's homes, schools, and communities from the pollution monitor may have resulted in some error in estimating individual children's pollutant exposures. The distance from the pollution monitor to the participating schools ranges from less than 1.6 km (~1 mile) to approximately 11 km (~7 miles). Additionally, the monitoring station is located about 1500 meters from the intersection of two interstate highways and is on a diesel bus route, likely resulting in higher measured pollutant concentrations than some of the study children were actually exposed to. The resulting exposure error was likely a combination of both Berkson and classical error (Zeger et al., 2000 and Bateson and Wright, 2010), possibly resulting in a bias towards the null and underestimates of the relative odds of a pediatric asthma visit associated with increased pollutant concentrations. Additionally, the larger effect estimates observed for some of the multi-day average pollutant concentrations could be a result of less error in exposure

measurements for multi-day versus single-day lag values. Also, confounding by unmeasured non-time varying covariates is likely minimal due to our use of a case-crossover study design, which controls for non-time-varying factors by design. This study was also limited by a lack of data regarding other potentially relevant pollutants including nitrogen dioxide, which is often highly correlated with some of the pollutants analyzed in this study. Although monitors for nitric oxide, nitrogen dioxide, and other nitrogen compounds were added to the Rochester monitoring site in 2011 and will be available for future studies, these subject data are from 2006–2009 and so those pollutant measurements were not available for our analyses. Finally, although residual confounding by weather or other unknown factors is possible, using alternate lag days to control for confounding by temperature and relative humidity did not substantially change our effect estimates.

As hypothesized, we observed associations between ambient traffic pollutant concentrations and asthma exacerbation among urban children. However, contrary to our hypothesis that the anti-inflammatory action of daily inhaled corticosteroids would counteract the negative respiratory effects of these pollutants, we observed greater relative odds of a pediatric asthma visit associated with increases in both ultrafine particles and carbon monoxide among children being consistently treated with these preventive medications, compared to those who were not. Our results suggest that for a subset of asthmatic children, such preventive medications are insufficient to protect against the negative effects of urban air pollution. However, further research is necessary to confirm this finding. Our study also suggests the need for more research into methods of decreasing these exposures and protecting asthmatic children.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Both the original clinical trial and this analysis were approved by the Research Subjects Review Board at the University of Rochester. Eligible children and their parents were provided a detailed explanation of the School-Based Asthma Therapy trial, and permission was obtained to contact each child's primary care provider to verify the child's need for corticosteroid treatment. Informed consent was then obtained during visits to the homes of eligible children.

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- Case-crossover design used to study associations between air pollutants and pediatric asthma.
- Ultrafine particles and carbon monoxide increased exacerbation risk in urban children.
- Stronger effects were observed among children receiving daily preventive medication.
- Some asthmatic children may be more susceptible to effects of pollutants.

Table 1

Characteristics of subjects who had an asthma visit treated with prednisone during the School-Based Asthma Therapy trial, and characteristics of all trial subjects, mean (s.d.) or n (%)

	Subjects who had an asthma visit treated with prednisone		All trial subjects	
	School-based intervention (n=31)	**Usual care (n=43)**	**School-based intervention (n=265)**	**Usual care (n=265)**
Age at baseline (yrs)	6.1 (2.0)	7.1 (1.8)	7.1 (2.0)	7.2 (1.9)
Age at asthma diagnosis (yrs)	3.6 (3.0)	3.3 (3.3)	3.7 (3.2)	3.8 (3.1)
Male	24 (77)	23 (54)	161 (60)	147 (55)
Race				
White	2 (7)	3 (7)	27 (10)	21 (8)
Black	21 (68)	27 (63)	167 (63)	168 (63)
Other	8 (26)	13 (30)	71 (27)	76 (29)
Hispanic	12 (39)	12 (28)	82 (31)	69 (26)
Insurance				
Medicaid	23 (74)	35 (81)	192 (73)	197 (74)
NY State public insurance	3 (10)	5 (12)	33 (13)	31 (12)
Private or other	5 (16)	2 (5)	35 (13)	28 (11)
No insurance	0 (0)	1 (2)	5 (2)	9 (3)
Mother has asthma	12 (39)	12 (28)	101 (38)	86 (33)
Father has asthma	5 (16)	12 (28)	46 (17)	51 (19)
Child has eczema	21 (68)	20 (47)	121 (46)	107 (40)
Family member has eczema	25 (81)	25 (58)	147 (56)	153 (58)
On preventive meds, baseline	26 (84)	33 (77)	185 (70)	174 (66)
Peak expiratory flow at baseline (L/min)	118.7 (38.7)	131.6 (58.8)	147.1 (62.0)	145.0 (66.6)
Forced expiratory volume in 1 second at baseline (L)	0.9 (0.4)	1.0 (0.4)	1.1 (0.4)	1.1 (0.4)
Symptom-free days in past 2 weeks at baseline	7.0 (4.9)	6.4 (5.0)	8.0 (5.0)	8.0 (1.8)
Smoker(s) in the home	15 (48)	22 (51)	140 (53)	145 (55)
Cotinine at baseline (ng/ml)	1.4 (2.2)	1.1 (1.5)	1.2 (1.6)	1.6 (2.8)
Mother is primary caregiver	27 (87)	38 (88)	238 (90)	233 (88)
Caregiver age (yrs)	34.5 (9.5)	33.0 (9.3)	33.9 (8.1)	34.5 (9.1)
Caregiver education				
Less than high school	10 (32)	16 (37)	79 (30)	74 (28)
High school grad/GED	8 (26)	10 (23)	81 (31)	85 (32)
Some college	11 (36)	14 (33)	76 (29)	76 (29)
College grad/grad sch.	2 (7)	3 (7)	29 (11)	30 (11)
Caregiver single	22 (71)	25 (58)	192 (73)	197 (74)

L/min: liters per minute; ng/ml: nanograms per milliliter

Table 2

Distribution of daily pollutant concentrations, temperature, and humidity during the study period (Sept. 2006 through June 2009)

			Percentiles						
Pollutant	**Days of data collection**	**24-hour mean (± SD)**	**Minimum**	**5th**	**25th**	**50th**	**75th**	**95th**	**Maximum**
Ultrafine particles (p/cm^3)	990	5151 (2359)	480	1954	3442	4843	6449	9575	14450
Accumulation mode particles (p/cm^3)	990	1054 (679)	108	280	525	899	1399	2329	4444
Fine particles (μg/m^3)	939	8.6 (5.9)	0.1	1.9	4.4	7.4	11.1	20.3	43.0
Carbon monoxide (ppm)	982	0.40 (0.16)	0.1	0.2	0.3	0.4	0.5	0.7	1.0
Sulfur dioxide (ppb)	1011	5.4 (7.7)	1.0	1.2	2.0	3.3	5.1	19.4	50.0
Ozone (ppb)	1008	26.1 (10.2)	1.5	11.5	18.8	25.2	33.0	43.6	64.7
Black carbon (μg/m^3)	923	0.68 (0.40)	0.05	0.20	0.37	0.61	0.90	1.40	2.44
Temperature (°C)	1034	9.8 (7.7)	−13.2	−6.6	1.4	10.4	18.7	24.6	29.4
Relative humidity (%)	1033	64.1 (14.0)	10.2	40.9	55.8	65.2	73.5	85.2	95.3

p/cm^3: parts per cubic centimeter; μg/m^3: micrograms per cubic meter; ppm: parts per million; ppb: parts per billion

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Table 3

Relative odds of an asthma visit associated with each interquartile range increase in mean pollutant concentrations, by lagged averaging time. All models adjusted for 7-day mean temperature (1 degree of freedom) and relative humidity (3 degrees of freedom)

Pollutant	Pollutant Averaging Time*	IQR	Number of Subjects	Number of Visits	Odds ratio	95% CI	p
Ultrafine particles (p/cm^3)	1-day	3007	65	85	0.89	0.64 – 1.24	0.48
	2-day	2514	65	85	1.05	0.76 – 1.46	0.76
	3-day	2224	64	85	1.19	0.86 – 1.64	0.30
	4-day	2088	63	84	1.27	0.90 – 1.79	0.17
	5-day	2011	61	83	1.19	0.80 – 1.77	0.40
	6-day	1913	60	82	1.19	0.78 – 1.81	0.43
	7-day	1841	60	82	1.06	0.67 – 1.68	0.79
Accumulation mode particles (p/cm^3)	1-day	874	65	85	0.73	0.50 – 1.08	0.12
	2-day	757	65	85	0.87	0.61 – 1.23	0.42
	3-day	688	64	85	0.98	0.70 – 1.36	0.89
	4-day	638	63	84	1.00	0.71 – 1.40	0.99
	5-day	603	61	83	0.89	0.61 – 1.30	0.56
	6-day	583	60	82	0.90	0.57 – 1.40	0.64
	7-day	573	60	82	0.90	0.55 – 1.45	0.66
Fine particles ($\mu g/m^3$)	1-day	6.7	61	80	0.88	0.61 – 1.27	0.50
	2-day	6.0	60	78	0.98	0.67 – 1.45	0.94
	3-day	5.3	60	77	1.03	0.71 – 1.51	0.86
	4-day	5.0	59	76	1.05	0.71 – 1.56	0.81
	5-day	4.8	59	76	0.95	0.62 – 1.47	0.83
	6-day	4.7	58	75	0.89	0.55 – 1.45	0.65
	7-day	4.3	58	74	0.92	0.55 – 1.52	0.74
Carbon monoxide (ppm)	1-day	0.19	70	92	1.10	0.77 – 1.57	0.59
	2-day	0.18	70	92	1.18	0.81 – 1.72	0.38
	3-day	0.17	70	92	1.35	0.92 – 1.97	0.12
	4-day	0.17	70	92	1.49	1.01 – 2.22	0.05
	5-day	0.17	70	92	1.55	1.02 – 2.35	0.04
	6-day	0.17	69	91	1.59	1.02 – 2.47	0.04
	7-day	0.17	69	91	1.63	1.03 – 2.59	0.04

Pollutant	Pollutant Averaging Time*	IQR	Number of Subjects	Number of Visits	Odds ratio	95% CI	p
Sulfur dioxide (ppb)	1-day	3.1	70	92	1.08	0.90 – 1.31	0.41
	2-day	2.8	70	92	1.10	0.90 – 1.36	0.34
	3-day	2.8	70	92	1.14	0.91 – 1.42	0.24
	4-day	2.6	70	92	1.09	0.89 – 1.34	0.40
	5-day	2.5	70	92	1.07	0.87 – 1.33	0.51
	6-day	2.4	70	92	1.07	0.85 – 1.35	0.55
	7-day	2.3	70	92	1.07	0.86 – 1.34	0.53
Ozone (ppb)	1-day	14.2	69	91	0.87	0.51 – 1.47	0.60
	2-day	13.1	69	91	0.75	0.42 – 1.34	0.33
	3-day	12.7	69	90	0.67	0.35 – 1.29	0.23
	4-day	12.9	69	90	0.54	0.25 – 1.16	0.11
	5-day	12.6	69	90	0.41	0.18 – 0.92	0.03
	6-day	12.9	69	90	0.41	0.16 – 1.01	0.05
	7-day	12.5	69	90	0.46	0.18 – 1.16	0.10
Black carbon ($\mu g/m^3$)	1-day	0.52	71	90	0.93	0.64–1.33	0.68
	2-day	0.43	71	90	1.05	0.76–1.46	0.77
	3-day	0.39	71	90	1.10	0.79–1.54	0.57
	4-day	0.36	71	89	1.20	0.85–1.70	0.30
	5-day	0.33	71	89	1.07	0.75–1.53	0.70
	6-day	0.31	71	88	0.94	0.64–1.37	0.73
	7-day	0.30	71	88	0.88	0.57–1.34	0.55

IQR: interquartile range; p/cm^3: parts per cubic centimeter; $\mu g/m^3$: micrograms per cubic meter; ppm: parts per million; ppb: parts per billion;

*1-day = lag day 0, same day as pediatric asthma visit; 2-day = mean of lag days 0 and 1; 3-day = mean of lag days 0–2; 4-day = mean of lag days 0–3; 5-day = mean of lag days 0–4; 6-day = mean of lag days 0–5; 7-day = mean of lag days 0–6

Table 4

Relative odds of an asthma visit associated with each interquartile range increase in mean pollutant concentrations among School-Based Asthma Therapy intervention and usual care groups, by lagged averaging time. All models adjusted for 7-day mean temperature (1 degree of freedom) and relative humidity (3 degrees of freedom)

			School-based intervention (n=31)			Usual care (n=43)		
Pollutant	**Pollutant averaging time***	**IQR**	**Number of visits**	**OR (95% CI)**	**p**	**Number of visits**	**OR (95% CI)**	**p**
Ultrafine particles (p/cm^3)	1-day	3007	37	1.11 (0.68–1.79)	0.69	48	0.72 (0.44–1.16)	0.18
	2-day	2514	37	1.40 (0.86–2.28)	0.18	48	0.80 (0.50–1.30)	0.37
	3-day	2224	37	1.49 (0.93–2.39)	0.10	48	0.94 (0.58–1.52)	0.80
	4-day	2088	37	1.42 (0.89–2.27)	0.14	47	1.10 (0.65–1.87)	0.71
	5-day	2011	37	1.22 (0.72–2.09)	0.46	46	1.21 (0.64–2.29)	0.55
	6-day	1913	36	1.41 (0.79–2.51)	0.25	46	1.14 (0.59–2.21)	0.70
	7-day	1841	36	1.26 (0.67–2.36)	0.47	46	1.03 (0.51–2.10)	0.93
Carbon monoxide (ppm)	1-day	0.19	40	1.44 (0.85–2.46)	0.18	52	0.87 (0.53–1.41)	0.57
	2-day	0.18	40	1.56 (0.89–2.75)	0.12	52	0.89 (0.52–1.51)	0.66
	3-day	0.17	40	1.66 (0.94–2.92)	0.08	52	1.08 (0.63–1.87)	0.78
	4-day	0.17	40	1.79 (1.00–3.23)	0.05	52	1.25 (0.71–2.21)	0.45
	5-day	0.17	40	1.95 (1.05–3.62)	0.03	52	1.25 (0.69–2.29)	0.46
	6-day	0.17	40	2.00 (1.03–3.87)	0.04	51	1.34 (0.71–2.52)	0.37
	7-day	0.17	40	2.05 (1.03–4.11)	0.04	51	1.37 (0.70–2.69)	0.35
Ozone (ppb)	1-day	14.2	40	0.92 (0.40–2.11	0.85	51	0.90 (0.45–1.82)	0.78
	2-day	13.1	40	0.56 (0.22–1.43)	0.23	51	0.98 (0.45–2.14)	0.97
	3-day	12.7	39	0.52 (0.18–1.52)	0.23	51	0.87 (0.37–2.08)	0.76
	4-day	12.9	39	0.35 (0.10–1.25)	0.11	51	0.79 (0.29–2.18)	0.65
	5-day	12.6	39	0.33 (0.10–1.12)	0.08	51	0.49 (0.16–1.53)	0.22
	6-day	12.9	39	0.35 (0.09–1.33)	0.12	51	0.46 (0.13–1.66)	0.24
	7-day	12.5	39	0.37 (0.09–1.45)	0.15	51	0.54 (0.15–1.94)	0.34

IQR: interquartile range; p/cm^3: parts per cubic centimeter; ppm: parts per million; ppb: parts per billion;

*1-day = lag day 0, same day as pediatric asthma visit; 2-day = mean of lag days 0 and 1; 3-day = mean of lag days 0–2; 4-day = mean of lag days 0–3; 5-day = mean of lag days 0–4; 6-day = mean of lag days 0–5; 7-day = mean of lag days 0–6