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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 ($\leq$2.5 micrograms [μm]; $PM_{2.5}$), carbon monoxide, sulfur dioxide, and ozone. We hypothesized that increased 1–7 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 to 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 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 ($\leq$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.

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 $\leq$2.5 μm diameter) concentration on the same and previous day (National Center for Environmental Assessment, 2009). Studies in children have reported decreases in pulmonary function and increases in respiratory symptoms and medication use associated with increased particulate pollutant concentrations (Weinmayr et al., 2010; Sacks et al., 2011; Yeh et al., 2011). However, only a few studies have examined respiratory effects of ultrafine particles ($\leq$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; Belleudi et al., 2010), and even fewer have examined ultrafine

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particle effects on respiratory function or asthma symptoms in children (Pekkanen et al., 1997; Tiitanen et al., 1999; 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; Desai and Oppenheimer, 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 Asthma Education and Prevention Program, 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 1–7 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 Asthma Education and Prevention Program, 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 ($\leq$0.1 μm) and accumulation mode particles (0.10–0.50 μm) (Wang et al., 2011a, 2011b). Concentrations of fine particles ($\leq$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., 2011a, 2011b, 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 to 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 m from the intersection of two interstate highways, and ranges from less than 1.6 km (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; 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