Effects of wintertime ambient air pollutants on asthma exacerbations in urban minority children with moderate to severe disease

Nathan Rabinovitch, MD,a Lening Zhang, PhD,b James R. Murphy, PhD,b Sverre Vedal, MD,c Steven J. Dutton, MSc,c and Erwin W. Gelfand, MDa Denver, Colo

Background: Urban minority children with asthma are at higher risk for severe exacerbations leading to hospitalizations and deaths. Because multiple studies have reported associations between air pollution and asthma worsening, elevated levels of air pollution are cited as a possible trigger for increased asthma morbidity in urban areas. Few studies have prospectively followed panels of children with asthma to determine whether air pollution levels are associated with clinically relevant outcomes such as asthma exacerbations.

Objective: To determine the association between levels of ambient air pollutants and asthma exacerbations in urban poor children with moderate to severe asthma.

Methods: A school-based panel of children with difficult-to-control disease was followed over a period of 3 consecutive winters in Denver, Colo. The panel consisted of predominantly urban African American children with moderate to severe asthma. Levels of Environmental Protection Agency criteria air pollutants were measured on a daily basis with concurrent monitoring of lung function, bronchodilator use, symptoms, and asthma exacerbations.

Results: After controlling for time-varying factors such as upper respiratory infections and meteorologic factors, a weak association was found between ambient carbon monoxide levels and asthma exacerbations. Results: After controlling for time-varying factors such as upper respiratory infections and meteorologic factors, a weak association was found between ambient carbon monoxide levels and bronchodilator use. Ozone levels were associated with daytime symptoms only. No association was observed between daily air pollution concentrations and daily levels of FEV1, peak flow, nighttime symptom scores, or asthma exacerbations over the 3-year period.

Conclusion: Ambient levels of Environmental Protection Agency criteria air pollutants in Denver do not lead to clinically significant asthma worsening in urban children with moderate to severe asthma during winter months when children are primarily indoors. (J Allergy Clin Immunol 2004;114:1131-7.)

Key words: Air pollution, asthma, minority, urban, children

Asthma morbidity is increased among minority urban children.1-9 One hypothesis to explain this phenomenon is that exacerbated environmental factors are more prevalent in the urban environment. These environmental factors include exposure to indoor allergens such as cockroach, environmental tobacco smoke, and air pollution.10 Several investigators have reported a relationship between acute exposure to increasing air pollution levels and asthma worsening. These include associations between short-term increases in levels of ambient particles smaller than 2.5 or 10 μm and increased hospitalizations,11,12 increased asthma symptoms, and decreased pulmonary function.13-17 Others have been unable to find any significant relationships.18,19

These earlier studies contain several potential deficiencies. First, the incidence of asthma triggers such as upper respiratory infections (URIs) and medication use on an individual level are not monitored, although these variables have the potential to modify asthma symptoms and pulmonary function.20,21 Second, although statistically significant decreases in pulmonary function were observed in several time-series studies in children with mild asthma,22 these decrements are too small to indicate clinically significant morbidity in children with stable asthma. Because of these problems in study design, it is difficult to extrapolate results from previous studies to infer that high particle levels are an important trigger in urban children with severe asthma who are at increased risk for asthma morbidity.

Here, we examined the relationship between air pollution and asthma, taking advantage of a well-defined group of asthmatic children who were followed daily. As these children attended the school daily, we monitored potential time-varying confounders to study the effects of air pollution in children at highest risk for asthma morbidity.

Abbreviations used

APCD: Air Pollution Control Division
EPA: Environmental Protection Agency
FEV1: Forced expiratory volume in 1 second
NAAQS: National Ambient Air Quality Standards
NAAEP: National Asthma Education and Prevention Program
NJMRC: National Jewish Medical and Research Center
PEF: Peak expiratory flow
PM2.5: Particulate matter ≤2.5 μm in aerometric diameter
PM10: Particulate matter ≤10 μm in aerometric diameter
URI: Upper respiratory infection

From "the Division of Allergy/Immunology, Department of Pediatrics, "the Division of Biostatistics, and "the Division of Environmental and Occupational Medicine, Department of Medicine, National Jewish Medical and Research Center. Supported by EPA R825702, Thrasher Research Fund 02816-8, Colorado Tobacco Research Program R2.001. Received for publication October 31, 2003; revised August 2, 2004; accepted for publication August 6, 2004. Reprint requests: Nathan Rabinovitch, MD, National Jewish Medical and Research Center, 1400 Jackson Street, Denver, CO 80206. E-mail: rabinovitch@njc.org. 0091-6749/$30.00 © 2004 American Academy of Allergy, Asthma and Immunology doi:10.1016/j.jaci.2004.08.026
TABLE I. Demographics and asthma severity

<table>
<thead>
<tr>
<th>Number of children</th>
<th>Mean age (y)</th>
<th>African American (%)</th>
<th>Admitted to intensive care unit for asthma (%)</th>
<th>Exacerbations within previous year* (%)</th>
<th>Daily inhaled steroid use (%)</th>
<th>Asthma severity† (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1 n = 41</td>
<td>9.6</td>
<td>76</td>
<td>46</td>
<td>90</td>
<td>68</td>
<td>NA‡</td>
</tr>
<tr>
<td>Year 2 n = 63</td>
<td>10.1</td>
<td>79</td>
<td>47</td>
<td>84</td>
<td>71</td>
<td>24 Mild</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>48 Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>28 Severe</td>
</tr>
<tr>
<td>Year 3 n = 43</td>
<td>11.7</td>
<td>56</td>
<td>56</td>
<td>91</td>
<td>79</td>
<td>2 Mild</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60 Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>38 Severe</td>
</tr>
</tbody>
</table>

*Exacerbations were defined as episodes requiring hospitalization or emergency department or urgent care visits or prednisone bursts.
†Daily asthma severity criteria were defined by NAEPP criteria.
‡Data on daily asthma severity as defined by the NAEPP guidelines were not collected in year 1.

METHODS

Population sample

This study was conducted during 3 consecutive winters in Denver, Colo, when ambient particulate levels were highest. In the first year (year 1) of the study, pollution and health outcomes data were collected daily over a 17-week period (November 15, 1999, to March 15, 2000) on a panel of 41 asthmatic children age 6 to 12 years enrolled in the Kunsberg School at the National Jewish Medical and Research Center (NJMRC) in Denver. During the second year (year 2), a larger group of children (n = 63) was followed from November 13, 2000, through March 23, 2001. In year 3, 43 children were followed from November 15, 2001, through March 22, 2002. Twenty-four children from year 1 participated in the study in year 2. Thirty-seven children from year 2 participated in year 3. Fifteen children participated in all 3 years of the study. Ethical and scientific approval for each year was obtained from the National Jewish Institutional Review Board.

Table I summarizes demographic and asthma severity characteristics on the basis of a screening questionnaire administered to the parents before each year of the study. Most of these children were classified as having moderate to severe asthma by National Asthma Education and Prevention Program (NAEPP) guidelines. School activities were not influenced by air pollution alerts so as not to bias any potential pollution effects—that is, children did not stay inside or change supervised medication use on high air pollution days.

Health outcomes

Asthma severity outcomes included asthma exacerbations (ie, asthma episodes severe enough to require oral prednisone use, visits to urgent care facilities, emergency departments, or hospitalizations). Other health outcomes included daily forced expiratory volume in 1 second (FEV₁), peak expiratory flow (PEF), asthma symptoms, and daily use of short-acting bronchodilators. Data on health outcomes were collected similarly in all years of the study.

Pulmonary function

Each subject was asked to perform forced expiratory maneuvers by using an Airwatch (Carlsbad, Calif) asthma monitor in the morning. These maneuvers were performed at the beginning of the school day (7:00-9:00 AM) before bronchodilator usage under the supervision of school nurses and/or study personnel and repeated at home between 5:00 PM and 11:00 PM. On weekends and other nonschool days, subjects performed 2 sets of maneuvers in the morning and evening with criteria similar to those performed on schooldays.

Bronchodilator use

Each child was given 2 Dosers (Meditrak, Hudson, Mass), 1 for use at school and 1 for home. The Doser is an electronic counter that records the number of bronchodilator (albuterol) activations in each 24-hour period. In addition, albuterol nebulizer treatments were recorded on the AM and PM diary cards. The number of nebulizer treatments for AM and PM was summed and converted to activation puff equivalents in the ratio of 2:1 (ie, each nebulizer use counted as 2 puffs). This resulted in a total 24-hour medication score taken from 8:00 AM to 8:00 AM.

Asthma symptoms

Subjects completed diaries twice daily describing current day and previous nighttime symptoms. The current day symptom scores reflected the severity of the current day’s asthma symptoms (cough/wheeze) in relation to play (filled out each evening), and the previous night’s symptom score reflected how the symptoms affected the previous night’s sleep (filled out each morning). The 5-point (0-4) score was based on how severe these symptoms were, with 0 representing no symptoms and 4 representing symptoms severe enough to not allow for play that day or sleep on the previous night. On nonschooldays and vacation days, subjects filled out diary cards in the morning and evening at approximately the same times as on schooldays. These diary cards were handed in to study personnel on Monday or on the day after vacation.

URLs and asthma exacerbations

Three questions related to URIs were asked on the diary cards: “Do you have a cold today?” “Did someone tell you that you have a fever today?”, and, “Do you have a sore throat today?” If a subject answered yes to any of the 3 questions, the subject was treated as having an URI on that day.

Children were asked daily whether they took inhaled steroids or prednisone and, if so, how many puffs or milligrams were taken. In years 1 and 2, children were asked whether they had used a bronchodilator within 4 hours of performing spirometry and whether they played outside after school. In year 3, children were asked whether anyone had smoked around them that day. On a weekly basis, children were asked whether and when they had been hospitalized or visited an emergency department or urgent care facility for their asthma. Answers to daily diary and weekly questions were cross-checked with parents and school nurses for accuracy.
Ambient air monitoring and meteorology

The air pollutants that were analyzed for this study included particulate matter ≤10 μm in aerometric diameter (PM10), particulate matter ≤2.5 μm in aerometric diameter (PM2.5), carbon monoxide (CO), nitrogen dioxide (NO2), sulfur dioxide (SO2), and ozone (O3). Twenty-four-hour daily averages taken from midnight to midnight were used for all pollutants except O3, for which the daily 1-hour maximum value was used.

In years 1 and 2, ambient PM2.5 and PM10 concentrations were monitored by using Environmental Protection Agency (EPA) reference method equipment located on a 10-foot high scaffolding approximately 100 yards from the school (PM2.5 and PM10 were measured by using individual monitors). A Partisol Plus model 2025 Sequential Air Sampler (Rupprecht and Patashnick Co, Albany, NY) was used for sampling 24-hour integrated PM2.5 following EPA Quality Assurance Guidance Protocol 2.12. Four Andersen model 3.1 high-volume samplers (Andersen Instruments Inc, Smyrna, Ga) running on successive days were used for sampling daily 24-hour integrated PM2.5 following EPA Quality Assurance Guidance Protocol m2.11. All siting, sampling, and data verification were performed under the guidance of the Air Pollution Control Division (APCD). Particulate filters were routinely transported to the APCD for gravimetric analysis following the listed EPA protocols. Adjacent to the scaffold at NJMRC was an existing community monitoring station operated by APCD and reporting hourly ambient CO. Ambient NO2, SO2, and O3 data were obtained from a community monitoring station located 7.1 miles north of the school, also operated by the APCD.

In year 3, ambient data were obtained from the same sources with the exception of the particulate data, which was obtained from the closest community monitoring station, located 2.8 miles west of NJMRC and operated by the APCD. This change was made in response to a strong correlation observed during the first 2 winters between the PM2.5 values measured locally and at a downtown monitoring station (Pearson product-moment correlation = 0.93) and between the PM10 values measured locally and at a downtown monitoring station (correlation = 0.84). Therefore, in year 3, all ambient data were collected from nearby community monitoring stations.

For all 3 years, temperature and relative humidity data for downtown Denver (2.8 miles from NJMRC) were obtained from the APCD, and barometric pressure for the Denver International Airport (16.4 miles from NJMRC) was obtained from the National Climatic Data Center.

Analyses

FEV1 and PEF values were analyzed as continuous variables. Because the symptom scores and medication usage were zero on many days, these variables were dichotomized. Daily medication use was coded as 0 if the subject did not take any rescue medications on that day and 1 otherwise. The daily symptom score was coded as 0 if the child had no asthma symptoms and 1 otherwise. Exacerbation was similarly analyzed as a dichotomized variable.

The SAS statistical analysis package (version 8.2; SAS Institute Inc, Cary, NC) was used for all analyses. For FEV1, PEF, and symptom scores, AM and PM data were analyzed separately. Other outcomes had only single daily values. We analyzed the 3 years of data separately (data not shown) as well as combined them. The procedure PROC MIXED was used when pulmonary function was the outcome variable, and PROC GENMOD was used when exacerbation, symptom, or medication score was the outcome variable. Only 1 pollutant variable at a time was entered into the model as a linear term. On exploration of single-year and combined-year data, no consistent pattern was observed across health outcomes at any lags up to 5 days after the exposure. Moving averages have been reported to give more robust estimates in previous studies13,14 by minimizing measurement errors on any single day. Therefore, a decision was made to examine the outcomes by using 3-day moving averages of the pollutant as well.

A set of predetermined covariates (daily average temperature, barometric pressure, and relative humidity) were added, as well as a set of covariates found during the course of the study to influence the outcome variables (time trend, weekend, holiday, URI, and child’s height). For analysis of the 3-year combined data, an indicator variable was added for each of the individual years. Because several children participated in multiple years of the study, each subject was specified as being nested in a specific year.

The final model for the FEV1 and PEF analysis included a spatial exponential covariance structure to handle serially correlated data.

### TABLE II. Distribution of air pollution concentrations and meteorologic measures

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number (%) of days collected</th>
<th>Mean</th>
<th>SD</th>
<th>Minimum value</th>
<th>25th quantile</th>
<th>Median</th>
<th>75th quantile</th>
<th>Maximum value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM2.5 (μg/m³)</td>
<td>322 (85)</td>
<td>10.8</td>
<td>7.1</td>
<td>1.8</td>
<td>6.3</td>
<td>8.9</td>
<td>13.2</td>
<td>53.5</td>
</tr>
<tr>
<td>PM10 (μg/m³)</td>
<td>361 (95)</td>
<td>28.1</td>
<td>13.2</td>
<td>6.0</td>
<td>18.0</td>
<td>26.0</td>
<td>34.0</td>
<td>102.0</td>
</tr>
<tr>
<td>CO (ppm)</td>
<td>378 (99)</td>
<td>1.0</td>
<td>0.4</td>
<td>0.3</td>
<td>0.7</td>
<td>0.9</td>
<td>1.2</td>
<td>3.5</td>
</tr>
<tr>
<td>NO2 (ppb)</td>
<td>377 (99)</td>
<td>24.9</td>
<td>14.2</td>
<td>0.0</td>
<td>15.0</td>
<td>26.6</td>
<td>35.0</td>
<td>54.3</td>
</tr>
<tr>
<td>SO2 (ppb)</td>
<td>381 (100)</td>
<td>2.4</td>
<td>2.3</td>
<td>0.0</td>
<td>0.6</td>
<td>2.0</td>
<td>3.6</td>
<td>15.7</td>
</tr>
<tr>
<td>O3 (ppb)</td>
<td>369 (97)</td>
<td>28.2</td>
<td>11.4</td>
<td>0.0</td>
<td>20.0</td>
<td>30.0</td>
<td>36.0</td>
<td>70.0</td>
</tr>
<tr>
<td>Relative humidity (%)</td>
<td>374 (98)</td>
<td>49.9</td>
<td>16.0</td>
<td>18.8</td>
<td>39.1</td>
<td>47.9</td>
<td>60.5</td>
<td>94.6</td>
</tr>
<tr>
<td>Barometric pressure (mm Hg)</td>
<td>381 (100)</td>
<td>624.8</td>
<td>39.7</td>
<td>614.2</td>
<td>621.8</td>
<td>625.1</td>
<td>627.6</td>
<td>636.5</td>
</tr>
<tr>
<td>Temperature (°F)</td>
<td>374 (98)</td>
<td>35.3</td>
<td>9.0</td>
<td>8.9</td>
<td>29.5</td>
<td>35.6</td>
<td>41.7</td>
<td>57.8</td>
</tr>
</tbody>
</table>

### TABLE III. Association between 3-day moving average pollutant levels and FEV1

<table>
<thead>
<tr>
<th>AM</th>
<th>Estimate*†</th>
<th>SE</th>
<th>P value</th>
<th>Estimate*†</th>
<th>SE</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM2.5</td>
<td>-0.003</td>
<td>0.009</td>
<td>.756</td>
<td>-0.004</td>
<td>0.011</td>
<td>.746</td>
</tr>
<tr>
<td>PM10</td>
<td>-0.010</td>
<td>0.008</td>
<td>.179</td>
<td>-0.011</td>
<td>0.010</td>
<td>.299</td>
</tr>
<tr>
<td>CO</td>
<td>-0.001</td>
<td>0.008</td>
<td>.932</td>
<td>0.015</td>
<td>0.010</td>
<td>.145</td>
</tr>
<tr>
<td>NO2</td>
<td>0.006</td>
<td>0.009</td>
<td>.497</td>
<td>-0.009</td>
<td>0.011</td>
<td>.407</td>
</tr>
<tr>
<td>SO2</td>
<td>0.010</td>
<td>0.007</td>
<td>.192</td>
<td>-0.009</td>
<td>0.011</td>
<td>.381</td>
</tr>
<tr>
<td>O3</td>
<td>0.015</td>
<td>0.008</td>
<td>.085</td>
<td>-0.000</td>
<td>0.012</td>
<td>.973</td>
</tr>
</tbody>
</table>

*Estimates are standardized per SD unit change in pollutant.
†The covariates used in this model include 3-day moving average pollutant, time trend, year, height, meteorologic factors (temperature, relative humidity, and pressure), URI, weekend, and holiday.
TABLE IV. Association between 3-day moving average pollutant levels and exacerbations

<table>
<thead>
<tr>
<th>Pollutant</th>
<th>Odds ratio* †</th>
<th>Lower</th>
<th>Upper</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM2.5</td>
<td>0.971</td>
<td>0.843</td>
<td>1.118</td>
<td>.679</td>
</tr>
<tr>
<td>PM10</td>
<td>1.016</td>
<td>0.911</td>
<td>1.133</td>
<td>.776</td>
</tr>
<tr>
<td>CO</td>
<td>1.012</td>
<td>0.913</td>
<td>1.123</td>
<td>.818</td>
</tr>
<tr>
<td>NO2</td>
<td>1.101</td>
<td>0.952</td>
<td>1.273</td>
<td>.193</td>
</tr>
<tr>
<td>SO2</td>
<td>1.048</td>
<td>0.939</td>
<td>1.170</td>
<td>.402</td>
</tr>
<tr>
<td>O3</td>
<td>0.910</td>
<td>0.785</td>
<td>1.056</td>
<td>.215</td>
</tr>
</tbody>
</table>

*Odds ratios are standardized per SD unit change in pollutant.
†The covariates used in this model include 3-day moving average pollutant meteorologic factors (temperature, humidity, and pressure), year, time trend, weekend, holiday, and URI.

A random intercept and slope (for the pollutant) were included in these models as well as all covariates mentioned. A first-order autoregressive structure was used in the analysis of exacerbation, medication use, and symptom score with the generalized estimating equations model. All of these covariates except height (which was significant only in the pulmonary function models) were added to these models as well (height was measured by the school nurses before the beginning of each year of the study).

RESULTS

Air pollution concentrations and meteorology

The distribution of air pollutant concentrations and meteorology for years 1, 2, and 3 is shown in Table II.

The average ambient pollution levels were within the National Ambient Air Quality Standards (NAAQS). Levels of O3, SO2, and NO2 were sometimes below the minimal detectable limits. Almost all of the pollutants were significantly correlated with each other; O3 was negatively correlated (data not shown).

Relationship between asthma health outcomes and pollutant levels

Analysis of these outcomes revealed that asthma symptoms correlated with medication usage (P < .01), and medication usage was negatively correlated with pulmonary function (P < .01). The following results are from the 3-year combined data using the 3-day moving-average pollutant levels.

Pulmonary function. Table III summarizes the slope estimates, SEs, and P values for the association between 3-day moving average levels of the individual pollutants and AM and PM FEV1. Over the 3-year period, no significant associations were observed between morning or evening pulmonary function (FEV1 or PEF) and any of the pollutants.

Medication use. The median levels of bronchodilator use for the 3 years of the study were 2 puffs/day. Over the 3-year period, no significant association was observed between increased daily use of bronchodilators and pollutants, except for CO, which was marginally significant (odds ratio: 1.065; CI: 1.001-1.133; P = .047).

Symptoms. Mean days with symptoms for the 3 years of the study were 31.3. Over the 3-year period, no significant association was observed between air pollution levels and increased asthma symptoms except for daily O3, which was associated with increased current day symptoms (odds ratio: 1.083; CI: 1.002-1.170; P = .045). Previous night symptoms were not associated with any pollutant.

Exacerbations. Over the 3 winters, children had 199 asthma exacerbations (year 1, 67; year 2, 86; year 3, 46). Approximately half the children had at least 1 asthma exacerbation in each of the study years (year 1, 25 children [61%]; year 2, 35 children [56%]; year 3, 17 children [40%]). Table IV summarizes the standardized odds ratios, 95% CIs, and P values for the association between 3-day moving average levels of the individual pollutant and the incidence of severe asthma exacerbations. Over the 3 years of the study, no significant associations were observed between asthma exacerbations and any of the pollutants.

Relative effects of URI and PM10 on asthma health outcomes. Fig 1, A and B, illustrates the relative effects of PM10 on asthma health outcomes compared with URIs, which were included in the same models as covariates. URI symptoms were strongly associated with decreases in both AM and PM FEV1 and PEF, as well as increases in medication usage, asthma symptoms, and exacerbations. A separate analysis revealed no association between the incidence of URIs and pollutant levels (data not shown).

DISCUSSION

There is consensus that the adverse health effects of exposure to ambient air pollution are not evenly distributed among the general population, but are either limited to or magnified in susceptible population subgroups. These subgroups largely consisted of those with pre-existing chronic illness, including asthma. We had access to children with asthma whose disease was more severe than that in subjects typically included in panel studies. If individuals with severe asthma were particularly susceptible to the effects of air pollution exposure, we expected to observe obvious adverse effects in this study.

In this panel study, daily variability in ambient air pollutant concentrations was not associated with significant increases in asthma severity. Increasing CO levels were marginally associated with medication use, and increased daytime symptoms were associated with O3 concentrations, but no consistent associations were observed between these pollutants and other health outcomes. No significant associations were observed with FEV1, PEF, nighttime asthma symptoms, or exacerbations over a 3-year period.

These negative findings are consistent with findings from 2 previous studies involving patients with asthma in Denver. Ostro et al24 reported no statistically significant
association between any of the criteria air pollutants (PM_{2.5}, \text{SO}_2, \text{NO}_2) and asthma symptoms in a panel of more than 200 adults with asthma. Similarly, Perry et al\textsuperscript{25} observed no association between pollutants (PM_{2.5}, \text{CO}, \text{SO}_2, \text{O}_3) and PEF, asthma symptoms, or bronchodilator usage. This finding is consistent with a large study in which no association was found between levels of PM_{10}, \text{SO}_2, or NO_2 and PEF, asthma symptoms, or bronchodilator use in children with asthma.\textsuperscript{18}

A limited number of studies have examined acute effects of air pollution on severe asthma exacerbations requiring hospitalization or prednisone use. Schwartz et al\textsuperscript{11} reported increased asthma hospitalizations, and Atkinson et al\textsuperscript{12} reported a similar outcome in patients with asthma living in 8 European cities. Such large-scale time-series studies lack information about individual-level changes in asthma triggers such as URIs, which are associated with asthma exacerbations\textsuperscript{18} and can potentially confound the association between air pollution and asthma.\textsuperscript{20} These associations must be interpreted with caution if they are not controlled for potential time-varying confounders. In our study, strong crude associations between air pollution and asthma outcomes were observed. However, after controlling for time-dependent covariates such as URIs and time trend, these associations disappeared.

Several panel studies reported associations between air pollution and pulmonary function. In these studies as well as our own, a time-series model with repeated measurements is used. This model minimizes any confounders that are not temporally related to increases in air pollution concentrations such as indoor air pollutants.\textsuperscript{27} For example, no change in the effect estimates for pollutants were observed when households with tobacco smokers (non-time-varying) or days with smoking exposure (time-varying) were included in the model as a covariate (data not shown).

**FIG 1. A,** Relative effects of URI and PM_{10} on FEV\textsubscript{1} and PEF. Illustrates the slope estimates and the 95% CIs for the association between FEV\textsubscript{1} or PEF vs 3-day moving average PM_{10} and URIs. **B,** Relative effects of URI and PM_{10} on asthma exacerbations, medication usage, and symptoms. Illustrates the odds ratios and the 95% CIs for the association between asthma exacerbations, medication usage, and symptoms vs 3-day moving average PM_{10} and URI.
In general, these panel studies report small effects on pulmonary function in patients with mild asthma. The clinical relevance of these small reversible changes in pulmonary function in children who are not at high risk for exacerbation is unclear and should not solely account for the increased respiratory morbidity seen in large epidemiologic studies. We observed a greater decline in lung function compared with those reported in patients with mild asthma. Nevertheless, these relatively large changes in pulmonary function are small in terms of clinical effect. For example, estimated declines in FEV\(_1\) per SD change in \(\text{PM}_{10}\) were approximately one fifth of the estimated declines on days with URI symptoms.

It has been suggested that children with more severe disease control their pulmonary function by decreasing exposures or increasing medications, thereby obscuring any small effects caused by pollutants. It is likely that children in our study spent much of their time indoors to avoid colder temperatures and were not fully exposed to ambient pollutant concentrations. If so, recommending that children with more severe asthma stay indoors during air pollution spikes would be a prudent intervention, because the effects of air pollution appeared to be minimized in this wintertime study. Our findings suggest that the level of ambient air pollution is not a strong predictor of the increased daily lung function variability found in children with more severe disease, even after controlling for recent bronchodilator use. These children were predominantly using inhaled corticosteroids, and some studies suggest that this may blunt the effects of air pollution. Adding daily inhaled steroid use into the model did not change the observed estimates, suggesting that there was no significant interaction with air pollutant effects. It may be difficult to observe small effects in patients with more severe asthma with wide day-to-day variability in lung function. In comparison, other triggers, such as URIs, caused significant effects on all outcome variables, including asthma exacerbations, demonstrating that the study had adequate power to measure effects of important triggers in this population.

As reported in the National Air Quality and Emissions Trends Report (2000), levels of some pollutants such as CO have been decreasing in Denver and across the United States since the early 1980s and 1990s, when some of the studies noted were performed. Almost all of the previous positive studies observed associations below the NAAQS, and none of these studies demonstrated thresholds below which there were no significant effects. It is possible that these studies demonstrated associations because of generally higher exposure levels than in this study, and that no effects on asthma can be detected below a specific pollutant threshold concentration. If so, it would be important for future studies to focus on evaluating threshold effects at pollutant concentrations well below the NAAQS.

Pollution levels in Denver during the study period were fairly representative of pollutant levels in large urban centers. Although levels of hydrogen ion and sulfate are lower than in regions where industrial sources are prevalent, the predominant source of ambient particulate is vehicular exhaust, as in most regions of the United States.

There are limitations to this study that are not dissimilar to those in previously published studies. As with all panel studies, this study was not designed to examine the effect of chronic air pollution exposure on asthma prevalence or severity. The role of summer \(O_3\) was not examined. This study did not examine individual susceptibility to air pollution within the panel or measure individual exposures. Personal exposure monitoring may be especially important in the urban poor population, in whom exposures to outdoor point sources are increased, and in wintertime studies, when children are primarily indoors.

In summary, no clinically significant associations were observed between increases in daily ambient wintertime air pollutant concentrations and asthma worsening in urban poor children with moderate to severe asthma over a 3-year period in Denver. Although we cannot rule out chronic air pollution effects or effects at higher pollutant concentrations, day-to-day variability in ambient wintertime air pollution levels presently found in many urban centers in the United States does not appear to play a major role in asthma severity among urban children with moderate to severe asthma.

We appreciate the assistance of the students and staff of the Kunsberg School at National Jewish Medical and Research Center and the Air Pollution Control Division of the Colorado Department of Public Health and Environment. We also thank Matt Strand for advice on statistical modeling and Diana Nabighian for her assistance in preparing this manuscript.

REFERENCES


