Effects of Ambient Air Pollution on Symptoms of Asthma in Seattle-Area Children Enrolled in the CAMP Study

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We observed a panel of 133 children (5–13 years of age) with asthma residing in the greater Seattle, Washington, area for an average of 58 days (range 28–112 days) during screening for enrollment in the Childhood Asthma Management Program (CAMP) study. Daily self-reports of asthma symptoms were obtained from study diaries and compared with ambient air pollution levels in marginal repeated measures logistic regression models. We defined days with asthma symptoms as any day a child reported at least one mild asthma episode. All analyses were controlled for subject-specific variables [age, race, sex, baseline height, and FEV_1 PC_{20} concentration (methacholine provocative concentration required to produce a 20% decrease in forced expiratory volume in 1 sec)] and potential time-dependent confounders (day of week, season, and temperature). Because of variable observation periods for participants, we estimated both between- and within-subject air pollutant effects. Our primary interest was in the within-subject effects: the effect of air pollutant excursions from typical levels in each child's observation period on the odds of asthma symptoms. In single-pollutant models, the population average estimates indicated a 30% [95% confidence interval (CI), 11–52%] increase for a 1-ppm increment in carbon monoxide lagged 1 day, an 18% (95% CI, 5–33%) increase for a 10-μg/m^3 increment in same-day particulate matter < 1.0 μm ($PM_{1.0}$), and an 11% (95% CI, 3–20%) increase for a 10-μg/m^3 increment in particulate matter < 10 μm (PM_{10}) lagged 1 day. Conditional on the previous day's asthma symptoms, we estimated 25% (95% CI, 10–42%), 14% (95% CI, 4–26%), and 10% (95% CI, 3–16%) increases in the odds of asthma symptoms associated with increases in CO, $PM_{1.0}$, and PM_{10}, respectively. We did not find any association between sulfur dioxide (SO_2) and the odds of asthma symptoms. In multipollutant models, the separate pollutant effects were smaller. The overall effect of an increase in both CO and $PM_{1.0}$ was a 31% (95% CI, 11–55%) increase in the odds of symptoms of asthma. We conclude that there is an association between change in short-term air pollution levels, as indexed by PM and CO, and the occurrence of asthma symptoms among children in Seattle. Although PM effects on asthma have been found in other studies, it is likely that CO is a marker for vehicle exhaust and other combustion by-products that aggravate asthma. *Key words*: ambient air pollution, asthma, carbon monoxide, children, panel study, particulate matter, sulfur dioxide, symptoms, within-subject effects. *Environ Health Perspect* 108:1209–1214 (2000). [Online 20 November 2000]
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The Clean Air Act (*1*) mandates that National Ambient Air Quality Standards be set to protect the most sensitive members of the population. Children with asthma are such a sensitive subpopulation. The relationship between asthma and outdoor air pollutants is of great interest. Special interest is centered on the effects of particulate matter (PM) air pollution because the U.S. Environmental Protection Agency (U.S. EPA) is attempting to change its PM regulations. Although common outdoor air pollutants have not been shown to cause asthma, as documented in a recent review (*2*), PM air pollution levels have been associated with a broad spectrum of measures of asthma aggravation. These adverse health effects include pulmonary function decrements, visits to emergency departments and hospital admissions, and increased medication use. Few studies have shown an association between PM and increases in asthma symptoms. In a study in Southern California, Delfino et al. (*3*) found that PM air pollution was associated with both symptoms and medication use in a panel of 25 children with asthma. The children with the most baseline symptoms were most at risk for aggravation associated with PM. Vedal et al. (*4*) reported that increased cough, phlegm production, and sore throat were associated with PM < 10 μm in aerodynamic diameter (PM_{10}) in children with asthma in Port Alberni, British Columbia, Canada, during an 18-month period. Gielen et al. (*5*) reported an association between black smoke (a marker of diesel exhaust) and acute respiratory symptoms in a panel of 61 children in the Netherlands. Romieu et al. (*6*) found that an increase of 20 μg/m^3 PM_{10} was associated with an 8% increase in lower respiratory symptoms in 5- to 7-year-old children.

More studies have found an association between gaseous pollutants, such as sulfur dioxide and nitrogen dioxide, and symptoms in children with asthma. For instance, asthma symptoms and medication use have been associated with air pollution levels in a number of different geographical locations such as Paris, France (*7*), where the strongest relationship was between asthma aggravation and SO_2 concentrations on the same day, and Sweden (*8*), where the strongest association was seen with NO_2. Von Mutius et al. (*9*) studied 1,854 children (9–11 years of age) with asthma. This questionnaire study reported increased risks of developing upper respiratory symptoms in winter months associated with mean SO_2 concentrations [odds ratio (OR) = 1.72; 95% confidence interval (CI), 1.19–2.49], mean NO_x concentrations (OR = 1.53; 95% CI, 1.01–2.31), and PM maximum values (OR = 1.62; 95% CI, 1.08–2.45). A combined pollutant metric showed the highest risk (OR = 2.10; 95% CI, 1.30–3.37). Peters et al. (*10*) found a strong association between both peak flow and symptom scores in children with asthma with average SO_2 and sulfate concentrations in Germany. Some studies used traffic indicators (traffic density or distance from a thoroughfare) as a surrogate for air pollution. Such studies have found that these traffic indicators are associated with significant increases in adverse respiratory outcomes in children with asthma (*11,12*).

In this study, we attempted to assess the effects of air pollution on daily symptoms of asthma aggravation in children on an individual level in Seattle, Washington. The children in the study are enrolled in the Childhood Asthma Management Program (CAMP) (*13*) and thus are well-characterized asthmatics. Seattle is in an air shed where SO_2 concentrations are very low and are not expected to aggravate asthma, as seen in the European studies (*7–10*). Previous studies have shown that PM air pollution in Seattle is associated with both increased visits to emergency

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departments for asthma (*14,15*) and hospital admissions for asthma (*16*).

Methods

CAMP is a National Heart, Lung, and Blood Institute-sponsored multicenter, randomized clinical trial involving seven cities in the United States: Albuquerque, New Mexico; Baltimore, Maryland; Boston, Massachusetts; Denver, Colorado; San Diego, California; Seattle; St. Louis, Missouri; and one in Canada (Toronto). Its main goal is to evaluate the long-term effects of daily inhaled anti-inflammatory medication on lung growth in children diagnosed with mild to moderate persistent asthma (*13*). We used data obtained before randomization (i.e., before the introduction of study medicine); these data were collected in the calendar period November 1993 through August 1995. Participants were children living in the greater Seattle area (133 of the 144 randomized at Seattle). Before randomization, each child completed questionnaires and visits; beginning with the second screening visit, each child received a daily diary card as well. The average number of days of diary data provided by each child before randomization was 58 (range 28–112 days). In the CAMP Air Pollution Ancillary Study, we matched the pre-randomization data with atmospheric data from the Puget Sound Clean Air Agency.

Study population. Children enrolled in CAMP were 5–12 years of age at the initial interview. They had a history of chronic mild to moderate asthma on the basis of one or more of the following for at least 6 months in the previous year: suffered from asthma symptoms more than once per week; used an inhaled bronchodilator twice or more per week, or needed asthma medication daily.

Study participants completed a pre-randomization screening period of 5–16 weeks. CAMP obtained informed consent, and questionnaires about demographic characteristics, asthma history, and home environment were completed. At the second screening visit, all anti-asthma medication except rescue albuterol was stopped, and children were asked to complete a diary card daily beginning that day. They recorded peak flow and symptoms for 28 days to confirm eligibility. A child's asthma was considered too mild if there were fewer than 8 days during the 28-day screening period with either a symptom score of at least 1 on a 0–3 scale or morning or evening peak flow < 80% of personal best, or if the sensitivity to methacholine [methacholine provocative concentration required to produce a 20% decrease in forced expiratory volume in 1 se (FEV_1 PC_{20}) concentration] was greater than 12.5 mg/mL. A child's asthma was considered too severe if, during the 28-day screening period, more than 8 puffs of albuterol were used on 3 consecutive days, if night awakening due to asthma averaged more than 1.5 times per week, if the mean diary card symptom score was > 2, or if he/she used medication other than albuterol to control asthma. Children who still qualified underwent three more visits in which additional baseline data were collected.

Asthma monitoring. The diary cards were completed daily each morning and evening by study participants. They recorded their morning and evening peak expiratory flow rate (PEFR), their use of medications (rescue inhaler and before exercise), whether they had night awakening due to asthma, and a symptom rating. We focused on a dichotomy of the symptom rating that distinguished between no asthma symptoms and at least one mild asthma symptom (including wheezing, coughing, chest tightness, and/or shortness of breath). We also obtained baseline covariate information including age, sex, race, height, weight, and FEV_1 PC_{20} concentration, a measure of bronchial hyperresponsiveness based on a methacholine challenge test.

Ambient air monitoring. Atmospheric data for the CAMP period November 1993 through August 1995 were provided by the Puget Sound Clean Air Agency for 6, 3, and 1 monitoring sites, respectively, measuring the daily carbon monoxide, atmospheric particles [PM; both by gravimetric reference methods (PM_{10}) and from nephelometers ($PM_{1.0}$)], and SO_2 in the greater Seattle area. No measurements of oxides of nitrogen were available during this period. CO and $PM_{1.0}$ were available throughout all 580 study days. PM_{10} was not monitored by any of the three sites on 16 study days, and SO_2 was not measured on 12 study days. The monitors are operated according to national guidelines set by the U.S. EPA. We converted the light scattering measurements from nephelometers to gravimetric units for ease of reporting because previous studies have shown nephelometer measurements capture fine PM in the greater Seattle air shed (*17*). We also obtained average air temperature from three sites. We used daily averages of CO, PM, and air temperature measurements to reduce the variability of measurements among sites and to better track the usual exposures for the region as a whole.

Statistical analysis. We used repeated-measures logistic regression models to account for the correlation among the repeated observations of the outcome variable. Specifically, we applied a marginal approach [generalized estimating equations (GEE) with an exchangeable working correlation matrix (*18,19*)] to estimate the population-averaged effect of air pollution on asthma symptoms, and a transition approach (*20*) to estimate the population-averaged effect conditioned on the previous day's outcome. We regressed the binary asthma symptom outcome on each exposure of interest, adjusting for subject-specific variables (age, race, sex, baseline height, and FEV_1 PC_{20} concentration) and potential time-dependent confounders (six indicators for day of week, linear splines of season, temperature lagged 2 days, and its quadratic term) with the Stata statistical package (*21*). Because children who experienced asthma symptoms on 1 day were probably more likely than those who did not to have asthma symptoms on the next day, the past history of asthma symptoms might significantly influence the present occurrence of asthma symptoms. Therefore, in the transition approach, we explicitly modeled the current asthma symptom as a function of the past response by including asthma symptoms reported on the previous day as an additional explanatory variable in the GEE model. We performed simple graphic checks examining residuals obtained from each model to assess how well our models fitted the study data. Two types of residuals were considered: residuals aggregated over all observations for each study participant (residuals per person), and residuals aggregated over all observations assembled on each study day (residuals per day). There was little evidence of any study participant or study day being influential.

In addition to analyzing the effect of air pollutants separately as linear terms by fitting individual pollutant in the model, we also considered multipollutant models in which CO, SO_2, and one type of PM were fitted simultaneously. Because we had no *a priori* knowledge of which lags of air pollutants were clinically relevant to the risk of days with asthma symptoms, we examined the same-day, 1-day, and 2-day lags of air pollution levels and selected the ones with the strongest association with asthma symptom days to include in the multipollutant models. We report the joint effects of the odds of asthma symptoms for a simultaneous change in two pollutants by adding the effects of both in the linear predictor with all other covariates held constant. The standard error is adjusted for the covariance of the two estimates by using a standard variance calculation for the sum of correlated variables.

Unlike many air pollution panel studies, we observed children at various times and in different seasons. Because we compared different children at different time points, differences in between- and within-subject air pollution effects were possible. Naïve application of the repeated measures logistic regression models implicitly assumes that the two effects are identical. We therefore explicitly separated these two components by fitting the between-subject (long-term) air pollutant

exposure, $\overline{X}_i$ (subject mean of air pollution concentration), and the within-subject (short-term) air pollutant exposure, X_{it}-$\overline{X}_i$ (deviation of daily air pollution level from subject mean air pollution level), in the models simultaneously (*22*). Because our objective was to evaluate the short-term effects of acute exposure on children with asthma, the within-subject air pollution effects are of interest. We do not report the between-subject effects because of concerns about residual between-subject confounding.

Results

There was a total of 7,658 pre-randomization daily diary records collected over 580 days between 3 November 1993 and 15 August 1995. Figure 1 summarizes by date the number of daily diary records provided by study participants. By protocol, each child completed a minimum of 28 days of records before randomization. As many as 112 days and an average of 58 days of records were collected from each child. Except for the 17 January 1995 through 28 March 1995 period when the clinic suspended recruitment activities, a range of 1–28 and an average of 13 diary records were collected per study day.

As shown in Table 1, the average age of children at randomization was 8.6 years, with an average age of 3.2 years when asthma was confirmed by a doctor. Twenty-four percent were from ethnic minorities and 20% had household incomes below $30,000. On average the group was very responsive to methacholine challenge (mean FEV_1 PC_{20} = 1.5 mg/mL) and all participants were responsive (maximum 12.2 mg/mL). All baseline characteristics were comparable between boys and girls in the study population ($p > 0.05$).

Table 2 summarizes the asthma-related events that the children reported on the diary card. All 133 children had had at least one mild asthma symptom on at least one day during the pre-randomization period. Thirteen of them had experienced at least one mild asthma episode on a daily basis. Most children (53%) had at least one night awakening for asthma, but overall, it only occurred on 8% of the diary record days. This is consistent with using too many night awakenings because of asthma as an exclusion criterion for randomization. Most participants also reported using rescue inhalers before exercise (78%) or for asthma signs (99%).

The air pollutant exposure levels and air temperature during the study period are summarized in Table 3. The air pollutant levels over 580 study days were all fairly low. The highest CO level (4.18 ppm) was observed during December 1994; this was the only day during the study when the CO level was > 4 ppm. Most of the CO levels were well below 3 ppm. PM concentrations were highest and most variable in the first 3 months of the study (November 1993 to January 1994); however, most of the measurements were < 60 μg/m^3. SO_2 levels were low throughout the entire study period, with a range of 1–21 ppb. During the 580-day study period, CO and PM levels were highly correlated, whereas SO_2 was only weakly correlated with other pollutants, as shown in Table 3.

Among the same-day to 2-day lags of air pollutant exposure, we found the 1-day lag CO and PM_{10} levels and the same-day $PM_{1.0}$ and SO_2 levels to have the strongest effects on asthma symptoms after controlling for subject-specific variables and time-dependent confounders. Table 4 shows the estimated odds of asthma symptoms for a unit increase in the within-subject pollutant exposure (1 ppm for CO, 10 μg/m^3 for PM, and 10 ppb for SO_2) from each of the regression models. We found an association between an increase in short-term air pollution levels and asthma

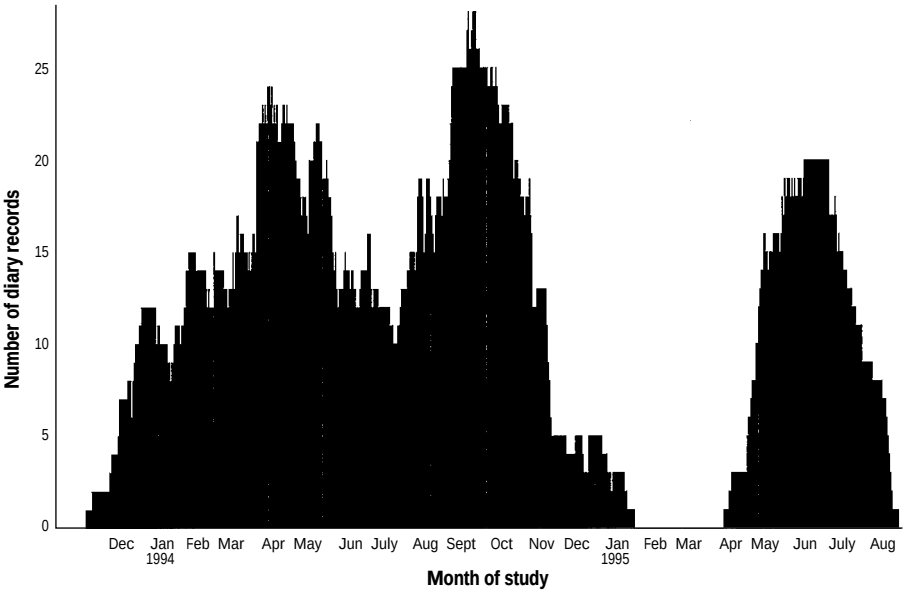

Figure 1. Number of daily diary records collected during the CAMP pre-randomization study period.

Table 1. Summary of baseline characteristics for 133 Seattle children in the CAMP pre-randomization period.

	Total (n = 133)		Male (n = 84)				Female (n = 49)			
Characteristics	Percent	Mean ± SD	Percent	Mean ± SD	Min	Max	Percent	Mean ± SD	Min	Max
Age (years)		8.6 ± 2.1		8.7 ± 2.1	5.1	13.0		8.5 ± 2.1	5.1	13.1
Age asthma confirmed (years)		3.2 ± 2.4		3.1 ± 2.3	0.2	10.0		3.5 ± 2.4	0.2	11.0
Duration of asthma (years)		5.4 ± 2.7		5.6 ± 2.8	0.2	11. 7		4.9 ± 2.6	0.5	10.7
Standing height (cm)		132.3 ± 13.7		132.9 ± 14.4	100.2	171.9		131.4 ± 12.7	105.1	157.5
Weight (kg)		32.3 ± 11.3		33.1 ± 12.6	14.2	73.0		31.0 ± 8.9	18.0	53.0
FEV_1 PC_{20} (mg/mL)		1.54 ± 2.18		1.39 ± 1.95	0.03	10.70		1.80 ± 2.53	0.061	12.20
Race										
White (non-Hispanic)	76		74				80			
Black	7		8				6			
Other	17		18				14			
Family income										
< $15,000	5		6				4			
$15,000–$29,999	15		14				16			
$30,000–$49,999	38		37				39			
At least $50,000	39		39				39			
Decline to answer	3		4				2			

Abbreviations: Max, maximum; Min, minimum.

symptoms for CO and PM, but not for SO_2. In the single-pollutant marginal (GEE) models, we found a 30% increase in the odds for a child to experience at least one asthma symptom for a 1 ppm increment in short-term CO, 18% and 11% increases for 10 μg/m^3 increments in short-term $PM_{1.0}$ and PM_{10}, respectively. The effects of air pollutant exposure were reduced in the transition models but were still elevated with the odds of symptoms relative to no symptoms estimated at 1.25 for CO lagged 1 day (95% CI, 1.10–1.42), 1.14 for same-day $PM_{1.0}$ (95% CI, 1.04–1.26), and 1.10 for PM_{10} lagged 1 day (95% CI, 1.03–1.16). This result is conditional on the previous day's symptoms, which were strongly associated with the current day's symptoms: the relative odds of any asthma symptoms given symptoms on the previous day was 4.6 in all transition models (95% CI, 3.6–5.9). Although previous day's symptoms was a strong predictor of current day's symptoms, it did not confound the air pollution–asthma association. The magnitudes of the air pollutant effects were essentially the same in both marginal and transition models with their confidence intervals overlapped. We examined all two-way interactions between the short-term air pollution level and each of the adjustment variables, but did not find any important effects. This included previous day's symptoms in the transition model, indicating that the air pollution effect on symptoms did not depend upon recent symptoms.

When these short-term pollutant effects were considered in the multipollutant models, all pollutant effects decreased. Only CO remained statistically important (Table 4). The effect of PM was no longer elevated after adjusting for other pollutants (CO and SO_2; marginal model 95% CI for $PM_{1.0}$, 0.98–1.26; 95% CI for PM_{10}, 0.95–1.19). With both $PM_{1.0}$ and SO_2 held constant, a 1 ppm increase in CO inflated the odds of asthma symptoms by 18% (17% in the transition model). We also considered the joint effect of a simultaneous change in both CO and PM (1 ppm increment in CO and 10 μg/m^3 increment in $PM_{1.0}$), with SO_2 held constant. For a simultaneous change in both CO and $PM_{1.0}$, we estimated the effect at 1.31-fold in the marginal model (95% CI, 1.11–1.55) and 1.26-fold in the transition model (95% CI, 1.11–1.44). For CO and PM_{10}, the effect was 1.22-fold in the marginal model (95% CI, 1.05–1.43) and 1.19-fold in the transition model (95% CI, 1.02–1.39).

Discussion

In this panel study of children with asthma, increased exposure to air pollutants, specifically CO and PM, was associated with increased odds of at least one mild asthma symptom. SO_2 was not associated with the odds of asthma symptoms. Although SO_2 is known to aggravate asthma, our SO_2 result is not surprising given its low concentration in Seattle. In contrast, CO is not known to aggravate asthma. Although we have also found CO effects on asthma in a previous analysis of asthma hospital admissions in

Table 2. Summary of diary records: experience of the 133 subjects during the CAMP pre-randomization study period.

	No. (%) of subjects	Mean ± SD	Minimum	Maximum
Event				
At least 1 asthma episode during the day	133 (100)[a]	0.6 ± 0.3[b]	0.03	1.0
At least 1 asthma episode daily	13 (10)			
Night awakening for asthma	71 (53)	0.08 ± 0.07	0.01	0.36
Absent from school for asthma	30 (23)	0.03 ± 0.02	0.01	0.09
Contacted doctor for asthma	21 (16)	0.03 ± 0.02	0.01	0.07
Medication				
Rescue inhaler before exercise (puffs/day)	104 (78)[c]	0.8 ± 0.9[d]	0.02	4.0
Rescue inhaler for asthma sign or low PEFR (puffs/day)	132 (99)	2.0 ± 1.4	0.13	6.5
Prednisone for asthma (pills/day)	8 (6)	0.3 ± 0.2	0.05	0.6
PEFR (L/min)				
AM	7,458[e]	228.3 ± 69.9[f]	30	600
PM	7,488	244.0 ± 67.7	30	540

[a]Number (%) of subjects ever having an event. [b]Values are the mean ± SD, minimum, and maximum of the fraction of days for subjects who ever had an event. [c]Number (%) of subjects ever taking medication. [d]Values are the mean ± SD, minimum, and maximum of the average dose among subjects who had ever had medication. [e]Number of records with completed PEFR. [f]Values are the mean ± SD, minimum, and maximum PEFR over all completed records.

Table 3. Correlation among air pollutants and temperature over 580 study days.

	Temperature (F)	CO (ppm)	$PM_{1.0}$ (μg/m^3)	PM_{10} (μg/m^3)	SO_2(ppb)
Percentiles					
Minimum	26.3	0.65	2.03	7.67	1
Mean	52.4	1.6	10.4	24.7	7.26
Median	52.3	1.47	7.28	21	7
Maximum	78.3	4.18	61.7	86.3	21
Correlations					
Temperature	1				
CO	–0.44	1			
$PM_{1.0}$	–0.48	0.82	1		
PM_{10}	–0.33	0.86	0.89	1	
SO_2	–0.07	0.31	0.31	0.38	1

Table 4. Percentiles of pollutants and estimates of odds ratios of asthma symptoms for a short-term 1 ppm increase in CO, a 10 μg/m^3 increase in PM, and a 10 ppb increase in SO_2.

	Odds ratio (95% confidence interval)	
Exposure	Marginal GEE	Transition GEE
Single-pollutant models		
$CO_{it} - \overline{CO}_i$ (ppm)		
Same day	1.22 (1.03, 1.45)	1.18 (1.02, 1.37)
1-Day lag	1.30 (1.11, 1.52)	1.25 (1.10, 1.42)
2-Day lag	1.26 (1.09, 1.46)	1.18 (1.04, 1.33)
$PM_{1.0it} - \overline{PM}_{1.0i}$ (μg/m^3)		
Same day	1.18 (1.05, 1.33)	1.14 (1.04, 1.26)
1-Day lag	1.17 (1.04, 1.33)	1.13 (1.03, 1.24)
2-Day lag	1.09 (0.98, 1.21)	1.04 (0.96, 1.13)
$PM_{10\,it} - \overline{PM}_{10i}$ (μg/m^3)		
Same day	1.09 (1.01, 1.18)	1.08 (1.01, 1.15)
1-Day lag	1.11 (1.03, 1.20)	1.10 (1.03, 1.16)
2-Day lag	1.08 (1.01, 1.17)	1.05 (1.00, 1.11)
$SO_{2\,it} - \overline{SO}_{2i}$ (ppb)		
Same day	1.07 (0.90, 1.27)	1.06 (0.90, 1.25)
1-Day lag	1.07 (0.90, 1.28)	1.06 (0.90, 1.26)
2-Day lag	1.00 (0.83, 1.20)	0.97 (0.81, 1.15)
Multipollutant models		
Model 1		
1-Day lag $CO_{it} - \overline{CO}_i$	1.18 (1.03, 1.36)	1.17 (1.02, 1.35)
Same day $PM_{1.0it} - \overline{PM}_{1.0\,i}$	1.11 (0.98, 1.26)	1.08 (0.96, 1.20)
Same day $SO_{2it} - \overline{SO}_{2i}$	1.00 (0.85, 1.19)	1.00 (0.85, 1.17)
Model 2		
1-Day lag $CO_{it} - \overline{CO}_i$	1.15 (0.92, 1.44)	1.13 (0.91, 1.41)
1-Day lag $PM_{10it} - \overline{PM}_{1.0i}$	1.06 (0.95, 1.19)	1.05 (0.95, 1.16)
Same day $SO_{2it} - \overline{SO}_{2i}$	1.02 (0.86, 1.21)	1.02 (0.87, 1.19)

i, indexes the individual; *t*, indexes day.

Seattle (*16*), it is unlikely that CO itself is causing the effects. Rather, ambient CO levels, particularly when quantified by spatial averaging, may be a good marker for ambient levels of combustion by-products that aggravate asthma.

Our PM results are consistent with findings from several previous studies. For example, among 83 African-American children with asthma 7 to 12 years of age in Los Angeles, California, Ostro et al. (*23*) reported a 9% increase in the reporting of shortness of breath for a 10 $\mu g/m^3$ increase in PM_{10}. Whittemore and Korn (*24*) found a 0.8% increase in asthma attacks for a 10 $\mu g/m^3$ increase in total suspended particulates in a group of asthmatics residing in the Los Angeles area. In both of these studies, significant effects were also seen for ozone concentrations. Pope et al. (*25*) studied a school-based sample of 34 children who wheezed and/or were diagnosed with asthma by a doctor; the authors reported a 5.1% increase in lower respiratory disease including trouble breathing, dry cough, and wheezing for a 10 $\mu g/m^3$ increase in PM_{10}. Similar findings were obtained by Vedal et al. (*4*), who reported an 8% increase in the odds of cough in a group of children with physician-diagnosed asthma. No association between PM_{10} and respiratory symptoms was found in non-asthmatic children, suggesting that children with asthma are more susceptible to adverse health effects of air pollution.

The CAMP Air Pollution Ancillary Study provided an excellent opportunity to investigate the air pollution–asthma relationship. During this pre-randomization phase of the trial, all participants suspended maintenance medications; therefore, this study is unique in its ability to evaluate the acute effects of air pollution without any confounding effects of routine preventive therapy. The extensive repeated within-subject data increased power for detection of any significant air pollution effects on children with asthma by comparing each child with himself or herself. In addition, collecting diary information on each child on a daily basis reduced possible recall bias. We controlled for seasonal confounding in two ways: *a*) we explicitly included seasonal adjustment terms in the model, and *b*) we partitioned air pollution exposure into within-subject and between-subject exposures so that we did not make the implicit assumption that the two effects were identical. In many air pollution panel studies, the variation in exposure between individuals is controlled by designs stipulating that all individuals are observed over identical time periods (however, missing data invariably negate much of this design advantage). We found that the magnitudes of the two exposure effects were quite different, which further confirmed to us the necessity for separating air pollutant effects explicitly. We did not report the between-subject exposure effects because we believe they may be biased by residual between-subject confounding.

There are several potential sources of bias that we should consider in interpreting our results. Although recall biases were unlikely given the data collection protocol, there might have been biases due to misreporting of an asthma episode on a given day. Asthma symptom ascertainment was only based on the subjective reporting by each child, without any clinical validation. However, because participating children and their parents were not aware that we were studying air pollution, their perceptions of air pollution conditions were unlikely to influence their reporting of asthma symptoms. In addition, the individual pollutant exposures could have been misclassified in this study because we substituted a regional average from ambient monitors for individual exposures. This may be particularly problematic for CO because these monitors are located in street canyons in Seattle where they are likely to pick up high levels of CO from vehicle exhaust. To compensate for this as much as possible, we used an average of six monitors to dampen the influence of local effects. Because previous research has shown that the street canyon monitors are correlated with more generally distributed "background" levels in Seattle (*26*), we believe the spatial average captures the important source of variation for this study—the day-to-day variation in CO levels. Furthermore, we had no information such as time–activity data to adjust individual participants' pollutant exposures. The actual air pollutant exposure level to ambient source pollutants for each study child is a function of the amount of time they spent outdoors, the pollutant-specific penetration rate, and building ventilation characteristics. PM has been shown to penetrate readily into a sample of homes in Seattle (*27*), and CO is also known to penetrate well. For these pollutants, ambient monitor measurements may reasonably represent personal exposure to their ambient source components. We also did not adjust for nonambient-source time-varying exposures such as cigarette smoke, indoor combustion from cooking and heating, or household sensitizing antigens. Because nonambient-source PM is independent of ambient-source PM over time (*28*), these exposures were unlikely to have introduced bias in our models. Finally, we were unable to consider other potential time-varying confounders and effect modifiers such as other outdoor pollutants, exposure to airborne pollens and molds, other meteorologic factors, and respiratory infections. We omitted rescue inhaler use related to asthma because we felt that it was an intermediate variable, but it could also be considered as a confounder.

We examined several lags of air pollutants in the analyses before selecting the final models. Because we had no prior clinical knowledge of which lags of air pollutants should be evaluated in relation to asthma symptoms, we selected the one for each air pollutant that demonstrated the strongest statistical association with asthma outcome. We considered lags up to 2 days to allow for both immediate acute effects and the delayed effects caused by build-up of late phase reactivity. However there is possible bias in this approach due to model selection. In a simulation study based on Seattle data, Lumley and Sheppard (*29*) showed that the potential for bias from this model selection strategy is not negligible. This model selection bias is smallest when the true association is moderately large. Because the magnitude of the true association is unknown, we cannot rule out some bias due to model selection in the present analyses.

In conclusion, we found that symptoms of asthma aggravation in a population of children with mild to moderate asthma were associated with air pollutants known to be emitted from combustion sources. The children in this study were a selected group and were all under a physician's care for asthma; thus they probably differ in this respect from the population of children reporting to hospital emergency departments for asthma symptoms. These results for daily symptoms complement the other Seattle-area studies that found air pollution health effects for emergency department visits (*12,13*) and hospital admissions (*14*). Taken together, these studies suggest that the health effects among asthmatics from short-term changes in air pollution levels are an important public health problem.

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