Effects of ambient air pollution on symptom severity and medication use in children with asthma

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Background: Exposure to air pollutants has been investigated as a possible cause of asthma attacks in children.

Objective: To investigate the short-term effects of air pollutants on a panel of 133 children with asthma who enrolled in the Childhood Asthma Management Program.

Methods: During screening, the children completed daily diary cards for an average of 58 days to indicate their medication use and asthma severity. We used ordinal logistic regression to compare the odds of a more serious relative to a less serious asthma attack, and we used a Poisson model to analyze medication use. In both analyses we accommodate dependence in the data and different periods of observation for study subjects.

Results: Our results indicate that a 10-$\mu g/m^3$ increase in particulate matter less than or equal to 2.5 μm ($PM_{2.5}$) lagged 1 day was associated with a 1.20 times increased odds of having a more serious asthma attack [95% confidence interval (CI), 1.05 to 1.37] and a 1.08-fold increase in medication use (95% CI, 1.01 to 1.15). A 10-$\mu g/m^3$ increase in particulate matter less than or equal to 10 μm (PM_{10}) increased the odds of a more serious asthma attack (odds ratio = 1.12; 95% CI, 1.04 to 1.22) and also increased medication use (relative risk = 1.05; 95% CI, 1.00 to 1.09).

Conclusions: Increases in $PM_{2.5}$ and PM_{10} are significantly associated with an increased risk of more severe asthma attacks and medication use in Seattle area children with asthma. We also found associations with carbon monoxide, but we believe that carbon monoxide is a marker for exposure to combustion byproducts.

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INTRODUCTION

Particulate matter (PM) is a complex aerosol of solid and liquid organic and inorganic material that may include dust, soot, smoke, pollens, acid droplets, and secondary aerosols. The Environmental Protection Agency (EPA) has recognized the harmful effects of PM_{10} (PM with an aerodynamic diameter ≤ 10 μm) for several years, instituting air quality standards in 1989. More recent research has indicated that particles 2.5 μm in diameter or smaller ($PM_{2.5}$) may be more strongly associated with asthma than coarse particles between 2.5 and 10 μm in diameter.[1–3] In 1997, the EPA established new additional federal guidelines specifically for $PM_{2.5}$.[4]

The association between air pollution and asthma exacerbations has been investigated using epidemiologic studies. In general, short-term increases in PM levels have been found to be significantly associated with lung function decrements,[1,5] use of asthma medications,[6] emergency depatment visits,[2,7,8] hospital admissions,[9] and symptoms.[5,6,9,10] The studies using symptoms have chosen to dichotomize symptoms into 2 levels, which are generally "no symptoms" vs "any symptoms." However, asthma attacks can range across many different levels including relatively mild coughing attacks to moderate episodes that might restrict a child's activity or to more severe episodes that require a visit to the emergency department. We incorporated severity into our analysis by treating severity of asthma symptoms as an ordered, categorical outcome.

We investigated the short-term effects of PM and carbon monoxide (CO) on asthma symptoms and medication use in a group of children with asthma from the Seattle, WA, area who were participating in the clinical trial Childhood Asthma Management Program (CAMP). The children were identified as having mild-to-moderate asthma. They were followed up for 28 to 112 days while using "as-needed" inhaled albuterol as their only asthma medication. For severe exacerbations, oral prednisone was added to this regimen. This period of rescue medication was part of the CAMP screening process and served to exclude children with very mild disease or severe disease.

Asthma symptoms vary by severity, duration, and frequency within individuals on a daily basis. We classified a child's daily asthma severity based on a self-reported daily diary card. We then related this asthma severity to daily pollution levels to determine whether increasing levels were associated with more severe asthma episodes. We also investigated whether or not there was an association between PM

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or CO with rescue inhaler use (albuterol) in the same group of children.

MATERIALS AND METHODS

Study Subjects

CAMP is a multicenter, randomized, clinical trial designed to gauge the effectiveness of 3 treatments for mild-to-moderate childhood asthma. Before being randomized to 1 of the 3 treatment groups, each of the CAMP participants underwent a run-in period in which they completed age-appropriate, daily diary cards. We selected children from the Seattle subset of CAMP using data from the run-in period for this substudy. CAMP children had mild-to-moderate asthma, as defined by the presence of symptoms or by the use of an inhaled bronchodilator at least twice weekly or the use of daily medication for asthma. Subjects were excluded from CAMP if the concentration of methacholine causing a 20% decrement in forced expiratory volume in 1 second (FEV_1PC_{20}), was greater than 12.5 mg/mL. FEV_1PC_{20} varied between 0.03 and 12.2 mg/mL (median = 0.73 mg/mL) in the subgroup of subjects we studied. Children were excluded from CAMP if they had any other clinically significant conditions.[11]

Table 1 summarizes the baseline variables for the children in our study. Most subjects were white (76%) and had family incomes that were greater than $30,000 (77%); the median family income for King County was approximately US$45,000 in 1994. The children were 5 to 13 years old at enrollment and, on average, were first diagnosed as having asthma 5.6 years earlier. More boys (84) than girls (49) were enrolled in the study.

On their diary cards, subjects reported AM and PM peak expiratory flow rate measures, the number of rescue inhaler puffs used for asthma signs, and whether their asthma caused them to wake up during the night, see a physician, or miss school. Participants also indicated a daily asthma severity code on their diary cards. From the original CAMP diary cards, we recategorized both the asthma severity code and rescue inhaler use outcome variables for this substudy. We collapsed the original 4-level severity code into 3 more distinct levels: (1) no asthma attacks; (2) any number of mild attacks; and (3) a more severe asthma episode that lasts more than 2 hours or results in shortened normal activity or seeing a physician for acute care. Because the children reported taking an even number of inhaler puffs 97% of the days, medication use was also recorded for the final Poisson models. We recategorized 1 puff with 2, 3 puffs with 4, etc, to better comply with the Poisson model assumptions.

Table 1. Baseline Characteristics (N = 133)

Characteristic	Percentage	Mean (SD)	Min	Max
Age at screening, y		8.6 (2.1)	5.1	13.1
Asthma duration, y		5.3 (2.7)	0.2	11.7
FEV_1PC_{20}, mg/mL		1.5 (2.2)	0.03	12.2
Height, ft		4.3 (0.5)	3.2	5.6
Weight, lb		71 (25)	31	161
Male sex	63%			
Race				
White (non-Hispanic)	76%			
African-American	7%			
Other	17%			

Abbreviation: FEV_1PC_{20}, 20% drop in forced expiratory volume in 1 second.

Air Pollution Monitoring

The Puget Sound Clean Air Agency (Seattle, WA) contributed air pollution and temperature data used in this study. The agency maintains a number of air pollution monitoring stations throughout the Puget Sound region. The data for this analysis come from 12 sites, 6 of which measure CO, 3 that measure temperature, and 3 that measure PM_{10} and $PM_{2.5}$ (PM_{10} gravimetrically, $PM_{2.5}$ by nephelometry).

We used nephelometers to estimate the mass concentration of $PM_{2.5}$ in the greater Seattle area. Nephelometers continuously measure light scattering from dry particles to determine a light scattering coefficient. Light scattering can provide an extremely sensitive tool for measurement of aerosol concentrations and particle size. Independent research in the Seattle area indicates that a 0.476×10^{-4}-m^{-1} increase in light scattering coefficient corresponds to a 10-$\mu g/m^3$ increase in $PM_{2.5}$ with a correlation of approximately 0.9.[1] During the study period, there were many days when both gravimetric $PM_{2.5}$ measurements and nephelometer readings were available from the same site. On these days, we were able to directly compare the 2 readings. We also found a high level of correlation ($r = 0.91$) between the gravimetric $PM_{2.5}$ measurements and nephelometers, as well as a similar linear relationship. Because the nephelometer readings were available on all study days, whereas the $PM_{2.5}$ readings were available on only approximately one third of the days, we decided to use nephelometers to estimate $PM_{2.5}$.

$PM_{2.5}$ and PM_{10} concentration were measured at 3 sites and CO concentrations at 6 sites in the Seattle area. We estimated population exposure to PM and CO by averaging over sites for each pollutant. By averaging, we attempted to diminish the influence of random sources of variation from a given site on a given day. Research conducted in Seattle[12] indicates that most of the variation in $PM_{2.5}$ can be attributed to time rather than location. Other results[13] suggest that the average of CO monitors used in this study may capture the variation in background ambient CO fairly well. We also calculated 1-, 2-, and 3-day lags for each pollutant to determine whether concentrations from 1, 2, or 3 days earlier are related to today's asthma severity.

CAMP subjects provided information on the zip code of their current family residence. From this information, it was possible to approximate a subject's general location relative to the pollution monitoring sites. Eleven subjects were removed from the analysis because they were found to live outside the greater Seattle area, leaving 133 children in the final analyses.

Statistical Methods

Ordinal logistic regression, specifically the proportional odds model, was used to analyze the asthma severity outcome. McCullagh[14] developed the proportional odds model as a general class of linear models to deal with ordinal data. This model takes into account the ordinal nature of the data to provide an odds ratio (OR) estimate comparing the odds of a more serious outcome relative with a less serious outcome. Consider a multinomial response variable Y with k ordinal outcomes; then the proportional odds model can be expressed as:

$$\text{logit}(Pr(Y > k)) = a_j + X'B, j = 1,2, \ldots, k - 1$$

Note that the regression coefficient B does not depend on j, implying that the relationship between X and Y is independent of j. The assumption of identical log-odds across the $k - 1$ cut points is called the proportional odds assumption, hence the name "proportional odds model." In this study, we are estimating the odds of any asthma attack vs no attacks and the odds of a severe asthma attack vs any mild attacks or no attack. The proportional odds assumption, which can be tested statistically, is that these 2 ORs are the same.[15] The proportional odds assumption held in our models.

In this longitudinal study, repeated measurements were taken on the same children. It is therefore necessary to assume that measurements taken on the same child will be more alike than measurements taken on different children. To account for this lack of independence, a generalized estimating equation approach was used with the robust "sandwich" estimator fixing the variance estimates of the coefficients.[16–18] Both the proportional odds and Poisson models were estimated using STATA 6.0 software using an independent working correlation matrix.[19] Previous research by Pepe and Anderson[20] indicates that failing to choose an independent working model could lead to biased inference when covariates vary over time, as they do in this study.

In addition to marginal proportional odds and Poisson models, we also fit transition models to the data. The transition models additionally controlled for the previous day's response without fitting interaction terms. In the ordinal models, we conditioned on the previous day's asthma severity, and in the Poisson models we controlled for whether the previous day's medication use was above, equal to, or below the subject's median medication use.

In this study population, air pollution levels changed both between individuals and within an individual from day to day. Children entered and left the study at different times and were measured for varying durations. Thus we expected difference in between-subject, $\bar{X}_i$, and within-subject, $X_{il} - \bar{X}_i$, pollution exposure. To explicitly separate these 2 effects, both the within-subject and between-subject exposures were fit in the models simultaneously. Because we were primarily interested in short-term pollutant effects, our primary predictor of interest became the within-subject changes in pollutant level. Differences in between-subject pollution effects were completely attributable to different periods of observations, so we could not completely rule out residual seasonal confounding in these estimates and therefore do not report them.

A number of baseline variables were considered as potential confounders, with age, sex, height baseline methacholine responsiveness (FEV_1PC_{20}), and race being included in the final model. We also adjusted for the daily effects of temperature, lagged 2 days as both a linear and centered quadratic term. Temperature does not vary much in the Seattle area, so we found this simple adjustment sufficient. In addition to the baseline variables and temperature, we also controlled for the day of the week (indicator variables) and used linear splines (7 *df*) to control for seasonality.

RESULTS

Table 2 characterizes the medication use and asthma severity information reported by the CAMP subjects on their diary cards. Severity was self-reported and based on both the number and duration of a subject's asthma attacks as defined in the methods. All 133 subjects experienced at least one asthma attack while they were on study, and no child reported the same asthma severity every day during their study period. One child reported the same rescue inhaler use (zero puffs) throughout the study period. Ninety-seven percent of all inhaler puffs were reported in even increments, and only 5% of the children reported an odd number of inhaler puffs on more than 25% of the days.

Measurements from at least one monitoring site for CO, $PM_{2.5}$, and air temperature were available for all 580 days of the study period, whereas PM_{10} measurements were available on 564 days. For $PM_{2.5}$ and CO, individual sites had at most 2% missing concentrations, whereas individual PM_{10} sites had between 4% and 18% missing. These daily averages are shown in Figure 1 fitted with a loess smooth line (span = 0.2). The daily measurements of CO, PM_{10}, $PM_{2.5}$, and temperature were also significantly correlated. $PM_{2.5}$ was correlated with PM_{10} ($r = 0.75$) and CO ($r = 0.82$), PM_{10} was correlated with CO ($r = 0.65$), and all 3 pollutants were negatively correlated with temperature.

A total of 7,356 and 7,403 person-days of diary card data were available for the asthma severity and inhaler use anal-

Table 2. Person-days of Rescue Inhaler Use by Reported Asthma Severity*

Asthma severity	Puffs taken from rescue inhaler					
	0	1–2	3–4	5–6	≥7	Total
No attacks	2870	76	37	10	1	2,994
Mild/moderate	401	1,794	1,549	562	196	4,502
Severe	4	0	5	13	56	78

*Data are from 133 subjects observed for 28 to 112 days.

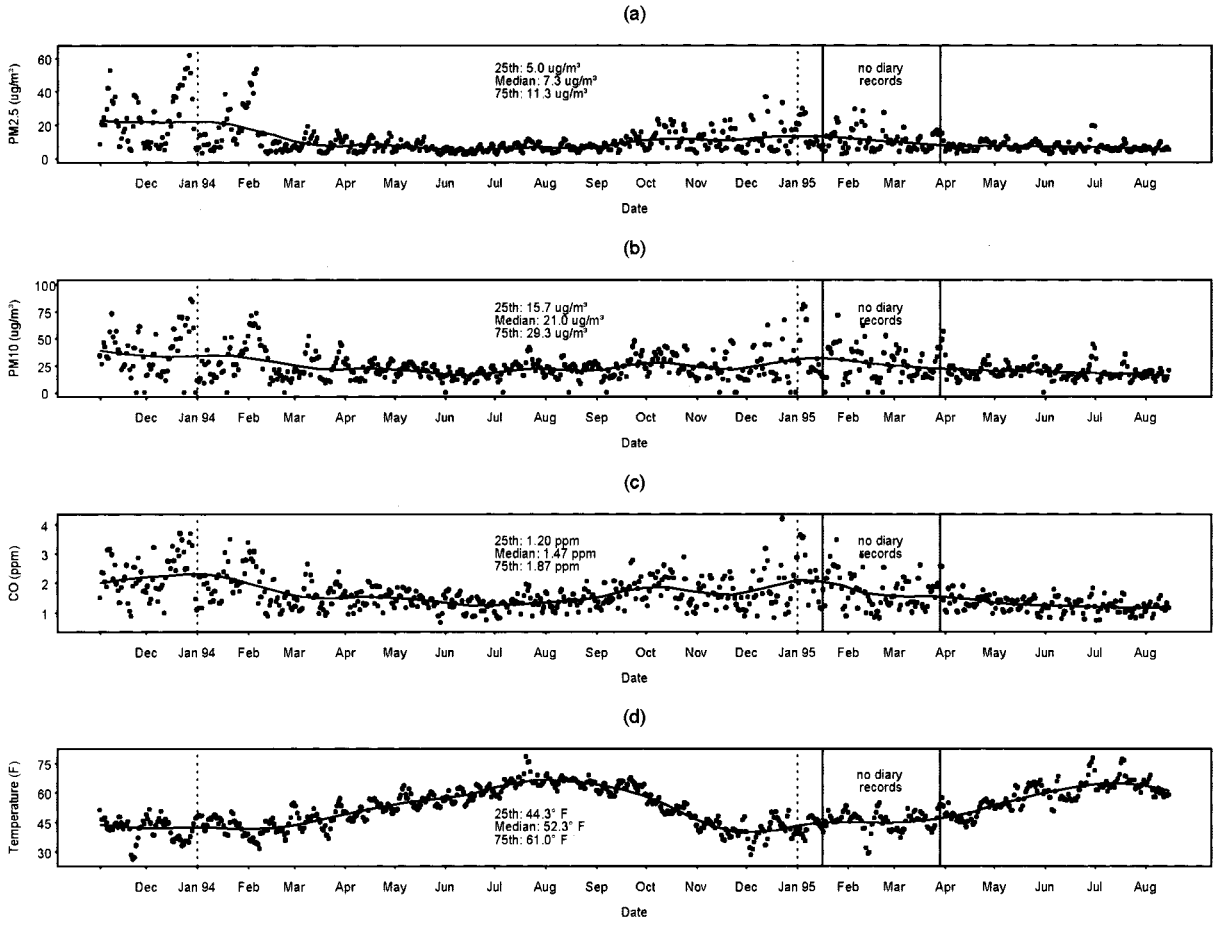

Figure 1. Averages of the pollution variables over the study period fitted using a loess smooth line: (a) $PM_{2.5}$ from 3 sites, (b) PM_{10} from 3 sites, (c) CO from 6 sites, and (d) temperature from 3 sites.

yses, respectively. We used all diary data in the $PM_{2.5}$ and CO models, but missing pollution data reduced the sample size in the PM_{10} models to 7,198 (severity) and 7,259 (inhaler) person-days. To make the models more comparable, we adjusted for the same confounders in every model, regardless of the pollutant or type of model. Specifically, we adjusted for 2-day lagged effects of temperature (linear and quadratic term), sex, baseline FEV_1PC_{20}, baseline height, race, day of the week, and season (using linear splines, 7 *df*).

Among 0- to 3-day lags of pollution exposure, we found that the 1-day lagged $PM_{2.5}$ and CO and the same-day PM_{10} levels were most significantly associated with increased asthma severity. Figure 2 presents the OR estimates and 95% confidence intervals (CIs) for the various lags of $PM_{2.5}$, PM_{10}, and CO from the ordinal models. For $PM_{2.5}$ and CO, the associations with asthma severity were strongest at the 1-day lag and became weaker as the lag time increased. Adjusting for confounders, a 10-$\mu g/m^3$ increase in 1-day lagged $PM_{2.5}$ was associated with a 1.20-fold increased odds of having a more serious asthma attack (95% CI, 1.05 to 1.37). When the previous day's asthma severity is also controlled for using the transition model, the OR decreases to 1.13 (95% CI, 1.03 to 1.23). A 0.67-ppm increase in the 1-day lagged CO levels was most strongly associated with an increased odds of having a more serious asthma attack (OR = 1.21 without transition, OR = 1.17 with transition); the same- and 2-day lags were also significant ($\alpha = 0.05$) in the CO proportional odds models. The association between PM_{10} and asthma severity was strongest at the zero-day lag, and also became weaker as the lag time increased. A 10-$\mu g/m^3$ increase in the same-day, within-subject PM_{10} levels was associated with a 1.12-fold increased odds of having a more serious asthma attack (OR = 1.10 with transition).

When we related rescue inhaler use to pollutant levels, we found the same pattern of stronger association at the 0- and 1-day lag followed by decreasing strength of association as lag days increased (Fig 3). However, associations of the pollutants with medication use were weaker than they were with asthma severity. We found the strongest associations of medication use with $PM_{2.5}$ and CO at the 1-day lags with weaker association for 2- and 3-day lags. A 10-$\mu g/m^3$ increase in the previous-day's $PM_{2.5}$ concentrations was asso-

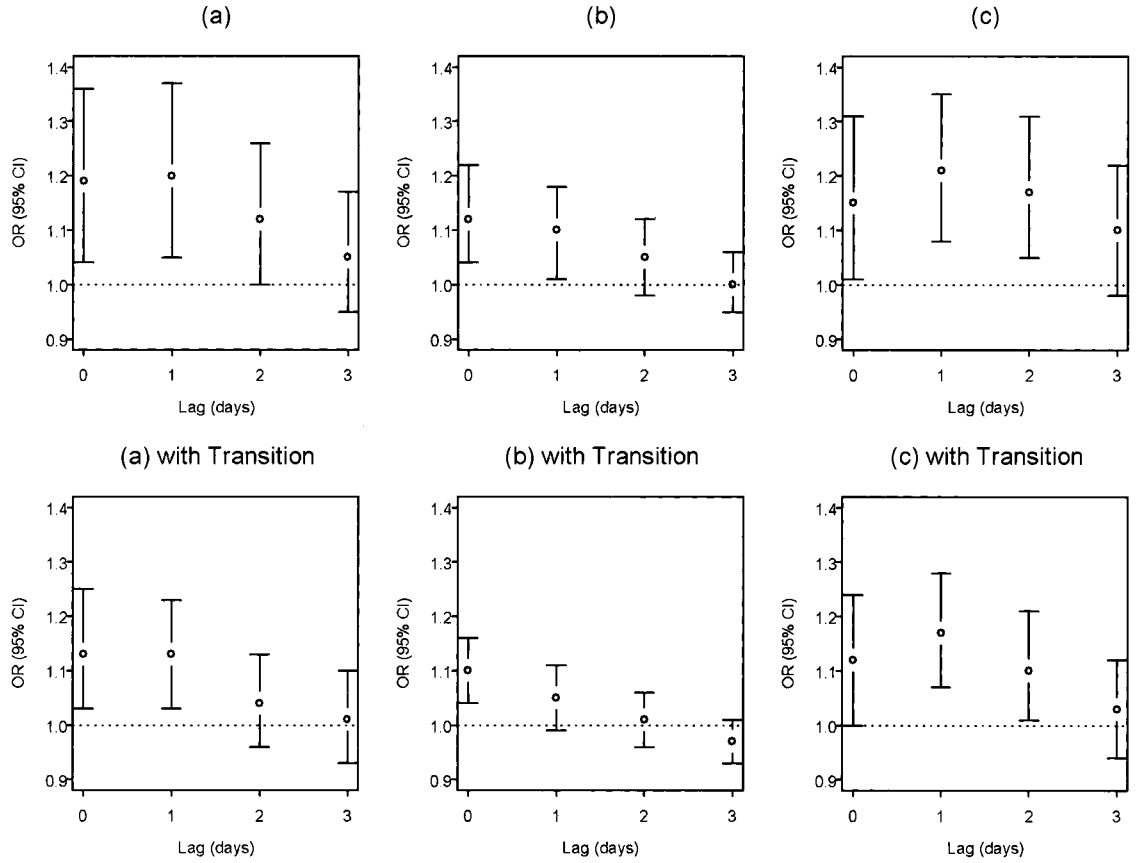

Figure 2. Estimated odds ratios for having a more serious asthma attack for short-term, within-subject increases in (a) $PM_{2.5}$ (10 $\mu g/m^3$), (b) PM_{10} (10 $\mu g/m^3$), and (c) CO (0.67 ppm). Transition models additionally control for the previous day's severity.

ciated with a 1.08-fold increase (95% CI, 1.01 to 1.15) in rescue inhaler use using the nontransition model. We also found significant associations between a 1-ppm increase in CO and increased rescue inhaler use in both the marginal [1-day relative risk (RR) = 1.09; 95% CI, 1.03 to 1.16] and transition models (1-day RR = 1.06; 95% CI, 1.01 to 1.10). For PM_{10}, the strongest association with medication use was at lag zero (RR = 1.05; 95% CI, 1.00 to 1.09).

We also fit multipollutant models in which PM levels were adjusted for ambient CO exposure (Table 3). Adjusting for CO concentration generally attenuated the PM effect. There was still an association of $PM_{2.5}$ and PM_{10} with asthma severity (OR = 1.16 and OR = 1.11, respectively), but there was no longer an association of PM with rescue inhaler use.

DISCUSSION

We investigated the association of PM and CO with asthma severity and medication use in a panel of children with mild-to-moderate asthma. Using ordinal logistic regression, we found that both higher PM and CO levels were significantly associated with greater odds of having a more severe asthma attack. Increases in these pollutants were also found to increase rescue inhaler use among these subjects. For both inhaler use and symptom reporting, associations with ambient PM and CO were strongest at the 0- or 1-day lag and became weaker at the 2- and 3-day lags.

Previous studies investigating the association of air pollution with asthma symptoms have chosen to dichotomize asthma symptoms into 2 levels.[3,5,6,10] In our analysis, we used the proportional odds model to incorporate the ordinal nature of asthma severity into the model. Our results indicate that elevated PM and CO concentrations are associated with both (1) any asthma symptoms (compared with no symptoms) and (2) more severe episodes (compared with no attacks or mild attacks). For example, a 10-$\mu g/m^3$ increase in the previous day's $PM_{2.5}$ concentration is associated with a 1.20-fold increased odds of an individual having any asthma attacks. The same increase in $PM_{2.5}$ is also associated with a 1.20 times increased odds of having a prolonged attack lasting more than 2 hours or having to see a physician for acute care.

To analyze the ordinal asthma severity outcome, we used the proportional odds model adapted for correlated responses. The basic assumption of the proportional odds model is that

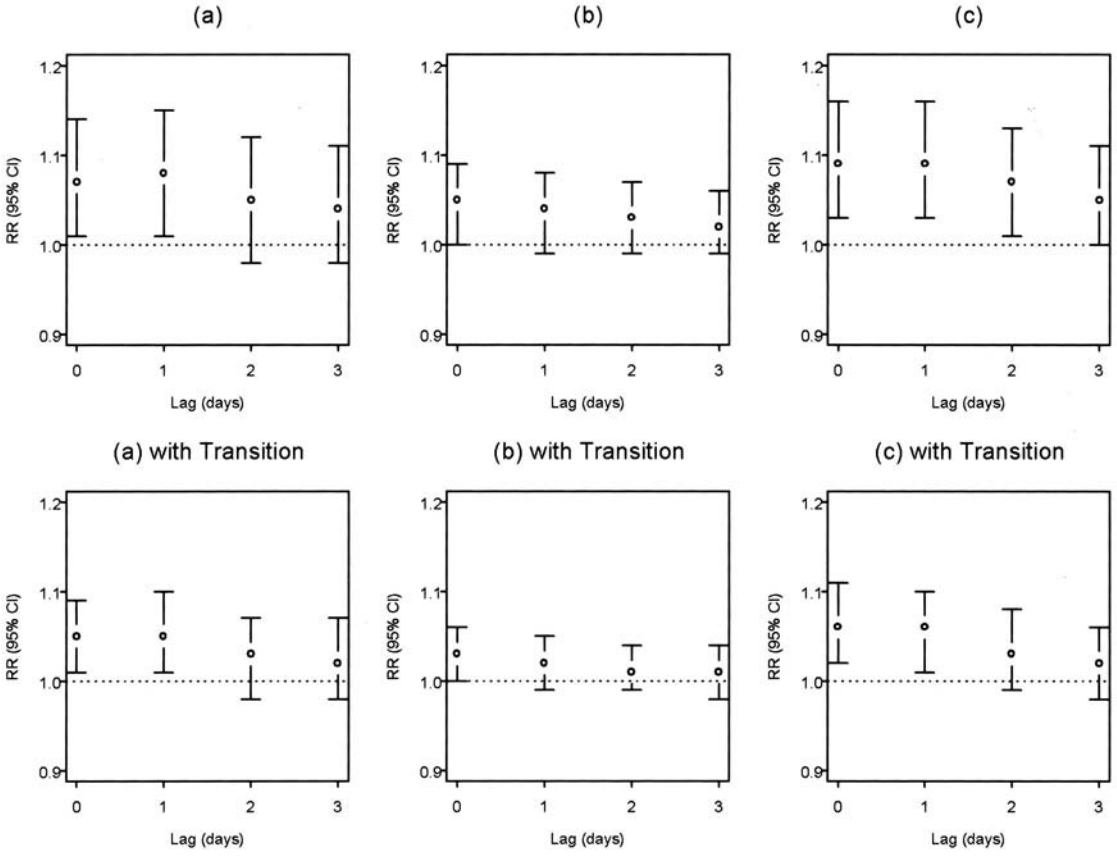

Figure 3. Estimated relative risks for inhaler use for a short-term increase in (a) $PM_{2.5}$ (10 $\mu g/m^3$), (b) PM_{10} (10 $\mu g/m^3$), and (c) CO (0.67 ppm). Transition models additionally control for the previous day's medication use.

Table 3. Odds Ratio (Asthma Severity) or Relative Risk (Inhaler use) Estimates for a Short-term 10-$\mu g/m^3$ Increase in $PM_{2.5}$ or PM_{10} Concentrations, Adjusted for Ambient CO Levels

Outcome and pollutant	OR/RR	95% CI
Asthma severity		
$PM_{2.5}$ (1-day lag)	1.16	1.03, 1.30
PM_{10} (same day)	1.11	1.03, 1.19
Inhaler use		
$PM_{2.5}$ (1-day lag)	1.04	0.98, 1.10
PM_{10} (same day)	1.02	0.99, 1.06

Abbreviations: $PM_{2.5}$, particulate matter less than or equal to 2.5 μm; PM_{10}, particulate matter less than or equal to 10 μm; CO, carbon monoxide; OR, odds ratio; RR, relative risk; CI, confidence interval.

the OR comparing severe asthma attacks with mild or no attacks is proportional to the OR comparing any asthma attacks vs no attacks. To test this assumption, we developed a score test for correlated ordinal data, based on procedure outlined by Stiger et al.[15] This test revealed that the proportional odds assumption held for within-subject changes in $PM_{2.5}$ ($P = .78$), PM_{10} ($P = .97$), and CO ($P = .37$).

Pollution levels were gathered from several sites around Seattle and then averaged to provide a general picture of air pollution on a particular day. It is not possible to determine exactly how well these pollution levels correspond to a child's personal exposure on that day. Factors such as the amount of time spent indoors and outdoors may affect the amount of pollution to which a child was exposed. However, PM, especially $PM_{2.5}$, has been found to penetrate from outdoor to indoor environments fairly well.[21] We also were not able to adjust for nonambient sources of PM, such as from cooking, cleaning, pets, or tobacco smoke. However, nonambient PM sources have been shown to be independent of ambient PM over time,[22] so these types of exposures are unlikely to be introducing bias into the models. Ascertaining CO levels was potentially more difficult than determining the PM levels due to the relatively low correlations between the CO monitoring sites. All of the CO monitor sites are located in areas of high traffic volume, so they may give readings that are higher than residential areas.[13] By choosing to average CO data from 6 sites throughout Seattle, we attempted to diminish the influence of random sources of variation in CO levels from any given site on a particular day that are not representative of population exposure.

We found stronger associations between asthma severity and rescue inhaler use with CO than with PM. However, a

direct association between CO and asthma exacerbation lacks biologic plausibility.[23] The primary effect of CO exposure is anoxia, which results in confusion, headache, and nausea. It is possible that CO serves as a marker for diesel and gasoline exhaust particles. A recent source apportionment analysis[24] found that concurrently measured CO was correlated with $PM_{2.5}$ from gasoline vehicles. These types of particles have been conjectured to be especially toxic in children and may be what is truly causing the asthma exacerbations.[25,26] They also have a relatively high content of semivolatile organic compounds, which are underreported by PM measurement equipment. The CO association would then be driven by either higher toxicity or higher measurement error in one component of the diverse PM mixture.

The method in which we explored pollution lags could also be problematic. When multiple lags are explored during model selection, it can potentially result in some bias. In a simulation study using Seattle data, it was shown that the potential for bias in studies using this type of model selection is not negligible when the magnitude of the true association is small.[27] Although we focused our analysis on the previous day's pollution levels, we did look at lags ranging from 0 to 3 days. However, our results are consistent with a 1-day lagged effect of $PM_{2.5}$, PM_{10}, and CO on asthma, with other lags being associated as well. Because we do not know the magnitude of the true association, we cannot rule out model selection bias in this analysis.

The diary card data are another potential source of bias. Children were asked to fill out their diary record twice daily, once in the morning and once at bedtime. Since this was done independently at home, actual compliance with this procedure is unknown. Although it is possible that some entries were completed later, the categorical and experiential nature of the severity and medication use information should facilitate recall. The severity categories are rather broad, so children should be able to remember that information fairly accurately, but remembering the number of puffs taken from their rescue inhalers could be more problematic. This recall error could be a factor in the weaker associations found in the medication models compared with the symptom severity models.

CONCLUSION

The prerandomization phase of the CAMP study provided an excellent opportunity to investigate the potential relationship between asthma severity and air pollution. During this time, each of the CAMP children suspended maintenance medications; therefore, the effects of routine preventive therapies do not confound this study. Each child completed several weeks of daily diary card information, which increased the power to find an association and allowed us to compare each child with himself or herself. We found that both asthma severity and medication use were associated with $PM_{2.5}$, PM_{10}, and CO concentrations in a population of children with mild-to-moderate asthma severity.

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