Acute Effects of Ambient Inhalable Particles in Asthmatic and Nonasthmatic Children

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Although increases in inhalable particle (PM_{10}) concentrations have been associated with acute reductions in the level of lung function and increased symptom reporting in children, including children with asthma, it is not clear whether these effects occur largely in asthmatic children, or even whether asthmatic children are more likely to experience these effects than children without asthma. To address these points, the following subgroups of children were selected from a survey population of all 2,200 elementary school children (6 to 13 yr of age) in a pulp mill community on the west coast of Vancouver Island: (*1*) all children with physician-diagnosed asthma (n = 75 participated), (*2*) all children with an exercise-induced fall in FEV_1 without diagnosed asthma (n = 57), (*3*) all children with airway obstruction ($FEV_1/FVC < 0.76$) without either of the above (n = 18), and (*4*) control children without any of the above (n = 56). The children were followed for as long as 18 mo with twice daily measurements of peak expiratory flow (PEF) and daily symptom diary recording. Maximum daily PM_{10} concentration was 159 $\mu m/m^3$ (median, 22.1), but only 8 d (1.2%) had concentrations above 100 $\mu g/m^3$. In an analysis that accounted for time-varying covariates, and serially correlated and missing data, for the entire sample of children, increases in PM_{10} were associated with reductions in PEF and increased reporting of cough, phlegm production, and sore throat. For the subgroup of children with diagnosed asthma, PEF in the time period with the highest PM_{10} concentrations fell by an estimated 0.55 L/min (95% CI, 0.06 to 1.05) for a 10 $\mu g/m^3$ PM_{10} increase above the mean daily PM_{10} concentration of 27.3 $\mu g/m^3$ and the odds of reported cough increased by 8% (95% CI, 0 to 16%); no consistent effects were observed in the other groups of children. It is concluded that children experience reductions in PEF and increased symptoms after increases in relatively low ambient PM_{10} concentrations, and that children with diagnosed asthma are more susceptible to these effects than are other children. Vedal S, Petkau J, White R, Blair J. Acute effects of ambient inhalable particles in asthmatic and nonasthmatic children.

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Exposure to short-term increases in outdoor particulate air pollution has been associated with increased respiratory symptom reporting and acute decreases in level of lung function in both asthmatic children (1) and adults (2), and in subjects without asthma (3–5). Similar associations have also been reported for most measures of acute respiratory morbidity, including use of asthma medications (1) and emergency room visits (6, 7) or hospitalizations (8–11) for respiratory conditions, as well as for mortality from respiratory illness (12–15). These studies have understandably prompted great concern since the associations reported persist even at inhalable particle (PM_{10}) concentrations well below the current U.S. 24-h ambient PM_{10} standard of 150 $\mu g/m^3$.

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Patients with preexisting respiratory or cardiac illnesses appear to be at particular risk of the most severe adverse health effects caused by exposure to inhalable particles such as death or hospitalization (11, 14). It is reasonable to presume that those with preexisting illnesses would also be especially susceptible to the less adverse health effects of such exposure such as increases in respiratory symptoms or reductions in level of lung function, although the data on which this is based are sparse. As one potentially susceptible subgroup, asthmatics are susceptible to adverse effects of increases in PM_{10} concentrations as demonstrated by the increased asthma emergency room visits observed to occur after increases in PM_{10} concentrations (6). It has not been clearly shown that asthmatics are more susceptible to the less adverse effects of inhalable particles, although again it is reasonable to suppose that they would be. In a previous, similarly designed study from Utah in which differential impacts on a sample of asymptomatic children and a sample with respiratory symptoms were investigated, it was concluded that the children with symptoms were more adversely affected (3). The purpose of this study was specifically to compare the acute effects of inhalable particle

pollution on peak expiratory flow and respiratory symptoms in asthmatic and nonasthmatic children.

Longitudinal studies such as these that attempt to relate changes in ambient particle concentrations to changes in respiratory health face many potential difficulties. Exposure to particles is often estimated by a monitoring site located at some distance from a large segment of the study population, which potentially results in considerable misclassification of the true exposure to outdoor particles. Further, other pollutants are strongly correlated over time with inhalable particle concentrations, which makes it difficult to attribute any observed associations to one component of the pollutant mix (16). Finally, although recent methodologic advances have combated difficulties resulting from missing (17) and serially correlated data (18, 19) in longitudinal data analysis, for the study of many acute health effects there remains uncertainty regarding the impact of using different statistical methods.

This study had several important advantages. First, the study population of children exposed to ambient particles was confined to a small geographic area, which should have allowed better estimation of exposure using a central monitoring site than other similarly designed studies. Second, the analysis of the study data employed various analytical methods performed in parallel. Such an approach allowed an assessment of the sensitivity of the study findings to the use of different statistical methods. Third, concentrations of the potentially important copollutants such as sulfur dioxide, ozone, or acid aerosol were very low in the study community. Finally, the study contained a relatively large number of children with a doctor's diagnosis of asthma, which provided the study with good power to identify specific impacts on this large and potentially susceptible subgroup of the population.

METHODS

Study Site and Population

The study was performed in Port Alberni, a community with a population of 30,000 located at the head of an ocean inlet on the west coast of Vancouver Island, British Columbia, Canada (Figure 1). Housing density is higher in the northern part of the community. Because Port Alberni is surrounded on three sides by hills and mountains, it is subject to frequent thermal inversions that trap air pollutants in the area, particularly during the winter. Industrial air contaminants are produced primarily by one pulp and paper mill (Figure 1) and to a lesser extent by two sawmills. The main sources of ambient particulate pollution are the pulp mill boilers and residential wood burning.

On the basis of data collected for a cross-sectional study of air pollution in the community involving 2,199 children (20), four groups of elementary school children were identified: (*1*) all children with a physician's diagnosis of current asthma based on an interviewer-administered questionnaire to parents (ASTHMA), (*2*) those without a physician's diagnosis of asthma who experienced at least a 9% fall in FEV_1 10 min after a 5-min free range run (exercise-induced fall [EIF]), (*3*) those without physician-diagnosed asthma or an exercise-induced fall in FEV_1, but who had airway obstruction on spirometry based on a FEV_1/FVC ratio less than 0.76 (OBSTRUCT), and (*4*) a control group of children matched by school classroom to the children in the previous three groups (CONTROL).

Health Outcomes

A letter of recruitment was mailed to the parent or guardian of each potential participating child. After obtaining informed consent, a research nurse visited each home and administered a modified American Thoracic Society children's respiratory questionnaire (20, 21) as had been done in the initial cross-sectional study. The nurse then instructed the child in the completion of a daily symptom and medication diary and in the performance of peak expiratory flows two times each day. Peak expiratory flow (PEF) was measured using a Mini-Wright peak flow meter. Three peak flow maneuvers were to be performed in the morning after getting up, and three maneuvers were to be repeated before bedtime. All six values were recorded by the child. The daily PEF value was defined as the maximum of the available morning and evening measurements. The diary required the child to write one or more numbers in a box for each day, with each number entered corresponding to positive responses to each of the following statements: "Compared to how I am usually, today I: 1) coughed more, 2) produced more phlegm (mucous) from my chest, 3) had more burning, itching or redness of my eyes, 4) had a more runny or stuffed nose, 5) had a more sore throat, 6) wheezed more, 7) had more chest tightness, 8) felt more short of breath." Use of regular asthma medications and extra asthma medication use were also recorded, but results of this analysis will not be reported here. If PEF measurements were recorded on a given day and no diary numbers were recorded, it was assumed that no worsened symptoms were present on that day for that child. Alternatively, if no PEF measurements were recorded and no diary numbers were recorded, both PEF and symptoms data were assumed to be missing on that day.

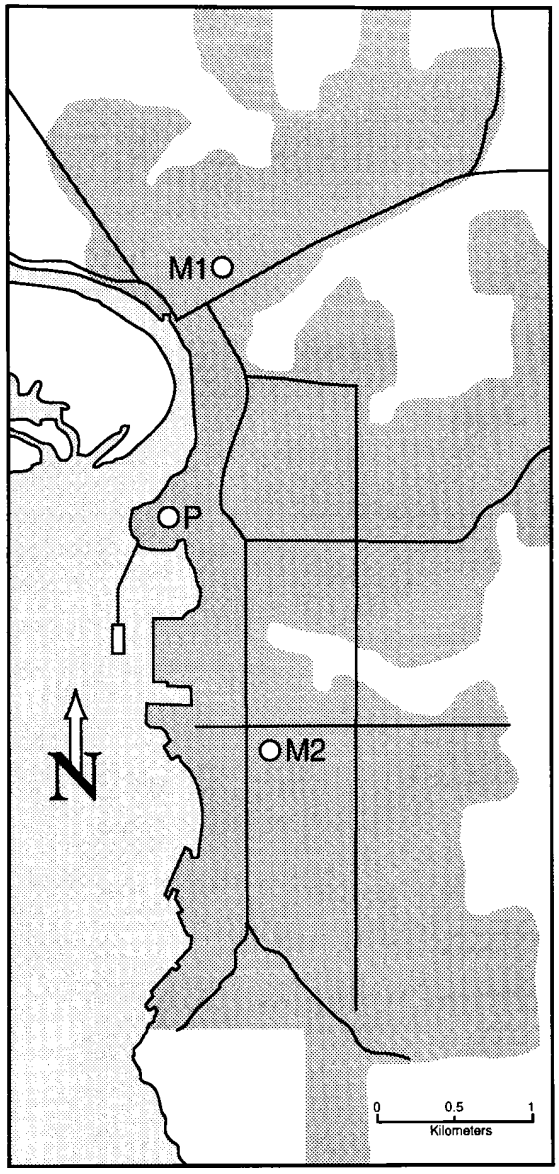

Figure 1. Port Alberni pulp mill (P) and PM_{10} monitor locations (M1 = NORTH SITE; M2 = SOUTH SITE). Only the NORTH SITE monitor data were used for the analysis. *Dark shading* represents residential area. Intermediate shading represents the Alberni Inlet.

Daily data were collected for each child from as early as May 1, 1990 (Day 1) through March 13, 1992 (Day 683), with no data collected during July and August of 1991. The nurse contacted each child in the study by telephone every 2 wk and personally collected the diary forms each month. Continued participation was encouraged with prizes awarded for periods of time enrolled in the study.

Ambient Air Monitoring and Meteorology

Daily outdoor air monitoring was performed to correspond to the period of time that the children recorded their symptom and peak flow data. Two particle monitoring sites (NORTH SITE and SOUTH SITE) were used (*see* Figure 1). Housing density was higher in the region of the NORTH SITE than the SOUTH SITE. At each monitoring station, PM_{10} samplers (Sierra-Andersen, Carmel, CA) were operated for each 24-h period from 9:00 A.M. to the following 9:00 A.M. PM_{10} concentrations were measured gravimetrically. Quality control consisted of frequent sampler calibration and inclusion of blank filters with each set of filters.

Meteorological data were obtained from Environment Canada. The daily precipitation and average daily temperatures obtained from a meteorological station at the community hospital contained no missing values. However, hourly humidity values were available for the daytime hours only, and after July 1, 1991, no humidity data were available on weekends or holidays. Further, after January 1, 1992, the wind speed and direction data from that station were available only when the humidity data were available. A complete set of hourly wind data for the period after January 1, 1992 was obtained from the Port Alberni airport and was substituted for the original data set after comparisons were made to ensure that the two sets of wind data were comparable. Unfortunately, no other reliable source of humidity data for Port Alberni was available; all missing daily humidity data (79 out of a total 683 d) therefore were estimated using a linear model ($R^2 > 0.76$) based on average daily temperature, a daily indicator of precipitation, the amount of daily precipitation, the average daily wind speed, and the average daily humidity from the closest neighboring community (74 km away) that had complete humidity data.

Particle counts were also measured at each monitoring site using a particle counter (CI-7300; Climet Industries, Redlands, CA). Particles were counted for six diameter size ranges: (*1*) 0.3 to 0.5 μm, (*2*) 0.5 to 0.7 μm, (*3*) 0.7 to 1 μm, (*5*) 5 to 10 μm, and (*6*) > 10 μm. Counts were obtained for the first minute of every hour over the entire monitoring period; therefore, 24 particle counts for six size ranges were made daily. Airborne pollen and mold counts were obtained at the SOUTH SITE using a Rotorod Sampler (Ted Brown Associates, Los Altos Hills, CA), which ran concurrently for 24 h with the PM_{10} monitor at that site. The findings on particle counts and aeroallergens will be reported elsewhere.

Analysis

Missing PM_{10} concentrations at each site were estimated using the EM algorithm (22). The pollution data used in the estimation procedure included daily PM_{10} and the particle counts at both sites as described above. Meteorological variables included daily average temperature, humidity, and wind speed and direction (hourly values represented as two-dimensional Cartesian coordinates and then averaged for each day), as well as an indicator of daily precipitation and the daily amount of precipitation. Preliminary analyses suggested the additional inclusion of day of the week and season (defined as four 3-mo blocks with winter = January through March).

Preliminary plots indicated the need to transform all of the pollution variables to correct for heteroscedasticity and non-normality before applying the EM algorithm. For the particle count data, the hourly counts were first transformed and a daily average based on all available data for that day was then computed. The effects of the meteorological and temporal variables were first removed from each of the 14 transformed daily pollution variables (PM_{10} concentrations and six particle counts at each of two sites) using a linear model containing the temporal variables described above, as well as all main effects and two-way interactions of the meteorological variables. Using the resulting residuals, the missing residuals from the 14 sets of particle pollution data were then simultaneously imputed with the EM algorithm. There were seven isolated days in which no pollution data of any type were available from either site; these days were assigned imputed residuals of zero after adjustment for the meteorological and temporal variables. Adding the fitted temporal and meteorological effects to these imputed residuals, we obtained imputed daily values of the pollution variables for those days where these variables were missing in the original data set, thus leading to a "complete" set of pollution data. The pattern and number of measured and imputed PM_{10} values from the NORTH SITE are shown in Figure 2. The PM_{10} concentrations in the "complete" data set were transformed to the natural logarithm scale for all of the subsequent analyses reported.

The association of both PEF and daily symptoms with PM_{10} was evaluated in three stages, with successive stages involving progressively more rigorous approaches. The first stage was an exploratory approach in which daily averages were calculated using all children who provided data on any given day. For PEF, the difference between each child's value for that day (i.e., the maximum of the available measurements on that day) and that child's mean daily PEF value during the study was first calculated; these differences were then averaged over all children contributing PEF data on that day to obtain the overall value for that day. This overall mean daily PEF was then regressed on the explanatory variables using ordinary least-squares regression. For symptoms, the overall value for each of the eight symptoms for each day was simply the prevalence of that symptom for all children contributing symptom data for that day. Symptoms were also grouped into the following symptom sets: Set 1 = cough or phlegm; Set 2 = eye, nose, or throat symptoms; Set 3 = wheeze, shortness of breath, or chest tightness; Set 4 = any symptom. Logistic regression was used for the analyses of these symptom data. Explanatory (independent) variables included a linear trend for time (via a counter indicating study day), daily meteorology (temperature, humidity and precipitation) and periodicity (day-of-the-week and month), in addition to PM_{10} concentration. Lags up to 15 d between the measured outcomes and the PM_{10} concentrations were explored both individually and sequentially. In addition, the cumulative effects of PM_{10} were explored by considering the average log PM_{10} over several previous days (cumulative lags) as explanatory variables.

In the second stage of the analysis, individual variability was taken into account. In a "fixed effects" analysis each subject was allowed an individual level (intercept), but the effects of PM_{10} and all of the covariates were taken to be common to all subjects. In a "random effects" analysis an individual level and PM_{10} effect were estimated for each subject, although the other covariate effects were still taken to be common to all subjects. The estimates of these separate PM_{10} effects for each subject were then combined (23, 24) to obtain an estimate of the "average" PM_{10} effect for the population from which this sample of subjects was drawn. The fixed effects and random effects analyses are directed at different objectives (25, 26); our main purpose in carrying out both analyses was to compare the results of the two approaches.

Ordinary least-squares regression (which is appropriate provided the variability of the data is similar for different subjects) was used to fit these models for PEF, and logistic regression (with the scale parameter set to the default of 1.0, thereby not incorporating overdispersion) was used to fit these models for the symptom response variables. Serial correlation in the data was not taken explicitly into account when fitting these models at the second stage.

In the third stage of the analysis, the serial correlation in the responses within subjects over days was taken into account to obtain more efficient estimates of regression coefficients and more accurate estimates of the corresponding standard errors. To accomplish this, all models were fit using the generalized estimating equations (GEE) approach (18, 19). The GEE approach is based on "borrowing strength" across the subjects; no attempt is made to model the relationship between the response variable and the predictor variables for individual subjects (a "subject-specific" approach). Rather, the approach models the "population-average" relationship between the response and the predictors, thus yielding estimates of the population-average PM_{10} effects (27–29).

This third stage can be considered an extension of the second stage "fixed effects" analysis, where the serial correlation is accounted for through the use of the GEE approach. However, the GEE approach will only allow a separate intercept for each subject through the use of a fixed offset rather than as a parameter to be estimated from the data. For any particular model fit, the individual offsets used in our

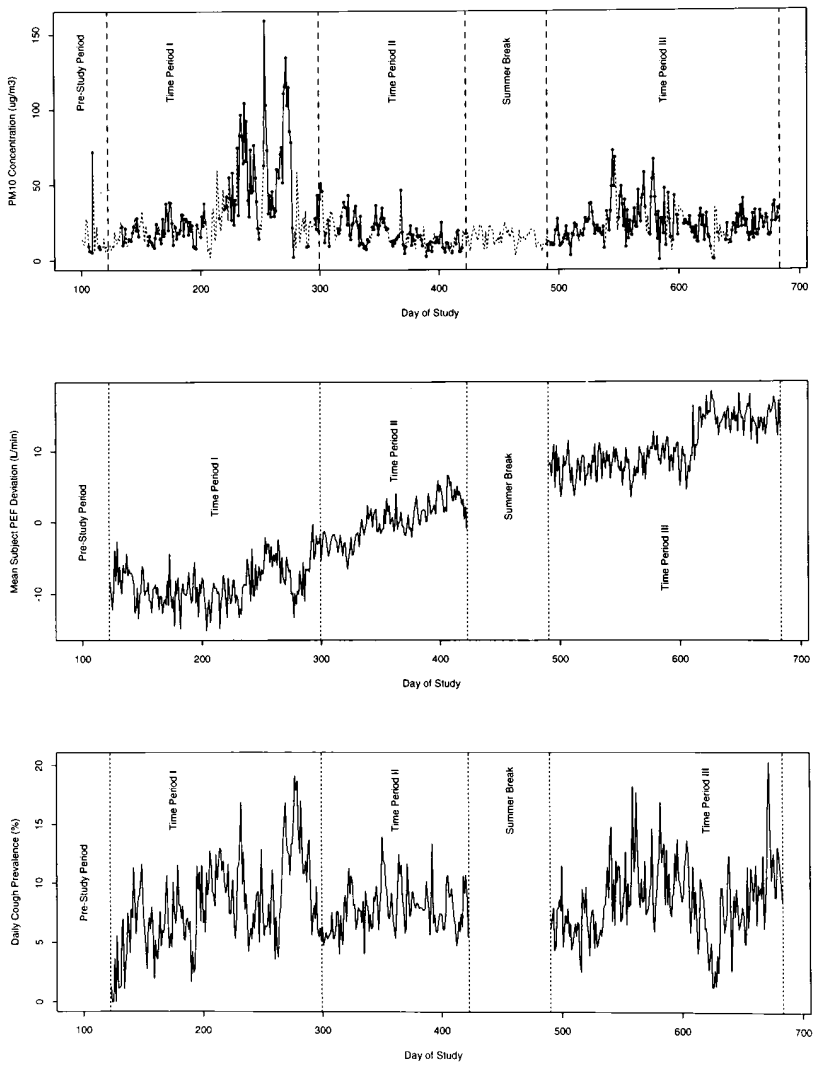

Figure 2. PM_{10} concentrations at the NORTH SITE, mean PEF deviation, and cough prevalence over the study period. *Dots* on the PM_{10} graph are actual measurements; *dotted lines* are estimates based on the EM algorithm (*see* METHODS: Analysis). *See* RESULTS (Health Outcomes) for definition of mean PEF deviation.

implementation of the GEE approach were the estimated intercepts from the corresponding second stage fixed effects model fit.

The GEE approach accounts for the correlation structure in the data through a specified working correlation model. These correlations are estimated from the data, and estimates of regression coefficients are then iteratively updated taking this correlation into account. As part of its outputs, the GEE approach provides robust estimates of the standard errors of the regression coefficients, which are asymptotically (as the number of subjects increases) valid irrespective of the working correlation used in the analysis and the actual correlation structure of the data.

In practice, the true correlation structure for the repeated observations over time within a subject is rarely known. The GEE approach therefore has strong appeal because it does not require the working correlation model to be correctly specified. Even the simplest working assumption—that the repeated observations over time within a subject are uncorrelated, which corresponds to choosing an independence working correlation model—allows asymptotically valid inferences. But this choice will be less efficient than alternate choices that more accurately reflect the true correlation structure over time. The GEE approach allows any knowledge about the true correlation structure to be incorporated into the estimation process through the specification of a working correlation model expected to be close to the true correlation structure. Sensitivity of the conclusions to the choice of working correlation model can be examined, and residual analyses can provide guidance as to the most appropriate choice. The GEE analyses reported here were carried out with either a working independence correlation model (the IND case) or a working first-order autocorrelation model (the AR1 case).

Implementation of the GEE approach is not always straightforward. Available public domain software is quite inefficient in the present context where there are a large number of observations over time for each subject. Furthermore, such software has very limited capacity to handle arbitrary patterns of missing data. To overcome these limitations, a customized version of GEE code was constructed that explicitly incorporated the pattern of missing data for each subject. Explicit formulas for the inverses of the working correlation matrices, appropriately taking into account the patterns of missing data, were also incorporated, thereby dramatically enhancing the computational efficiency of the iterative algorithm leading to the GEE estimates of the regression coefficients.

RESULTS

Participation

From the initial cross-sectional study, 127 children were identified with a physician's diagnosis of current asthma (ASTHMA),

TABLE 1

PERCENT PARTICIPATION, DEMOGRAPHIC DATA, SYMPTOM REPORTING (PERCENTAGE OF SUBJECT-STUDY DAYS), AND PEF VARIABILITY IN THE PARTICIPATING SAMPLE CLASSIFIED BY GROUP*

	Sample Groups			
	ASTHMA	EIF	OBSTRUCT	CONTROL
Subjects, n	75	57	18	56
Participation, %	59	56	62	36
Age, mean yr (SD)	10.3 (1.9)	10.4 (1.8)	11.0 (1.8)	10.3 (2.0)
Male, %	59	46	44	39
White, %	83	75	78	96
Cough, %	8.6	5.6	13.9	9.0
Phlegm, %	3.9	3.7	11.6	5.2
Eye symptoms, %	2.2	0.6	0.6	1.4
Nose symptoms, %	11.0	9.0	8.7	10.3
Sore throat, %	4.1	3.3	6.0	5.0
Wheeze, %	3.8	0.9	1.7	1.5
Chest tightness, %	3.2	0.8	0.6	0.9
Dyspnea, %	4.5	2.4	1.8	1.8
PEF variability, L/min				
Diurnal, mean (SD)	19.5 (9.6)	16.8 (7.9)	19.1 (10.4)	15.2 (8.9)
Day-to-day, mean (SD)	24.1 (9.6)	19.2 (7.3)	19.0 (9.0)	18.1 (6.9)

Definition of abbreviations: ASTHMA = doctor's diagnosis of asthma; EIF = no ASTHMA, but exercise-induced fall in FEV_1; OBSTRUCT = no ASTHMA or EIF, but $FEV_1/FVC < 0.76$; CONTROL = none of the above.

* *See* METHODS for definition of symptoms and RESULTS (Health Outcomes) for definitions of PEF variability.

101 with a significant exercise-induced fall in FEV_1 who did not have a diagnosis of asthma (EIF), and another 29 with evidence of airway obstruction without a diagnosis of asthma or an exercise-induced fall in FEV_1 (OBSTRUCT). A total of 157 control students were identified. Of the 213 children for whom agreement to participate was obtained, 208 provided useable PEF and diary data. Two of these children were not included in the analyses because of concerns regarding the validity of their PEF records, leaving a total of 206 children for analysis. The participation rates for the three "case" groups was higher than that of the CONTROL group (Table 1), with 75 children in the ASTHMA group, 57 children in the EIF group, 18 children in the OBSTRUCT group, and 56 children in the CONTROL group being included in the analysis. An average of 84% of the children remaining in the study provided data on any given day. The age distribution was similar in the four groups of children (Table 1), but the ASTHMA group included relatively more male children and the CONTROL group included relatively more white children.

Subjects were recruited into the follow-up study over time (Figure 3). Also shown in Figure 3 is that participation fell off after the summer break in 1991. The first children in the three "case" groups began contributing data in May 1990; the group of CONTROL children did not begin contributing data until January 1991. Because the PM_{10} data were not regularly collected until September 1990, data were analyzed beginning on September 1, 1990 (Day 124) and ending on March 13, 1991 (Day 683). This period of 560 days will be referred to as the study period. Because no response data were collected during the 1991 summer break, the data from Day 423 to Day 490 were excluded, leaving 492 d with response data to be analyzed during the study period.

Health Outcomes

The distributions of symptom reporting and PEF variability during the study period were compared across the four groups of children. Diurnal PEF variability for each child was defined as the mean of the absolute daily differences in the daily maximal morning and evening values. Day-to-day PEF variability for each child was defined as the standard deviation of the residuals from a linear regression for each child of daily PEF value on day-of-study. Diurnal PEF variability was higher in the ASTHMA and OBSTRUCT groups than in either the EIF group or the CONTROL group (Table 1). Day-to-day PEF variability was higher in the ASTHMA group than in all of the other three groups. The percentage of subject-study days in which a symptom was reported was higher for wheeze, chest tightness, dyspnea, and eye symptoms in the ASTHMA group than in the other three groups, but it was not higher for cough or for any of the other symptoms (Table 1).

For purposes of illustration, each child's mean PEF during the study period, and the difference between each child's PEF value for each day and their mean PEF (the daily PEF deviation), were calculated. The mean of these daily deviations for each day for all children contributing data on that day is shown in Figure 2. The gradual increase reflects the growth of children over the study period. Also shown in Figure 2 is the prevalence of one of the symptom outcomes, reported cough, for each day of the study period for the children contributing data on that day. There was considerable day-to-day variability in both PEF and cough.

PM_{10} Concentrations and Meteorological Conditions

During the study period, of the 492 d in which response data were collected, PM_{10} measurements were available for 377 d (77%) at both the NORTH and SOUTH sites: PM_{10} was available at both sites on 326 d and at neither site on 64 d. The observed PM_{10} concentrations for the study period ranged from 0 to 159 $\mu g/m^3$ at the NORTH SITE, with the highest concentrations observed during the winter of 1990 (Figure 2 and Table 2); measured concentrations were lower at the SOUTH SITE. As described in METHODS, missing PM_{10} data were estimated from the EM algorithm. Meteorological data are also presented in Table 2.

The quality of the PM_{10} data from the SOUTH SITE was questioned after inspecting correlations between the measured log PM_{10} concentrations and log daily particle counts at both sites, as well as their respective correlations with the meteorological data. At the NORTH SITE, correlations between the PM_{10} concentrations and particle counts in the 0.7 to 1 μm and 1 to 5 μm ranges were 0.75 and 0.78, respectively, whereas at the SOUTH SITE these were 0.34 and 0.36, respectively. The particle counts at the SOUTH SITE correlated better with PM_{10} concentrations at the NORTH SITE than with PM_{10} concentrations at the SOUTH SITE. Also, the correlation between PM_{10} and daily temperature was $-0.43°$ C at the NORTH SITE, but only $-0.09°$ C at the SOUTH SITE. Although no technical reasons could be identified for the apparent poor quality of the SOUTH SITE PM_{10} measurements, it was elected to use only the NORTH SITE PM_{10} data to reflect the entire community's exposure. Because the proportion of the population residing to the south of the SOUTH SITE was relatively small, given the lower housing density in the southern part of the community, most of the population's exposure would have been better estimated by the NORTH SITE monitor, even if there had been no concerns about the quality of the SOUTH SITE measurements.

Health Outcomes and PM_{10}

The first-stage (exploratory) analysis of the same-day associations between the health outcomes and PM_{10}, before any adjustment for temporal or meteorological variables, showed associations in the hypothesized directions for PM_{10} with PEF,

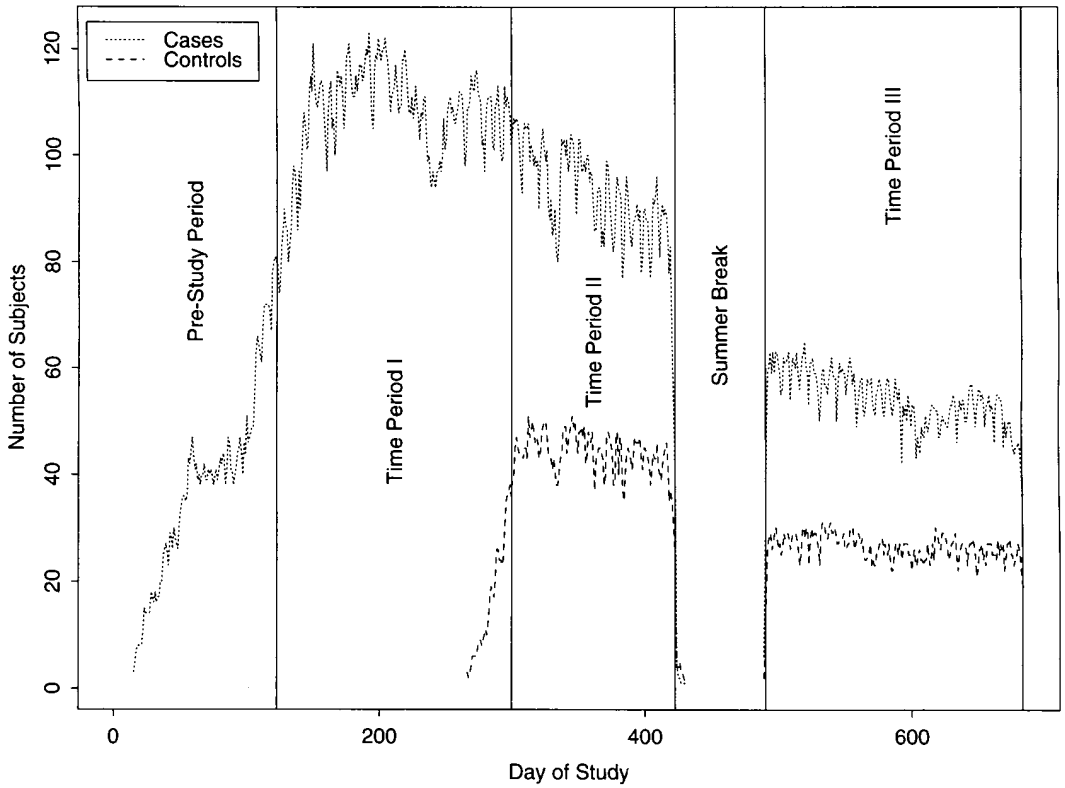

Figure 3. Recruitment of children into the study was incremental. The CONTROL group began contributing data on Day 266. "Cases" refers to the ASTHMA, EIF, and OBSTRUCT groups of children (*see* METHODS). The time periods refer to the periods used for the stratified analyses (*see* RESULTS: Comparison of Asthmatic and Nonasthmatic Children). After the summer of 1991, the participation rate decreased substantially for all groups.

cough, nose symptoms, and throat soreness (Table 3). Analyses of symptoms grouped into sets (*see* METHODS) showed associations for Sets 1 (cough or phlegm), 2 (eye, nose, or throat symptoms) and 4 (any symptom), but not for Set 3 (wheeze, dyspnea, or chest tightness). Adjustment for a linear trend (time) over the study period did not influence the associations substantially, except for PEF for which the size of the regression coefficient was halved (Table 3). The decrease in the estimated standard error of the PEF coefficient with the adjustment for this linear trend resulted from the control of PEF "growth" over the study period (Figure 2). The statistical significance of the association between PM_{10} and PEF was greatly weakened with additional adjustment for the meteorological variables (temperature, humidity, and precipitation). This was true to a lesser extent for cough and symptom Set 1.

TABLE 2

DAILY AVERAGE PM_{10} CONCENTRATION, TEMPERATURE, HUMIDITY, AND PRECIPITATION FOR THE STUDY PERIOD*

		Percentile			
	Minimum	10th	50th	90th	Maximum
North Site PM_{10}, $\mu g/m^3$	0.2	9.7	22.1	48.6	159.0
South Site PM_{10}, $\mu g/m^3$	0.5	6.4	16.1	30.0	66.5
Temperature, ° C	−8.4	1.1	7.2	15.5	20.2
Humidity, %	30.0	66.2	85.8	95.4	97.9
Precipitation, mm†	0.0	0.0	0.2	21.0	102.0

* Based on actually measured values only.
† 234 of the 492 study days (48%) had no precipitation.

Finally, with additional adjustments for day-of-the-week and month (periodicity), the same-day associations with cough, nose symptoms, and sore throat, and symptom Sets 1, 2, and 4 persisted (Table 3). Results of all subsequent analyses presented, including the second and third stage analyses, are based on models that include all of the time-varying covariates (linear time trend, meteorology, and periodicity).

Analyses were performed for PM_{10} concentrations on individual days preceding the health outcomes (the lagged analysis). Associations were observed with PEF and with cough, phlegm, and throat soreness for most of the lagged associations for as long as 7 d. The strongest associations tended to be at lags of 2, 3, and 4 d. Examination of the effects of individual lags for as long as 15 d showed some strong effects on PEF and some of the symptoms for the 12- to 14-d lags as well.

Results of the second-stage analysis for the same-day effects with the fixed effects approach were similar to those of the first stage analysis with the regression coefficients being similar to those presented for the first stage analysis (Table 3) and the standard errors from this individual subject-based analysis being slightly larger than in the first-stage analysis. The impact of the random effects analysis in the second stage was to further increase the size of the estimated standard errors for every outcome such that no same-day PM_{10} effects were statistically significant ($p < 0.05$) in the random effects analysis. Results of individual day lag analysis with the fixed effects models for days lagged from 1 to 7 d before the health outcome were also similar to those of the first-stage analysis. Again, the impact of the random effects models was largely to increase the size of the standard errors such that only the ef-

TABLE 3

ESTIMATED EFFECTS*—REGRESSION COEFFICIENT (STANDARD ERROR)—OF AN INCREASE IN PM_{10} CONCENTRATION ON SAME-DAY PEF AND SYMPTOMS: IMPACT OF CONTROL FOR TIME-VARYING COVARIATES†

		Covariates		
Outcome‡	No Covariates	Time	Time + Meteorology	Time + Meteorology + Periodicity
PEF	−1.63 (0.57)‖	−0.76 (0.17)‖	−0.26 (0.18)	−0.18 (0.17)
Cough	0.09 (0.02)‖	0.10 (0.02)‖	0.06 (0.03)§	0.07 (0.03)§
Phlegm	0.02 (0.03)	0.02 (0.03)	0.01 (0.03)	0.05 (0.04)
Eye symptoms	−0.06 (0.05)	−0.05 (0.05)	0.01 (0.06)	0.02 (0.07)
Nose symptoms	0.06 (0.02)‖	0.07 (0.02)‖	0.08 (0.03)‖	0.06 (0.03)§
Sore throat	0.07 (0.03)§	0.09 (0.03)‖	0.10 (0.04)§	0.10 (0.04)§
Wheeze	0.03 (0.04)	0.05 (0.04)	0.07 (0.05)	−0.03 (0.05)
Chest tightness	0.05 (0.05)	0.07 (0.05)	0.11 (0.06)§	0.05 (0.06)
Dyspnea	0.00 (0.04)	0.01 (0.04)	0.05 (0.04)	−0.00 (0.05)
Set 1	0.09 (0.02)‖	0.09 (0.02)‖	0.05 (0.02)§	0.06 (0.03)§
Set 2	0.05 (0.02)‖	0.06 (0.02)‖	0.07 (0.02)‖	0.06 (0.02)‖
Set 3	0.02 (0.03)	0.03 (0.03)	0.07 (0.04)§	−0.01 (0.04)
Set 4	0.06 (0.02)‖	0.06 (0.02)‖	0.06 (0.02)‖	0.04 (0.02)§

* Based on the first-stage analysis (*see* METHODS).

† "Time" is a number corresponding to the study day; "Meteorology" includes daily mean temperature, humidity, and precipitation (*see* METHODS); "Periodicity" includes variables for day of the week and month of study.

‡ *See* METHODS for definition of symptoms: Set 1 = cough or phlegm; Set 2 = eye, nose, or throat symptoms; Set 3 = wheeze, chest tightness, or dyspnea; Set 4 = any respiratory symptom.

§ $0.01 \leq p < 0.05$.

‖ $p < 0.01$.

fects on cough and symptom Set 1 at most of the day lags were statistically significant in the random effects analysis.

To provide guidance for the definitive analysis to be carried out at the third stage, the residuals from the second stage fits (least-squares residuals for the PEF data and deviance residuals for the symptom data) were subjected to a detailed diagnostic investigation. No major difficulties were identified with respect to homogeneity (across individuals) of variances and dispersion, systematic departures from the presumed linear form of fitted relationships, outlying data values, or highly influential points. Beyond these aspects, the feature of main interest was the strength of the serial correlation in these residuals. For any particular fit, autocorrelations were evaluated for each subject separately. Consistent with the results of the first stage analyses, the fits based on same-day pollution clearly indicated positive serial correlation at several of the low lags (the average Lag 1 autocorrelation, which was always the strongest, was around 0.5 for PEF and between 0.3 and 0.6 for the different symptoms). The corresponding partial autocorrelations suggested a third-order autoregressive structure for the PEF data (although the Lag 1 partial autocorrelation was substantially stronger than those at Lags 2 and 3) and a first-order autoregressive structure for each of the symptom responses. In particular, this indicated that the GEE analyses to be carried out as the definitive third-stage analyses would be more efficient if based on an autoregressive rather than on an independence, working correlation structure.

The third-stage (GEE) analysis accounted for the serial correlation in the data using either an independence (IND) or a first-order autoregressive (AR1) working correlation model. After adjusting for all of the time-varying covariates included in the previous analyses, same-day PM_{10} was associated with cough, nose symptoms, and sore throat, and with symptom Sets 1 (cough or phlegm) and 2 (eye, nose, or throat symptoms) with an IND working correlation model (statistically significant only for cough and the symptom sets). With the AR1 working correlation model, all of these associations with same-day PM_{10} were substantially weakened, and none were statistically significant. Differences between the IND and AR1 fits were also observed in the individual day lag analyses. For the IND fits, associations between PM_{10} and PEF were observed at lags of 2 and 4 d, and at several of the day lags for as long as 7 d for cough, phlegm, sore throat, and symptom Set 1; associations with symptom Sets 2 and 4 (any symptom) were observed at lags of 1 and 2 d, respectively. For the AR1 fits, the associations with PEF at lags of 2 and 4 d were similar, but associations with cough, phlegm, sore throat, and symptom Set 1 were observed at only a few of the day lags. Other associations with individual symptoms and symptom sets for the IND and AR1 fits were observed for the rare individual day lag, sometimes in the nonhypothesized direction.

A 1- to 4-d cumulative lag effect (*see* Analysis in METHODS) appeared to be a reasonable choice for the final form of the PM_{10} effect to be fitted to all of the outcomes for the following reasons: (*1*) as detailed above, for most of the health responses, no same-day PM_{10} effects were observed, and the statistical significance of PM_{10} effects tended to weaken for individual day lags beyond 4 d; (*2*) the same-day effect for PEF was based in part on PEF measurements made on the morning of the same day in which PM_{10} was measured (hence, many of the PEF measurements would have preceded the PM_{10} measurement); (*3*) previous studies have found similar lagged effects (*4*). Comparison of the three models that included either same-day and individual lags 1, 2, 3, and 4 effects, same-day and a 1- to 4-d cumulative lag effect, or a 1- to 4-d cumulative lag effect only, also indicated that the 1- to 4-d cumulative lag effect provided an adequate summary of the short-term effects of PM_{10} on the health responses. The 1- to 4-d cumulative lag PM_{10} regression coefficients estimated by the GEE approach with an AR1 working correlation model are shown in Table 4; the estimated effects for a 10 $\mu g/m^3$ PM_{10} concentration increase above the observed mean daily PM_{10} concentration of 27.3 $\mu g/m^3$ are also tabulated. For the models including only a 1- to 4-d cumulative lag PM_{10} effect, reduced PEF and increases in several symptoms (particularly cough, phlegm,

TABLE 4

ESTIMATED EFFECTS (AND REGRESSION COEFFICIENTS FROM FITTED MODEL*) OF AN INCREASE IN PM_{10} CONCENTRATION ON PEF (L/min) AND SYMPTOMS (ODDS RATIO) IN THE ENTIRE SAMPLE OF CHILDREN

	Effect		Regression Coefficient	
Outcome	Estimate†	95% CI	Estimate	SE
PEF	−0.27	−0.54–−0.01	−0.880	0.426
Cough	1.07	1.02–1.11	0.202	0.066
Phlegm	1.07	1.00–1.13	0.202	0.095
Eye symptoms	1.05	0.97–1.13	0.144	0.123
Nose symptoms	1.04	1.00–1.08	0.110	0.062
Throat soreness	1.06	1.01–1.11	0.184	0.083
Wheeze	1.03	0.96–1.10	0.090	0.111
Chest tightness	1.06	0.97–1.16	0.198	0.147
Dyspnea	1.01	0.94–1.08	0.027	0.108
Cough/phlegm	1.06	1.02–1.10	0.188	0.058
Eye/nose/throat	1.03	0.99–1.06	0.091	0.056
Wheeze/tight/dyspnea	1.02	0.96–1.08	0.066	0.094
Any symptom	1.03	1.00–1.06	0.092	0.049

* Using third-stage (GEE) analysis for AR1 working correlation model (*see* METHODS: Analysis).

† Estimated for a 10 $\mu g/m^3$ increase above the mean daily PM_{10} concentration of 27.3 $\mu g/m^3$, using a 1- to 4-d cumulative lag PM_{10}.

sore throat, and symptom Set 1) were associated with an increase in PM_{10} concentration in the entire sample of children.

Comparison of Asthmatic and Nonasthmatic Children

Up to this point no account has been taken of the study sampling design in which children were selected based on criteria for inclusion into the ASTHMA, EIF, OBSTRUCT, or CONTROL groups (*see* METHODS). Children in the OBSTRUCT group were not included in the following analyses because of the small size of this group (n = 18). Also, although CONTROL children began providing data on Day 266, recruitment of the full group of CONTROL children was completed around March 1991 (study Day 300). The analysis therefore was carried out separately for each of three time periods: Period I from September 1990 to March 1991 (Day 124 to Day 299), Period II from March to June 1991 (Day 300 to Day 422), and Period III from September 1991 to March 1992 (Day 491 to Day 683). Therefore, no CONTROL children were included in the analysis for time Period 1. Time Period III was the period after the 1991 summer break when the number of children participating in the study had decreased considerably (Figure 3). Also, with this stratification into time periods, some children contributed only a few days of data in a given time period; children contributing 10 or fewer days of data to a given time period were not included in the analyses for that time period. The resulting number of children contributing data in the ASTHMA, EIF, and CONTROL groups, respectively, were: 75, 56, and 0 for time Period I; 61, 42, and 55 for time Period II; and 36, 25, and 32 for time Period III. To correspond to the results presented in Table 4, all of the results presented for this analysis by group and time period are based on the third-stage (GEE) analyses using an AR1 working correlation model and a 1- to 4-d cumulative lag PM_{10} effect.

For time Period I, an association between PM_{10} and PEF was observed only in the ASTHMA group (Figure 4). For time Period II, the PM_{10} coefficient for PEF in the ASTHMA group was almost identical to that for time Period I, but it was not statistically significant, whereas the estimate of effect in the EIF group was similar to that for the ASTHMA group, and also nonsignificant. The CONTROL group showed no association between PM_{10} and PEF in time Period II. For time Period III, when the number of children contributing data had fallen substantially, the only association observed between PM_{10} and PEF was an association in the nonhypothesized direction for the CONTROL group.

For cough, consistent associations with PM_{10} across time periods were observed only in the ASTHMA group of children (Figure 4). For the remaining symptoms and the symptom sets, no consistent associations were observed for any group. A few of these effects were statistically significant for the ASTHMA group, but there was no consistency across time period. Some of the rare statistically significant effect estimates for the EIF or CONTROL groups, most notably the highly significant estimate for eye symptoms for the CONTROL group in time Period III ($p < 0.001$), were in the nonhypothesized direction.

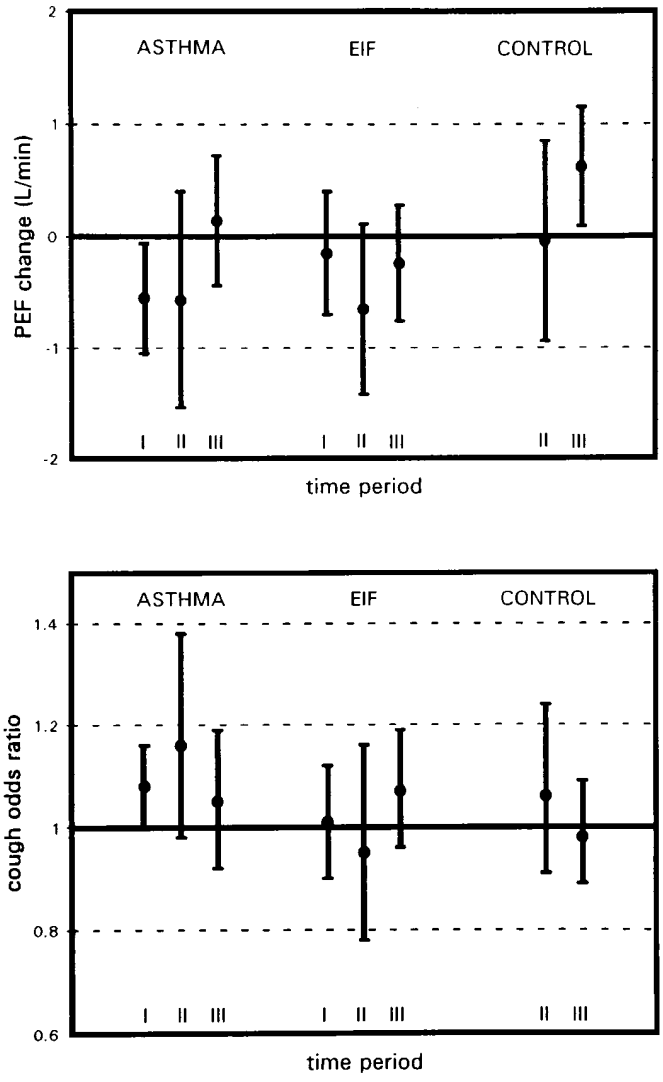

Figure 4. Estimated effects of an increase in PM_{10} concentration on PEF and cough stratified by child groups (ASTHMA, EIF, CONTROL) and time periods (I, II, III). Effects are calculated for a 10-$\mu g/m^3$ increase in the 1- to 4-d cumulative lag PM_{10} above the mean daily PM_{10} concentration of 27.3 $\mu g/m^3$ using the coefficients estimated in the third-stage (GEE) analysis with the AR1 working correlation model (*see* METHODS). CONTROL children did not contribute data in time period I. Relatively fewer children contributed data during time period III (*see* Figure 3). The smaller group of children in the OBSTRUCT group were not included in this stratified analysis.

DISCUSSION

In this population-based study of school children, short-term increases in PM_{10} concentrations were associated with reductions in the level of PEF and increased reporting of cough, phlegm production, and sore throat. In the examination of the subgroups of children, the meaningful associations were largely limited to the subgroup of children with a reported physician's diagnosis of asthma. The findings add to the already large number of studies on the adverse health effects associated with particulate air pollution (30, 31). In particular, they provide insight into subgroup susceptibility to the less adverse effects of inhalable particles. The study also provides some insight into the sensitivity of the findings to the statistical methods used in analyzing the data.

It would seem reasonable to expect that asthmatic children might be more susceptible to the adverse effects of particulate air pollution as a result of sensitivity to either the irritant or inflammatory effects of inhaled particles. The associations for PEF and cough within the subgroup of children with physician-diagnosed asthma were reasonably consistent. Interestingly, the other symptoms that might indicate worsening of asthma such as wheeze, chest tightness, or dyspnea did not

show consistent associations with PM_{10} in the asthmatic children. This may merely reflect the higher daily prevalence of cough compared with these other symptoms. Although some associations within the subgroup with exercise-induced fall in FEV_1 were observed, there was little consistency, with some significant effects being observed in only one time period, and other effects being in the nonhypothesized direction. For the control group of children, who had no physician's diagnosis of asthma, no exercise-induced bronchospasm, and no baseline airway obstruction, there was no consistent evidence for adverse effects associated with increases in ambient PM_{10} concentrations.

In stratifying our analysis by time period and groups of children we unavoidably reduced our statistical power and the consequent ability to detect statistically significant associations within specific strata. Therefore, although the associations observed for the asthmatic children were reasonably consistent, they were not always statistically significant. In addition, for time Period III we observed estimates of effect that were inconsistent and sometimes opposite in direction to those hypothesized. The children who remained in the study after the final summer were a selected subset of an already somewhat selected sample, recalling the initial participation rates. We have no explanation for the counter-intuitive findings in the control children for Period III, other than to note that our power for that period was lower than for the first two periods, and that the dynamics influencing the children to continue participating in the study at that stage were largely unknown and may have resulted in an unusual group of children supplying data during that final period.

Stratification by time period allowed a comparison of effect estimates for a period with modest PM_{10} concentrations (Period I) and a period with low PM_{10} concentrations (Period II), corresponding to the first fall and winter seasons of the study and the first spring season, respectively (Figure 2). The effect estimates for PEF were essentially identical for asthmatic children in the two time periods, although their standard errors differed. In Period II the highest measured PM_{10} concentration was 50 $\mu g/m^3$, which suggests that the effects of particle exposures occur at even lower concentrations. When the few days with PM_{10} concentrations above 40 $\mu g/m^3$ were excluded from the analysis, no meaningful change in this effect estimate was observed, suggesting that similar effects were observed even at concentrations below 40 $\mu g/m^3$.

The degree of rigor of the statistical analyses had a substantial effect on the size of both the effect estimates and their standard errors. In general, as expected, substantial reduction in the effect estimates was observed with the successive addition of time-varying covariates to the models, especially with the addition of the meteorological variables. But, with the exception of the inclusion of a linear time trend for PEF, the addition of the time-varying covariates had only modest effects on the standard errors of the effect estimates. Accounting for serial correlation also had a substantial effect, as was apparent when comparing the assessed significance of estimates based on the fixed effects models (second stage), in which no attempt was made to account for serial correlation, and the GEE models (third stage), whose estimates are asymptotically valid regardless of the true correlation structure in the data. In the present context where the response data are positively serially correlated, ignoring the serial correlation leads to underestimation of the standard errors of the effect estimates, thereby potentially resulting in unjustified claims of significance; our rationale for using the GEE approach was to avoid this difficulty. Interestingly, although the primary impact of specification of a better working correlation model (i.e., AR1 rather than IND), as expected, was to improve the efficiency of the GEE estimates (that is, to produce effect estimates with smaller standard errors), substantial differences were occasionally seen in the effect estimates obtained with the IND and AR1 fits.

No attempt was made to validate either the diary symptom reporting or the PEF measurements. The nurse research assistant checked the diary reports and PEF records from each child every 2 wk in order to attempt to detect unusual patterns of response. Some assurance that these outcome measures reflected the outcomes of interest is provided by the observed variation in the measures across the sampled groups of children. As expected, asthmatic children had greater variability in PEF both over a day and from day to day, although children in the OBSTRUCT group also had high diurnal PEF variability (Table 2). In addition, increased reporting of wheeze, chest tightness, dyspnea, and eye symptoms was seen in the asthmatic group of children. No differences across the groups were observed for either cough or phlegm production or for the nose or throat symptoms.

Lagged associations between the health outcome measures and PM_{10} concentrations were in the hypothesized directions and were of considerable strength in the range from 1 d to 1 wk. This suggests that the effect is other than an acute irritant effect of particle exposure, and it raises the possibility that particle exposure has an inflammatory effect. The estimated size of the cough effect for the entire sample of children for a 10 $\mu g/m^3$ increase in PM_{10} concentration was larger than that estimated from a group of similar studies (7 versus 1%, respectively) (30), although even larger effects have been observed (4). The effect on PEF, however, was approximately 0.1%, which was similar to that estimated from a similar group of studies (30). We also observed some significant associations for individual lags as long as 2 wk, which persisted after adjustment for shorter term lags. Although others have also observed lagged effects as long as these (32–34), plausible explanations are lacking.

This study has several potential advantages compared with other similarly designed studies. First, given the relatively small geographic area in which all of the children's schools and residences were located, the PM_{10} monitoring site should have provided a good estimate of the relevant ambient concentrations relative to studies in which a single monitoring site was used to reflect concentrations over a large urban area. This should have the effect of reducing misclassification of the ambient particle exposure. Nevertheless, misclassification of overall particle exposure must also have been present in this study, given the importance of indoor particle concentrations in determining total particle exposure; for longitudinal studies of individual subjects, however, such misclassification may be less significant than for cross-sectional studies (35). Second, in spite of a kraft pulp mill being the main source of particulate pollution in this study community, pilot data showed only low concentrations of sulfur-related compounds such as methyl mercaptan, hydrogen sulfide, and sulfur dioxide. Similarly, concentrations of ozone and acid aerosol are very low in this community. Therefore, confounding of the PM_{10} associations by other air pollutants is unlikely. Confounding by meteorological conditions also seems unlikely given the control for temperature, humidity, and precipitation in the analyses. Third, as a population-based study, estimated effects from this population sample should be generalizable to other community settings. This is particularly valuable when attempts are made to estimate impacts of particle pollution exposure for a community.

Some care should nevertheless be taken in interpreting the findings of this study. Although one might suspect that having data on individual subjects avoids the potential weaknesses of

an ecologic type of study design in which data are not available at the level of individuals, this is not necessarily the case. For a longitudinal study of daily responses such as this, it would be necessary to have individual data on covariates on a daily basis in order to attempt to avoid biases caused by unmeasured changes in covariates over time. For example, exposure to environmental tobacco smoke might produce the outcomes of interest in our study. If this exposure varied over time and was associated somehow with ambient particle concentrations (for example, with closing of windows during periods of high particle pollution), confounding of our associations of interest could occur. Because we have no information on daily environmental tobacco smoke exposure or other similar exposures, this study is still potentially susceptible to the biases that can affect any ecologic study.

References

1. Pope, C. A., D. W. Dockery, J. D. Spengler, and M. Raizenne. 1991. Respiratory health and PM_{10}: a daily time-series analysis. *Am. Rev. Respir. Dis.* 46:90–97.
2. Ostro, B., M. J. Lipsett, M. B. Wiener, and J. C. Selner. 1991. Asthmatic responses to airborne acid aerosols. *Am. J. Public Health* 81:694–702.
3. Pope, C. A., and D. W. Dockery. 1992. Acute health effects of PM_{10} pollution of symptomatic and asymptomatic children. *Am. Rev. Respir. Dis.* 145:1123–1128.
4. Schwartz, J., D. W. Dockery, L. M. Neas, D. Sypij, J. H. Ware, J. D. Spengler, P. Koutrakis, F. E. Speizer, and B. G. Ferris, Jr. 1994. Acute effects of summer air pollution on respiratory symptom reporting in children. *Am. J. Respir. Crit. Care Med.* 150:1234–1242.
5. Neas, L. M., D. W. Dockery, P. Koutrakis, D. J. Tollerud, and F. E. Speizer. 1995. The associations of ambient air pollution with twice daily peak expiratory flow rate measurements in children. *Am. J. Epidemiol.* 141:111–122.
6. Schwartz, J., D. Slater, T. V. Larson, W. E. Pierson, and J. Q. Koenig. 1993. Particulate air pollution and hospital emergency room visits for asthma in Seattle. *Am. Rev. Respir. Dis.* 147:826–831.
7. Sunyer, J., M. Saez, C. Murillo, J. Castellsague, F. Martinez, and J. M. Anto. 1993. Air pollution and emergency room admissions for chronic obstructive pulmonary disease: a 5-year study. *Am. J. Epidemiol.* 137: 701–705.
8. Schwartz, J. 1994. Air pollution and hospital admissions for the elderly in Birmingham, Alabama. *Am. J. Epidemiol.* 139:589–599.
9. Schwartz, J. 1994. PM_{10}, ozone and hospital admissions for the elderly in Minneapolis-St. Paul. *Arch. Environ. Res.* 49:366–373.
10. Thurston, G. D., K. Ito, C. G. Hayes, D. V. Bates, and M. Lippmann. 1994. Respiratory hospital admission and summertime haze air pollution in Toronto, Ontario: consideration of the role of acid aerosols. *Environ. Res.* 65:271–290.
11. Burnett, R. T., R. Dales, D. Krewski, R. Vincent, T. Dann, and J. F. Brook. 1995. Associations between ambient particulate sulfate and admissions to Ontario hospitals for cardiac and respiratory disease. *Am. J. Epidemiol.* 142:15–22.
12. Fairley, D. 1990. The relationship of daily mortality to suspended particulates in Santa Clara County, 1980–1986. *Environ. Health Perspect.* 89:159–168.
13. Pope, C. A., J. Schwartz, and M. R. Ransom. 1992. Daily mortality and PM_{10} pollution in Utah Valley. *Arch. Environ. Res.* 47:211–217.
14. Schwartz, J., and D. W. Dockery. 1992. Increased mortality in Philadelphia associated with daily air pollution concentrations. *Am. Rev. Respir. Dis.* 145:600–604.
15. Schwartz, J. 1993. Air pollution and daily mortality in Birmingham, Alabama. *Am. J. Epidemiol.* 137:1136–1147.
16. Kinney, P. L., and H. Ozkaynak. 1991. Associations of daily mortality and air pollution in Los Angeles county. *Environ. Res.* 54:99–120.
17. Laird, N. M. 1988. Missing data in longitudinal studies. *Stat. Med.* 7:305–315.
18. Liang, K. Y., and S. L. Zeger. 1986. Longitudinal data analysis using generalized linear models. *Biometrika* 73:13–22.
19. Zeger, S. L., and K. Y. Liang. 1986. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* 42:121–130.
20. Vedal, S., J. Blair, and B. Manna. 1991. Adverse respiratory health effects of ambient inhalable particle exposure. Paper no. 91-180.56. *Air Waste Manage. Assoc.* 1–16.
21. Ferris, B. G., Jr. 1978. Epidemiology Standardization Project. *Am. Rev. Respir. Dis.* 118(6 Part 2):36–47.
22. Dempster, A. P., N. M. Laird, and D. B. Rubin. 1977. Maximum likelihood from incomplete data via the EM algorithm (with discussion). Series B 39. *J. Royal Stat. Soc.* 1–38.
23. Korn, E. L., and A. S. Whittemore. 1979. Methods for analyzing panel studies of acute health effects of air pollution. *Biometrics* 35:795–802.
24. Gumpertz, M., and S. G. Pantula. 1989. A simple approach to inference in random coefficient models. *Am. Stat.* 43:203–210.
25. Laird, N. M., and J. H. Ware. 1982. Random effects models for longitudinal data. *Biometrics* 38:963–974.
26. Gibbons, R. D., D. Hedeker, I. Elkin, C. Waternaux, H. C. Kraemer, J. B. Greenhouse, M. T. Shea, S. D. Imber, S. M. Sotsky, and J. T. Watkins. 1993. Some conceptual and statistical issues in analysis of longitudinal psychiatric data. *Arch. Gen. Psychiatry* 50:739–750.
27. Zeger, S. L., K. Y. Liang, and P. A. Albert. 1988. Models for longitudinal data: a generalized estimating equation approach. *Biometrics* 44:121–130.
28. Zeger, S. L., and K. Y. Liang. 1992. An overview of methods for the analysis of longitudinal data. *Stat. Med.* 11:1825–1839.
29. Liang, K. Y., and S. L. Zeger. 1993. Regression analysis for correlated data. *Annu. Rev. Public Health* 14:43–68.
30. Dockery, D. W., and C. A. Pope. 1994. Acute respiratory effects of particulate air pollution. *Annu. Rev. Public Health* 15:107–132.
31. Pope, C. A., D. W. Dockery, and J. Schwartz. 1995. Review of epidemiologic evidence of health effects of particulate air pollution. *Inhal. Toxicol.* 7:1–18.
32. Dockery, D. W., J. H. Ware, B. G. Ferris, Jr., F. E. Speizer, and N. R. Cook. 1982. Change in pulmonary function in children associated with air pollution episodes. *J. Air Pollut. Control Assoc.* 32:937–942.
33. Ostro, B. E., and S. Rothschild. 1989. Air pollution and acute respiratory morbidity: an observational study of multiple pollutants. *Environ. Res.* 50:238–247.
34. Ransom, M. R., and C. A. Pope. 1992. Elementary school absences and PM_{10} pollution in Utah Valley. *Environ. Res.* 58:204–219.
35. Wallace, L. 1996. Indoor particles: a review. *J. Air Waste Manage. Assoc.* 46:98–126.