

## Pulmonary Function Changes in Children Associated with Fine Particulate Matter

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During winter months many neighborhoods in the Seattle metropolitan area are heavily affected by particulate matter from residential wood burning. A study was conducted to investigate the relationship between fine particulate matter and pulmonary function in young children. The subjects were 326 elementary school children, including 24 asthmatics, who lived in an area with high particulate concentrations predominately from residential wood burning. FEV<sub>1</sub> and FVC were measured before, during and after the 1988-1989 and 1989-1990 winter heating seasons. Fine particulate matter was assessed using a light-scattering instrument. Analysis of the relationship between light scattering and lung function indicated that an increase in particulate air pollution was associated with a decline in asthmatic children's pulmonary function. FEV<sub>1</sub> and FVC in the asthmatic children dropped an average of 34 and 37 ml respectively for each 10<sup>-4</sup> m<sup>-1</sup> increase in  $\sigma_{sp}$ . This  $\sigma_{sp}$  increase corresponds to an increase in PM<sub>2.5</sub> of 20  $\mu\text{g}/\text{m}^3$ . It is concluded that fine particulate matter from wood burning is significantly associated with acute respiratory irritation in young asthmatic children. © 1993 Academic Press, Inc.

### INTRODUCTION

Suspended particulate air pollution is associated with decreased lung function and increased prevalence of respiratory disease symptoms in young children under 12 years of age (Dockery *et al.*, 1982). In this 2-year study of the relationship between pulmonary function changes in third and fourth grade children and air pollutant alerts in Steubenville, Ohio, researchers found a decline in pulmonary function tests associated with increasing 24-hr concentrations of total suspended particulate matter (TSP). Peak values of TSP ranged from 27 to 422  $\mu\text{g}/\text{m}^3$ . The pulmonary function declines were small but persisted for up to 2 weeks. The elimination of children with reported prevalence of coughs, colds, and other respiratory symptoms did not change the estimated mean effect. Similar findings were reported from The Netherlands (Dassen *et al.*, 1986) in a study of children aged 6-11 years before and during an air stagnation episode, although the effects of allergy and chronic respiratory disease were not evaluated. Data reported by Ware and associates (1986) show increased respiratory symptoms in children aged 6 through 9 years when enrolled initially and exposed chronically to elevated levels of particulate matter, as well as sulfur dioxide. Particulate air pollution has been shown to be related to work loss and restricted activity days (Ostro, 1983).

The sources of particulate matter in the above studies were mainly industrial and automotive. Another source of particulate matter is from residential wood burning. Many communities, including Seattle, have geographical areas with high concentrations of fine particulate matter from wood burning during the winter heating season.

Studies in the United States have explored the relationship between wood burning and health. Honicky and co-workers (1985) conducted a survey of 31 children aged 1 to 7 years who lived in homes using wood stoves and 31 children whose homes had no wood stoves. A significant increase in the severity of respiratory symptoms was seen in the exposed children. There was no difference in the prevalence of asthma between the two groups of children. Butterfield *et al.* (1989) also found more respiratory symptoms, especially wheezing, in children aged 1 to 5½ years living in homes with wood stoves. The use of a wood-burning stove was found to be a risk factor for lower respiratory tract infection (bronchiolitis or pneumonia) in American Indian children who were 24 months or younger (Morris *et al.*, 1990). A study of lung function in children carried out in Montana found poorer lung function associated with increased levels of ambient air pollution, mostly total suspended particulate matter (Johnson *et al.*, 1990).

The evidence is not completely consistent. For example, Tuthill (1984) found no association between wood stove usage and symptoms of respiratory disease in children from kindergarten through sixth grade. In Seattle, a questionnaire study suggest that young children aged 1–5 years living in a high wood smoke area had a pattern of more respiratory symptoms and disease than similar children living in a less polluted area nearby (Browning *et al.*, 1990). Although a trend was noted, it was not found to be statistically significant. A limitation of prior research is that none of the above studies provided either indoor or outdoor air monitoring data nor did they evaluate susceptible populations.

In Seattle, due to a combination of residential wood burning and the topography of the city, some areas along creek drainages have quite high concentrations of fine particulate matter on cold, clear nights, whereas nearby areas on adjacent ridges have two to three times lower concentrations. Particulate matter with a diameter less than 10 µm (PM<sub>10</sub>) was measured during three heating seasons in one such residential valley in north Seattle (Larson *et al.*, 1989; Maykut and Larson, 1991). These PM<sub>10</sub> measurements were found to be highly correlated with the local air pollution control agency's estimate of particulate matter using a light-scattering detection device. Source apportionment of the particulate matter showed that more than 80% is produced by wood-burning devices during the nighttime hours (Larson *et al.*, 1992). Furthermore, indoor–outdoor ratios of fine particles are high in residential communities in homes without cigarette smokers. Three studies document such infiltration. Quackenboss and colleagues have reported an indoor/outdoor ratio of 0.63 for PM<sub>10</sub> in homes of nonsmokers in Tucson, and Dockery and Spengler reported a similar ratio of 0.55 for total suspended particulate matter in Steubenville, Ohio. Sexton *et al.* characterized the indoor/outdoor ratio in residences using wood stoves and found indoor–outdoor ratios ranging from 0.50 to 0.70.

In the present study, we conducted repeated spirometric measurements in young children in two residential neighborhoods during two heating seasons. Fine particulate matter was measured as light-scattering coefficient using a nephelometer, an instrument with output that correlates well with PM<sub>2.5</sub> (Waggoner and Weiss, 1980; EPA, 1982). Statistical analysis indicated a strong association between light-scattering coefficient and decline in pulmonary function. Two preliminary reports of these data have been presented (Koenig *et al.*, 1990a,b).

## METHODS

Our study extended over two heating seasons, 1988–1989 and 1989–1990. The

subjects during the first study year were 326 children, including 24 with asthma, from two participating elementary schools drawn from the target area (Fig. 1). During the second study year, only 20 children, all of whom had asthma, were studied. Fourteen of these asthmatics had been studied in Year 1. Consent forms approved by the University of Washington Human Subjects' Committee describing the study were sent home with all third through sixth grade children. Information on parental smoking, the presence of a wood stove in the home, allergy, or asthma was obtained on the consent form. In the first year, all children who returned a signed consent were studied; in Year 2, only asthmatics were studied. Questionnaires were sent to nonparticipants to determine whether they differed as a group from participants.

Spirometry was conducted according to the 1987 American Thoracic Society

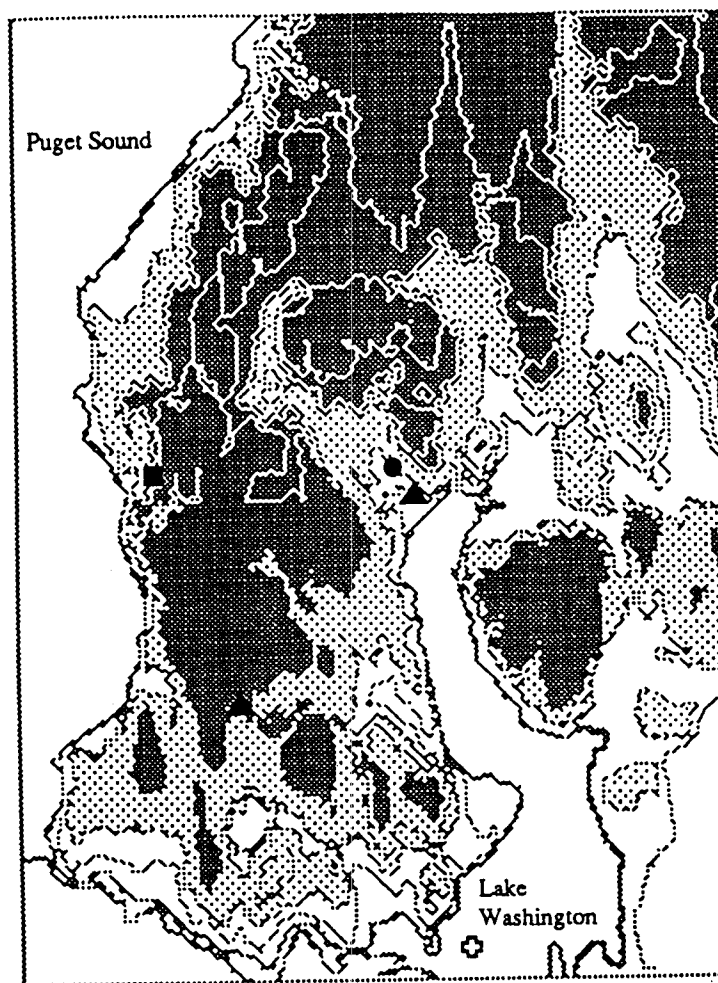


FIG. 1. Topographic map of north Seattle showing the locations of the two elementary schools and two nephelometer monitoring sites. The monitoring site close to School 1 was used to study the pulmonary effects of fine particulate matter. The highest concentrations of particulate matter are found in the residential valley near School 1. A second nephelometer, operated by the Puget Sound Air Quality Control Agency, is located on a ridge as shown (see Fig. 3 for a comparison of the two nephelometers). ●, School 1; ■, School 2; ▲, nephelometer.

(ATS) guidelines (Gardner *et al.*, 1987) with adjustments for young children (requiring a 3-sec duration rather than 6 sec) (Sly and Robertson, 1990). Each of the pulmonary function coaches was instructed in the ATS guidelines for spirometry. Three Ohio 822 (SensorMedics, Yorba Linda, CA) or one Vitalograph (Lenexa, KY) spirometers were used. As discussed later, our results did not depend upon the choice of spirometer. All spirometers were calibrated with a 3-liter syringe and stopwatch each morning prior to making measurements. All values were converted to standard body temperature pressure-saturated (BTPS) values. In 1988–1989 when over 300 children were tested, we tested on 6 days at each time period. In each 6-day period, we tested alternately at the schools, so that all the testing was not on Days 1, 2, and 3 at one school and 4, 5, and 6 at the other. All testing was carried out either at the 10:30 AM recess or the 11:30 to 1:00 lunch hour. During 1989–1990 when only the asthmatic children were tested, all children were tested on the same day. We tested at one school during recess and at the other during lunch break, always in that order. All subjects had been in the school building for at least 2 hr, thus they were acclimated to the indoor temperature and humidity. The children were asked to perform three acceptable tracings on each measurement day. From these records forced expiratory volume in 1 sec ( $FEV_1$ ) and forced vital capacity (FVC) were calculated. The best  $FEV_1$  and FVC from each set of three acceptable tracings was used. Height was measured at each study period. Each child was asked if he or she had been ill during the preceding week. Normal medication use was allowed. All children who were well enough to be in school were tested. Baseline spirometry was performed prior to the heating season in September, during the heating season in December and February, and after the season in May during both years. During the second winter, spirometry was performed five times (September, early December, late December, February, and May).

Light-scattering ( $\sigma_{sp}$ ) data were collected with an integrating nephelometer at a site located in a residential valley one-half mile southeast of School 1 (see Fig. 1), in order to obtain information on the airborne concentrations of fine particulate matter. The average nephelometer reading for the 12-hr nighttime period (7:00 PM to 7:00 AM) preceding each functional measurement from this site was used in the statistical analysis. Data from another nephelometer operated by the Puget Sound Air Pollution Control Agency were obtained for the entire duration of the first year's study, in order to examine spatial variability. This monitor was located on a ridge immediately south of the study area (see Fig. 1) and reflects the lower concentrations found on ridges. In order to verify the relationship between light scattering and  $PM_{2.5}$ , samples were collected on Teflon filters using low-volume air samplers with a flow rate of 4 liters/min and 10- $\mu$ m inlets (Marple *et al.*, 1987). Temperature and relative humidity were obtained from local weather records. The relationship between  $FEV_1$  or FVC and measurements of  $\sigma_{sp}$ , height, and other independent variables was explored using the mixed-effects model (Laird and Ware, 1982). The use of the mixed-effects model allowed us to estimate the average slopes of  $FEV_1$  and FVC values against  $\sigma_{sp}$ . A more detailed description of our statistical methods is given in the Appendix. Due to the limited numbers of repeated measurements, the only random-effects parameters included in the analysis were the intercepts. Light-scattering coefficient, height, and potential confounding variables, including temperature, humidity, recent illness, and type of spirometer, were considered as fixed effects.

## RESULTS

Table 1 provides a breakdown of the children in the study area during the first and second year of the study. The total number of children in the appropriate grades in the participating schools during this year was 762; 326 participated in the study. The table shows the percentage of children with self-reported asthma, parental smoking, and household use of wood heat. In general, nonparticipants did not enter the study because they did not receive the forms. As a group they did not differ from participants in smoking prevalence (16% vs 22%) or wood stove or fireplace use (43% vs 40%). All asthmatic children still attending the schools, a total of 14, participated in the second year of the study as well as 6 new recruits from the third grade (children who had been too young for the first year's study).

Table 2 lists the best of three acceptable FEV<sub>1</sub> values at each indicated measurement period for the individual asthmatic children participating in our study. Table 3 compares FEV<sub>1</sub> and FVC regression coefficients for the children in the first year of our study with those from children in a larger study by Dockery and co-workers (1982). Generally, the coefficients for height, age, and gender found in our study match those obtained in the larger study.

The light-scattering values are graphed in Fig. 2. There is not a complete data set for the 1988–1989 heating season. In both years, light-scattering values are low in September and again in May and the highest peaks are in December, January, and February. Figure 3 plots the relationship between  $\sigma_{sp}$  at the valley location versus  $\sigma_{sp}$  at the ridge location. The values are higher at the valley site; the two measurements are correlated ( $r = 0.76$ ). This demonstrates that any relationship between  $\sigma_{sp}$  and lung function found using the higher values found at the valley site will underestimate the magnitude of the relationship for the entire study population.

Figure 4 shows the relationship between PM<sub>2.5</sub>, a gravimetric measurement, and  $\sigma_{sp}$ . Although these data were taken in 1991, they demonstrate a well-established fact—that  $\sigma_{sp}$  is a good indicator of fine particulate matter in urban areas. Our observed relationship between  $\sigma_{sp}$  and PM<sub>2.5</sub> is consistent with that found in other studies (Waggoner and Weiss, 1980). Based on these results we estimated the following conversion factor between  $\sigma_{sp}$  and PM<sub>2.5</sub> at this site:  $10^{-4} \text{ m}^{-1} = 20.4 \text{ } \mu\text{g}/\text{m}^3$ .

The main results for the statistical analysis of the relationship between 12-hr nighttime averages of  $\sigma_{sp}$  and pulmonary function measurements taken the following morning are reported in Tables 4 and 5. The slopes are reported in both units of  $10^{-4} \text{ m}^{-1}$  ( $\sigma_{sp}$ ) and  $\mu\text{g}/\text{m}^3$  (PM<sub>2.5</sub>) to aid the reader. Both the slopes for

TABLE 1  
CHARACTERISTICS OF CHILDREN IN THE STUDY AREA

	Year 1	Year 2
Total studied <sup>a</sup>	326	20
Males	49.7%	50%
Asthmatics	7.7%	100%
Allergies	27.3%	100%
Smokers in home	22.3%	11.8%

<sup>a</sup> Total children in participating schools = 762.

TABLE 2  
FEV<sub>1</sub> VALUES IN ASTHMATIC CHILDREN DURING THE 1988-1989 AND 1989-1990 HEATING SEASON

Subject	September 1988	December 1988	February 1989	May 1989	September 1989	December 1989	December 1989	February 1989	May 1990
27	1.53	1.78	1.56	1.78	1.53	1.68	1.76	1.79	1.87
37	1.75	1.79	1.91	2.08					
38	1.77	1.69	1.72	1.88					
68	1.65	1.14	1.85	1.90	2.02	1.71	1.95	2.01	2.03
75	2.03	1.96	2.18	2.21	2.18	2.64	2.66	2.59	2.88
96	2.78	1.81	2.83	3.03	3.05	2.71	2.99	2.98	2.94
120	1.81	1.96	2.03	2.16					
526	1.64	1.55	1.53	1.64	1.68	1.71	1.76	1.69	1.76
536	1.45	1.53	1.54	1.53	1.52	1.32	1.71	1.53	1.27
538	1.59	1.75	1.78	2.03	1.95	1.98	1.98	1.85	1.98
556	1.92	1.90	2.03	2.08	2.28	2.20	2.31	2.13	2.48
566	1.96	1.98	1.97	1.97	1.95	1.98	1.98	2.02	2.15
568	2.36	2.25	3.07	3.06					
585	2.10	1.95	2.08	2.08	2.17	2.20	2.37	2.29	2.37
590	1.88	1.96	1.92	2.07	2.12	2.09	2.09	2.07	2.15
603	1.98	1.78	1.83	1.92	2.17	2.20		1.96	2.26
623	2.95	2.83	3.01	3.01					
628	2.13	2.33	2.36	2.52					
633	2.24	1.89	2.47	2.69	2.60	2.53	2.59	2.67	3.09
634	1.95	2.14	1.95	2.11	2.39	2.42	2.53	2.62	2.81
641	2.07	2.35		2.19					
650	2.44	2.75	3.02	2.83					
658	2.96	2.93	2.94	2.89					
669	1.87	2.01	1.82	2.24					
810					1.74	1.87	1.71	1.80	1.87
811					1.19	1.43	1.27	1.04	1.21
813					1.25		1.21	2.42	1.32
815					1.20	1.52	1.68	1.19	1.12
816					1.85	1.90	1.95	1.68	1.92
817					1.64	1.63	1.74	1.74	1.60
Mean	2.03	2.00	2.16	2.25	1.92	1.99	2.01	2.01	2.05
SD	0.41	0.42	0.52	0.45	0.40	0.40	0.47	0.49	0.59

TABLE 3  
REGRESSION COEFFICIENTS FOR ln(FEV<sub>1</sub>) AND ln(FVC) VERSUS RACE, GENDER, AND HEIGHT

	Dockery <i>et al.</i> (1982)		Present study	
	Estimate	SE	Estimate	SE
FEV <sub>1</sub>				
Constant	-0.0464	0.0031	-0.055	0.043
ln(height)	2.5805	0.0103	2.468	0.102
Race	-0.1334	0.0021	—	—
Gender	-0.0642	0.0043	-0.064	0.013
Gender × ln(height)	-0.0298	0.0298	—	—
	$R^2 = 0.7665$		$R^2 = 0.6734$	
FVC				
Constant	-0.1486	0.0032	-0.097	0.046
ln(height)	2.4130	0.0108	2.335	0.108
Race	-0.1343	0.0021	—	—
Gender	-0.0642	0.0043	-0.0321	0.014
Gender × ln(height)	-0.0346	0.0148	—	—
	$R^2 = 0.7256$		$R^2 = 0.6131$	

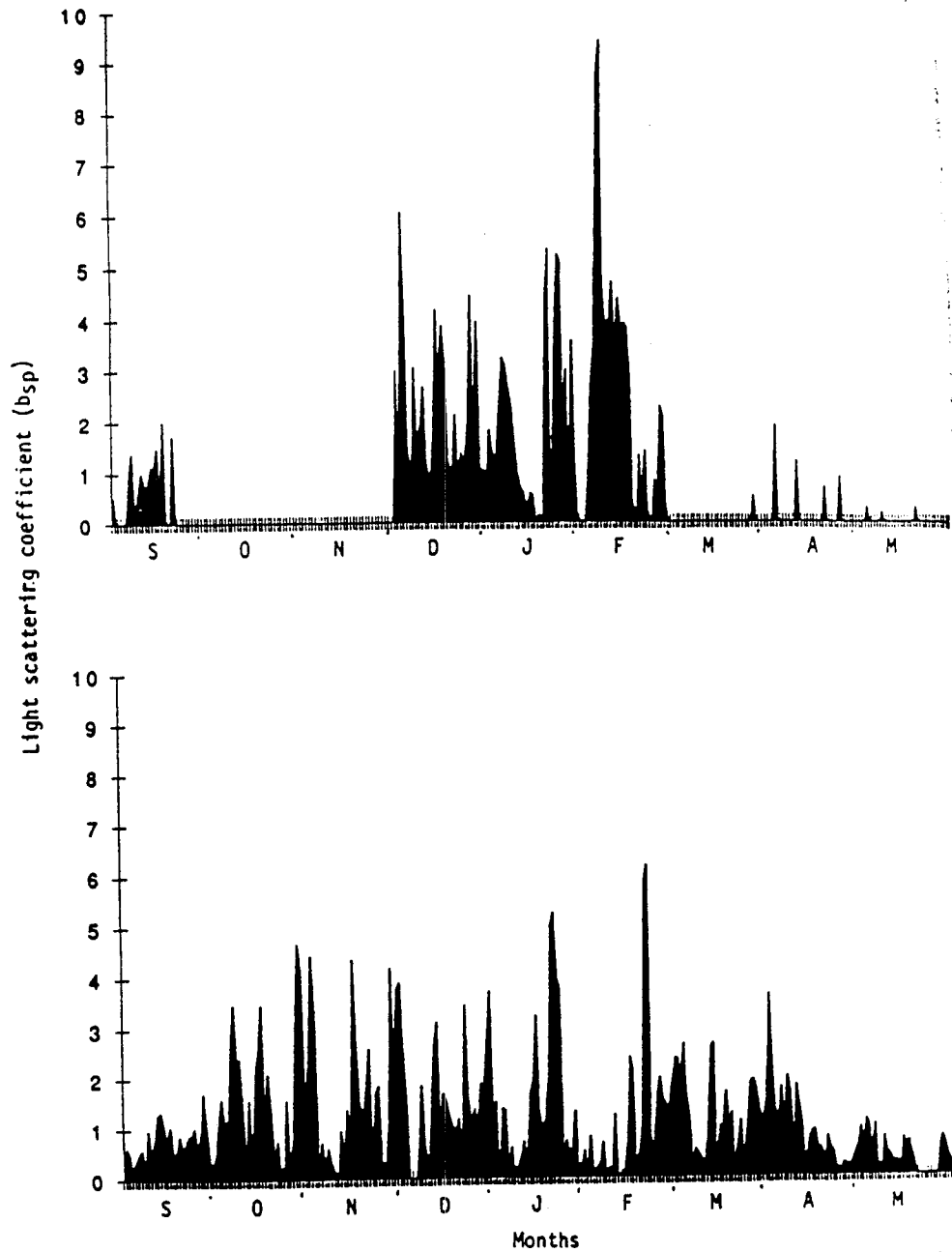


FIG. 2. Twelve-hour nighttime averages of light-scattering coefficient in the study area, for the 1988-1989 (top) and the 1989-1990 heating seasons (bottom). Measurements were not taken during October and November, 1988, and in March, 1989.

$FEV_1$  and FVC against  $\sigma_{sp}$  are significant at the 1% level for the asthmatic children, whereas those for the nonasthmatic children are not significant.

Temperature was a significant variable for changes in pulmonary function in the nonasthmatic children but not in the asthmatic children. The results in Table 4 and

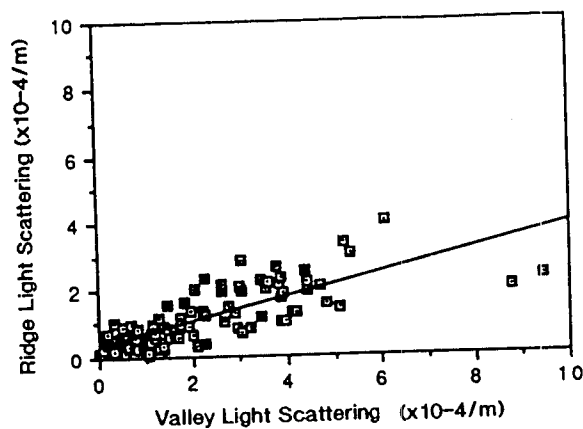


FIG. 3. Matched values of  $\sigma_{sp}$  taken from the two nephelometers whose sites are shown in Fig. 1. Generally, the values are higher at the valley site; the two measurements are correlated ( $r = 0.76$ ).

5 are based upon 30 subjects with 155 valid observations for the asthmatic children and 298 subjects with 550 valid observations for the nonasthmatic children.

The inclusion of parental smoking and household use of wood heat as independent variables in the analysis did not change the basic conclusions; however, substantial amounts of missing data on these two variables preclude reliable significance tests. Furthermore, recent illness, type of spirometer, and relative humidity were all nonsignificant.

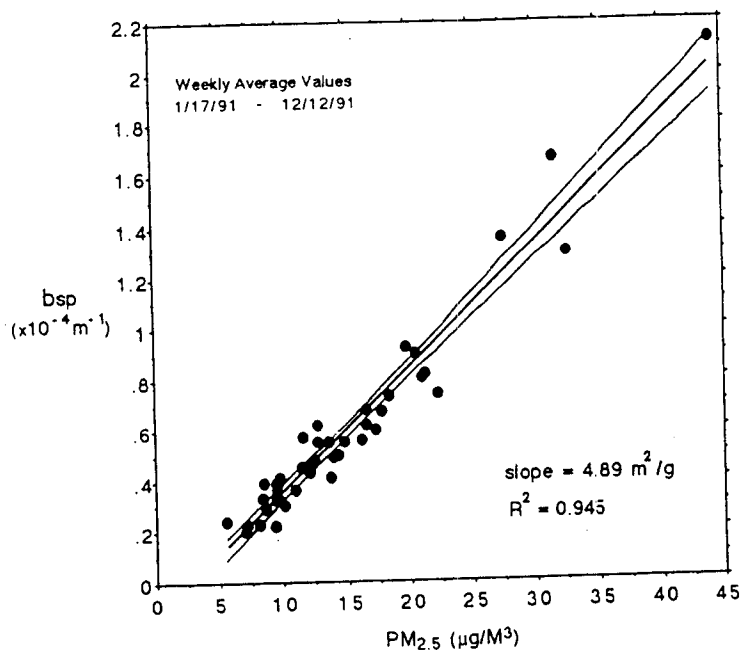


FIG. 4. Relationship between weekly average PM<sub>2.5</sub> and the corresponding light-scattering values. Data shown here are for all of 1991.



TABLE 4  
PARAMETER ESTIMATES IN THE MIXED-EFFECTS MODEL FOR ASTHMATIC CHILDREN<sup>a</sup>

	FEV <sub>1</sub> <sup>b</sup>			FVC <sup>b</sup>		
	Estimate	SE	Estimate/SE	Estimate	SE	Estimate/SE
Intercept <sup>c</sup>	-3.598	0.453	-7.95	-4.188	0.450	-9.32
$\sigma_{sp}$ <sup>d</sup>	-0.034	0.011	-3.10	-0.037	0.009	-3.98
Height <sup>e</sup>	0.099	0.008	12.71	0.117	0.008	15.10

<sup>a</sup> There were 30 subjects with 155 valid observations for the asthmatic children and 298 subjects with 550 valid observations for the nonasthmatic children. The tests of healthy children were conducted during the 1988-1989 heating season; testing of the children with asthma was conducted during that period and also during the 1989-1990 heating season.

<sup>b</sup> Measured in liters.

<sup>c</sup> The intercept is the value of lung function when all other parameters are set to zero. Other reported parameters refer to slopes of lung function values versus the listed quantity. A negative value for the slope indicates a decrease in lung function.

<sup>d</sup> Measured in units of  $10^{-4} \text{ m}^{-1}$ ; the equivalent values of the slope in terms of  $\text{PM}_{2.5}$  are  $-0.0017$  and  $-0.0018$  liters/ $(\mu\text{g}/\text{m}^3)$  for FEV<sub>1</sub> and FVC, respectively.

<sup>e</sup> Height is measured in inches.

Results were essentially the same when lags of 48 and 72 hr were included between 12-hr average nighttime particulate measurements and the pulmonary function measurements.

## DISCUSSION

In the earlier Six City Study report of children in Steubenville (Dockery *et al.*, 1982), a group median estimate of the slope between FVC and total suspended particulate was  $-0.081 \text{ ml}/\mu\text{g}/\text{m}^3$  for all children. When the estimate of a similar relationship (FVC/measure of fine particle concentration, shown in Table 4) is

TABLE 5  
PARAMETER ESTIMATES IN THE MIXED-EFFECTS MODEL FOR NONASTHMATIC CHILDREN<sup>a</sup>

	FEV <sub>1</sub> <sup>b</sup>			FVC <sup>b</sup>		
	Estimate	SE	Estimate/SE	Estimate	SE	Estimate/SE
Intercept <sup>c</sup>	-2.819	0.207	-13.59	-3.430	0.232	-14.81
$\sigma_{sp}$ <sup>d</sup>	0.003	0.004	0.79	0.007	0.004	1.75
Height <sup>e</sup>	0.089	0.0034	26.09	0.107	0.0038	27.77
Temperature <sup>f</sup>	-0.004	0.001	-3.07	-0.005	0.001	-4.29

<sup>a</sup> There were 30 subjects with 155 valid observations for the asthmatic children and 298 subjects with 550 valid observations for the nonasthmatic children. The tests of healthy children were conducted during the 1988-1989 heating season; testing of the children with asthma was conducted during that period and also during the 1989-1990 heating season.

<sup>b</sup> Measured in liters.

<sup>c</sup> The intercept is the value of lung function when all other parameters are set to zero. Other reported parameters refer to slopes of lung function values versus the listed quantity. A negative value for the slope indicates a decrease in lung function.

<sup>d</sup> Measured in units of  $10^{-4} \text{ m}^{-1}$ ; the equivalent values of the slope in terms of  $\text{PM}_{2.5}$  are  $-0.00015$  and  $+0.00034$  liters/ $(\mu\text{g}/\text{m}^3)$  for FEV<sub>1</sub> and FVC, respectively.

<sup>e</sup> Height is measured in inches.

<sup>f</sup> Temperature is measured in Fahrenheit.

made using the present data, the estimated mean FVC decrease per unit increase of  $PM_{2.5}$  is  $-1.8$  and  $+0.34$  ml/ $\mu\text{g}/\text{m}^3$  for asthmatic and nonasthmatic children, respectively. The FVC change per unit increase in  $PM_{2.5}$  for the asthmatic children in our study is more pronounced than the FVC changes in the Dockery study which may be due solely to an increased sensitivity to airborne irritants in children with asthma or may suggest that fine particulate matter is more irritating than general industrial TSP.

The pollutants emitted into the air when wood is burned are products of incomplete combustion (Koenig *et al.*, 1988; Larson and Koenig, 1993). Much of this material is released as particulate matter in sizes less than  $1\ \mu\text{m}$  making it highly respirable. As a product of incomplete combustion, wood smoke resembles environmental tobacco smoke, for which numerous studies have shown deleterious effects on the respiratory health of children (Samet *et al.*, 1987). Thus, particulate emissions from residential wood burning may be more irritating than general industrial TSP, due to its respirable size fraction and its chemical composition. Furthermore, other gaseous constituents of wood smoke, such as formaldehyde, are also respiratory irritants (Tuthill, 1984) and the fine particles associated with lung function changes in our study may be a surrogate for another agent.

This study found that asthmatic children showed a greater response to particulate air pollution than did healthy children. Prior studies have suggested increased susceptibility to particulate air pollution among asthmatics. Stern and others (1989) reported significantly lower  $FEV_1$  and FVC values in children aged 7–12 when comparing two communities with different levels of air pollution, including inhalable particles. They also reported a significant relationship between air pollution and wheeze, and a significant relationship between use of a gas cooking stove and asthma. Dockery and co-workers (1989) reported that chronic cough, bronchitis, and chest illness were positively associated with fine particulate matter ( $PM_{15}$ ), including fine sulfates, in a group of children studied in the Harvard Six City Study. Although not statistically significant, the authors concluded that there was a stronger association between fine particulate matter and symptoms in asthmatics compared with nonasthmatics. The results from the present study indicate that increases in particulate air pollution are associated with declines in asthmatic children's pulmonary function. Since both asthma morbidity and mortality are increasing (Gergen and Weiss, 1990) some researchers suggest a relationship between poor air quality and the increasing asthma prevalence (Scott, 1990). In general there is increasing concern that present levels of air pollution in the United States may cause or aggravate respiratory illness.

There are several limitations to this study including the small sample size and the lack of personal exposure data for the children, as well as unequal measurement periods between the nonasthmatic and asthmatic children. Another limitation is the lack of measurement of traditional indoor air pollutants such as dust mites and molds which also affect asthma. However, there is no reason to believe that levels of these natural pollutants correlate with outdoor particulate matter concentrations. Dust mites are known to peak in the fall prior to the heating season (Platts-Mills *et al.*, 1987). Indoor concentrations of nitrogen dioxide from gas cooking stoves have been associated with respiratory symptoms in children (Samet *et al.*, 1987); however, the use of gas for residential cooking in Seattle is rare. Finally, due to the relatively infrequent measurement of pul-

monary function, this study could not examine the duration of the observed acute effects.

In summary, the 12-hr average of fine particulate matter measured by light scattering in a wood-burning community is strongly associated with acute changes in pulmonary function in asthmatic children exposed during a winter heating season, and the magnitude of this relationship is larger than previous estimates for the effects of TSP on young children.

#### APPENDIX: STATISTICS METHODS

Suppose that there were  $N$  children and that the  $i$ th child had  $n_i$  sets of measurements on  $FEV_1$ ,  $\sigma_{sp}$ , height, and temperature. Then the following mixed-effects model (also called a random-effects model) can be used to study the relationship between  $FEV_1$  and  $\sigma_{sp}$  while controlling for the effects of height and temperature.

$$Y_{ij} = \alpha + a_i + \beta X_{ij} + \gamma H_{ij} + \epsilon T_{ij} + e_{ij},$$

for  $i = 1, \dots, N$  and  $j = 1, \dots, n_i$ . In this model,  $Y_{ij}$ ,  $X_{ij}$ ,  $H_{ij}$ , and  $T_{ij}$  are, respectively, the  $j$ th measurements of  $FEV_1$ ,  $\sigma_{sp}$ , height, and temperature for the  $i$ th child,  $\alpha$  and  $(\beta, \gamma, \epsilon)$  are the population intercept and slopes;  $a_i$  is the intercept for the  $i$ th child, and  $(e_{i1}, \dots, e_{in_i})$  are the random noises assumed to be multivariate normal with zero mean. The parameters  $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\epsilon$  are called fixed effects, whereas the  $a_i$ 's are called random effects. We are mainly interested in  $\beta$ , which is the average slope of  $FEV_1$  on  $\sigma_{sp}$ . Other potential confounding variables may also be included in this model. A similar model is used to study the effect of  $\sigma_{sp}$  on FVC.

We fit the mixed-effects models separately for asthmatic and nonasthmatic children. The parameter estimates and standard error estimates were obtained by the restricted maximum likelihood method described in Laird and Ware (1982). The REML program from the Harvard School of Public Health was utilized. In screening for significant fixed effects parameters, we started with a model that contained all the measured potential confounders and then deleted nonsignificant parameters successively.

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