Acute Effects of Summer Air Pollution on Respir Symptom Reporting in Children

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A daily diary of respiratory symptoms was collected from the parents of 1,844 school children in six U.S. cities to study the association between ambient air pollution exposures and respiratory illness. A cohort of approximately 300 elementary school children in each of six communities were asked to keep a daily log of the study child's respiratory symptoms for one year. Daily measurements of ambient sulfur dioxide, nitrogen dioxide, ozone, inhalable particles (PM_{10}), respirable particles ($PM_{2.5}$), light scattering, and sulfate particles were made, along with integrated 24-h measures of aerosol strong acidity. The analyses were limited to the five warm season months between April and August. Significant associations were found between incidence of coughing symptoms and incidence of lower respiratory symptoms and PM_{10}, and a marginally significant association between upper respiratory symptoms and PM_{10}. There was no evidence that other measures of particulate pollution including aerosol acidity were preferable to PM_{10} in predicting incidence of respiratory symptoms. Significant associations in single pollutant models were also found between sulfur dioxide or ozone and incidence of cough, and between sulfur dioxide and incidence of lower respiratory symptoms. A change in 24-h PM_{10} concentration from 20 to 50 $\mu g/m^3$ was associated with a relative odds of 1.53 (95% CI 1.20–1.95) for the incidence of lower respiratory symptoms, a relative odds of 1.22 (95% CI 1.03–1.45) for the incidence of coughing, and a relative odds of 1.22 (95% CI 0.98–1.52) for the incidence of upper respiratory symptoms. A change in 24-h ozone concentration of 30 parts per billion (ppb) was associated with a relative odds of 1.22 (95% CI 0.96–1.49) for the incidence of coughing. The relationship between ozone and incidence of cough was independent of other pollutants. However, the relationship between sulfur dioxide and incidence of lower respiratory symptoms appeared to derive only from a few influential observations, and could be confounded by PM_{10}. Aerosol acidity was not associated with the incidence of any respiratory symptom. The highest daily PM_{10} concentration was 117 $\mu g/m^3$ during the study, indicating that these relationships occurred at concentrations below the ambient air quality standard. **Schwartz J, Dockery DW, Neas LM, Wypij D, Ware JH, Spengler JD, Koutrakis P, Speizer FE, Ferris BG Jr. Acute effects of summer air pollution on respiratory symptom reporting in children. Am J Respir Crit Care Med 1994;150:1234–42.**

Recent studies have reported that short-term exposures to particulates (1–4) or ozone (5–7) are associated with acute, reversible decrements in pulmonary function. Acute exposure to pollution has been associated with excess early mortality in episodes of high pollution (8) and in longer term studies across a broad range of pollution values (9–15). Air pollution also has been associated with croup symptoms in preschool children (16), hospital admissions for respiratory illness (17–20), respiratory symptoms in preschool children (21), and increased symptoms and medication use in asthmatics (3). Recent studies have suggested that aerosol strong acidity may be an important factor for chronic prevalence rates (22), asthma symptoms (23), and acute mortality (24). Many studies have analyzed sulfate (SO_4) ion concentrations as a marker of the concentration of various aerosol acids. Identifying the specific component of the mixture of pollutants in the ambient air which is responsible for acute health effects remains a critical need.

Daily diary studies of respiratory symptoms represent an attractive approach to investigate the possible acute effects of air pollution. While the significance of reversible changes in lung function has been debated, respiratory symptoms are clearly outcomes that produce discomfort and morbidity in their victims. In longitudinal studies of symptom reporting over time, the population serves as its own control, eliminating a possible source of confounding found in cross-sectional studies. The use of daily questionnaires allows the separate investigation of risk factors for symptom incidence and risk factors for the duration of respiratory symptoms. Recent studies have used such approaches to diary data to examine possible associations with respiratory symptoms (25–28).

This report presents results from a study of the association between respiratory symptoms in a sample of elementary school children in six U.S. cities and daily air pollution measurements including aerosol acidity measurements.

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METHODS

The Six Cities Study of respirable particles and sulfur oxides is a longitudinal study of the effects of exposure to respirable particles and sulfur oxides on the respiratory health of children and adults (29). A stratified random sample of 1,844 children in grades two through five from six U.S. cities (Watertown, MA; Kingston-Harriman, TN; St. Louis, MO; Steubenville, OH; Portage, WI; and Topeka, KS) was enrolled in a year-long diary study starting in September 1984. Children were selected from stratum based on the presence of indoor sources of air pollution (gas stoves and parental smoking) determined from a questionnaire administered to the whole cohort. The families participated in an indoor air pollution study which has been described previously (30, 31). Parents completed a daily report on the child's respiratory (and other) symptoms. Symptom reports were collected every 2 wk over the phone and parents mailed in the written diaries monthly. One community, Watertown, was examined in the 1984/85 school year. Children in two communities, Kingston and St. Louis, were examined in 1985/86; two communities, Steubenville and Portage, in 1986/87; and finally one community, Topeka, in 1987/88. The diaries recorded symptoms in 13 categories (Table 1).

Air Pollution Measurements

Ambient air pollution was measured daily during the diary study at a central monitoring station located in a residential area in each community. Sulfur dioxide (SO_2), nitrogen dioxide (NO_2), and ozone (O_3) were measured hourly and the daily mean calculated for each day with at least 18 h of observation. Particulate matter was collected by a dichotomous sampler with aerodynamic size cut at 10 μm (PM_{10}) and 2.5 μm ($PM_{2.5}$). Mass concentrations were determined by beta-attenuation. Elemental sulfur, as an index of SO_4, was measured from the $PM_{2.5}$ filters by X-ray fluorescence. A nephelometer continuously measured light scattering by the very fine particulate fraction.

Aerosol acidity (H^+) was measured daily. The Harvard aerosol impactor was used to collect particulates less than 2.5 μm aerodynamic diameter on teflon filters. Impactors were equipped with an ammonia (NH_3) gas denuder to prevent neutralization of collected acid aerosols. The filters were removed immediately after sampling and placed in a vial of doubly distilled ion-free water, sealed and returned to the Harvard School of Public Health for pH and ion analysis. Before shipping and immediately upon receipt, the concentration of hydrogen was determined by ion selection electrode (32).

Temperature was measured at the nearest National Oceanographic and Atmospheric Administration weather station.

Analytic Methodology

The symptoms recorded on the diary (Table 1) are not independent. Rather, they occur in discrete combinations. Factor analysis combined with medical judgment yielded four discrete respiratory complexes: lower respiratory symptoms, defined as reports of at least two of cough, chest pain, phlegm, and wheeze; upper respiratory symptoms, defined as the report of at least two of hoarseness, sore throat, and fever; cough alone, defined as the report of cough without any other symptom; and rhinitis, defined as the report of runny nose without lower or upper respiratory symptoms as just defined. Rhinitis was not analyzed in this report.

The same factors that promote the development of respiratory symptoms may not necessarily determine the duration of those symptoms. For example, in these data the number of lower respiratory symptom events is much higher in the winter than in the summer, but the mean duration is unaffected by season. Because the mean duration of respiratory symptoms is more than one day, prevalence data are highly autocorrelated, which complicates the analytical strategy. This analysis therefore focuses on the incidence of symptoms. Incident cases were defined by a positive report of a symptom complex by an individual who had not reported that symptom on the previous day. When symptom incidence is analyzed, only subjects free of the symptoms on the previous day are at risk.

Although each individual contributing to the incidence rate on a specific day was by definition symptom-free on the previous day, the incidence rates for respiratory symptoms may still exhibit autocorrelation. Autocorrelation (or serial correlation) refers to the tendency for incidence rates close together in time to be correlated. For example, symptoms of infectious origin may occur because other subjects had the symptoms on the same or previous days. In addition, time-dependent covariates such as weather and air pollution often exhibit serial correlation, which could lead to serial correlation in daily symptom reporting. The standard logistic regression model assumes independence of the daily incidence rates, after controlling for the covariates. If all appropriate covariates are included in the model, this condition may be met, but if important covariates are omitted or inadequately controlled for, serial correlation in the data will

TABLE 1

SYMPTOMS RECORDED ON DAILY DIARIES AND DESCRIPTIONS OF SYMPTOMS GIVEN TO PARTICIPANTS

Hoarseness:	Hoarse or dry throat; raspy voice; laryngitis.
Sore throat:	Any soreness or irritation of the throat; strep throat; tonsillitis.
Cough:	Sporadic, intermittent, or protracted coughing.
Phlegm from chest:	Phlegm or mucus coughed up from the lungs or area of the throat below the voice box; congestion in the lungs.
Pain in chest:	Aching, irritation or feeling of constriction in lungs; shortness of breath
Wheezing:	Wheezing or whistling sound from the chest.
Fever:	An above average temperature recorded by thermometer at any point during the day or evening.
Ear pain or discharge:	Ear ache or ear infection; discharge of fluid from the ears.
Runny nose:	Nasal or sinus congestion; postnasal drip; phlegm or mucus from back of throat; sneezing; itching of nasal passages.
Burning, aching, or red eyes:	Sensations of burning, itching, or aching in the eyes or eyelids; red or watery eyes.
Restricted activities:	Interruption in the child's daily routine resulting from any illness; e.g., child stays home from school or on a nonschool day remains indoors.
Saw doctor:	Any appointment or visit with a health practitioner, whether regularly scheduled or not.
Hospitalized:	Admitted to hospital or clinic as an in-patient for one night or more.

remain, and the residuals will exhibit autocorrelation. At a minimum, this can lead to biased estimates of the standard errors of the regression coefficients, and inefficient estimates of the coefficients themselves. Liang and Zeger (33, 34) have described methods for fitting logistic regression models where the covariance structure exhibits autocorrelation. In addition, this methodology allows for robust variance estimates when multiple independent subsets of the data are available. In this study, although the data from each city could be considered independent, city of residence was treated as a categorical explanatory variable to account for differences between communities unrelated to the air pollution exposures. Therefore, robust variance estimates could not be calculated. Statistically insignificant ($p > 0.10$) autoregression parameters in the covariance model were dropped. If no autocorrelation exists in the data, the effect estimates are the same as from the usual logistic regression models. This approach has been successfully implemented in previous diary studies of air pollution and respiratory symptoms (21, 25), and preliminary analyses of these data (35).

Respiratory symptoms peak in the winter, primarily because of infectious disease epidemics. In contrast, ozone and aerosol acidity peak in the warm months and are near their minimal detectable limits in the winter. This creates considerable potential for confounding and errors in variables. To avoid these problems, the analysis was restricted to data from the nonwinter months, April through August (153 days) in each community.

A logistic regression of respiratory symptoms against a continuous pollution variable assumes that the logit (logarithm of the odds) of the symptom rate varies linearly (with no threshold) with the pollutant. Identifying possible threshold values or other nonlinearities in the concentration–response relationship in a major public health concern. Local nonparametric smoothing provides an attractive method for investigating such issues. Local smoothing is a generalization of a moving average, where the predicted value of the outcome at x_i, the exposure on day i, is taken to be the mean of the outcomes in a neighborhood around x_i. Usually, a weighted mean is taken, with weights that decline with distance from x_i. The Generalized Additive Model (36) extends this concept to include multiple covariates, and allows its use in models for discrete outcomes, such as logistic regression. The logit of symptom rates is fit to a continuous function of pollution concentration, defined by local nonparametric smoothing controlling for covariates. The improvement in model fit compared with a linear relationship is evaluated with a chi-square test, with a nonsignificant test suggesting that the data are consistent with a linear trend. Smoothed plots of symptom rates versus pollution, controlling for cofactors, allow the visual evaluation of the shape of the concentration–response relationship.

Because of the multiple pollutants being considered, a sequential analytic strategy was utilized. Preliminary regressions showed that the incidence of respiratory symptoms was highly correlated with the previous day's mean temperature and the previous day's temperature squared. There was little additional correlation with current day's temperature, or temperature for more than one day lag. Interaction terms were used to test for city-specific temperature dependence, and included where significant ($p < 0.10$). Incidence of respiratory symptoms was then regressed separately against each pollutant controlling for previous day's temperature (and its square), day of the week, and city of residence. Pollutants that were significant in these regressions were then analyzed in multiple pollutant models. The effects estimated for each pollutant from the logistic model are reported as estimated odds ratios and 95% confidence intervals (95% CI) scaled to a characteristic range of exposures approximately equal to the interquartile range.

Following a pollution episode, incident respiratory symptoms may develop immediately or possibly several days later (3). Associations of incident respiratory symptoms were considered with pollution concentration on the current day, the previous day, and the mean of up to four previous days was assessed for each pollutant. Significant pollution relationships detected in the initial logistic regressions were examined using Generalized Additive Models (37).

RESULTS

Table 2 shows the percentile distribution of daily mean pollution, temperature, and the respiratory symptom incidence combined over the six cities for the five nonwinter months. The maximal 24-h concentration of PM_{10} was 117 $\mu g/m^3$, compared with a National Ambient Air Quality Standard (NAAQS) of 150 $\mu g/m^3$. For sulfur dioxide the maximal 24-h average was 82 ppb compared with the 24-h standard of 140 ppb. The maximal 24-h mean aerosol acidity concentration observed during this period (372 $nmol/m^3$) corresponds to an equivalent exposure to pure sulfuric acid of 18.2 $\mu g/m^3$. No ambient air quality standard has been promulgated for acid aerosols. Thus this study examines the effects of exposure to air pollution at levels below the current standards. There was strong day-to-day correlation between the measures of particulate mass concentrations (Table 3) were high, with correlation coefficients greater than 0.75. Aerosols acidity had weaker associations with particle mass, with correlation coefficients between 0.55 and 0.76. The gaseous pollutants, sulfur dioxide, nitrogen dioxide, and ozone, had weaker correlations with particle mass and with each other.

Incidence of Cough

Incidence of cough without other symptoms was serially correlated after controlling for day of week, city, and previous day's temperature. The pattern was well described by an autoregressive model of order one, which was used in all analyses.

Upon estimating the additional effect of daily mean concentrations of individual pollutants, the best goodness-of-fit χ^2 was found for incidence of cough with increased PM_{10} on the previous day (odds ratio [OR] for 30 $\mu g/m^3$ = 1.22, 95% CI = 1.03–1.45). A better association, measured by χ^2 goodness-of-fit statistic was obtained for the mean PM_{10} over the previous 3 d (OR for 30 $\mu g/m^3$ = 1.29, 95% CI = 1.07–1.56). Fitting a Generalized Additive Model showed that cough incidence increased monotonically with PM_{10} concentration (Figure 1) and that the deviation from linearity was not statistically significant (p = 0.81).

The only other single pollutant significantly associated with cough incidence was mean O_3 on the previous day (OR for 30 ppb O_3 = 1.27, 95% CI = 1.05–1.54). Two- and 3-day averaged O_3 gave a poorer fit. The locally smoothed fit by the Generalized Additive Model showed cough incidence to increase with ozone (Figure 2). Although the concentration–response association was less regular than with PM_{10}, the test for deviation from linearity was not significant (p = 0.31).

Cough incidence was not significantly associated with SO_2 (OR for 10 ppb = 0.99, 95% CI = 0.90–1.10), with NO_2 (OR for 10 ppb = 1.10, 95% CI = 0.96–1.26), nor with NO_2 on the previous day (OR for 10 ppb = 1.10, 95% CI = 0.96–1.25). For longer averaging times, the estimated effect of the average concentration over the previous 4 d was statistically significant for SO_2 (OR for 10 ppb = 1.16, 95% CI = 1.02–1.32) and also for NO_2 (OR for 10 ppb = 1.35, 95% CI = 1.11–1.63). However, the local nonparametric smooth of the 4-d mean NO_2 concentration showed increased cough incidence rates up to approximately the median concentration (~ 13 ppb) after which no further increase was observed. The test for deviation from linearity was significant (p = 0.01). For SO_2, the local smooth showed increased cough incidence only above a 4-d mean of 20 ppb, that is, less than 5%

TABLE 2

DISTRIBUTION OF 24-H MEAN POLLUTION, TEMPERATURE, AND HEALTH OUTCOMES FOR NONWINTER MONTHS (APRIL–AUGUST) COMBINED OVER SIX CITIES

Variable	Days (no.)	10%	25%	50%	75%	90%	Max
Air pollutants							
SO_2, ppb	830	0.8	1.4	4.1	8.2	17.9	81.9
NO_2, ppb	809	5.0	8.3	13.3	18.3	24.1	44.2
O_3, ppb	898	23.0	29.2	36.9	45.5	54.1	87.0
PM_{10}, $\mu g/m^3$	657	13.0	20.0	30.0	41.0	53.0	117.0
$PM_{2.5}$, $\mu g/m^3$	660	7.2	12.0	18.0	27.0	37.0	86.0
$PM_{2.5}$ Sulfur, $\mu g/m^3$	660	0.8	1.4	2.5	4.0	5.9	15.1
H^+, $nmol/m^3$	684	3.1	8.5	18.1	35.4	61.0	371.7
Weather							
Temperature, °F	918	52	61	71	77	82	
Health outcomes*							
Cough		0	0	3.1	5.8	8.6	
Lower respiratory symptoms		0	0	0	2.9	3.4	
Upper respiratory symptoms		0	0	0	3.1	5.7	

* Incident cases/1,000 child-days.

TABLE 3

CORRELATION OF 24-H MEAN POLLUTION CONCENTRATIONS AND TEMPERATURE FOR NONWINTER MONTHS (APRIL–AUGUST) COMBINED OVER SIX CITIES

	PM_{10}	$PM_{2.5}$	Nephelometer	$PM_{2.5}$ Sulfur	H^+	SO_2	NO_2	O_3
PM_{10}	1.0							
$PM_{2.5}$	0.92	1.0						
Nephelometer	0.76	0.88	1.0					
$PM_{2.5}$ Sulfur	0.80	0.93	0.90	1.0				
H^+	0.55	0.69	0.69	0.76	1.0			
SO_2	0.53	0.55	0.35	0.50	0.23	1.0		
NO_2	0.36	0.35	0.21	0.28	0.03	0.51	1.0	
O_3	0.32	0.25	0.19	0.26	0.13	−0.09	−0.28	1.0
Temperature	0.40	0.38	0.38	0.40	0.32	−0.03	−0.11	0.35

TABLE 4

REGRESSION MODELS FOR COUGH INCIDENCE, CONTROLLING FOR TEMPERATURE, CITY, AND DAY OF THE WEEK*

Pollutant	Exposure†	Odds Ratio	95% CI	*t* Statistic	Goodness-of-fit χ^2
PM_{10}	(30 $\mu g/m^3$)‡	1.28	1.07–1.54	2.77	738.5
Ozone	(30 ppb)§	1.23	0.99–1.54	1.89	739.5
SO_2	(10 ppb)‖	1.15	1.02–1.31	2.25	744.4
NO_2	(10 ppb)‖	1.27	1.04–1.56	2.40	748.8
$PM_{2.5}$	(20 $\mu g/m^3$)‡	1.19	1.01–1.42	2.07	741.0
$PM_{2.5}$ Sulfur	(5 $\mu g/m^3$)‡	1.23	0.95–1.59	1.62	741.4
Nephelometry	(1 km^{-1})‡	1.21	1.02–1.45	2.19	NA¶
H^+	(25 $nmol/m^3$)	1.06	0.87–1.29	0.62	NA¶
Two-Pollutant Models					
PM_{10}	(30 $\mu g/m^3$)‡	1.27	1.06–1.52	2.67	732.4
Ozone	(30 ppb)§	1.20	0.96–1.49	1.62	
PM_{10}	(30 $\mu g/m^3$)‡	1.22	0.99–1.50	1.86	738.7
SO_2	(10 ppb)‖	1.08	0.93–1.25	1.04	
PM_{10}	(30 $\mu g/m^3$)‡	1.21	0.99–1.47	1.91	741.7
NO_2	(10 ppb)‖	1.17	0.94–1.46	1.44	
Ozone	(30 ppb)§	1.23	0.99–1.52	1.84	741.6
NO_2	(10 ppb)‖	1.27	1.04–1.55	2.37	
NO_2	(10 ppb)‖	1.19	0.95–1.51	1.53	747.0
SO_2	(10 ppb)‖	1.09	0.94–1.30	1.16	
Ozone	(30 ppb)§	1.23	0.98–1.53	1.84	737.5
SO_2	(10 ppb)‖	1.15	1.01–1.31	2.22	

* Restricted to 762 d with complete air pollution data.
† Increment in pollution used to estimate odds ratios.
‡ Mean of previous 72 h.
§ Mean of previous 24 h.
‖ Mean of previous 96 h.
¶ Missing observations of nephelometry and hydrogen ion imply that tests compared with other pollutants are not appropriate.

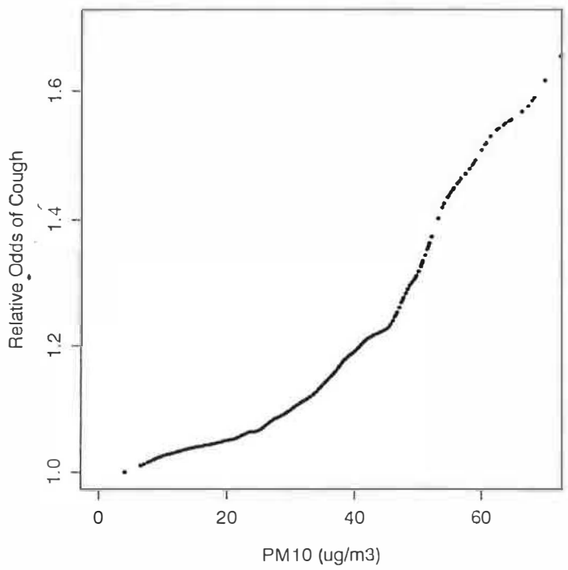

Figure 1. Relative odds of incidence of coughing smoothed against 3-d mean PM_{10} ($\mu g/m^3$), controlling for temperature, city, day of the week, and ozone concentration.

of the data. Again, the test for nonlinearity was significant ($p = 0.002$). An analysis testing for an association with 4-d mean SO_2 restricted to days below 20 ppb was far from statistical significance ($p = 0.54$). Thus, at the relatively low SO_2 and NO_2 ambient concentrations observed in this study, no clear associations with cough incidence could be observed.

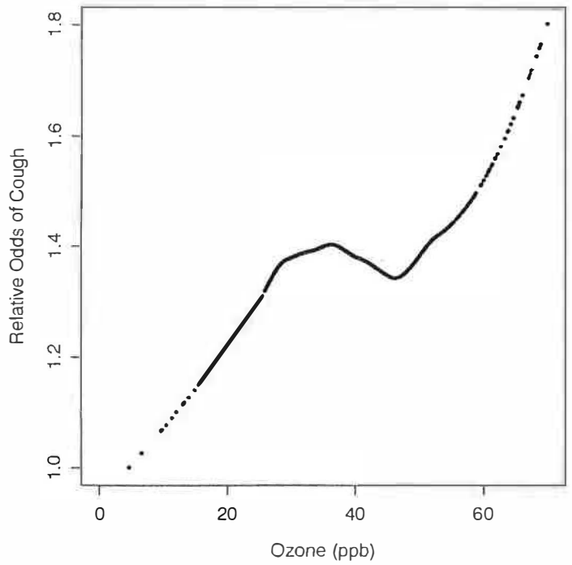

Figure 2. Relative odds of incidence of coughing smoothed against 24-h mean ozone (ppb), controlling for temperature, city, day of the week, and PM_{10} concentration.

The pollutants associated with the incidence of coughing, i.e., PM_{10}, O_3, SO_2, and NO_2 were examined in multiple pollutant models, restricted to those days that had no missing values of any of the four pollutants (Table 4). For comparison, the one-pollutant models were reestimated on the restricted data sets (Table 4).

The associations for PM_{10} (OR for 30 $\mu g/m^3$ = 1.27, 95% CI = 1.06–1.52) and O_3 (OR for 30 ppb = 1.20, 95% CI = 0.96–1.49) when simultaneously considered in the linear logistic model (Table 4) were both similar to the associations for the single-pollutant models. This suggests that the effects of PM_{10} and O_3 on cough incidence are independent and additive on the logit scale. The goodness-of-fit χ^2 for this model was substantially better than any other two-pollutant models or the univariate model for PM_{10} (χ^2 = 6.1, 1 degree of freedom [df], $p = 0.27$).

The effect estimates for PM_{10} and O_3 each only slightly changed when other pollutants were considered in two-pollutant models (Table 4). The models with SO_2 and NO_2 had poorer goodness-of-fit statistics. The log odds ratio for SO_2 was reduced by almost half in the model with PM_{10}, suggesting its association was substantially due to confounding with particles. The NO_2 log odds ratio was reduced by about one-third also suggesting some confounding with PM_{10}.

Other measures of particulate matter on the previous 3 d also were associated with cough incidence, although the associations and statistical significance of these were weaker; $PM_{2.5}$ (OR for 20 $\mu g/m^3$ = 1.19, 95% CI = 1.01–1.42), fine particle sulfur (OR for 5 $\mu g/m^3$ = 1.23, 95% CI = 0.95–1.59), and nephelometry (OR for 1 km^{-1} = 1.21, 95% CI = 1.02–1.45).

Aerosol acidity H^+ over the previous 3 d was not significantly associated with cough incidence (OR for 25 $nmol/m^3$ = 1.06, 95% CI = 0.87–1.29). Local smoothing with the Generalized Additive Model showed no increase in cough incidence until concentrations exceeded 50 $nmol/m^3$, approximately the 80th percentile. Above 50 $nmol/m^3$ the incidence of cough increased with concentration up to approximately 150 $nmol/m^3$ and then decreased. Thus there was little evidence that H^+ was more strongly associated with incidence of cough than the mass concentration of inhalable particles (PM_{10}).

Incidence of Lower Respiratory Symptoms

There was no significant serial correlation in the incidence of lower respiratory symptoms. Of the criteria pollutants, the strongest association ($p = 0.0005$) was with inhalable particles (PM_{10}) on the previous day (OR for 30 $\mu g/m^3$ = 1.53, 95% CI 1.20–1.95) (Table 5). Sulfur dioxide also was associated with incidence of lower respiratory symptoms (OR for 10 ppb = 1.28, 95% CI 1.13–1.46, $p = 0.0011$), as was ozone (OR for 30 ppb = 1.35, 95% CI 1.00–1.84). In two-pollutant models (not shown) the estimated effects of inhalable particles were stable on inclusion of other pollutants, whereas the estimated effects of sulfur dioxide, ozone, and nitrogen dioxide were all substantially reduced (and not statistically significant) after adjusting for particle concentrations.

The incidence of lower respiratory symptoms was most strongly associated with each of these pollutants with a lag of 1 d. The association for each fell off when pollution was averaged over several previous days. The results when different components of the particulate fraction were examined (Table 5) showed no evidence that either the finer fraction ($PM_{2.5}$), the sulfur fraction, or the acidic fraction was more potent than PM_{10} in increasing the incidence of respiratory symptoms. Aerosol acidity (H^+) was not significantly associated with lower respiratory symptom incidence ($p = 0.22$). A test for increased incidence associated with episodes of aerosol acidity (60 $nmol/m^3$) was also insignificant.

TABLE 5
LOWER RESPIRATORY SYMPTOMS REGRESSED ON INDIVIDUAL AIR POLLUTANTS ON THE PREVIOUS DAY AFTER CONTROLLING FOR TEMPERATURE, DAY OF WEEK, AND CITY OF RESIDENCE

Pollutant*	Exposure†	Odds Ratio	95% CI	*t* Statistic
Mean Gases				
SO_2	10 pb	1.28	1.13–1.46	3.27
O_3	30 ppb	1.35	1.00–1.84	1.96
NO_2	10 ppb	1.20	0.98–1.47	1.73
Particulate measures				
PM_{10}	30 $\mu g/m^3$	1.53	1.20–1.95	3.47
$PM_{2.5}$	20 $\mu g/m^3$	1.44	1.15–1.82	3.13
$PM_{2.5}$ Sulfur	5 $\mu g/m^3$	1.82	1.28–2.59	3.35
Nephelometry	1 km^{-1}	1.36	1.14–1.63	3.33
H^+	25 $nmol/m^3$	1.05	0.25–1.30	0.44

* Mean of previous 24 h.
† Values represent incremental increase in each pollutant for estimated odds ratio.

When smoothed plots of the relative odds of the incidence of lower respiratory symptoms versus individual pollutants were examined, a monotonic concentration response relationship was seen with PM_{10} (Figure 3), and the test for deviation from linearity was not significant. No increase in the incidence of lower respiratory symptoms was seen with SO_2 until concentrations exceeded 22 ppb (Figure 4), nor with hydrogen ion until concentrations exceeded 110 nm/m^3 (Figure 5), which only occurred on a few days. For ozone, the smoothed plot revealed a pattern of increasing lower respiratory symptom incidence with increasing ozone concentration as high as about 40 ppb, at which point no further increase in rates with increasing ozone was seen.

Incidence of Upper Respiratory Symptoms

No significant serial correlation was observed in any models of the incidence of upper respiratory symptoms. None of the measured air pollutants was significantly associated with incidence of upper respiratory symptoms. PM_{10} 2 d before the event was associated with increased incidence of upper respiratory symptoms (OR for 30 $\mu g/m^3$ = 1.22, 95% CI 0.98–1.52, $p = 0.076$) as was $PM_{2.5}$ 2 d before (OR for 20 $\mu g/m^3$ = 1.22, 95% CI 1.00–1.49,

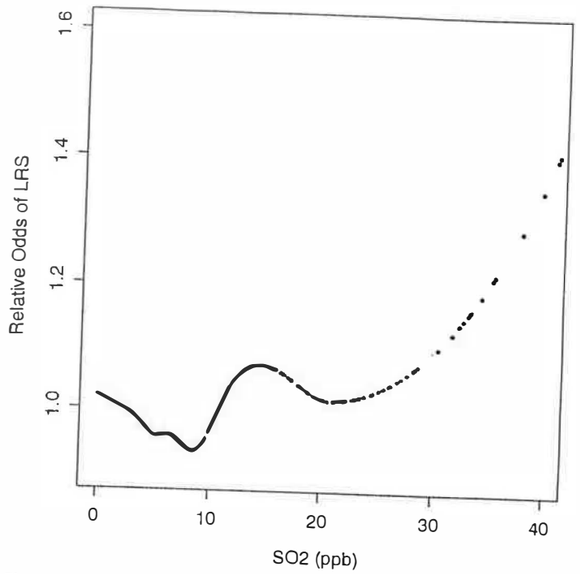

Figure 4. Relative odds of incidence of LRS smoothed against 24-h mean SO_2 concentration on the previous day, controlling for temperature, city, and day of the week.

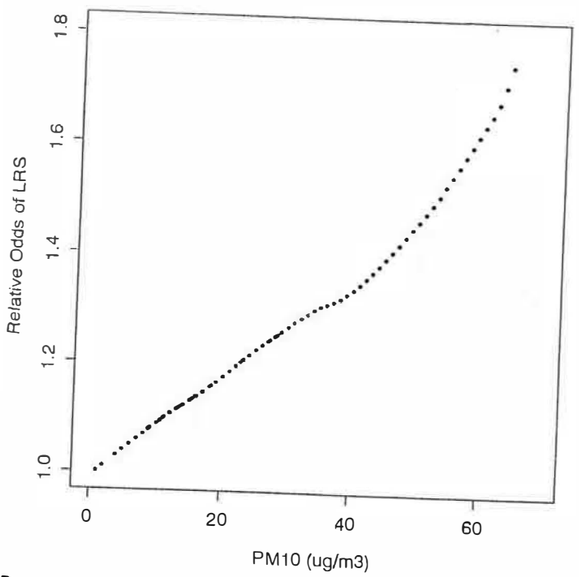

Figure 3. Relative odds of incidence of lower respiratory symptoms (LRS) smoothed against 24-h mean PM_{10} ($\mu g/m^3$) on the previous day controlling for temperature, day of the week, and city.

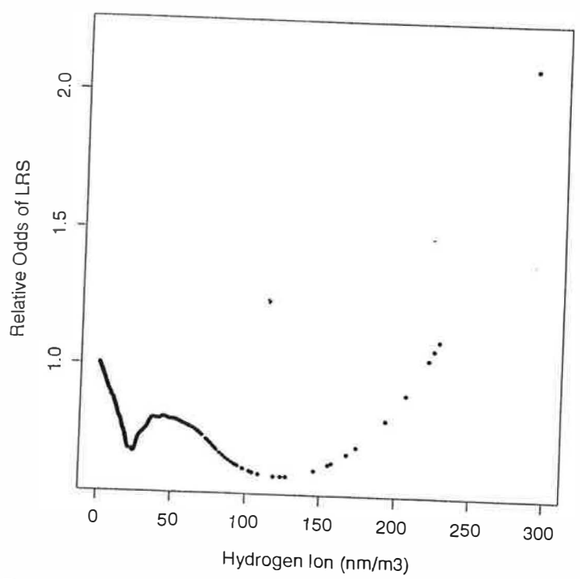

Figure 5. Relative odds of incidence of LRS smoothed against 24-h mean H^+ concentration on the previous day, controlling for temperature, city, and day of the week.

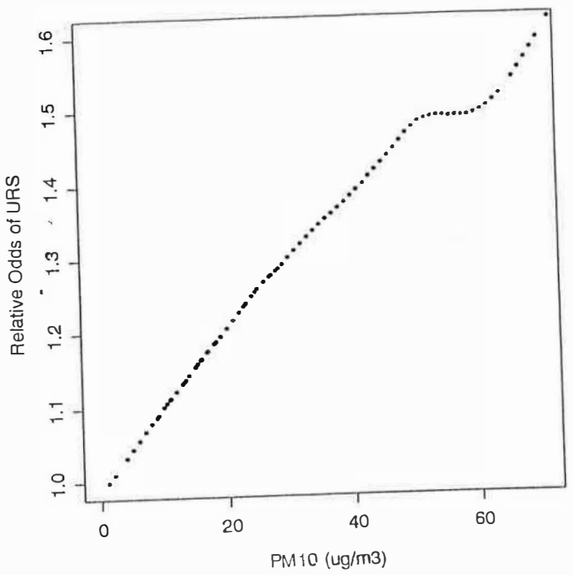

Figure 6. Relative odds of incidence of upper respiratory symptoms (URS) smoothed against 24-h mean PM_{10} concentration 2 d earlier, controlling for temperature, city, and day of the week.

p = 0.056). Hydrogen ion 2 d before was weakly associated (OR for 25 nmol/m³ = 1.06, 95% CI 0.98–1.15, p = 0.15). When the shape of the relationship was examined in the Generalized Additive Model, incidence of upper respiratory symptoms showed an exposure-dependent increase across the entire range of PM_{10} concentrations (Figure 6). The test for improved fit compared with a linear model on the logistic scale was not significant (p = 0.67).

In contrast, hydrogen ion showed no consistent association with incidence of upper respiratory symptoms until concentrations exceeded 110 nmol/m³. This relationship was similar to that for the incidence of lower respiratory symptoms.

DISCUSSION

Particulate matter concentration was associated with the incidence of all of the respiratory symptoms examined in this study. The association was strongest with incidence of lower respiratory symptoms and weakest with incidence of upper respiratory symptoms. All of the particulate measures (PM_{10}, $PM_{2.5}$, fine sulfate, nephelometry) had essentially the same association with the incidence of these respiratory symptoms. While the high correlation among the various measures of particulate matter (ranging from 0.72 between PM_{10} and nephelometry to 0.94 between $PM_{2.5}$ and its sulfur fraction) precludes drawing strong conclusions regarding the relative importance of these measures, there is certainly nothing in these data to suggest that measures other than PM_{10} are better predictors of the incidence of respiratory symptoms.

In contrast, the correlation between PM_{10} and hydrogen ion concentration is only 0.54 in these data, and the difference in the correlations with respiratory incidents is striking. While measurement error is a larger fraction of the variability of the hydrogen ion measure than of the PM_{10} measurements, a dummy variable for high acid concentrations was likewise insignificant. The nonparametric smoothed curves indicated that hydrogen ion might have a threshold for effect at 110 nmol/m³. However, the small number of days above these concentrations makes confounding a possible alternative explanation. The Utah Valley studies (3, 4, 17, 19) reported associations of PM_{10} with respiratory symptoms and hospitalization in a location with essentially no SO_2 and a particulate aerosol with no detectable acidity. This fits well with our finding of an association with PM_{10}, but not with aerosol strong acidity. The exposure-dependent increase in symptoms seen across the entire range of PM_{10} certainly suggests that the effect is principally related to particle mass, and not specifically to the acidic components. Acid may increase the particulate effect if it is in high enough concentrations, however. This may relate to neutralization of lower concentrations of acidic aerosols by ammonia in the breathing zone (38). Further investigation of any role of aerosol acidity in modulating the effects of PM_{10} is needed to clarify this.

Table 6 summarizes the associations reported here in comparison with previously reported associations between inhalable particulate concentrations and respiratory symptoms. Overall there is good agreement among the studies, particularly given that there were differences in the definition of symptom complexes between the studies. The consistency of findings in both summer studies in Six Cities and winter studies in Utah suggests that the associations are not limited to photochemically produced aerosols.

The observed association with other pollutants was not as clear. SO_2 was associated with the incidence of cough symptoms and of lower respiratory symptoms. For both of these endpoints, the association was weaker than that for PM_{10}. The SO_2 association was also due to a few influential observations, and disappeared when those observations were excluded. No association was seen across the bulk of the range of variation of SO_2. Although this may reflect a threshold for the effect of SO_2, results dependent on a few influential observations must be viewed with caution. The SO_2 results were confounded with the PM_{10} correlations for both outcomes. The better fit of the PM_{10} models, coupled with the strong evidence of a monotonic increase in symptoms with PM_{10} across the entire range of its variation suggest that the PM_{10} relationship is more plausible. This is further supported by the evidence from other studies.

TABLE 6

ODDS RATIOS AND 95% CONFIDENCE INTERVALS FOR A 30 μg/m³ INCREASE IN PM_{10} ASSOCIATED WITH RESPIRATORY SYMPTOMS IN RECENT DIARY STUDIES

	Cough		Lower Respiratory Symptoms		Upper Respiratory Symptoms	
Study*	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI
Six Cities	1.22	1.03–1.45	1.53	1.20–1.95	1.22	0.98–1.52
Switzerland† (21)	1.41	1.17–1.70	NA		1.23	1.06–1.43
Utah Valley 1990–91 (4)						
Asymptomatic children	1.20	1.04–1.38	1.12	0.85–1.32	1.02	0.84–1.24
Symptomatic children	1.24	1.10–1.34	1.22	1.08–1.37	1.17	1.04–1.32
Utah Valley 1989–90‡ (3)	NA		1.16	1.03–1.31	1.11	1.02–1.21

* Numbers in parentheses refer to references.
† PM_{30} converted to PM_{10} a ratio of PM_{10}/PM_{30} = 0.65.
‡ Increased use of asthma medication was associated with air pollution, which may have dampened the effect on symptoms.

Ozone was also associated with cough incidence. Ozone had the best goodness-of-fit statistic after PM_{10} in the single-pollutant models for incidence of cough. Its coefficient was essentially unchanged when it was considered in models with other pollutants, suggesting little evidence that the association was due to confounding with the other pollutants. Overall, the weight of the evidence suggests ozone as the most likely other pollutant associated with cough incidence. The estimated coefficient for ozone in the two-pollutant model was marginally insignificant, but this likely reflects the lower sample size caused by the greater number of days with missing PM_{10} data. The relationship between ozone and incidence of lower respiratory symptoms, in contrast, was only marginally significant, and the shape of the exposure–response relationship was implausible. This relationship is probably influenced by confounding with other factors.

One limitation of this study is the use of central station outdoor monitoring of pollution as the estimate for individual exposure. However, the study areas are small communities or defined areas of larger communities so that spatial scales are not large (< 10 km). More importantly, in this study design, the sample day is the unit of measurement. Although there may be spatial or other differences between individual and ambient exposure estimates, these will only affect the effect estimates if they vary day-to-day and specifically if these differences covary with ambient pollution. Thus errors in individual exposure are likely to be random and bias the estimated effect with respect to personal exposure towards the null. Moreover, we are not attempting to estimate the effect of personal exposure, but rather the effect of day-to-day variations in ambient exposure of respiratory symptom incidence. This is the relevant exposure for standard setting.

Misclassification of the reports of respiratory symptoms in children by the parents is also possible. This would introduce a bias if reporting varied with perceived air pollution concentrations. However, because air pollution concentrations were low in this study, almost all below the standards set to protect public health, it is unlikely that parents were aware of, or modified their reporting in association with exposures.

Chamber studies of exposure to 80 ppb ozone in exercising young adults have reported increased coughing symptoms as well as decreased pulmonary function (39). Given the exercise protocol in these studies, the cumulative daily dose was undoubtedly higher than those seen in our study. Ozone exposure has been associated with increased respiratory symptoms in asthmatics (40) and weakly associated with respiratory symptoms in a general population of adults (41). Higher doses of ozone have been associated with evidence of cell damage, mediator release, and inflammatory response in bronchoalveolar lavage fluid (42). Oxidant exposure has been associated with the incidence of chest discomfort (25) and the duration (but not incidence) of coughing episodes in a diary study of student nurses (43).

Recent studies have found associations between acute exposure to airborne particles and a continuum of effects including reductions in lung function (1–4), increased respiratory symptoms in mildly asthmatic schoolchildren (3), increased need for asthma medication in those children, increased hospital emergency room visits for asthma and other respiratory conditions (44–47), increased hospitalization admissions for asthma and other respiratory ailments (17–19), and increased daily mortality, particularly for respiratory conditions (10–15). Asthmatics are not the only people who appear to show these effects. Decreased lung function and increased symptoms were seen in nonasthmatic schoolchildren (4), and a test for heterogeneity of response of lung function to particles in a general population sample of schoolchildren in Steubenville showed no evidence for heterogeneity (48). Increased symptoms also were reported in a Swiss diary study (21), and increased hospital and pediatrician visits for croup have also been associated with particulate air pollution (16). Increased school absences have also been associated with particulate air pollution in a general population study (49). Acute respiratory morbidity also has been associated with particulate concentrations in adults (41). Exposure to particulates and SO_2 has been linked to increased bronchial secretion during colds (50). The consistency of these findings across the full range of acute respiratory responses argues strongly for the causality of these associations. Although confounding can not be eliminated as an explanation for these epidemiologic findings, in such time series studies the principal confounder is likely to be weather factors that have not been perfectly controlled. The studies mentioned previously cover two continents, and include locations where particle concentrations peak in the winter as well as locations where they peak in the summer. Humid and dry climates are included. These contrasts in climate suggest that the observed air pollution associations are independent of weather. In this study only data from warm weather months were used, which reduces possible confounding by weather or epidemics.

Indirectly supporting evidence is provided by studies linking longer term exposure to particles to chronic respiratory responses. These include a cross-sectional comparison of these cities finding a strong association between rates of acute bronchitis and PM_{15} annual concentrations (28), and a long-term follow-up of Seventh Day Adventists which found an association between integrated particle exposure and the prevalence of chronic bronchitis in adults (51).

Thus, this study suggests that episodes of particulate air pollution, measured by PM_{10}, $PM_{2.5}$, nephelometry, or sulfate concentrations, are associated with increased incidence of cough, lower respiratory symptoms, and also upper respiratory symptoms. These data did not support the hypothesis that the acidity of the particulates was associated with incidence of these symptoms. Ozone episodes were also associated with cough incidence. Thus increased symptom reporting was observed in association with summer haze events, which are characterized by high ozone and fine particle concentrations. The acidity of particles during these summer haze episodes was not specifically associated with respiratory symptom incidence.

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Longitudinal Changes in Lung Function among Asbestos-exposed Workers

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To prospectively identify the determinants of persistent or accelerated loss of lung function among workers occupationally exposed to asbestos and assess the relative contribution of cigarette smoking, asbestos-induced pleural fibrosis, and specific findings from bronchoalveolar lavage and high resolution CT scans, we examined the determinants of lung function changes in 117 subjects occupationally exposed to asbestos for at least 1 yr in a high exposure setting. A minimum of 20 yr was required between the first exposure to asbestos and entry into the study. Baseline studies included an independent assessment of dyspnea, lung volumes, diffusing capacity of carbon monoxide (D_{LCO}), a chest radiograph, a high resolution CT (HRCT) scan, and bronchoalveolar lavage (BAL). Subjects were observed for an average of 2 yr (range, 0.5 to 4.0 yr), and lung function was measured on at least two separate occasions (mean, 4.1 separate tests). During the period of observation, there was an average 1.5% decrease in the TLC and a 2.5% decrease in the D_{LCO}. In this longitudinal data set, after controlling for age, height, pack-years of cigarette smoking, and follow-up time, persistently lower measures of TLC were independently related to moderate to severe dyspnea ($p = 0.005$), diffuse pleural thickening ($p = 0.007$), and higher concentrations of fibronectin in BAL fluid ($p = 0.01$). Interstitial lung disease either on the chest radiograph or HRCT scan was not independently associated with persistently lower measures of TLC during the period of observation. However, none of the clinical variables we examined were associated with an accelerated decline in TLC. After controlling for age, height, and follow-up time, persistently lower measures of D_{LCO} were independently related to moderate to severe dyspnea ($p = 0.006$), increased pack-years of cigarette smoking ($p = 0.00001$), honeycombing on HRCT scan ($p = 0.0009$), and higher concentrations of lymphocytes ($p = 0.0008$), neutrophils ($p = 0.0005$), eosinophils ($p = 0.03$), and fibronectin ($p = 0.02$) in the BAL fluid. Importantly, higher concentrations of neutrophils and eosinophils in the BAL fluid were significantly associated with an accelerated decline in gas exchange during the period of observation. These results indicate that among asbestos-exposed subjects, prognostically important risk factors include symptoms of dyspnea, cigarette smoking, diffuse pleural thickening, honeycombing on HRCT scan, and higher concentrations of inflammatory cells and fibronectin in the BAL fluid. **Schwartz DA, Davis CS, Merchant JA, Bunn WB, Galvin JR, Van Fossen DS, Dayton CS, Hunninghake GW. Longitudinal changes in lung function among asbestos-exposed workers. Am J Respir Crit Care Med 1994;150:1243–9.**

Asbestosis and asbestos-induced pleural fibrosis are traditionally thought to be slowly progressive disorders. Radiographic evidence of disease progression appears to be associated with advanced age (1–3), increased evidence of asbestos-induced lung disease on the chest radiograph (1, 4–7), more extensive occupational exposure to asbestos (2, 5, 8–10), and cigarette smoking (1, 7, 9). Progressive restrictive physiology has been reported to be associated with cumulative asbestos exposure (8, 11–13), cigarette smoking (11), and either the presence of asbestosis (8) or of diffuse pleural thickening (4, 8) on the chest radiograph. Excess declines in diffusing capacity have been associated with higher concentrations of neutrophils in bronchoalveolar lavage (BAL) fluid (14). Risk factors such as advanced age, more extensive occupational exposure to asbestos, cigarette smoking, and specific radiographic abnormalities, which are found to be associated with disease progression, are particularly important when one considers that, among those with asbestosis, as much as 20% of the attributable mortality appears to be caused by progressive, interstitial fibrosis (15). Beyond the inherent clinical utility of these prognostic factors, specific risk factors may be particularly useful in identifying populations that may warrant aggressive therapeutic trials to diminish the risk of disease progression.

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