Are There Sensitive Subgroups for the Effects of Airborne Particles?

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Recent studies have shown that particulate air pollution is a risk factor for hospitalization for heart and lung disease; however, little is known about what subpopulations are most sensitive to this pollutant. We analyzed Medicare hospital admissions for heart disease, chronic obstructive pulmonary disorders (COPD) and pneumonia in Chicago, Cook County, Illinois, between 1985 and 1994. We examined whether previous admissions or secondary diagnoses for selected conditions predisposed persons to having a greater risk from air pollution. We also considered effect modification by age, sex, and race. We found that the air-pollution-associated increase in hospital admissions for cardiovascular diseases was almost doubled in subjects with concurrent respiratory infections. The risk was also increased by a previous admission for conduction disorders. For COPD and pneumonia admissions, diagnosis of conduction disorders or dysrhythmias increased the risk of particulate matter < 10 μm in aerodynamic diameter (PM_{10})-associated admissions. Persons with asthma had twice the risk of a PM_{10}-associated pneumonia admission and persons with heart failure had twice the risk of PM_{10}-induced COPD admissions. The PM_{10} effect did not vary by sex, age, and race. These results suggest that patients with acute respiratory infections or defects in the electrical control of the heart are a risk group for particulate matter effects. *Key words*: effect modification, hospital admissions, particulate air pollution. *Environ Health Perspect* 108:841–845 (2000). [Online 28 July 2000]
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Particulate air pollution has been associated with increases in daily deaths and hospital admissions in studies all over the world (*1–15*). These associations are now well documented but little is known, as yet, of the characteristics of persons that put them at increased risk of adverse events related to particulate air pollution. This has been identified as a key data gap (*16*).

Schwartz and Dockery (*17*) reported that persons older than 65 years of age had a somewhat increased risk of death, and this has been confirmed in other studies (*18*). A more detailed examination of particulate matter-related risk by deciles of age (*19*) showed the risk beginning to increase at approximately 40 years of age and reaching its maximum for those 75 years of age and older.

In addition to age, several studies suggest that persons with respiratory illness are at increased risk for cardiovascular effects associated with air pollution. An examination of death certificates on high- and low-air pollution days reported a substantial difference in the proportion of deaths from cardiovascular causes that had respiratory disease as a contributing cause of death (*19*). A recent follow-up study of a cohort of persons with chronic obstructive pulmonary disease (COPD) in Barcelona, Spain, found an association between particulate air pollution and all-cause mortality in the cohort (*20*). The magnitude of the risk per microgram per cubic meter of exposure was substantially greater than that for the general population. Controlled exposure of animals with chronic bronchitis and control animals to concentrated air particles also demonstrated a potentiating effect of chronic lung disease in the response to airborne particles (*21*). This has led to the hypothesis that the cardiovascular effects of air pollution are predominantly in persons with chronic lung disease. There has been even less done to examine potential modifiers of the effects of airborne particles on hospital admissions.

The existing literature on comorbidity shows that comorbidity per se seems to increase the risk of adverse outcomes (*22–30*). Little is known about the role of these comorbidities as effect modifiers for the effects of air pollution.

This study uses data from the Medicare system to examine potential short-term and long-term medical conditions that may increase a person's risk of hospital admissions associated with particulate air pollution. In addition, we examine potential effect modification by age, race, and sex.

Materials and Methods

Health data. The Health Care Financing Administration (Baltimore, MD) maintains records of every hospital admission for Medicare participants in the United States. Persons in this database have a unique identifier. Using this identifier, we traced every hospital admission for heart and lung disease for each person in Cook County, Illinois, between 1985 and 1994. We chose Cook County because it is the most populous county in the United States with daily monitoring for particulate matter with aerodynamic diameter < 10 μm (PM_{10}). The data were then analyzed to look at effect modification by concurrent and preexisting conditions as well as by age, race, and sex.

To establish a baseline risk, we computed daily counts of hospital admissions for cardiovascular disease (CVD) [*International Classification of Disease, 9th edition*, World Health Organization, Geneva (ICD-9) code 390–429], pneumonia (ICD-9 code 480–487), and COPD (ICD-9 code 490–496, excluding 493). The association between these daily counts and PM_{10} was examined for the years 1988–1994, when daily PM_{10} monitoring data were available in Chicago.

Once our baseline risks were established, we examined three classes of potential effect modifiers. First, we looked at whether previous admissions for selected conditions predisposed persons to having a greater risk from air pollution. For each of the three admission categories (CVD, pneumonia, and COPD), we considered 10 causes (defined by a previous admission) as effect modifiers: COPD (ICD-9 code 490–496 except 493), asthma (ICD-9 code 493), acute bronchitis (ICD-9 code 466), acute respiratory illness (ICD-9 code 460–466), pneumonia (ICD-9 code 480–487), CVD (ICD-9 code 390–429), myocardial infarction (ICD-9 code 410), congestive heart failure (ICD-9 code 428), conduction disorders (ICD-9 code 426), and dysrhythmias (ICD-9 code 427).

To test the hypothesis that persons with these conditions had higher risks of subsequent PM_{10}-related admissions, we computed separate daily counts of admissions for our three target causes, stratified by whether or not the person admitted had been previously admitted for the hypothesized predisposing condition. Separate analyses were then performed within each strata to see if the effects of PM_{10} differed by strata.

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The second set of potential predisposing conditions included secondary diagnoses associated with the index admission. These could represent the presence of a chronic condition (e.g., COPD) that has not resulted in a previous hospital admission. They could also represent acute conditions that may have increased the subjects' sensitivity to air pollution. For example, if respiratory infections modified the effect of particulate matter on the cardiovascular health of persons with underlying heart disease, then the risk of a hospital admission for heart disease might be different in persons with infections. If this were true, then the risk ratio of a 10-μg/m^3 increase of PM_{10} on cardiovascular admissions of persons with a concurrent respiratory infection would be different from the ratio in persons without respiratory infection. To test these hypotheses, we computed separate daily counts of admissions for events with and without the concurrent conditions hypothesized to increase sensitivity to air pollution. These were taken as the same 10 conditions in the first analysis with certain exclusions for pairing that would be illogical. That is, the concurrent diagnosis of a specific cardiac condition was not treated as an effect modifier for admissions for any cardiovascular condition. Likewise, pneumonia and COPD were not possible concurrent conditions for each other.

The third set of predisposing conditions considered was being older than 75 years of age, nonwhite, and female. These were examined for all three outcomes.

We obtained weather data for O'Hare Airport from the EarthInfo CD-ROM (EarthInfo CD NCDC Surface Airways, EarthInfo Inc., Boulder, CO), and we obtained air pollution data from the U.S. Environmental Protection Agency Aerometric Information Retrieval System network (*31*).

Methods

We analyzed the data with a generalized additive robust Poisson regression model (*32*). This approach has become the norm in such studies (*14*,*33*,*34*). In the generalized additive model the outcome is assumed to depend on a sum of nonparametric smooth functions for each variable that models the potential nonlinear dependence of daily admission on weather and season. The model is of the form:

$$\log[E(Y_t)] = \alpha_0 + S_1(X_1) + \ldots + S_p(X_p)$$

where $E(Y_t)$ is the expected value of the daily count of admissions Y_t and S_i are the smooth functions of the covariates X_i. We examined temperature, previous day's temperature, relative humidity, barometric pressure, and day of week covariates. The locally weighted running-line smoother, loess (*35*), was chosen to estimate the smooth function.

To control for weather variables and day of the week, we chose the smoothing parameter that minimized the Akaike's information criterion (*36*).

To model seasonality we chose the smoothing parameter that minimized the sum of the autocorrelation of the residuals while removing seasonal patterns. Two autoregressive terms (*37*) were added in the model to eliminate the remaining serial correlation from the residuals. We used the mean of PM_{10} on the day of the admission and the day before the admission as our exposure variable. This gives results that are similar to those obtained fitting a full distributed lag model (*38*). PM_{10} was treated linearly.

Our baseline models used the daily counts of CVD, pneumonia, and COPD admissions as outcomes. We then subdivided those counts by the presence or absence of the potential effect modifier and reestimated our regressions on those subgroups.

We considered effect modification to be indicated when the estimates of PM_{10} in the group with the condition was outside of the 95% confidence interval (CI) of the effect estimate in persons without the condition.

Results

Table 1 shows the mean daily admissions for COPD, cardiovascular, and pneumonia both overall and in the presence of the potential effect modifiers. For some effect modifiers such as conduction disorders or myocardial infarctions, the counts in conjunction with our respiratory outcomes are low, which limits power. In general, the numbers are lower for examining effect modification by previous admissions than for effect modification by concurrent diagnosis. This is as expected because many clinically relevant comorbidities may never have resulted in a hospital admission.

Table 2 shows the 25th, 50th, and 75th percentile values for the environmental variables. The mean value for PM_{10} is 33 μg/m^3. The daily values for PM_{10} were computed as the average of 10 monitors, two of which measured PM_{10} almost every day and the others less frequently (*38*).

Table 3 shows the mean daily counts of CVD, COPD, and pneumonia by sex, age groups, and race. The distribution by sex is almost even, although the counts of admissions for males are generally lower (approximately 10%) than for females, particularly for cardiovascular diseases. The counts of CVD, COPD, and pneumonia admissions were similar for people 65–75 or 75 years of age and older.

Tables 4–6 show the results for the effect PM_{10} overall and stratifying by concurrent diagnosis and previous admissions. These are expressed as the percentage increase for 10 μg/m^3 PM_{10}.

Table 4 shows the results for CVD. A 10-μg/m^3 increase in PM_{10} was associated with a 1.31% (5% CI, 0.97%; 95% CI, 1.66%) increase in hospital admissions for heart disease in all elderly persons. A concurrent (not previous) diagnosis of COPD modified the risk of PM_{10}-associated admissions for heart disease. However, significant associations were still seen between PM_{10}

Table 1. Mean daily counts of admissions, Chicago 1986–1994, for COPD, CVD, and pneumonia overall and by concurrent diagnosis and by previous admissions.

	By concurrent diagnosis			By previous admissions		
	COPD	CVD	Pneumonia	COPD	CVD	Pneumonia
Overall	7.8	102.1	26.5	7.8	102.1	26.5
Respiratory disease						
Acute bronchitis	0.1	0.9	0.3	0.8	1.6	0.9
Acute respiratory infections	0.3	1.3	0.3	0.9	1.8	1.0
Pneumonia	0.4	4.0	NA	1.6	7.3	6.4
Asthma	0.1	1.8	0.9	0.9	1.5	0.7
COPD	NA	13.4	6.9	2.7	2.0	1.4
Cardiovascular disease						
CVD	4.7	NA	14.7	2.1	54.7	7.2
Conduction disorders	0.2	NA	0.6	0.0	1.0	0.2
Cardiac dysrhythmias	1.4	NA	4.6	0.4	9.9	1.5
Congestive heart failure	1.8	NA	7.3	0.9	24.2	3.1
Myocardial infarction	0.1	NA	0.4	0.3	11.4	1.0

NA, not applicable.

Table 2. 25th, 50th, and 75th percentile values for the environmental variables in Chicago, 1988–1994.

Temperature (°F)	Relative humidity	Barometric pressure	PM_{10} (μg/m^3)
35	62	29.2	23
51	70	29.3	33
67	79	29.4	46

Table 3. Mean daily counts of admissions by sex, race, and age groups, Chicago, 1986–1994.

Group	COPD	CVD	Pneumonia
Overall	7.8	102.1	26.5
Female	4.2	59.4	14.7
Nonwhite	1.6	21.0	5.2
Age > 75 years	3.7	55.1	17.4

and heart disease admissions in persons without COPD listed as either a comorbidity or a cause of previous admission (Table 4). A significant association was also seen in persons without any respiratory disease as a concurrent diagnosis, although the risk is much lower than in persons with respiratory disease. However, the risk associated with PM_{10} was roughly doubled in subjects with concurrent respiratory infections and the risk estimates in those subjects were outside the 95% CI of the risk in patients without concurrent respiratory infections.

A previous admission for conduction disorders (e.g., heart block) increased the risk of a PM_{10}-related subsequent admission for any heart condition, and a weaker indication of effect modification was seen for persons with previous admission for dysrhythmias. In contrast heart failure and previous myocardial infarctions were highly insignificant as effect modifiers.

Table 5 shows the results for COPD. Overall, there is a 1.89% (95% CI, 0.8–3.0) increase in COPD admissions for a 10-$\mu g/m^3$ increase in PM_{10}.

The results of the stratified analysis suggest that preexisting heart disease modifies the risk of COPD admissions on high particle days. Previous admissions for any cardiovascular disease increased the risk of a PM_{10}-associated COPD admission approximately 2.5-fold. A previous heart failure admission caused an even more striking increase in the PM_{10} effect. Previous admissions for dysrhythmias and conduction defects were rare (Table 1) with no power to examine effect modifications. Listings as concurrent diagnoses were more common and here they joined heart failure in increasing the risk of PM_{10}-associated COPD admissions. For COPD there was also some indication that concurrent pneumonia or an acute respiratory infection admission in the last year increased risk. The low numbers made these estimates less precise, however.

The percentage increase in pneumonia admission (Table 6) for 10 $\mu g/m^3$ PM_{10} is higher than for COPD or CVD with an increase of 2.34% (95% CI, 1.66–3.0).

As with COPD, persons with heart disease appeared at higher risk of pneumonia hospital admissions associated with particulate air pollution. Here diagnoses suggestive of impaired autonomic control of the heart, such as conduction disorders or dysrhythmias, were associated with increased risk for PM_{10} effects on pneumonia admissions. Unlike COPD, no difference was seen for congestive heart failure. Persons with asthma had twice the risk of a PM_{10}-induced pneumonia admission as persons without asthma.

Table 7 shows the results by sex, age, and race. None of the effect size estimates for any of the stratification variables were outside of the 95% CI for the opposite strata. There was a tendency for the effect of PM_{10} on CVD admissions to be higher for females, whereas the effect on pneumonia admissions was higher for males. In general, we found somewhat larger effects on whites compared to nonwhites, and for persons older than 75 years of age compared to younger persons.

Discussion

In this analysis we examined whether the effect of PM_{10} on the risk of hospital admission for heart and lung disease was different depending on the presence of comorbidities. We found that PM_{10} was associated with hospital admissions for all three causes (CVD, COPD, and pneumonia) and we found not a general increase in PM_{10} related risk with comorbidities, but a specific pattern that is suggestive of potential mechanisms and consistent with other recent epidemiologic and toxicologic findings.

One major finding of this study is that preexisting cardiovascular disease, particularly impaired autonomic control (conduction defects and dysrhythmias) and heart failure, substantially increased the risk of respiratory admissions associated with airborne particles.

In fact, recent human studies have shown that exposure to particulate air pollution is a risk factor for reduced heart rate variability (*39–41*). Reduced heart rate variability is an adverse response and a risk factor for arrhythmia. A new study of defibrillator discharges in patients with implanted cardioverter defibrillators found that discharges were associated with air pollution (*42*). Exposure to combustion

Table 4. Percentage increase in hospital admissions for CVD in all persons and by concurrent diagnosis and previous admissions.

	PM_{10}	2.5% CI	97.5% CI
All persons	1.31	0.97	1.66
By concurrent diagnosis			
Respiratory disease			
All respiratory disease			
With	1.65	1.10	2.20
Without	0.98	0.64	1.33
Acute bronchitis			
With	2.50	–0.47	5.55
Without	1.07	0.76	1.37
Acute respiratory infections			
With	2.71	0.18	5.30
Without	1.06	0.76	1.37
Pneumonia			
With	1.95	0.55	3.36
Without	1.03	0.72	1.35
COPD			
With	1.59	0.85	2.34
Without	1.08	0.75	1.41
By previous admissions			
Respiratory disease			
All respiratory disease			
With	1.18	0.45	1.91
Without	1.08	0.76	1.41
COPD			
With	1.48	–0.40	3.40
Without	1.09	0.78	1.40
Asthma			
With	1.71	–0.43	3.89
Without	1.08	0.77	1.39
Cardiovascular disease			
Conduction disorders			
With	2.89	0.22	5.63
Without	1.07	0.76	1.38
Cardiac dyshrethmias			
With	1.61	0.75	2.48
Without	1.04	0.72	1.36

Increases are for a 10-$\mu g/m^3$ increase in PM_{10}.

Table 5. Percentage increase in hospital admissions for COPD in all persons and by concurrent diagnosis and previous admissions.

	PM_{10}	2.5% CI	97.5% CI
All persons	1.89	0.80	2.99
By concurrent diagnosis			
Respiratory disease			
Pneumonia			
With	4.00	–0.45	8.65
Without	1.51	0.47	2.57
Cardiovascular disease			
Conduction disorders			
With	2.34	–4.42	9.59
Without	1.60	0.58	2.64
Cardiac dysrhythmias			
With	3.09	0.64	5.60
Without	1.43	0.33	2.55
Congestive heart failure			
With	2.90	0.77	5.08
Without	1.39	0.24	2.55
By previous admissions			
Respiratory disease			
Acute respiratory infections			
With	3.20	–1.38	8.01
Without	1.70	0.66	2.76
Cardiovascular disease			
CVD			
With	2.90	0.99	4.85
Without	1.18	–0.01	2.39
Congestive heart failure			
With	4.37	1.43	7.40
Without	1.14	0.05	2.24
Within 1 year	6.04	2.10	10.14

Increases are for a 10-$\mu g/m^3$ increase in PM_{10}.

Table 6. Percentage increase in hospital admissions for pneumonia in all persons and by concurrent diagnosis and previous admissions.

	PM_{10}	2.5% CI	97.5% CI
All persons	2.34	1.66	3.02
By concurrent diagnosis			
Respiratory disease			
Asthma			
With	4.18	1.01	7.46
Without	2.07	1.46	2.69
Cardiovascular disease			
Conduction disorders			
With	7.92	4.28	11.69
Without	1.99	1.37	2.61
Cardiac dysrhythmias			
With	–	–	–
Without	–	–	–
By previous admissions			
Cardiovascular disease			
Cardiac dysrhythmias			
With	3.47	1.21	5.79
Without	2.08	1.45	2.71

Increases are for a 10-$\mu g/m^3$ increase in PM_{10}.

Table 7. Effect modification by sex, race, and age groups for 10 μg/m^3 PM_{10}.

	COPD		CVD		Pneumonia	
	%	(95% CI)	%	(95% CI)	%	(95% CI)
All persons	1.89	(0.80, 2.99)	1.31	(0.97, 1.66)	2.34	(1.66, 3.02)
Male	1.34	(–0.14, 2.84)	1.07	(0.62, 1.51)	2.65	(1.81, 3.5)
Female	2.19	(0.81, 3.59)	1.21	(0.83, 1.6)	1.91	(1.11, 2.72)
White	1.65	(0.51, 2.81)	1.20	(0.86, 1.55)	2.45	(1.77, 3.14)
Non-white	1.07	(–1.11, 3.3)	0.70	(0.1, 1.3)	1.91	(0.69, 3.14)
Age > 75	2.20	(0.72, 3.69)	1.28	(0.88, 1.69)	2.12	(1.38, 2.86)
Age ≤ 75	1.33	(0.03, 2.65)	0.93	(0.51, 1.35)	2.52	(1.57, 3.48)

Figures shown are the percentage increase in admissions (95% CI).

particles has also been associated with arrhythmia in an animal model (*43*) and changes in ST segments have been noted as well (*44*). This is the first study to suggest persons with defects in the electrical control of the heart are also at higher risk of respiratory illness after exposure to airborne particles.

These data also suggest that persons admitted to hospitals for pneumonia during an air pollution episode may be at high risk for clinically significant conduction disorders during that hospital admission.

Patients with congestive heart failure were at greater risk of hospital admissions for COPD in association with airborne particles. Heart failure and COPD is not an uncommon combination. The finding that these patients are at higher risk for admissions associated with particulate air pollution is new but is also consistent with several other recent reports. The spontaneous hypertensive rat develops a model of heart failure, and recent studies have reported greater sensitivity to particulate air pollution in these rats. These include both electrocardiogram abnormalities (*44*) and pulmonary toxicity (*45,46*). Similarly, in an epidemiologic study, Hoek et al. (*47*), found a higher relative risk of death with an increase in PM_{10} for congestive heart failure deaths than other deaths. The potential role of COPD in those heart failure deaths was not examined.

Another consistent pattern in our data is of acute respiratory infections increasing susceptibility to airborne particles. Acute bronchitis, or more generally acute upper respiratory illnesses, as well as pneumonia, increased susceptibility to particle-associated admissions for CVD and COPD. The notion that air pollution exacerbates acute respiratory infections is well supported by studies which report associations between airborne particles and hospital admissions for respiratory infections (*48,49*). Zelikoff et al. (*50*) exposed rats infected with streptococcus to concentrated air particles and reported a significant increase in bacterial burdens and in the extent of pneumonia compared to animals exposed to filtrated air. This suggests an impaired immune response. Similarly, exposure to combustion particles enhances influenza infections in mice (*51*).

An impaired defense to respiratory infection is a major reason that persons with COPD require hospital admission. If airborne particles result in further impairment the effect modification we observe makes good sense. The effect modification for heart disease admissions is more relevant. This modification is consistent with the earlier report of Schwartz (*19*), who found greater reports of respiratory complications on death certificates with an underlying cause of heart disease if the death occurred on a day with high levels of airborne particles.

Although airborne particle exposure has been associated with increased exacerbation of asthma (*2,12,48,52–59*), this paper is the first to suggest that asthmatics are more susceptible to PM_{10}-induced pneumonia exacerbation or to cardiovascular effects. The effects on pneumonia admissions are plausible, given the impaired ability to fight off infections in asthmatics with mucus plugs and the evidence the airborne particles impair the lungs' ability to fight off bacterial and viral infections, as noted earlier. The increased cardiovascular sensitivity, albeit weaker, is interesting. If airborne particles affect the cardiovascular system via the role of the lung in autonomic control, it is possible that asthmatics would be more sensitive to those effects. Animal models of asthma showed that combustion particles enhance the asthmatic response to aeroallergen challenges (*59*). This suggests an enhancement of pulmonary response in asthmatics. On the other hand, the diagnosis of asthma is problematic in the elderly, and crossover with COPD is possible. The possibility that this explains our results is reduced by our failure to find previous hospital admission for COPD was an effect modifier for the effect of particles on cardiovascular admissions.

We must acknowledge several potential limitations of this study. First, we considered only previous admissions that occurred within Cook County. Hence persons with previous admissions elsewhere would be misclassified to our reference group. The effect of this would be to reduce the difference in PM_{10} effect between the two groups. Nevertheless, we identified some interesting interactions. We cannot exclude the possibility that there are areas we missed for this reason. We also examined interactions in a log relative risk model, which is inherently multiplicative. Although we believe this is justified because doubling the population exposed would be expected to double the pollution associated admissions, it results in a more conservative definition of interaction than would an additive risk model. Finally, our exposure is clearly measured with error. Most of this error is Berkson error (*60*) and hence will introduce no bias, and Zeger et al. (*60*) showed that the remaining error would have to have pathologic correlations with other variables to result in an upward bias.

Another important result from this study, of course, is an estimate of the magnitude of the effect of airborne particles on public health. The PM_{10} concentrations in Chicago during this period were associated with approximately 1,600 additional admissions per year for heart disease, 740 additional admissions per year for pneumonia, and 170 additional admissions per year for COPD. These are not trivial increases in serious morbidity.

The results of our study should be replicated in additional cities, although they do begin to fill in some missing information about the effects of airborne particles on health.

More generally airborne particles have been associated with a broad range of systemic changes including heart rate variability (*39–41*), increased peripheral neutrophils (*61–63*), increased plasma viscosity (*64*), an increase in blood pressure (*65*), and the outcomes mentioned previously. The role of these systemic changes as potential sources of the specific effect modifications we have seen should be an area of fruitful research in the future.

References and Notes

1. Katsouyanni K, Touloumi G, Spix C, Schwartz J, Balducci F, Medina S, Rossi G, Wojtyniak D, Sunyer J, Bacharova L, et al. Short term effects of ambient sulphur dioxide and particulate matter on mortality in 12 European cities: results from time series data from the APHEA project. Br Med J 314:1658–1663 (1997).
2. Pope CA, Dockery DW, Schwartz J. Review of epidemiologic evidence of health effects of particulate air pollution. Inhal Toxicol 7:1–18 (1995).
3. Schwartz J. Air pollution and daily mortality: a review and meta analysis. Environ Res 64:36–52 (1994).
4. Dominici F, Samet J, Zeger SL. Combining evidence on air pollution and daily mortality from the largest 20 US cities: a hierarchical modeling strategy. R Stat Soc Ser A, in press.
5. Burnett RT, Dales RE, Raizenne ME, Krewski D, Summers PW, Roberts GR, Raad-Young M, Dann T, Brooke T. Effects of low ambient levels of ozone and sulfates on the frequency of respiratory admissions to Ontario hospitals. Environ Res 65:172–194 (1994).
6. Anderson HR, Spix C, Medina S, Schouten JP, Castellsague J, Rossi G, Zmirou D, Touloumi G, Wojtyniak B, Ponka A, et al. Air pollution and daily admissions for

chronic obstructive pulmonary disease in 6 European cities: results from the APHEA project. Eur Respir J 10:1064–1071 (1997).
7. Schwartz J. Short term fluctuations in air pollution and hospital admissions of the elderly for respiratory disease. Thorax 50:531–538 (1995).
8. Schwartz J. Air pollution and hospital admissions for heart disease in eight U.S. counties. Epidemiology 10:17–22 (1999).
9. Schwartz J. Air pollution and hospital admissions for the elderly in Minneapolis. Arch Environ Health 49:366–374 (1994).
10. Schwartz J. Air pollution and hospital admissions for the elderly in Birmingham, Alabama. Am J Epidemiol 139:589–598 (1994).
11. Schwartz J. Air pollution and hospital admissions for the elderly in Detroit, MI. Am J Respir Crit Care Med 150:648–655 (1994).
12. Pope CA III. Respiratory disease associated with community air pollution and a steel mill, Utah valley. Am J Public Health 79:623–628 (1989).
13. Saldiva PH, Pope CA, Schwartz J, Dockery DW, Lichtenfels AJ, Salge JM, Barone I, Bohm GM. Air pollution and mortality in elderly people: a time series study in Sao Paulo, Brazil. Arch Environ Health 50:159–163 (1995).
14. Schwartz, J. Air pollution and hospital admissions for cardiovascular disease in Tucson. Epidemiology 8:371–177 (1997).
15. Delfino RJ, Murphy Moulton AM, Becklake MR. Emergency room visits for respiratory illnesses among the elderly in Montreal: association with low level ozone exposure. Environ Res 76:67–77 (1998).
16. National Research Council. Research Priorities for Airborne Particulate Matter. Washington, DC:National Academy Press, 1998.
17. Schwartz J, Dockery DW. Increased mortality in Philadelphia associated with daily air pollution concentrations. Am Rev Respir Dis 145:600–604 (1992).
18. Samet JM, Zeger SL, Berhane K. The association of mortality and particulate air pollution. In: Particulate Air Pollution and Daily Mortality. The Phase I Report of the Particle Epidemiology Evaluation Project. Boston, MA:Health Effects Institute, 1995.
19. Schwartz J. What are people dying of on high air pollution days? Environ Res 64:26–35 (1994).
20. Sunyer J, Schwartz J, Tobias A, MacFarlane D, Garcia J, Anto JM. Patients with chronic obstructive pulmonary disease are a susceptible population of dying due to urban particles. Am J Epidemiol 151(1):50–56 (2000).
21. Godleski JJ, Sioutas C, Katler M, Koutrakis P. Death from inhalation of concentrated air particles in animal models of pulmonary disease. Am J Respir Crit Care Med 153:A15 (1996).
22. Matsui K, Goldman L. Comorbidity as a correlate of length of stay for hospitalized patients with acute chest pain. J Gen Intern Med 11:262–268 (1996).
23. Charlson M, Szatrowshi TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol 47:1245–1251 (1994).
24. Monane M, Kanter DS, Glynn RJ, Avorn J. Variability in length of hospitalization for stroke. The role of managed care in an elderly population. Arch Neurol 53:848 (1996).
25. Hallstrom AP, Cobb LA, Yu BH. Influence of comorbidity on the outcome of patients treated for out-of-hospital ventricular fibrillation. Circulation 93:2019–2022 (1996).
26. Malenka DJ, Mclerran D, Roos N, Fisher ES, Wennberg JE. Using administrative data to describe case-mix: a comparison with the medical record. J Clin Epidemiol 47:1027–1032 (1994).
27. Romano PS, Roos LL, Jollis JG. Adapting a clinical comorbidity index for use with ICD-9-CM administrative data: differing perspectives. J Clin Epidemiol 46:1075–1079 (1993).
28. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9CM administrative databases. J Clin Epidemiol 45:613–619 (1992).
29. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40:373–383 (1987).
30. Librero J, Peiró S, Ordiñana R. Chronic comorbidity and outcomes of hospital care: length of stay, mortality, and readmission at 30 and 365 days. J Clin Epidemiol 52:171–179 (1999).
31. Nehls GJ, Akland GG. Procedures for handling aerometric data. J Air Pollut Control Assoc 23:180–184 (1973).
32. Hastie T, Tibshirani R. Generalized Additive Models. London:Chapman and Hall, 1990.
33. Schwartz J. Generalized additive models in epidemiology. In: International Biometric Society, Invited Papers. 17th International Biometric Conference, 8–12 August 1994, Hamilton, Ontario, Canada. Washington, DC:International Biometric Society, 1994;55–80.
34. Rossi G, Vigotti MA, Zanobetti A, Repetto F, Giannelle V, Schwartz J. Air pollution and cause specific mortality in Milan, Italy, 1980–1989. Arch Environ Health 54:158–164 (1999).
35. Cleveland WS, Devlin SJ. Robust locally-weighted regression and smoothing scatterplots. J Am Stat Assoc 74:829–836 (1988).
36. Akaike H. Information theory and an extension of the maximum likelihood principal. In: 2nd International Symposium on Information Theory (Petrov BN, Csaki F, eds). Budapest:Akademiai Kaiado, 1973;267–281.
37. Brumback BA, Ryan LM, Schwartz J, Neas LM, Stark PC, Burge HA. Transitional regression models with application to environmental time series. J Acoust Soc Am 95(449):16–28 (2000).
38. Schwartz J. The distributed lag between air pollution and daily deaths. Epidemiology 11:320–326 (2000).
39. Pope CA III, Verrier RL, Lovett EG, Larson AC, Raizenne ME, Kanner RE, Schwartz J, Villegas GM, Dockery DW. Heart rate variability associated with particulate air pollution. Am Heart J 138:890–899 (1999).
40. Gold DR, Litonjua A, Schwartz J, Lovett E, Larson A, Nearing B, Allen G, Verrier M, Cherry R, Verrier R. Ambient pollution and heart rate variability. Circulation 101(11):1267–1273 (2000).
41. Liao D, Creason J, Shy C, Williams R, Watts R, Zweidinger R. Daily variation of particulate air pollution and poor cardiac autonomic control in the elderly. Environ Health Perspect 107:521–525 (1999).
42. Peters A, Liu E, Verrier RL, Schwartz J, Gold DR, Mittelman M, Baliff J, Allen G, Monahan K, Dockery DW. Air pollution and incidences of cardiac arrhythmia. Epidemiology 11(1):11–17 (2000).
43. Godleski JJ, Verrier RL, Koutrakis P, Catalano P. Mechanisms of Morbidity and Mortality from Exposure to Ambient Air Particles. Health Effects Institute Research Report 91. Cambridge, MA:Health Effects Institute, 2000.
44. Watkinson WP, Campen MJ, Kodavanti UP, Ledbetter AD, Costa DL. Effects of inhaled residual oil fly ash particles on electrocardiographic and thermoregulatory parameters in normal and compromised rats [Abstract]. Am J Respir Crit Care Med 157:A150 (1998).
45. Watkinson WP, Campen MJ, Costa DL. Cardiac arrhythmia induction after exposure to residual oil fly ash particles in a rodent model of pulmonary hypertension. Toxicol Sci 41:209–216 (1998).
46. Kodavanti UP, Jackson MC, Richards J, Ledbetter A, Costa DL. Differential pulmonary responses to inhaled emission particulate matter (PM) in systemically hypertensive vs. normotensive rats [Abstract]. Am J Respir Crit Care Med 157:A260 (1998).
47. Hoek G, Brunekreef B, van Wijnen JH. Cardiovascular mortality response to air pollution is strongest for heart failure and thrombotic causes of death [Abstract]. Epidemiology 10:S177 (1999).
48. Bates DV, Szito R. Hospital admissions and air pollutants in southern Ontario: the acid summer haze effect. Environ Res 43:317–331 (1987).
49. Pope CA III. Respiratory disease associated with community air pollution and a steel mill, Utah valley. Am J Public Health 79:623–628 (1989).
50. Zelikoff JT, Nadziejko C, Fang T, Gordon C, Premdass C, Cohen MD. Short term, low-dose inhalation of ambient particulate matter exacerbates ongoing pneumococcal infections in *Streptococcus Pneumoniae*-infected rates. In: Proceedings of the Third Colloquium on Particulate Air Pollution and Human Health (Phalen RF, Bell YM, eds). Irvine, CA:Air Pollution Health Effects Laboratory, University of California, 1999;8-94–8-101.
51. Clarke RW, Hemenway DR, Frank R, Kleeberger SR, Longphre MV, Jakab GJ. Particle associated sulfate exposure enhances murine influenza mortality [Abstract]. Am J Respir Crit Care Med 155:A245 (1997).
52. Pope CA, Dockery DW, Spengler JD, Raizenne ME. Respiratory health and PM_{10} pollution: a daily time series analysis. Am Rev Respir Dis 144:668–674 (1991).
53. Schwartz J, Koenig J, Slater D, Larson T. Particulate air pollution and hospital emergency visits for asthma in Seattle. Am Rev Respir Dis 147:826–831 (1993).
54. Thurston GD, Ito K, Lippman M, Hayes CG, Bates DV. Respiratory hospital admissions and summertime haze air pollution in Toronto, Ontario: consideration of the role of acid aerosols. Environ Res 65:271–290 (1994).
55. Norris G, YoungPong SN, Koenig JQ, Larson TV, Sheppard L, Stout JW. An association between fine particles and asthma emergency department visits for children in Seattle. Environ Health Perspect 107:489–493 (1999).
56. Hamada K, Goldsmith CW, Kobzik L. Air pollutant aerosols allow airway sensitization to allergen in juvenile mice. Am J Resp Crit Care Med A28 (1999).
57. Lambert AL, Selgrade M, Dong W, Winsett D, Gilmour M. Enhanced allergic sensitization by residual oil fly ash particles is mediated by soluble metal constituents [Abstract]. Am J Respir Crit Care Med 159:A26 (1999).
58. Dailey LA, Madden MC, Devlin RB. Do airway epithelial cells from normal and asthmatic donors respond differently to an in vitro challenge with a particulate pollutant? [Abstract]. Am J Respir Crit Care Med 157:A598 (1998).
59. Gilmour MI, Winsett D, Selgrade MJ, Costa DL. Residual oil fly ash exposure enhances allergic sensitization to house dust mite in rats and augments immune-mediated inflammation [Abstract]. Am J Respir Crit Care Med 155:A244 (1997).
60. Zeger SL, Thomas D, Dominici F, Samet JM, Schwartz JM, Dockery D, Cohen A. Exposure measurement error in time–series studies of air pollution: concepts and consequences. Environ Health Perspect 108:419–426 (2000).
61. Salvi S, Blomberg A, Rudell B, Kelly F, Sandstrom T, Holgate ST, Frew A. Acute inflammatory responses in the airways and peripheral blood after short-term exposure to diesel exhaust in healthy human volunteers. Am J Respir Crit Care Med 159:702–709 (1999).
62. Tan WC, van Eeden S, Qiu DW, Liam BL, Dyachokova Y, Hogg JL. Particulate air pollution, bone marrow stimulation and the pathogenesis of excess cardiovascular and pulmonary deaths. Am J Respir Crit Care Med 155:1441–1447 (1997).
63. Gordon T, Nadziejko C, Schlesinger R, Chen LC. Pulmonary and cardiovascular effects of acute exposure to concentrated ambient particulate matter in rats. Toxicol Lett 96–97:285–288 (1998).
64. Peters A, Doering A, Wichmann HE, Koenig W. Increased plasma viscosity during an air pollution episode: a link to mortality? Lancet 349(9065):1582–1587 (1997).
65. Peters A, Stieberv J, Doering A, Wichmann HE. Is systolic blood pressure associated with air pollution? [Abstract]. Epidemiology 10(4):S177 (1999).