Who is Sensitive to the Effects of Particulate Air Pollution on Mortality?

A Case-Crossover Analysis of Effect Modifiers

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Background: Populations susceptible to the effects of particulate matter have begun to be characterized, but the independent contributions of specific factors have not been explored.

Methods: We used a case-crossover study to examine PM_{10}-associated mortality risk during 1988–1991 among 65,180 elderly residents of Cook County, Illinois, who had a history of hospitalization for heart or lung disease. We assessed how the effect was independently modified by specific diagnoses and personal characteristics.

Results: We found a 1.14% (95% confidence interval [CI] = 0.44% to 1.85%) increased risk of death per 10 $\mu g/m^3$ increase in ambient PM_{10} concentration. Persons with heart or lung disease—but no specific diagnosis of myocardial infarction, diabetes, congestive heart failure, chronic obstructive pulmonary disorder, or conduction disorders—were at 0.74% (−0.29% to 1.79%) increased risk. Persons with a history of myocardial infarction had a 2.7-fold higher risk (CI = -2.1 to 7.4). Those with diabetes carried a 2.0-fold higher risk (CI = -1.5 to 5.5). Risk appeared to decrease with age among elderly men and increase with age among elderly women, but the estimated 3-way interaction was not precise enough to exclude the null. We found no indication that susceptibility varied by group-level socioeconomic measures.

Conclusion: Among a frail population, individuals diagnosed with myocardial infarction or diabetes were at greatest risk of death associated with high concentrations of PM_{10}. These results suggest that their susceptibility may derive from prior vascular damage to the heart.

(*Epidemiology* 2004;15: 143–149)

Editors' note: *A commentary on this article appears on page 131.*

Submitted 7 May 2003; final version accepted 18 November 2003.

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Supported in part by Environmental Protection Agency grant R827353.

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ISSN: 1044-3983/04/1502-0143
DOI: 10.1097/01.ede.0000112210.68754.fa

High concentrations of particulate air pollution have been found to be associated with higher rates of daily deaths and hospital admissions in studies conducted throughout the industrialized world.[1–5] Similar relationships have been reported in a variety of locations reflecting a wide range of particulate matter (PM) and gas copollutant concentrations.[6–8] These associations are not confounded by secular time trends, seasonal patterns, influenza epidemics,[9] or weather.[5,10–13]

Decreased heart rate variability,[14–17] increased peripheral neutrophils,[18,19] and increased plasma viscosity[20] could be involved in the mechanism by which increased concentrations of PM are associated with increased risk of mortality and morbidity. However, not all groups of people respond to PM exposure in the same way.[21–29] Although certain subpopulations seem to exhibit an enhanced response, much remains to be learned about which personal characteristics make some people especially sensitive to the adverse effects of particulate matter, and what the independent contributions are when several characteristics are present in combination. The National Research Council has identified this as a key research gap.[30] Further identification of susceptible populations may direct investigators toward more specific biologic mechanisms for the observed effects of PM on human health.

The results of single-factor subgroup analyses have shown that people with chronic obstructive pulmonary disorder,[22] conduction disorders,[23,28] congestive heart failure,[24,25,28] diabetes,[21,23,27] and myocardial infarction[26] are at greater risk of adverse events associated with air pollution in general and particulate matter in particular. In this study, we used a case-crossover design that allows for the examination of effect modification at the level of the individual rather than at the group level. As an alternative analytic methodology to Poisson regression, the case-crossover approach allows for the direct modeling of interaction terms rather than depending on multiple subgroup analyses. Consequently, we have the ability to model several potential effect modifiers simultaneously, which may allow for the assessment of independent effects of several modifiers in the same analysis. Direct modeling of interaction terms also allows us to look at

modifiers using continuous variables such as age and higher dimension interactions. Case-crossover analyses control for seasonal confounding, thus avoiding the issues of modeling seasonal patterns in Poisson regression.

METHODS

Health Data

Cook County, Illinois (Chicago area) was selected for study because it was the most populous county in the United States for which we had daily monitoring of particulate matter. The Center for Medicare and Medicaid Services (CMS) provides financial reimbursement of inpatient hospital admission costs for all U.S. citizens age 65 years and older; this center also retains detailed data on morbidity. Data did not include information on cause of death. We extracted available data on the incidence of all-cause mortality and history of Medicare-reimbursable hospital admissions from persons who were admitted to the hospital with a primary or secondary diagnosis of heart disease (International Classification of Diseases, 9th Revision [ICD-9]: 390–429) or lung disease (ICD-9: 460–519) between 1986 and 1991. This population was chosen because they were thought to be at generally higher risk for mortality as a result of transient exposure to high concentrations of particulate matter. We restricted this population to those who had residential addresses in Cook County, Illinois, and had validated dates of death between 1988 and 1991. Deaths occurring in 1986 or 1987 were excluded as a result of lack of data on air pollution during that time; information on deaths occurring after 1991 was not available. We excluded individuals who died within 15 days of discharge from the hospital to ensure that time spent in the hospital could not be chosen as reference periods in the case-crossover study design.

We classified each person according to their diagnoses, in prior hospital admissions, of any of the following conditions: myocardial infarction (ICD-9: 410), diabetes (ICD-9: 250), congestive heart failure (ICD-9: 428), chronic obstructive pulmonary disorder (COPD; ICD-9: 490–492), or conduction disorders (ICD-9: 426–427). Secondary as well as primary diagnoses were included.

Sociodemographic Data

We extracted information from the CMS data on each person's date of birth, sex, and zip code of residence. Each zip code area was matched to the 1990 U.S. census data to determine the area's median household income, percentage of adults who had completed a bachelor's degree, and percentage of adults who spoke a language other than English in the home. The deaths in this study came from 150 zip codes.

Environmental Data

We obtained the air pollution concentration data on particulate matter smaller than 10 μm in diameter (PM_{10}) from U.S. Environmental Protection Agency's Aerometric Information Retrieval System for monitors in Cook County, Illinois. We computed a daily mean PM_{10} concentration using an algorithm that accounts for the different monitor-specific means and variances.[5]

We obtained meteorologic data, measured at Chicago O'Hare Airport in Cook County, Illinois, from the EarthInfo CD-ROM (EarthInfo CD NCDC Surface Airways, EarthInfo Inc., Boulder, CO). Weather-related variables used in our analyses included daily mean temperature, relative humidity, and barometric pressure.

Statistical Analysis

We investigated the association between daily PM_{10} concentrations and mortality using a case-crossover design. The case-crossover design is a variant of the case-control design, used to study the effects of transient exposures on acute events.[31] This design samples only cases and compares each case's exposure during a time period just before the case-defining event (hazard period) with that subject's own exposure in other reference periods (control periods). Because each subject serves as his or her own control, there is perfect matching on all measured or unmeasured subject characteristics that do not vary over time.

We used a symmetric bidirectional case-crossover design. In this design, reference periods are symmetrically spaced in time, both before and after the hazard period, which minimizes potential time-varying confounding by season or time trends.[32] In this study, the hazard period was defined as the day of death, and PM_{10} exposure was modeled as the mean of exposure on the day of death (lag 0) and the day before death (lag 1). We matched 18 reference days to each hazard day. Nine reference days were the 6–14 days before the hazard day and 9 were the 6–14 days after the hazard day. Hazard days that could not be matched to the full complement of referent days were excluded rather than sacrificing the symmetry of the matching. Selection bias is possible in case-crossover studies when some days in a time series are unevenly sampled as hazard or reference (control) days. This can occur, for example, at the beginning of the series when the need to sample control days before the first event day means some days contribute to reference periods without contributing to hazard periods. This can be corrected using the method of Bateson and Schwartz[33] who showed that the selection bias in any set of data could be estimated by calculating the effect of exposure using the same model and set of covariate data, but selecting a counterfactual time series composed of a single event on each day of the study period on which an event actually was observed. Because exposure and outcome are independent by construction, any estimated effect is an estimate of the selection bias. Conditional logistic regression analyses were conducted using PROC PHREG in SAS (SAS Software Release 8.2; SAS Institute, Cary, NC,

2001). The selection bias was estimated and the resulting estimate was subtracted from the naive effect estimate.

We controlled for 4 meteorologic covariates in each model. We modeled today's mean temperature as a quadratic function to allow for a possible nonlinear effect; and yesterday's mean temperature, today's mean humidity, and today's mean barometric pressure as linear functions. PM_{10} was modeled linearly. Because day-of-the-week effects were not explicitly controlled for in our study design, we included 6 day-of-the-week indicator variables in each model. To investigate the potential modification of the effect of PM_{10} on the risk of mortality by various medical history and sociodemographic factors, we added to the model different sets of interaction terms that were the product of the PM_{10} measurement and the several potential effect modifiers.

We define relative effect modification (REM) to be the ratio of (1) the log odds ratio of the outcome associated with exposure among a population with a particular characteristic to (2) the same log odds ratio in a population without that characteristic.

RESULTS

Among the residents of Cook County, Illinois, who were at least 65 years of age, there were 65,180 deaths during 1988–1991 in the population of persons who had been previously admitted to the hospital for a Medicare-reimbursable diagnosis of heart or lung disease during 1986–1991. Table 1 shows the number of individuals who had a specific prior diagnosis of myocardial infarction, diabetes, congestive heart failure, COPD, or conduction disorders, alone or in combination with the other specific diagnoses. Table 2 shows the distribution, across 150 zip codes, of 3 socioeconomic factors ascertained from the 1990 U.S. Census. Table 3 shows the distribution of environmental factors for Cook County during the study period.

TABLE 1. Distribution of 5 Specific Primary and Secondary Diagnoses Among Study Sample of 65,180 Cook County, Illinois, Residents

Diagnosis	One Diagnosis*	Multiple Diagnoses	Total
Myocardial infarction	677	5480	6157
Diabetes	3596	9382	12,978
Congestive heart failure	5760	21,163	26,923
Chronic obstructive pulmonary disease	5452	10,951	16,403
Conduction disorders	7756	19,590	27,346

*Individuals who may have had more than 1 diagnosis of heart or lung disease but had only 1 of the 5 specific diagnoses in the table.

Our basic model assessed the effect of PM_{10} on the risk of mortality while controlling for mean temperature on the day before death, and mean temperature, mean relative humidity, and mean barometric pressure on the day of death. The basic model also controlled for day-of-the-week effects. We found that for each 10 $\mu g/m^3$ increase in the concentration of PM_{10}, there was a 1.14% (95% confidence interval [CI] = 0.44% to 1.85%) increase in the risk of dying among the study population.

We extended this basic model to include 5 interaction terms simultaneously representing the independent interactions between PM_{10} concentration and each of the 5 specific medical histories of interest: myocardial infarction, diabetes, congestive heart failure, COPD, and conduction disorders. The results are shown in Table 4. In this model, the effect of each 10 $\mu g/m^3$ increase in the concentration of PM_{10} was estimated at 0.74% (-0.29% to 1.79%) among persons with heart and lung diseases but none of the 5 specific diagnoses. The effect of PM_{10} on the risk of mortality was higher among those with a prior diagnosis of myocardial infarction (1.98%), diabetes (1.49%), and congestive heart failure (1.28%). The mortality risk associated with a prior diagnosis of COPD (0.58%) or conduction disorders (0.64%) was similar to the risk among persons with heart and lung diseases but none of the specific diagnoses.

We also extended our basic model to include an interaction term for patient's sex (Table 5). The increase in risk of death associated with PM_{10} was 1.3% (0.3% to 2.3%) per 10 $\mu g/m^3$ increase in PM_{10} in men and 1.00% (0.1% to 1.9%) per 10 $\mu g/m^3$ increase in PM_{10} in women. When we added a continuous linear interaction term for age, the increase in risk of death associated with a 10 $\mu g/m^3$ increase in PM_{10} was 0.04% higher (-0.7% to 0.8%) for each added decade in age above 65 years. Modeling an interaction term for sex, for age, and a 3-way interaction between PM_{10}, sex, and age, we

TABLE 2. Distribution of Sociodemographic Factors Among 5-digit Zip Codes (N = 150) in Cook County, Illinois, From 1990 U.S. Census

Demographic Factor	Mean	Standard Error	Minimum	Maximum
Median household income (US dollars)	34,000	13,000	7000	150,000
Percent with bachelor's degree	22	16	4	89
Percent speaking languages other than English at home	21	15	0	62

TABLE 3. Distribution of Environmental Factors Measured in Cook County, Illinois, During 1988–1991

	Mean	Standard Error	Minimum	Maximum
PM_{10}*	37.6	15.5	3.7	128
Temperature (°C)†	10.7	11.0	−23.3	31.7
Humidity (%)†	69	12	36	98
Pressure (In. Hg)†	29.3	0.2	28.5	30.1

*PM_{10} measurements obtained from the U.S. EPA AIRS network for monitors in Cook County, IL.
†Meteorologic measurements from O'Hare Airport, Chicago IL (Earth-Info, Boulder, CO).

found that there was substantial effect modification of the risk of mortality (Table 5). Risk with PM_{10} appeared to decrease with age among men and increase with age among women, although these patterns were based on imprecise estimates.

To assess the potential interaction between PM_{10} and zip code-level socioeconomic factors, we extended the basic model with continuous linear interaction terms for PM_{10} and zip code-level data on income, educational attainment, and language other than English in the home. The risk of dying associated with a 10 $\mu g/m^3$ increase in the concentration of PM_{10} was increased by 0.2% (-0.3% to 0.7%) with a 10% increase in the prevalence of residents having at least a bachelor's degree, and was unchanged with either a $10,000

TABLE 4. Modification of the Effect of PM_{10} Concentrations on Mortality by Prior Diagnoses

Specific Condition	Percent Increased Risk (per 10 $\mu g/m^3$)	(95% CI)	Relative Effect Modification (REM)*	(95% CI†)
Myocardial infarction (n = 6157)	1.98	(−0.25 to 4.26)	2.65	(−2.09 to 7.39)
Diabetes (n = 12,978)	1.49	(−0.06 to 3.07)	2.00	(−1.47 to 5.47)
Congestive heart failure (n = 26,923)	1.28	(−0.06 to 2.64)	1.72	(−1.28 to 4.72)
Chronic obstructive pulmonary disease (n = 16,403)	0.58	(−0.82 to 2.00)	0.78	(−1.40 to 2.96)
Conduction disorders (n = 27,346)	0.64	(−0.61 to 1.90)	0.85	(−1.21 to 2.91)
None of the above conditions‡	0.74	(−0.29 to 1.79)	1.0	

$$*REM = \left(\frac{\beta_X}{\beta_Y}\right).$$

$$^{\dagger}Var\left[\frac{\beta_X}{\beta_Y}\right] \approx \left(\frac{\beta_X}{\beta_Y}\right)^2\left[\left(\frac{Var(\beta_X)}{(\beta_X)^2}\right) + \left(\frac{Var(\beta_Y)}{(\beta_Y)^2}\right)\right], \qquad (\text{since } Cov(\beta_X, \beta_Y) = 0)$$

‡Reference category.

TABLE 5. Modification of the Effect of Short-term Changes in Ambient Particulate Matter Concentrations on Mortality by Age and Sex

Age (years)	Men		Women		Total	
	Effect (%)	95% CI	Effect (%)	95% CI	Effect (%)	95% CI
65	2.0¶	(0.3 to 3.8)	0.1¶	(−1.6 to 1.9)	1.1‖	(−0.12 to 2.3)
75	1.5¶	(−0.2 to 3.1)	0.7¶	(−1.1 to 2.4)	1.1‖	(−0.1 to 2.3)
85	0.9¶	(−0.7 to 2.5)	1.2¶	(−0.5 to 3.0)	1.2‖	(−0.0 to 2.4)
95	0.3¶	(−1.3 to 1.9)	1.8¶	(0.03 to 3.6)	1.2‖	(0.0 to 2.4)
All	1.3§	(0.4 to 2.3)	1.0§	(0.1 to 1.9)	1.1‡	(0.4 to 1.9)

*All models control for weather and day of the week (and all time-invariant factors).
†Confidence intervals are pointwise and based on linear model results.
‡Model A: Main effect of PM_{10}
§Model B: Main effect of PM_{10} plus (Gender*PM_{10}).
‖Model C: Main effect of PM_{10} plus (Age*PM_{10}).
¶Model D: Main effect of PM_{10} plus (Gender*PM_{10}) plus (Age*PM_{10}) plus (Gender*Age*PM_{10}).

increase in median household income (-0%; -0.6% to 0.6%) or a 10% increase in the prevalence of residents who spoke a language other than English at home (0%; -0.4% to 0.4%).

DISCUSSION

There is a substantial body of epidemiologic literature showing a clear and consistent association between high concentrations of ambient PM_{10} and negative health effects.[1–3] Of great interest is the biologic mechanism by which PM_{10} could be causing this morbidity and mortality. One avenue by which investigators can offer direction is by assessing whether there are subgroups of people who are especially sensitive to the health effects of PM_{10}. Identification of sets of individuals who have an enhanced response to PM_{10} may suggest possible mechanisms of physiological assault, as well as provide data that can be used for more detailed risk assessment.

The case-crossover study design focuses the examination of potential modification of the effect of PM_{10} on individuals by making them the unit of analysis. This study design allows analyses beyond single-factor subgroups (marginal analyses) and models multiple potential interaction terms simultaneously. This can facilitate the examination of the independent effects of specific modifiers in a setting where most people have multiple comorbidities. Case-crossover designs also allow for the modeling of continuous multiplicative effects between 2 continuous variables rather than the usual categorical assessment.

Our study population was people age 65 years or older who had previously been admitted to the hospital for a Medicare-reimbursable diagnosis of heart or lung disease. Over the entire population, a 10 $\mu g/m^3$ increase in the concentration of PM_{10} was associated with a 1.14% (95% CI = 0.44% to 1.85%) increase in the risk of death, which is consistent with that observed in other locations.[1–3] Compared with the people who did not have any specific diagnosis of myocardial infarction, diabetes, congestive heart failure, COPD, or conduction disorders, we found somewhat stronger effects of PM_{10} on the risk of mortality among person with a prior diagnosis of myocardial infarction, diabetes, or, to a lesser degree, congestive heart failure. Our measures of effect modification had large confidence intervals because we modeled 5 interaction terms simultaneously controlling for the other modifiers. Still, they suggest specific populations that may be especially sensitive to the effects of PM_{10}.

Our data suggest that people with COPD or conduction disorders are at no more risk than people with more general heart or lung conditions once the presence of additional comorbidities was controlled for. Sunyer[22] investigated the association between PM_{10} and all-cause mortality among a population with COPD and found that patients admitted to intensive-care units and those with a higher rate of emergency room visits were at greater risk of dying. Their case definition, which required an emergency visit for COPD, likely defined a more seriously ill class than our definition, which included people with COPD noted as a secondary diagnosis for admissions for other purposes. Also, their comparison population was the general population of Barcelona, whereas ours required an admission for heart and lung disease. Hence, these 2 sets of results suggest that effect modification may occur only with severe COPD.

In a study using the same general source population of elderly residents as ours, Zanobetti[23] found that the air pollution-associated increased risk of hospital admissions for cardiovascular disease was almost doubled among subjects with concurrent respiratory infections. Having a previous hospital admission for conduction disorders also increased risk. They did not assess effect modification by COPD status. For outcomes of COPD and pneumonia admissions, previous diagnoses of conduction disorders or dysrhythmias increased the risk of PM_{10}-associated admissions.[23] Mann and colleagues reported that a history of arrhythmia increased the risk of hospital admission for ischemic heart disease associated with air pollution, but they did not examine particulate matter specifically, because of lack of data on daily measurements. In our study population, most people had more than 1 of the 5 specific diagnoses. It may be that people with COPD are at increased risk of death associated with PM, but their risk is increased by their constellation of comorbidities rather than the specific diagnosis of COPD. The same explanation may apply to conduction disorders. Our results do support previous findings that diabetes[21,27,29] and congestive heart failure[24,25,28] substantially increase the risk of morbidity and mortality associated with ambient particulate matter. Although air pollution has been shown to be a risk factor for myocardial infarction, we know of no previous data suggesting that a history of myocardial infarction can modify the risk of death associated with particulate air pollution.

These analyses are based on claims for reimbursement by the hospitals that treated these patients. The interpretation of these results could be limited by how accurately these data characterized the true prevalence of the considered diseases. We used both the primary and secondary diagnoses on each hospital admission record. No differentiation was made for the number of times a specific diagnosis was mentioned after the first. Although Medicare records collected by CMS may not completely predict the point-prevalence of each disease condition at all times, there is little indication that the cumulative set of diagnoses from prior hospital admission records would fail to capture the specific conditions that our analyses focused on. Although diabetes, in particular, is not likely to be an admitting diagnosis, it may be mentioned secondarily as a complication, or possibly to increase financial reimbursement that the hospital could claim from the government.

The precision with which we were able to estimate the effect modification was somewhat low, but the ranking of comorbidities in order of the estimated strength of the modification may point to a vulnerability to the effects of particulate matter shared by patients with diabetes and those who have sustained a myocardial infarction. A prospective cohort study showed that among people who have had one or more myocardial infarctions, the impact of diabetes on survival is similar to that of a prior myocardial infarction, indicating that the history of both conditions further worsened survival.[34] This suggested a similar mechanism mediating the adverse effects of myocardial infarction and diabetes on mortality—possibly related to remodeling of the left ventricle.[34,35] Capillaries in the pulmonary endothelium regulate levels of circulating substances that affect cardiovascular homeostasis and seem to be affected early in acute lung injury.[36] Particulate-induced sympathovagal imbalance could be a precipitating event that would correspond with increased mortality among people with diabetes, prior myocardial infarction, or congestive heart failure but not necessarily among those with COPD.

Endothelial function is one aspect of cardiovascular health that is impaired among patients with diabetes.[37,38] A recent clinical study examined effects of air pollution on vascular and endothelial function.[39] Healthy adults inhaled 150 $\mu g/m^3$ of concentrated ambient fine particles and ozone (120 ppb) for 2 hours. Basal brachial artery vasoconstriction was demonstrably higher (ie, diameter was diminished) with the pollution inhalation than with clean air inhalation, but no important differences were observed for blood pressure or other measures of vascular dilation.

Patients with diabetes are generally at increased risk of death, and this risk appears to be related in part to higher levels of C-reactive protein, decreased heart rate variability, increased plasma fibrinogen levels, and other markers of increased systemic inflammation.[40–42] Particulate air pollution has also been associated with all of these factors.[15,18,43,44] If patients with diabetes have already overwhelmed their compensatory mechanisms for dealing with these risks, interaction is plausible.

We found that the effect of PM_{10} was apparently not modified by age or sex, although there was a suggestion of joint interaction (Table 5). Our analysis avoided the use of subgroups (with possible problems of small numbers) by taking advantage of the study design to model the effects of age and sex jointly. Among people age 65 years and older, men were found to have the highest increased risk associated with PM_{10} at the youngest ages (65 years), and the increased risk of dying associated with PM_{10} diminished among older men. The pattern was reversed in women. Women were seen to have the lowest increased risk of dying associated with PM_{10} at the youngest ages (65 years), and the effect of PM_{10} was stronger among the older women. Sunyer et al.[22] have also found a similar pattern of joint effect modification by age and sex with the eldest women appearing to have a greater risk of mortality associated in PM_{10}. Hong et al.[45] found that elderly women were most susceptible to the adverse effects of PM_{10} on the risk of acute mortality from stroke. Sunyer et al.[22] suggested that differing particulate deposition patterns between men and women may partly explain the sex difference.

We did not find effect modification by the socioeconomic factors we examined. This result is also consistent with other studies that have assessed socioeconomic factors at group levels such as county or city.[13] Although our study examined a finer stratification of geographic unit by looking across 5-digit zip codes, it seems likely that the variability within each geographic unit was larger than the variability between units, which might obscure any true effect. It may be that information on socioeconomic factors needs to be collected at a much finer geographic level such as census block groups and census tracts.[46] In studies that have used individual-level data on education, the observed effect of particulate air pollution on all-cause mortality is higher among people with lower educational attainment.[47]

Our study suggested the modification of effects of PM_{10} on all-cause mortality by personal characteristics, but only when those characteristics were measured on the individual level. We have identified several subpopulations that seem to exhibit an enhanced response to PM_{10} exposure based on their specific medical histories and individual characteristics. The further epidemiologic identification of individual traits associated with increased risk from particulate air pollution will continue to direct ongoing research into biologic mechanisms and provide critical data for risk assessment.

REFERENCES

1. Schwartz J, Dockery DW. Increased mortality in Philadelphia associated with daily air pollution concentrations. *Am Rev Respir Dis*. 1992;145: 600–604.
2. Katsouyanni K, Touloumi G, Samoli E, et al. Confounding and effect modification in the short-term effects of ambient particles on total mortality: results from 29 European cities within the APHEA2 project. *Epidemiology*. 2001;12:521–531.
3. Katsouyanni K, Touloumi G, Spix C, 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. Air Pollution and Health: a European Approach. *BMJ*. 1997;314:1658-1663.
4. Samet JM, Dominici F, Curriero FC, et al. Fine particulate air pollution and mortality in 20 US cities, 1987–1994. *N Engl J Med*. 2000;343: 1742–1749.
5. Zanobetti A, Schwartz J, Dockery DW. Airborne particles are a risk factor for hospital admissions for heart and lung disease. *Environ Health Perspect*. 2000;108:1071–1077.
6. Atkinson RW, Anderson HR, Sunyer J, et al. Acute effects of particulate air pollution on respiratory admissions results from APHEA 2 Project. Air Pollution and Health: a European Approach. *Am J Respir Crit Care Med*. 2001;164:1860–1866.
7. Goldberg MS. Particulate air pollution and daily mortality: who is at risk? *J Aerosol Med*. 1996;9:43–53.

8. Le Tertre A, Medina S, Samoli E, et al. Short term effects of particulate air pollution on cardiovascular diseases in eight European cities. *J Epidemiol Community Health*. 2002;56:773–779.
9. Braga AL, Zanobetti A, Schwartz J. Do respiratory epidemics confound the association between air pollution and daily deaths? *Eur Respir J*. 2000;16:723–728.
10. Samet J, Zeger S, Kelsall J, et al. Does weather confound or modify the association of particulate air pollution with mortality? An analysis of the Philadelphia data, 1973–1980. *Environ Res*. 1998;77:9–19.
11. Schwartz J. Air pollution and hospital admissions for heart disease in eight US counties. *Epidemiology*. 1999;10:17–22.
12. Schwartz J. Assessing confounding, effect modification, and thresholds in the association between ambient particles and daily deaths. *Environ Health Perspect*. 2000;108:563–568.
13. Samet JM, Zeger SL, Dominici F, et al. The National Morbidity, Mortality, and Air Pollution Study. Part II: Morbidity and mortality from air pollution in the United States. *Res Rep Health Eff Inst*. 2000;94:5–70.
14. Pope CA III, Verrier RL, Lovett EG, et al. Heart rate variability associated with particulate air pollution. *Am Heart J*. 1999;138:890–899.
15. Gold DR, Litonjua A, Schwartz J, et al. Ambient pollution and heart rate variability. *Circulation*. 2000;101:1267–1273.
16. Liao D, Creason J, Shy C, et al. Daily variation of particulate air pollution and poor cardiac autonomic control in the elderly. *Environ Health Perspect*. 1999;107:521–525.
17. Magari SR, Schwartz J, Williams PJ, et al. The association between personal measurements of environmental exposure to particulates and heart rate variability. *Epidemiology*. 2002;13:305–310.
18. Salvi S, Blomberg A, Rudell B, et al. 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*. 1999;159:702–709.
19. Gordon T, Nadziejko C, Schlesinger R, et al. Pulmonary and cardiovascular effects of acute exposure to concentrated ambient particulate matter in rats. *Toxicol Lett*. 1998;96--97:285-288.
20. Peters A, Doring A, Wichmann HE, et al. Increased plasma viscosity during an air pollution episode: a link to mortality? *Lancet*. 1997;349:1582–1587.
21. Goldberg MS, Bailar JC III, Burnett RT, et al. Identifying subgroups of the general population that may be susceptible to short-term increases in particulate air pollution: a time-series study in Montreal, Quebec. *Res Rep Health Eff Inst*. 2000;97:7–113.
22. Sunyer J, Schwartz J, Tobias A, et al. Patients with chronic obstructive pulmonary disease are at increased risk of death associated with urban particulate air pollutions: a case-crossover analysis. *Am J Epidemiol*. 2000;151:50–56.
23. Zanobetti A, Schwartz J, Gold D. Are there sensitive subgroups for the effects of airborne particles? *Environ Health Perspect*. 2000;108:841–845.
24. Goldberg MS, Burnett RT, Bailar JC III, et al. Identification of persons with cardiorespiratory conditions who are at risk of dying from the acute effects of ambient air particles. *Environ Health Perspect*. 2001;109(suppl 4):487–494.
25. Kwon HJ, Cho SH, Nyberg F, et al. Effects of ambient air pollution on daily mortality in a cohort of patients with congestive heart failure. *Epidemiology*. 2001;12:413–419.
26. Peters A, Dockery DW, Muller JE, et al. Increased particulate air pollution and the triggering of myocardial infarction. *Circulation*. 2001;103:2810–2815.
27. Zanobetti A, Schwartz J. Are diabetics more susceptible to the health effects of airborne particles? *Am J Respir Crit Care Med*. 2001;164:831–833.
28. Mann JK, Tager IB, Lurmann F, et al. Air pollution and hospital admission for ischemic heart disease in persons with congestive heart failure or arrhythmia. *Environ Health Perspect*. 2002;110:1247–1252.
29. Zanobetti A, Schwartz J. Cardiovascular damage by airborne particles: are diabetics more susceptible? *Epidemiology*. 2002;13:588–592.
30. National Research Council. *Research Priorities for Airborne Particulate Matter: I. Immediate Priorities and Long-Term Research Portfolio*. Washington, DC: National Academy Press; 1998.
31. Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. *Am J Epidemiol*. 1991;133:144–153.
32. Bateson TF, Schwartz J. Control for seasonal variation and time trend in case-crossover studies of acute effects of environmental exposures. *Epidemiology*. 1999;10:539–544.
33. Bateson TF, Schwartz J. Selection bias and confounding in case-crossover analyses of environmental times-series data. *Epidemiology*. 2001;12:654–661.
34. Mukamal KJ, Nesto RW, Cohen MC, et al. Impact of diabetes on long-term survival after acute myocardial infarction. *Diabetes Care*. 2001;24:1422–1427.
35. Nesto RW, Zarich S. Acute myocardial infarction in diabetes mellitus: lessons learned from ACE inhibition. *Circulation*. 1998;97:12–15.
36. Orfanos SE, Armaganidis A, Glynos C, et al. Pulmonary capillary endothelium-bound angiotensin-converting enzyme activity in acute lung injury. *Circulation*. 2000;102:2011–2018.
37. Williams SB, Cusco JA, Roddy MA, et al. Impaired nitric oxide-mediated vasodilation in patients with non-insulin-dependent diabetes mellitus. *J Am Coll Cardiol*. 1996;27:567–574.
38. Johnstone MT, Creager SJ, Scales KM, et al. Impaired endothelium-dependent vasodilation in patients with insulin-dependent diabetes mellitus. *Circulation*. 1993;88:2510–2516.
39. Brook RD, Brook JR, Urch B, et al. Inhalation of fine particulate air pollution and ozone causes acute arterial vasoconstriction in healthy adults. *Circulation*. 2002;105:1534–1536.
40. Gerritsen J, Dekker JM, TenVoorde BJ, et al. Glucose tolerance and other determinants of cardiovascular autonomic function: the Hoorn Study. *Diabetologia*. 2000;43:561–570.
41. Resnick HE, Howard BV. Diabetes and cardiovascular disease. *Annu Rev Med*. 2002;53:245–267.
42. Ford ES. Body mass index, diabetes, and C-reactive protein among US adults. *Diabetes Care*. 1999;22:1971–1977.
43. Schwartz J. Air pollution and blood markers of cardiovascular risk. *Environ Health Perspect*. 2001;109(suppl 3):405–409.
44. Gold DR, Litonjua A, Schwartz J, et al. Ambient pollution and heart rate variability. *Circulation*. 2000;101:1267–1273.
45. Hong YC, Lee JT, Kim H, et al. Effects of air pollutants on acute stroke mortality. *Environ Health Perspect*. 2002;110:187–191.
46. Krieger N, Chen JT, Waterman PD, et al. Geocoding and Monitoring US socioeconomic inequalities in mortality and cancer incidence: does choice of area-based measure and geographic level matter?—The Public Health Disparities Geocoding Project. *Am J Epidemiol*. 2002;156:471–482.
47. Krewski D, Burnett RT, Goldberg MS, et al. Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of Particulate Air Pollution and Mortality. Investigators' Report Part 2: sensitivity analyses. *Res Rep Health Eff Inst.* A Special Report of the Institute's Particle Epidemiology Reanalysis Project; July 2000;137–141.