Who is Sensitive to the Effects of Particulate Air Pollution on Mortality? A Case-Crossover Analysis of Effect Modifiers

Thomas F. Bateson* and Joel Schwartz*†

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 μg/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.

(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.¹⁰⁻¹³ Decreased heart rate variability,¹⁴⁻¹⁷ increased peripheral neutrophils,¹⁸,¹⁹ and increased plasma viscosity²⁰ 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 infarction²⁶ 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...
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.

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

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

*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.

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.

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 10μg/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.

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

<table>
<thead>
<tr>
<th>Demographic Factor</th>
<th>Mean</th>
<th>Standard Error</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median household income (US dollars)</td>
<td>34,000</td>
<td>13,000</td>
<td>7000</td>
<td>150,000</td>
</tr>
<tr>
<td>Percent with bachelor’s degree</td>
<td>22</td>
<td>16</td>
<td>4</td>
<td>89</td>
</tr>
<tr>
<td>Percent speaking languages other than English at home</td>
<td>21</td>
<td>15</td>
<td>0</td>
<td>62</td>
</tr>
</tbody>
</table>
found that there was substantial effect modification of the risk of mortality (Table 5). Risk with PM\textsubscript{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\textsubscript{10} and zip code-level socioeconomic factors, we extended the basic model with continuous linear interaction terms for PM\textsubscript{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 μg/m\textsuperscript{3} increase in the concentration of PM\textsubscript{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 3. Distribution of Environmental Factors Measured in Cook County, Illinois, During 1988–1991

<table>
<thead>
<tr>
<th>Factor</th>
<th>Mean</th>
<th>Standard Error</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM\textsubscript{10}*</td>
<td>37.6</td>
<td>15.5</td>
<td>3.7</td>
<td>128</td>
</tr>
<tr>
<td>Temperature (°C)†</td>
<td>10.7</td>
<td>11.0</td>
<td>-23.3</td>
<td>31.7</td>
</tr>
<tr>
<td>Humidity (%)†</td>
<td>69</td>
<td>12</td>
<td>36</td>
<td>98</td>
</tr>
<tr>
<td>Pressure (In. Hg)†</td>
<td>29.3</td>
<td>0.2</td>
<td>28.5</td>
<td>30.1</td>
</tr>
</tbody>
</table>

*PM\textsubscript{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).

### TABLE 4. Modification of the Effect of PM\textsubscript{10} Concentrations on Mortality by Prior Diagnoses

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

*REM = \frac{\beta_1}{\beta_0}.

\text{Var} \left[ \frac{\beta_i}{\beta_j} \right] = \frac{\text{Var}(\beta_i)}{(\beta_j)^2} + \left[ \frac{\text{Var}(\beta_j)}{(\beta_i)^2} \right] + \left[ \frac{\text{Cov}(\beta_i, \beta_j)}{(\beta_i)^2(\beta_j)^2} \right].

\text{since Cov}(\beta_i, \beta_j) = 0

†Reference category.

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

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Men</th>
<th>95% CI</th>
<th>Women</th>
<th>95% CI</th>
<th>Total</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>65</td>
<td>2.0†</td>
<td>(0.3 to 3.8)</td>
<td>0.1†</td>
<td>(−1.6 to 1.9)</td>
<td>1.1†</td>
<td>(−0.12 to 2.3)</td>
</tr>
<tr>
<td>75</td>
<td>1.5†</td>
<td>(−0.2 to 3.1)</td>
<td>0.7†</td>
<td>(−1.1 to 2.4)</td>
<td>1.1†</td>
<td>(−0.1 to 2.3)</td>
</tr>
<tr>
<td>85</td>
<td>0.9†</td>
<td>(−0.7 to 2.5)</td>
<td>1.2†</td>
<td>(−0.5 to 3.0)</td>
<td>1.2†</td>
<td>(−0.0 to 2.4)</td>
</tr>
<tr>
<td>95</td>
<td>0.3†</td>
<td>(−1.3 to 1.9)</td>
<td>1.8†</td>
<td>(0.03 to 3.6)</td>
<td>1.2†</td>
<td>(0.0 to 2.4)</td>
</tr>
<tr>
<td>All</td>
<td>1.3†</td>
<td>(0.4 to 2.3)</td>
<td>1.0‡</td>
<td>(0.1 to 1.9)</td>
<td>1.1‡</td>
<td>(0.4 to 1.9)</td>
</tr>
</tbody>
</table>

*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\textsubscript{10}.
§Model B: Main effect of PM\textsubscript{10} plus (Gender*PM\textsubscript{10}).
□Model C: Main effect of PM\textsubscript{10} plus (Age*PM\textsubscript{10}).
□Model D: Main effect of PM\textsubscript{10} plus (Gender*PM\textsubscript{10}) plus (Age*PM\textsubscript{10}) plus (Gender*Age*PM\textsubscript{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.\textsuperscript{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.\textsuperscript{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\textsuperscript{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 definitions, 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\textsuperscript{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.\textsuperscript{23} Mann and colleagues reported that a history of arrhythmias 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$_{10}$ 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\textsuperscript{21,27,29} and congestive heart failure\textsuperscript{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 μg/m³ 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, death, and this risk appears to be related in part to higher other measures of vascular dilation.40 Levels of C-reactive protein, decreased heart rate variability, and other biologic mechanisms and provide critical data for risk assessment. 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 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 PM₁₀ 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 PM₁₀ 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


