The Effect of Particulate Air Pollution on Emergency Admissions for Myocardial Infarction: A Multicity Case-Crossover Analysis

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Recently, attention has focused on whether particulate air pollution is a specific trigger of myocardial infarction (MI). The results of several studies of single locations assessing the effects of ambient particulate matter on the risk of MI have been disparate. We used a multicity case-crossover study to examine risk of emergency hospitalization associated with fine particulate matter (PM) with aerodynamic diameter < 10 µm (PM$_{10}$) for > 300,000 MUs during 1985–1999 among elderly residents of 21 U.S. cities. We used time-stratified controls matched on day of the week or on temperature to detect possible residual confounding by weather. Overall, we found a 0.65% [95% confidence interval (CI), 0.3–1.0%] increased risk of hospitalization for MI per 10 µg/m$^3$ increase in ambient PM$_{10}$ concentration. Matching on apparent temperature yielded a 0.64% increase in risk (95% CI, 0.1–1.2%). We found that the effect size for PM$_{10}$ doubled for subjects with a previous admission for chronic obstructive pulmonary disease or a secondary diagnosis of pneumonia, although these differences did not achieve statistical significance. There was a weaker indication of a larger effect on males but no evidence of effect modification by age or the other diagnoses. We also found that the shape of the exposure–response relationship between MI hospitalizations and PM$_{10}$ is almost linear, but with a steeper slope at levels of PM$_{10}$ < 50 µg/m$^3$. We conclude that increased concentrations of ambient PM$_{10}$ are associated with increased risk of MI among the elderly.

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admissions were traced back to 1985, ensuring at least 1 year of data before the start of the particle data.

Daily monitoring of PM$_{10}$ is not done in all U.S. cities. We selected the following 21 cities with daily monitoring of PM and representing a geographic distribution across the country: Birmingham, Alabama; Boulder, Colorado; Canton, Ohio; Chicago, Illinois; Cincinnati, Ohio; Cleveland, Ohio; Colorado Springs, Colorado; Columbus, Ohio; Denver, Colorado; Detroit, Michigan; Honolulu, Hawaii; Houston, Texas; Minneapolis–St. Paul, Minnesota; Nashville, Tennessee; New Haven, Connecticut; Pittsburgh, Pennsylvania; Provo–Orem, Utah; Salt Lake City, Utah; Seattle, Washington; Steubenville, Ohio; and Youngstown, Ohio.

For most cities, the metropolitan county encompassed the city and much of its suburbs, but we used multiple counties for Minneapolis–St. Paul (Ramsey and Hennepin, MN), Birmingham (Blount, Jefferson, St. Clair, Shelby, and Walker, AL), Steubenville (Jefferson, OH, and Brooke and Hancock, WV), and Youngstown (Columbiana and Mahoning, OH).

Environmental data. We obtained PM$_{10}$ data from the U.S. Environmental Protection Agency’s Aerometric Information Retrieval System (Nehls 1973). Many of the cities have more than one monitoring location, requiring a method to average over multiple locations. We computed local daily mean PM$_{10}$ concentrations using an algorithm that accounts for the different monitor-specific means and variances (Zanobetti et al. 2000a). Not all cities have daily PM$_{10}$ for the full range of years from 1986 to 1999; therefore, each city was analyzed for those years when daily PM$_{10}$ was available.

These PM$_{10}$ series had some occasional missing observations, and we replaced the missing values with the predicted values from a random effect, whether PM$_{10}$ was modeled linearly. To confirm the report of Braga et al. (2001) that the association was predominant with PM$_{10}$ on the day of the event, we examined effects at exposure from lag day 0 to lag day 2. If we could confirm a primary association with lag day 0, we used this for the subsequent analysis described below.

As a sensitivity analysis, we tested an alternate referent selection scheme that matched on AT (rounded to the same degrees Celsius) and used indicator variables to control for day of the week. Because matching on two covariates controls for interactions between the covariates, this controls for the possibility that the temperature effects vary by month. It also renders moot any question of whether the nonlinear dependence of MIs with temperature was modeled correctly. Previous day’s temperature was controlled using a cubic spline in this analysis, as well.

Case-crossover analyses lend themselves to the analysis of effect modification. Factors such as sex are controlled by matching in the design of the study, but we can still test for effect modification with interaction terms or a stratified analysis. We chose stratified analyses, because if a characteristic modifies the effect of PM$_{10}$, it might also modify the effect of weather or other covariates. A stratified analysis controls for this. Specifically, we conducted stratified analyses by sex, age (<75 vs. ≥75), and previous admission for chronic disease such as atrial fibrillation, COPD, CHF, and diabetes, and secondary diagnosis for pneumonia as an acute modifier.

In a second stage of the analysis, the city-specific results were combined using the multivariate meta-regression technique of Berkey et al. (1998). To be conservative, we report the results incorporating a random effect, whether or not there was a significant heterogeneity.

Finally, we assessed the shape of the dose–response relationship by fitting a piecewise linear spline, with slope changes at 20 µg/m$^3$ and 50 µg/m$^3$. We combined these estimates using a random effect meta-analysis as well.

Results

There were 302,453 hospital admissions for MI in the 21 cities during the study period. Table 1 shows the counts for all of the cities.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>302,453</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>65–75</td>
<td>145,983 (48)</td>
</tr>
<tr>
<td>&gt;75</td>
<td>156,470 (52)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>147,246 (49)</td>
</tr>
<tr>
<td>Female</td>
<td>155,207 (51)</td>
</tr>
<tr>
<td>Secondary diagnosis</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>13,588 (4)</td>
</tr>
<tr>
<td>Previous admissions</td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>32,455 (11)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>28,912 (10)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>49,732 (16)</td>
</tr>
</tbody>
</table>
broken into categories by age group, sex, and previous and secondary diagnosis. Table 2 shows the distribution of environmental factors by city, including the study period, the total population, PM, AT, and the counts of hospital admissions for MI. The average PM$_{10}$ across all cities was 27 µg/m$^3$.

We first looked at the lag structure of the association between PM$_{10}$ and the risk of hospitalization for MI by simultaneously estimating the effect of PM$_{10}$ from lag days 0 to 2. The combined estimates of percent change in risk (and 95% confidence interval (CI)) of emergency hospitalization for MI are shown in Figure 1 together with the estimate of lag day 0 alone. The PM$_{10}$ effect is mainly associated with the change in risk on the day of hospitalization; therefore, the rest of the analysis was done for lag day 0. Figure 1 also shows the percent change of the combined estimates for PM$_{10}$ at lag day 0 from the sensitivity analysis, where the control periods were chosen using the same time-stratified approach but such that exposures on the case day were compared with exposures occurring on days of the same month with the same value of AT (TEMP) as the case day.

The results shown in Figure 1 using the two different referent selection schemes are consistent and show a very similar estimated effect. Overall, we found that for each 10 µg/m$^3$ increase in the concentration of PM$_{10}$, there was a 0.65% (95% CI, 0.3–1%) increase in the risk of hospitalization for an MI among the study population. When matching by AT (TEMP in Figure 1), we found a 1.3% change (95% CI, 1.5–1.6) versus females (0.5%; 95% CI, 0.3–0.9) in the risk of hospitalization for MI, compared with a 0.6% change (95% CI, 0.3–1) in subjects without a secondary diagnosis of pneumonia. No significant heterogeneity was found when combining the stratified results.

None of the other effect modifiers we examined (age, sex, CHF, atrial fibrillation, diabetes) showed much evidence for effect modification except perhaps for sex, with a suggestive difference for males (0.9%; 95% CI 0.2–1.5) versus females (0.4%; 95% CI, 0.2–0.6). Finally, the shape of the exposure–response relationship between MI hospitalizations and PM$_{10}$ is shown in Figure 3. The exposure response is almost linear, but with a steeper slope at levels of PM$_{10}$ < 50 µg/m$^3$.

**Discussion**

We found a significant association between airborne particles and the risk of emergency MI hospitalization in a multicity study. This association was only with PM$_{10}$ on the same day, suggesting that airborne particles are acting as a trigger of an MI. We did not find evidence of effect modification by age, and weak evidence by sex, but we found a doubled risk in subjects with a secondary diagnosis of pneumonia or a previous admission for COPD. Diabetes, CHF, and atrial fibrillation did not modify the risk. These results greatly expand the number of locations in which an association between PM$_{10}$ and MI has been investigated and, by using a uniform analytical strategy, provide a clearer indication of the lag between exposure and response.

The estimated effect for a 10 µg/m$^3$ increase in PM$_{10}$ on emergency MI admissions (0.65%; 95% CI, 0.3–1.0) was higher than the estimates recently published for all-cause mortality (Schwartz et al. 2003). This suggests that MI is a more specific outcome, and the lag structure found indicates a rapid pathway. In the same article (Schwartz et al. 2003), we
also showed that the effects of PM$_{10}$ on hospi-
tal admissions for all other cardiovascular causes are not greatly different from the effects on MI admissions.

Recent studies of intermediate markers also provide support for a causal association. These include an observation of increased plasma fibrinogen in a human exposure chamber study (Ghio et al. 2000). Results for C-reactive protein concentrations have been mixed (Brook et al. 2003; Donaldson et al. 2001; Peters et al. 2001b; Pope et al. 2004b), but PM exposure was associated with decreased plaque stability in an animal model for arteriosclerosis (Suwa et al. 2002). In a Los Angeles panel study in patients with COPD (Linn et al. 1999) and in a large cross-sectional German study of older adults (Ibald-Mulli et al. 2001), higher levels of air pollution were associated with higher blood pressure. Another study in Boston (Zanobetti et al. 2004) suggested that changes in PM$_{2.5}$ led to within-
person increases in resting and exercise blood pressure among vulnerable patients with cardiovascular disease. These studies provide a limited but growing understanding of mecha-
nisms underlying these findings, suggesting that pollution may lead to acute or chronic vasoconstriction and/or atherosclerosis, per-
haps due to systemic inflammation, changes in autonomic function, or oxidative stress.

Our finding that secondary diagnosis of pneumonia or a previous admission for COPD appears to increase the risk is consistent with previous findings. For example, cardiovascular deaths on high-pollution days have been reported to be three times as likely to include respiratory complications (Schwartz 1994b). In a study using Poisson models, we found that a secondary diagnosis for acute respiratory infec-
tion, acute bronchitis, pneumonia, and COPD modified the risk of any admission for heart disease (Zanobetti et al. 2000b). D’Ippoliti et al. (2003) also analyzed several comorbid-
ties, and they did not find effect modification. Their study showed some indication of a higher effect for conduction disorders, a slightly higher effect in females, and a higher effect with increasing age group.

Previous studies have reported PM$_{10}$ (Atkinson et al. 2001; Ofteledal et al. 2003; Zanobetti et al. 2000a) effects on respiratory admissions. However, the small percentage increase in pneumonia associated with a 10 µg/m$^3$ increase in PM$_{10}$ cannot explain the doubling of the effect of PM$_{2.5}$ on MI admis-
sions. Persons with COPD often have under-
lying coronary artery disease through their joint association with smoking, and this may explain some or all of the observed effect modi-
fication. We also did not find effect modifica-
tion by sex and age, even if we found a slightly higher effect in males. The weak evidence for effect modification by age groups indicates that the adverse effect of particles is not limited to the extremely elderly population.

The indication of a somewhat higher slope at PM$_{10}$ concentrations $< 50$ µg/m$^3$ is consist-
tent with a previous report for all-cause mor-
tality (Schwartz 2000). Other studies have assessed exposure response for particle using nonparametric smoothing (Schwartz 1994a; Schwartz and Zanobetti 2000) or natural spline (Daniels et al. 2000) and similarly found little evidence for a threshold and more sup-
port for steepers slopes at low concentrations.

There is a substantial body of epidemiolo-
gy literature showing a clear and consistent association between concentrations of ambient PM and negative health effects (Anderson et al. 2003; Brunekreef and Holgate 2002; Dockery 2001; Katsouyanni et al. 1996; Samet et al. 2000). Less clear is the biologic mechanism by which PM could be causing this morbidity and mortality. One avenue by which investi-
gators can offer direction is identifying which outcomes are most strongly and consistently associated with PM$_{10}$ and conditions that modify that outcome. Epidemiologic research continues to narrow the focus around specific outcomes, from mortality to cause-specific mortality and from hospitalization for cardio-
vascular disease to MI and examination of specific modifiers.

The further epidemiologic identification of individual traits that are associated with increased risk of mortality and morbidity from increased concentrations of PM air pollu-
tion will continue to direct ongoing research into the biologic mechanism and provide critical data for risk assessment and inform policy makers.

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**Figure 2.** Stratified analysis for several effect modi-
fiers: combined random-effect estimated change in risk (and 95% CI) of hospitalization for MI associ-
ated with a 10 µg/m$^3$ increase in daily PM$_{2.5}$ on the same day. W/out, without.

**Figure 3.** Combined random-effect estimated of the dose–response relationship between MI emerg-
cy hospital admissions and PM$_{2.5}$ computed by fitting a piecewise linear spline, with slope changes at 20 µg/m$^3$ and 50 µg/m$^3$. 


