Ischemic Heart Disease Events Triggered by Short-Term Exposure to Fine Particulate Air Pollution

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Background—Recent evidence suggests that long-term exposure to particulate air pollution contributes to pulmonary and systemic oxidative stress, inflammation, progression of atherosclerosis, and risk of ischemic heart disease and death. Short-term exposure may contribute to complications of atherosclerosis, such as plaque vulnerability, thrombosis, and acute ischemic events. These findings are inconclusive and controversial and require further study. This study evaluates the role of short-term particulate exposure in triggering acute ischemic heart disease events.

Methods and Results—A case-crossover study design was used to analyze ischemic events in 12,865 patients who lived on the Wasatch Front in Utah. Patients were drawn from the cardiac catheterization registry of the Intermountain Heart Collaborative Study, a large, ongoing registry of patients who underwent coronary arteriography and were followed up longitudinally. Ambient fine particulate pollution (particles with an aerodynamic diameter ≤2.5 μm; PM$_{2.5}$) elevated by 10 μg/m$^3$ was associated with increased risk of acute ischemic coronary events (unstable angina and myocardial infarction) equal to 4.5% (95% confidence interval, 1.1 to 8.0). Effects were larger for those with angiographically demonstrated coronary artery disease.

Conclusions—Short-term particulate exposures contributed to acute coronary events, especially among patients with underlying coronary artery disease. Individuals with stable presentation and those with angiographically demonstrated clean coronaries are not as susceptible to short-term particulate exposure. (Circulation. 2006;114:2443-2448.)

Key Words: air pollution ■ angina ■ coronary disease ■ ischemia ■ myocardial infarction

Exposure to elevated concentrations of ambient particulate matter (PM) air pollution has been implicated as a risk factor for cardiovascular disease and mortality. Long-term repeated exposure to PM has been linked to ischemic heart disease. The empirical patterns of PM mortality associations are consistent with the hypothesis that PM exposure contributes to pulmonary and systemic oxidative stress, inflammation, atherosclerosis, and increased risk of ischemic heart disease and death. Long-term PM exposure has been associated with subclinical chronic inflammatory lung injury and subclinical atherosclerosis. In heritable hyperlipidemic rabbits, PM exposure accelerated progression of atherosclerotic plaques and increased vulnerability to plaque rupture. PM-potentiated vascular inflammation and atherosclerosis also were observed in a recent study of apolipoprotein E–deficient (hyperlipidemic) mice exposed to environmentally relevant concentrations of fine PM.

Editorial p 2430
Clinical Perspective p 2448

Short-term PM exposures also may play a role in triggering acute ischemic heart disease events. Short-term elevated PM exposures and related inflammation may contribute to acute complications of atherosclerosis by increasing the risk of atherosclerotic plaque rupture, thrombosis, and precipitation of acute ischemic events. Evidence that short-term exposure to PM air pollution can trigger myocardial infarction (MI) has been observed in several general population studies. Increased short-term PM exposure also has been associated with ischemic stroke, ECG ST-segment depression, increased plasma viscosity, increased circulating markers of inflammation, and changes in cardiac autonomic function as indicated by various measures of heart rate variability. Related evidence also shows that short-term PM exposure is associated with vasculature alterations. For example, PM- and ozone exposure–induced arterial vasoconstriction in healthy adults was associated with impaired vascular reactivity and endothelial function in patients with diabetes, and increased blood pressure in cardiac rehabilitation patients and adults with lung disease. Evidence of pathophysiological or mechanistic pathways that plausibly link PM exposure to cardiopulmonary disease and death is reviewed and discussed in more detail elsewhere.

The present study evaluates the role of environmentally relevant short-term increases in exposures in triggering acute ischemic heart disease events. This study takes advantage of...
a large, ongoing, and unique registry of well-characterized patients who underwent coronary arteriography and who have been followed up over time. The research participants lived in a well-defined area with long-term daily monitoring of particulate air pollution and with substantial daily variability in PM concentrations resulting from densely populated mountain valley topography and frequent temperature inversions. The specific objective of this study is to explore the potential role of short-term exposure to fine PM in triggering acute ischemic heart disease events in these well-characterized cardiac catheterization patients.

Methods

Study Area and Participants

Approximately 80% of the population of Utah resides on a relatively narrow strip of land that fronts the west side of the Wasatch mountain range. The Wasatch Front area is bordered on the east by the Wasatch Mountains and on the west largely by the Great Salt Lake, Utah Lake, and smaller mountain ranges. It is ~10 to 15 miles wide from east to west and ~80 miles long from north to south with 3 nearly contiguous metropolitan areas: the city of Ogden and surrounding communities to the north with a 2003 total population of 469 000, Salt Lake City and surrounding communities located in the center with a 2003 total population of 1 005 000, and Provo/Orem and surrounding communities to the south with a 2003 total population of 407 000.

Study participants included patients drawn from the cardiac catheterization registry of the Intermountain Heart Collaborative Study, a population of patients undergoing coronary arteriography at the LDS Hospital (Salt Lake City, Utah). At the time of index hospitalization, these patients presented with 1 of 3 general clinical conditions that indicated coronary angiography: acute MI, an unstable pattern of chest pain suggesting unstable angina (such as progressive symptoms or symptoms at rest), or a stable pattern of chest pain suggesting stable angina (exertional symptoms only, including a positive stress test result) or stable noncoronary syndromes necessitating angiography. Male and female patients of unrestricted age were included in the registry. The study was approved by the institutional review board of the hospital.

A total of 26 643 participants were enrolled between 1994 and 2004, including mostly patients from throughout Utah and from neighboring western states. The present analysis includes the 12 865 study participants who lived in the Wasatch Front study area and who had their event on a day when air pollution and weather data were available. This analysis also included identifiable subsequent MI events. Participants were followed up until death or December 31, 2004. Deaths were determined from electronic hospital records, State of Utah Health Department death certificates, and national Social Security Administration death records. MI events subsequent to the index hospitalization were identified by searching the Intermountain Healthcare electronic medical records database.

Baseline Participant Variables

Baseline participant variables, including various individual risk factors, were determined or derived from physician-provided information on the standard angiographic report form used at the LDS Hospital. These included age, gender, smoking, body mass index (BMI), congestive heart failure (CHF), hypertension, hyperlipidemia, diabetes, family history of early coronary artery disease (CAD), and number of severely diseased coronary vessels. Smoking included active or previous (>10 pack-years) tobacco use. BMI was calculated from height and weight. CHF was physician reported based on clinical symptoms. Hypertension was physician reported for systolic blood pressure $\geq 140$ mm Hg, diastolic blood pressure $\geq 90$ mm Hg, or use of antihypertensive agents. Hyperlipidemia was physician reported for total cholesterol $\geq 200$ mg/dL, low-density lipoprotein level $\geq 130$ mg/dL, or use of cholesterol-lowering med-
less variability in estimated exposures. As reported in Table 1, the means and the standard deviations for the monitored plus estimated data were similar to the monitored data.

**Statistical Analysis**

In this analysis, the primary exposure variable was PM$_{2.5}$, but PM$_{10}$ was also considered. Concentrations on the concurrent day and previous 1 to 3 days and 2- to 4-day lagged moving average concentrations were evaluated. The primary outcome variables were presentation with MI or unstable angina at the time of index hospitalization and subsequent incident MI during follow-up (after the index hospitalization), analyzed separately and in pooled analysis. Elevated concentrations of PM air pollution were hypothesized to increase the risk of these acute coronary events. Stable presentation at the index hospitalization also was analyzed as an outcome variable. However, because treatment for stable presentation is more likely to be elective with regard to its timing, it was hypothesized that this presentation is less associated with particulate air pollution.

This analysis uses the case-crossover design, which is an adaptation of the retrospective case-control design. This approach matches exposures at the time of or shortly before the event of interest with ≥1 periods when the event did not occur (control or referent periods) and evaluates potential excess risk using conditional logistic regression. Details of the use of conditional logistic regression in case-crossover studies with application to air pollution exposure are given elsewhere. Because individuals who experience an acute event serve as their own controls, there is perfect matching on all participant-specific characteristics that do not vary over time; thus, this approach controls for participant-specific risk factors by design. Furthermore, by choosing matching referent periods close in time (before and after the event) and on the same day of the week, this approach structures the analysis so that various time-dependent risk factors such as day of the week, seasonality, long-term time trends, and long-term changes in individual characteristics between multiple events for the same patient also are controlled for by design. In this analysis, referent or control period exposures were matched on day of the week in the same month and year as the ischemic event, resulting in up to 4 control periods per event. The details of this specific time-stratified referent selection approach and a statistical exposition on why it allows unbiased conditional logistic regression estimates and avoids bias that can occur as a result of time trends in air pollution exposure are presented elsewhere. Temperature and dewpoint temperature were included as linear and quadratic terms in the conditional logistic regression model. Additionally, analyses stratified by various baseline participant variables, risk factors, and number of severely diseased coronary vessels were conducted.

The authors had full access to the data and take full responsibility for their integrity. All authors have read and agree to the manuscript as written.

**Results**

Baseline participant characteristics are summarized in Table 2. Of those presenting with MI or unstable angina, only 21% had a history of smoking; however, most were hypertensive or hyperlipidemic.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MI + Unstable Angina (n=4818)</th>
<th>Stable Presentation (n=8047)</th>
<th>Subsequent MI (n=1173)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>63±13</td>
<td>60±16</td>
<td>65±13</td>
</tr>
<tr>
<td>Male gender, %</td>
<td>69</td>
<td>55</td>
<td>68</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>21</td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td>BMI, kg/m$^2$</td>
<td>29±6</td>
<td>28±6</td>
<td>30±14</td>
</tr>
<tr>
<td>MI, %</td>
<td>41</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>CHF, %</td>
<td>12</td>
<td>15</td>
<td>21</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>60</td>
<td>39</td>
<td>58</td>
</tr>
<tr>
<td>Hyperlipidemia, %</td>
<td>60</td>
<td>31</td>
<td>50</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>22</td>
<td>14</td>
<td>24</td>
</tr>
<tr>
<td>Family history, %</td>
<td>45</td>
<td>21</td>
<td>35</td>
</tr>
<tr>
<td>Risk factors, %*</td>
<td>0</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>22</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>19</td>
<td>25</td>
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<tr>
<td></td>
<td>3</td>
<td>26</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>4+</td>
<td>11</td>
<td>11</td>
</tr>
</tbody>
</table>

Proportions are given in percent; averages, in mean±SD.

*Risk factors include CHF, hypertension, hyperlipidemia, diabetes, and family history of early CAD.

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<table>
<thead>
<tr>
<th>Monitoring Sites</th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
<th>Maximum</th>
</tr>
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<tr>
<td>Ogden PM$_{2.5}$</td>
<td>3589</td>
<td>28.5</td>
<td>16.5</td>
<td>163</td>
</tr>
<tr>
<td>Ogden PM$_{10}$</td>
<td>4381</td>
<td>28.5</td>
<td>16.5</td>
<td>163</td>
</tr>
<tr>
<td>Ogden PM$_{2.5}$</td>
<td>773</td>
<td>10.8</td>
<td>10.6</td>
<td>108</td>
</tr>
<tr>
<td>Ogden PM$_{10}$</td>
<td>4381</td>
<td>10.9</td>
<td>9.7</td>
<td>108</td>
</tr>
<tr>
<td>SLC Hawthorne PM$_{2.5}$</td>
<td>2634</td>
<td>27.7</td>
<td>17.4</td>
<td>162</td>
</tr>
<tr>
<td>SLC Hawthorne PM$_{10}$</td>
<td>4381</td>
<td>27.2</td>
<td>16.8</td>
<td>162</td>
</tr>
<tr>
<td>SLC Hawthorne PM$_{2.5}$</td>
<td>2309</td>
<td>11.3</td>
<td>11.9</td>
<td>94</td>
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<tr>
<td>SLC Hawthorne PM$_{10}$</td>
<td>4382</td>
<td>10.6</td>
<td>10.8</td>
<td>94</td>
</tr>
<tr>
<td>Provo/Orem, Lindon PM$_{2.5}$</td>
<td>4057</td>
<td>32.7</td>
<td>21.1</td>
<td>240</td>
</tr>
<tr>
<td>Provo/Orem, Lindon PM$_{10}$</td>
<td>4381</td>
<td>32.5</td>
<td>20.8</td>
<td>240</td>
</tr>
<tr>
<td>Provo/Orem, Lindon PM$_{2.5}$</td>
<td>2332</td>
<td>10.1</td>
<td>9.8</td>
<td>82</td>
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<tr>
<td>Provo/Orem, Lindon PM$_{10}$</td>
<td>4383</td>
<td>10.6</td>
<td>11.1</td>
<td>144</td>
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<tr>
<td>SLC AMC PM$_{2.5}$</td>
<td>2260</td>
<td>35.9</td>
<td>20.4</td>
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<td>SLC North PM$_{10}$</td>
<td>4032</td>
<td>45.1</td>
<td>25.1</td>
<td>199</td>
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</tbody>
</table>
and many also had CHF, diabetes, or a family history of early CAD. When CHF, hypertension, hyperlipidemia, diabetes, and family history of early CAD were treated as underlying individual “risk factors,” the majority of the MI and unstable angina participants had multiple risk factors. In comparison, those with stable presentation were relatively less likely to smoke and had less underlying chronic cardiovascular disease.

Table 3 presents estimated increased risk (and 95% confidence intervals [CIs]) for acute coronary events associated with a 10-μg/m³ increase in concurrent-day PM$_{2.5}$. Index MI/unstable angina and subsequent MI were not significantly different in terms of their associations with PM$_{2.5}$. On the basis of estimates from pooled analysis, a 10-μg/m³ increase in PM$_{2.5}$ was associated with a 4.5% (95% CI, 1.1 to 8.0) increase in risk of presenting with an acute coronary event. The effect estimate was nearly the same when observations using imputed PM data were excluded. The association between PM$_{2.5}$ and stable presentation was negative and not statistically significant.

Figure 1 presents risk estimates for different lag structures. Increased risk was more strongly associated with PM$_{2.5}$ than with PM$_{10}$. Although there is autocorrelation in daily PM exposures, the strongest associations were with concurrent-day or the 2-day-lagged moving average (mean of the concurrent and previous day), indicating the relative importance of more recent exposure. The distributed lag structure also partially reflects the fact that clinical presentation and subsequent angiography follow onset of symptoms.

Figure 2 presents PM$_{10}$ risk estimates for all acute coronary events after stratification by event type and individual characteristics. The PM$_{2.5}$ effect estimates were nearly the same for unstable angina, index MI, and subsequent MI, indicating that pooling these events was appropriate. Observed differences in PM$_{2.5}$ effect estimates for age, gender, smoking, BMI, underlying disease, and risk factor strata were not statistically significant ($P>0.05$). However, significantly larger PM$_{2.5}$ effect estimates were observed for individuals who had at least 1 severely diseased coronary vessel compared with those who did not (interaction $P=0.01$). Excluding participants who, on the basis of coronary arteriography, were found not to have seriously diseased coronary arteries clearly resulted in stronger PM$_{2.5}$ associations.

**Discussion**

The results of this analysis indicate that short-term ambient PM$_{2.5}$ exposure is associated with acute ischemic heart disease events. Similar results have been observed in a study of MI events in Boston, a study of first MI hospitalization in Rome, a study of emergency hospitalizations for MI in 21 US cities, and a study of hospital readmissions for MI, angina, dysrhythmia, or heart failure of MI survivors in 5 European cities. The present study is unique with regard to its use of a large registry of well-characterized patients who underwent coronary arteriography and lived in a well-defined geographic area with adequate long-term daily pollution monitoring. No other study has been able to explore differential effects for patients with differing levels of angiographically demonstrated CAD. Although the effect estimates of a 10-μg/m³ increase in PM$_{2.5}$ are relatively small (during winter temperature inversions, 24-hour PM$_{2.5}$ concentrations can exceed 100 μg/m³), these effects may be of significant public health importance because such exposure to fine PM is relatively ubiquitous in urban environments and essentially involuntary.

A primary strength of the case-crossover study design used in this analysis is that the effect estimates are probably not due to

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** Percent increase in risk (and 95% CI) of acute coronary events associated with 10 μg/m³ of PM$_{2.5}$ or PM$_{10}$ for different lag structures. av Indicates average.
confounding by age, gender, smoking, underlying chronic disease, or other individual-level characteristics. In this case-crossover study design, individuals serve as their own controls, and individual-level characteristics are controlled for by design. Similarly, long-term time trends, seasonality, day of the week, and long-term changes in individual characteristics between multiple events for the same patient are controlled for by matching. Furthermore, it has been demonstrated that the time-stratified referent selection strategy used in this analysis allows unbiased conditional logistic regression estimates and avoids the bias that can occur as a result of time trends in air pollution exposure.43,44

Although this study includes well-defined and characterized subjects, the design allows only the evaluation of pollution-related risk for those who had an event, required index catheterization, and were available for study entry. It is unclear how these limitations affect the generalizability of the results, but they place the emphasis of analysis on events that are less likely to have been fatal. In this study, only $\approx$5% of index MI events were fatal, defined as death within 30 days of the event. Although a quantitative review of the literature suggests that there may be differential effects of PM pollution on fatal versus nonfatal events, the use of different study designs and PM measures requires some caution when comparing effect estimates.5 Furthermore, clinical presentation and subsequent angiography follow onset of symptoms and in some cases may be on a different calendar date, resulting in some exposure misclassification and affecting the estimated distributed lag structure.

The results of this study provide some information regarding the related issue of plausibility. Is it plausible that clinically relevant ischemic cardiovascular events could be triggered by environmentally relevant exposures of only a day or 2? It seems implausible that short-term PM exposure could trigger a clinically relevant ischemic cardiac event in someone without pre-existing CAD. In fact, PM$_{2.5}$ associations with acute ischemic heart disease events were observed only for individuals who had at least 1 severely diseased coronary vessel (with $\approx$70% stenosis as determined at angiography). These findings are consistent with the suggestion that short-term elevated PM exposure and related inflammation contribute to acute complications of atherosclerosis, including plaque vulnerability, thrombosis, and acute ischemic events, but only in persons with existing disease.

A primary limitation of the design used in this study is that it allowed analysis of only very short-term acute exposure and its potential to trigger ischemic heart disease events. As discussed elsewhere, long-term repeated exposure to elevated concentrations of PM may contribute to oxidative stress, low- to moderate-grade inflammation, and the initiation and progression of atherosclerosis and related cardiovascular disease.1,4,5,7 Further study is required to evaluate long-term risk. However, this study does provide evidence that short-term exposure to elevated concentrations of fine particulate air pollution contributes to the triggering of acute ischemic heart disease events. Individuals with stable presentation and without seriously diseased coronary vessels are not as susceptible to risk from short-term exposure to fine particulate pollution.

**Sources of Funding**

This study was supported by Deseret Foundation, Salt Lake City, Utah, and funds from the Mary Lou Fulton Professorship, Brigham Young University, Provo, Utah.

**Disclosures**

None.

**References**


**CLINICAL PERSPECTIVE**

It has previously been demonstrated that long-term exposure to particulate air pollution contributes to cardiovascular disease, including the progression of atherosclerosis and risk of ischemic heart disease and death. This study extends that risk to include short-term exposures of ~24 hours of ambient fine particulate air pollution. By analyzing 12,865 patients who lived on the Wasatch Front in Utah, we determined that short-term particulate exposures are associated with a significantly increased risk of acute ischemic coronary events, especially for those with established coronary artery disease. This information emphasizes that even short-term pollution episodes of only 1 or a few days may put patients at risk. Although any single high-air-pollution day results in only a modest increase in the risk of an acute ischemic event, the additive risk over time may result in substantial adverse clinical impact. The present study suggests that future research should investigate effective interventions to reduce the cardiovascular risks associated with high-air-pollution days. On the basis of these results, patients with established heart disease might do well to move to areas with a lower burden of fine particulate air pollution levels. If moving is not possible, patients may at best be wise to stay indoors during the more polluted days and to ensure adequate filtering of their indoor air. Given the ubiquitous and involuntary nature of the exposure, this study provides support for the need for increased public efforts to improve overall air quality.
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Circulation. 2006;114:2443-2448; originally published online November 13, 2006; doi: 10.1161/CIRCULATIONAHA.106.636977
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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