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# Relation of Heart Failure Hospitalization to Exposure to Fine Particulate Air Pollution

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Cardiopulmonary disease has been associated with particulate matter (PM) air pollution. There is evidence that exposure to elevated PM concentrations increases risk of acute ischemic heart disease events, alters cardiac autonomic function, and increases risk of arrhythmias. It is plausible, therefore, that PM exposure may exacerbate heart failure (HF). A case-crossover study design was used to explore associations between fine PM (PM<sub>2.5</sub>; particles with an aerodynamic diameter  $\leq 2.5 \mu\text{m}$ ) and 2,628 HF hospitalizations. Patients lived on Utah's Wasatch Front and were drawn from those hospitalized at Intermountain Healthcare facilities with a primary diagnosis of HF. A 14-day lagged cumulative moving average of  $10 \mu\text{g}/\text{m}^3$  PM<sub>2.5</sub> was associated with a 13.1% (95% confidence interval 1.3 to 26.2) increase in HF admissions. The strongest PM<sub>2.5</sub>-HF associations were for elderly patients who had previously been admitted for HF and who required only a short period of hospitalization. HF hospitalizations are associated with lagged cumulative exposure to PM<sub>2.5</sub> of approximately 2 weeks. In conclusion, particulate air pollution may play a role in precipitating acute cardiac decompensation in otherwise well-managed patients with HF, perhaps through effects of PM on myocardial ischemia, cardiac autonomic function, and/or arrhythmic effects. © 2008 Elsevier Inc. All rights reserved. (Am J Cardiol 2008;102:1230-1234)

Exposure to elevated concentrations of ambient particulate matter (PM) air pollution has been associated with cardiopulmonary disease and mortality.<sup>1-8</sup> This study analyzes hospitalization data of patients with heart failure (HF) who lived in a well-defined area with long-term daily monitoring of particulate air pollution and with substantial temporal variability in PM concentrations due to densely populated mountain valley topography and frequent temperature inversions. It is hypothesized that elevated PM concentrations are associated with increased risk of HF hospitalization. Also, because hospitalization follows onset of symptoms, which likely follow a period of cumulative exposure, a distributed lag structure relating exposure to hospitalization of a few days or more is hypothesized.

## Methods

More than 2 million people, approximately 80% of Utah's population, live on the Wasatch Front, a narrow area of land that is bordered on the east by the Wasatch Mountain range and on the west by the Great Salt Lake, Utah Lake, and smaller mountain ranges. This area is approximately 10 to 15 miles wide from east to west and approximately 80 miles long from north to south. It contains 3 nearly contiguous

metropolitan areas, including the Ogden area to the North, the Salt Lake City area located in the center, and the Provo/Orem area to the south. Study participants included patients who were hospitalized with a primary discharge diagnosis of HF at Intermountain Healthcare. All patients had been admitted to Utah Valley Regional Medical Center, American Fork Hospital, Alta View Hospital, Cottonwood Hospital, LDS Hospital, or McKay-Dee Hospital for the years 1994 to 2006. These 6 hospitals accounted for approximately 60% of hospital admittances in the study area. Hospitalizations were identified by searching the Intermountain Healthcare electronic medical records data warehouse for HF International Classification of Diseases, ninth edition (ICD-9) diagnosis codes, as discussed elsewhere.<sup>9</sup> The study was approved by the Intermountain Healthcare Urban Central Region institutional review board. There were a total of 3,747 HF admissions including patients from throughout the state of Utah and from neighboring Western states. The present analysis includes the 2,618 admittances (including readmittances) of patients who lived in the Wasatch Front study area and who had their event on a date when air pollution and weather data were available. Individual patient variables included date and time of admission, date and time of discharge, age, gender, race, and zip code of residence.

Common weather patterns are shared across the Wasatch Front study area. PM concentrations are elevated during low-level temperature inversion episodes due to trapping of local emissions in a stagnant air mass near the valley floor. Daily weather data were collected from the National Weather Service (Salt Lake City International Airport station) for the time period January 1, 1993 through December 31, 2006. These data included temperature, dew point temperature, barometric pressure, and clearing index. The clear-

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Table 1  
Summary of pollution concentration data 1993 to 2006

Monitoring Sites		n (days)	Mean ( $\mu\text{g}/\text{m}^3$ )	SD	Max
Ogden	PM <sub>2.5</sub> monitored	1,005	10.6	9.9	108
Ogden	PM <sub>2.5</sub> monitored + imputed	5,108	10.7	9.3	108
SLC, Hawthorne	PM <sub>2.5</sub> monitored	3,007	11.1	11.2	94
SLC, Hawthorne	PM <sub>2.5</sub> monitored + imputed	5,109	11.9	11.8	104
Provo/Orem, Lindon	PM <sub>2.5</sub> monitored	3,021	10.1	9.3	82
Provo/Orem, Lindon	PM <sub>2.5</sub> monitored + imputed	5,113	10.6	10.7	142

PM<sub>2.5</sub> refers to particles with an aerodynamic diameter  $\leq 2.5$  micrometer cut point.

Table 2  
Descriptive information regarding the hospitalized patients with HF

Number of Admissions	2,618
Age (yrs)	67 $\pm$ 15
Men	57%
Race (white)	90%
Readmissions	38%
Length of stay (days)	6 $\pm$ 9

Data presented as proportions (%) or averages (mean  $\pm$  SD).

ing index ranges from 0 to 1,050. Low index values reflect stagnant air conditions; high values reflect greater diffusion pollution potential.

Particulate air pollution data for PM<sub>10</sub> (particles with an aerodynamic diameter  $\leq 10 \mu\text{m}$ ), and PM<sub>2.5</sub> (particles with an aerodynamic diameter  $\leq 2.5$ ) were obtained from the Utah Department of Environmental Quality, Division of Air Quality, Salt Lake City, Utah. Data from monitoring sites along the Wasatch Front from January 1, 1993 to December 31, 2006 were collected. Monitoring was conducted in accordance with the US Environmental Protection Agency federal reference method.<sup>10</sup> In Ogden and Provo/Orem, PM<sub>10</sub> monitoring was conducted at a single community-based site with monitoring completeness of 83% and 93%, respectively. In Salt Lake City, the centrally located monitoring site, the Salt Lake City Air Monitoring Center (SLC AMC) was replaced by another site (SLC Hawthorne) with concurrent overlapping monitoring for over a year. Daily PM<sub>10</sub> data were available from  $\geq 1$  of these 2 sites for 95% of the days. In addition, PM<sub>10</sub> data were collected from another Salt Lake City monitoring site (SLC North). Daily PM<sub>10</sub> concentrations between all of the Wasatch Front sites were highly correlated ( $r = 0.72$  to  $0.94$ ). For PM<sub>2.5</sub>, daily monitoring at the SLC Hawthorn and Lindon sites and every third day monitoring at the Ogden site began in January 1998. Missing values for PM<sub>2.5</sub> at specific monitors were estimated using available PM<sub>2.5</sub>, PM<sub>10</sub>, and clearing index data using a 2-stage statistical approach reported in more detail elsewhere.<sup>8</sup> First, PM<sub>10</sub> concentration ratios between monitors were calculated and missing PM<sub>10</sub> values were estimated based on these ratios and monitored PM<sub>10</sub> data at the nearest monitoring site without missing data. Second, for each of the 3 Wasatch Front metropolitan areas, the PM<sub>2.5</sub>/PM<sub>10</sub> ratios were estimated for 10 different air stagnation (clearing index  $\leq 100$ ; 101 to 200; 201 to 500; 501 to 999; 1,000 to 1,050) and seasonal periods (winter months December to February vs non-winter months) using regression models and missing

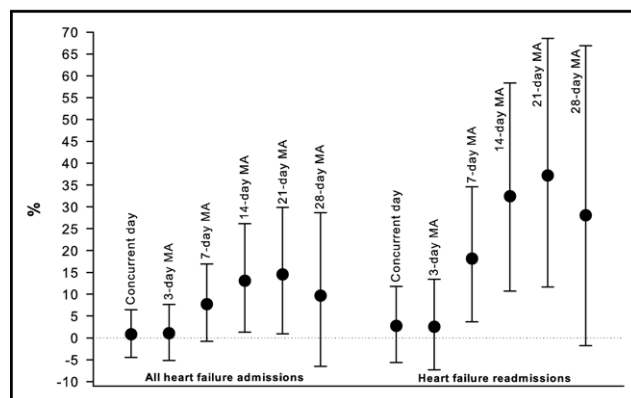


Figure 1. Percent increase in risk and 95% CIs of HF admissions and readmissions, associated with a  $10 \mu\text{g}/\text{m}^3$  of PM<sub>2.5</sub> for selected lagged moving average (MA) exposures 0 to 28 days.

PM<sub>2.5</sub> concentrations were estimated based on these ratios.

The analysis of HF hospitalizations and ambient PM<sub>2.5</sub> was based on the case-crossover design, which is an adaptation of the retrospective case-control design.<sup>8,11,12</sup> This approach matches exposures at the time of or shortly before the event of interest with  $\geq 1$  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.<sup>13,14</sup> Because patients with HF 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. By choosing matching referent periods close in time (before and after the event) and on the same day of the week, the analysis is structured such that time-dependent risk factors including day of week, seasonality, and long-term time trends are also controlled for by design. In this analysis, referent or control period exposures were matched on day of week in the same month and year as the HF hospitalization, resulting in  $\leq 4$  control periods per hospitalization event date. The details of this specific time-stratified referent selection approach, and a statistical exposition on why it allows for unbiased conditional logistic regression estimates and avoids bias that can occur due to time trends in air pollution exposure is presented elsewhere.<sup>13,14</sup>

Analyses using all hospitalizations and analyses stratified by gender, age, length of stay, and first HF admissions

Table 3

Percent increase in risk and 95% CIs of HF hospital admission associated with 10  $\mu\text{g}/\text{m}^3$  PM<sub>2.5</sub> lagged moving average of 14 days for all admissions, readmissions, and stratified by various subgroups

Variable	All HF Admissions		Readmissions	
	n	% Increase (95% CI)	n	% Increase (95% CI)
All	2,618	13.1 (1.3, 26.2)*	999	32.4 (10.7, 58.4) <sup>†</sup>
Men	1,495	13.4 (-1.7, 30.7) <sup>‡</sup>	570	29.2 (2.7, 62.6)*
Women	1,123	12.7 (-5.1, 33.9)	429	41.5 (5.4, 89.9)*
Age <65 yrs	977	3.5 (-13.5, 23.8)	376	-3.1 (-26.5, 27.8)
Age ≥65 yrs	1,641	19.6 (4.0, 37.5)*	623	64.1 (28.6, 109) <sup>†</sup>
Length of stay 0–2 days	682	24.4 (-0.8, 56.0) <sup>‡</sup>	244	68.9 (12.5, 154)*
Length of stay 3–7 days	1,395	10.8 (-4.6, 28.7)	528	35.7 (5.9, 73.9)*
Length of stay 8+ days	541	6.5 (-15.9, 34.8)	227	2.6 (-28.5, 47.1)
First HF admissions	1,619	2.1 (-11.3, 17.5)	—	—
Subsequent HF admits	999	32.4 (10.7, 58.4) <sup>†</sup>	—	—

\* p < 0.05.

<sup>†</sup> p < 0.01.

<sup>‡</sup> p < 0.10.

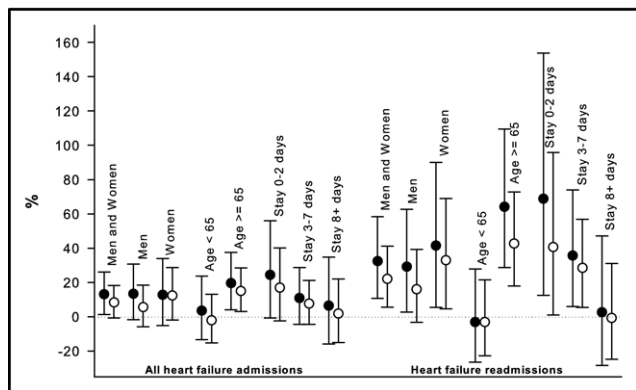


Figure 2. Percent increase in risk and 95% CIs of HF admissions and readmissions associated with 10  $\mu\text{g}/\text{m}^3$  of PM<sub>2.5</sub> lagged moving average of 14 days stratified by gender, age, and length of hospital stay. Closed and open circles are estimates from models including and excluding weather variables, respectively.

versus readmissions were conducted. PM<sub>2.5</sub> concentrations for different lag structures, including concurrent day and lagged moving average concentrations  $\leq 28$  days (including the concurrent day), were evaluated. To control for weather variables, the 14-day lagged moving average (including concurrent day and previous 13 days) of temperature, dew point temperature, and barometric pressure (as both linear and quadratic terms) were included in the conditional logistic regression models.

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

## Results

A summary of the PM<sub>2.5</sub> concentration data and basic descriptive information regarding the HF hospitalizations is provided in Tables 1 and 2, respectively. Figure 1 presents risk estimates of PM<sub>2.5</sub> for different lag structures. The strongest associations were with 14-day or 21-day lagged moving average PM<sub>2.5</sub> concentrations. Although the 21-day

lagged moving average has slightly larger point estimates of the risk effect estimates, the 14-day lagged moving average had the strongest statistical associations based on largest effect estimate relative to standard error of the estimate and lowest p value. Increased risk was not significantly associated with concurrent-day or previous-day concentrations of PM<sub>2.5</sub>.

Table 3 lists the percent increased risk and 95% CI of HF hospital admission associated with 10  $\mu\text{g}/\text{m}^3$  PM<sub>2.5</sub> lagged moving average of 14 days for all admissions and admissions stratified by various subgroups. When all admissions were included in the analysis, statistically significant associations between PM<sub>2.5</sub> and HF admissions were observed. The PM<sub>2.5</sub> effect estimates were not significantly different for men versus women. The effect estimates were larger for those >65 years of age versus younger patients, and larger PM effects were observed for those that required shorter hospitalization. Furthermore, the PM<sub>2.5</sub> effects were seen primarily in patients who had previously been hospitalized for HF. Approximately 38% of the admissions were readmissions. Table 3 also lists the results from analyses that included only admissions of patients who had previously been admitted. Again, in this subset of readmissions, the strongest PM<sub>2.5</sub> associations were for elderly patients, who required a relatively short period of hospitalization.

Figure 2 presents the PM<sub>2.5</sub> hospitalization risk estimates and 95% CI from models that included 14-day lagged moving averages for both PM<sub>2.5</sub> and the weather variables (temperature, dew point temperature, and barometric pressure, as linear and quadratic terms) and from models that did not include the weather variables. The PM<sub>2.5</sub> risk effect estimates were not highly sensitive to controlling for weather variables in the models but, in general, the inclusion of weather variables resulted in somewhat larger pollution effect estimates.

## Discussion

This study indicates that lagged cumulative exposures to PM<sub>2.5</sub> of 1 to several weeks are significantly associated with increased risk of HF exacerbations, as represented by hospitalization with a primary discharge diagnosis of HF. This

study has both limitations and strengths. Although the study area had a relatively reliable long-term network of PM monitoring sites, missing PM<sub>2.5</sub> concentration data required some imputation based on existing PM<sub>2.5</sub>, PM<sub>10</sub>, and air stagnation data. A primary limitation of the case-crossover design used in this study is that it only allows for analysis of relatively short-term PM<sub>2.5</sub> exposure and its potential to exacerbate existing HF. Nevertheless, this study design provides effect estimates that are not likely due to confounding by age, gender, smoking, or other subject-level characteristics because subjects serve as their own controls and subject-level characteristics are controlled for by design. Similarly, long-term time trends, seasonality, day of week and long-term changes in patient 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 for unbiased conditional logistic regression estimates and avoids bias that can occur due to time trends in air pollution exposure.<sup>13,14</sup>

HF associations with PM were also observed in a large daily time-series analysis of PM<sub>2.5</sub> and cardiovascular and respiratory hospitalizations using a national database constructed from United States Medicare files.<sup>15</sup> A 10  $\mu\text{g}/\text{m}^3$  increase in concurrent-day PM<sub>2.5</sub> was associated with a 1.28% (95% CI 0.78 to 1.78) increase in HF admissions. An analysis of PM air pollution and HF hospital admissions for Medicare recipients in 7 cities found a 10  $\mu\text{g}/\text{m}^3$  increase in concurrent-day PM<sub>10</sub> associated with a 0.72% (95% CI 0.35 to 1.10) increase in HF admissions.<sup>16</sup> In our analysis, similar effect sizes for concurrent-day PM<sub>2.5</sub> associations were observed (0.81% and 2.74% increase in all HF admissions and readmissions, respectively), but due to sample size considerations these estimates had much larger CIs (Figure 1) and were not statistically significant. In our analysis, substantially larger PM<sub>2.5</sub> effects were observed for lagged cumulative exposures of approximately 2 weeks.

The distributed lag structure of approximately 14 days may reflect the importance of cumulative PM<sub>2.5</sub> exposure and that the onset of symptoms may follow elevated exposure with hospitalization after onset of symptoms related to HF exacerbation. The peaking of the size of the effect estimate at 2 or 3 weeks and then the decline in the estimated effect suggests a trade-off between the importance of cumulative exposure and the proximity in time of exposure. In a previous case-crossover study, we found that short-term exposure to PM<sub>2.5</sub> was associated with the triggering of acute ischemic heart disease events, especially in patients with underlying coronary artery disease.<sup>8</sup> A much shorter lag structure of approximately 1 to 4 days was observed, suggesting that proximity in time may be more important than long-term cumulative exposure in triggering ischemic events in persons with existing coronary artery disease. Several time-series studies, however, have explored the effects of PM on risk of mortality using longer time scales or extended distributed lags of  $\leq 40$  days.<sup>17–19</sup> PM mortality effect estimates were larger when time scales longer than a few days were used. A more comprehensive review of the mortality effects of longer term exposures to PM concludes that adverse effects of PM exposure are dependent on both exposure concentrations and length of exposure and longer-

term exposures have larger, more persistent cumulative effects than short-term exposures.<sup>19</sup>

An analysis of the American Cancer Society (ACS) prospective cohort, a study of long-term exposure and mortality, reported similar air pollution associations with HF related mortality risk as observed in the present study.<sup>3</sup> Long-term elevated exposure of 10  $\mu\text{g}/\text{m}^3$  PM<sub>2.5</sub> was associated with a 13% (95% CI 5 to 21) increased risk of mortality from the cause-of-death grouping that included dysrhythmias, HF, and cardiac arrest. Although they did not focus on HF specifically, the Harvard Six Cities<sup>1,5</sup> and the Women's Health Initiative<sup>7</sup> studies reported larger associations between long-term PM<sub>2.5</sub> exposure and the risk of cardiovascular disease. The Harvard Six Cities study<sup>5</sup> reported that long-term elevated exposure of 10  $\mu\text{g}/\text{m}^3$  PM<sub>2.5</sub> was associated with a 28% (95% CI 13 to 44) increased risk of cardiovascular mortality and the Women's Health Initiative study<sup>7</sup> reported that long-term elevated exposure of 10  $\mu\text{g}/\text{m}^3$  PM<sub>2.5</sub> was associated with a 24% (95% CI 9 to 41) increased risk of first cardiovascular event and a 76% (95% CI 25 to 147) increased risk of death from cardiovascular causes.

The mechanisms underlying the link between PM exposure and exacerbation of HF are not fully elucidated. Previous research results linking short-term PM exposures to acute ischemic heart disease events,<sup>8,20</sup> ischemic stroke,<sup>21</sup> electrocardiographic ST-segment depression,<sup>22</sup> increased plasma viscosity,<sup>23</sup> increased circulating markers of inflammation,<sup>24–26</sup> changes in cardiac autonomic function as indicated by various measures of heart rate variability,<sup>26–28</sup> and increased risk of arrhythmias<sup>29,30</sup> are suggestive of potential impacts of PM on HF. More detailed discussions of the pathophysiological or mechanistic pathways that plausibly link PM exposure and cardiopulmonary disease and death are provided elsewhere.<sup>3,4,6</sup> These results, however, suggest that exposure to air pollution may exacerbate HF by triggering decompensation through effects of PM on myocardial ischemia, cardiac autonomic function, and/or arrhythmic effects.

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