

# Increased Particulate Air Pollution and the Triggering of Myocardial Infarction

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**Background**—Elevated concentrations of ambient particulate air pollution have been associated with increased hospital admissions for cardiovascular disease. Whether high concentrations of ambient particles can trigger the onset of acute myocardial infarction (MI), however, remains unknown.

**Methods and Results**—We interviewed 772 patients with MI in the greater Boston area between January 1995 and May 1996 as part of the Determinants of Myocardial Infarction Onset Study. Hourly concentrations of particle mass  $<2.5$   $\mu\text{m}$  ( $\text{PM}_{2.5}$ ), carbon black, and gaseous air pollutants were measured. A case-crossover approach was used to analyze the data for evidence of triggering. The risk of MI onset increased in association with elevated concentrations of fine particles in the previous 2-hour period. In addition, a delayed response associated with 24-hour average exposure 1 day before the onset of symptoms was observed. Multivariate analyses considering both time windows jointly revealed an estimated odds ratio of 1.48 associated with an increase of  $25 \mu\text{g}/\text{m}^3$   $\text{PM}_{2.5}$  during a 2-hour period before the onset and an odds ratio of 1.69 for an increase of  $20 \mu\text{g}/\text{m}^3$   $\text{PM}_{2.5}$  in the 24-hour period 1 day before the onset (95% CIs 1.09, 2.02 and 1.13, 2.34, respectively).

**Conclusions**—The present study suggests that elevated concentrations of fine particles in the air may transiently elevate the risk of MIs within a few hours and 1 day after exposure. Further studies in other locations are needed to clarify the importance of this potentially preventable trigger of MI. (*Circulation*. 2001;103:2810-2815.)

**Key Words:** myocardial infarction ■ air pollution ■ heart disease ■ epidemiology

Epidemiological analyses throughout the world have shown that high 24-hour average levels of ambient particulate air pollution are associated with an increase in all-cause, respiratory, and cardiovascular disease mortality<sup>1-4</sup>; nevertheless, little information is available on the effect of shorter-term exposures. The harmful effects of elevation of ambient concentrations of particulate matter are well documented in multiple studies of hospital admissions and emergency department visits for respiratory diseases.<sup>1,4</sup> In addition, increased hospital admissions for cardiovascular diseases have been associated with particulate air pollution in studies of numerous American, Canadian, and European cities.<sup>5-9</sup> These results indicate that ambient particulate air pollution is a risk factor not only for respiratory diseases but also for acute cardiovascular events.

Inhaled particles could lead to acute exacerbation of cardiovascular disease through pulmonary inflammation triggering systemic hypercoagulability.<sup>10</sup> Increases in plasma viscosity<sup>11</sup> and C-reactive protein<sup>12</sup> were observed in randomly selected healthy adults after episodes of high particulate air pollution. Increased heart rate,<sup>13,14</sup> decreased heart

rate variability,<sup>15-17</sup> and increased risk of implanted cardioverter-defibrillator discharges<sup>18</sup> associated with episodes of particulate air pollution indicate an autonomic nervous system response.

The US Environmental Protection Agency has promulgated a new ambient air quality standard for fine particles (particulate matter  $<2.5$   $\mu\text{m}$  aerodynamic diameter,  $\text{PM}_{2.5}$ ).<sup>19</sup> This new standard regulates 24-hour and annual average concentrations and does not address transient elevations (minutes to hours) in fine-particle concentration. There are no published data on the risk of myocardial infarction (MI) in human populations after transient exposures to elevated concentrations of ambient fine particles.

We therefore evaluated the effect of short-term exposure to fine-particle air pollution on the risk of acute MIs, comparing data from the Determinants of Myocardial Infarction Onset Study (Onset Study) with hourly measurements of fine particles in Boston. We used a case-crossover design<sup>20,21</sup> to specifically assess the risk of exposure to high levels of  $\text{PM}_{2.5}$  and the timing of the impact of this exposure on the onset of MI.

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## Methods

### Study Design

The design of the Onset Study has been described in detail elsewhere.<sup>20–23</sup> In brief, we used a case-crossover study design to assess the change in risk of acute MI during a brief “hazard period” after exposure to potential triggers of MI onset. An important feature of the case-crossover design is that control information for each patient is based on his or her own past exposure experience. Self-matching results in freedom from confounding by risk factors that are stable over time within an individual but often differ between study subjects.

### Patient Population

The Onset Study is a multicenter case-crossover study conducted between 1989 and 1996 in 64 centers throughout the United States.<sup>24</sup> Participants were interviewed a median of 4 days after their MI. We analyzed data from 772 Onset Study participants living in the greater Boston area collected between January 20, 1995, and May 25, 1996. Data were collected in 6 centers with  $\geq 50$  cases (455 cases), 6 centers with 25 to 49 cases (209 cases), and 14 centers with  $< 25$  cases (108 cases).

Interviewers identified eligible cases by reviewing coronary care unit admission logs and patients’ charts. For inclusion in the study, patients were required to meet all of the following criteria: symptom onset while in the greater Boston area,  $\geq 1$  creatine kinase level above the upper limit of normal for the clinical laboratory performing the test, positive MB isoenzymes, an identifiable onset of pain or other symptoms typical of infarction, and the ability to complete a structured interview. The protocol was approved by the Institutional Review Board at each participating center, and informed consent was obtained from each patient.

Detailed chart reviews and patient interviews were conducted by trained research personnel.<sup>22,23</sup> Data were collected on standard demographic variables as well as risk factors for coronary artery disease. The interview identified the time, place, and characteristics of MI pain and other symptoms.

### Air Pollution Measurements

Daily air pollution measurements were collected at a Harvard School of Public Health–operated monitoring site in South Boston starting January 15, 1995.<sup>18</sup>  $PM_{2.5}$  and  $PM_{10}$  concentrations were measured continuously with a Tapered Element Oscillating Microbalance (Rupprecht and Patashnick model 1400A TEOM). Elemental carbon concentration was determined continuously with an Aethalometer (Magee Scientific Inc), a light-absorption method to measure “black carbon.” Ozone concentration was measured with a UV photometer analyzer (TECO model 49, Thermal Environmental). CO concentration was measured with a continuous nondispersive infrared analyzer (Bendix model 8501-5CA). Relative humidity and temperature were measured continuously (Vaisala model MP113Y). The Massachusetts Department of Environmental Protection measured concentrations of sulfur dioxide and nitrogen dioxide hourly in Chelsea, which is  $\approx 7.5$  km north of the South Boston site. We calculated 24-hour mean values when  $\geq 16$  valid hourly measurements were available.

### Statistical Analyses

The analysis of case-crossover data is an application of standard methods for stratified data analysis.<sup>20,21</sup> The stratifying variable is the individual patient, as in a crossover experiment. For each subject, 1 case period was matched to 3 control periods exactly 24 hours apart. Thus, by matching time of day for case and control periods, potential confounding by the circadian pattern of MI onset or diurnal patterns in the air pollution were controlled.

Conditional logistic regression analyses were used to analyze the data. Exposure to particles and gases were entered into the model as continuous variables. Odds ratios are expressed for a change in air pollution concentrations from the 5th to the 95th percentile for all measurements available. Separate models were constructed to eval-

TABLE 1. Characteristics of the Study Population (n=772)

Age, y	
Mean $\pm$ SD	61.6 $\pm$ 13.4
< 50	164 (21)
50–69	365 (47)
70+	243 (32)
Sex	
Male	489 (63)
Female	283 (37)
Medical history	
Prior myocardial infarction	237 (31)
Prior angina	174 (23)
Any coronary artery disease	302 (39)
Hypertension	319 (41)
Diabetes mellitus	143 (19)
Obese	261 (34)
Ever smoker	558 (72)
Current smoker	246 (32)

Values are n (%).

uate the impact of hourly and 24-hour average air pollution concentrations on the onset of MI.

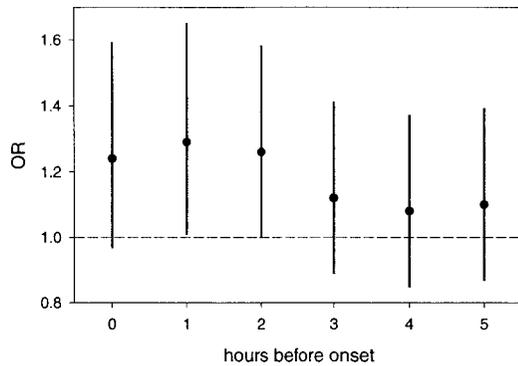
We also evaluated the effect of hourly (2-hour average) and daily (24-hour average) exposures jointly in 1 model. Control periods were selected as multiples of 24 hours starting 3 days before the date and time of the onset of the symptoms. In addition, multivariate analyses adjusting for season, day of the week, and meteorological parameters on the same time scales were estimated. The final model included sine and cosine functions with periods of 1 year plus  $\frac{1}{2}$ ,  $\frac{1}{3}$ ,  $\frac{1}{4}$ ,  $\frac{1}{5}$ , and  $\frac{1}{6}$  of a year. It also included quadratic terms for minimum temperature and relative humidity during the 2-hour and 24-hour period of exposure and an indicator for the day of week. Results are presented as odds ratios (OR) and 95% CI.

The unidirectional case-crossover analyses might be sensitive to trends in the outcome and the exposure.<sup>25,26</sup> Therefore, control periods close to the event were chosen to minimize the impact of a potential trend. Particulate air pollution concentrations increased over time ( $0.4 \mu\text{g}/\text{m}^3$  per 100 days,  $P=0.0002$ ). Although there was weak evidence of a linear downward trend in the number of cases ( $-0.05$  cases per 100 days,  $P=0.23$ ), the sampling fraction of cases decreased substantially during 1996. Consequently, a downward bias of the estimates would have been expected. This could be demonstrated by choosing control periods  $> 5$  days before the event. The bidirectional design has been shown to give unbiased estimates when full case ascertainment was present.<sup>26</sup> Analyses of the present data, however, indicated a bias with the bidirectional design due to incomplete case ascertainment during 1996.

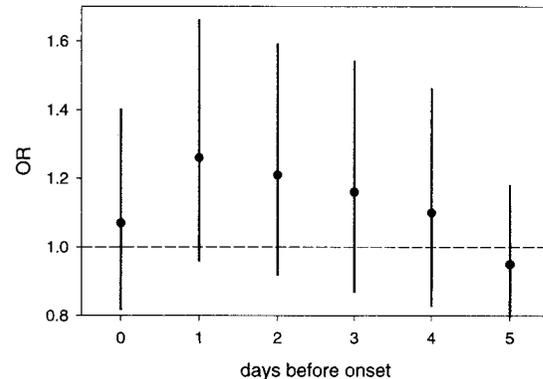
## Results

The baseline characteristics of the study population are shown in Table 1. The distribution of 24-hour average and 1-hour average concentrations of the particulate and gaseous air pollutants is presented in Table 2.  $PM_{2.5}$  and  $PM_{10}$  were highly correlated, whereas the coarse fraction of  $PM_{10}$ , ie, difference of  $PM_{10}$  and  $PM_{2.5}$ , and the gaseous pollutants were only moderately correlated with  $PM_{2.5}$ .

Figures 1 and 2 show results from the conditional logistic regression models, in which  $PM_{2.5}$  was entered as a linear continuous variable. Odds ratios are expressed for an hourly change of  $25 \mu\text{g}/\text{m}^3$  in  $PM_{2.5}$  (Figure 1) or a daily change of



**Figure 1.** Univariate analyses for association between onset of MI and hourly concentrations of PM<sub>2.5</sub>. Odds ratios and 95% CIs for an increase of 25 μg/m<sup>3</sup> PM<sub>2.5</sub>.



**Figure 2.** Univariate analyses for association between onset of MI and 24-hour average concentrations of PM<sub>2.5</sub>. Odds ratios and 95% CIs for an increase of 20 μg/m<sup>3</sup> PM<sub>2.5</sub>.

20 μg/m<sup>3</sup> PM<sub>2.5</sub> (Figure 2) corresponding the 5th to 95th percentile intervals (Table 2).

A positive association between the onset of MI and the concentrations of PM<sub>2.5</sub> was observed within the first 3 hours (Figure 1) that was statistically significant for the PM<sub>2.5</sub> concentrations 1 hour and 2 hours before the onset of

symptoms of an MI. Exposures before this time period seemed to have little impact on the risk of acute MI. In addition, a more delayed response to air pollution was observed when 24-hour averages of the particles were considered (Figure 2). A positive association was observed with

**TABLE 2. Distribution of the Air Pollutants for the Time Period January 15, 1995, to May 25, 1996, in Boston, Mass**

	n	Mean	SD	5%	50%	95%	Correlation With PM <sub>2.5</sub>	
							1-Hour	24-Hour
<b>Particles</b>								
PM <sub>2.5</sub> , μg/m <sup>3</sup>								
1-hour	11 457	12.1	8.9	2.6	9.7	29.6	1.00	
24-hour	490	12.1	6.8	4.6	10.4	24.3		1.00
PM <sup>10</sup> , μg/m <sup>3</sup>								
1-hour	11 698	19.4	12.8	4.5	16.7	43.7	0.87	
24-hour	497	19.4	9.4	7.8	17.6	37.0		0.90
Coarse mass, μg/m <sup>3</sup>								
1-hour	11 357	7.3	6.6	-0.7	6.2	19.4	0.33	
24-hour	490	7.4	4.4	1.6	6.8	15.2		0.38
Black carbon, μg/m <sup>3</sup>								
1-hour	11 466	1.34	1.21	0.27	0.97	3.71	0.68	
24-hour	488	1.35	0.72	0.49	1.18	2.83		0.74
<b>Gases</b>								
Ozone, ppb								
1-hour	10 884	19.8	14.8	1	18	46	-0.03	
24-hour	460	19.9	10.0	6	19	36		0.10
Carbon monoxide, ppm								
1-hour	11 843	1.09	0.58	0.30	1.00	2.10	0.54	
24-hour	497	1.09	0.40	0.49	1.07	1.78		0.57
Nitrogen dioxide, ppm								
1-hour	11 671	0.023	0.013	0.007	0.021	0.047	0.51	
24-hour	494	0.024	0.009	0.011	0.022	0.039		0.60
Sulfur dioxide, ppm								
1-hour	11 796	0.007	0.010	0	0.005	0.023	0.38	
24-hour	497	0.007	0.007	0.001	0.006	0.020		0.43

**TABLE 3. Odds Ratios for 2-Hour (1 Hour Before Onset) and 24-Hour Average (on the Previous Day) Concentrations of PM<sub>2.5</sub> Considered Jointly**

	Quintile					Trend Test <i>P</i>
	I	II	III	IV	V	
2-hour average PM <sub>2.5</sub>						
Range, μg/m <sup>3</sup>	0–5.2	5.3–7.9	7.9–11.5	11.6–17.0	17.1–74.8	
Odds ratios (CI)	1.00	1.15 (0.90, 1.48)	1.09 (0.84, 1.41)	1.27 (0.99, 1.64)	1.44 (1.12, 1.87)	0.025
24-hour average PM <sub>2.5</sub>						
Range, μg/m <sup>3</sup>	1.6–6.4	6.5–8.6	8.7–11.5	11.6–16.2	16.3–52.2	
Odds ratios (CI)	1.00	1.12 (0.87, 1.45)	1.15 (0.89, 1.48)	1.31 (1.01, 1.69)	1.32 (1.01, 1.72)	0.008

elevated concentrations between 24 and 48 hours before the onset of the symptoms.

A combined analysis considered 2-hour averages (between 60 and 180 minutes before the onset of symptoms) and 24-hour averages (between 24 and 48 hours before the onset of the symptoms) jointly, with pollution levels divided into quintiles (Table 3). When concentrations of PM<sub>2.5</sub> were elevated immediately before the onset of symptoms as well as

1 day before the onset of symptoms, the risk of an MI was increased.

Table 4 summarizes the association between ambient air pollution as a continuous measure and the risk of onset of MI. The estimates of the combined analyses of 2-hour averages and 24-hour averages were larger than the analyses considering the time periods individually. Statistically significantly elevated risks of MI were observed for PM<sub>2.5</sub>. The coarse

**TABLE 4. Odds Ratios for 2-Hour and 24-Hour Average Concentrations of Single Pollutants Estimated Jointly.**

	Increase (5th to 95th Percentile)	Unadjusted OR (95% CI) (n=772)	Adjusted* OR (95% CI) (n=764)
<b>Particles</b>			
PM <sub>2.5</sub> , μg/m <sup>3</sup>			
2-hour	25	1.43 (1.13, 1.81)	1.48 (1.09, 2.02)
24-hour	20	1.44 (1.11, 1.86)	1.62 (1.13, 2.34)
PM <sub>10</sub> , μg/m <sup>3</sup>			
2-hour	40	1.45 (1.11, 1.88)	1.51 (1.06, 2.15)
24-hour	30	1.31 (0.99, 1.73)	1.66 (1.11, 2.49)
Coarse mass, μg/m <sup>3</sup>			
2-hour	15	1.13 (0.92, 1.40)	1.16 (0.89, 1.51)
24-hour	15	1.18 (0.85, 1.64)	1.39 (0.89, 2.15)
Black carbon, μg/m <sup>3</sup>			
2-hour	3	1.32 (1.06, 1.65)	1.27 (0.97, 1.68)
24-hour	2	1.08 (0.84, 1.39)	1.21 (0.87, 1.70)
<b>Gases</b>			
Ozone, ppb			
2-hour	45	1.05 (0.76, 1.46)	1.31 (0.85, 2.03)
24-hour	30	1.21 (0.88, 1.67)	0.94 (0.60, 1.49)
Carbon monoxide, ppm			
2-hour	1.0	1.27 (0.98, 1.63)	1.22 (0.89, 1.67)
24-hour	0.6	0.99 (0.77, 1.27)	0.98 (0.70, 1.36)
Nitrogen dioxide, ppm			
2-hour	0.040	1.20 (0.91, 1.59)	1.08 (0.76, 1.53)
24-hour	0.030	1.03 (0.77, 1.39)	1.19 (0.81, 1.77)
Sulfur dioxide, ppm			
2-hour	0.020	1.00 (0.87, 1.14)	0.96 (0.83, 1.12)
24-hour	0.020	0.92 (0.71, 1.20)	0.91 (0.67, 1.23)

Estimates are calculated for a change from 5th to 95th percentile of the pollutants.

\*Adjusted for season, meteorological parameters, and day of the week.

fraction of PM<sub>10</sub>, black carbon, and the gaseous air pollutants including carbon monoxide, NO<sub>2</sub>, SO<sub>2</sub>, and ozone showed positive associations, but none were statistically significant.

A strong seasonal pattern was observed, with increased risks of MI between May and December. Temperature and humidity immediately before the onset of symptoms were not associated with the onset of symptoms, but the 24-hour averages of higher temperatures and lower humidity 1 day before the onset of symptoms showed an increased risk. After adjustment for seasonal and meteorological conditions, the association of PM<sub>2.5</sub> with the onset of MI was sustained (Table 4).

### Discussion

Elevated concentrations of fine particles (PM<sub>2.5</sub>) were associated with a transient risk of acute MI onset. High 24-hour average concentrations of fine particles were also associated with an elevated risk of MI with a 24-hour delay. The elevated risks during 2 separate time periods appear to be independent of each other. In addition, even changes from low to moderate ambient concentrations were associated with an increased risk of MI, although PM<sub>2.5</sub> concentrations were below the new standards.<sup>23</sup> Particles >2.5 μm, which consist primarily of resuspended crustal material, showed a substantially smaller association than particles <2.5 μm. Other pollutants, such as black carbon, carbon monoxide, nitrogen dioxide, and sulfur dioxide, showed positive associations, but none of them achieved statistical significance in the single-pollutant multivariate analyses.

These results are consistent with time-series analyses on hospital admissions for cardiac diseases.<sup>5-9</sup> Hospital admission data collected for administrative purposes were positively associated with 24-hour average particle mass concentrations collected for regulatory compliance monitoring. The effect of ambient particles on hospital admissions was reported to vary between an immediate response on the same day<sup>5-7,9</sup> and a 1-day lagged response.<sup>8</sup>

There are several biological effects of ambient particles that may lead to cardiac events. First, particles deposited in the alveoli lead to activation of cytokine production by alveolar macrophages<sup>27</sup> and epithelial cells<sup>28</sup> and to recruitment of inflammatory cells.<sup>29</sup> Second, increases in plasma viscosity<sup>11</sup> and C-reactive protein<sup>12</sup> have been observed in randomly selected healthy adults in association with episodes of high particulate air pollution. Third, acceleration of heart rates and diminished heart rate variability in association with air pollution have been documented in elderly persons<sup>13,15-17</sup> and in a random population sample.<sup>14</sup> One study reported that heart rate variability started to decrease within hours of exposure.<sup>17</sup> Controlled-exposure experiments in dogs exposed to concentrated ambient particles indicated changes in the ECG within an hour of the onset of exposure.<sup>30</sup> Fourth, ambient concentrations of PM<sub>2.5</sub> have been associated with ventricular fibrillation and an increased number of therapeutic interventions in patients with implanted cardioverter-defibrillators.<sup>18</sup>

A proposed mechanism for triggering of MI is that onset occurs when a vulnerable but not necessarily stenotic atherosclerotic plaque disrupts in response to hemodynamic stress; there-

after, hemostatic and vasoconstrictive forces determine whether the resultant thrombus becomes occlusive.<sup>31</sup> As reviewed above, particulate air pollution is associated with hemodynamic and hemostatic alterations, which may contribute to MI onset.

Previous studies have shown that physical<sup>23,32</sup> and psychological<sup>24</sup> stress as well as substances such as cocaine<sup>22</sup> can trigger the onset of MI. In this report, we demonstrate that transient exposures to an environmental factor, ie, ambient air pollution, appear to increase the risk of an acute MI.

The available evidence suggests that the mechanisms responsible for the impact of ambient particles on MI may be similar to the mechanisms responsible for triggering by other stressors. If these findings are substantiated, susceptible subgroups could be identified and possible pharmacological interventions could be developed to protect the public from transient exposures to ambient particles, such as that experienced during rush-hour traffic.

### Limitations

The case-crossover design controls for chronic risk factors for MI such as sex, age, and hypertension. Confounding may occur because of time-varying risk factors,<sup>26</sup> such as time of day, season, or weather. These potential confounders, however, were considered in the multivariate analyses.

Another potential limitation of the study is that only 1 air pollution monitoring site was available. Air pollution measurements throughout the east coast indicate that the elevated concentrations of particulate matter during the summer months are due to regional transport.<sup>33</sup> For 11 months, starting in October 1995, concurrent PM<sub>2.5</sub> measurements were collected every other day in South Boston and 3 other sites in eastern Massachusetts. There was high concordance between these 24-hour samples, with Pearson correlation between South Boston and downtown Boston (Beacon Hill, 3 km northwest) of 0.86, Lynn (16 km north) of 0.86, and Brockton (27 km south) of 0.81. On a larger scale, a high correlation (0.76) was found between daily concentrations of fine particles measured at sites 200 km apart in Washington and Philadelphia.<sup>33</sup> Data on the correlation between hourly concentrations of fine particles at different locations within a metropolitan area are not available.

### Conclusions

Knowledge of the induction time between the exposure to particulate air pollution and adverse health effects is crucial to understanding the biological mechanisms responsible for these associations and to setting of standards that reduce the risk for the population. The present study suggests that elevated concentrations of fine particles may transiently increase the risk of MI for several hours as well as for several days after exposure. As a consequence, 24-hour averages might underestimate the association between air pollution and acute cardiovascular events.

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