



STATEMENT

Synopsis of Research Report 124 Part I

HEALTH
EFFECTS
INSTITUTE

Air Pollutants, Personal Activities, and the Onset of Myocardial Infarction

BACKGROUND

Ambient particulate matter (PM) is a complex mixture of particles suspended in the air. The size, chemical composition, and other physical and biological properties of these particles vary with location and time. Despite wide variations in PM composition and levels, epidemiologic studies in many different places have reported associations between exposure to PM and increases in illness and death. Yet several critical questions about the effects of PM remain. One is how to identify those characteristics of particles—especially size and chemical composition—that make them potentially harmful to human health. To protect the population in general, and groups considered to be most vulnerable to the adverse effects of PM in particular, the US Environmental Protection Agency (EPA) in 1997 promulgated National Ambient Air Quality Standards for PM_{2.5} (particles equal to or smaller than 2.5 µm in aerodynamic diameter) and PM₁₀ (the size considered respirable in humans). Within the particle mixture, some scientists believe that the fraction containing ultrafine particles (smaller than 0.1 µm) may be particularly toxic.

To address some of the key issues in PM research, in 1998 HEI issued Request for Applications 98-1, “Characterization of Exposure to and Health Effects of Particulate Matter”. A primary objective stated in the RFA was to evaluate the effects of exposure to ambient particles on people who might be more susceptible than healthy people. To that end, HEI funded two researchers to conduct epidemiologic studies that would assess the possible impact of exposure to PM on important cardiovascular events: Dr Annette Peters (GSF-National Research Center for Environment and Health, Institute of

Epidemiology, Neuherberg, Germany) to explore nonfatal myocardial infarction (MI); and Dr Douglas Dockery (Harvard School of Public Health, Boston, Massachusetts) to investigate arrhythmic episodes that trigger a response from an implanted cardioverter defibrillator (pacemaker) in patients with cardiovascular conditions. (The Dockery Investigators’ Report, Review Committee’s Commentary, HEI Statement, and an Integrated Discussion of the Peters and Dockery studies comprise Part II of HEI Research Report 124.)

APPROACH

Peters and colleagues hypothesized that onset of a nonfatal MI is associated with exposure to particulate air pollution within 2 hours before the event, and specifically with the *number of ultrafine particles* rather than the *mass of fine particles*. The investigators also wanted to evaluate whether activities, such as strenuous physical exertion or spending time in traffic, in the hours before the MI were associated with its onset.

To pursue these possibilities, Peters and colleagues studied 851 patients in hospitals in and around Augsburg, Germany, who had survived an MI; via a diary questionnaire, 691 of these subjects provided hourly details about their activities in the 4 days before MI onset. The investigators measured levels of ultrafine particles, PM_{2.5}, and PM₁₀ in ambient air in the city of Augsburg. They also obtained information about weather conditions and the levels of gaseous pollutants (nitrogen dioxide [NO₂], carbon monoxide [CO], sulfur dioxide [SO₂], and ozone [O₃]) in the city from a local agency, the Bavarian Air Monitoring Network.

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Peters and colleagues predominantly used a case–crossover analysis to determine whether exposure to pollutants was associated with onset of MI. In this approach, each subject serves as his or her own control and comparisons are made between different time periods for each subject. Exposure to pollutants during a specified time period relevant to the occurrence of MI onset (the case period; eg, 1 hour before) was compared with exposure during different time periods (control periods; eg, 24 or 48 hours before the case period). For ultrafine particles and PM_{2.5}, the investigators evaluated hourly intervals up to 6 hours before and daily intervals up to 5 days before the onset of MI. To evaluate the effect of specific activities on risk of MI onset, the investigators conducted unidirectional case–crossover analyses; that is, they selected control periods before, but not after, onset of MI because the symptoms of and hospitalization for the MI would have affected the subject's subsequent activities. For other potential risk factors that would not be affected by MI onset—such as pollutant concentrations measured in the community—the investigators compared the results from unidirectional analyses with those from bidirectional analyses, in which control periods were selected both before and after the outcome of interest. They also compared these estimates of effects with results obtained from a more typical Poisson regression analysis of time-series data.

RESULTS AND INTERPRETATION

No statistically significant associations were found between the onset of a nonfatal MI and ultrafine particle levels concurrent with, 1 to 6 hours before, or up to 5 days before the event. Thus, these results do not support a role for exposure to ultrafine particles in the acute induction of a nonfatal MI. Other epidemiologic studies, however, have found associations between ultrafine particle levels and different cardiovascular endpoints. The negative results in the current study may mean that ultrafine particles, in fact, are not associated with the onset of a nonfatal MI. Another possibility is that these results were affected by the location of the site for monitoring ultrafine particles: an Augsburg monastery away from an urban setting that may be influenced by vehicle emissions. Measurements from these monitors therefore may not reflect particles that might have induced cardiovascular effects in this population. In other studies in which effects of ultrafine particles were detected, the monitors might have measured more of these traffic-related particles. Note, however, that an association between ultrafine particles

from vehicle emissions and health effects has not been established.

No statistically significant associations were found between the onset of a nonfatal MI and concurrent PM_{2.5} levels or levels 1 to 6 hours earlier. This contrasts with the results of an earlier study by Peters and colleagues with a smaller number of participants conducted in Boston, Massachusetts; that study found evidence for an association between MI onset and PM_{2.5} levels in the previous 2 hours. The investigators suggested several possible explanations for the different results from the two studies. Among them were (1) the population in the current study included a higher proportion of men, a substantially higher proportion of people with hypertension, and a lower proportion of subjects with previous infarctions; (2) the possibility that subjects in the current study were taking more up-to-date and hence more protective medications for cardiovascular disease; and (3) differences in the characteristics of PM_{2.5} between Boston and Augsburg. Alternatively, the observation in Boston that PM_{2.5} levels shortly before MI onset were associated with the event may have been due to chance.

In the current study, PM_{2.5} levels 2 days before the event were associated with onset of MI. The increase in relative risk depended on the method of selecting control periods: relative risk was 18% in unidirectional analyses and 8% in bidirectional analyses (based on an increase in PM_{2.5} levels of 7.7 µg/m³). These increases in relative risk were similar to those reported for PM_{2.5} 1 and 2 days before MI in Peters' earlier Boston study. Little or no association with MI onset was found in the current study between same-day PM_{2.5} levels or levels 1, 3, 4, or 5 days earlier. PM₁₀ levels 1 and 2 days before onset of MI were associated with increased relative risk (7% and 9%, respectively) in bidirectional analyses, but the associations were not significant.

Associations similar to those observed for PM_{2.5} were found between the gaseous pollutants NO₂, CO, and SO₂ and MI onset: increases in relative risk of 5% to 10% in bidirectional analyses on certain days (NO₂—same day and up to 2 days earlier; CO—2 to 4 days earlier; and SO₂—2 days earlier). These results, which parallel the associations described in Peters' Boston study, are of interest because most of the NO₂ and CO in cities is attributable to car traffic. At the same time, although SO₂ is emitted from vehicles, its ambient levels result primarily from other sources, especially the combustion of coal in industrial uses and in generating electricity. The finding that O₃ levels were not associated with MI

onset suggests that exposure to this pollutant in the time frame examined has no effect.

Time spent in traffic (including time in cars, on public transport, or riding bicycles) 1 or 2 hours earlier increased the relative risk of MI onset by 2- to 3-fold compared with control periods. The increase in relative risk was similar for all modes of transportation. As has been described in other studies, strenuous activities such as playing tennis or soccer or dancing—concurrently or 1 to 6 hours before MI onset—were also strongly associated with MI onset: an 8-fold maximum increase in relative risk was noted 1 hour before the event. Less strenuous activity and time spent outdoors were also associated with increases in relative risk of MI onset, ranging from 0.5- to 4-fold. However, subjects were interviewed about activities preceding their MIs at a median of 9 days after the event. Thus, subjects might not have remembered their activities accurately or might have developed a distorted view of activities in the hours immediately preceding the event because they dwelled more on that time period than on earlier days (recall bias).

CONCLUSIONS

This important study investigated specific hypotheses about exposure to particulate pollutants and the induction of a major cardiac event, nonfatal MI. It also provided valuable information about associations between the onset of MI and other possible triggers, such as gaseous pollutants, and—through the use of information obtained from individual subjects—activities such as time spent outdoors or in traffic.

The investigators' hypothesis that levels of ultrafine or fine particles up to 2 hours before the event would be associated with MI induction was not supported. The

reasons for the differences in effect estimates for $PM_{2.5}$ in the hours before MI onset reported in the current study and in Peters' earlier study in Boston need to be resolved by additional studies of this design.

In the current study, effect estimates for $PM_{2.5}$ levels 2 days before MI onset were associated with a small increase in relative risk, similar to estimates reported for $PM_{2.5}$ levels 1 and 2 days before the event in Peters' Boston study. This provides some support for an association between $PM_{2.5}$ levels in this time frame and MI onset. Studies are needed to determine the mechanistic pathways that underlie these reported associations. These data also support results from current time-series studies, some of which describe similar associations between $PM_{2.5}$ and hospitalizations for MI and other cardiovascular conditions. In the current study, the increases in relative risk of MI onset associated with levels of the gaseous pollutants NO_2 , CO, and SO_2 were similar to the increases in relative risk associated with levels of $PM_{2.5}$. Thus, the question remains as to which pollutants—and sources of these pollutants—are responsible for the effects observed.

The finding that time spent in traffic was associated with increased relative risk of nonfatal MI onset is important new information. In this study, time spent in cars, on public transport, or riding bicycles was much more strongly associated with induction of a nonfatal MI than any of the air pollutants measured at a central site in Augsburg. It is not clear whether the increased relative risk associated with time spent in traffic resulted from stressors such as noise and anxiety or from exposure to traffic-related air pollutants; it is also possible that recall bias may have influenced to some extent the size of the estimated risk. Further studies that focus on exposure in places near to traffic may help resolve this issue.

Particulate Air Pollution and Nonfatal Cardiac Events

Part I. Air Pollution, Personal Activities, and Onset of Myocardial Infarction in a Case–Crossover Study

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INVESTIGATORS' REPORT

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