RESEARCH REPORT

HEALTH EFFECTS INSTITUTE

Number 124
June 2005

Particulate Air Pollution and Nonfatal Cardiac Events

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

Annette Peters, Stephanie von Klot, Margit Heier, Ines Trentinaglia, Josef Cyrys, Allmut Hörmann, Michael Hauptmann, H Erich Wichmann, and Hannelore Löwel

Part II. Association of Air Pollution with Confirmed Arrhythmias Recorded by Implanted Defibrillators

Douglas W Dockery, Heike Luttmann-Gibson, David Q Rich, Mark S Link, Joel D Schwartz, Diane R Gold, Petros Koutrakis, Richard L Verrier, and Murray A Mittleman

Includes Commentaries by the Institute's Health Review Committee

HEALTH
EFFECTS
INSTITUTE

The Health Effects Institute was chartered in 1980 as an independent and unbiased research organization to provide high quality, impartial, and relevant science on the health effects of emissions from motor vehicles, fuels, and other environmental sources. All results are provided to industry and government sponsors, other key decisionmakers, the scientific community, and the public. HEI funds research on all major pollutants, including air toxics, diesel exhaust, nitrogen oxides, ozone, and particulate matter. The Institute periodically engages in special review and evaluation of key questions in science that are highly relevant to the regulatory process. To date, HEI has supported more than 220 projects at institutions in North America, Europe, and Asia and has published over 160 Research Reports and Special Reports.

Typically, HEI receives half of its core funds from the US Environmental Protection Agency and half from 28 worldwide manufacturers and marketers of motor vehicles and engines who do business in the United States. Other public and private organizations periodically support special projects or certain research programs. Regardless of funding sources, HEI exercises complete autonomy in setting its research priorities and in reaching its conclusions.

An independent Board of Directors governs HEI. The Institute's Health Research Committee develops HEI's five-year Strategic Plan and initiates and oversees HEI-funded research. The Health Review Committee independently reviews all HEI research and provides a Commentary on the work's scientific quality and regulatory relevance. Both Committees draw distinguished scientists who are independent of sponsors and bring wide-ranging multidisciplinary expertise.

The results of each project and its Commentary are communicated widely through HEI's home page, Annual Conference, publications, and presentations to professional societies, legislative bodies, and public agencies.

HEI STATEMENT

Synopsis of Research Report 124 Part I

Air Pollutants, Personal Activities, and the Onset of Nonfatal 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 PM_{10} (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 PM_{10} in ambient air in the city of Augsburg. They also obtained information about weather conditions and the levels of gaseous pollutants (nitrogen dioxide [NO_2], carbon monoxide [CO], sulfur dioxide [SO_2], and ozone [O_3]) in the city from a local agency, the Bavarian Air Monitoring Network.

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

Continued

This Statement, prepared by the Health Effects Institute, summarizes a research project funded by HEI and conducted by Dr Annette Peters at GSF-National Research Center for Environment and Health, Neuherberg, Germany. The following Research Report contains both the detailed Investigators' Report and a Commentary on the study prepared by the Institute's Health Review Committee.

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 $\mu g/m^3$). 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. PM_{10} 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 NO_2, CO, and SO_2 and MI onset: increases in relative risk of 5% to 10% in bidirectional analyses on certain days (NO_2—same day and up to 2 days earlier; CO—2 to 4 days earlier; and SO_2—2 days earlier). These results, which parallel the associations described in Peters' Boston study, are of interest because most of

the NO_2 and CO in cities is attributable to car traffic. At the same time, although SO_2 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 O_3 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.

Library of Congress Catalog Number for the HEI Report Series: WA 754 R432.
The paper in this publication meets the minimum standard requirements of the ANSI Standard Z39.48-1984 (Permanence of Paper) effective with Report 21 in December 1988; and effective with Report 92 in 1999 the paper is recycled from at least 30% postconsumer waste with Reports 25, 26, 32, 51, 65 Parts IV, VIII, and IX, 91, 105, 117, and 128 excepted. These excepted Reports are printed on acid-free coated paper.

HEI STATEMENT
Synopsis of Research Report 124 Part II

Association of Particulate Air Pollution with Arrhythmias Recorded by Implanted Defibrillators

INTRODUCTION

Epidemiologic studies have reported associations between short-term changes in concentrations of particulate matter (PM) or its components and hospital admissions for and increased mortality from cardiovascular diseases. How exposure to PM may be linked to exacerbation of cardiovascular disease is not well understood. In 1998 HEI issued Request for Applications 98-1, "Characterization of Exposure to and Health Effects of Particulate Matter", to characterize exposure to and evaluate the health effects of PM. A key component of the RFA was to evaluate the effects of exposure to ambient particles in people who might be more susceptible to particle effects than healthy individuals; people with cardiovascular conditions are considered one of those groups.

HEI funded two researchers to conduct epidemiologic studies to assess the possible impact of short-term exposure to PM on important cardiovascular events. One was Dr Annette Peters (GSF-National Research Center for Environment and Health, Neuherberg, Germany) who studied the effects of air pollution on the induction of nonfatal myocardial infarction. The second was Dr Douglas Dockery (Harvard School of Public Health, Boston MA), whose study is described here.

APPROACH

Dockery and colleagues hypothesized that short-term increases in ambient (outdoor) concentrations of PM would increase the risk of possibly life-threatening arrhythmias—rapid, and in some cases rapid and irregular, heart rhythms—in patients with implanted cardioverter defibrillators (ICDs). An ICD is programmed to respond when the heart rate exceeds a preset number of beats per minute. The ICD records and stores the heartbeat pattern before, during, and after every detected arrhythmic episode. (If necessary, the ICD delivers an electrical stimulus to return the heart rate to a normal rhythm.) By evaluating the patients' ICD tracings, the investigators assessed whether pollutant concentrations were associated with arrhythmias recorded by the ICD.

Many patients with cardiovascular disease and different cardiac conditions are fitted with an ICD to immediately treat arrhythmias that develop in the lower chambers of the heart, the ventricles. If not treated rapidly, ventricular arrhythmias may cause sudden death. Thus, ICDs are designed to react to ventricular arrhythmias with a rapid heart beat because they are life-threatening. Arrhythmias may also originate in the upper chambers of the heart, the atria; these atrial arrhythmias (generally referred to as supraventricular arrhythmias) are not immediately life-threatening. Most supraventricular arrhythmias do not stimulate a rhythm in the ventricles rapid enough to trigger an ICD electrogram tracing.

Single-chamber ICDs monitor only the ventricles; newer dual-chamber ICDs monitor both the ventricles and the atria, making it easier to distinguish between ventricular and supraventricular arrhythmias when tracings are reviewed later.

Dockery and colleagues studied 195 patients treated at the New England Medical Center's Cardiac Electrophysiology and Pacemaker Laboratory in Boston MA. The patients were Massachusetts residents who lived within 40 km (25 miles) of the Harvard School of Public Health and who had been followed for more than 60 days (average follow-up 3.2 years). Of the 195 patients, 81% had single-chamber ICDs and 19% had dual-chamber ICDs. The average age at implantation was 63.6; 74% of the participants were male; and 83% were white. For their cardiac conditions, the majority of patients were prescribed multiple cardiac medications, predominantly β-blockers, antiarrhythmic drugs, and digoxin.

Continued

This Statement, prepared by the Health Effects Institute, summarizes a research project funded by HEI and conducted by Dr Douglas W Dockery at the Harvard School of Public Health, Boston MA. The following Research Report contains both the detailed Investigators' Report and a Commentary on the study prepared by the Institute's Health Review Committee.

The investigators measured concentrations of different fractions of PM and its components: fine particles ($PM_{2.5}$; aerodynamic diameter $\leq$ 2.5 μm), ultrafine particles (measured as particle number concentration; generally representative of particles with aerodynamic diameter $\leq$ 0.1 μm), black carbon (BC; the carbon component of PM that absorbs light), and sulfate. However, because they had information about ultrafine particles and sulfate levels for less than 3 years of the 7-year study period, they included these PM components in only a few of their analyses.

They also obtained information about concentrations of the gaseous pollutants nitrogen dioxide (NO_2), carbon monoxide (CO), sulfur dioxide (SO_2), and ozone (O_3) in the Boston metropolitan area. The effects of pollutant concentrations on the day of the event (lag day 0) and up to 3 days before the event (lag days 1–3) were assessed as single days, as the mean of lag days 0 and 1, and as the distributed lag, that is, estimated for all lag days simultaneously.

Dockery and colleagues used logistic regression models to determine whether exposure to pollutants was associated with arrhythmias. For many analyses the investigators reported estimates of effects of individual pollutants on all arrhythmias combined, and separately on ventricular and supraventricular arrhythmias. They also used the patients' clinical information in some analyses to determine whether specific characteristics would modify a pollutant's effects. The effect modifiers evaluated were diagnosis at ICD implantation (these included coronary artery disease compared with other cardiac diagnoses; ejection fraction [the fraction of total blood pumped out of the ventricle with every heartbeat]; and a history of heart attacks); cardiac medications prescribed; multiple arrhythmias during the follow-up period; and more than one arrhythmia within 3 days. They also evaluated whether the distance of patients' residences from the air pollution monitors affected the estimates of a pollutant's effect.

This study followed a smaller pilot study in Boston by Dockery and colleagues that also examined pollutant effects on patients with implanted ICDs. That study had reported weak associations between ICD discharges and ambient concentrations of PM and NO_2; associations were stronger in a subgroup analysis of those who had had multiple ICD discharges.

RESULTS AND INTERPRETATION

Unlike the pilot study, the cardiologist on the current study evaluated all the ICD tracings recorded (1912) and excluded 232 events because they did not meet the criteria for an arrhythmia; he identified 1342 tracings as ventricular and 346 as supraventricular arrhythmias. At least one ventricular or supraventricular arrhythmia was identified in 92 of the 195 patients.

Associations between $PM_{2.5}$ or BC and ventricular arrhythmias or all arrhythmias combined were weakly positive (and not statistically significant) at lag days 0 and 1, and were not found at days 2 and 3. Associations between $PM_{2.5}$ or BC and supraventricular arrhythmias were larger but also nonsignificant. Associations between CO, NO_2, or O_3 and the different types of arrhythmias were similar to those reported for $PM_{2.5}$ and BC in parallel analyses.

Associations for SO_2 with all arrhythmias combined or ventricular arrhythmias were positive (increase in relative risks of 6%–14%) at lag days 0, 1, 2, and 3. When analyzed as single days, for all arrhythmias combined these increases were statistically significant for days 0, 2, and 3; and for ventricular arrhythmias they were statistically significant for days 2 and 3. Larger associations (increase in relative risks of 15%–25%) were reported for SO_2 with supraventricular arrhythmias; the relative risk was statistically significant for lag day 1.

Of the several possible effect modifiers evaluated, few showed any effects. However, experiencing a ventricular arrhythmia within the 3 days before another ventricular arrhythmia increased the relative risk associated with $PM_{2.5}$, BC, SO_2, CO, and NO_2 concentrations (an increase in relative risk of 28%–75%, depending on the pollutant). Taking β-blockers was associated with decreased effects of pollutants on supraventricular arrhythmias. No consistent pattern of altered risk was found in relation to a patient's distance of residence from the pollutant monitors. These associations, produced by appropriate exploratory analyses, need to be validated in future studies.

CONCLUSIONS

This important study investigated specific hypotheses about exposure to particulate pollutants and the induction of a major clinical endpoint,

cardiac arrhythmias that could be fatal if not for the intervention of the ICD. Overall, the study's results indicate that, in patients with an ICD, ambient concentrations of $PM_{2.5}$ or BC on the day of or up to 3 days before the event are only weakly, if at all, associated with the induction of any type of nonfatal arrhythmia. These results reported for particulate pollutants parallel some of those described in the investigators' earlier pilot study in the Boston area. Thus, these results do not strongly support one of the investigators' main study hypotheses, that increased ambient concentrations of particulate air pollutants would be associated with increased incidence of arrhythmias. For sulfate and ultrafine particles, fewer measurements were made and not many analyses were performed or reported. Thus, conclusions are difficult to draw from the results in this report about associations between these particulate pollutants and arrhythmias.

Compared with all other pollutants, associations between arrhythmias and SO_2—a pollutant derived primarily from stationary sources in this study area—were more likely to be statistically significant and more robust, especially for supraventricular arrythmias. It is not clear, however, whether the associations reported for SO_2 and arrhythmias are due to SO_2 per se or reflect the activity of another pollutant associated with SO_2. NO_2, CO, and O_3 showed weak associations with all arrhythmias combined, similar to those reported for $PM_{2.5}$ and BC. These results differ from the pilot study, in which NO_2 was the only pollutant, gaseous or particulate, found to be significantly associated with ICD discharges in the overall study population.

The sources that emit the different pollutants are not clear: in the area of the current study, NO_2, CO, and $PM_{2.5}$ are associated primarily with vehicular emissions but SO_2 is associated primarily with stationary sources. Methods are needed to accurately identify the sources of emissions and to evaluate the relative contributions to health effects from stationary and mobile sources.

A strength of this study was the care taken to characterize the tracings recorded by the ICDs. This allowed nonarrhythmic events to be excluded from the analyses and ventricular arrhythmias to be distinguished from supraventricular arrhythmias. As expected, because the ICD is programmed to primarily treat arrhythmias that originate in the ventricles, the majority of arrhythmias identified were ventricular in origin. Thus, effect estimates for particulate or gaseous pollutants and ventricular arrhythmias were similar to those reported for all arrhythmias combined.

The estimated effects of particulate pollutants and SO_2 on supraventricular arrhythmias were larger than those reported for ventricular arrhythmias and all arrhythmias combined. These results are intriguing and suggest new avenues for research on the cardiovascular effects of air pollution.

The results about supraventricular arrhythmias should be interpreted with caution, however. Of the tracings recorded, supraventricular arrhythmias comprised only 15%; thus the statistical power to draw conclusions about associations between pollutant concentrations and this type of arrhythmia is somewhat low. In addition, the supraventricular arrhythmias recorded by ICDs used in this study are only a small set of the total supraventricular arrhythmias that actually occur.

Another strength of this study was using information on each patient's cardiac history, function, and medications to explore whether these characteristics would modify the effects of pollutants on arrhythmias. Possibly of most clinical significance, several pollutants—$PM_{2.5}$, BC, NO_2, CO, and SO_2—showed a significant positive association with ventricular arrhythmias among patients who had had another ventricular arrhythmia within the previous 3 days. In studies in which multiple subgroup analyses are performed, some results may be due to chance; thus, these associations should be interpreted cautiously. Given that the results were similar for many of the pollutants, they also increase the challenge of determining whether a particular pollutant or source may be responsible for the observed associations or may vary simultaneously over time with the responsible pollutant or pollutants. Nonetheless, they suggest that air pollutant effects may be most important for individuals in whom cardiac electrophysiology is most compromised.

Although the results of this study are not definitive, they suggest topics for further research that could be fruitful. Obviously, a study in which a substantially larger number of arrhythmias are recorded, through increasing the number of subjects involved, the length of follow-up, or both, is needed. The results also indicate that future studies need to pay

careful attention to distinguishing supraventricular from ventricular arrhythmias; newer generations of ICDs should facilitate this distinction. Given the intriguing results related to supraventricular arrhythmias, other methods for investigating the effects of exposure to pollutants on this common subset of cardiac arrhythmias should be sought. At this point it is still not clear whether effects on cardiac arrhythmias are an important mechanism through which exposure to air pollution, and especially particulate pollution, exerts an effect on cardiovascular conditions.

CONTENTS

Research Report 124

HEALTH EFFECTS INSTITUTE

Particulate Air Pollution and Nonfatal Cardiac Events

HEI STATEMENT for Each Research Project Health Effects Institute

These Statements are nontechnical summaries of the Investigators' Reports and the Health Review Committee's Commentaries.

INVESTIGATORS' REPORTS AND COMMENTARIES

When an HEI-funded study is completed, the investigators submit a final report. The Investigators' Report is first examined by three ouside technical reviewers and a biostatistician. The report and the reviewers' comments are then evaluated by members of the HEI Health Review Committee, who had no role in selecting or managing the project. During the review process, the investigators have an opportunity to exchange comments with the Review Committee and, if necessary, revise the report.

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

Annette Peters, Stephanie von Klot, Margit Heier, Ines Trentinaglia, Josef Cyrys, Allmut Hörmann, Michael Hauptmann, H Erich Wichmann, and Hannelore Löwel

GSF-National Research Center for Environment and Health, Institute of Epidemiology, Health Economics and Health Care Management, Neuherberg, Germany; Ludwig-Maximilians-Universität, München, Germany; National Cancer Institute, Bethesda, Maryland, USA

Continued

Commentary on Part I Health Review Committee

The Commentary about the Investigators' Report is prepared by the HEI Health Review Committee and staff. Its purpose is to place the study into a broader scientific context, to point out its strengths and limitations, and to discuss remaining uncertainties and implications of the findings for public health.

Part II. Association of Air Pollution with Confirmed Arrhythmias Recorded by Implanted Defibrillators

Douglas W Dockery, Heike Luttmann-Gibson, David Q Rich, Mark S Link, Joel D Schwartz, Diane R Gold, Petros Koutrakis, Richard L Verrier, and Murray A Mittleman

Departments of Environmental Health and Epidemiology, Harvard School of Public Health; Cardiac Electrophysiology and Pacemaker Laboratory, New England Medical Center; Beth Israel Deaconess Medical Center; Harvard Medical School; Boston, Massachusetts

Continued

Publishing history: In March 2005, Part I of this document was posted as a preprint on *www.healtheffects.org* ; in June 2005, the whole document was posted as a preprint and then finalized for print.

Citation for Research Report 124 in its entirety:

Health Effects Institute. June 2005. Particulate Air Pollution and Nonfatal Cardiac Events. Parts I and II. Research Report 124. Health Effects Institute, Boston MA.

Citation for Part I only:

Peters A, von Klot S, Heier M, Trentinaglia I, Cyrys J, Hörmann A, Hauptmann M, Wichmann H-E, Löwel H. March 2005. Air pollution, personal activities, and onset of myocardial infarction in a case–crossover study, Part I. In: Particulate Air Pollution and Nonfatal Cardiac Events. Research Report 124. Health Effects Institute, Boston MA.

Citation for Part II only:

Dockery DW, Luttmann-Gibson H, Rich DQ, Link MS, Schwartz JD, Gold DR, Koutrakis P, Verrier RL, Mittleman MA. June 2005. Association of air pollution with confirmed arrhythmias recorded by implanted defibrillators, Part II. In: Particulate Air Pollution and Nonfatal Cardiac Events. Research Report 124. Health Effects Institute, Boston MA.

When specifying a section of this report, cite it as a chapter of the whole document.

INVESTIGATORS' REPORT

Particulate Air Pollution and Nonfatal Cardiac Events

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

Annette Peters, Stephanie von Klot, Margit Heier, Ines Trentinaglia, Josef Cyrys, Allmut Hörmann, Michael Hauptmann, H Erich Wichmann, and Hannelore Löwel

ABSTRACT

We conducted a prospective case–crossover study to assess the association of particulate air pollution with onset of nonfatal myocardial infarction (MI)*. Patients who had survived MIs between February 1999 and July 2001 were identified based on the Coronary Event Registry in Augsburg, Southern Germany. The study included 851 MI subjects with known date and time of MI who had survived the first 24 hours and had completed the Registry's standard interview. Of these subjects, 691 provided case and control information for subject-specific MI triggers collected by a diary assessing the 4 days before symptom onset. The exposures of interest were the total number concentration (TNC) of particles as an indicator for ultrafine particles and the mass of particles with an aerodynamic diameter no larger than 2.5 μm ($PM_{2.5}$). We conducted conditional logistic regression analyses using different control-selection strategies in a case–crossover approach, and Poisson regression analyses of the time-series data.

The specific study hypotheses were not confirmed by the study. Little or no association was found between an increase in the concentration of particulate air pollution ($PM_{2.5}$ and TNC) and MI onset hours later. In addition, no association was seen between TNC and MI onset within 5 days after exposure. Analyses suggested, however, an association between an interquartile range (IQR) increase in $PM_{2.5}$ concentrations and MI onset 24 to 95 hours later. Further case–crossover analyses with 16 bidirectional control periods found an effect with comparable increases in $PM_{2.5}$ and sulfur dioxide (SO_2) concentrations lagged 2 days (odds ratio [OR] 1.08 [95% confidence interval {CI} 0.99, 1.17] for a 7.7-μg/m^3 increase in $PM_{2.5}$; and OR 1.06 [95% CI 1.01, 1.11] for a 1.5-μg/m^3 increase in SO_2). The estimates obtained by the case–crossover analyses differed depending on the control-selection strategies, and ranged from a 6% to 18% increased relative risk per 7.7-μg/m^3 increase in $PM_{2.5}$ concentrations. However, the biases were not explained by confounding due to trend or season. In addition, positive effect estimates were observed for PM_{10}, carbon monoxide (CO), and nitrogen dioxide (NO_2) lagged 2 days and negative estimates for O_3 lagged 2 days, but for these pollutants results from case–crossover analyses and time-series analyses differed somewhat. Subject-specific triggers such as strenuous activities and time spent outdoors or time spent in traffic, as reported by subjects, were associated with MI onset 1 hour later. We found no evidence that these activities confounded the associations between air pollutant concentrations and MI onset. Strenuous outdoor activities were particularly associated with an increased relative risk of MI onset. The study suggested relatively large effect estimates for triggering of MI by $PM_{2.5}$. It further indicated that microenvironments such as those with high levels of traffic-related pollutants might be associated with the onset of MI.

*A list of abbreviations and other terms appears at the end of the Investigators' Report.

This Investigators' Report is Part I of Health Effects Institute Research Report 124. The Report also includes a Commentary by the Health Review Committee and an HEI Statement about the research project conducted by Peters and associates; the Part II Investigators' Report for research conducted by Dockery and colleagues, and the Health Review Committee's Commentary and the HEI Statement about the Dockery research project; and an Integrative Discussion that compares and contrasts the two studies. Correspondence concerning this Investigators' Report may be addressed to Dr Annette Peters, GSF-National Research Center for Environment and Health, Institute of Epidemiology, Ingolstädter Landstr. 1, 87564 Neuherberg, Germany; *peters@gsf.de*.

Although this document was produced with partial funding by the United States Environmental Protection Agency under Assistance Award R82811201 to the Health Effects Institute, it has not been subjected to the Agency's peer and administrative review and therefore may not necessarily reflect the views of the Agency, and no official endorsement by it should be inferred. The contents of this document also have not been reviewed by private party institutions, including those that support the Health Effects Institute; therefore, it may not reflect the views or policies of these parties, and no endorsement by them should be inferred.

INTRODUCTION

Ambient particulate air pollution has been associated with increased all-cause mortality, as well as with respiratory and cardiovascular disease mortality in epidemiologic analyses throughout the world (Schwartz 1991; Bascom et al 1996; Katsouyanni et al 1997; Pope and Dockery 1999). The harmful effects of elevated ambient concentrations of PM are well documented in multiple studies of hospital admissions and emergency department visits for respiratory diseases (Bascom et al 1996; Pope and Dockery 1999). In addition, in studies in American, Canadian, and European cities, the increase of hospital admissions for cardiovascular diseases was associated with increased particulate air pollution (Burnett et al 1995; Schwartz and Morris 1995; Burnett et al 1997a; Poloniecki et al 1997; Schwartz 1997, 1999, 2001b; Prescott et al 1998; Zanobetti et al 2000). These results indicate that ambient particulate air pollution is a risk factor not only for respiratory diseases, but also for acute cardiovascular events.

MI is one of the main causes of deaths from cardiovascular disease and might be contributing substantially to hospital admissions for cardiovascular events due to the association with particulate air pollution (Dockery 2001). It has been hypothesized that MIs might be triggered by ambient particle concentrations based on the observation that important inflammatory markers associated with an increased risk of MI (Danesh et al 2000) are elevated in response to increased particle concentrations (Seaton et al 1995). Those include increased plasma viscosity (Peters et al 1997a), fibrinogen (Pekkanen et al 2000; Schwartz 2001a), and C-reactive protein (Peters et al 2001b).

Evidence that elevated concentrations of particulate air pollution might trigger MI has been published (Peters et al 2001a). In that study, 772 MI patients were interviewed in the greater Boston area between January 1995 and September 1996 as part of the Determinants of Myocardial Infarction Onset Study. Hourly concentrations of $PM_{2.5}$, 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 an MI onset increased in association with elevated concentrations of fine particles in the 2-hour period preceding the onset of symptoms. In addition, a delayed response, associated with 24-hour average concentrations 1 day before the onset of symptoms, was observed. Analyses that considered both the 2-hour and 24-hour time windows jointly revealed an estimated OR of 1.48 per 25-$\mu g/m^3$ increase in $PM_{2.5}$ concentrations during a 2-hour period before the onset, and an OR of 1.62 for an increase of 20 $\mu g/m^3$ $PM_{2.5}$ in the 24-hour period before the onset (95% CIs 1.09, 2.02 and 1.13, 2.34, respectively). CO and NO_2 in some instances showed positive, but not statistically significant, associations with the onset of MI. That study suggested that elevated concentrations of fine particles in the air may transiently elevate the MI risk within both a few hours and 1 day after the exposure. Eilstein and colleagues (2001) reported on the association between daily concentrations of ambient air pollutants and MIs in Strasbourg, France. The data were analyzed using Poisson regression analyses adjusting for trend, season, influenza, weather, and day of the week. Positive associations between MI onset and concentrations of CO, SO_2, and PM_{13} on the same day were reported; but none of the associations was statistically significant. In contrast, NO_2 and nitrogen monoxide (NO) lagged 5 days showed statistically significant associations with the daily variation in MIs. In addition, ozone (O_3) lagged 1 day was also statistically significantly associated with the number of MIs during the summer months. In London, UK, hospital admissions because of MI increased when concentrations of black smoke, NO_2, CO, and SO_2 had been elevated on the day before the MI (Poloniecki et al 1997).

Ambient aerosols are a complex suspension of particles of different physical and chemical properties in a gas phase. The mass of particles within a cubic meter of air nominally below certain cut-points, such as 10 µm or 2.5 µm, represent one approach to characterizing the ambient aerosols. These metrics have largely been used to establish the association between particulate air pollution and acute increases in cardiopulmonary disease morbidity and mortality (Pope 2000). Alternatively, one might take the number concentration of ambient particles to characterize the prominence of high concentrations of particles freshly generated by combustion processes (Wichmann and Peters 2000). The TNC of particles is dominated by the ultrafine particle fraction, which is defined as particles being smaller than 100 nm (Tuch et al 1997). Based on toxicologic data, it has been hypothesized that these particles with large active surfaces but little mass might also have the potential to elicit cardiovascular effects (Seaton et al 1995; Oberdörster 2000; Donaldson et al 2001; Frampton 2001). However, until now, little evidence has been presented of the link between ultrafine particles and cardiovascular disease exacerbation. A time-series mortality study indicated that both fine and ultrafine particles might be associated with respiratory as well as cardiovascular disease mortality in Erfurt (Wichmann et al 2000). In the Exposure and Risk Assessment for Fine and Ultrafine Particles in Ambient Air (ULTRA) study, both $PM_{2.5}$ and the ultrafine number concentrations were associated with an increased risk of ischemia (Pekkanen et al 2002).

SPECIFIC AIMS

This study was designed to assess the association of nonfatal MI onset with particulate air pollution and to prospectively apply the case–crossover method. Subjects were drawn from the Coronary Event Registry in Augsburg, Southern Germany (Löwel et al 1991). The air pollutants of interest were the TNC (as an indicator of ultrafine particles) and $PM_{2.5}$. The study's objective was to test the following specific hypotheses:

1. The onset of MI is associated with an acute exposure to particulate air pollution within hours.
2. The association of MI is stronger with an acute exposure to TNC than to $PM_{2.5}$.

For registration in the Coronary Event Registry in Augsburg, MI survivors were routinely interviewed. Because we planned to evaluate these hypotheses taking into account personal activities known to trigger MIs, we designed an additional questionnaire to collect data on known MI triggers up to 4 days before the onset of symptoms.

Average population exposure to ambient particles would be estimated on the basis of continuous measurements taken at a central background monitoring site. TNC would be measured with a condensation particle counter (CPC), and hourly measurements of $PM_{2.5}$ would be taken with a tapered element oscillating microbalance (TEOM). Hourly mean concentrations of the gaseous air pollutants (CO, O_3, SO_2, and NO_2) and the meteorological variables (temperature, relative humidity, and air pressure) would be obtained through the Bavarian Air Monitoring Network.

METHODS AND STUDY DESIGN

STUDY LOCATION

The study area comprised the City of Augsburg and two adjacent districts referred to as County Augsburg (or Augsburg Land) and County Aichach-Friedberg (see Figure 19 for a map of the study area). In 1998, these three administrative districts had approximately 610,000 total inhabitants (City of Augsburg 254,000; County of Augsburg 235,000; and County of Aichach-Friedberg 121,000). Of the total inhabitants of the region, 198,000 men and 201,000 women were within the age range of 25 to 74 years and were living in the study area in 1998. Inhabitants of this area in this age range formed the study population of the Coronary Event Registry Augsburg. (From the Registry, subjects for the current study were recruited.)

The City of Augsburg is the administrative center of the northwestern region of Bavaria; the two adjacent districts are predominantly rural. Small and middle-sized industrial entities are located in the northeastern part of the City of Augsburg. In addition, there is a small regional airport in the northeast of the city. City planning has designated these as industrial sites. Therefore, the emissions from these sites contribute little to the air pollution concentrations in the City of Augsburg if the predominantly westerly winds prevail. The terrain is moderately flat at 500 m above sea level. In the adjacent counties, the landscape is dominated by smooth hills at 400 to 600 m above sea level.

AIR POLLUTION MEASUREMENTS

$PM_{2.5}$ and TNC Measurements at the HEI Site

Particulate exposures were estimated on the basis of measurements taken at a central background monitoring site in the cloister garden (orchard) of St Stephan, a Benedictine monastery, located within ancient city walls 1 km to the north of the downtown area on the high banks of the river Lech (Figure 1). Figure 2 shows the surroundings of

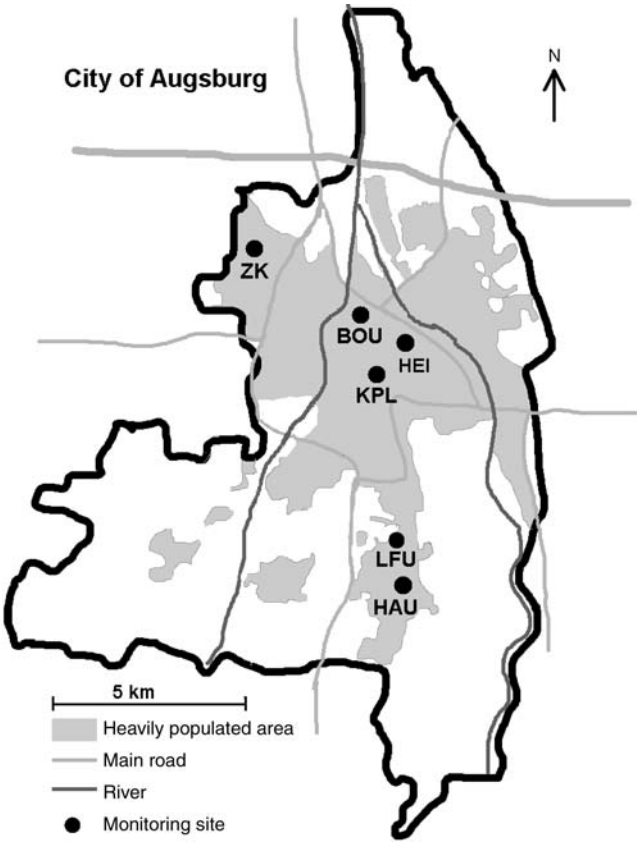

Figure 1. Map of air pollution measurement sites and the subject recruitment hospital in Augsburg. ZK is Zentralklinikum (Central Hospital); BOU is Bourges-Platz; HEI is the HEI site; KPL is Königsplatz; LFU is Landesamt für Umweltschutz; and HAU is Haunstetten.

the HEI site. The orchard is enclosed by a wall about 3 m high. The measurement device within this garden was 15 m from the nearest wall. The nearest street with virtually no traffic is at a distance of 20 m; the next minor street with low traffic intensity is 50 m away; and the nearest major street about 125 m to the east. The nearest stationary air pollution source is a thermal power station (powered by gas) at a distance of 300 m. Its stack is 60 m high and its emissions are unlikely to have an impact on the pollution concentrations of the measuring site.

Continuous measurement devices were used to obtain hourly measurements of fine and ultrafine particles. $PM_{2.5}$ was measured continuously from February 1, 1999 through July 31, 2001 with a TEOM model 1400A (Patashnick and Rupprecht, German distributor: MLU, Essen, Germany; Patashnick 1991). The particles were sampled at a flow rate of 3 L/min. To select fine particles, a $PM_{2.5}$ cyclone (R&P PM-2.5 Inlet [flow rate of 16.7 L/min No. 10-002319) was used. The TEOM was operated at 50°C to avoid the impact of water condensation on the particle mass measurements. The particles were collected on a filter mounted on a rotating glass fiber rod; the rotation of the rod was proportional to the weight of the filter. This instrument provided the basis for the continuous calculation of $PM_{2.5}$ mass concentration, expressed in micrograms per cubic meter of air. The measurements were given for standard temperature (25°C) and pressure (1 mbar). The device was serviced regularly based on the operating procedures (Peters et al 2002).

The impact of heating the aerosol as part of the TEOM measurement procedures was evaluated by additional $PM_{2.5}$ measurements taken every second day by means of a Harvard impactor (HI) (Marple et al 1987) at a flow rate of 10 L/min. Filters were collected between September 1999 and January 2001. In the HI, large particles impact on an oiled impactor plate and are thereby eliminated from the sample. After their passage through the device, small particles are collected on a 37-mm Teflon filter with a pore size of 2 µm (Anderson; BGI Inc, Waltham MA). In contrast to the TEOM, measurements in this device were taken at ambient temperature and pressure. Duplicates and field blanks were obtained for 10% of the measurements. The procedures were based on the ULTRA Standard Operating Procedure (Pekkanen and Timonen 2000) with slight modifications (Peters et al 2002). Blank values proved to be problematic; however, no corrections for blanks were included in the analyses on the basis of recommendations from the HEI Quality Assurance officer.

The $PM_{2.5}$ HI data were recalculated for 25°C and 1 mbar to be directly comparable with the $PM_{2.5}$ TEOM data. The $PM_{2.5}$ concentrations measured by the HI were clearly higher than those obtained by the TEOM (Figure 3). The daily ratios between TEOM and HI were mostly below 1, on average 0.78. This value is comparable with the results of other studies comparing various filter-based particulate matter samplers with the TEOM (Allen et al 1997; Cyrys et al 2001). In all studies, the values obtained with the TEOM were lower than the corresponding values obtained with the comparison sampler. The TEOM/HI ratio for the ambient aerosol was 0.74 in Erfurt (Cyrys et al 2001) and between 0.64 and 0.89 at several US locations (Allen et al 1997). The heating of the TEOM filter to 50°C was suggested to cause

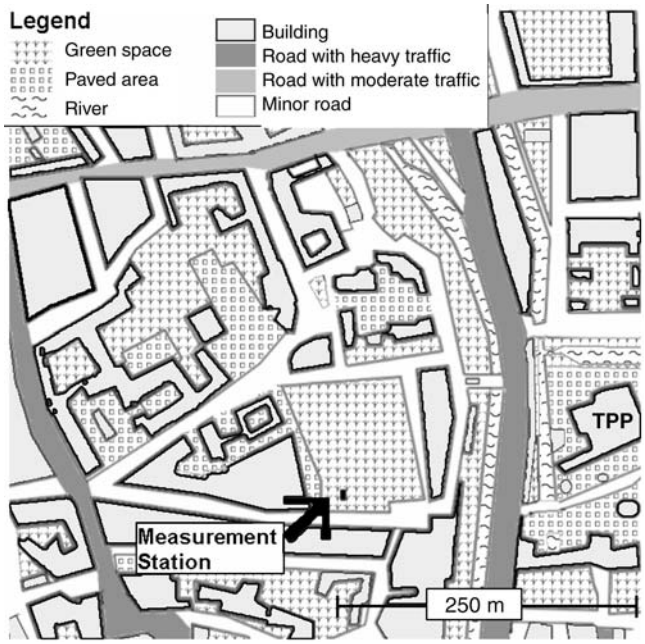

Figure 2. Surroundings of HEI measurement site in a cloister garden. Note the two roads with heavy traffic within 125 to 200 m to the east and west, the road with moderate traffic about 300 m to the north, and the thermal power plant (TPP).

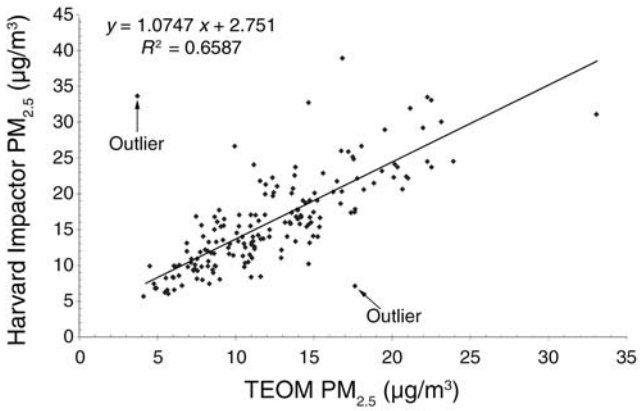

Figure 3. Comparison of $PM_{2.5}$ measured at the HEI site by the TEOM and HI between September 1999 and January 2001. (The TEOM readout applied automatic correction of y = 3.0 + 1.03 $PM_{2.5}$ unscaled.)

some volatilization of particulate semivolatile material. This may be the reason for differences in particle mass obtained with the TEOM method compared with a filter-based gravimetric method. In fact, we saw slightly higher TEOM/HI ratios in summer (TEOM/HI = 0.81, n = 59), when the temperature differences between the two samplers were lower, than in winter (TEOM/HI = 0.73, n = 21). (December through February was defined as winter and June through August as summer.)

Nevertheless, the $PM_{2.5}$ concentrations measured by the TEOM and by the HI were highly correlated. After excluding two outliers (identified by comparing the time series for the two variables) the Spearman correlation coefficient was 0.83 and the squared correlation was 0.66 (Figure 3). This high correlation allowed a recalculation of the TEOM data that used 5.97 $\mu g/m^3$ for the intercept and 1.11 for the slope, instead of the default values 3 $\mu g/m^3$ for the intercept and 1.03 for the slope.

As a marker for ultrafine particles, TNC was measured with a CPC (3022A; TSI, Aachen, Germany; Agarwal and Sem 1980), which counted particles between 0.007 µm and 3.0 µm. Independent of their size, particles were sampled at a flow rate of 5 mL/sec at a height of 1.7 m. The device was operated in high flow mode. Within the instrument, particles passed a compartment saturated with n-butanol at a temperature of 36.1°C. In the condensation chamber, lower temperature (10°C) caused the butanol to condense onto the particles. A laser spectrometer counted the particles and calculated the number of particles per cubic centimeter.

Quality control procedures included daily and weekly instrument inspections based on the standard operating procedures (Peters et al 2002). The CPC was serviced and calibrated twice during the 2.5 years of the study. Comparison measurements within the area were performed twice with a second CPC during the year 2000. During the first set of measurements acquired in June and July 2000, an obstruction of the sample line caused by an insect was identified. The data from the parallel measurements were used to adjust the data at the monitoring site. A second set of measurements were obtained in November and December 2000 and the data are reported below (see text discussion of Tables 6 and 7 and Figure 15 in Results / Air Pollution Measurements). During this period, TNC was also measured at the site of the Bavarian Air Monitoring Network at Bourges-Platz and at Haunstetten (described in the next section).

TNC data were recorded as 1-minute averages (February 1999 to April 2000) or as 30-second averages (April 2000 to July 2001). All data were inspected for plausibility and implausible values were set to missing on the basis of the 1-minute or 30-second averages (Peters et al 2002). If two-thirds or more of the hourly data were available after the implausible values were removed, 1-hour average concentrations were calculated.

Pollutants and Weather Variables Measured at Additional Sites

Hourly mean concentrations of the gaseous air pollutants (CO, O_3, SO_2, NO_2, and NO) and the meteorological variables (temperature, relative humidity, and air pressure) were obtained through the Bavarian Air Monitoring Network.

Total suspended particles (TSP) were measured only until December 1999 and then PM_{10} was measured starting in February 2000 by the Bavarian Air Monitoring Network. Gaseous pollutants, PM_{10}, and TSP were measured at Bourges-Platz, which is north of the city center and 1 km northwest of the HEI site at St Stephan (Figure 1). It is situated at the northern end of a public park; the next street is 12 m away. SO_2 was measured with UV fluorescence (Monitor labs, ML 8850 [M]); nitrogen oxides (NO_2 and NO) with chemiluminescence (Ecophysics CLD 700 AL); CO with gas filter correlation (API300A); and TSP and PM_{10} by means of β-absorption (ESM Eberline FH62 I-N). Measurements of gases were recorded as ½-hour averages; particle measurements at this site were recorded as 3-hour averages.

Weather parameters were measured at Haunstetten on the roof of a building adjacent to the air hygiene measurement station at a height of 15 m. O_3 was also measured at the Haunstetten site, at a background air monitoring site on the outskirts of the City of Augsburg that was operated until April 2001. It was located 5 km south of the city center; the nearest street was 4 m away. Bavarian Air Monitoring Network had established a new site in Haunstetten in 2000 called the Landesamt für Umweltschutz (LFU) site, also a background station and 100 m to the nearest, very quiet, street. O_3 and weather data were used from this station for the time period May to July 2001. O_3 measurements at both Haunstetten sites were based on UV absorption (Thermo Instruments, TE 49).

AUGSBURG CORONARY EVENT REGISTRY

Hospitalized MI survivors were routinely interviewed for the Coronary Event Registry Augsburg as part of the KORA-Initiative (Cooperation for Health Research in the Region of Augsburg) (Löwel et al 1991). Subjects were recruited for the HEI study from the Registry between February 1999 and July 2001. The Registry had been established as part of the MONICA (MONItoring of trends and determinants in CArdiovascular disease) project in 1985; the procedures for hospitalization due to cardiovascular complications are described in detail elsewhere (Lewis et

al 1990). The study was approved by the review board for the KORA-Initiative.

Briefly, patients with a possible diagnosis of MI were identified daily by routine monitoring of hospitalizations at Zentralklinikum Central Hospital; in six hospitals further away but within the study area, and in four hospitals outside of the study area, interviews for the Registry were conducted once a week. Admission diagnoses for our screening purposes included: acute MI, chest pain, angina pectoris, cardiac arrhythmia, pulmonary embolism, cardiac insufficiency, cardiac arrest, syncope or any other form of unconscious condition, hypertension, hypertensive crisis, coronary heart disease, myocardial ischemia, cardiogenic shock, cardiomyopathy, valvular heart disease, angiography, digitalis intoxication, percutaneous transluminal coronary angioplasty, pacemaker, death on arrival, aneurysm, carditis, myocarditis, hyperkalemia, no admission diagnosis.

After transfer to the general ward, patients with continued suspicion or clinical confirmation of transmural or nontransmural acute MI were informed of the purpose of the Coronary Event Registry by their ward physician. Informed consent was obtained and an appointment for an interview was made. Demographic characteristics, medical history, and smoking behavior were collected.

For the current case–crossover study, questions with respect to environmental tobacco smoke (ETS) exposures, respiratory infections, and absence from the study area in the week before the MI were added. After the subjects' discharge, we requested their medical records and abstracted information on the basis of a standardized protocol.

HEI DIARY

During the interview for the Coronary Event Registry, further information on the subjects' activities before the onset of symptoms was collected with a diary–questionnaire designed for the case–crossover study (see Appendix A). The diary was based on the questionnaire from the Triggers and Mechanisms of Myocardial Infarction Study (Willich et al 1993) and the questionnaire of the Determinants of the Onset of Acute Myocardial Infarction Study (Mittleman et al 1993). It assessed the 4 days preceding the MI in a semistructured interview (Peters et al 2002). The diary was tested in a pilot phase with the result that a first page was designed to record whether the subjects were able to answer all questions for each day. Diary recordings included time of MI, sleeping periods, activity levels during the day, time spent outdoors, means of transportation used, location within the study area, angina pectoris symptoms, occurrence of extreme anger or joy, and dust or solvent exposures. Activities that took place between 0 and 59 minutes after each clock hour were ascribed to that hour. An activity code was developed based on a modified classification of a metabolic equivalent unit (MET) used in the Determinants of MI Onset Study (Mittleman et al 1993) (Table 1). Time spent outdoors was coded if the person had spent more than 15 minutes of the considered hour outdoors. Means of transportation used included: walking, bicycling, riding a motorbike, and using a car or public transportation (buses and trains). (For brevity, using some form of transportation may be referred to as time spent in traffic.) Typical and atypical angina pectoris symptoms were recorded, such as chest pain, shortness of breath, cold sweat, nausea without vomiting, vomiting, and a doctor's visit because of chest pain. A coding list for the locations within the study area was developed by taking into account geographical differences, administrative postal units (zip codes), and anticipated differences in ambient air pollution (based on spatial measurements of NO_2 in 1987).

The research nurses were provided with written instructions for coding and data entry (Peters et al 2002). All subjects with unclear information were discussed by the nurses and the investigators.

DEFINITION OF MI AND TIME OF ONSET

The MI definition derived from the MONICA Project was adopted for the Augsburg Coronary Event Registry during the HEI study. MI diagnosis was based on the following criteria:

1. chest pain for more than 20 minutes that could not be relieved by nitrates;
2. changes in an electrocardiogram (ECG) that suggested an evolving MI; and
3. subsequent increases in the level of either creatine kinase, aspartate aminotransferase, or lactate dehydrogenase to more than twice the upper limit of normal enzyme levels.

The final decision about diagnosis was based on a computer algorithm to avoid biases (Lewis et al 1990; Peters et al 2002). A recurrent infarction occurring within 28 days of the index event was not counted as a separate event but was considered a complication of the index event.

The Coronary Event Registry differentiated between definite MIs, possible MIs, and cardiac arrests based on these criteria:

1. A definite MI was classified as present if
   - the clinical diagnosis from the ECG had been a transmural acute MI;

Table 1. Activity Codes for the HEI Diary[a]

Code for Activity Level	Primary Description	Types of Activities Included
1	Sleeping (MET 1)	
2	Lying down, reclining (MET 1)	Sunbathing, lying on a couch watching television
3	Sitting, very light exertion, light exertion (MET 2–4)[b]	Eating, reading, sitting watching television, personal care, standing in line, strolling, car driving, office work, slow walking, bowling, dusting, sweeping
5	Moderate exertion (deep breathing, MET 5)	Normal walking, slow biking, hunting, fishing, slow dancing, down-hill skiing, riding, curling, ice-skating, table tennis, cleaning windows, cleaning, raking leaves, light gardening, hanging wallpaper, interior painting, light restaurant work
6	Vigorous exertion (with panting, overheating, MET 6)	Slow jogging, speed-walking, tennis, swimming, cross-country skiing, sportive skiing, fast biking, ice hockey, circuit training, aerobics, volleyball, handball, badminton, mountain climbing, shoveling snow, pruning trees, mowing with a push mower, heavy gardening (digging, pulling out weeds), heavy household repairs, climbing up and down a ladder, overhead work, laying bricks, factory assembly work, heavy restaurant work
7	Heavy exertion (with gasping, sweating, MET 7)	Running, fast jogging, soccer, basketball, squash, pushing a car stuck in snow, moving boulders, changing tires, shoveling heavy snow, mixing cement, putting down wall-to-wall carpet, climbing stairs with more than a 20-kg load, using a sledgehammer
8	Extreme or peak exertion (MET 8)	Sprinting, fast running, jogging uphill, aggressive sports with frequent sprints and no rest, pushing or pulling with all one's might, unusually extreme work

[a] Table based on information and MET levels described in Mittleman et al 1993.

[b] MET 2 through MET 4 were combined into code 3 to simplify the interview.

- the clinical diagnosis from the ECG had been a non–Q-wave acute MI, the symptoms had been typical, atypical, or possible (insufficient data), and pathological elevation of enzymes had been documented; or
- the clinical diagnosis from the ECG had not been complete but symptoms had been typical and a pathological elevation of enzymes had been documented.

2. A possible MI was classified as present if

- the clinical diagnosis from the ECG had been a non–Q-wave acute MI or had been incomplete, the symptoms had been typical, and there had been no pathological elevation of serum enzymes; or
- the clinical diagnosis from the ECG had been neither transmural nor non–Q-wave acute MI, but the symptoms had been typical.

3. An ischemic cardiac arrest with successful resuscitation was classified as present if

- such an event had been documented but the criteria were not sufficient to specify a possible or definite MI.
- Pain, pressure, burning sensation in the chest for more than 20 minutes, or several attacks in short succession were regarded as typical symptoms. One attack of pain, pressure, burning sensation in the chest for less than 20 minutes, other pains (in shoulder, arm, hand, neck, jaw, upper abdomen, or shoulder blades) that could not be explained by other diseases, and complaints such as vomiting, nausea, dyspnea, syncope, perspiration, sensation of impending doom were regarded as atypical symptoms.

The time of onset was obtained from Coronary Event Registry questionnaire data and the medical records. It was defined as the time when angina pectoris symptoms (chest pain or chest tightness) that persisted for more than 20 minutes started and could not be relieved by nitrates. If symptoms were atypical, or several attacks of pain occurred in short succession, then the time of MI onset was defined as the time when the pain had been most severe. If no interview had been conducted, the time of onset was approximated by the time of admittance to the hospital. A detailed description of the algorithm is provided in the operations manual for this study (Peters et al

2002). The time of onset was defined as in the Coronary Event Registry; however, somewhat stricter criteria were applied for the HEI study:

1. symptoms fulfilled the MI criteria, and
2. the patient was able to recall the time of onset or the time when symptoms had been most severe.

Because the time of MI onset had a key role in this study, it was corrected on the basis of the medical records if the recording in the diary differed from the time obtained from the medical records. The medical records often contained notes on the sequence of events preceding the hospitalization, taken by the ambulance physician and the emergency room physician. Of 906 interviewed patients with confirmed MIs, 740 completed the HEI diary and had a known time of onset. Of these 740, 569 subjects (77%) during the interview reported exactly the same time as was identified by the medical record abstraction; for 12% there was a difference of 1 hour forward or backwards compared to the medical record abstraction; for 5.4% the time of onset was between 2 and 24 hours earlier; for 0.7% the time was more than 1 day earlier; for 3.2% the time was between 2 and 24 hours later; and for 1.4% the onset was a day or more later.

STATISTICAL METHODS AND DATA ANALSYES

The analytical plan we proposed and further developed as part of the operations manual foresaw a case–crossover data analysis using conditional logistic regression (Mittleman et al 1995). The initial approach was to match one case period (defined as a time period for a subject within hours before the MI event) to three control periods (defined as periods for the same subject some time before the case period; eg, 24, 48, and 72 hours) (Figure 4).

The formula below shows the likelihood of an analysis of a 1:M matched case–control study (a case is denoted as 0; a control as $j = 1, \ldots, M$; and matched sets $i = 1, \ldots, \ell$)

$$\Pr(y=1 \mid x) = \prod_{i=1}^{\ell} \frac{1}{1+\sum_{j=1}^{M} \exp\left[\beta\left(x_{ij} - x_{i0}\right)\right]}. \qquad (1)$$

where x_{ij} is the vector of exposures of the jth subject in the ith matched set (Breslow and Day 1980). Exposure variables were binary (interview-derived data such as activities reported) or continuous (measured air pollution and weather parameters).

Detailed descriptions of the analyses for air pollution and subject-specific risk factors are provided below and the possible biases are discussed. The analyses with air pollution as factor of interest in case and control periods considered the case–crossover design and applied different control-selection strategies to reflect the ongoing discussion on possible biases. In addition, Poisson regression analyses were applied to conduct the analyses by a different method. Confounder selection was done within the different approaches, but most extensively in the Poisson regression analyses, by which most of the sensitivity analyses were preformed. The final decisions on how to proceed with data analysis were based on the integrated

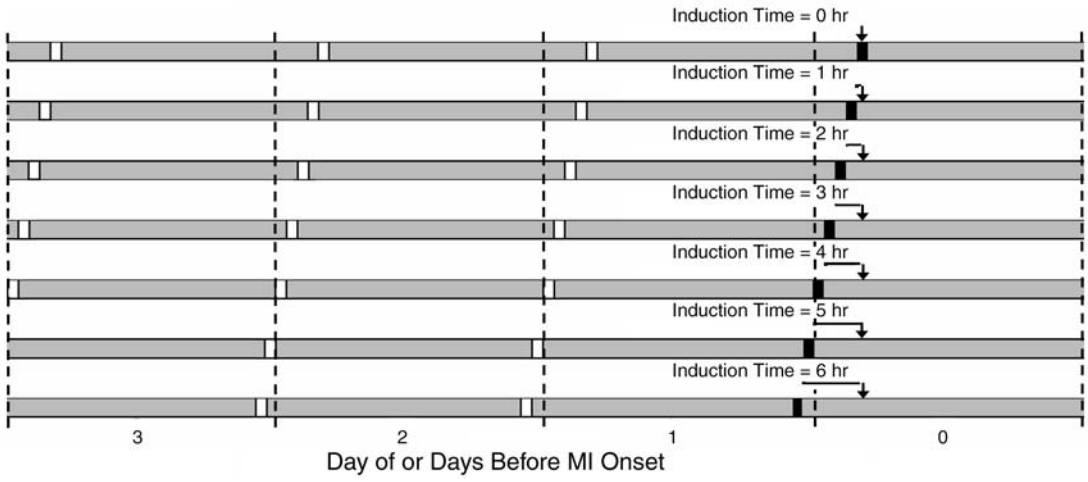

Figure 4. Selection of case periods (wide black bars) **and control periods** (white bars) **for the unidirectional case–crossover analyses considering a 1:3 match between 1-hour case and control periods.** The arrow is the time of MI onset and the induction time (——) is the time between MI onset and the case period being evaluated.

knowledge from the different approaches. The results of analyses with subject-specific activities as the factors of interest in case and control periods can be presented in the framework of Mantel-Haenszel estimators as well as conditional logistic regression analyses. We chose the latter for most of the analyses, but present an example for the Mantel-Haenszel approach in the Statistical Methods and Data Analyses section below.

Particulate and Gaseous Air Pollution As Triggers of MI

The analyses of the association between air pollution concentrations and MI onset were conducted in the subset of 851 subjects who had completed the Registry's interview and for whom information on the date and hour of MI onset was available (see Figure 16).

Case–Crossover Analyses The case–crossover approach controls for time-invariant confounders by design because the cases themselves serve as their own controls. Time-of-day was kept constant for case and control periods to limit confounding by known and unknown risk factors that may be associated with circadian rhythms and are responsible for MIs occurring more frequently in the morning hours. This appeared to be necessary, because air pollutants also show elevated levels in the morning.

One-hour and 24-hour average concentration measurements of particulate and gaseous air pollution, taken at central measuring sites, formed the basis for characterizing the average ambient particle exposure of the population.

To determine the induction time (specific aim 1), 1-hour average concentrations of air pollution 0 (concurrent), 1, 2, 3, 4, 5, and 6 hours prior to the event were considered as exposure windows for the case periods. (The concurrent hour spans minutes 0–59; the first hour spans minutes 60–119; and so forth.) Control periods were scheduled 24, 48, and 72 hours prior to the respective case period (Figure 4). These analyses were conducted for $PM_{2.5}$ and TNC (specific aim 2) and for other recorded pollutants. The analyses were conducted in SAS using PROC PHREG, version 8.2.

Additional analyses were conducted that considered 24-hour average pollutant concentrations and explored induction times of 0 to 5 days. Three 24-hour control periods directly preceding the respective case period were chosen (Figure 5). This allowed a comparison of the estimates obtained in this study with the estimates obtained in the MI Onset Study in Boston (Peters et al 2001a).

In order to estimate the latency period directly, spline functions were used to model the associations between particle exposures and MI onset (De Boor 1978; Hauptmann et al 2000, 2002). The case period was always the hourly profile from 1 to 96 hours prior to the event. Three different approaches were selected for 96-hour control periods:

1. three control periods per case period lagged 4 days (unidirectional design);
2. three to four control periods per case period stratified by month (bidirectional design); and
3. three control periods stratified by 4-week periods (bidirectional design).

A detailed description of the methods is provided in Appendix B.

Control-Selection Strategies The results obtained by Poisson regression analyses and by conditional logistic regression analyses were compared in simulation studies (Bateson and Schwartz 1999; Lumley and Levy 2000; Levy et al 2001a). Bateson and Schwartz (1999) had concluded that a symmetric bidirectional sampling regimen for control periods would reduce the bias so that it is negligible, whereas unidirectional control sampling would introduce bias. Lumley and Levy (2000) suggested stratified sampling of control periods to provide unbiased effect estimates. We performed additional analyses to compare the different approaches (Figure 5):

1. bidirectional control periods spaced 7 days apart, considering 4 control periods in total;
2. bidirectional control periods spaced 1 day apart, minimum of 7 days before and after the MI, considering 16 control periods in total;
3. stratified sampling considering the same weekdays within a month as a matched set; and
4. Poisson regression analyses of a time series.

Confounding Possible confounders are factors that vary over time (such as season or meteorological parameters), that may be associated with both the exposure of interest (pollutant concentration) and the outcome of interest (nonfatal MI), and that are not part of the causal pathway between the exposure and the outcome. Season might be a confounder because TNC and some of the gaseous pollutants tended to be higher in winter than in summer in Augsburg. Although no evidence for seasonal variation in MI frequency was found in Augsburg, season was still included in the modeling strategy to be consistent with other analyses of air pollution health effects. Models that included season as sine and cosine terms suggested a seasonal effect in the unidirectional design based on the Akaike information criterion (AIC), but not in the bidirectional design. In the unidirectional design, control periods were chosen (1) close to the case periods, (2) without a

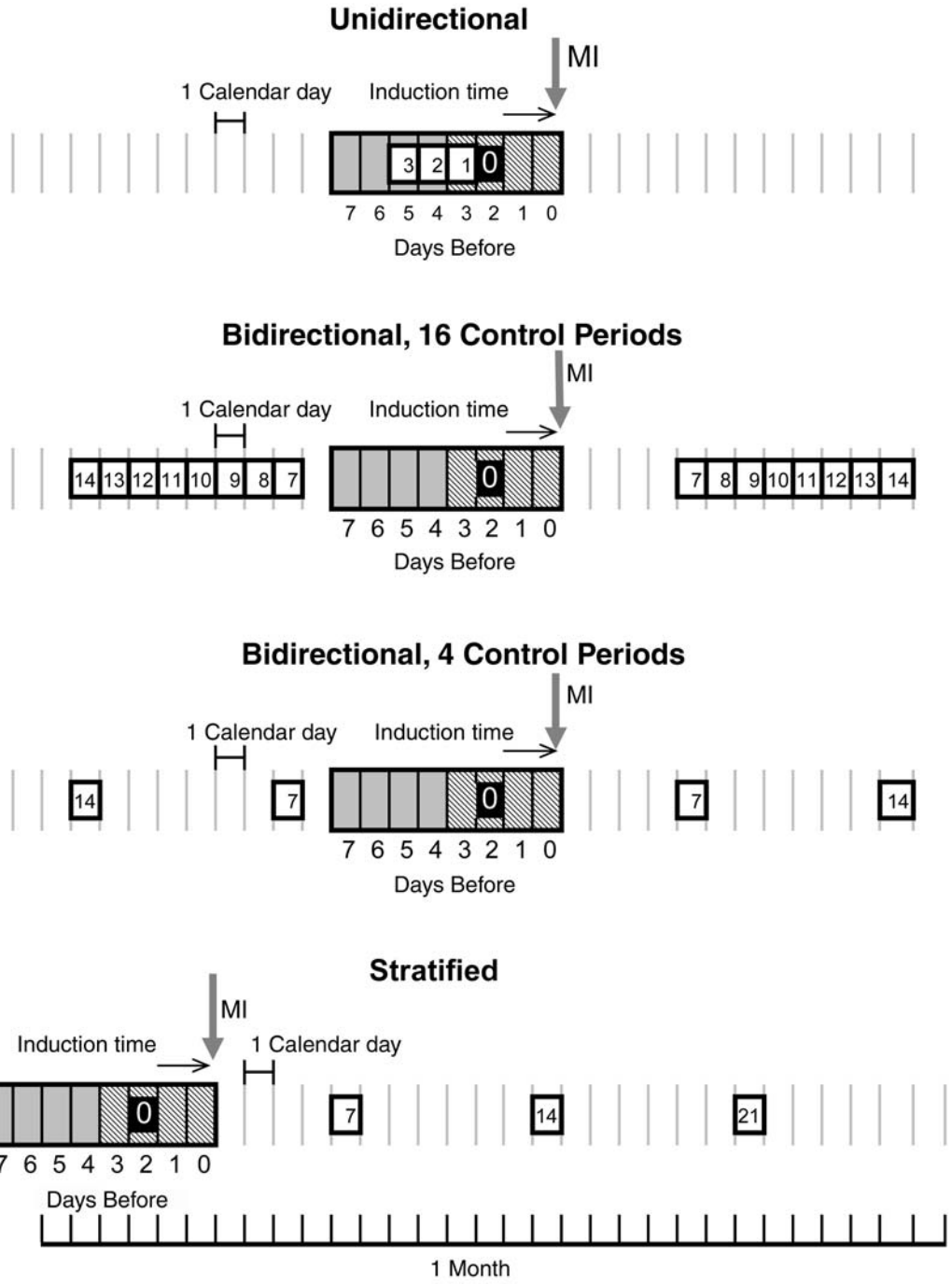

Figure 5. Different selections of control periods considered in the case–crossover analyses shown for a 24-hour average air pollutant exposure lagged 2 days. Black squares are case periods and open squares are control periods. Days with hatch marks show the time period covered by subjects' diary data. See text explanation.

winter-summer contrast, and (3) showed only minimal seasonal pattern. Therefore, season was only included in the sensitivity analyses. Temperature was anticipated to be associated with both TNC and $PM_{2.5}$ as well as with nonfatal MIs. The meteorological variables were considered as hourly and as 24-hour averages and dose-response functions were assessed. Indicators for the day of the week were included to eliminate a possible influence of weekdays whenever this was not controlled by design, as it was in the bidirectional or stratified control selections. Based

on the sensitivity analyses and the results from the models using penalized splines for the Poisson regression analyses, which found little evidence for confounding by time-varying factors, we present most of the results from case–crossover analyses based on univariate models.

Poisson Regression Analyses Daily MI counts were calculated and constituted the dependent variable in Poisson regression analyses. The statistical modeling was based on previous work of the investigators (Wichmann et al 2000). Possible confounders considered included trend, season, weather variables, and day-of-the-week indicators. Generalized additive models were used to allow for nonparametric functions for the confounders. All final models were estimated using the software R, package mgcv (version 1.7.1) (Wood 2001). Thin-plate regression penalized splines (Wood and Augustin 2002; Wood 2003) were tested for the continuous confounder variables time trends, daily average temperature, daily average relative humidity, and daily average air pressure. The number of degrees of freedom (*df*) of the smooth function depended on the weight of the penalty (smoothing parameter) in the penalized likelihood function. The decision on the adequate smoothing parameter was based on an algorithm by Wood, which automatically searches the minimum generalized cross-validation score (Wood 2000). The confounder variables were sequentially considered by basing the decisions on statistical tests and plausibility assessed in sensitivity analyses described below. The final model included a smooth term for trend with approximately 2 *df*. A smooth term for temperature with approximately 4 *df*, a linear term for air pressure, and indicators for the day of the week were introduced in the model.

Single lagged days were considered in addition to 5-day, 15-day, 30-day, and 45-day moving averages. All results are presented as relative risks (RRs; or odds ratios) per IQR of the pollutants.

Sensitivity Analyses Sensitivity analyses for the case–crossover analyses evaluated the final models by: (1) altering the season and weather modeling; (2) stratifying subject-specific characteristics, such as concurrent illnesses (eg, underlying cardiovascular diseases) and smoking; (3) stratifying subjects with respect to their whereabouts in the study area; and (4) excluding subjects with an uncertain MI diagnosis.

Sensitivity analyses for the Poisson regression analyses were performed to assess the impact of the confounder modeling on the air pollution effect estimates. These models were estimated in S-PLUS (version 6.0) with a convergence criterion set at 10^{-12}. The confounder variables were sequentially considered by basing the decisions on a combination of AIC and negative autocorrelation of the errors in partial autocorrelation plots. Partial autocorrelation plots indicated that an overall positive autocorrelation was present in raw time series of MIs. Generally, the events are considered to be independent, and autocorrelation is thought to be introduced through time-varying factors such as season or weather. Therefore, the absence of autocorrelation can be used as a criterion to assess overfitting of the models. Strong negative autocorrelation was induced by any attempt to model seasonality, either with locally weighted smoothing scatterplot (LOESS) functions with spans ranging from 0.1 to 0.8, or with natural spline functions, allowing for 3 *df* per year. Consequently, only a linear term for trend was retained. A second-order polynomial for temperature and a linear term for air pressure improved the model fit without introducing further negative autocorrelation. In particular, after inclusion of the air pressure, the shape of the temperature association obtained its parametric form. Results of the sensitivity analyses are reported for $PM_{2.5}$ lagged 2 days.

Subject-Specific Risk Factors Analyzed

For this study, we developed a questionnaire on known MI triggers to evaluate subject-specific risk factors in addition to central-site monitoring of ambient air pollution concentrations. The analyses were conducted for the subset of 691 subjects who had provided information for at least the 6 hours before MI onset and one control period. Before considering them jointly in a model, the effects of each risk factor were assessed in separate models. Activities of the MI survivors were available on an hourly basis. The activity intensity was recorded and physical activities were defined as activity code 5 or higher (MET 5) and strenuous activities as code 6 or higher (MET 6) (Table 1; Mittleman et al 1993). One-hour periods in the 0 to 6 hours prior to the event were defined as case periods and the 24-, 48-, and 72-hour periods before the event were defined as control periods. If an effect of pollution could be observed at 6 hours before MI onset, then we also investigated exposures 7 to 12 hours prior to MI onset. The unidirectional approach was fixed by design because data had been collected retrospectively for the 4 days preceding the event.

Generally speaking, data for a case–crossover study can be analyzed in the same manner as a matched-case–control study (Mittleman et al 1995). The distribution of the exposure (herein referred to as the factor) of interest in the case period versus the distribution of the factor of interest in the control periods in each matched set is quantified. In the simplest analysis (Figure 6), when one case period is matched to one control period (1:1 matched design) and the factor of interest is dichotomous (present or not present; positive or negative), the number of matched sets

is counted for all four combinations (see Figure 6). In the 1:1 matched design, the Mantel-Haenszel OR is calculated by dividing the number of subjects who reported engaging in the factor of interest only during the case period by those who did report engaging in the same factor only during the control period:

$$\mathrm{OR}_{\mathrm{mh}} = \frac{f_{10}}{f_{01}} . \tag{2}$$

To quantify the exposure effect, the concordant pairs are uninformative. For the test of the null hypothesis, the McNemar test for equality of proportions in matched samples can be used.

$$\chi^2 = \frac{(|f_{10} - f_{01}| - 1)^2}{(f_{10} - f_{01})} . \tag{3}$$

The 95% confidence limits (L = lower; U = upper) are calculated by solving the equations

$$\frac{f_{10} - \mathrm{CI_L} f_{01} - \frac{1}{2}(1 + \mathrm{CI_L})}{\sqrt{(f_{10} + f_{01})\mathrm{CI_L}}} = 1.96, \tag{4}$$

$$\frac{f_{10} - \mathrm{CI_U} f_{01} + \frac{1}{2}(1 = \mathrm{CI_U})}{\sqrt{(f_{10} + f_{01})\mathrm{CI_U}}} = -1.96. \tag{5}$$

An example is given in Figure 6 for any time spent in traffic and MI onset (for details see the section Results / Subject-Specific Triggers / Time Spent in Traffic). Figure 6 presents the number of concordant and discordant pairs considering 1 hour before MI onset as the case period and the same hour of the preceding day as the control period (1:1 matching). The OR is 60/21 = 2.86 using equation (2), and the 95% CI is 1.74, 4.70 using equations (4) and (5). The conditional logistic regression yields the identical result.

In the more general analysis of M control periods in each stratum, as used in the present study, the observations are represented by a $2 \times (M + 1)$ format, where the entry f_{11}, for example, is the number of matched sets in which the case period and exactly one of the control periods are both positive (Figure 7). The formula for the odds ratio in a 1:M matched case–control study, allowing for a varying number of control periods per case period, is

FIGURE 6. THE 2 × 2 FORMAT FOR MATCHED CASE–CONTROL STUDIES AS APPLIED TO CASE–CROSSOVER ANALYSES

The top panel demonstrates the general format in which a factor of interest in a case period is compared with the same factor in a control period. In this format, the case and control periods are designated "yes" and "no" on the basis of whether the factor of interest did or did not occur. f = number of pairs of matched case and control periods in each block.

The first subscripted number after the f indicates "yes" [1] or "no" [0] for the case period; that is, the factor of interest did or did not occur during the case period. The second subscripted number indicates the same information for the control period. The relation of interest is between discordant pairs [$\boldsymbol{f_{10}}$ and $\boldsymbol{f_{01}}$], which are shown in boldface italic type. Information about the subjects in each of these groups is used for data analysis.

Example from the Current Study. The bottom panel shows an example from the current case–crossover analysis of time spent in traffic (the factor of interest) 1 hour before MI onset (case period of interest) and 24 hours earlier (control period of interest). A total of 613 subjects provided pertinent data via diary interviews.

During the case period, 73 subjects ***did*** *report* time spent in traffic and 540 subjects ***did not*** *report* time spent in traffic. One group of interest is the 60 subjects who ***did*** *report* time spent in traffic during the case period and ***did not*** *report* time spent in traffic during the control period; the other group of interest is the 21 subjects who ***did not*** *report* time spent in traffic during the case period and ***did*** *report* time spent in traffic during the control period: their answers about time spent in traffic were discordant between the case and control periods. These two groups are used for data analysis.

Format for 2 × 2 Comparison

Case Period \ Control Period	No	Yes
Yes	$\boldsymbol{f_{10}}$	f_{11}
No	f_{00}	$\boldsymbol{f_{01}}$

Example: Did the Subject Report Time Spent in Traffic?

During Case Period: 1 Hour Before MI Onset \ During Control Period: 24 Hours Before Case Period	No	Yes
Yes	***60***	13
No	519	***21***

$$\mathrm{OR}_{\mathrm{mh}=}\frac{\sum_{M}\sum_{m=1}^{M}\frac{(M+1-m)f_{1(m-1)}}{M+1}}{\sum_{M}\sum_{m=1}^{M}\frac{mf_{0m}}{M+1}}. \qquad (6)$$

Figure 7 presents the number of concordant and discordant pairs considering the 1 hour before MI onset as case period and the same hours of the 3 preceding days as control periods (1:3 matching). Here it is important to note that 1:1, 1:2, and 1:3 matched pairs exist depending on the

FIGURE 7. THE 2 × (*M*+1) FORMAT FOR MATCHED CASE–CONTROL STUDIES AS APPLIED TO CASE–CROSSOVER ANALYSES

Much of this figure is identical to Figure 6. The difference is that the factor of interest in the one case period is compared with the same factor in *one or more* selected control periods (in this figure, we stop at three). As in Figure 6, the first subscripted number after the *f* indicates "yes" [1] or "no" [0] for the case period.

The labels at the top of the grid (none, 1, 2, ..., *M*) show the number of control periods in which the factor of interest *did occur.* Thus, the second subscripted number after the *f* is the same number as above: the factor of interest occurred in none (0) of the three possible control periods; or in any 1, 2, or all 3 control periods. As in Figure 6, the relations of interest are those between discordant pairs.

Example from the Current Study. The bottom panel shows an example from the same case–crossover analysis of time spent in traffic (factor of interest) 1 hour before MI onset (case period of interest) and corresponding control periods 24 hours earlier *on each of the 3 preceding days*. The number of control periods that can be matched with a case period (1:1, 1:2, or 1:3) depends on the completeness of the subjects' diary information.

Of all 623 subjects who provided any diary information, 81 provided information about 1 of 3 control periods (1:1 matching), 131 about 2 of 3 control periods (1:2 matching), and 411 about all 3 control periods (1:3 matching). In the 1:3 matching analysis (the left-hand set of eight boxes), 358 subjects reported time spent in traffic in ***none*** of the control periods; 38 reported time spent in traffic in ***any 1*** control period; 9 in ***any 2*** control periods; and 6 in ***all 3*** control periods.

As in Figure 6, the numbers in bold italic type are the subject groups of interest because the answers about time spent in traffic are discordant between the case and control periods.

Format for 2 × (*M*+1) Comparison

Number of Control Periods in Which the Factor of Interest Did Occur

Case Period: The Factor of Interest Did or Did Not Occur	None	1	2	3	…	*M*
Yes	f_{10}	f_{11}	f_{12}	f_{13}	…	f_{1M}
No	f_{00}	f_{01}	f_{02}	f_{03}	…	f_{0M}

Example: Did the Subject Report Time Spent in Traffic?

Number of Control Periods in Which the Subject Did Report Time Spent in Traffic

Case Period 1 Hour Before MI Onset: The Subject Did or Did Not Report Time Spent in Traffic	Matching	1:3				1:2			1:1	
		None	1	2	3	None	1	2	No	Yes
Yes		**35**	**13**	**4**	4	**10**	**3**	1	**5**	0
No		323	**25**	**5**	**2**	106	**9**	**2**	75	**1**
		[358]	[38]	[9]	[6]					
		411				131			81	

completeness of the diaries. When applying equation (6) the following result is obtained.

$$\frac{\left[\left(3f_{10}+2f_{11}+f_{12}\right)/4\right]+\left[\left(2f_{10}+f_{11}\right)/3\right]+\left(f_{10}/2\right)}{\left[\left(f_{01}+2f_{02}+3f_{03}\right)/4\right]+\left[\left(f_{01}+2f_{02}\right)/3\right]+\left(f_{01}/2\right)}=$$

$$\frac{\left\{\left[(3\times35)+(2\times13)+(1\times4)\right]/4\right\}+\left\{\left[(2\times10)+3\right]/3\right\}+\left(5/2\right)}{\left\{\left[25+(2\times5)+(3\times2)\right]/4\right\}+\left\{\left[9+(2\times2)\right]/3\right\}+\left(1/2\right)}=2.91$$

The results for the conditional logistic regression (OR 3.11) show small numerical deviations from the number calculated based on the formula (OR 2.91), which are attributable to the numerical procedures in obtaining the estimates in conditional logistic regression analyses.

Our primary approach was to analyze the association of the prevalence of subject-specific triggers with the outcome (MI). This implied that effect estimates of two induction times might contain at least some of the same subjects whenever the duration of the induction time was longer than 1 hour. To compare this study with previous investigations, odds ratios were calculated controlling for subsequent reporting of an activity in the case period (end of an activity instead of prevalence). In addition, analyses were performed that considered sex, age, concurrent illnesses, smoking, and the usual frequency of strenuous activities. This latter factor was approximated with the frequency of the engagement in the activity on the 3 control days. The sensitivity of the results was evaluated with several approaches:

1. instead of the 1:3 matching, a 1:24 matching was done, controlling for time-of-day with indicator variables;
2. subjects who were not able to recall activities on all 4 days were excluded; and
3. 1-hour case periods in the 24 to 30 hours before the event were matched to 1-hour control periods 24 hours earlier (ie, 48 to 54 hours before the event).This approach was used as an example of no association and was called a referent control analysis.

Similar approaches as described above were used for means of transportation (including bicycling, riding in a car, riding a motorbike, and using public transportation) and for time spent outdoors. Sometimes physical activities or some means of transportation (such as bicycling) are also outdoor activities. Therefore, the impact of activities engaged in outside was jointly analyzed and interactions were examined. Activities such as extreme emotional distress, or solvent or dust exposures were reported too seldom to allow formal assessments of the associations.

RESULTS

AIR POLLUTION MEASUREMENTS

Air pollution measurements at the HEI site were conducted between February 1, 1999 and July 31, 2001. For $PM_{2.5}$ and TNC, Table 2 describes the distribution of the 1-hour and the 24-hour average concentrations at the HEI site; 24-hour average concentrations of $PM_{2.5}$ never exceeded 65 µg/m^3. Occasionally, values above 100 µg/m^3 were recorded on hourly levels: the maximum of 355 µg/m^3 $PM_{2.5}$ was observed on New Years Evening 2000. There was no strong seasonal variation in the $PM_{2.5}$ concentrations (Figure 8). This was also confirmed by the TSP and PM_{10} measurements at the official air hygiene station at Bourges-Platz (Figure 8). On average, $PM_{2.5}$ concentrations

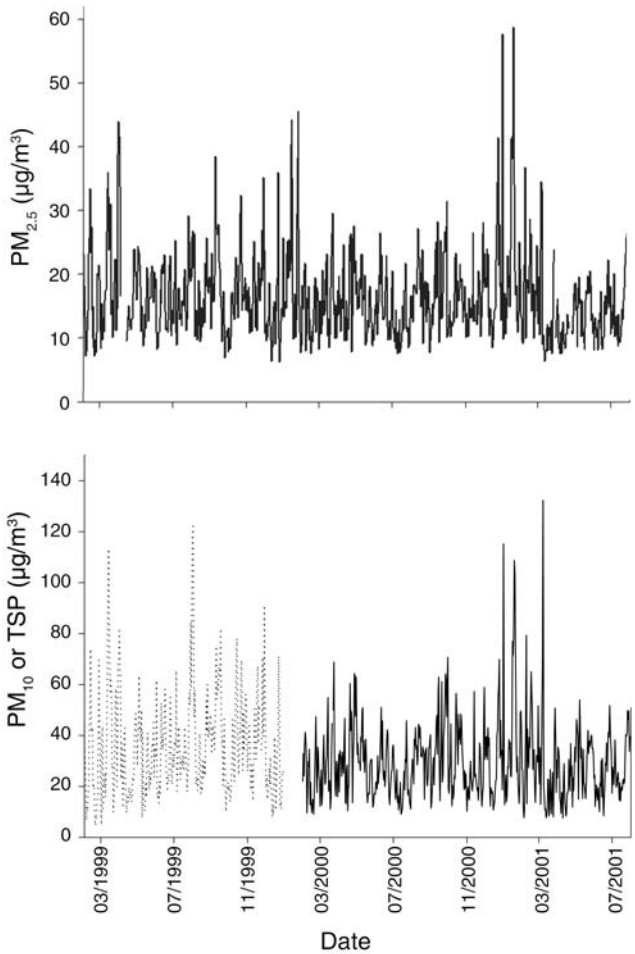

Figure 8. $PM_{2.5}$ concentrations at the HEI site (top panel) **and TSP (.....) and PM_{10} (——) concentrations at Bourges-Platz** (bottom panel).

decreased 0.89 μg/m^3 per year with a 95% CI of 0.28, 1.50; and $PM_{2.5}$ represented 50% of the PM_{10} measurement and 42% of the TSP measurement. During the study period, 24-hour-average PM_{10} concentrations never exceeded 150 μg/m^3. For PM_{10} and $PM_{2.5}$ and for TSP and $PM_{2.5}$, 24-hour averages were highly correlated (Table 3). Unfortunately, TSP and PM_{10} measurements conducted at the Bourges-Platz site did not overlap; when viewed sequentially, however, either TSP or PM_{10} were recorded on 94.7% days of the study period. A clear diurnal pattern with elevated concentrations during morning and evening hours was observed for $PM_{2.5}$ measured at the HEI site (Figure 9). The

Table 2. Comparison of Particle Measurements at Two Sites[a]

	n	%	Mean	Minimum	25%	50%	75%	Maximum	IQR
HEI Site[b]									
1-Hour averages									
$PM_{2.5}$	21,402	97.7	16.3	−6.9[c]	10.7	14.5	19.8	355.2[d]	9.1
TNC	18,639	82.6	12,318	1048	7326	10,001	15,245	89,676	7919
24-Hour averages									
$PM_{2.5}$	897	98.3	16.3	6.1	11.6	14.9	19.3	58.5	7.7
TNC	763	80.5	12,292	3666	8426	10,934	14,702	39,147	6276
Bourges-Platz									
3-Hour averages									
TSP[e]	2661	99.6	35.7	3.0	19.0	31.0	46.0	376.0	27.0
PM_{10}[f]	4373	99.9	29.5	3.0	16.0	26.0	39.0	500.0	23.0
24-Hour averages									
TSP	332	99.4	35.7	4.6	21.0	32.7	44.9	122.1	23.9
PM_{10}	546	99.8	29.5	7.6	18.6	26.6	36.5	132.3	17.9

[a] *n* = the total number of available measurements; % = proportion of the total possible measurements. $PM_{2.5}$, TSP, and PM_{10} are reported in μg/m^3; TNC is reported in number/cm^3.

[b] Measurements at the HEI site were taken between February 1999 and July 2001.

[c] Negative values may occur based on measurement principle.

[d] Maximum value was recorded on January 1, 2001, 0 AM (midnight).

[e] TSP was measured from February 1999 until December 31, 1999.

[f] PM_{10} was measured from February 1, 2000 through July 2001.

Table 3. Spearman Correlation Coefficients for 24-Hour Averages of Pollutant Concentrations and Temperature

	$PM_{2.5}$	TSP	PM_{10}	CO	NO_2	NO	SO_2	O_3	Temperature
TNC	0.37	0.31	0.32	0.51	0.69	0.52	0.69	−0.33	−0.38
$PM_{2.5}$		0.89	0.92	0.57	0.67	0.59	0.58	−0.24	0.05
TSP			—[a]	0.67	0.66	0.63	0.46	−0.16	0.18
PM_{10}				0.55	0.69	0.61	0.60	−0.19	0.15
CO					0.71	0.70	0.63	−0.41	−0.33
NO_2						0.76	0.75	−0.31	−0.09
NO							0.56	−0.61	−0.17
SO_2								−0.27	−0.32
O_3									0.58

[a] No overlap of measurement periods.

range of the diurnal variation amounted to 35% of the mean concentrations. On weekdays, higher concentrations of $PM_{2.5}$ were observed than on weekends, with a maximal range of 15% of the mean concentration of $PM_{2.5}$ (Figure 9).

The TNC averaged 12,000 particles/cm^3. High day-to-day variability was indicated by the graphical presentations of the time course of 24-hour average concentrations (Figure 10). TNC was higher during the winter months than during the summer months. Again, a clear diurnal pattern and higher concentrations on weekdays than on weekends were observed (Figure 11). The range of the average diurnal variation was 60% of the mean TNC; TNCs were 34% higher on Wednesdays than on Sundays. TNC was only moderately correlated with $PM_{2.5}$ for 1-hour averages (Table 4), and correlations were slightly lower for 24-hour averages (Table 3).

Table 5 describes the 1-hour and 24-hour averages of the gaseous pollutants. Moderate CO, NO_2, and O_3 concentrations were recorded, with occasionally high 1-hour concentrations. NO_2 had no strong seasonal pattern, whereas the seasonal pattern of CO was more pronounced (Figure12). SO_2 concentrations were low throughout the study period with a clear seasonal pattern. Temperature

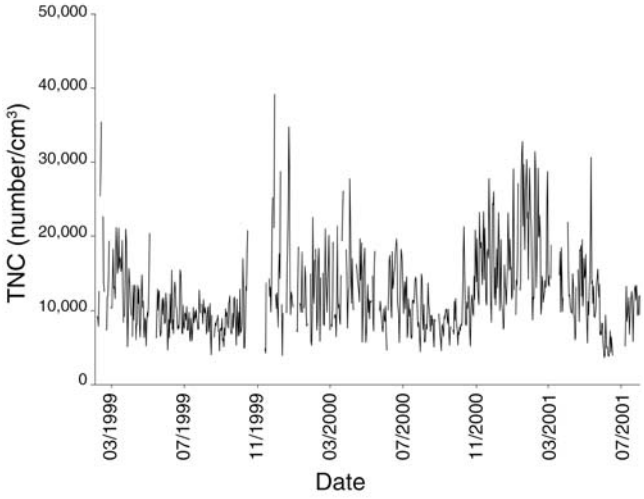

Figure 10. Daily TNCs at the HEI site.

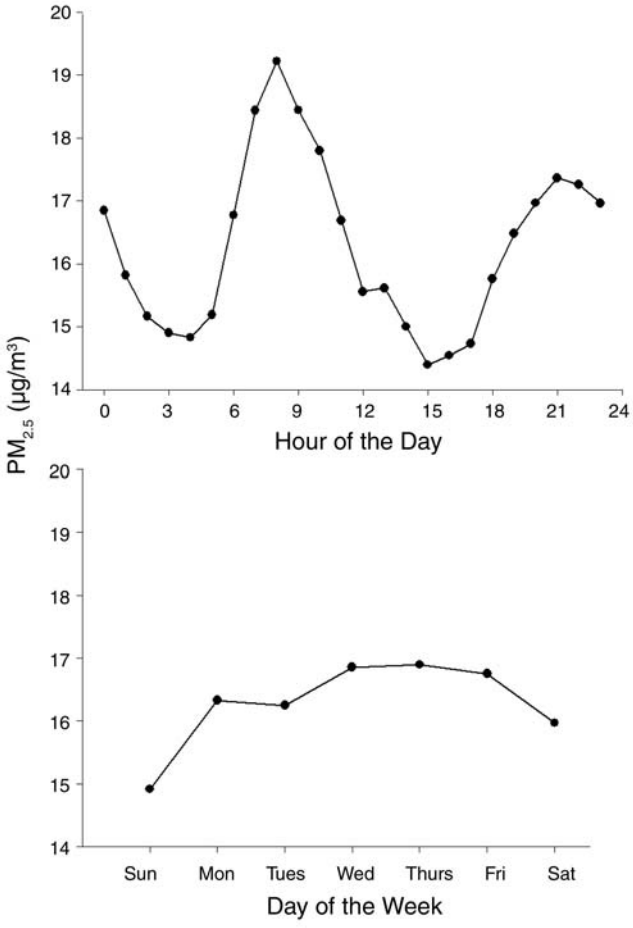

Figure 9. Circadian (upper panel) **and weekly** (lower panel) **variation of $PM_{2.5}$ at the HEI site.**

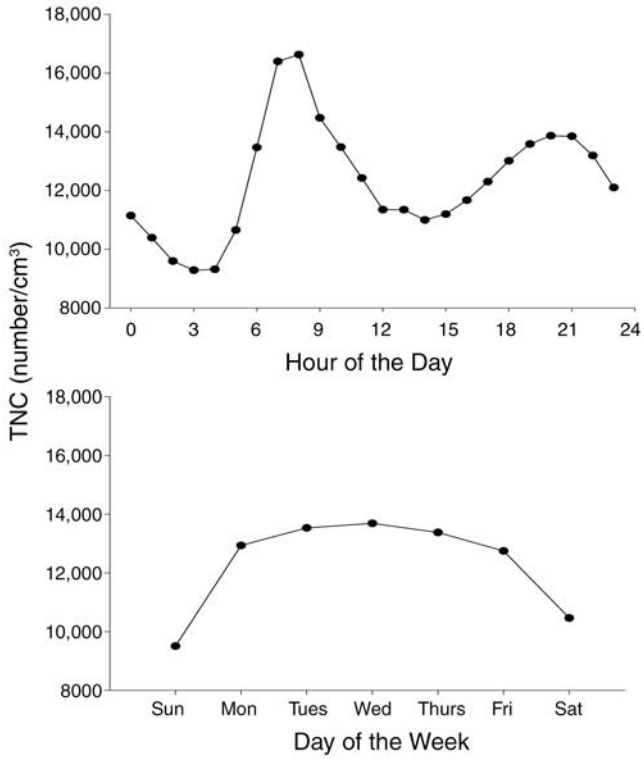

Figure 11. Circadian (upper panel) **and weekly** (lower panel) **variation of TNCs at the HEI site.**

values indicated a moderate climate with only occasional 24-hour averages below −10°C or above 25°C (Table 5). Moderate correlations were observed between the pollutants NO_2, CO, $PM_{2.5}$ and SO_2, both on a 1-hour and 24-hour averaged basis. NO_2, NO, and CO had the highest correlations with each other. The correlations between the gaseous pollutants and TNC were comparable to the correlations between the gaseous pollutants and $PM_{2.5}$ on a 24-hour basis and for the 1-hour averages (Tables 3 and 4). There was no correlation between O_3 and the other pollutants, but there was a positive correlation with temperature, which was also reflected in the seasonal variation as shown in Figure 12. Figure 13 shows the correlations for TNC and for $PM_{2.5}$ with the other pollutants separated by season. Whereas moderate correlations of TNC with the pollutants were present in the winter, in summer they were markedly reduced. The correlations between $PM_{2.5}$ and TSP or PM_{10} were unaffected by season. During summer, the correlations between $PM_{2.5}$ and the gaseous pollutants CO, NO_2, NO, and SO_2 were slightly weaker than in winter. $PM_{2.5}$ was inversely correlated with O_3 and temperature in the winter, but both showed a small positive correlation during the summer months.

Table 4. Spearman Correlation Coefficients for 1-Hour Averages of Pollutant Concentrations and Temperature

	$PM_{2.5}$	CO	NO_2	NO	SO_2	O_3	Temperature
TNC	0.42	0.53	0.68	0.50	0.53	−0.39	−0.31
$PM_{2.5}$		0.52	0.58	0.50	0.48	−0.35	−0.01
CO			0.71	0.64	0.51	−0.41	−0.29
NO_2				0.67	0.55	−0.42	−0.12
NO					0.45	−0.48	−0.12
SO_2						−0.24	−0.28
O_3							0.51

At the HEI site, duplicate measurements of TNC were performed with a second CPC during 1-week periods in winter 2000/2001. For the week of February 5–12, 2001, Figure 14 shows the parallel measurements from the HEI-site primary CPC and the second CPC device located nearby in a small shed adjacent to the garden walls (15 m away from the primary CPC container). The correlation between the two measurement devices was 0.99 (Spearman correlation coefficient).

Figure 15 (top panel) shows the parallel measurements of TNC at the HEI site and at Bourges-Platz for the week of December 11–18, 2000. The HEI site in the cloister garden was considered to be influenced by urban background; the

Table 5. Comparison of Gaseous Pollutant and Temperature Measurements at Two Sites[a]

	n	%	Mean	Minimum	25%	50%	75%	Maximum	IQR
Bourges-Platz									
1-Hour averages									
CO	21,005	95.8	0.51	0.10	0.25	0.40	0.60	8.30	0.35
NO_2	21,668	99.0	35.8	8.0	24.0	32.5	44.0	131.0	20.0
NO	21,668	99.0	17.7	1.0	3.5	8	19	468.5	15.5
SO_2	21,544	98.4	3.3	2.0	2.0	2.0	3.0	125.0	1.0
24-Hour averages									
CO	873	95.5	0.51	0.10	0.31	0.45	0.62	2.17	0.31
NO_2	900	98.7	35.8	13.6	27.6	34.4	42.0	79.5	14.4
NO	900	98.7	17.7	1.2	5.9	11.0	22.1	166.5	16.2
SO_2	896	98.2	3.3	2.0	2.0	2.4	3.5	23.2	1.5
Haunstetten and Landesamt für Umweltschutz									
1-Hour averages									
O_3	21,813	99.7	43.5	3.0	14.5	39.5	63.0	204.5	48.5
Temperature	21,817	99.7	10.8	−17.2	4.5	10.7	16.4	35.0	11.9
24-Hour averages									
O_3	909	99.7	43.5	3.0	27.1	43.7	59.3	117.9	32.2
Temperature	909	99.7	10.8	−12.7	4.8	10.9	17.0	27.3	12.1

[a] *n* = the total number of available measurements; % = the proportion of the total possible measurements. All gases are reported in µg/m^3 except for CO, which is given in mg/m^3. Temperatures are in °C.

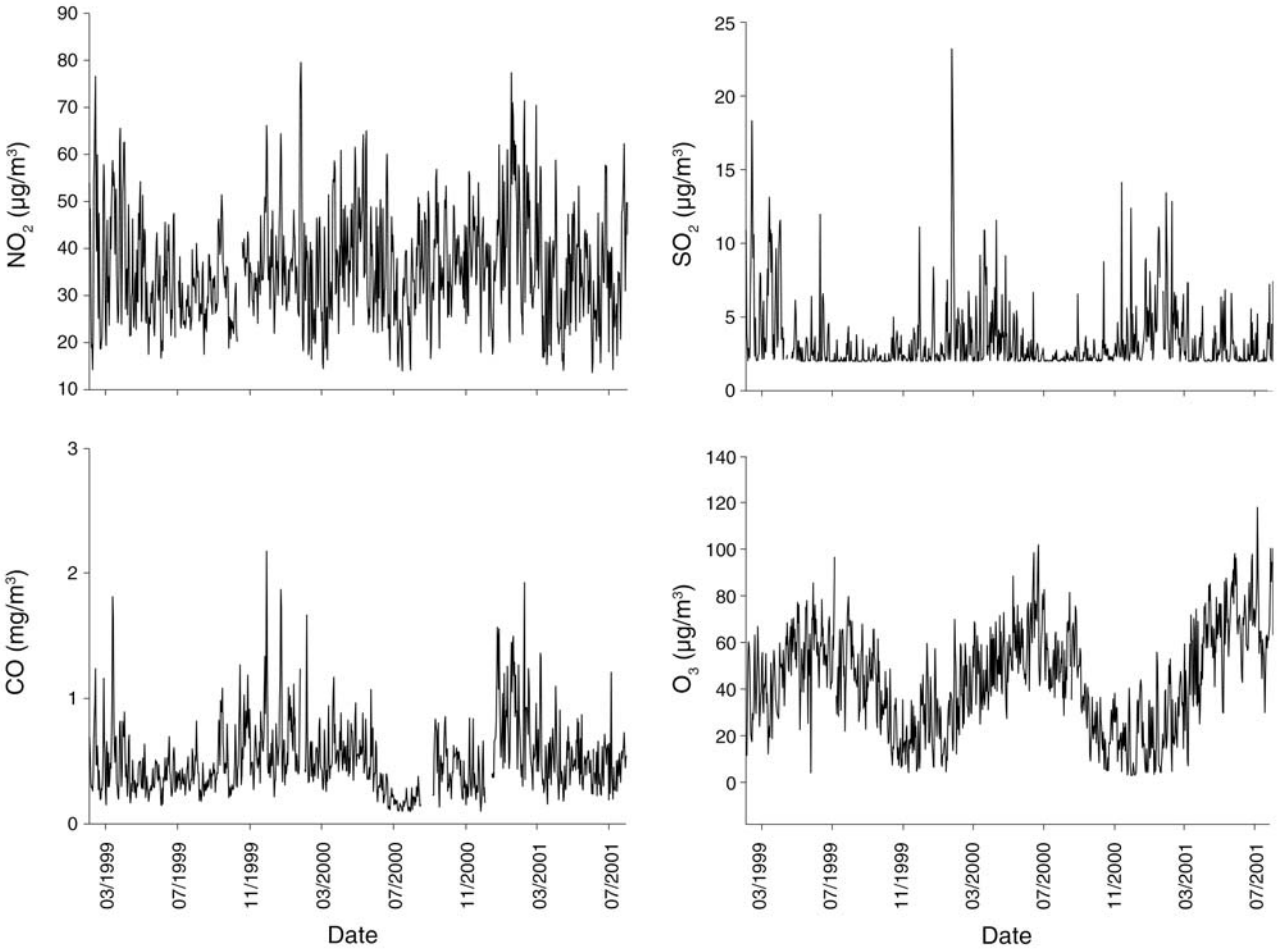

Figure 12. NO_2, CO, SO_2, and O_3 concentrations measured at Bourges-Platz.

station at Bourges-Platz was influenced by traffic. However, the uniformity of the time courses (Figure 15) and the strong correlation (r = 0.95) between the TNC measured at both sites (Table 6) suggest that, although the central HEI monitoring site was considered to measure background pollution, the patterns measured reflect quite well the traffic-related air pollution pattern in Augsburg. Nevertheless, the maximum values were lower at the HEI site than at Bourges-Platz; this was also reflected by the average TNC values at the HEI site (12,028/cm^3) and at Bourges-Platz (15,466/cm^3).

For the week of December 4–11, 2000, Figure 15 (bottom panel) shows the time courses of TNC measured at the HEI site and at Haunstetten (5 km south of the city center) along with the wind direction measured at Haunstetten.

Table 7 describes the correlations between different TNC measurements at the Haunstetten and HEI sites for the week of December 4–11, 2000. The correlations between the TNC measurements at Haunstetten and at the HEI site for this earlier week (Table 7) are weak compared with the correlation observed for the TNC measurements at the HEI site and at Bourges-Platz for the later week (December 11–18, 2000; Table 6).

The reason for these weaker correlations might be the pronounced change of the wind direction during the later week, as documented in the bottom panel of Figure 15. On December 8, the wind direction changed rapidly from northeast to southwest. From that time on, the wind was coming from a very busy main street located southwest from the measurement site at Haunstetten. Thus, higher TNC was measured at Haunstetten compared with TNC measured at the HEI site (Figure 15, bottom panel), which was much less influenced by the freshly generated ultrafine particles from mobile sources. After stratifying the measured data by wind direction, the Spearman correlation coefficients for the relation between TNC (HEI site) and TNC (Haunstetten) increased from 0.69 (Table 7) to 0.85 for wind directions from the northeast, and from 0.65

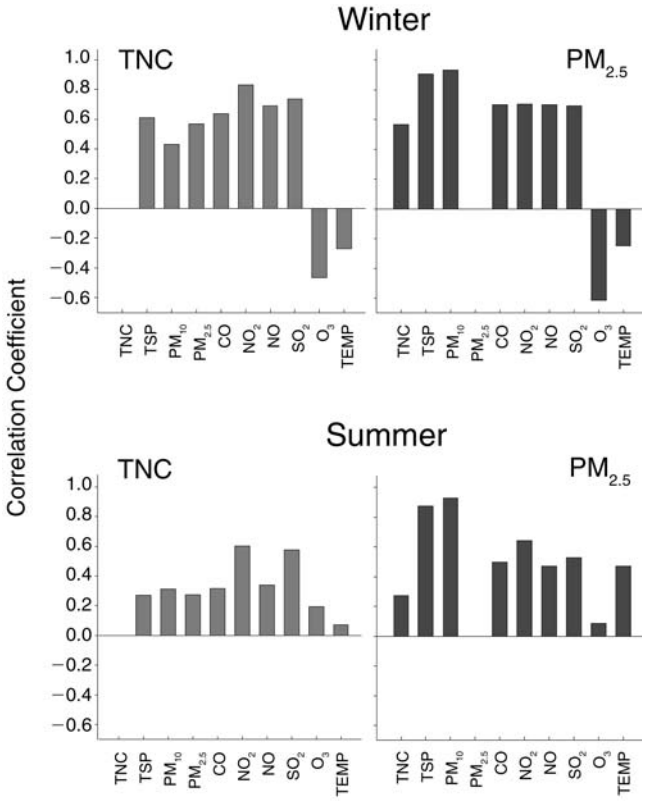

Figure 13. Spearman correlation coefficients for TNC (left panels) **or $PM_{2.5}$** (right panels) **compared with air pollutant concentrations or temperature by season.**

to 0.75 for wind directions from the southwest. The corresponding TNC were: (1) for northeastern winds: 17,759/cm^3 at the HEI site and 14,384/cm^3 at Haunstetten; and (2) for southwestern winds: 14,530/cm^3 at the HEI site and 21,912/cm^3 at Haunstetten. The results indicate a spatial variability particularly dependent on the wind direction, but over time a substantial correlation within the study area as well.

Tables 6 and 7 also show correlations between TNC and gaseous pollutant concentrations. NO and NO_2 measured at Bourges-Platz were highly correlated with TNC measured both at the HEI site and at Bourges-Platz during the week of December 11–18. Surprisingly, SO_2 measured at Bourges-Platz showed the strongest correlation with TNC measured at the HEI site; and SO_2 measured at Haunstetten showed the strongest correlation with TNC also measured at Haunstetten for the earlier week (December 4–10).

DESCRIPTIONS OF SUBJECTS AND SUBGROUPS

Altogether, 906 patients who had survived more than 24 hours after they were hospitalized for MI were interviewed by nurses for the Coronary Event Registry Augsburg between February 1999 and July 2001; all patients had had an MI as defined by the computer algorithm used in the MONICA project. Reasons for not interviewing included (1) a patient refused to participate, (2) the patient died before the interview, (3) other medical reasons that precluded an

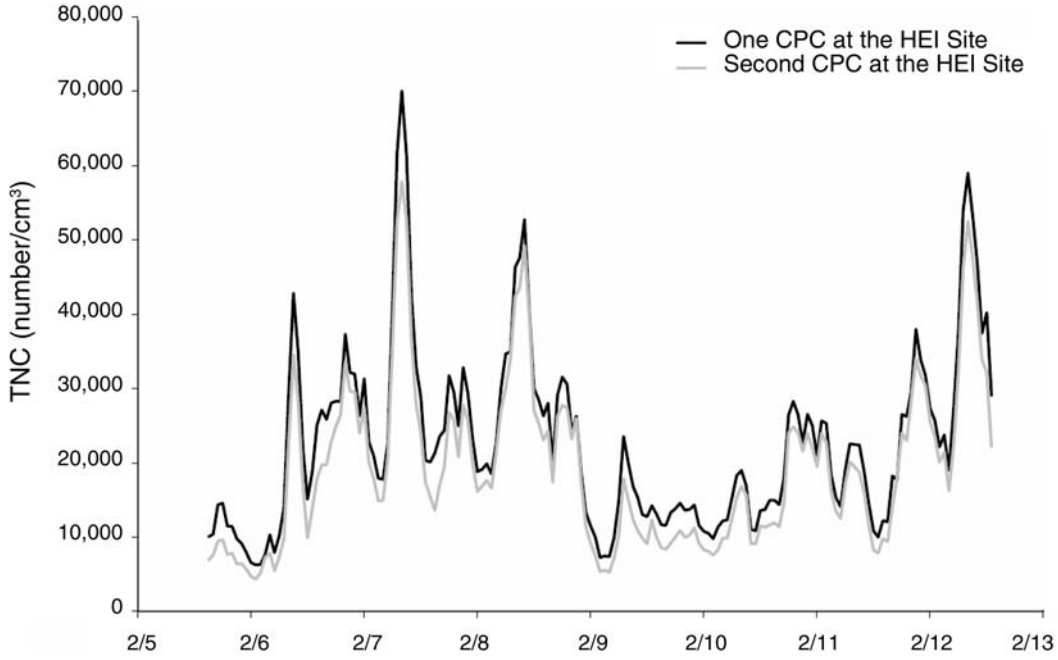

Figure 14. Comparison of TNC measurements from two CPCs within the cloister garden at the HEI site in February 2001.

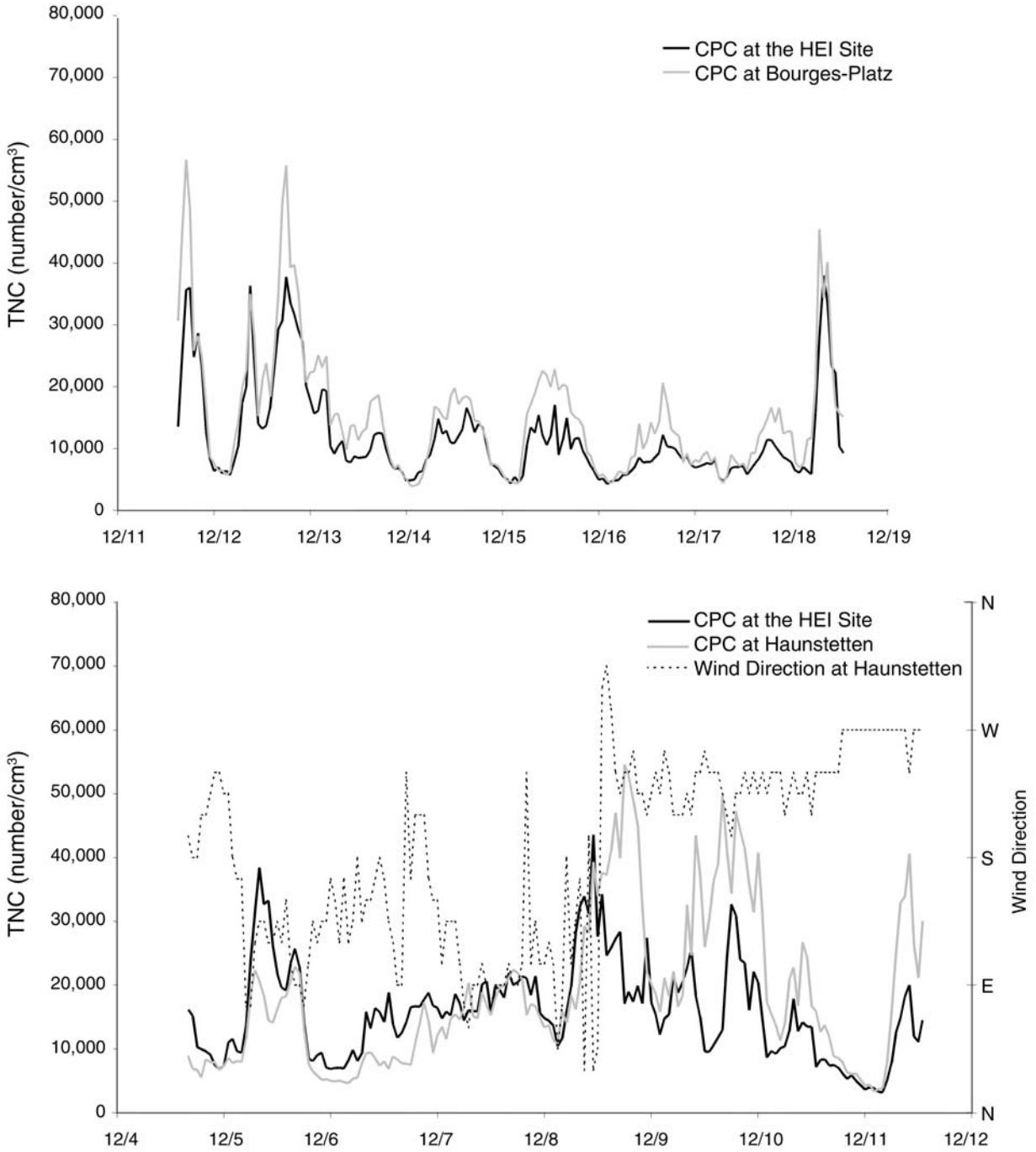

Figure 15. Comparison of TNC measurements from three CPCs in December 2000. Top panel: one at the HEI site and the other at Bourges-Platz; bottom panel: one at the HEI site and the other at Haunstetten (this panel also shows the effects of wind direction at Haunstetten). Note that measurements in each panel span different sets of dates.

interview, (4) the patient was transferred to another hospital, and (5) the patient was discharged before an interview could take place. For at least 50% of the subjects, the interview was conducted 9 or fewer days after the MI.

Of the 906 MI patients who were interviewed, for 851 (94%) the time of MI onset was validated as required for the HEI study (Figure 16). The primary analyses of the association between ambient air pollution concentrations and MI onset were based on this group of 851 subjects. Of these, 740 (87%) agreed to continue with the HEI diary questionnaire at the end of the Coronary Event Registry's interview and provided information for at least 1 day out of 4. The reasons 111 subjects did not participate at this stage included language problems, only a vague memory of all events associated with the MI, and refusal to proceed.

Of the 740 subjects who had a known time of onset and had provided diary information, when we later analyzed subject-specific information about possible triggers of MI we excluded 49 subjects (7%) because the information for either the selected case period or control period or both was incomplete; this left 691 subjects with a verified time of MI onset and diary data that could be matched for case

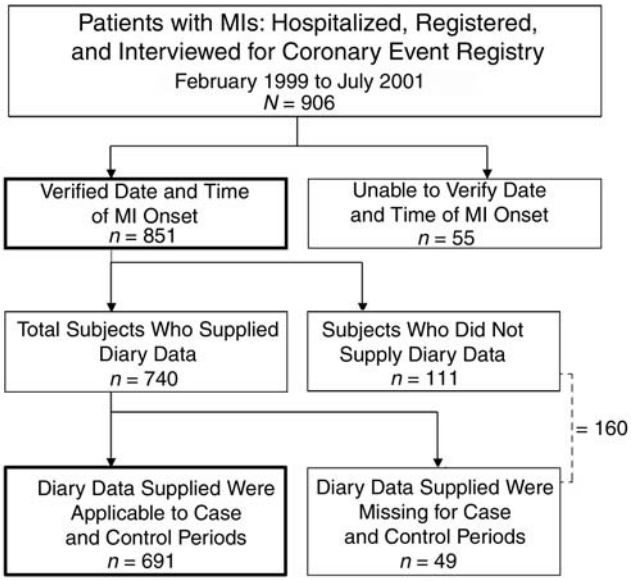

Figure 16. Graphic presentation of the study population and inclusion and exclusion criteria for certain types of analyses. The total population was 906 patients who (a) were hospitalized for an MI and registered with the Coronary Event Registry with a diagnosis of MI based on MONICA criteria; (b) completed the Registry's questionnaire; (c) were recruited for the study; and (d) survived the first 24 hours in a hospital. (The characteristics of these 906 patients are compared by subgroups in Table 8.) The 851 subjects for whom the date and time of MI onset could be verified formed the basis for analyses relating air pollution and MI onset. Of the 740 subjects who supplied some diary data, the data for 691 subjects were applicable to both case and control periods. This group formed the basis for analyses relating air pollution and subject-specific triggers.

Table 6. Spearman Correlation Coefficients for 1-Hour Averages of TNC Measured at the HEI and Bourges-Platz Sites and Gaseous Pollutants Measured at Bourges-Platz, December 11–18, 2000[a]

	Bourges-Platz				
	TNC	NO	NO_2	CO	SO_2
TNC at HEI	0.95	0.80	0.93	0.40	0.59
TNC at Bourges-Platz		0.89	0.95	0.38	0.61
NO at Bourges-Platz			0.81	0.30	0.64
NO_2 at Bourges-Platz				0.53	0.60
CO at Bourges-Platz					0.26

[a] n = 167, except for correlations with CO, for which n = 93.

Table 7. Spearman Correlation Coefficients for 1-Hour Averages of TNC and Gaseous Pollutants Measured at the HEI, Haunstetten, and Bourges-Platz Sites, December 4–11, 2000[a]

	Haunstetten	Bourges-Platz			Haunstetten
	TNC	NO	NO_2	SO_2	SO_2
TNC at HEI	0.69	0.62	0.56	0.78	0.64
TNC at Haunstetten		0.15	0.24	0.57	0.73
NO at Bourges-Platz			0.58	0.63	0.31
NO_2 at Bourges-Platz				0.44	0.30
SO_2 at Bourges-Platz					0.57

[a] n = 166.

and control periods. These 691 subjects were used for the analyses of air pollution and possible triggers of MI.

Table 8 describes the characteristics of: (1) the total possible study population (all 906 MI patients who had a Registry interview); (2) the patients without (55) and with (851) validated information for the time of MI onset; and (3) those subjects with verified time of MI onset and without (160) and with (691) diary data. Only the statistical tests to compare subjects' characteristics by subgroups used all 906 patients who had been interviewed for the Coronary Event Registry. For these analyses, the 906 patients were divided into three subgroups: 55 patients who had a Registry interview but for whom the time of MI onset was unknown; 160 subjects for whom the time of MI onset was known, but who either (a) provided no diary data, or (b) supplied diary data that were not applicable to selected case or control periods during data analysis; and 691 subjects with known time of MI onset and complete diary data applicable to both case and control periods (Table 8 and Figure 16).

Table 8. Description of Subjects with Confirmed MIs Recruited from the Augsburg Coronary Event Registry[a]

	Interviewed Subjects (N = 906)		Subjects Without a Known Time of MI Onset (n = 55)		Subjects with a Known Time of MI Onset (n = 851)		Subjects with a Known Time of MI Onset and Incomplete Diary Data[b] (n = 160)		Subjects with a Known Time of MI Onset and Complete Diary Data[c] (n = 691)		
Characteristic	n	%	n	%	n	%	n	%	n	%	P Value[d]
Age (years)—Mean	60		61		60		62		60		0.045[e]
25–34	7	1	—	—	7	1	1	0	6	1	0.22[f]
35–44	64	7	1	2	63	7	5	3	58	8	
45–54	184	20	12	22	172	20	31	19	141	20	
55–64	292	32	19	35	273	32	49	31	224	32	
65–74	359	40	23	42	336	39	74	46	262	38	
Male	704	78	45	82	659	77	127	79	532	77	0.61[f]
German	857	95	52	95	805	95	149	93	656	95	0.61[g]
Occupational status											
Blue-collar worker	391	43	24	44	367	43	77	48	290	42	0. 22[f]
White-collar worker	304	34	15	27	289	34	39	24	250	36	
Civil servant	58	6	5	9	53	6	13	8	40	6	
Self-employed	111	12	8	15	103	12	24	15	79	11	
Other	42	5	3	5	39	5	7	4	32	5	
Education[h]											
Low education	687	76	38	69	649	76	117	73	532	77	0.37[f]
High education	182	20	13	24	169	20	37	23	132	19	

Table continues next page

[a] n = number of subjects in each category; % = the proportion of the number of subjects given at the top of each pair of columns.

[b] Of the 851 subjects with a known time of onset, this group of 160 either did not provide diary data or the available data were not applicable to selected case and control periods.

[c] A total of 740 subjects provided diary data; however, the data from only 691 of those were applicable to selected case and control periods.

[d] The tests were conducted based on three different subgroups: 55 subjects without a known time of MI onset; 160 subjects with a known time of MI onset and either incomplete or no diary data; and 691 subjects with a known time of MI onset and complete diary data applicable to case and control periods.

[e] Tukey test.

[f] Chi-square test.

[g] Exact Fisher test.

[h] Low = 8 to 11 years; high = more than 11 years.

[i] Wilcoxon test.

The group of 691 subjects with complete diary data (Table 8) was compared with two other groups: (a) the 55 patients without a known time of MI onset (this group was included only in this set of analyses and excluded thereafter); and (b) the 160 subjects with a known time of MI onset and either incomplete or no diary data. When compared with the group of 691 subjects, the other two groups (1) were older; (2) had a smaller percentage of subjects with typical symptoms; (3) before MI onset, had more conditions associated with cardiovascular disease; (4) were more

Table 8 (*continued*). Description of Subjects with Confirmed MIs Recruited from the Augsburg Coronary Event Registry[a]

	Interviewed Subjects (N = 906)		Subjects Without a Known Time of MI Onset (n = 55)		Subjects with a Known Time of MI Onset (n = 851)		Subjects with a Known Time of MI Onset and Incomplete Diary Data[b] (n = 160)		Subjects with a Known Time of MI Onset and Complete Diary Data[c] (n = 691)		
Characteristic	n	%	n	%	n	%	n	%	n	%	P Value[d]
First MI	766	85	46	84	720	85	125	78	595	86	0.11[g]
Survival ≥ 28 days	901	99	54	98	847	100	160	100	687	99	0.30[g]
MI diagnosis											
Definite	775	86	51	93	724	85	131	82	593	86	0.26[g]
Possible	128	14	4	7	124	15	28	18	96	14	
Cardiac arrest	3	0	—	—	3	0	1	1	2	0	
Symptoms of MI											
Typical	838	92	46	84	792	93	145	91	647	94	0.0078[g]
Atypical	37	4	2	4	35	4	8	5	27	4	
Other	31	3	7	13	24	3	7	4	17	2	
Conditions associated with cardiovascular disease before MI onset											
Angina pectoris	232	26	13	24	219	26	56	35	163	24	0.011[f]
Hypertension	622	69	40	73	582	68	125	78	457	66	0.010[f]
Diabetes mellitus	212	23	16	29	196	23	53	33	143	21	0.0022[f]
None of these	202	22	11	20	191	22	18	11	173	25	0.0007[f]
Smoking status											
Smoker	299	33	15	27	284	33	36	23	248	36	0.011[f]
Exsmoker	294	32	21	38	273	32	65	41	208	30	
Never-smoker	313	35	19	35	294	35	59	37	235	34	
Hospitals											
Central Hospital	723	80	49	89	674	79	115	72	559	81	0.0078[f]
Other	183	20	6	11	177	21	45	28	132	19	
Days between MI onset and interview—Median											
	9		12		9		10		9		<0.0001[i]

[a] n = number of subjects in each category; % = the proportion of the number of subjects given at the top of each pair of columns.

[b] Of the 851 subjects with a known time of onset, this group of 160 either did not provide diary data or the available data were not applicable to selected case and control periods.

[c] A total of 740 subjects provided diary data; however, the data from only 691 of those were applicable to selected case and control periods.

[d] The tests were conducted based on three different subgroups: 55 subjects without a known time of MI onset; 160 subjects with a known time of MI onset and either incomplete or no diary data; and 691 subjects with a known time of MI onset and complete diary data applicable to case and control periods.

[e] Tukey test.

[f] Chi-square test.

[g] Exact Fisher test.

[h] Low = 8 to 11 years; high = more than 11 years.

[i] Wilcoxon test.

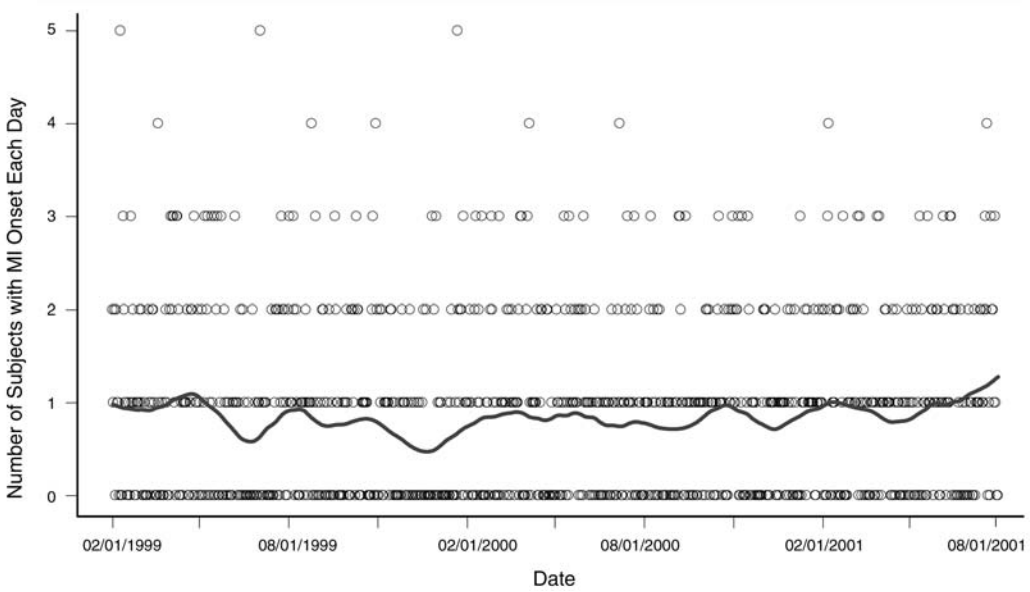

Figure 17. Out of 851 subjects who had a known time of MI onset, the number of subjects who experienced MI onset on each day from February 1, 1999 to July 31, 2001. Nonparametric function (curve showing LOESS with span of 0.1) did not identify seasonal variation or an overall trend.

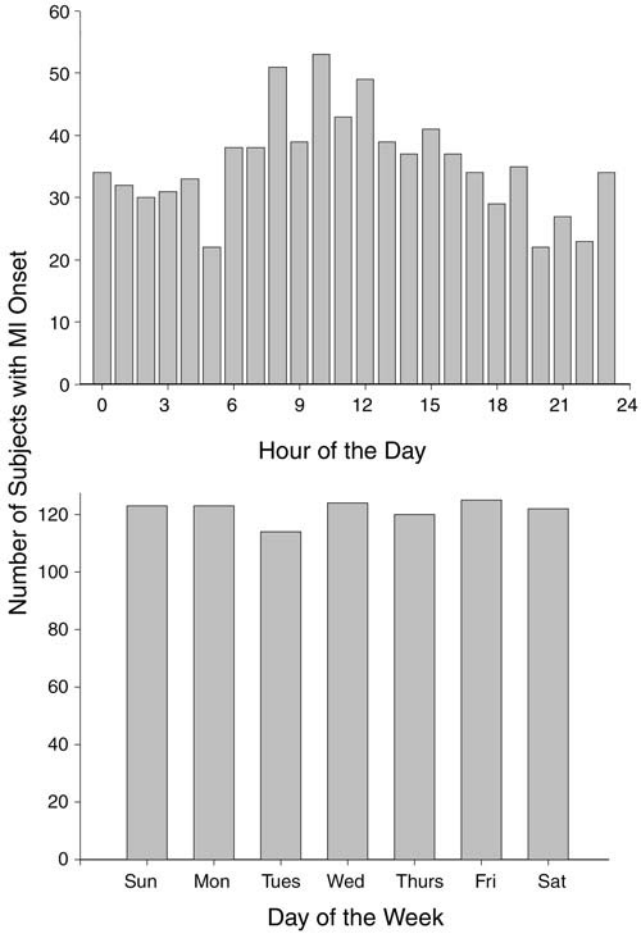

Figure 18. Circadian (upper panel) **and weekly** (lower panel) **variation of MI onset for 851 subjects who had a known time of onset.**

often treated in other hospitals than in the Central Hospital; and (5) the time between MI onset and interview was longer. Among these three groups of interviewed subjects, there were no differences in gender, occupational status distribution, frequency of a first MI, and 28-day survival.

(The medical record abstraction of the patients who were not interviewed by the Coronary Event Registry within the HEI study period is still ongoing; therefore, no final estimates of the proportion of patients not interviewed can be given to date. In 1999, 78% of all hospitalized patients had been interviewed.)

Figure 17 illustrates the time series of MI onset for each day over the study period for the 851 subjects with known date and hour of MI onset. On average, data were gathered for 0.94 subjects per day, ranging from 0 to 5 subjects each day. No trend in the number of subjects each day and no seasonal pattern were observed (Figure 17). Figure 18 shows the number of MIs for each hour of the day and day of the week for the same group of 851 subjects. For the hour of day, 32% of the MIs occurred between 6:00 AM and noon (hours 6 and 12); 28% between noon and 6:00 PM (hours 12 and 18); only 20% occurred between midnight and 6:00 AM (hours 0 and 6) and between 6:00 PM and midnight (hours 18 and 24). The highest numbers of MIs occurred on Wednesdays and Fridays, but the differences among days of the week were not statistically significant.

Figure 19 shows the subject distribution within the study area. Of 740 subjects with diary information, 302 MI events (41%) occurred within the City of Augsburg, 92 MI events (12%) in County Aichach-Friedberg, 228 MI events (31%)

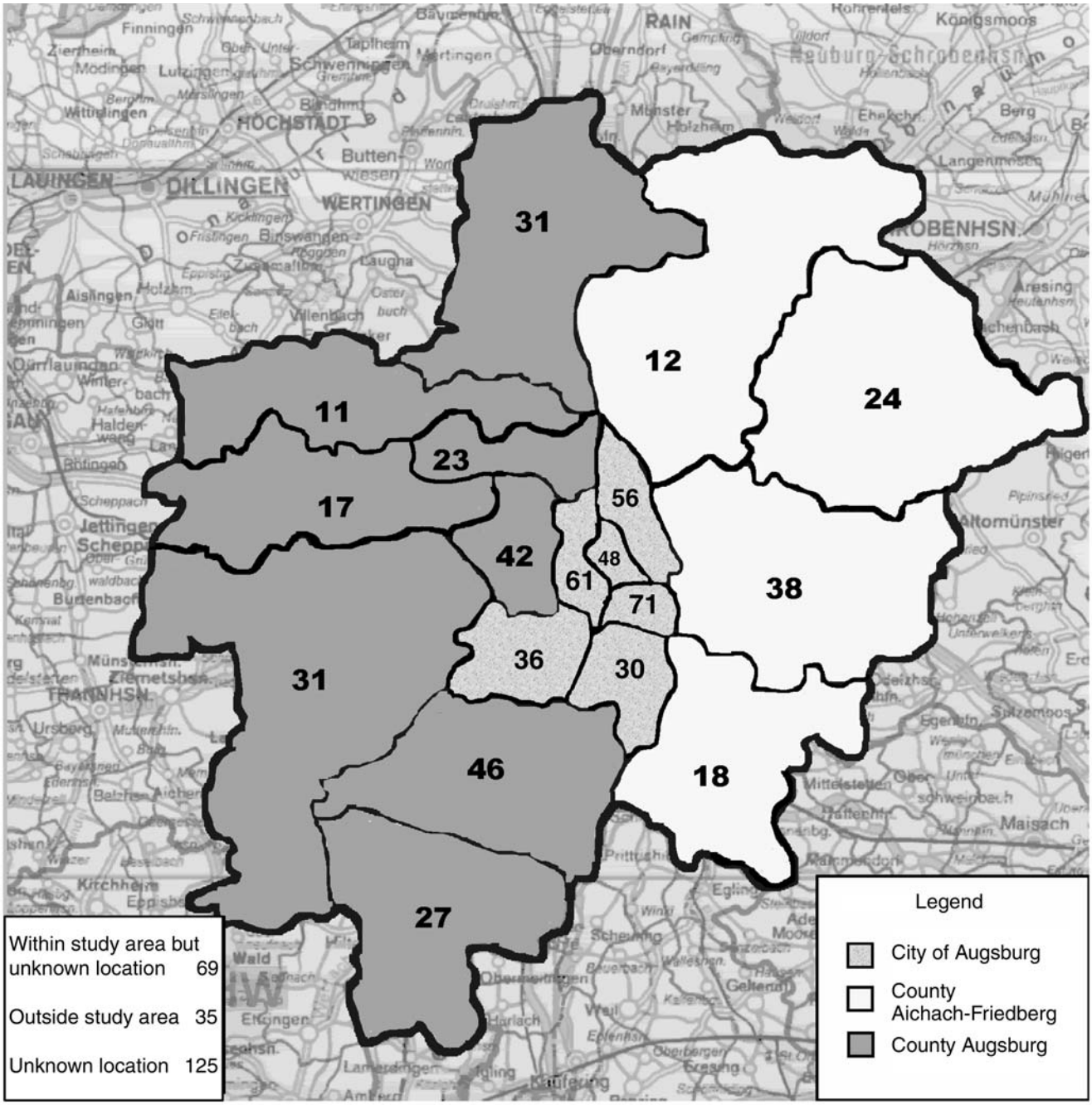

Figure 19. Distribution of the locations within the study area of 851 subjects at the onset of their MI symptoms. The number of subjects in each sector is shown; additional subjects with unknown locations or locations outside the study area are summarized in the lower left block.

in County Augsburg, 69 MI events (9%) were within the study area but with unknown location, 35 MI events (5%) were outside the study area, and 14 MI events (2%) did not have location information. The smallest number of MI events was recorded in the western areas adjacent to the highway in the County Augsburg, and in the northeast and the southeast of the County Aichach-Friedberg.

AIR POLLUTION AND MI ONSET

The analyses of the association between air pollution and MI onset were conducted for the 851 interviewed subjects who had survived 24 hours and had valid information on time and date of MI onset. The results of the primary analyses addressing specific aim 1 and 2 are shown in Table 9. We used a unidirectional control sampling process

spaced 24 hours apart to control for circadian variation. Case periods were defined as 1-hour average concentrations of particles either concurrently or up to 6 hours before the symptom onset. Control periods were selected 24, 48, and 72 hours earlier. No association between the hourly concentrations of $PM_{2.5}$ or TNC and MI onset was observed.

For 24-hour averages, a positive association was observed for 2-day-lagged $PM_{2.5}$ concentrations and MI onset. In addition, the relative risk of MI increased by 13% in association with TNC lagged 3 days. Here again, three unidirectional control periods were selected 24, 48, and 72 hours earlier.

To estimate the latency period directly, spline functions were used to model the associations between particle exposures and the relative risk of MI onset. The case period was always the hourly exposure profile from 1 to 96 hours prior to the event. Three different approaches were selected for 96-hour control periods:

1. three control periods per case period lagged 4 days (unidirectional design),
2. three or four control periods per case period stratified by month (bidirectional design), and
3. three control periods stratified by 4-week periods (bidirectional design).

The linear spline model with one interior knot made evident that $PM_{2.5}$ concentrations contributed differently to the relative risk of an MI onset at different times within the 96-hour period preceding the event (Figure 20). This model produced the best model fit, and the estimated location of the interior knot in this model can be interpreted as the estimated induction time (Table 10). The estimate was 82 hours with a 95% CI covering 24 to 95 hours. There was some evidence that the more flexible cubic spline with no interior knot also fitted the data well (Table 10). The visual inspection of the cubic spline curves suggested a shorter induction time of 48 to 72 hours (Figure 20). More flexible models such as quadratic or cubic splines with one interior knot did not result in a better fit. For $PM_{2.5}$, the induction time patterns observed were very similar for the two bidirectional control period selections (Table 10). In addition, the results were generally very similar for the unidirectional control period selection.

Table 9. Effect Estimates of $PM_{2.5}$ or TNC Obtained from Univariate Case–Crossover Analyses for 851 Subjects with Known Time of MI Onset[a]

	$PM_{2.5}$			TNC		
	Odds Ratio	95% CI	*P* Value	Odds Ratio	95% CI	*P* Value
1-Hour averages[b]						
Concurrent	0.98	0.88 , 1.10	0.79	1.01	0.91 , 1.13	0.81
1-Hour lag	0.97	0.87 , 1.09	0.62	0.99	0.88 , 1.11	0.84
2-Hour lag	0.93	0.83 , 1.04	0.21	0.95	0.84 , 1.06	0.35
3-Hour lag	0.98	0.88 , 1.09	0.72	1.01	0.90 , 1.13	0.83
4-Hour lag	0.96	0.86 , 1.07	0.48	1.03	0.93 , 1.15	0.54
5-Hour lag	0.94	0.84 , 1.05	0.26	1.00	0.89 , 1.13	0.96
6-Hour lag	0.90	0.80 , 1.01	0.064	0.93	0.82 , 1.05	0.23
24-Hour averages[c]						
Same day	0.95	0.83 , 1.08	0.42	0.99	0.85 , 1.14	0.84
1-Day lag	1.10	0.96 , 1.25	0.17	1.00	0.86 , 1.16	0.97
2-Day lag	1.18	1.03 , 1.34	0.014	1.04	0.90 , 1.20	0.58
3-Day lag	1.07	0.94 , 1.22	0.30	1.13	0.98 , 1.31	0.10
4-Day lag	0.94	0.83 , 1.07	0.38	1.00	0.86 , 1.16	0.97
5-Day lag	0.90	0.79 , 1.02	0.099	0.94	0.81 , 1.09	0.39

[a] Control-selection method: unidirectional with three control periods.

[b] Estimates and CIs calculated for one IQR: 1-hour average 9.1 $\mu g/m^3$ $PM_{2.5}$ and 7800/cm^3 TNC.

[c] Estimates and CIs calculated for one IQR: 24-hour average 7.7 $\mu g/m^3$ $PM_{2.5}$ and 6400/cm^3 TNC.

For TNC, there was no evidence that the relative risk of MI onset differed for exposures at different times during the 96-hour period prior to MI onset (Table 10).

Based on these results, the data for 2-day-lagged $PM_{2.5}$ concentrations and MI onset were calculated using different control period selections and Poisson regression analyses (Figure 21). The observed associations were halved when bidirectional control period selections were applied compared to the unidirectional design. Results were slightly higher when 16 control periods before and after the event had been considered, instead of only 4 control periods (Figure 5). The smallest estimates were observed when

Table 10. Analysis of Deviance Comparing Induction Time Models of $PM_{2.5}$ or TNC for 851 Subjects with Known Time of MI Onset

	$PM_{2.5}$				TNC			
	At Number of Hours	Model		Likelihood Ratio[a]	At Number of Hours	Model		Likelihood Ratio[a]
Model		*df*	Deviance	*P* Value		*df*	Deviance	*P* Value
Three Control Periods per Case Period Lagged 4 Days								
4-Day average exposure model		1	2238.1	—		1	1689.2	—
Linear spline								
One interior knot[b,c]	82	4	2230.9	0.064	95	4	1683.8	0.15
Quadratic spline								
No interior knot		3	2233.4	0.091		3	1688.0	0.54
One interior knot[b]	78	5	2231.4	0.151	95	5	1683.5	0.22
Cubic spline								
No interior knot		4	2232.8	0.15		4	1688.0	0.73
One interior knot[b]	71	6	2231.3	0.23	95	6	1682.7	0.25
Three to Four Control Periods per Case Period Stratified by Month								
4-Day average exposure model		1	2391.6	—		1	1794.1	—
Linear spline								
One interior knot[b,d]	82	4	2381.6	0.018	95	4	1791.3	0.42
Quadratic spline								
No interior knot		3	2386.3	0.068		3	1793.4	0.68
One interior knot[b]	77	5	2382.4	0.055	83	5	1788.5	0.23
Cubic spline								
No interior knot		4	2383.2	0.038		4	1790.8	0.34
One interior knot[b]	73	6	2382.5	0.104	81	6	1788.6	0.35
Three Control Periods per Case Period Stratified by 4-Week Periods								
4-Day average exposure model		1	2253.3	—		1	1703.5	—
Linear spline								
One interior knot[b,e]	83	4	2242.9	0.016	17	4	1699.4	0.25
Quadratic spline								
No interior knot		3	2248.3	0.085		3	1702.2	0.53
One interior knot[b]	78	5	2243.6	0.046	29	5	1697.2	0.18
Cubic spline								
No interior knot		4	2244.4	0.031		4	1698.0	0.14
One interior knot[b]	74	6	2243.7	0.087	95	6	1696.5	0.22

[a] Compared with the 4-day-average exposure model.

[b] Location of knot based on profile likelihood search, estimation of knot location included in degrees of freedom.

[c] Estimated knot location can be interpreted as estimated induction time with 95% CI: 24–95 hours for $PM_{2.5}$; 77–95 hours for TNC.

[d] Estimated knot location can be interpreted as estimated induction time with 95% CI: 57–89 hours for $PM_{2.5}$; 2–95 hours for TNC.

[e] Estimated knot location can be interpreted as estimated induction time with 95% CI: 67–89 hours for $PM_{2.5}$; 2–95 hours for TNC.

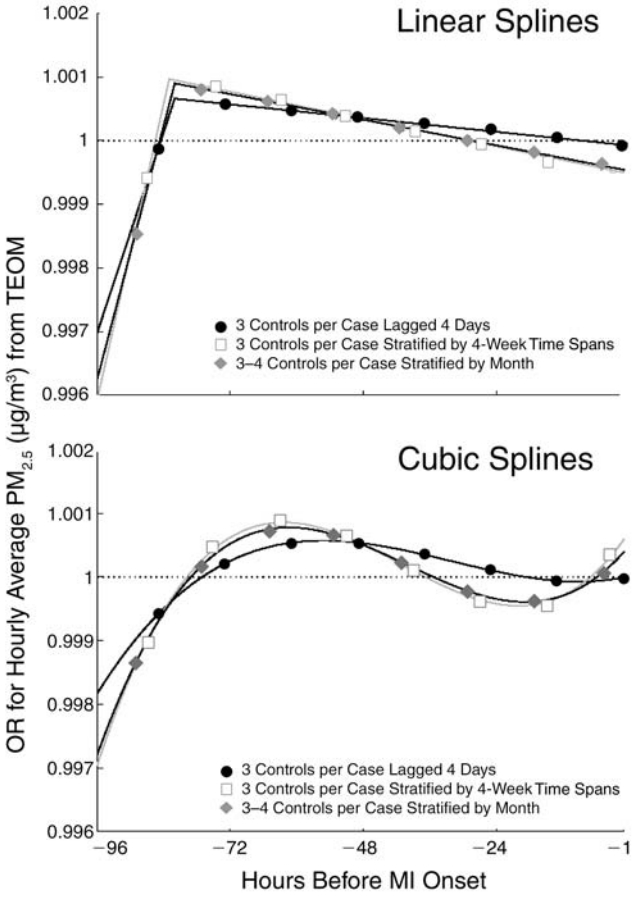

Figure 20. Linear splines with one interior knot (upper panel) **and cubic splines with no interior knot** (lower panel) **for determining the induction time between $PM_{2.5}$ exposure and MI onset for 851 subjects who had a known time of MI onset, comparing data analyzed with different selections of control periods.** $PM_{2.5}$ was measured using a TEOM. Case = case period; control = control period.

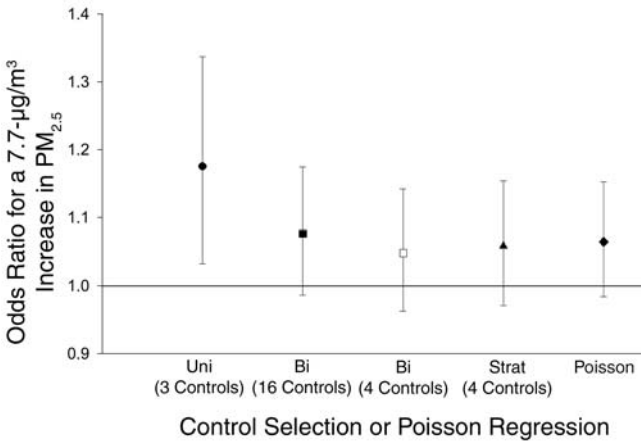

Figure 21. Comparison of the effect estimates per 7.7-µg/m^3 increase in 24-hour average $PM_{2.5}$ lagged 2 days and MI onset for 851 subjects who had a known time of onset; obtained from case–crossover analyses with different selections of control periods (unidirectional, bidirectional, and stratified) **and from Poisson regression analyses.**

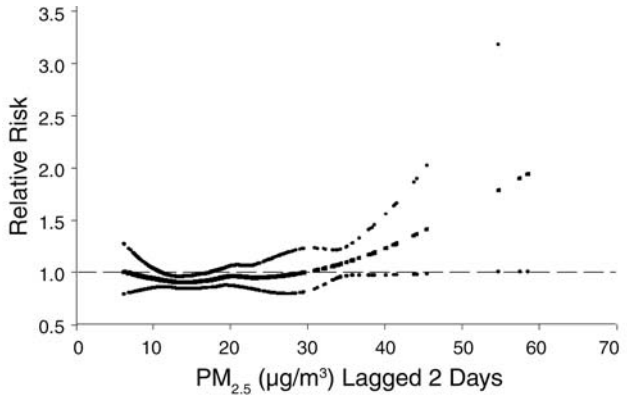

Figure 22. Nonparametric function (LOESS with span of 0.8) for the dose–response curve (center) **between 24-hour average $PM_{2.5}$ concentrations lagged 2 days and MI onset for 851 subjects who had a known time of onset.** Upper and lower curves describe the 95% CI.

control periods were selected on the same day of the week within the same month. Poisson regression analyses gave similar results as for the bidirectional approaches.

Table 11 compares the results from the bidirectional case–crossover analyses and the Poisson regression analyses for particulate air pollution. Confounder selection for the Poisson regression analyses indicated that trend, season, and weather had only weak associations with MI onset. The final model consisted of a P-spline for trend with approximately 2 *df*, a P-spline for 24-hour average temperature with approximately 4 *df* and a linear term for air pressure and day-of-the-week indicators. The case–crossover analyses were rather robust against confounding by time-varying factors. Therefore, the results are presented for the univariate analyses in Table 11. (Sensitivity analyses are provided later in this section.) Both methods suggested a weak association between $PM_{2.5}$ lagged 1 day or 2 days and MI onset. A 5-day mean moving average was positive but had a large confidence interval (Table 11). Figure 22 shows a nonparametric function of the association between $PM_{2.5}$ lagged 2 days and MI onset (LOESS with a span of 0.8) in the Poisson regression model. It indicated that, in particular, $PM_{2.5}$ concentrations above 30 µg/m^3 were associated with MI onset. The estimation of the relative risk for decile increases in $PM_{2.5}$ in case–crossover analyses showed results consistent with those of the LOESS function.

Moving averages for 15, 30, and 45 days were calculated and used as exposure variables in Poisson regression analyses. They suggested that there might be an association with longer cumulative exposure. The largest effect estimates were observed for 30-day moving averages of $PM_{2.5}$

Table 11. Effect Estimates of 24-Hour Averages of $PM_{2.5}$, TNC, or PM_{10} on Relative Risk of MI Obtained from Univariate Case–Crossover or Multivariate Time-Series Analyses for 851 Subjects with Known Time of MI Onset

		Case–Crossover[a]		Time-Series[b]	
	IQR[c]	Odds Ratio	95% CI	Relative Risk	95% CI
$PM_{2.5}$					
Same day	7.7	1.03	0.94 , 1.12	0.97	0.89 , 1.07
1-Day lag	7.7	1.07	0.98 , 1.16	1.04	0.96 , 1.13
2-Day lag	7.7	1.08	0.99 , 1.17	1.07	0.98 , 1.15
3-Day lag	7.7	1.01	0.92 , 1.10	1.03	0.95 , 1.11
4-Day lag	7.7	0.96	0.88 , 1.04	0.98	0.90 , 1.07
5-Day lag	7.7	0.93	0.85 , 1.02	0.98	0.90 , 1.06
5-Day mean (lag 0–4 days)	5.8	1.03	0.94 , 1.14	1.03	0.94 , 1.12
15-Day mean (lag 0–14 days)	4.0			1.03	0.95 , 1.13
30-Day mean (lag 0–29 days)	2.7			1.09	1.01 , 1.18
45-Day mean (lag 0–44 days)	2.1			1.08	1.00 , 1.17
TNC					
Same day	6500	1.01	0.90 , 1.13	1.04	0.93 , 1.16
1-Day lag	6500	0.97	0.87 , 1.08	0.95	0.86 , 1.05
2-Day lag	6500	1.02	0.91 , 1.14	0.99	0.89 , 1.09
3-Day lag	6500	1.05	0.94 , 1.17	1.02	0.92 , 1.13
4-Day lag	6500	0.98	0.88 , 1.10	0.98	0.88 , 1.09
5-Day lag	6500	0.97	0.87 , 1.09	0.99	0.89 , 1.10
5-Day mean (lag 0–4 days)	5500	1.01	0.86 , 1.20	0.97	0.86 , 1.10
15-Day mean (lag 0–14 days)	5000			1.00	0.88 , 1.14
30-Day mean (lag 0–29 days)	5000			1.07	0.92 , 1.25
45-Day mean (lag 0–44 days)	4500			1.06	0.92 , 1.23
PM_{10}[d]					
Same day	18	1.03	0.94 , 1.12	0.99	0.91 , 1.08
1-Day lag	18	1.07	0.98 , 1.16	1.02	0.94 , 1.11
2-Day lag	18	1.09	1.00 , 1.18	1.01	0.94 , 1.10
3-Day lag	18	1.04	0.95 , 1.13	1.04	0.96 , 1.13
4-Day lag	18	0.99	0.91 , 1.08	1.00	0.92 , 1.08
5-Day lag	18	0.96	0.88 , 1.05	0.99	0.91 , 1.07
5-Day mean (lag 0–4 days)	15	1.08	0.97 , 1.19	1.02	0.93 , 1.12
15-Day mean (lag 0–14 days)	10			0.99	0.90 , 1.09
30-Day mean (lag 0–29 days)	8			1.13	1.01 , 1.25
45-Day mean (lag 0–44 days)	7			1.12	1.00 , 1.25

[a] Control-selection method: bidirectional, 16 control periods.

[b] Poisson regression. Adjusted for trend (penalized spline, ~2 *df*), temperature (penalized spline, ~4 *df*), linear air pressure, and day-of-the-week indicators.

[c] IQRs are given in $\mu g/m^3$ for $PM_{2.5}$ and PM_{10} and in number/cm^3 for TNC.

[d] From February 1999 to December 1999, PM_{10} was estimated from TSP by multiplying the TSP measurement by a factor of 0.83.

and PM_{10}. There was no evidence of an association between TNC and MI onset.

Table 12 summarizes the associations between gaseous pollutants and MI onset for an IQR increase. NO_2 and SO_2 concentrations, on the same day and for lags 1 through 3, were positively associated with MI onset. The effect estimates obtained from the case–crossover analyses ranged between 1.05 (95% CI 0.95, 1.09) per 15-$\mu g/m^3$ increase in NO_2 lagged 2 days and 1.06 (95% CI 1.01, 1.11) per 1.5-$\mu g/m^3$ increase in SO_2 lagged 2 days; positive estimates were observed for CO only for lag 2 and 3 (OR 1.09 [95% CI 0.99, 1.20] and OR 1.07 [95% CI 0.97, 1.20], respectively). Nevertheless, results were inconsistent across methods for NO_2, CO, and SO_2 and with MI onset (Table 12, Figure 23).

Table 12. Effect Estimates of 24-Hour Averages of Gaseous Air Pollutants on Relative Risk of MI Obtained from Univariate Case–Crossover or Multivariate Time-Series Analyses for 851 Subjects with Known Time of MI Onset

		Case–Crossover[a]		Time-Series[b]	
	IQR[c]	Odds Ratio	95% CI	Relative Risk	95% CI
NO_2					
Same day	15	1.05	0.95 , 1.16	1.05	0.95 , 1.17
1-Day lag	15	1.07	0.97 , 1.18	1.04	0.94 , 1.15
2-Day lag	15	1.05	0.95 , 1.16	1.01	0.92 , 1.12
3-Day lag	15	1.03	0.93 , 1.14	1.02	0.92 , 1.13
4-Day lag	15	0.95	0.86 , 1.05	0.97	0.88 , 1.07
5-Day lag	15	0.92	0.83 , 1.01	0.96	0.87 , 1.06
5-Day mean (lag 0–4 days)	10	1.05	0.95 , 1.17	1.02	0.93 , 1.12
15-Day mean (lag 0–14 days)	8			1.02	0.92 , 1.13
30-Day mean (lag 0–29 days)	6			1.09	0.99 , 1.20
45-Day mean (lag 0–44 days)	6			1.07	0.96 , 1.20
CO					
Same day	0.31	0.99	0.90 , 1.09	0.99	0.90 , 1.08
1-Day lag	0.31	0.99	0.89 , 1.09	0.97	0.89 , 1.05
2-Day lag	0.31	1.09	0.99 , 1.20	0.98	0.90 , 1.07
3-Day lag	0.31	1.07	0.97 , 1.18	1.05	0.97 , 1.14
4-Day lag	0.31	1.05	0.95 , 1.15	1.01	0.93 , 1.10
5-Day lag	0.31	0.94	0.85 , 1.04	1.03	0.94 , 1.12
5-Day mean (lag 0–4 days)	0.24	1.09	0.96 , 1.24	1.00	0.91 , 1.09
15-Day mean (lag 0–14 days)	0.23			1.03	0.92 , 1.16
30-Day mean (lag 0–29 days)	0.21			1.09	0.97 , 1.22
45-Day mean (lag 0–44 days)	0.19			1.11	0.99 , 1.24
SO_2					
Same day	1.5	1.03	0.98 , 1.08	1.02	0.96 , 1.07
1-Day lag	1.5	1.04	0.99 , 1.09	1.02	0.97 , 1.08
2-Day lag	1.5	1.06	1.01 , 1.11	1.03	0.98 , 1.08
3-Day lag	1.5	1.04	0.99 , 1.09	1.05	1.01 , 1.10
4-Day lag	1.5	1.01	0.96 , 1.06	1.03	0.99 , 1.08
5-Day lag	1.5	0.97	0.92 , 1.03	1.01	0.96 , 1.06
5-Day mean (lag 0–4 days)	1.5	1.08	1.00 , 1.17	1.06	0.99 , 1.14
15-Day mean (lag 0–14 days)	1.3			1.07	0.99 , 1.16
30-Day mean (lag 0–29 days)	1.4			1.13	1.02 , 1.24
45-Day mean (lag 0–44 days)	1.5			1.13	1.01 , 1.26
O_3					
Same day	32	1.01	0.86 , 1.18	1.03	0.90 , 1.18
1-Day lag	32	0.93	0.79 , 1.08	1.03	0.91 , 1.18
2-Day lag	32	0.82	0.70 , 0.96	0.96	0.84 , 1.09
3-Day lag	32	0.82	0.70 , 0.96	0.95	0.83 , 1.07
4-Day lag	32	0.90	0.77 , 1.05	0.98	0.86 , 1.10
5-Day lag	32	0.91	0.78 , 1.06	0.94	0.83 , 1.06
5-Day mean (lag 0–4 days)	30	0.77	0.61 , 0.97	0.98	0.85 , 1.14
15-Day mean (lag 0–14 days)	30			0.97	0.82 , 1.14
30-Day mean (lag 0–29 days)	30			0.98	0.81 , 1.19
45-Day mean (lag 0–44 days)	29			0.96	0.78 , 1.19

[a] Control-selection method: bidirectional, 16 control periods.

[b] Poisson regression. Adjusted for trend (penalized spline, ~2 *df*), temperature (penalized spline, ~4 *df*), linear air pressure, and day-of-the-week indicators.

[c] IQRs are given in $\mu g/m^3$ except for CO, which are given in mg/m^3.

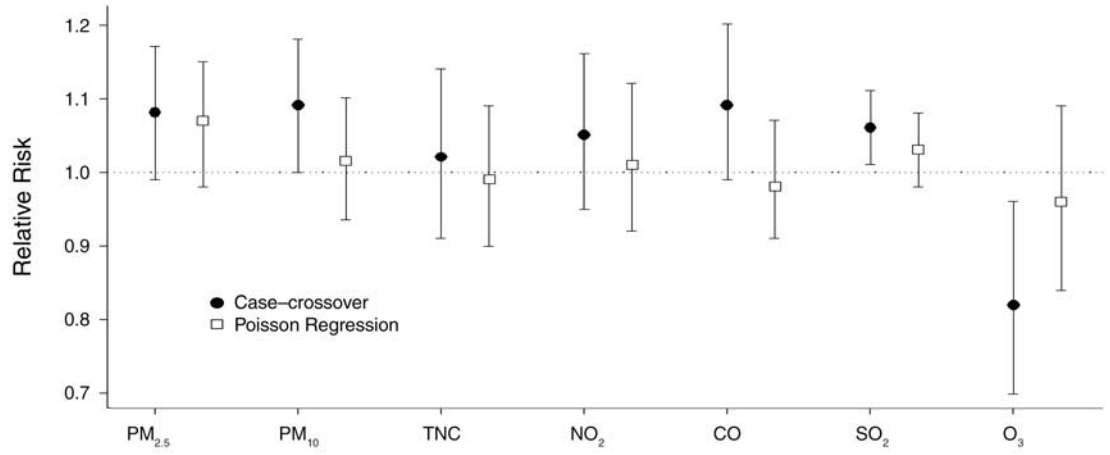

Figure 23. Comparison of the effect estimates obtained by case–crossover and Poisson regression analyses per IQR increase in the 24-hour average for each air pollutant lagged 2 days (as given in Tables 11 and 12) **and MI onset for 851 subjects who had a known time of onset.**

Estimates obtained for a 30-day moving average of SO_2 were consistent with an increased relative risk of longer cumulative air pollution exposures. O_3 concentrations showed inconsistent results for both case–crossover and Poisson regression analyses. Stratification by season also showed no association between O_3 and MI onset in summer or winter by Poisson regression analyses. Figure 23 summarizes the results for case–crossover and Poisson regression analyses with respect to air pollution concentrations 2 days before MI onset. Consistent estimates were observed for $PM_{2.5}$; PM_{10}, CO, and O_3 showed differences between the point estimates obtained by the two different methods although their confidence intervals overlap. Figure 24 summarizes the estimates for the 30-day moving averages. An increased relative risk of MI onset is shown for all measures of cumulative particulate and gaseous air pollution other than O_3.

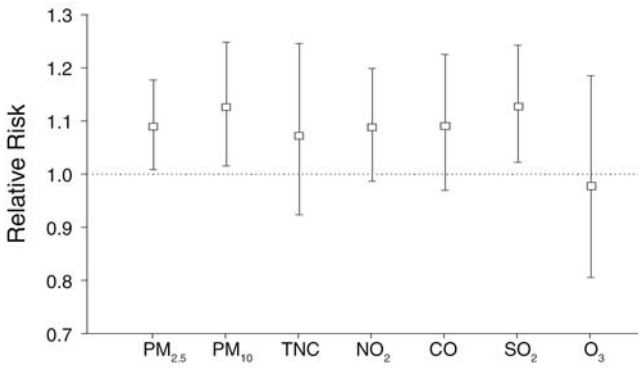

Figure 24. Effect estimates obtained by Poisson regression analyses per IQR increase for the 30-day moving average of each air pollutant (as given in Tables 11 and 12) **for 851 subjects who had a known time of MI onset.**

Sensitivity analyses are presented with respect to confounder modeling for all different case–crossover approaches considered and for Poisson regression analyses in Table 13. Model 4 was selected based on the AIC and on examination of the partial autocorrelation in the Poisson regression analyses. Model 6 was selected by minimizing the generalized cross-validation in the Poisson regression analyses. Additional control for season and weather did not influence the effect estimates for the unidirectional approaches. The bidirectional approaches showed smaller effect estimates when season and weather were considered. Even the results obtained by Poisson regression analyses were only slightly different with respect to the different model specifications.

Analyses of effect modification according to patient characteristics for the 2-day lagged concentrations of $PM_{2.5}$ were conducted using a bidirectional symmetric case–crossover method with 16 control periods (Table 14). Results indicated that subjects having had their first MI had slightly smaller estimates. Subjects with either a history of angina or subjects who recorded symptoms before MI onset showed large and, despite their small number, relatively strong associations with $PM_{2.5}$. Never-smokers were at higher relative risk of MI onset when $PM_{2.5}$ concentrations increased, whereas little association was noted between $PM_{2.5}$ and MI onset among exsmokers and current smokers (Table 14).

Subject-specific information could be used to exclude subjects who had been outside the study area during relevant time periods (Figure 25). At least two-thirds of a 24-hour period had to be spent within the study region to fulfill the criterion of belonging to the study area during case or control periods. Generally, slightly smaller effect estimates were calculated for case periods within the study area.

Table 13. Comparison of Effect Estimates per 7.7-μg/m^3 Increase in 24-Hour Averages of $PM_{2.5}$ Lagged 2 Days (48 Hours Before MI Onset) Obtained from Case–Crossover and Time-Series Analyses

	Case–Crossover								Time-Series[a]	
	I Unidirectional		II Bidirectional (16 Control Periods)		III Bidirectional (4 Control Periods)		IV Stratified		V	
Model	Odds Ratio[b]	95% CI	Odds Ratio[c]	95% CI	Odds Ratio[c]	95% CI	Odds Ratio[c]	95% CI	Odds Ratio[c]	95% CI
1	1.175	1.033 , 1.337	1.077	0.988 , 1.174					1.059	0.981 , 1.142
2	1.179	1.035 , 1.343	1.078	0.988 , 1.175	1.049	0.964 , 1.141	1.059	0.972 , 1.154	1.056	0.979 , 1.140
3	1.170	1.028 , 1.333	1.060	0.970 , 1.160					1.062	0.982 , 1.148
4	1.176	1.031 , 1.341	1.060	0.969 , 1.160	1.032	0.944 , 1.128	1.047	0.957 , 1.145	1.059	0.979 , 1.146
5	1.170	1.026 , 1.336	1.065	0.973 , 1.166	1.033	0.945 , 1.130	1.045	0.954 , 1.144	1.063	0.981 , 1.151
6	1.175	1.030 , 1.340	1.068	0.976 , 1.168	1.036	0.947 , 1.132	1.054	0.964 , 1.153	1.065	0.985 , 1.153
7	1.177	1.030 , 1.344	1.077	0.983 , 1.179	1.039	0.950 , 1.136	1.056	0.965 , 1.156	1.069	0.988 , 1.157

Models Adjusted For

1 Not adjusted for temperature, linear air pressure, relative humidity, or day of the week.
2 Day of the week: for analyses III and IV, by design; for analyses I, II, and V: with indicator variables.
3 Temperature (quadratic), linear air pressure.
4 Temperature (quadratic), linear air pressure, day of the week.
5 Temperature (quadratic), air pressure (quadratic), relative humidity (quadratic), day of the week: for analyses III and IV, by design; for analyses I, II, and V: with indicator variables.
6 Temperature (penalized spline, 4.4 *df*), linear air pressure, day of the week: for analyses III and IV, by design; for analyses I, II, and V: with indicator variables.
7 Temperature (penalized spline, 4.4 *df*), linear air pressure, relative humidity (penalized spline, 7.8 *df*), day of the week: for analyses III and IV, by design; for analyses I, II, and V: with indicator variables.

[a] Poisson regression.

[b] Not controlled for trend.

[c] Controlled for trend: analyses II, III, and IV by design; analysis V with a linear trend term for Models 1 through 5, and with a penalized spline of trend with 1.8 *df* for Models 6 and 7.

SUBJECT-SPECIFIC TRIGGERS ANALYZED

For a sample of 20 subjects, Figure 26 shows subject-specific activities as recorded in the HEI diary between October 26 and November 10, 2000. The midnight notations defined the day numbers by which interviewers recorded activity data. The right end of each line is the time of MI onset and the lines show any kind of activity. Sleeping periods, strenuous activities, time being outdoors, and time spent in traffic are indicated as recorded in the diary. Figure 27 shows the same data for the same 20 subjects, but now displayed as 24-hour periods before the time of MI onset. Table 15 shows the frequency of the subject-specific activities expressed as a proportion of persons who reported the activity and the average duration in person-hours of each activity per 24 person-hours. The frequencies are given for 24-hour intervals preceding the hour of MI onset (Figure 27).

Diary data applicable to case and control periods were provided by 691 subjects. All of these subjects slept during the three 24-hour intervals before MI onset, with an average sleep duration of 8 to 9 hours. The average duration increased to 12.5 hours for the time period 72 to 96 hours preceding the MI, which most likely reflects the fact that persons who had an MI during night time had not engaged in any activity other than sleeping during this time period (Figure 27). Lying awake was highly prevalent before the MI and might be regarded as an indicator for symptoms preceding the acute event. Other than hospitalized subjects, nearly everybody reported some activity, even those who only reported sleeping for the respective time interval (Figure 27). Approximately 50% of the subjects had engaged in moderate to strenuous physical activities (in Table 1, defined as activity code 5 or higher [MET 5]) with a mean duration of 2 hours. Strenuous activity

Table 14. Effect Estimates (Obtained from Univariate Case–Crossover Analyses) of 24-Hour Averages of $PM_{2.5}$ 2 Days Before MI Onset for Various Subject Characteristics of the 851 Subjects with Known Time of MI Onset[a]

Characteristic	*n*	%	Odds Ratio[b]	95% CI	*P* Value	Test for Heterogeneity of These Subgroups (*P* Value)
All	830	100	1.08	0.99 , 1.17	0.090	—
First MI	702	85	1.04	0.94 , 1.14	0.48	0.047
Survival ≥ 28 days	826	100	1.08	0.99 , 1.18	0.067	0.13
Definite MI	706	85	1.07	0.97 , 1.17	0.17	0.57
Definite or possible MI	827	100	1.08	0.99 , 1.18	0.082	
Angina pectoris	213	26	1.16	0.98 , 1.37	0.077	0.30
Hypertension	567	68	1.10	0.99 , 1.22	0.070	0.49
Diabetes mellitus	191	23	1.04	0.87 , 1.25	0.65	0.69
None of these	187	23	1.03	0.84 , 1.25	0.79	0.59
Smoker	273	33	1.04	0.90 , 1.21	0.60	
Exsmoker	268	32	0.99	0.85 , 1.16	0.92	
Never-smoker	289	35	1.20	1.04 , 1.39	0.012	0.17
Symptoms recorded	172	21	1.21	1.01 , 1.44	0.034	
No symptoms recorded	658	79	1.04	0.94 , 1.15	0.44	0.15

[a] Control-selection method: bidirectional, 16 control periods. *n* = out of 851 subjects with known time of MI onset, $PM_{2.5}$ data plus information on these characteristics was available for 830 subjects during the specified 2-day period. % = the proportion of the 830 subjects (first row).

[b] OR for one IQR (7.7 µg/m³ $PM_{2.5}$).

(defined as activity code 6 or higher [MET6]) was rare, but it occurred twice as often during the 24 hours preceding the MI than during earlier time intervals. Figure 28 shows the average periods of time with strenuous activities and being outdoors. However, these data have to be interpreted with caution because matching between the case and control periods was neglected, thus leading to biased inference. The strenuous activities participants had been engaged in just before MI onset were (a) sports like tennis, soccer, biking, or dancing, (b) heavy gardening, or (c) exertion at work.

More than one-third of the subjects had used cars for transportation during the 4 days before onset of MI; on average, 1 person-hour per 24 person-hours had been spent in a car. Public transportation and bicycles were used by less than 10% of the subjects; motorbike use was below 1%. Approximately one-fourth of the subjects were walking when they left home; on average, subjects spent 30 minutes walking. The average time subjects spent outdoors was approximately 90 minutes.

Feelings of extreme joy or extreme anger were rare (no information on intermediate-level emotions was gathered as part of the project design). Exposure to solvents and dusts was rare (we added this question because, in the pilot phase, one subject had reported painting in the hours before MI onset).

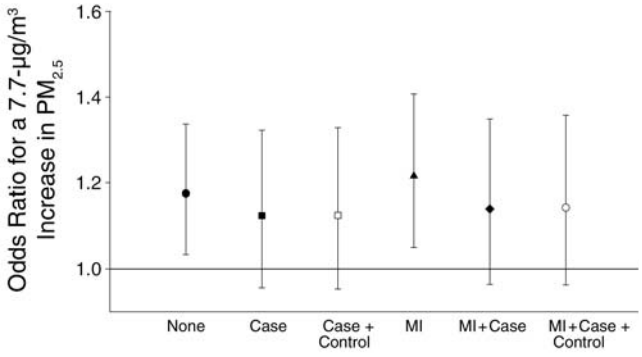

Figure 25. Comparison of the effect estimates obtained by case–crossover analyses (unidirectional design, 1:3 matching) **for MI onset and a 7.7-µg/m³ increase in 24-hour averages of $PM_{2.5}$ lagged 2 days.** Out of the 851 subjects who had a known time of MI onset, subjects were assigned to analytic subgroups on the basis of being within the study area for specific time periods. None = no restriction to study area; all 851 subjects. Case or Control (or both) = subjects were within the study area for at least 16 hours of the case or control period (or both). MI = subjects were within the study area the day before MI onset.

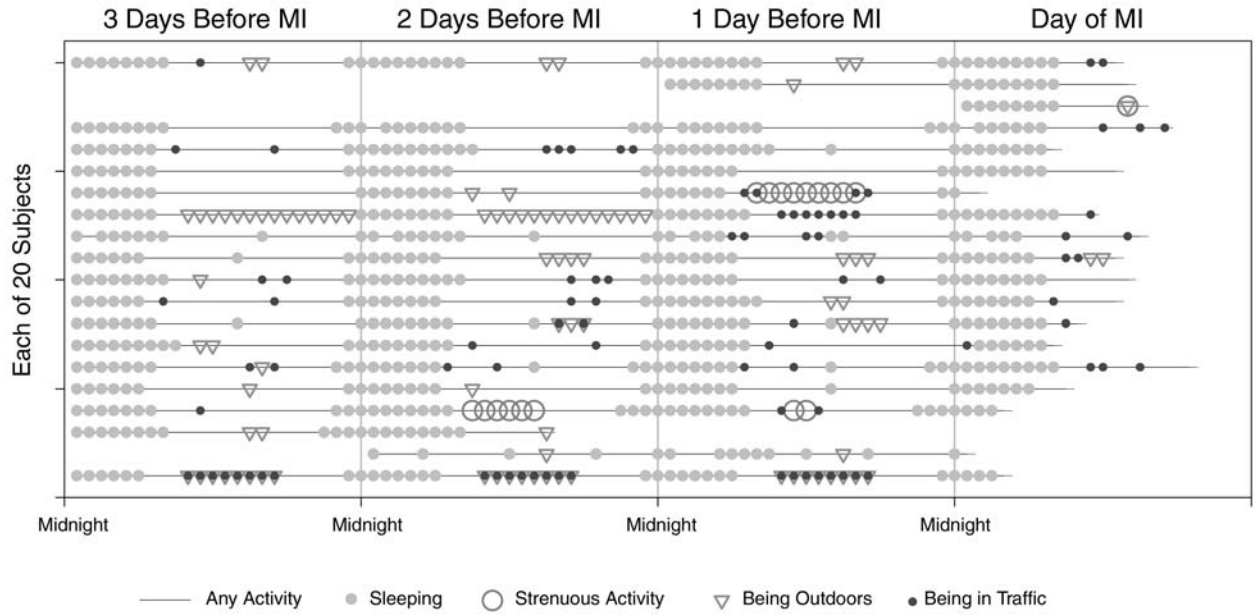

Figure 26. Example of activities recorded in the HEI diary for a subset of 20 subjects whose MIs had occurred between October 26 and November 10, 2000. Days are defined as midnight to midnight when applied to the diary data acquired during interviews about activities before MI onset.

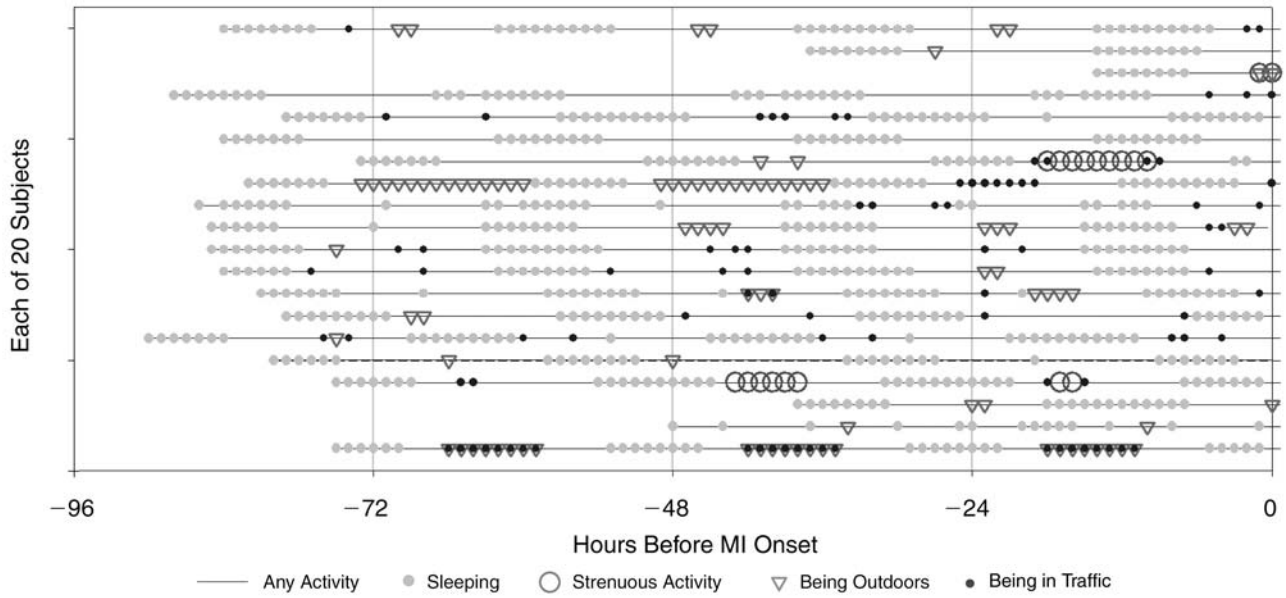

Figure 27. Example of activities recorded in the HEI diary for the same subset of 20 subjects shown in Figure 26. The time axis defines the hours before MI onset.

Physical Activity

Table 16 describes the results of the conditional logistic regression analyses of the effect of engaging in physical activity for 631 subjects. These analyses were performed with the unidirectional 1:3 matching of control periods spaced 24, 48, and 72 hours apart. Walking was associated with MI onset 1 to 2 hours afterward. The results for activities with moderate to extreme physical activity confirmed that an MI onset might be twice as likely 1 or 2 hours after the activity. A clear association was shown for strenuous activities, which were associated with an eightfold higher relative risk for an MI during the following hour.

When controlling for subsequent activities, the odds ratio for an induction time of less than 1 hour was unchanged by

Table 15. Proportion of Subjects Who Reported These Items on the Questionnaire During the 96 Hours Before MI Onset

	Hours Before MI[a]							
	0–23 (n = 691; p-h = 16,484)		24–47 (n = 691; p-h = 15,637)		48–71 (n = 624; p-h = 13,602)		72–96 (n = 531; p-h = 6236)	
	% of Subjects[b]	Hours/ 24 Hours[c]	% of Subjects[b]	Hours/ 24 Hours[c]	% of Subjects[b]	Hours/ 24 Hours[c]	% of Subjects[b]	Hours/ 24 Hours[c]
Activity and code[d]								
Sleep (Code 1)	100	8.33	100	9.1	100	9.2	98	12.5
Lay awake (Code 2)	16	0.41	11	0.32	8	0.25	6	0.24
Any exertion (Codes 3, 5–8)	100	15	97	15	93	15	73	11
Physical activity (Codes 5–8)	59	2.20	49	1.94	47	1.96	25	1.77
Strenuous activity (Codes 6–8)	15	0.64	8	0.44	7	0.37	4	0.40
Means of transportation								
Car	45	1.2	36	1.0	35	1.1	21	0.9
Public transportation	7.7	0.22	6.2	0.15	6.1	0.20	3.6	0.15
Bicycle	9.4	0.20	7.2	0.15	6.3	0.15	2.1	0.08
Motorcycle	0.7	0.04	0.9	0.05	0.5	0.02	0.4	0.03
Walking	33	0.62	26	0.54	25	0.57	12	0.48
Emotions								
Joy	1.2	0.02	0.3	0.01	0.5	0.01	0.4	0.02
Anger	3.8	0.06	2.7	0.04	3.1	0.06	1.8	0.11
Other								
Time spent outside	55	1.7	45	1.4	42	1.3	20	1.1
Exposure to solvents	1.2	0.03	1.2	0.05	1.1	0.06	0.4	0.01
Exposure to dust	2.5	0.12	2.5	0.14	2.0	0.13	2.2	0.23

[a] n = the total number of subjects who provided diary data within each time period. p-h = the total person-hours for which diary data had been provided during these time frames.

[b] % = the proportion of total subjects [at the top of the column] who reported this item within the specified 24 hours.

[c] The average number of hours of duration within each 24-hour period.

[d] Activity codes refer to Table 1.

definition because the activity was designated as concurrent. Strenuous exertion 1 hour earlier was associated with a twofold relative risk (OR 2.39 [95% CI 1.00, 5.69]) for MI onset; the relative risk for the period 2 to 5 hours before the MI was unaltered. The OR for an MI 6 hours later was 2.8 (95% CI 0.74, 10.6).

Time spent outdoors, which often accompanies physical activity, was also associated with a fourfold increase in the relative risk of MI onset during the following hour (OR 4.12 [95% CI 2.66, 6.38]).

In analyses with a 1:24 matching, where only full 24-hour sets were allowed, nearly identical results were obtained (Table 17). When only subjects who had provided

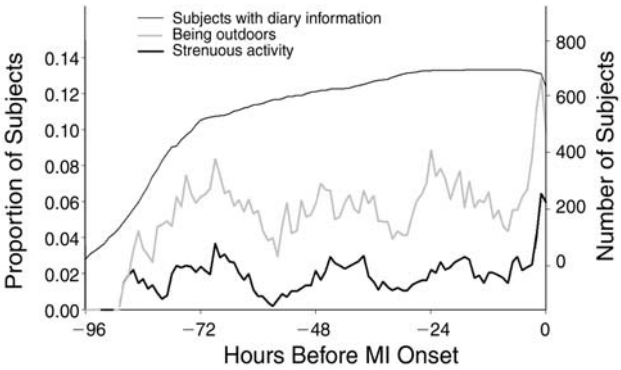

Figure 28. Proportion of 691 subjects who reported strenuous activities and time spent outdoors before MI onset. The time axis moves backward from the time of MI onset.

Table 16. Effect Estimates of Subject-Specific Activities During the 6 Hours Before MI Onset Obtained from Univariate Case–Crossover Analyses (Restricted to Activities Within the Study Area)[a]

Hours Before MI	% of Subjects[b]	Odds Ratio	95% Confidence Intervals	*P* Value
Walking (Codes 3 and 5)				
Concurrent	3.4	0.95	0.49 , 1.84	0.89
1	4.7	2.39	1.28 , 4.43	0.006
2	4.5	2.66	1.46 , 4.86	0.001
3	3.0	0.86	0.47 , 1.58	0.63
4	2.5	1.36	0.65 , 2.85	0.42
5	1.9	1.70	0.71 , 4.08	0.24
6	1.9	1.31	0.53 , 3.21	0.56
Physical Activity (Codes 5–8)				
Concurrent	13.2	1.65	1.12 , 2.43	0.012
1	16.0	2.84	1.95 , 4.13	< 0.0001
2	13.6	2.33	1.58 , 3.42	< 0.0001
3	10.1	1.55	1.03 , 2.34	0.036
4	9.6	2.30	1.46 , 3.62	0.0003
5	7.7	1.56	0.96 , 2.55	0.076
6	7.8	1.40	0.84 , 2.35	0.201
Strenuous Activity (Codes 6–8)				
Concurrent	6.1	5.52	2.80 , 10.9	< 0.0001
1	6.6	8.05	3.97 , 16.3	< 0.0001
2	3.9	3.41	1.68 , 6.92	< 0.0001
3	2.2	2.37	1.03 , 5.42	0.041
4	2.2	2.46	1.08 , 5.62	0.032
5	2.1	2.50	1.01 , 6.17	0.047
6	2.8	7.74	2.51 , 23.8	0.0004
Time Spent Outside				
Concurrent	10.0	1.59	1.02 , 2.46	0.039
1	13.1	4.12	2.66 , 6.38	< 0.0001
2	10.4	2.67	1.75 , 4.08	< 0.0001
3	8.3	1.53	1.00 , 2.34	0.052
4	6.5	1.80	1.07 , 3.04)	0.028
5	5.9	1.78	1.03 , 3.08	0.039
6	5.6	1.62	0.91 , 2.89	0.099

[a] Control-selection method: unidirectional, three control periods. Activity codes refer to Table 1.

[b] From the 691 subjects with known time of MI onset and complete diary data. Subjects who traveled outside the study area were excluded. The proportion of the remaining subjects who reported participating in these activities during the time frame of interest is given.

information for all three control periods were included, the odds ratios were slightly lower. These analyses were conducted based on the reasoning that these subjects might have recorded their activities more accurately than

Table 17. Comparison of Effect Estimates Obtained from Case–Crossover Analyses of the Frequency of Subject-Specific Activities (Restricted to Activities Within the Study Area)

	n[a]	Odds Ratio	95% CI
Control Selection			
Strenuous exertion			
1:3 Matching[b]	622	8.05	3.97 , 16.3
1:24 Matching[c]	622	7.92	4.80 , 13.1
1:3 Matching complete sets[d]	407	5.45	2.44 , 12.1
Time spent outside			
1:3 Matching[b]	623	4.12	2.66 , 6.38
1:24 Matching[c]	624	3.12	2.33 , 4.18
1:3 Matching complete sets[d]	407	3.43	2.02 , 5.82
Time spent in traffic[e]			
1:3 Matching[b]	623	3.11	2.10 , 4.60
1:24 Matching[c]	624	2.86	2.17 , 3.79
1:3 Matching complete sets[d]	407	3.50	2.21 , 5.53
Referent Control Analysis[e]			
Strenuous exertion	555	1.00	0.25 , 4.00
Time spent outside	558	1.29	0.69 , 2.44
Time spent in traffic[f]	558	0.83	0.45 , 1.52

[a] Number of subjects included in analyses. Subjects who traveled outside the study area were not included.

[b] All available control periods spaced 24, 48, and 72 hours apart.

[c] 24 control periods from 24–47 hours before MI (controlling for hour of the day).

[d] Three control periods spaced 24, 48, and 72 hours apart.

[e] One case period 25 hours before MI; 1 control period 49 hours before MI.

[f] Time spent in cars, in public transportation, or on motorcycles or bicycles.

subjects who remembered less about the 3 days before MI onset. The analyses, however, indicate that activity reporting may have underestimated participation when only one or two control periods were available because strenuous activities often are performed only every other day or even less often. The referent control analysis should provide a negative control and, indeed, no associations were observed.

Further analyses revealed possible interactions between physical activities and time spent outdoors; the interactions are systematically addressed in the following section. Subgroup analyses indicated consistent results for strenuous activity and time spent outdoors in the different subgroups considered (Table 18). Slightly increased estimates associated with strenuous activity were observed for subjects with diabetes mellitus or for those who had never smoked; however, the differences were not statistically significant. Time spent outdoors might be a trigger for persons

Table 18. Effect Estimates of Strenuous Activity and Time Spent Outside 1 Hour Before MI Onset Obtained from Univariate Case–Crossover Analyses for Various Subject Characteristics (Restricted to Activities Within the Study Area)[a]

			Strenuous Activity				Time Spent Outside			
Characteristic	*n*	%	Odds Ratio	95% CI	*P* Value	Test for Heterogeneity of These Subgroups (*P* Value)	Odds Ratio	95% CI	*P* Value	Test for Heterogeneity of These Subgroups (*P* Value)
All	622[b]	100	8.05	3.97 , 16.3	<0.0001	—	4.12	2.66 , 6.38	<0.0001	—
First MI	533[b]	86	7.55	3.71 , 15.4	<0.0001	0.99	4.48	2.78 , 7.24	<0.0001	0.36
Survival ≥ 28 days	618[b]	99	8.05	3.97 , 16.3	<0.0001		4.20	2.70 , 6.54	<0.0001	0.55
Definite MI	535[b]	86	7.36	3.60 , 15.0	<0.0001	0.99	4.33	2.72 , 6.90	<0.0001	0.51
Definite or possible MI	620[b]	100	8.05	3.97 , 16.3	<0.0001	—	4.10	2.65 , 6.36	<0.0001	—
Angina pectoris	148	24	8.99	0.94 , 86.4	0.057	0.92	2.37	1.03 , 5.42	0.0412	0.13
Hypertension	415[b]	67	8.06	2.95 , 22.0	<0.0001	1.00	3.61	2.16 , 6.04	<0.0001	0.36
Diabetes mellitus	130	21	13.5	1.61 , 11.4	0.017	0.60	5.28	1.82 , 15.3	0.0022	0.61
None of these	156	25	8.88	2.96 , 26.7	<0.0001	0.81	7.86	2.63 , 23.5	0.0002	
Smoker	226	36	6.39	2.04 , 20.0	0.001		5.02	2.36 , 10.7	<0.0001	
Exsmoker	184[b]	30	8.59	2.83 , 26.1	0.0001		5.94	2.65 , 13.3	<0.0001	
Never-smoker	212	34	10.3	2.19 , 48.8	0.003	0.87	2.30	1.08 , 4.90	0.0311	0.19
Symptoms recorded	151[b]	24	9.19	1.89 , 44.7	0.006		8.76	2.46 , 31.2	0.0008	
No symptoms recorded	471	76	7.77	3.53 , 17.1	<0.0001	0.85	3.62	2.26 , 5.80	<0.0001	0.20

[a] Control-selection method: unidirectional with three control periods. *n* = number of subjects included in the analyses. % = the proportion of all 622 subjects (first row). Subjects who traveled outside the study area were not included.

[b] An additional subject was analyzed for time spent outdoors; for those data, *n* = +1.

without a prior history of cardiovascular disease or diabetes. In addition, never-smokers seemed to be less affected by time spent outdoors than smokers or exsmokers.

Time Spent in Traffic

Table 19 presents the results of the conditional logistic regression analyses of the effect of time spent in traffic within the study area. All forms of transportation were associated with increased relative risk of MI onset; using cars, public transportation, motorcycles, or bicycles 1 hour before the event increased the relative risk of MI onset between 2.6- and 4-fold. (Motorbike use was too infrequent to be assessed as a trigger by itself.) Although the largest relative risk was associated with traveling 1 hour before the MI, the OR was 2.99 (95% CI 1.97, 4.53) after adjusting for physical activity, strenuous activity, being outside, and the presence of extreme anger (Figure 29). (Extreme anger by itself was too infrequent to obtain a reliable estimate of the underlying association with an MI onset [OR 0.57 {95% CI 0.06, 5.33}].) Time spent in traffic was also associated with MI onset 2 to 4 hours later. Time spent in traffic before this time period might also have been associated with increased relative risks, but the number of subjects who reported that activity was small, which introduced statistical variability.

For most subjects, activity code 5 (moderate exertion) was assigned to using a bicycle. The results for cycling were confounded by being outside and moderate to severe exertion at the same time. The adjusted OR for using a bicycle was 1.77 (95% CI 0.59, 5.31).

Restricting the analyses to subjects with a first MI produced results similar to those that included all subjects

Table 19. Effect Estimates of Time Spent in Traffic During the 6 Hours Before MI Onset Obtained from Univariate Case–Crossover Analyses (Restricted to Activities Within the Study Area)[a]

Hours Before MI	% of Subjects[b]	Odds Ratio	95% CI	*P* Value
Any Means of Transportation[c]				
Concurrent	8.0	2.06	1.31 , 3.23	0.002
1	12.1	3.11	2.10 , 4.60	1.3×10^{-8}
2	8.9	1.91	1.24 , 2.93	0.003
3	5.5	1.69	1.03 , 2.77	0.038
4	5.6	1.46	0.88 , 2.40	0.143
5	6.8	1.90	1.18 , 3.04	0.008
6	6.1	1.15	0.67 , 1.96	0.614
Cars				
Concurrent	5.6	1.69	1.00 , 2.86	0.049
1	8.3	2.63	1.68 , 4.12	2.2×10^{-5}
2	6.5	1.76	1.07 , 2.88	0.025
3	4.2	1.70	0.94 , 3.08	0.081
4	4.0	1.30	0.73 , 2.30	0.371
5	5.3	1.84	1.09 , 3.12	0.023
6	5.0	1.35	0.73 , 2.47	0.336
Public Transportation				
Concurrent	0.5	6.46	0.62 , 67.7	0.119
1	1.2	4.03	1.15 , 14.1	0.029
2	0.9	7.11	0.75 , 67.6	0.088
3	0.3	1.00	0.19 , 5.32	1
4	0.9	2.54	0.67 , 9.71	0.172
5	0.6	3.09	0.67 , 14.1	0.146
6	0.3	0.22	0.04 , 1.16	0.074
Bicycles				
Concurrent	1.8	2.92	1.08 , 7.87	0.034
1	2.4	3.77	1.48 , 9.56	0.005
2	1.6	2.49	0.94 , 6.58	0.065
3	1.0	1.98	0.71 , 5.56	0.194
4	0.7	1.80	0.43 , 7.48	0.419
5	0.9	1.37	0.40 , 4.78	0.617
6	0.7	2.80	0.56 , 13.9	0.208

[a] Control-selection method: unidirectional, three control periods.

[b] Proportion of 691 subjects with known time of MI onset and complete diary data who reported these activities during the time frame of interest. Subjects who traveled outside the study area were not included.

[c] Any means of transportation includes time spent in cars, in public transportation, or on motorcycles or bicycles.

(Table 20). Excluding the subjects who had not survived 28 days did not change the estimates. History of cardiovascular disease or diabetes did not change the relative risk of MI onset after time spent in traffic. Analyses with smokers and exsmokers produced estimates comparable to those that included all subjects, but never-smokers seemed to be at higher relative risk (Figure 29, Table 20). For subjects who had recorded any kind of symptoms before their MIs, it was possible that use of transportation might have been associated with the evolving MI. However, no difference in relative risk was observed between subjects with and without symptoms preceding MI onset. If anything, the relative risk appeared to be higher for subjects who had not reported symptoms.

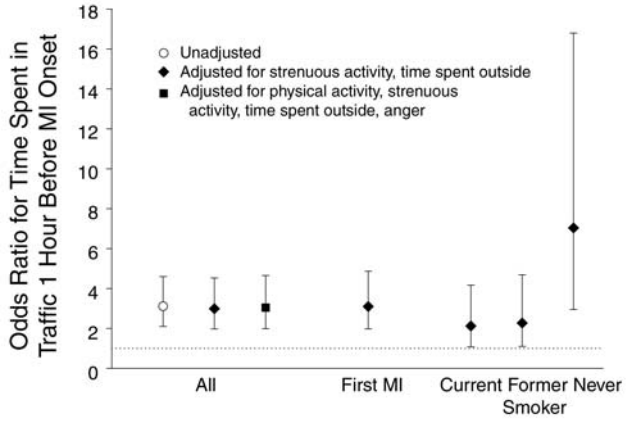

Figure 29. Estimates for time spent in traffic (cars, public transportation, motorcycles, and bicycles) **1 hour before MI onset for 691 subjects who reported this activity; estimated from case–crossover analyses with 1:3 matching.**

Signs and Symptoms of MI Onset

Symptoms as possible indicators for an evolving MI were relatively rare (Table 21). Nevertheless, their occurrences were more frequent 1 day before MI onset than they had been 4 days before. The most common symptoms were angina pectoris and shortness of breath. Atypical symptoms such as vomiting, cold sweat, and nausea were very rare. Table 22 describes the results of the conditional logistic regression analyses with respect to symptoms and sleepless hours during the night. These are not considered as triggers but might be potent indicators for an evolving acute event. Cardiac symptoms including angina pectoris preceded MI onset by 4 to 6 hours. Within 1 hour before MI onset, subjects were lying awake 4 to 6 times more often than on the days before the event.

Temperature

High temperatures were associated with an increased relative risk of MI obtained from a nonparametric function that assessed the dose–response relation between ambient 24-hour temperatures and MI onset (LOESS with a span of 0.8). No evidence for adverse health effects of cold

Table 20. Effect Estimates of Time Spent in Traffic 1 Hour Before MI Onset Obtained from Univariate Case–Crossover Analyses for Various Subject Characteristics (Restricted to Activities Within the Study Area)[a]

Characteristic	*n*	%	Odds Ratio	95% CI	*P* Value	Test for Heterogeneity of These Subgroups (*P* Value)
All	623	100	3.11	2.10 , 4.60	<0.0001	—
First MI	534	86	3.14	2.07 , 4.78	<0.0001	0.90
Survival ≥ 28 days	619	99	3.11	2.10 , 4.60	<0.0001	
Definite MI	536	86	2.64	1.74 , 4.02	<0.0001	0.06
Definite or possible MI	621	100	3.21	2.16 , 4.76	<0.0001	—
Angina pectoris	148	24	3.65	1.64 , 8.13	0.002	0.65
Hypertension	416	67	3.58	2.20 , 5.83	<0.0001	0.34
Diabetes mellitus	130	21	3.87	1.68 , 8.94	0.002	0.56
None of these	156	25	2.83	1.24 , 6.48	0.014	0.80
Smoker	226	36	2.29	1.22 , 4.32	0.010	
Exsmoker	185	30	2.38	1.22 , 4.61	0.011	
Never-smoker	212	34	7.09	3.02 , 16.6	<0.0001	0.079
Symptoms recorded	152	24	2.47	1.00 , 6.08	0.049	
No symptoms recorded	471	76	3.28	2.12 , 5.07	<0.0001	0.58

[a] Time spent in cars, in public transportation, or on motorcycles or bicycles. Control-selection method: unidirectional with three control periods. *n* = number of subjects included in the analyses; % = the proportion of all 623 subjects (first row). Subjects who traveled outside the study area were not included.

Table 21. Proportion of Subjects Who Reported Symptoms or a Physician's Visit During the 96 Hours Before MI Onset

	Hours Before MI[a]							
	0–23 (*n* = 691; p-h = 16,484)		24–47 (*n* = 691; p-h = 15,637)		48–71 (*n* = 624; p-h = 13,602)		72–96 (*n* = 531; p-h = 6236)	
	% of Subjects[b]	Hours/ 24 Hours[c]	% of Subjects[b]	Hours/ 24 Hours[c]	% of Subjects[b]	Hours/ 24 Hours[c]	% of Subjects[b]	Hours/ 24 Hours[c]
Symptom								
Any	19	0.34	9.4	0.15	5.9	0.1	1.8	0.07
Angina pectoris	16	0.26	8.4	0.12	5.0	0.06	1.4	0.05
Shortness of breath	2.6	0.04	2.5	0.03	1.5	0.02	0.79	0.02
Vomiting	0.14	0	0	0	0	0	0	0
Cold sweat	1.9	0.02	0.87	0.01	1.3	0.01	0.20	0
Nausea	1.3	0.05	0.29	0.02	0.33	0.03	0	0
Physician's visit	0.87	0.01	0	0	0.33	0	0.20	0.01

[a] *n* = the total number of subjects who provided diary data within each time period. p-h = the total person-hours for which diary data had been provided during these time frames.

[b] % = the proportion of total subjects [at the top of the column] who reported this item within the specified 24 hours.

[c] The average number of hours of duration within each 24-hour period.

Table 22. Effect Estimates of Symptoms During the 6 Hours Before MI Onset Obtained from Univariate Case–Crossover Analyses (Restricted to Symptoms That Occurred Within the Study Area)[a]

Hours Before MI	% of Subjects[b]	Odds Ratio	95% CI	*P* Value
Any Symptoms				
Concurrent	1.0	0.93	0.31 , 2.74	0.893
1	1.4	2.28	0.84 , 6.18	0.106
2	1.2	2	0.70 , 5.67	0.193
3	0.9	2	0.56 , 7.15	0.286
4	2.2	9.26	2.03 , 42.2	0.004
5	1.6	4.42	1.48 , 13.2	0.008
6	1.3	6	1.54 , 23.3	0.01
Angina Pectoris				
Concurrent	0.8	0.83	0.25 , 2.78	0.765
1	0.9	1.87	0.61 , 5.72	0.27
2	0.7	1.55	0.45 , 5.25	0.486
3	0.6	1.51	0.39 , 5.83	0.552
4	1.9	18.3	2.32 , 144	0.006
5	1.0	4.11	1.18 , 14.3	0.027
6	0.9	5.05	1.25 , 20.3	0.023
Lying Awake				
Concurrent	3.4	4.75	2.11 , 10.7	1.6×10^{-4}
1	1.8	5.64	1.76 , 18.1	0.004
2	2.1	2.93	1.17 , 7.38	0.022
3	1.5	1.71	0.56 , 5.22	0.348
4	1.9	2.75	0.98 , 7.76	0.056
5	1.5	1.27	0.44 , 3.65	0.653
6	2.2	3.68	1.08 , 12.5	0.037

[a] Control-selection method: unidirectional, three control periods.

[b] Proportion of 691 subjects with known time of MI onset and complete diary data who reported these symptoms during the time frame of interest. Subjects who traveled outside the study area were not included.

temperatures was observed for the 851 subjects for whom the time of MI onset was verified. The estimation of the relative risk of deciles of temperature in case–crossover analyses showed results consistent with those of the LOESS function.

INTERACTIONS

Evidence for interactions between strenuous activity and being outside was found on a descriptive level as well as in conditional logistic regression analyses. One hour before MI onset, 38% of all outdoor activities had been strenuous and 76% of the strenuous activities had been outside. In comparison, during the control period, 13% of all outdoor activities were strenuous and 40% of all strenuous activities were outside. Strenuous activity outside was associated with a large odds ratio that was (1) significantly larger than the relative risk estimates for strenuous activity inside or for being outside without strenuous activity, and (2) larger than the product of these two marginal odds ratios; this indicates a strong interaction between strenuous activity and time spent outside (Table 23). The estimates of the effect of strenuous activity inside and outside were both relatively imprecise, although estimates were substantially higher for strenuous activity outside. Considering time spent in traffic did not change the effect estimates substantially.

A possible association between air pollution and personal activities may be indirect and may be caused by season and weather variables. For example, subjects were more likely to engage in strenuous activity in the 24 hours preceding their MIs during the summer months (17%, 0.7 person-hours per 24 person-hours) compared to the winter months (12%, 0.5 person-hours per 24 person-hours). Furthermore, subjects were also more likely to be outdoors during the summer season (62%, 2 person-hours per 24 person-hours) than during winter (46%, 1 person-hour per 24 person-hours). The effect estimates, however, were largely unchanged after adjusting for season with sine and cosine functions and periods of 1year down to one-fifth of a year, and also after adjusting for weather variables (quadratic functions for temperature, air pressure, and relative humidity) and day of the week. An OR of 7.9 (95% CI 3.8, 16.5) was estimated for strenuous activity and an OR of 3.9 (95% CI 2.5, 6.2) for being outside. Also, the estimates for the air pollution effects remained relatively unchanged after controlling for season and weather (Table 13). Therefore, no strong confounding of the air pollution estimates was evident. Nevertheless, models attempting to estimate the air pollution effects adjusted for subject-specific activities used the unidirectional design and three selected control periods spaced 24 hours apart. The estimated OR for a 2-day lag of $PM_{2.5}$ was 1.21 (95% CI 1.02, 1.43), controlling for strenuous activities, being outdoors, and their interaction 1 hour before MI onset, which is comparable to the unadjusted OR of 1.18 (95% CI 1.03, 1.34).

Exercise was considered as an effect modifier because of its potential to increase dosage of pollutants and to alter the pathophysiologic reaction to particles. In addition, time spent in traffic was tested as a possible effect modifier because it can increase the exposure to more harmful particles. Two possible mechanisms for effect modification were considered (Figure 30): (1) if air pollution exists concurrently with both triggers, a possible interaction between triggers may develop that results in modified relative risks;

Table 23. Interactions Between Strenuous Activity or Time Spent in Traffic and Ambient $PM_{2.5}$ or Temperature Obtained by Multivariate Case–Crossover Analyses with Control Periods Selected Within the Diary Data[a]

		Inside, Strenuous Activity		Outside, Strenuous Activity		Outside, No Strenuous Activity		Time Spent in Traffic	
Model	*n*	Odds Ratio[b]	95% CI	Odds Ratio[b]	95% CI	Odds Ratio[b]	95% CI	Odds Ratio[c]	95% CI
All data	622	2.15	0.72 , 6.40	26.8	8.05 , 89.0	2.56	1.57 , 4.19		
All data	622	2.23	0.73 , 6.81	27.6	8.15 , 93.7	2.16	1.30 , 3.60	3.04	2.00 , 4.61
2-Hour $PM_{2.5}$ ≤ 18.5 µg/m^3	375	2.02	0.44 , 9.28	15.8	3.47 , 71.9	1.74	0.88 , 3.44	2.45	1.39 , 4.31
2-Hour $PM_{2.5}$ >18.5 µg/m^3	134	5.51	0.54 , 55.7	12.2	1.35 , 110	2.25	0.63 , 7.96	3.5	1.31 , 9.37
5-Day mean $PM_{2.5}$ ≤ 18.5 µg/m^3	427	2.93	0.74 , 11.6	30.3	6.79 , 136	2.27	1.24 , 4.16	2.71	1.60 , 4.57
5-Day mean $PM_{2.5}$ >18.5 µg/m^3	132	1.23	0.11 , 13.7	11.4	1.34 , 97.1	0.83	0.24 , 2.91	4.01	1.67 , 9.62
2-Hour temperature ≤ 17°C	471	1.7	0.40 , 7.21	37.5	4.73 , 297	2.3	1.20 , 4.41	2.98	1.82 , 4.89
2-Hour temperature >17°C	125	5.98	0.59 , 60.1	25	4.69 , 133	2.23	0.84 , 5.94	5.78	1.68 , 19.9

[a] Interactions are compared with a model that does not stratify for $PM_{2.5}$ or temperature. For the case and control periods, $PM_{2.5}$ levels or temperatures were within prespecified intervals. Control periods were selected as those during which subjects had provided diary data. The *n* value of 622 is the total number of subjects who provided diary data about these activities; the remaining *n* values are the number of subjects included in each analysis because concurrent $PM_{2.5}$ or temperature data were also available.

[b] Referent group: inside, no strenuous activity.

[c] Referent group: not in traffic.

and (2) ambient pollution levels at one time may induce an individual's vulnerability to triggers that occur later. Five different time windows for possible air pollution effects were selected: elevated $PM_{2.5}$ concentrations (1) 1 and 2 hours before MI onset; (2) 24 hours before MI onset; (3) 48 to 72 hours before MI onset; (4) during the 120 hours before MI onset; and (5) 30 days before MI onset. The cut-point for elevated $PM_{2.5}$ was 18.5 µg/m^3, which was approximately equivalent to the 75th percentile (Table 2). All control periods that did not contain the same pollutant concentrations as that specified for the case period were dropped. Thereby the number of matched sets was reduced (Table 23).

Only the results for analyses of the 2-hour average $PM_{2.5}$ concentrations and the 5-day moving averages of $PM_{2.5}$ are presented; the estimates of the strenuous activity outside were approaching infinity for increases in same-day or 2-day lagged 24-hour average $PM_{2.5}$ concentrations and for

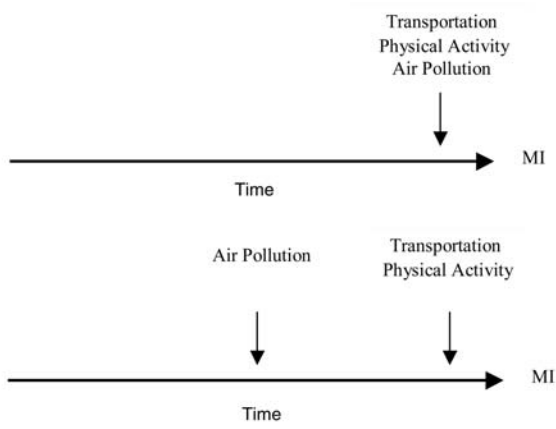

Figure 30. Possible time courses of interactions between subject-related triggers and ambient air pollution. Air pollution might enhance a person's susceptibilty of potential triggers when the pollution and trigger are present concurrently (upper panel); or it might induce vulnerability to potential triggers when they occur at a later time (lower panel).

increases in 30-day moving averages of $PM_{2.5}$. This was due to the fact that all discordant pairs had had strenuous outdoor activity in the case period coded. Other than strenuous activity outside, all triggers were strongly associated with MI onset when $PM_{2.5}$ concentrations had been high 2 hours before MI onset (Table 23). The estimates for exposures during time spent in traffic were not affected. When the 5-day moving average of $PM_{2.5}$ was above 18.5 $\mu g/m^3$, strenuous activity and being outdoors had smaller effect estimates compared to situations in which $PM_{2.5}$ concentrations stayed lower during case and control periods. In contrast, the association between exposures during time spent in traffic and MI onset was stronger in periods with high average $PM_{2.5}$ concentrations than in periods with low $PM_{2.5}$ concentrations.

Hot days were associated with larger relative risks of MI after strenuous activity inside. Analyses of effect modification by cold days (identified as temperatures below 5°C) did not result in interpretable estimates (data not shown).

DISCUSSION AND CONCLUSIONS

AIR POLLUTION AND MI ONSET

Main Findings of the Study

The aim of the study was to evaluate the possibility that particulate matter acts as a trigger for MI. The study assessed the association between ambient particulate matter in the hours and days before MI onset in MI survivors. Particulate air pollution was characterized by $PM_{2.5}$ and by TNC as a marker for ultrafine particles.

No association was found between 1-hour average concentrations of $PM_{2.5}$ or TNC and MI onset (specific aim 1). Elevated $PM_{2.5}$ concentrations were associated with MI onset 24 to 95 hours later as indicated by a formal estimation of the induction time. Positive associations were statistically significant or borderline significant from Poisson regression and case–crossover analyses for MI onset associated with 1-day- or 2-day-lagged $PM_{2.5}$ concentrations. No consistent association was observed for TNC and the relative risk of MI onset in contrast to the hypothesis formulated as specific aim 2.

The study was designed using a case–crossover format to allow subject-specific data collected through interviews to be used. Substantial differences in the relative risk estimates of air pollution effects were detected if different control-selection strategies were used. Unidirectional control periods selected adjacent to the case period resulted in a 23% increased relative risk of MI onset per 10-$\mu g/m^3$ increase in $PM_{2.5}$ (95% CI 4%, 46%). Using bidirectional control period selection (as described in Bateson and Schwartz 2001) resulted in a 10% increased relative risk of MI onset for a 10-$\mu g/m^3$ increase in $PM_{2.5}$ (95% CI −1%, 23%). Stratified analyses, which selected control periods from the same day of the week within the same month (as recommended by Lumley and Levy 2000) resulted in an 8% increased relative risk of MI onset for a 10-$\mu g/m^3$ increase in $PM_{2.5}$ (95% CI −4%, 20%). Poisson regression analyses produced estimates of 9% for MI onset for a 10-$\mu g/m^3$ increase in $PM_{2.5}$ (95% CI −2%, 20%) after adjusting for trend, weather, and day of the week.

The case–crossover design allows the assessment of transient risk factors based on a case series (Maclure and Mittleman 2000). It controls for chronic risk factors for acute events, such as an MI. Risk factors, for example, could be gender, age, or hypertension (Mittleman et al 1995). We chose the case–crossover design because subject-specific information about transient risk factors was accessible and could be considered in the analyses (information about individuals can only be ascertained retrospectively for a limited set of case periods over a limited period of time). The case–crossover design might add little, however, to the analyses of a case series in association with ambient air pollution if state-of-the-art Poisson regression analysis methods also can be applied (Neas et al 1999).

Seasonal variation and trends have been identified as potent factors that might introduce bias in case–crossover analyses (Greenland 1996; Navidi 1998). The data collected as part of this study lacked a strong seasonal pattern. A downward trend was identified in the exposure and no trend was identified in MI onset among subjects. However, this would result in an underestimation of the true association in the unidirectional design compared to the bidirectional design, which is presumably unbiased. Season and trend seem to be unlikely explanations to account for the substantial differences observed between the unidirectional and bidirectional analyses.

One explanation might be the fact that all control selection approaches assume that the presence of the factor of interest within the selected control periods is not associated with the event under study. For the bidirectional designs this implies that the $PM_{2.5}$ concentrations preceding the MI for several weeks are not related to MI onset. The relative risks associated with 15-day, 30-day, and 45-day moving averages were estimated in Poisson regression analyses based on earlier reports (Zeger et al 1999; Schwartz 2000b, 2001b; Zanobetti et al 2002). In those studies, evidence was found that 30-day moving averages of $PM_{2.5}$ were associated with an increased relative risk of MI onset. Such a delayed effect could affect the estimates

obtained from the stratified approach. Another explanation could be the different underlying study base. The bidirectional case–crossover and the Poisson regression analyses estimated the relative risk for subjects from Augsburg who were at risk of developing an MI during the entire study period. The unidirectional approach, however, might only assess the risk of developing an MI in subjects during vulnerable periods, such as a week before an MI. The latter group consists of fewer, and possibly more vulnerable, subjects at risk of developing an MI than is true for the entire population of the Augsburg study area.

The different bidirectional approaches produced comparable results to the Poisson regression analyses. The estimates from models with 16 bidirectional control periods produced slightly larger effect estimates than the other control selections. It has been argued that this might be due to a selection bias; a correction procedure has been proposed (Bateson and Schwartz 2001).

Given the uncertainties in the control period selections, many analytical approaches were used and the results presented. Within the scope of the project, we were unable to further unravel the reasons for the differences in the analyses. We therefore summarized our results on the basis of the more conservative bidirectional estimates. Also, the estimates for other particulate or gaseous pollutants are only presented for the bidirectional control period selection and the Poisson regression analyses.

Particulate and Gaseous Air Pollutants

$PM_{2.5}$ concentrations lagged 1 to 2 days were associated with MI onset. In addition, evidence for a cumulative association over 30 to 45 days was found in Poisson regression analyses. No association was found for PM_{10} concentrations 0 to 5 days before MI onset, despite its substantial correlation with $PM_{2.5}$. We examined the data for outliers, but exclusion of outliers did not resolve the discrepancies. Longer cumulative particle exposures such as 30-day moving averages of PM_{10} indicated the presence of negative associations. $PM_{2.5}$ concentrations measured at the HEI site with a TEOM were moderate without a clear seasonal pattern. They accounted for approximately half of the measured PM_{10} concentrations at the nearby official measurement site at Bourges-Platz. Parallel measurements with an HI indicated that volatile components of the particles were lost through the heating process. The observed $PM_{2.5}$ TEOM/HI ratio was consistent with those for the ambient aerosol in Erfurt (Cyrys et al 2001) and for several US locations (Allen et al 1997). There was weak evidence that more material was lost during winter than during summer, as reported earlier (Allen et al 1997). However, a lack of seasonality was observed for all three fractions of particles: $PM_{2.5}$, PM_{10}, and TSP. NO_2 also did not show a strong seasonal pattern, indicating that the source strength of both NO_2 and particles might not be substantially reduced during the summer. The effects observed for $PM_{2.5}$ in the Poisson regression analyses appeared to be five- to tenfold higher than the effects reported per 10-μg/m^3 increase in PM_{10} for hospital admissions due to heart disease (Schwartz 1997, 1999, 2001b; Prescott et al 1998; Zanobetti et al 2000) or ischemic heart disease (Burnett et al 1995; Schwartz and Morris 1995). The estimate for the 24-hour average $PM_{2.5}$ lagged 2 days from the unidirectional analyses revealed the same magnitude as the estimate for the 24-hour average $PM_{2.5}$ lagged 1 day in the Onset study, which observed a 27% increase in relative risk per 10-μg/m^3 increase in $PM_{2.5}$ (Peters et al 2001a).

In the present study, TNC was not associated with MI onset. Earlier, it had been found to be a valid proxy measurement for the number concentrations of ultrafine particles (Wichmann et al 2000). In that study in Erfurt, a correlation of 0.9 between TNC and ultrafine particle number concentrations was observed between 1995 and 1998. Ultrafine particles contributed on average 87% to TNC. The contribution of particles with a diameter above 500 nm to the TNC is negligible. In another study, accumulation-mode particles had a share of approximately 10% to 20% in the TNCs measured at different European locations (Pitz et al 2001; Ruuskanen et al 2001). In our study, parallel measurements of TNC at different locations within the City of Augsburg, although limited in number, showed good correlation. The parallel measurements, however, also indicated that the measurements might highly depend on the wind direction, as shown for Haunstetten in the south of Augsburg. The measurements revealed that the peaks were lower at the HEI site, pointing out that the site reflected urban background concentrations compared to other locations. Consequently, the contribution of traffic-related exposures to the true personal exposure of particles from outdoor origin might have been underestimated by the TNC measurements at the HEI site. The spatial distribution of ultrafine particles has only been investigated in Helsinki, Finland (Buzorius et al 1999). There, correlations up to 0.8 were found for different locations. However, those locations might all have been influenced by the same overall traffic pattern.

Gaseous pollutants such as NO, NO_2, or CO might be thought to be highly correlated with total particle concentrations. However, only weak to moderate correlations were observed between these gaseous pollutants and TNC. When TNC was measured at the same location as the gases (Bourges-Platz), the correlations increased. For the gaseous pollutants NO_2 and CO, positive associations were observed

for a 2-day lag as well as for a 30-day moving average in Poisson regression analyses. Burnett and colleagues (1997a) found evidence of an association of all gaseous pollutants with cardiac hospital admissions. Eilstein and colleagues (2001) showed that MIs were associated with NO and NO_2 with a 5-day lag. Evidence of an association between CO and hospital admissions for ischemic heart disease has also been reported (Schwartz and Morris 1995). However, in two-pollutant models the estimate for PM_{10} was stronger than the estimate for CO. Furthermore, CO was implicated to be associated with hospital admissions for congestive heart failure (Schwartz and Morris 1995; Burnett et al 1997b). In England one study found weak associations for all gaseous and particulate pollutants and hospital admissions for ischemic heart disease (Wordley et al 1997; Anderson et al 2001). Poloniecki and colleagues (1997) found associations between acute MI hospital admissions and gaseous pollutants as well as black smoke.

We observed associations between SO_2 and MI onset, although the average SO_2 concentrations were very low (3.3 $\mu g/m^3$ in Augsburg). An RR between 1.04 and 1.06 was estimated for a 1.5-$\mu g/m^3$ increase in SO_2 on the same day of MI onset and up to 3 days before. SO_2 displayed a clear seasonal pattern of maximum concentrations during the winter months. SO_2 concentrations above 10 $\mu g/m^3$ occurred on only 25 days during the winter months from November until March. On these days temperatures were very low (average -0.5°C) and $PM_{2.5}$ was highly concentrated (average 26.5 $\mu g/m^3$).

SO_2 in high concentrations (2.8 mg/m^3) affects the upper respiratory tracts of asthmatic subjects and is able to cause bronchial constriction as evidenced in controlled exposure experiments (Koenig 1999). Furthermore, panel studies of people with asthma have indicated decreases in peak expiratory flow measurements during prolonged episodes of several days with SO_2 concentrations exceeding 200 $\mu g/m^3$ (Peters et al 1996).

In an analysis of 20 cities in the US, no evidence of an association between SO_2 and mortality from all causes was found after adjusting for PM_{10} (Samet et al 2000). Similarly, an analysis of 10 US cities indicated that the associations between daily PM_{10} and daily mortality from all causes were not confounded by gaseous pollutants (Schwartz 2000a). In the Air Pollution and Health: A European Approach (APHEA) study, SO_2 was associated with mortality from all causes (Katsouyanni et al 1997); a 3% increased relative risk was observed in association with 50 $\mu g/m^3$ SO_2. The APHEA II project, based on 29 cities, showed that the PM_{10} results were not confounded by SO_2 levels (Katsouyanni et al 2001). Whereas the SO_2 concentrations steadily decreased between the mid-1980s to the end of the 1990s in Erfurt, Germany (Ebelt et al 2001), the RR between SO_2 concentrations and daily mortality increased (Spix et al 1993; Wichmann et al 2000).

Data from London, UK, also indicated that, of the pollutants evaluated, SO_2 had the most robust association with hospital admissions for acute MI (Poloniecki et al 1997). (In that study, the SO_2 concentrations were as low as those we recorded in Augsburg.) Data from Valencia, Spain, also showed a remarkably robust association between SO_2 and hospital admissions for heart disease (Ballester et al 2001). Unlike London, in Valencia the effect was strongest in the summer months. SO_2 was also associated with hospital admissions for ischemic disease in the APHEA II project in seven European areas (Sunyer et al 2003). In persons below age 65, the effect was robust after adjusting for PM_{10}.

Consistent with those findings, an association was observed between SO_2 concentrations and heart rate variability in a controlled exposure study in which healthy subjects and subjects with asthma were exposed to 200 ppb SO_2 for 1 hour (Tunnicliffe et al 2001).

Personal exposure measurements by Sarnat and colleagues (2001) indicated that $PM_{2.5}$ concentrations recorded by personal monitors were correlated with ambient $PM_{2.5}$ and ambient SO_2 concentrations. In contrast, SO_2 concentrations from personal monitors were correlated with ambient $PM_{2.5}$ concentrations but not correlated with ambient SO_2. Consequently, ambient SO_2 concentrations might be a marker for personal exposures to ambient $PM_{2.5}$ concentrations. Therefore, it may be difficult to separate out which effects are from $PM_{2.5}$ and which are from SO_2 if they are indicators of the same sources. However, when $PM_{2.5}$ and SO_2 originate from different sources, the effects of $PM_{2.5}$ dominate the health effects in two-pollutant models, as suggested by most of the large multicenter studies.

In the present study, the effects of O_3 were inconsistent between the estimates of the case–crossover analyses and the Poisson regression analyses. O_3 concentrations below 10 $\mu g/m^3$ were recorded on 58 days with relatively cold temperatures (average 3.8°C) and elevated $PM_{2.5}$ concentrations (average 21.2 $\mu g/m^3$). High concentrations of SO_2 and low concentrations of O_3 might serve as indicators for air pollution mixtures that might trigger an MI.

Emission inventories have been studied for the O_3 precursors CO, nitrogen oxides, and hydrocarbons in Augsburg (Slemr et al 2002). Based on measurements at a receptor site northeast of the City of Augsburg in March and October 1998, the authors came to the following conclusions (Klemp et al 2002): The primary source of these pollutants

was traffic emissions. One study detected a higher share of domestic heating and stationary sources in March 1998 than in October 1998, based on the alkane profile. That project also found that emissions of these precursors were significantly higher on weekdays than on weekends, and that the nonmethylated hydrocarbons were more reactive on weekdays than on weekends. The weekday variations for $PM_{2.5}$ and the TNCs observed in the present study matches well with those earlier findings. The hydrocarbon composition in the current study resembled those found in other large German cities (Klemp et al 2002); thus, the composition of emissions in Augsburg was judged to be characteristic of German cities.

The study presented here has only very limited power to assess effect modification of the air pollution associations by subjects' characteristics. A previously diagnosed cardiovascular disease such as angina, hypertension, or MI increased the relative risk that a subject would experience an MI in association with $PM_{2.5}$. In addition, the associations were stronger for subjects who reported symptoms that had occurred during the 4 days before MI onset. These results indicate that subjects with underlying cardiac disease are at greater relative risk of an MI associated with air pollution. No increased relative risk was observed for subjects with diabetes, as has been suggested by other time-series analyses of hospital admissions due to cardiovascular disease (Zanobetti and Schwartz 2002); but the group of subjects in our study might have been too small or too narrowly defined to observe such an association. Never-smokers showed a larger relative risk in association with $PM_{2.5}$ than current smokers or exsmokers. One possible explanation of this could be that the contribution of ambient particles to the total personal exposure to particles was larger in never-smokers than in the other groups. Whereas both never-smokers and exsmokers do not currently experience particle exposure while smoking, one might hypothesize that never-smokers are less likely to be exposed to environmental tobacco smoke than exsmokers. Furthermore, we considered whether another subject characteristic might help explain this effect in never-smokers. Approximately 25% of never-smokers had diabetes; it is unlikely that this characteristic would have a role in the result for never-smokers because subjects with diabetes did not show an increased risk. On the other hand, 25% of never-smokers had angina. Because both subgroups (never-smokers and those with angina) showed increased relative risks, it is possible that each condition influenced the increased risk associated with the other condition.The results observed in this study differed substantially from those observed in Boston (Peters et al 2001a). In particular, the immediate effect of $PM_{2.5}$ at 2 hours before MI onset that was found in the Boston study was not observed in the current study. Similar criteria for the definition of MI were used in the Boston and current studies. However, the subjects included in Boston and Augsburg differed in some respects: (1) Proportionally more women were included in Boston than in Augsburg. (2) Although the Boston study did not limit age and the Augsburg study did, no difference in the age distribution was observed in Augsburg. (3) The Augsburg study had a lower proportion of subjects who had had a previous MI, but a substantially higher proportion of subjects with hypertension. (4) It is possible that the treatment of the patients with cardiovascular disease changed with time: subjects were recruited between 1995 and 1997 in Boston and 1999 and 2001 in Augsburg; advancements in medications might have protected some individuals in Augsburg more than in Boston. (5) Although effect modification by subject-specific characteristics cannot be excluded, no obvious explanation can be derived from comparing subject-specific characteristics. Another substantial difference between the two studies is the pollution mix. $PM_{2.5}$ concentrations in Boston were dominated by long-range transport of sulfate-rich particles during the summer months. In Augsburg, in contrast, local sources dominated the measured $PM_{2.5}$ concentrations at the HEI site. Unfortunately, the pathophysiologic mechanisms leading from deposition of particles in the airways to MI onset are not yet well enough understood to discuss the potency of different aerosol mixes.

SUBJECT-SPECIFIC TRIGGERS AND MI ONSET

The analyses of the diary data indicated that the activities of strenuous exercise, time spent outdoors, and time spent in traffic might be triggers of MIs. All three activities were associated with MI onset during the following hour (discussed in detail below). In this study, anger was not associated with MI onset, as has been reported elsewhere (Verrier and Mittleman 1996; Moller et al 1999). The diary only requested extreme emotions such as those caused by the death of a relative or by a divorce, which had been indicated to be associated with MIs. Emotional distress might however be underestimated compared to a questionnaire that requests many levels of emotions. Other known triggers such as sexual activity (Muller et al 1996) or taking cocaine (Mittleman et al 1999) or marijuana (Mittleman et al 2001) were not assessed in the study because such questions would have dramatically lowered the number of subjects willing to participate and the response rates to questionnaires; in addition, these factors are thought to play only a minor role in the lives of subjects in the age range studied in Augsburg.

Exercise

An increased relative risk of MI onset after strenuous exertion was found; the highest relative risks associated with exertion were in the concurrent hour and 1 hour before the event. Earlier studies with case–crossover designs found an increased relative risk of MI (Mittleman et al 1993; Willich et al 1993; Hallqvist et al 2000) or sudden death (Albert et al 2000) shortly after vigorous exertion. Although these studies used different selection strategies for control periods, the relative risk increase reported for a time window of approximately 1 hour before the onset of MI was similar in all these studies including ours.

In 1993, Mittleman and colleagues reported that exertion only during the hour immediately before the onset of MI was associated with a relative risk increase (RR for heavy exertion of 5.9). In 2000, Hallqvist and colleagues showed very similar results, and analyses of higher time resolution patterns found the highest relative risk for concurrent exposure (OR 4), and a somewhat lower relative risk for every earlier 15 minutes up to 45 minutes (OR ~2). In 2000 Albert and colleagues reported on only the concurrent 1 hour, and in 1993 Willich and colleagues reported only on the concurrent 30 minutes. In the present study, the unadjusted analyses showed an OR of 5.5 for exertion during the hour concurrent with MI onset, and an OR of 8 for the hour before; there was also an increased risk in the earlier hours. The results of the concurrent hour are comparable with respect to the analyses and show nearly the same results.

The difference for longer times before MI onset is caused by different control period–selection strategies and activity classifications. Mittleman and colleagues (1993) calculated the effect for an induction time of 1 to 2 hours, excluding those who continued their activities, and used the usual annual frequency of physical activity as control. In our study, controlling for exercise in the preceding hour led to an OR of 2.4 (95% CI 1.00, 5.69) for the hour before the MI and an OR of about 1 for the 2 to 6 hours before, which suggests a very good correspondence to the results of Mittleman and colleagues (1993).

One difference between our study and that of Mittleman and colleagues (1993) may be due to different diary designs for recording the time of MI onset and information about activities. In the Mittleman study, the timing of activities was reported in time intervals before the onset of MI. In our study, both the onset of MI and the timing of activities were allocated within hourly segments. This resulted in a possible measurement error of ± 1 hour for the time of MI onset and thus for the induction time. In other studies, the same data may not have been much more precise; but our approach could in part explain the discrepancy between our results and those of earlier studies. In our interview protocol, we recorded activities concurrent with MI onset in the hour designated as "the concurrent hour" and earlier activities in the "hour before MI onset". Thus, with the variable of ± 1 hour for the time of MI onset in our study, our results from the effect period 0–2 hours might in fact correspond to those found for the 1-hour induction time by Mittleman and colleagues (1993); and our results for the 0-hour induction time might be comparable to those for ongoing physical exertion reported by Hallqvist and associates (2000). The apparent difference in results could be caused by the different diary designs.

An important finding from previous studies for public health was that regular exercise protects against an MI triggered by exertion (Mittleman et al 1993; Willich et al 1993; Albert et al 2000). No information was available in the current study on the frequency of exercise; however, it might be approximated from the exercise frequency during the 3 control days. The present study confirmed the protective effects of regular exercise.

Analyses according to patient characteristics showed larger effect estimates for subjects with diabetes and for never-smokers; however, none of the tests for heterogeneity indicated substantially different responses for subjects with different characteristics.

Time Spent in Traffic

Time spent in traffic, whether in cars, buses, or streetcars, or on bicycles or motorcycles, was associated with MI onset 1 hour later. Car travel constituted the largest proportion of time spent in traffic, but no information was collected about whether the subjects had been driving or the reasons for travel. Adjusting for the other triggers, such as physical activities or time spent outdoors, which would apply to a bicycle ride, did not change the effect estimates.

Time spent in traffic is a rather crude measure of exposure. A combination of different factors such as stress and traffic-related air pollution may contribute to the observed associations. Stress during driving (eg, driving in dense traffic) could not be accounted for because information about only extreme emotional distress was available. Considering extreme emotional distress in the analysis did not change the odds ratio for time spent in traffic either. The association also held when only time spent in public transportation was considered, which ruled out that stress while driving was responsible for the observed association.

In some analyses, we considered only those subjects without a history of symptoms for the 4 days before MI onset; thus the effects of car trips to consult a doctor due to an evolving MI were omitted. The odds ratio for subjects

without symptoms was actually slightly higher than that for subjects with symptoms. The odds ratio associated with time spent in traffic more than doubled for never-smokers. This finding is consistent with the one for exposures to ambient $PM_{2.5}$. Again, a possible explanation would be that traffic-related particles during transport contributed more to the total personal exposure to particles for never-smokers than for other groups.

Studies on personal exposure to $PM_{2.5}$ have indicated that passengers in cars and buses have higher exposures than people in outdoor background locations (Praml and Schierl 2000; Adams et al 2001). The concentrations recorded varied by the route driven and might resemble those at curbsides. Concentrations in streetcars were comparable with those in buses in Munich, Germany (Praml and Schierl 2000). In Munich as well as in Augsburg, streetcars share the streets with buses and cars. Cyclists had approximately half of the particle exposures of people traveling by car or bus (Bevan et al 1991; van Wijnen et al 1995; Adams et al 2001; Rank et al 2001). Higher ventilation rates increase the amount of particles deposited (van Wijnen et al 1995; Adams et al 2001; Rank et al 2001), but in congested situations, cyclists might be able to leave the polluted microenvironments faster than people in cars or buses (Adams et al 2001).

In the present study no information was available for the kind of street traveled. The concentrations measured during traveling highly depend on the traffic density (Adams et al 2001). In the current study, the results for bicycle use might be affected by the route traveled because the study did not distinguish between bicycle rides on busy streets and recreational cycling in the countryside. In the diary interview, subjects also reported time spent walking before MI onset. Although there was an association with walking 1 hour before MI onset, this association was reduced to null after adjusting for physical activity and time spent outdoors. In this respect, the results for walking differed from those for time spent traveling by car, public transportation, or bicycle.

The exposure studies summarized above indicate that one of the possible reasons for the association of time spent in traffic with an increased MI risk might be exposure to elevated air pollution concentrations. To further substantiate this finding, one would like to have two things at hand: (1) hourly measurements of the personal exposure to traffic-related particles during the 4 days before MI onset; and (2) hourly grading of the stress level throughout the entire 4-day period before MI onset. When designing the diary we considered the possibility of obtaining more information on traffic density, streets traveled, and duration of travel. However, it became clear at the design stage of the diary that it would be impossible to collect reliable data for the case and control periods. Given these limitations, a simpler measure was chosen, namely to record the time spent in traffic by a retrospective interview to assess traffic-related exposures. In addition, we had considered having an assessment of the emotional strain associated with daily activities including time spent in traffic. Again, instruments used earlier, such as the questionnaire from the onset study (Verrier and Mittleman 1996), were not applicable to the diary format. The pilot phase of the HEI study showed that the quality of data collected would depend highly on the patients' ability to follow the flow of the interview; this substantially restricted the items to be assessed.

In other studies, evidence was found that particles accumulated macrophages in the lungs of children living near major roads (Bunn et al 2001) and of policemen occupationally exposed to high concentrations of traffic-related pollution (Giovagnoli et al 1999). A recently published study from The Netherlands indicated that subjects living near major roads had a nearly twofold higher risk of mortality due to cardiopulmonary diseases (Hoek et al 2002). An increased risk of mortality due to ischemic heart disease has been documented in occupationally exposed persons such as policemen regulating traffic (Forastiere et al 1994). Whereas those studies indicate that long-term traffic exposures are associated with increased mortality, the data presented here might also suggest that short-term exposures could trigger nonfatal MIs.

INTERACTIONS BETWEEN SUBJECT-SPECIFIC TRIGGERS AND PARTICLE CONCENTRATIONS

These analyses were based on the assumptions that air pollution concentrations do not have an impact on the level of activities, on the choice of a certain means of transportation, or on extreme emotional distress. These seemed to be reasonable because subjects do not know air pollution levels. However, weather conditions might covary both with the air pollution concentrations and, for example, with the likelihood of outdoor activities. Indeed, outdoor activities were more frequent during the summer months than during the winter months. However, adjustment for season and weather did not change the associations for subject-specific triggers such as strenuous exercise or time spent outdoors. There was, however, a strong interaction between strenuous activity and time spent outdoors because strenuous outdoor activities, in particular, were found to trigger MIs. These interactions largely account for the overall effect of strenuous activity. But even time spent outdoors without strenuous activities doubled the relative risk of MI.

Activities that modify the magnitude of personal exposure to particles (such as time spent outdoors, exercising, or time spent in traffic) might also be considered as confounders. In analyses that combined subject-specific activities (or triggers) and $PM_{2.5}$ concentrations, we found no evidence that the air pollution associations were confounded by subject-specific triggers. Furthermore, the subject-specific triggers such as exercise, time spent outdoors, or time spent in traffic were also analyzed as effect modifiers because such activities may considerably modify the subject-specific exposures. To address this question, we stratified the analyses based on the $PM_{2.5}$ values during case and control periods. Prolonged high $PM_{2.5}$ exposures as indicated by 5-day moving averages were not associated with an increased relative risk for the subject-specific triggers. In this group of analyses, both case and control periods were times with high $PM_{2.5}$ concentrations. The results for strenuous activity and time spent outdoors might be interpreted as the $PM_{2.5}$ concentrations contributing to the observed relative risk and subject-specific triggers having less impact themselves. However, time spent in traffic showed larger estimates when $PM_{2.5}$ concentrations were elevated during case and control periods. Very cautiously, one might interpret this observation to indicate that after particles accumulate in the lung, further exposures to traffic-related pollutants might be harmful.

Although these results have to be interpreted with caution, because the sample size was small and because interactions between levels of ambient $PM_{2.5}$ and subject-specific triggers have not been assessed earlier, the results point toward possible interactions between ambient concentrations of $PM_{2.5}$ and subject-specific triggers of MI.

ULTRAFINE PARTICLES

TNC was used as a measure of ultrafine particle number concentrations, which contribute approximately 90% to TNC and are highly correlated with TNC (Wichmann et al 2000; Ruuskanen et al 2001). The present study did not observe an association between the TNC, as measured by the HEI monitor, and MI onset. Also NO_2, which showed the highest correlations with TNC, did not show a consistent association in Poisson regression analyses or in case–crossover analyses.

The first epidemiologic evidence of possible health effects of ultrafine particles was collected in a pilot study in Erfurt with 27 adult subjects with asthma (Peters et al 1997b). A stronger decrease in the peak expiratory flow was observed for ultrafine particle number concentrations than for fine particle mass concentrations.

In a second study with 53 subjects with asthma in Erfurt (von Klot et al 2002), increases in asthma symptoms and medication use were observed in relation to exposure to both fine and ultrafine particles; however, those health effects could not be attributed solely to the ultrafine particles. The results of lung function measurements were confirmed by a Finnish study of adults with asthma (Penttinen et al 2001), but not by studies of children with asthma (Pekkanen et al 1997; Tiittanen et al 1999); no association between symptoms or medication use was apparent in any of the Finnish studies.

In another prospective study, the association between mortality and fine and ultrafine particles was investigated by collecting mortality data over a 3.5-year period from August 1995 to December 1998 (Wichmann et al 2000). The measurement site was located approximately 50 m from the nearest busy road. Mortality increased in association with ambient particles after adjusting for season, influenza epidemics, day of the week, and weather conditions. Associations between particle number and particle mass concentrations were observed in different size classes of particles for different lag times. Immediate effects (lag 0 or 1 day) and delayed effects (lag 4 or 5 days) were found. The immediate effects seemed to be more closely associated with the mass concentrations (ie, in the larger size ranges) than with the number concentrations (ie, in the smaller size ranges); for more delayed effects the opposite was suggested. This pattern, however, could not be separated clearly, and distributed lag models comprising the days 0 to 5 showed similar results for both particle measures. The more immediate effects were on respiratory function and the more delayed effects were on cardiovascular function. Yet these effects could not be distinguished statistically.

The ULTRA study (Pekkanen et al 2002) indicated that $PM_{2.5}$ and ultrafine particles might independently be associated with ST-segment depressions. The association between particles and signs of ischemia were found with a 2-day lag, which is consistent with the results for $PM_{2.5}$ observed in the present study.

In the current study, TNC was not associated with MI onset. The placement of the HEI monitor within a cloister that was more remote from mobile sources of these particles (125 m from a major road) than the GSF measurement site in Erfurt (50 m from a major road) (Wichmann et al 2000) or the ultrafine particle measurement site in Helsinki (Buzorius et al 1999) may account in part for differences in findings among these studies. A plausible hypothesis has been put forward linking ultrafine particles to cardiovascular disease (Seaton et al 1995; Donaldson et al 2001; Frampton 2001); and rapid translocation of

5-nm carbonaceous particles from the lung to the blood has been documented (Nemmar et al 2002); future studies might further elucidate the role of ultrafine particles in the exacerbation of cardiovascular diseases.

PLAUSIBILITY

Epidemiologic evidence is accumulating that combustion-related particulate air pollution is an important environmental risk factor for cardiopulmonary mortality. Many studies are beginning to provide incomplete but intriguing results suggesting that particle-induced pulmonary and systemic inflammation, accelerated atherosclerosis, and altered cardiac autonomic function may be part of the pathophysiologic pathways that link particulate air pollution with cardiovascular mortality (Peters and Pope 2002).

First, it has been shown that particles deposited in the alveoli lead to activation of cytokine production by alveolar macrophages (Crystal 1991) and epithelial cells (Dye et al 1999), to recruitment of inflammatory cells (Driscoll et al 1997), and to stimulation of bone marrow to produce white blood cells (Terashima et al 1997; Tan et al 2000).

Second, increases in plasma viscosity (Peters et al 1997a), fibrinogen (Pekkanen et al 2000; Schwartz 2001a), and C-reactive protein (Peters et al 2001b) have been observed in samples from randomly selected healthy adults in association with particulate air pollution.

Third, acceleration of heart rates and diminished heart rate variability in association with air pollution have been documented in older persons (Liao et al 1999; Pope et al 1999a,b; Gold et al 2000), in a random sample of the Augsburg population ages 25 to 74 (Peters et al 1999), and in occupational groups (Magari et al 2001). Some of the studies on heart rate variability have reported an immediate response within hours (Gold et al 2000; Magari et al 2001) or on the same day (Liao et al 1999; Pope et al 1999b). That effects can be quite immediate was also suggested by Pope and colleagues (2001), who showed that exposure to passive smoke decreased heart rate variability within 2-hour–exposure windows in a controlled quasi-experimental setting. In addition to the immediate effects, in some studies effects on heart rate seemed to be cumulative in association with prolonged exposure to elevated air pollution concentrations (Peters et al 1999; Pope et al 1999a).

Fourth, for patients with implanted cardioverter defibrillators, an increased number of therapeutic interventions (discharges) have been associated with ambient concentrations of air pollution. (Peters et al 2000). $PM_{2.5}$ and NO_2 (both lagged 2 days) were associated with discharges from implanted cardioverter defibrillators. These findings were supported by a larger study with 195 patients that showed a 2-day-lagged SO_2 concentration of 4.1 ppb was associated with ventricular arrhythmia (OR 1.13 [95% CI 1.03, 1.25]; Dockery et al 2005). Furthermore, the study also suggested an association between ambient air pollution concentrations and supraventricular arrhythmias.

Fifth, endothelial dysfunction has been induced by controlled particle exposures (Brook et al 2002) and increases in blood pressure have been observed in association with elevated concentrations of ambient particles (Linn et al 1999; Ibald-Mulli et al 2001).

Finally, in a study with a rabbit model of hyperlipidemia, exposure to inhaled particles induced advanced stages of atherosclerotic plaque that are predisposed to rupture (Suwa et al 2002).

Consistent with these observations, the Finnish subgroup of patients with coronary artery disease participating in the ULTRA study showed ischemic reactions during a submaximal exercise test in association with ambient particulate matter (Pekkanen et al 2002). More specifically, a threefold risk for ST-segment depressions was observed in association with a 10-$\mu g/m^3$ increase in $PM_{2.5}$ lagged 2 days. In addition, evidence for an effect of ultrafine particles was also found with a 2-day lag.

It has been proposed that the onset of MI is triggered by the disruption of a vulnerable but not necessarily stenotic atherosclerotic plaque in response to hemodynamic stress; thereafter, hemostatic and vasoconstrictive forces determine whether the resultant thrombus becomes occlusive (Muller et al 1994).

The association between particulate matter and MI onset in MI survivors from the onset study was assessed in the larger Boston area (Peters et al 2001a). In analyses that assessed both immediate and 24-hour average concentrations of $PM_{2.5}$ jointly in one model, an OR of 1.48 was estimated for an increase of 25 $\mu g/m^3$ $PM_{2.5}$ during a 2-hour period before MI onset, and an OR of 1.62 was calculated for an increase of 20 $\mu g/m^3$ $PM_{2.5}$ in the 24-hour period 1 day before MI onset (95% CIs 1.09, 2.02 and 1.13, 2.34, respectively). Although the association with 24-hour average $PM_{2.5}$ lagged 1 day seems to be consistent with the data reported for the current study, we found no evidence for an immediate MI onset within hours after elevated air pollution exposure.

At this time, both the exact time course of effects initiated by particle deposition in the lung and the role of underlying cardiopulmonary disease in determining susceptibility remain unclear. Major disturbances in cardiac rhythm, such as ventricular fibrillation or tachyarrhythmia, are thought to be responsible for sudden cardiac death (Spooner et al 2001a). Sudden cardiac death has also been associated with the conventional risk factors for ischemic heart disease

such as smoking, hypertension, and diabetes, but it also occurs in apparently healthy individuals with low-risk-factor profiles (Spooner et al 2001b). Genetic factors have been thought to be largely responsible for these unexpected events (Spooner et al 2001b). In a case–crossover study in Seattle, Checkoway and colleagues (Checkoway et al 2000; Levy et al 2001b) investigated 362 cases of sudden cardiac death in patients without any evidence of cardiovascular disease before death. They found no association between ambient PM_{10} concentrations and sudden cardiac death; the risk estimates were negative and not statistically significant. In Seattle, air pollution concentrations are only moderate (Checkoway et al 2000); the main difference between the Seattle case–crossover study and other studies on MI survivors might be the absence of progressed atherosclerotic disease. Results from the current study support this argument: In subgroup analyses of subjects with a history of angina or subjects who reported angina during the 4 days before MI onset, we found slightly larger effect estimates with smaller standard errors than we found for subjects without a history of angina or without angina symptoms during the 4 days before MI onset.

STRENGTHS AND LIMITATIONS

The present study was prospectively planned and conducted as a case–crossover study to address the association between ambient particulate air pollution and MI onset. In addition to monitoring air pollution concentrations at central sites, subject-specific data were collected in a diary. In a semistructured interview, information on subjects' activities and whereabouts in the study area were collected for each hour of the 4 days before MI onset. This is a unique aspect of the study because it provides an opportunity to consider subject-specific information as effect modifiers and to evaluate different exposure levels and different activity levels both. Future studies might consider calculating particle intake or particle deposition based on the information obtained about exercise level and location within the study area.

We recruited subjects who had survived longer than 24 hours after MI onset in the area of Augsburg. Selection bias may have occurred because not all potential subjects were interviewed and only a portion of those interviewed provided diary information. Reasons for nonparticipation in the diary study included language problems or severity of disease and were unlikely to be correlated to the air pollution exposure. This possible selection bias could have led to either an under- or overestimation, but most likely the results of the present study were not affected.

Selection bias might also have occurred in bidirectional case–crossover analyses of air pollution exposures because the control periods, but not the case periods, were selected before and after the study period (February 1999–July 2001); thus, exposure and conditions in the control periods may not be identical with the representation of exposure and conditions in the hazard period (when a subject was at risk of developing an MI) (Bateson and Schwartz 2001). Case–crossover analyses were compared with Poisson regression analyses and agreement was found when bidirectional control periods were selected. Information bias may have occurred in the diary data due to recall bias. Because we used a case–crossover approach, no control group was available to directly address the possibility of recall bias. Earlier work that evaluated the role of exercise in triggering MIs had included a population-based control group matched for age, sex, and precinct (Willich et al 1993). That study found comparable results for strenuous activity when using both the case–crossover approach and the case–control approach. Those interviews took place and average of 13 days after the MI.

To examine the possible role of recall bias, we retrospectively assessed the subjects' activities during the 4 days before MI onset using a time-activity diary questionnaire. The interview took place 9 days after the MI event for about half the subjects. On the first page of the diary form, the nurse interviewer coded the patient's ability (or inability) to answer questions related to any day. The same importance was given to all 4 days before the event. Overall, the subjects accepted the diary questions and appreciated the interest in their own personal circumstances. Subjects sometimes had difficulty remembering their activities and, in particular, the exact time or duration; on the other hand, some subjects may have rehearsed the last days before the event to find reasons for their fate. It is also possible that subjects' memories of their activities are stronger for the hours before an MI than for the days before. Consequently, an overestimation of engaging in activities in case periods [the hour or hours before the MI], or an underestimation of engaging in activities in control periods [a day or more before the case period], or both could have inflated the effect estimates of these activities.

We evaluated this possible information bias by conducting analyses in a subgroup of subjects that remembered activities (strenuous activity, time spent outside, and time spent in traffic) on all 4 days; the case period was 1 hour before MI onset and the control periods were 24, 48, and 72 hours earlier (1:3 matching). In these analyses, for

example, we saw smaller effect estimates for strenuous activities (Table 17). This could be due to an information bias; however, it also could be caused by a better estimation of the usual frequency of activities when three control periods were used in the case–crossover analyses (1:3 matching). To control for a potential problem in remembering exact timing, these analyses were repeated with a 1:24 matching, in which hours 24–47 before MI onset were used as control periods. These results were nearly identical to those found with the 1:3 matching analysis, which further indicated that only a minor recall bias might have been present. In addition, we conducted a referent control analysis in which we chose one case period 25 hours before MI onset and one control period 49 hours before MI onset; in this analysis, we did not observe an association between any of the activities and MI onset (see Table 17). These latter results indicate that information bias may have been only a minor problem.

Misclassification of the population's average exposures to ambient air pollution might have occurred due to the use of one central monitoring site. However, high correlations between $PM_{2.5}$ and PM_{10} measured at different sites within the City of Augsburg could be seen. More measurement error can be expected for 1-hour averages than for 24-hour averages, a fact that might be partly responsible for the lack of an association between 1-hour average air pollution concentrations and MI onset. In addition, the spatial variability of TNC was assessed by monitors at different sites and surprisingly high correlations were found. However, there was also evidence that local sources of pollution might have highly influenced TNCs. Furthermore, the HEI site might not have adequately reflected the population average exposures to freshly emitted ultrafine particles. It cannot be excluded that this measurement error is responsible for the null association observed between TNC and MI onset. The available measurements based on particle mass or particle number all assume that all particles have the same toxicity per unit mass or per unit number. However, recent analyses on source apportionment of $PM_{2.5}$ have indicated that effects associated with exposure to PM vary by source because of differences in particle composition, mass, and numbers (Laden et al 2000; Schwartz 2003). For example, we observed no consistent association with PM_{10} concentrations lagged 0 to 5 days and MI onset when we employed different statistical models (Figure 23) although the values were highly correlated with $PM_{2.5}$. This might be due to the fact that the larger particles in PM_{10} are primarily derived from soil, whereas $PM_{2.5}$ particles are primarily derived from combustion. Pollutant sources contribute variably to size classes of particles, and particles in different size classes vary in their toxicity based on their chemical composition and surface properties. Therefore, the $PM_{2.5}$ and TNC particle metrics used might represent with considerable measurement error the relevant properties of the particles for health effects.

Time-varying confounders such as season, weather, and days of the week might have affected the estimates of associations both between air pollution and MI onset and between the subject-specific triggers and MI onset. The possible confounders considered in case–crossover as well as Poisson regression analyses by adjusting for them, and sensitivity analyses revealed little confounding due to these variables. In addition to the sensitivity analyses presented, models with more aggressive trend control were explored. In these analyses, however, strong negative autocorrelation was induced by the additional degrees of freedom and the AIC increased; this indicates that the model selected for the analyses was parsimonious. In addition, trend and season have been identified as factors leading to biases in unidirectional analyses; however, although unidirectional and bidirectional control selections resulted in substantial differences in the effect estimates for particulate air pollution, the predicted biases would have been in a different direction than we observed from our data. One might argue that the larger effect estimates observed in this study compared to other hospital admission data analyses are a sign of residual confounding. Given that no strong evidence for confounding was observed, alternative explanations should be considered. This study was unique in that a case period was well defined and the time of MI onset was known with precision rather than taken as the time of hospital admission.

The case–crossover analyses matched subjects to themselves so that confounding by time-invariant conditions was eliminated. On the other hand, within-person confounding might have occurred. Time-of-day was kept constant in all primary case–crossover analyses and thereby the influence of diurnal patterns was eliminated by design. The study had the ability to control simultaneously for activities (assessed in the diary) and environmental exposures (such as air pollution concentrations and temperature). No evidence for confounding of the air pollution associations by subject-specific triggers was found. Nevertheless, unmeasured variables like medication intake might have had an impact on the onset of MI and could not be taken into account in the analyses of air pollution with MI onset or subject-specific triggers and MI. The ability of the study to address interactions between subject-specific characteristics and ambient air pollution exposures or between the same characteristics and subject-specific triggers was

very limited due to the small sample size. Subgroup analyses, however, suggested that (1) subjects with or without a history of cardiovascular disease varied in risk of MI; (2) age and gender might be important determinants for susceptibility to triggers of MIs; and (3) factors such as age, gender, and disease status could modify induction times. It was beyond the power of the present study to address these issues thoroughly because of the small sample size. In addition, analyses of strenuous outdoor activities resulted in large odds ratios; however, this result might be regarded only as the basis for developing new hypotheses that warrant further investigation.

We conducted a large number of analyses to evaluate the study data. In this Report, we presented all approaches taken based on the approved analytic plan and the revised versions as discussed with the HEI Research Committee. Of course, the possibility cannot be excluded that the observed associations are chance findings. The debate within the field of epidemiology about the use and significance of *P* values and the implications for interpreting results of epidemiologic research on the basis of *P* values is ongoing (Goodman 2001; Poole 2001; Weinberg 2001). Many of the analyses presented in this report are not independent tests of an association, but are related analyses designed to establish consistency. For example, different methods were used to specify the lag structures of the effects, which we specifically used to address part of specific aim 1.

The subjects whose data were analyzed with respect to air pollution or subject-specific triggers had mostly similar characteristics compared to all patients interviewed by the Registry between February 1999 and July 2001. The characterization of pollutant emissions in Augsburg has been classified as being characteristic for German cities (Klemp et al 2002). Therefore, the results of this study might be generalizable to other sites in Germany where patients have suffered nonfatal MIs. One concern might be that the present study included only subjects with nonfatal MIs because subject-specific activity could not have been assessed retrospectively if the MIs had been fatal. The population who had suffered fatal MIs might have been more or less sensitive to external or subject-specific triggers. Therefore, in the extreme, a study might by chance observe no association with air pollution although, in truth, a positive association exists between air pollution and fatal MIs. However, given the data on hospital admissions for ischemic disease (Burnett et al 1995; Schwartz and Morris 1995; Eilstein et al 2001; Peters et al 2001a), this design seemed reasonable. The choice of design might limit the generalizability of the results to all MIs, both fatal and not. The results of the study would be applicable to patients with fatal MIs only under the assumption that MI severity would not affect the analysis of susceptibility to certain triggers. In addition, one also could perceive selection biases if certain activities would shift the proportions of nonfatal and fatal MIs. Data on fatal MIs for the time period February 1999 through July 2001 were collected by the Registry, but were not included because they were beyond the scope of the current study. Future research should address the effect of air pollution on fatal MIs and identify possible biases that might be present when research is focused only on nonfatal MIs.

CONCLUSIONS

The specific study hypotheses were not supported by the study. No association was found between elevated concentrations of particulate air pollution and MI onset hours later. In addition, no association was seen between ultrafine particles and MI onset within 5 days after exposure. For $PM_{2.5}$ and SO_2, using case–crossover analyses with 16 bidirectional control periods, the data suggested an association between 24-hour average concentrations lagged 2 days (OR 1.08 [95% CI 0.99, 1.17] for a 7.7-μg/m^3 increase in $PM_{2.5}$ and OR 1.06 [95% CI 1.01, 1.11] for a 1.5-μg/m^3 increase in SO_2). Neither an immediate association between particulate matter and MI onset within hours was observed, nor was there evidence of an association with TNC as a marker for ultrafine particles. The estimates obtained by the case–crossover analyses differed depending on the control-selection strategies; however, the biases were not, as would be predicted by confounding, based on season or trend. Subject-specific triggers such as strenuous activities, time spent outdoors, and time spent in traffic were identified and were associated with MI onset 1 hour later. No evidence of confounding of the air pollution associations by subject-specific triggers was observed. Strenuous outdoor activities were particularly associated with an increased relative risk of MI onset.

In addition, the study suggested that time spent in traffic, which possibly exposes subjects to high levels of traffic-related pollutants, might pose a relative risk of MI onset. Based on our current knowledge, it is impossible to apportion the relative contributions of risk factors such as stress or traffic-related air pollution to adverse effects such as MI onset. Nevertheless, patients vulnerable to acute coronary events are likely to profit from recent efforts to improve air quality in urban areas by cleaner vehicles and improved city planning.

ACKNOWLEDGMENTS

The authors would like to thank the following persons for supporting and contributing to the study: The Abbot of

St Stephan monastery allowed us to place the HEI monitoring site within the cloister garden, and Father Alkuin and Brother Leonard serviced the measurement station. Mike Pitz, Thomas Tuch, Klaus Koschine, Martina Zeiler, and Christian Harmarth conducted the air pollution measurements, serviced the devices, and performed quality control procedures. Joachim Heinrich and Wolfgang Kreyling provided oversight to the air pollution measurements. Thomas Gratza, Johannes Gostomschik, and Hans-Herbert Roth helped select the measurement site and provided access to the laboratories of the City of Augsburg for storage and field laboratory procedures. Peter Rabl conducted the spatial variability measurements and provided access to the Bavarian Air Monitoring Network, and Franz Ofner was the contact for obtaining the data measured by the Bavarian Air Monitoring Network. Katrin Zetzsche and Michael Mosetter processed and verified the air pollution data.

Special thanks to the research nurses Petra Pitschi, Gabriele Zimmermann, and Christine Winter who conducted the interviews. Their active participation and the discussions with them were important for the diary portion of the study. All of the nurses and Gabriele Orlik also abstracted data from medical records. Anita Schuler and Dorothea Lukisch conducted the quality control procedures and were essential for implementing the study within the Registry. Ursula Kaup managed the Coronary Event Registry data.

Verena Morgenstern helped with the analyses as a research assistant; Andrea Rückerl and Kathrin Wolf assisted in writing the Report; and Hanna Kirchmair corrected and edited the Report.

Furthermore, the authors would like to acknowledge Murray A Mittleman, Douglas W Dockery, and Joel Schwartz for discussions on the methodologic aspects of the study and the analyses; and Nicole Janssen for providing information on personal monitoring of traffic-related air pollution exposures.

Finally, the authors thank HEI for its support, the HEI Research Committee for its fruitful oversight, and in particular Aaron Cohen for his sustained contributions to the study.

REFERENCES

Adams HS, Nieuwenhuijsen MJ, Colvile RN, McMullen MA, Khandelwal P. 2001. Fine particle ($PM_{2.5}$) personal exposure levels in transport microenvironments, London, UK. Sci Total Environ 279:29–44.

Agarwal JK, Sem GJ. 1980. Continous flow, single-particle-counting condensation nucleus counter 6100. J Aerosol Sci 11:343–357.

Albert CM, Mittleman MA, Chae CU, Lee IM, Hennekens CH, Manson JE. 2000. Triggering of sudden death from cardiac causes by vigorous exertion. N Engl J Med 343:1355–1361.

Allen G, Sioutas C, Koutrakis P, Reiss R, Lurmann FW, Roberts PT. 1997. Evaluation of the TEOM method for measurement of ambient particulate mass in urban areas. J Air Waste Manage Assoc 47:682–689.

Anderson HR, Bremner SA, Atkinson RW, Harrison RM, Walters S. 2001. Particulate matter and daily mortality and hospital admissions in the west midlands conurbation of the United Kingdom: Associations with fine and coarse particles, black smoke and sulphate. Occup Environ Med 58:504–510.

Ballester F, Tenias JM, Perez-Hoyos S. 2001. Air pollution and emergency hospital admissions for cardiovascular diseases in Valencia, Spain. J Epidemiol Community Health 55:57–65.

Bascom R, Bromberg PA, Costa DA, Devlin R, Dockery DW, Frampton MW, Lambert W, Samet JM, Speizer FE, Utell M. 1996. Health effects of outdoor air pollution. Am J Respir Crit Care Med 153:3–50.

Bateson TF, Schwartz J. 1999. Control for seasonal variation and time trend in case crossover studies of acute effects of environmental exposures. Epidemiology 10:539–544.

Bateson TF, Schwartz J. 2001. Selection bias and confounding in case–crossover analyses of environmental time-series data. Epidemiology 12:654–661.

Bevan MAJ, Proctor CJ, Baker-Rogers J, Warren ND. 1991. Exposure to carbon monoxide, respirable suspended particulates, and volatile organic compounds while commuting by bicycle. Environ Sci Technol 25:788–791.

Breslow NE, Day NE. 1980. The Analysis of Case-Control Studies: Statistical Methods in Cancer Research Vol 1, International Agency for Research on Cancer Scientific Publications No. 32. IARC, Lyon, France.

Brook RD, Brook JR, Urch B, Vincent R, Rajagopalan S, Silverman F. 2002. Inhalation of fine particulate air pollution and ozone causes acute arterial vasoconstriction in healthy adults. Circulation 105:1534–1536.

Bunn HJ, Dinsdale D, Smith T, Grigg J. 2001. Ultrafine particles in alveolar macrophages from normal children. Thorax 56:932–934.

Burnett RT, Cakmak S, Brook JR, Krewski D. 1997a. The role of particulate size and chemistry in the association between summertime ambient air pollution and hospitalization for cardiorespiratory diseases. Environ Health Perspect 105:614–620.

Burnett RT, Dales R, Krewski D, Vincent R, Dann T, Brook JR. 1995. Associations between ambient particulate sulfate and admissions to Ontario hospitals for cardiac and respiratory diseases. Am J Epidemiol 142:15–22.

Burnett RT, Dales RE, Brook JR, Raizenne ME, Krewski D. 1997b. Association between ambient carbon monoxide levels and hospitalization for congestive heart failure in elderly in 10 Canadian cities. Epidemiology 8:162–174.

Buzorius G, Hämeri K, Pekkanen J, Kulmala M. 1999. Spatial variation of aerosol number concentration in Helsinki city. Atmos Environ 33:553–565.

Checkoway H, Levy D, Sheppard L, Kaufman J, Koenig J, Siscovick D. 2000. A Case–Crossover Analysis of Fine Particulate Matter Air Pollution and Out-of-Hospital Sudden Cardiac Arrest. Research Report 99. Health Effects Institute, Cambridge MA.

Crystal RG. 1991. Alveolar macrophages. In: The Lung: Scientific Foundations (Crystal RG, JB West, eds), pp 527–535. Raven Press, New York NY.

Cyrys J, Dietrich G, Kreyling W, Tuch T, Heinrich J. 2001. $PM_{2.5}$ measurements in ambient aerosol: Comparison between Harvard impactor (HI) and the tapered element oscillating microbalance (TEOM) system. Sci Total Environ 278:191–197.

Danesh J, Whincup P, Walker M, Lennon L, Thomson A, Appleby P, Gallimore JR, Pepys MB. 2000. Low grade inflammation and coronary heart disease: Prospective study and updated meta-analyses. BMJ 321:199–204.

de Boor C. 1978. A Practical Guide to Splines. Applied Mathematical Science Number 27. Springer, New York NY.

Dockery DW. 2001. Epidemiologic evidence of cardiovascular effects of particulate air pollution. Environ Health Perspect 109(Suppl 4):483–486.

Dockery DW, Luttmann-Gibson H, Rich DQ, Schwartz JD, Gold DR, Koutrakis P, Link MS, Verrier RL, Mittleman MA. 2005. Particulate Air Pollution and Nonfatal Cardiac Events, Part II: Association of Air Pollution with Confirmed Arrhythmias Recorded by Implanted Defibrillators. Research Report 124. Health Effects Institute, Boston MA.

Donaldson K, Stone V, Seaton A, MacNee W. 2001. Ambient particle inhalation and the cardiovascular system: Potential mechanisms. Environ Health Perspect 109(Suppl 4):523–527.

Driscoll KE, Carter JM, Hassenbein DG, Howard BW. 1997. Cytokines and particle-induced inflammatory cell recruitment. Environ Health Perspect 105:1159–1164.

Dye JA, Adler KB, Richards JH, Dreher KL. 1999. Role of soluble metals in oil fly ash-induced airway epithelial injury and cytokine gene expression. Am J Physiol 277:L498–L510.

Ebelt S, Brauer M, Cyrys J, Tuch T, Kreyling WG, Wichmann HE, Heinrich J. 2001. Air quality in postunification Erfurt, East Germany: Associating changes in pollutant concentrations with changes in emissions. Environ Health Perspect 109:325–333.

Eilstein D, Quenel P, Hedelin G, Kleinpeter J, Arveiler D, Schaffer P. 2001. Air pollution and myocardial infarction, Strasbourg France, 1984–89. Rev Epidemiol Sante Publique 49:13–25.

Forastiere F, Perucci CA, Di Pietro A, Miceli M, Rapiti E, Bargagli A, Borgia P. 1994. Mortality among urban policemen in Rome. Am J Ind Med 26:785–798.

Frampton MW. 2001. Systemic and cardiovascular effects of airway injury and inflammation: Ultrafine particle exposure in humans. Environ Health Perspect 109(Suppl 4):529–532.

Giovagnoli MR, Alderisio M, Cenci M, Nofroni I, Vecchione A. 1999. Carbon and hemosiderin-laden macrophages in sputum of traffic policeman exposed to air pollution. Arch Environ Health 54:284–290.

Gold DR, Litonjua A, Schwartz J, Lovett E, Larson A, Nearing B, Allen G, Verrier M, Cherry R, Verrier R. 2000. Ambient pollution and heart rate variability. Circulation 101:1267–1273.

Goldberg MS, Bailar JC III, Burnett RT, Brook JR, Tamblyn R, Bonvalot Y, Ernst P, Flegel KM, Singh RK, Valois M-F. 2000. Identifying Subgroups of the General Population That May Be Susceptible to Short-Term Increases in Particulate Air Pollution: A Time-Series Study in Montreal, Quebec. Research Report 97. Health Effects Institute, Cambridge MA.

Goodman SN. 2001. Of P-values and Bayes: A modest proposal. Epidemiology 12:295–297.

Greenland S. 1996. Confounding and exposure trends in case-crossover and case-time-control designs. Epidemiology 7:231–239.

Hallqvist J, Moller J, Ahlbom A, Diderichsen F, Reuterwall C, De Faire U. 2000. Does heavy physical exertion trigger myocardial infarction? A case-crossover analysis nested in a population-based case-referent study. Am J Epidemiol 151:459–467.

Hauptmann M, Berhane K, Langholz B, Lubin JH. 2001. Using splines to analyse latency in the Colorado Plateau uranium miners cohort. J Epidemiol Biostatistics 6:417–424.

Hauptmann M, Pohlabeln H, Lubin JH, Jockel KH, Ahrens W, Bruske-Hohlfeld I, Wichmann HE. 2002. The exposure-time-response relationship between occupational asbestos exposure and lung cancer in two German case-control studies. Am J Ind Med 41:89–97.

Hauptmann M, Wellmann J, Lubin JH, Rosenberg PS, Kreienbrock L. 2000. Analysis of exposure-time-response relationships using a spline weight function. Biometrics 56:1105–1108.

Hoek G, Brunekreef B, Goldbohm S, Fischer P, van den Brandt PA. 2002. Association between mortality and indicators of traffic-related air pollution in the Netherlands: A cohort study. Lancet 360:1203–1209.

Ibald-Mulli A, Stieber J, Wichmann HE, Koenig W, Peters A. 2001. Effects of air pollution on blood pressure: A population-based approach. Am J Public Health 91:571–577.

Katsouyanni K, Touloumi G, Samoli E, Gryparis A, Le Tertre A, Monopolis Y, Rossi G, Zmirou D, Ballester F, Boumghar A, Anderson HR, Wojtyniak B, Paldy A, Braunstein R, Pekkanen J, Schindler C, Schwartz J. 2001. Confounding and effect modification in the short-term effects of ambient particles on total mortality: Results from 29 European cities within the APHEA2 project. Epidemiology 12:521–531.

Katsouyanni K, Touloumi G, Spix C, Schwartz J, Balducci F, Medina S, Rossi G, Wojtyniak B, Sunyer J, Bacharova L, Ponka A, Anderson HR. 1997. Short term effects of ambient sulphur dioxide and particulate matter on mortality in 12 European cities: Results from time series data from the APHEA project. BMJ 314:1658–1663.

Klemp D, Mannschreck K, Pätz HW, Habram M, Matuska P, Slemr F. 2002. Determination of anthropogenic emission ratios in the Augsburg area from concentration ratios: Results from long-term measurements. Atmos Environ 36:S61–S80.

Koenig JQ. 1999. Air pollution and asthma. J Allergy Clin Immunol 104:717–722.

Laden F, Neas LM, Dockery DW, Schwartz J. 2000. Association of fine particulate matter from different sources with daily mortality in six U.S. cities. Environ Health Perspect 108:941–947.

Levy D, Lumley T, Sheppard L, Kaufman J, Checkoway H. 2001a. Referent selection in case-crossover analyses of acute health effects of air pollution. Epidemiology 12:186–192.

Levy D, Sheppard L, Checkoway H, Kaufman J, Lumley T, Koenig J, Siscovick D. 2001b. A case-crossover analysis of particulate matter air pollution and out-of-hospital primary cardiac arrest. Epidemiology 12:193–199.

Lewis M, Löwel H, Winter C, Zimmermann G, Pitschi P, Göpfert E, Luktisch D, Schwartzwälder I, Koenig W, Bolte H-D, Hörmann A, Schneider A, Janku D, Kaup W, Keil U. 1990. MONICA-Augsburg Coronary Event Registry: Handbook for the Registration of Hospitalized Events. GSF-Institut für Medizinische Informatik und Systemforschung Arbeitsgruppe Epidemiologie, Neuherberg, Germany.

Liao D, Creason J, Shy C, Williams R, Watts R, Zweidinger R. 1999. Daily variation of particulate air pollution and poor cardiac autonomic control in the elderly. Environ Health Perspect 107:521–525.

Linn WS, Gong H, Clark KW, Anderson KR. 1999. Day-to-day particulate exposure and health changes in Los Angeles area residents with severe lung disease. J Air Waste Manage Assoc 49:108–115.

Löwel H, Lewis M, Hormann A, Keil U. 1991. Case finding, data quality aspects and comparability of myocardial infarction registers: Results of a south German register study. J Clin Epidemiol 44:249–260.

Lumley T, Levy D. 2000. Bias in the case-crossover design: Implications for studies of air pollution. Environmetrics 11:689–704.

Maclure M, Mittleman MA. 2000. Should we use a case-crossover design? Annu Rev Public Health 21:193–221.

Magari SR, Hauser R, Schwartz J, Williams PL, Smith TJ, Christiani DC. 2001. Association of heart rate variability with occupational and environmental exposure to particulate air pollution. Circulation 104:986–991.

Marple VA, Rubow KL, Turner W, Spengler JD. 1987. Low flow rate sharp cut impactors for indoor air sampling: Design and calibration. J Air Pollut Control Assoc 37:1303–1307.

Mittleman MA, Lewis RA, Maclure M, Sherwood JB, Muller JE. 2001. Triggering myocardial infarction by marijuana. Circulation 103:2805–2809.

Mittleman MA, Maclure M, Robins JM. 1995. Control sampling strategies for case-crossover studies: An assessment of relative efficiency. Am J Epidemiol 142:91–98.

Mittleman MA, Maclure M, Tofler GH, Sherwood JB, Goldberg RJ, Muller JE (Determinants of Myocardial Infarction Onset Study Investigators). 1993. Triggering of acute myocardial infarction by heavy physical exertion: Protection against triggering by regular exertion. N Engl J Med 329:1677–1683.

Mittleman MA, Mintzer D, Maclure M, Tofler GH, Sherwood, JB, Muller JE. 1999. Triggering of myocardial infarction by cocaine. Circulation 99:2737–2741.

Moller J, Hallqvist J, Diderichsen F, Theorell T, Reuterwall C, Ahlbom A. 1999. Do episodes of anger trigger myocardial infarction? A case-crossover analysis in the Stockholm Heart Epidemiology Program (SHEEP). Psychosom Med 61:842–849.

Muller JE, Mittleman MA, Maclure M, Sherwood JB, Tofler GH. 1996. Triggering myocardial infarction by sexual activity. Low absolute risk and prevention by regular physical exertion. Determinants of Myocardial Infarction Onset Study Inverstigators. JAMA 275(18):1405–1409.

Muller JE, Abela GS, Nesto RW, Tofler, GH. 1994. Triggers, acute risk factors and vulnerable plaques: The lexicon of a new frontier. J Am Coll Cardiol 23:809–813.

Navidi W. 1998. Bidirectional case-crossover designs for exposures with time trends. Biometrics 54:596–605.

Neas LM, Schwartz J, Dockery D. 1999. A case-crossover analysis of air pollution and mortality in Philadelphia. Environ Health Perspect 107:629–631.

Nemmar A, Hoet PH, Vanquickenborne B, Dinsdale D, Thomeer M, Hoylaerts MF, Vanbilloen H, Mortelmans L, Nemery B. 2002. Passage of inhaled particles into the blood circulation in humans. Circulation 105:411–414.

Oberdörster G. 2000. Toxicology of ultrafine particles: In vivo studies. Phil Trans Royal Soc A 358:2719–2740.

Patashnick HREG. 1991. Continuous PM_{10} measurements using the tapered element oscillating microbalance. J Air Waste Manage Assoc 41:1079–1083.

Pekkanen J, Brunner EJ, Anderson HR, Tiittanen P, Atkinson RW. 2000. Daily concentrations of air pollution and plasma fibrinogen in London. Occup Environ Med 57:818–822.

Pekkanen J, Peters A, Hoek G, Tiittanen P, Brunekreef B, de Hartog J, Heinrich J, Ibald-Mulli A, Kreyling WG, Lanki T, Timonen KL, Vanninen E. 2002. Particulate air pollution and risk of ST-segment depression during repeated submaximal exercise tests among subjects with coronary heart disease: The Exposure and Risk Assessment for Fine and Ultrafine Particles in Ambient Air (ULTRA) study. Circulation 106:933–938.

Pekkanen J, Timonen KL. 2000. Exposure and Risk Assessment for Fine and Ultrafine Particles in Ambient Air (ULTRA). Kuopio University Printing Office, Kuopio, Finland.

Pekkanen J, Timonen KL, Ruuskanen J, Reponen A, Mirme A. 1997. Effects of ultrafine and fine particles in urban air on peak expiratory flow among children with asthmatic symptoms. Environ Res 74:24–33.

Penttinen P, Timonen KL, Tiittanen P, Mirme A, Ruuskanen J, Pekkanen J. 2001. Ultrafine particles in urban air and respiratory health among adult asthmatics. Eur Respir J 17:428–435.

Peters A, Dockery DW, Muller JE, Mittleman MA. 2001a. Increased particulate air pollution and the triggering of myocardial infarction. Circulation 103:2810–2815.

Peters A, Döring A, Wichmann HE, Koenig W. 1997a. Increased plasma viscosity during air pollution episode: A link to mortality? Lancet 349:1582–1587.

Peters A, Fröhlich M, Döring A, Immervoll T, Wichmann HE, Hutchinson WL, Pepys MB, Koenig W. 2001b. Particulate air pollution is associated with an acute phase response in men. Eur Heart J 22:1198–1204.

Peters A, Goldstein IF, Beyer U, Franke K, Heinrich J, Dockery DW, Spengler JD, Wichmann HE. 1996. Acute health effects of exposure to high levels of air pollutants in Eastern Europe. Am J Epidemiol 144:570–581.

Peters A, von Klot S, Heier M, Trentinaglia I, Kaup U, Hörmann A, Cyrys J, Zetzsche K, Pitschi P, Winter C, Zimmerman GA, Schuler A, Löwel H. 2002. Particulate Air Pollution and the Onset of Myocardial Infarction: A Case-Crossover Study—Study Manual for Field Work and Data

Management. GSF-Institute of Epidemiology, Neuherberg, Germany.

Peters A, Liu E, Verrier RL, Schwartz J, Gold DR, Mittleman M, Baliff J, Oh JA, Allen G, Monahan K, Dockery DW. 2000. Air pollution and incidence of cardiac arrhythmia. Epidemiology 11:11–17.

Peters A, Perz S, Doring A, Stieber J, Koenig W, Wichmann HE. 1999. Increases in heart rate during an air pollution episode. Am J Epidemiol 150:1094–1098.

Peters A, Pope CA III. 2002. Cardiopulmonary mortality and air pollution. Lancet 360(9341):1184–1185.

Peters A, Wichmann HE, Tuch T, Heinrich J, Heyder J. 1997b. Respiratory effects are associated with the number of ultra-fine particles. Am J Respir Crit Care Med 155:1376–1383.

Pitz M, Kreyling WG, Hölscher B, Cyrys J, Wichmann H-E, Heinrich J. 2001. Change of the ambient particle size distribution in East Germany between 1993 and 1999. Atmos Environ 35:4357–4366.

Poloniecki JD, Atkinson RW, de Leon AP, Anderson HR. 1997. Daily time series for cardiovascular hospital admissions and previous day's air pollution in London, UK. Occup Environ Med 54:535–540.

Poole C. 2001. Commentary: Positivized epidemiology and the model of sufficient and component cause. Int J Epidemiol 30:707–709.

Pope CA III. 2000. Epidemiology of fine particulate air pollution and human health: Biologic mechanisms and who's at risk? Environ Health Perspect 108(Suppl 4):713–723.

Pope CA III, Dockery DW. 1999. Epidemiology of particle effects. In: Air Pollution and Health (Holgate ST, Samet JM, Koren HS, Maynard RL, eds) pp 673–705. Academic Press, San Diego CA.

Pope CA III, Dockery DW, Kanner RE, Villegas GM, Schwartz J. 1999a. Oxygen saturation, pulse rate, and particulate air pollution. Am J Respir Crit Care Med 159:365–372.

Pope CA III, Eatough DJ, Gold DR, Pang Y, Nielsen KR, Nath P, Verrier RL, Kanner RE. 2001. Acute exposure to environmental tobacco smoke and heart rate variability. Environ Health Perspect 109:711–716.

Pope CA III, Verrier RL, Lovett EG, Larson AC, Raizenne ME, Kanner RE, Schwartz J, Villegas GM, Gold DR, Dockery DW. 1999b. Heart rate variability associated with particulate air pollution. Am Heart J 138:890–899.

Praml G, Schierl R. 2000. Dust exposure in Munich public transportation: A comprehensive 4-year survey in buses and trams. Int Arch Occup Environ Health 73:209–214.

Prescott GJ, Cohen GR, Elton RA, Fowkes FG, Agius RM. 1998. Urban air pollution and cardiopulmonary ill health: A 14.5 year time series study. Occup Environ Med 55:697–704.

Preston DL, Lubin JH, Pierce DA, McConney ME. 1996. Epicure Release 2.0. HiroSoft International Corporation, Seattle WA.

Rank J, Folke J, Jespersen PH. 2001. Differences in cyclists and car drivers exposure to air pollution from traffic in the city of Copenhagen. Sci Total Environ 279:131–136.

Ruuskanen J, Tuch T, ten Brink H, Peters A, Khlystov A, Mirme A, Kos GPA, Brunekreef B, Wichmann HE, Buzorius G, Vallius M, Kreyling WG, Pekkanen J. 2001. Concentration of ultrafine, fine and $PM_{2.5}$ particles in three European cities. Atmos Environ 35:3729–3738.

Samet JM, Dominici F, Curriero FC, Coursac I, Zeger SL. 2000. Fine particulate air pollution and mortality in 20 US cities, 1987–1994. N Engl J Med 343:1742–1749.

Sarnat JA, Schwartz J, Catalano PJ, Suh HH. 2001. Gaseous pollutants in particulate matter epidemiology: Confounders or surrogates? Environ Health Perspect 109:1053–1061.

Schwartz J. 1991. Particulate air pollution and daily mortality: A synthesis. Public Health Rev 19:39–60.

Schwartz J. 1997. Air pollution and hospital admissions for cardiovascular disease in Tucson. Epidemiology 8:371–377.

Schwartz J. 1999. Air pollution and hospital admissions for heart disease in eight US counties. Epidemiology 10:17–22.

Schwartz J. 2000a. Assessing confounding, effect modification, and thresholds in the association between ambient particles and daily deaths. Environ Health Perspect 108:563–568.

Schwartz J. 2000b. Harvesting and long term exposure effects in the relation between air pollution and mortality. Am J Epidemiol 151:440–448.

Schwartz J. 2001a. Air pollution and blood markers of cardiovascular risk. Environ Health Perspect 109(Suppl 3):405–409.

Schwartz J. 2001b. Is there harvesting in the association of airborne particles with daily deaths and hospital admissions? Epidemiology 12:55–61.

Schwartz J. 2003. Daily deaths associated with air pollution in six US cities and short-term mortality displacement in Boston. In: Revised Analysis of Time-Series Studies of Air Pollution and Health. Special Report. Health Effects Institute, Boston MA.

Schwartz J, Morris R. 1995. Air pollution and hospital admissions for cardiovascular disease in Detroit, Michigan. Am J Epidemiol 142:23–35.

Seaton A, MacNee W, Donaldson K, Godden D. 1995. Particulate air pollution and acute health effects. Lancet 345:176–178.

Slemr F, Friedrich R, Seiler W. 2002. The research project EVA: General objectives and main results. Atmos Environ 36:S1–S6.

Spix C, Heinrich J, Dockery D, Schwartz J, Volksch G, Schwinkowski K, Collen C, Wichmann HE. 1993. Air pollution and daily mortality in Erfurt, East Germany, 1980–1989. Environ Health Perspect 101:518–526.

Spooner PM, Albert C, Benjamin EJ, Boineau R, Elston RC, George AL Jr, Jouven X, Kuller LH, Maccluer JW, Marban E, Muller JE, Schwartz PJ, Siscovick DS, Tracy RP, Zareba W, Zipes DP. 2001a. Sudden cardiac death, genes, and arrhythmogenesis: Consideration of new population and mechanistic approaches from a National Heart, Lung and Blood Institute workshop, Part I. Circulation 103:2361–2364.

Spooner PM, Albert C, Benjamin EJ, Boineau R, Elston RC, George AL Jr, Jouven X, Kuller LH, Maccluer JW, Marban E, Muller JE, Schwartz PJ, Siscovick DS, Tracy RP, Zareba W, Zipes DP. 2001b. Sudden cardiac death, genes, and arrhythmogenesis: Consideration of new population and mechanistic approaches from a National Heart, Lung and Blood Institute workshop, Part II. Circulation 103:2447–2452.

Sunyer J, Ballester F, Tertre AL, Atkinson R, Ayres JG, Forastiere F, Forsberg B, Vonk JM, Bisanti L, Tenias JM, Medina S, Schwartz J, Katsouyanni K. 2003. The association of daily sulfur dioxide air pollution levels with hospital admissions for cardiovascular diseases in Europe (the Aphea-II study). Eur Heart J 24:752–760.

Suwa T, Hogg JC, Quinlan KB, Ohgami A, Vincent R, van Eeden SF. 2002. Particulate air pollution induces progression of atherosclerosis. J Am Coll Cardiol 39:935–942.

Tan WC, Qiu D, Liam BL, Ng TP, Lee SH, van Eeden SF, D'Yachkova Y, Hogg JC. 2000. The human bone marrow response to acute air pollution caused by forest fires. Am J Resp Crit Care Med 161:1213–1217.

Terashima T, Wiggs B, English D, Hogg JC, van Eeden SF. 1997. Phagocytosis of small carbon particles (PM_{10}) by alveolar macrophages stimulates the release of polymorphonuclear leukocytes from bone marrow. Am J Respir Crit Care Med 155:1441–1447.

Tiittanen P, Timonen KL, Ruuskanen J, Mirme A, Pekkanen J. 1999. Fine particulate air pollution, resuspended road dust and respiratory health among symptomatic children. Eur Respir J 13:266–273.

Tuch T, Brand P, Wichmann HE, Heyder J. 1997. Application of a mobile aerosol spectrometer for characterizing ambient aerosol particles in Eastern Germany. Atmos Environ 31:4193–4197.

Tunnicliffe WS, Hilton MF, Harrison RM, Ayres JG. 2001. The effect of sulphur dioxide exposure on indices of heart rate variability in normal and asthmatic adults. Eur Respir J 17:604–608.

von Klot S, Wölke G, Tuch T, Heinrich J, Dockery DW, Schwartz J, Kreyling WG, Wichmann HE, Peters A. 2002. Increased asthma medication use in association with ambient fine and ultrafine particles. Eur Respir J 20:691–702.

van Wijnen JH, Verhoeff AP, Jans HW, van Bruggen M. 1995. The exposure of cyclists, car drivers and pedestrians to traffic- related air pollutants. Int Arch Occup Environ Health 67:187–193.

Verrier RL, Mittleman MA. 1996. Life-threatening cardiovascular consequences of anger in patients with coronary heart disease. Cardiol Clin 14:289–307.

Wichmann HE, Peters A. 2000. Epidemiological evidence of the effects of ultrafine particle exposure. Phil Trans Royal Soc A 358:2751–2769.

Wichmann H-E, Spix C, Tuch T, Wölke G, Peters A, Heinrich J, Kreyling WG, Heyder J. 2000. Daily Mortality and Fine and Ultrafine Particles in Erfurt, Germany, Part I: Role of Particle Number and Particle Mass. Research Report 98. Health Effects Institute, Cambridge MA.

Weinberg CR. 2001. It's time to rehabilitate the P-value. Epidemiology 12:288–290.

Willich SN, Lewis M, Löwel H, Arntz HR, Schubert F, Schroder R (Triggers and Mechanisms of Myocardial

Infarction Study Group). 1993. Physical exertion as a trigger of acute myocardial infarction. N Engl J Med 329:1684–1690.

Wood SN. 2000. Modelling and smoothing parameter estimation with multiple quadratic penalties. J R Stat Soc B 62:413–428.

Wood SN. 2001. mgcv: GAMs and Generalized Ridge Regression for R. R News 1:20–24.

Wood SN. 2003. Thin plate regression splines. J R Stat Soc B 65:95–114.

Wood SN, Augustin NH. 2002. GAMs with integrated model selection using penalized regression splines and applications to environmental modelling. Ecol Modell 157:157–177.

Wordley J, Walters S, Ayres JG. 1997. Short term variations in hospital admissions and mortality and particulate air pollution. Occup Environ Med 54:108–116.

Zanobetti A, Schwartz J. 2002. Cardiovascular damage by airborne particles: Are diabetics more susceptible? Epidemiology 13:588–592.

Zanobetti A, Schwartz J, Gold DR. 2000. Are there sensitive subgroups for the effects of airborne particles? Environ Health Perspect 108:841–845.

Zanobetti A, Schwartz J, Samoli E, Gryparis A, Touloumi G, Atkinson R, Le Tertre A, Bobros J, Celko M, Goren A, Forsberg B, Michelozzi P, Rabczenko D, Aranguez RE, Katsouyanni K. 2002. The temporal pattern of mortality responses to air pollution: A multicity assessment of mortality displacement. Epidemiology 13:87–93.

Zeger SL, Dominici F, Samet J. 1999. Harvesting-resistant estimates of air pollution effects on mortality. Epidemiology 10:171–175.

APPENDIX A. Sample Questionnaire to Elicit Information About Symptoms and Activities on the Day of and for 3 Days Before the Subject's MI

We would like to ask about your activities on the day of your myocardial infarction before pain started: Please tell us what you did and where you stayed:

Int.: Document the daily activities only until myocardial infarction begins (Start of pain that led to maximum pain). Enter answer codes into the appropriate column:

Quest. No.	Additional questions concerning activities before the myocardial inf.	Answer 1= yes, 2= no, 3= n.a.			
		B 1	B 2	B 3	B 4
	diary denied:	|_|			
1	When did you wake up? *code: got up=**AS**, lie awake=**W***	|_|	|_|	|_|	|_|
2	Did you leave the house during the day? When? Several times?	|_|	|_|	|_|	|_|
2 a	Where did you go? *Int.: Enter numbers from the grid or make notes*	|_|	|_|	|_|	|_|
2 b	Which means of transport did you use that day? *code: by feet=**F**, bicycle = **R**, car=**A**, motorcycle = **M** public transportation= **B***	|_|	|_|	|_|	|_|
3	Did you stay outside during that day? How long? Several times? *Int.: mark with a cross in col. and enter term*	|_|	|_|	|_|	|_|
4	Did you engage in strenuous activities or sports? Several times? *Int.: please code the number from the list 'level of strain' here.*	|_|	|_|	|_|	|_|
5	Did you feel tightness in your chest or other symptoms of angina pectoris like vomiting, nausea, dyspnea, or cold perspiration? When? *code: vomiting = **E**, nausea=**Ü**, dyspnea=**AN**, cold perspiration=**KS**, angina pectoris=**AP***	|_|	|_|	|_|	|_|
6	Have you been concerned about any unusual events? When? *code: pleasure= **+**, annoyance = –*	|_|	|_|	|_|	|_|
7	Has your respiratory tract been strained by unusual exposures, e.g. dusts / fumes? *code: dust=**ST**, solvents/paints=**L***	|_|	|_|	|_|	|_|
8	Have you been sleeping or dozing during the day? *code: sleeping=**S***	|_|	|_|	|_|	|_|
9	When did you go to bed? *code: sleeping=**S***	|_|	|_|	|_|	|_|
10	Did you wake up at night on repeated occasions? *code: lie awake=**W***	|_|	|_|	|_|	|_|

B 1 - Day of myocardial infarction (questionnaire continued)

date: |__|__|.|__|__|.|__|__| weekday:_____

MI hour	time	activity	sleeping	location	means of transport.	outside activities	activity-code*	symptoms	emotion/ unusual ev.
0:00									
1:00									
2:00									
3:00									
4:00									
5:00									
6:00									
7:00									
8:00									
9:00									
10:00									
11:00									
12:00									
13:00									
14:00									
15:00									
16:00									
17:00									
18:00									
19:00									
20:00									
21:00									
22:00									
23:00									

mark hour of cardiac infarction below MI ❍ *not plausible* * *units from level of strain scale*

APPENDIX B. Using Splines to Estimate the Induction Time in a Case–Crossover Study on Air Pollution and Myocardial Infarction†

INTRODUCTION

We applied a spline function model to data from a case–crossover study on air pollution and myocardial infarction.

Splines are piecewise polynomial functions and have been described earlier by de Boor (1978). Theoretically, induction time patterns could be described by estimating separate risk parameters for exposures received or activities reported in short time intervals prior to the event for the case period and the corresponding index time for the control periods. However, the number of parameters would be large, and all the parameters could not be estimated due to limited data and high correlations. Spline functions are used to reduce the large number of parameters that would have to be estimated in such a nonparametric approach. Cubic splines induce only mild restrictions and retain great flexibility for approximating smooth functions. The model that includes average exposure, which corresponds to a constant induction time curve, is nested within the spline formulation.

STATISTICAL METHODS

Let $x(t)$ be the average exposure measured during the hour from $t-1$ to t hours prior to the event of a case period or the corresponding index time for a control period. Thus, $x(1)$, ..., $x(96)$ represent the 4-day (96-hour) hourly exposure history, and $\sum_{t=1}^{96} x(t)/96$ is the 4-day average exposure.

We start with the general model for the odds ratio,

$$\log(\mathrm{OR}) = \sum_{t=1}^{96} \beta(t)x(t),$$

where $\theta_1, \ldots, \theta_{96}$ are parameters that fully describe the induction time curve. In general, data are insufficient to estimate the full set of parameters $\theta_1, \ldots, \theta_{96}$. Our approach is then to apply mild constraints to the θ_t parameters and estimate a functional form that describes their behavior.

Suppose

$$\log(\mathrm{OR}) = \sum_{t=1}^{96} s(t;\theta)x(t),$$

where $s(t;\theta)$ is a function of time t and a parameter vector θ that models the hour-specific odds ratio per unit of exposure; that is, $s(t;\theta)$ is the odds ratio per unit of exposure received t hours in the past. The weighted sum

$$\sum_{t=1}^{96} s(t;\theta)x(t)$$

represents the odds ratio for the exposure profile $x(1), \ldots, x(96)$ compared to a zero profile (ie, a nonexposed individual).

B-splines are used to model $s(t;\theta)$ (Hauptmann et al 2000). Splines are smooth (ie, continuously differentiable) piecewise polynomial functions. They are segmented by interior knots. Cubic splines have certain optimal properties for approximating curves (de Boor 1978). The parameters cannot be interpreted directly, but the estimated spline function can be plotted.

Spline models with different numbers and placements of knots are not nested. Therefore, the number and placement of knots cannot be evaluated by likelihood ratio tests. To assure a smooth curve and to avoid overfitting, we considered linear, quadratic, and cubic splines with a small number of interior knots, that is, with no or one interior knot. For one interior knot, a profile likelihood search is performed by evaluating the deviance of models for a series of possible knot locations. For a cubic spline with one interior knot, five spline parameters have to be estimated and the knot position has to be determined. For details see the next section.

The simple log-linear odds ratio model in average exposure is included in the spline model when the induction time function is constant over time, that is $s(t;\theta) = \beta$ for all t. In this instance, β is the odds ratio per unit of average exposure. A likelihood ratio test is performed to test if the data are consistent with no variation in the hour-specific risk (ie, average exposure).

This method has been applied in epidemiologic studies to estimate lung cancer latency with respect to smoking and occupational exposure to asbestos and radon (Hauptmann et al 2000, 2001, 2002).

For the current application, we used the following two air pollution exposures: $PM_{2.5}$ hourly average as measured with a TEOM ($\mu g/m^3$) and a CPC (number/cm^3). Although the exposure during the case period was always the hourly exposure profile 96 hours prior to the event, we used three different approaches to select 96-hour control periods:

- three control periods per case period lagged 4 days (unidirectional) (Figure B.1);
- three or four control periods per case period stratified by month (bidirectional) (Figure B.2); and

† Excerpts from an article by Michael Hauptmann, September 22, 2002. Correspondence: Dr Michael Hauptmann, Biostatistics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Boulevard, Bethesda MD 20892.

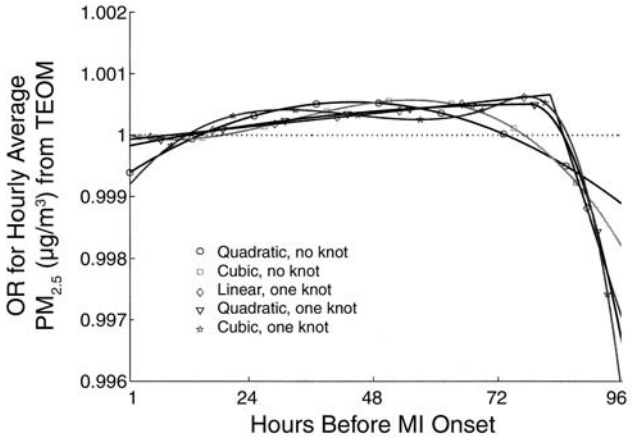

Figure B.1. Effect estimates of $PM_{2.5}$ concentrations on MI onset for 851 subjects who had a known time of onset: Comparison of five spline models using three unidirectional control periods lagged 4 days per case period. $PM_{2.5}$ was measured using a TEOM.

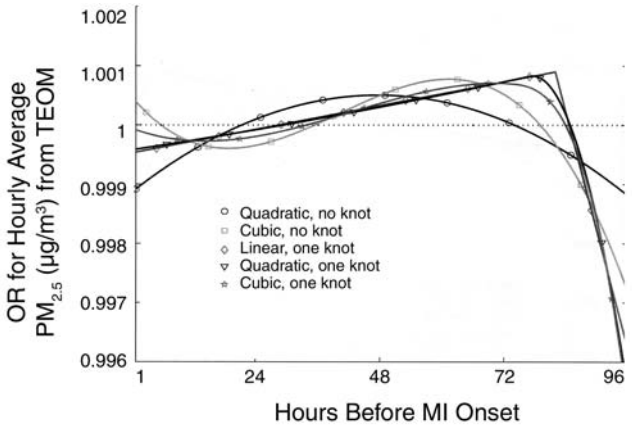

Figure B.2. Effect estimates of $PM_{2.5}$ concentrations on MI onset for 851 subjects who had a known time of onset: Comparison of five spline models using three to four control periods per case period stratified by month. $PM_{2.5}$ was measured using a TEOM.

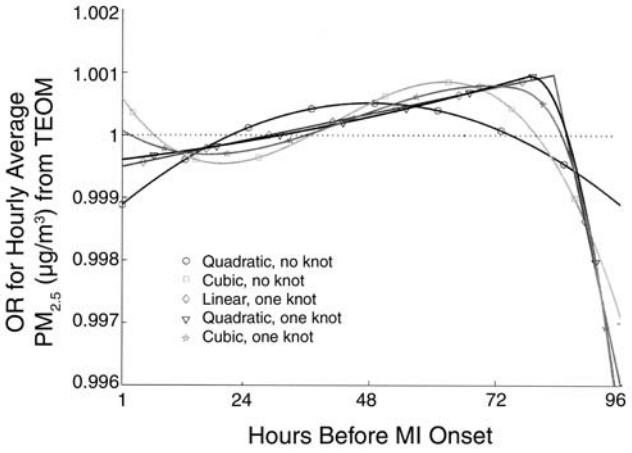

Figure B.3. Effect estimates of $PM_{2.5}$ concentrations on MI onset for 851 subjects who had a known time of onset: Comparison of five spline models using three control periods per case period stratified by 4-week time spans. $PM_{2.5}$ was measured using a TEOM.

- three control periods per case period stratified by 4-week time spans (bidirectional) (Figure B.3).

The control periods were matched to the case periods and conditional logistic regression models were used. No adjustment for possible confounders was attempted.

Case and control periods for which more than 75% of the 96 hourly exposure measurements were missing were deleted from the analysis. For all other periods, missing values were imputed by the mean of the next adjacent nonmissing values. If there was no nonmissing adjacent value on one side of the missing value, the nonmissing adjacent value on the other side was imputed.

SPLINE FUNCTION ESTIMATION

The function $s(t;\theta)$ is modeled using a B-spline as described by de Boor (1978). A spline of order k on the interval $[a,b]$ consists of polynomials of order k on the $m+1$ segments defined by m inner knots $a < t_1 < \ldots < t_m < b$. Adjacent polynomials are smoothly joined, so that the polynomials and their first and second derivatives agree at the knots.

Using a numerically favorable representation of splines, the space of splines can be spanned with $m+k$ basis functions $B_i(t)$, called B-splines. The knot list has to be augmented by $2k$ associated arbitrary "slack" knots. Without loss of generality, let

$$t_{-(k-1)} = a - (k-1),$$
$$t_{-(k-2)} = a - (k-2), \ \ldots, \ t_0 = a, \text{ and}$$
$$t_{m+1} = b, \ t_{m+2} = b+1, \ \ldots, \ t_{m+k} = b + k - 1.$$

Starting with $B_{i,1}(t) = 1$ if $t_i \le t < t_{i+1}$ and zero otherwise, the B-spline basis functions are defined by the recurrent relation

$$B_{i,k}(t) = \frac{t - t_i}{t_{i+k-1} - t_i} B_{i,k-1}(t) + \frac{t_{i+k} - t}{t_{i+k} - t_{i+1}} B_{i+1,k-1}(t).$$

The spline function has the form

$$s(t;\theta) = \sum_{i=-(k-1)}^{m} \theta_i B_{i,k}(t).$$

Calculations are performed in Epicure (Preston et al 1996). The spline parameters are estimated by maximizing the likelihood function.

When the best location of a single interior knot is estimated by a profile likelihood search, the maximum likelihood estimator is determined by evaluating the likelihood function for the series $a + 1, a + 2, \ldots, b - 1$ of possible locations of the single interior knot.

APPENDIX C. Quality Assurance Audit Statement

The conduct of the Peters' study was subjected to periodic, independent audits by a team from Hoover Consultants. This team consisted of auditors with experience in toxicology and epidemiology, a practicing board-certified physician epidemiologist, and an air monitoring expert. The audits included in-process monitoring of study activities for conformance to the study protocol and examination of records and supporting data. The dates of each audit are listed below with the phase of the study examined.

Written reports of each inspection were provided to the Director of Science of the Health Effects Institute, who transmitted these findings to the Principal Investigator. These quality assurance audits demonstrated that the study was conducted by a well-coordinated, experienced team according to the study protocol and standard operating procedures. The Investigators' Report appears to be an accurate representation of the study.

Date	Phase of Study Audited
2/14–16/2000	This audit consisted of a review of the study proposal, progress reports from year one and year two (5 months), instructions for data entry, methods used to identify myocardial infarction, patient eligibility, gathering and abstraction of medical records, administrative files in Augsburg, patient tracking information, comparison of medical records to form entries, tracking log maintained by PI, coding instructions, audit of diary data, staff training and qualifications. This audit also included an observation of a patient interview in the Central Hospital in Augsburg and observation of data entry of diary information, also performed in Augsburg. A site visit was made to the air monitoring station at St Stephan Cloister where TEOM and Harvard impactor $PM_{2.5}$ measurements were examined. Data collection from the monitoring station was assessed in terms of equipment operation, maintenance, and calibration.
10/22–24/2001	The audit team reviewed the progress reports since the previous audit, follow-up of previous audit findings, and the updated study manual. A sample of every tenth subject was selected and, of these, time permitted a complete audit of all data for 29 subjects. Computer algorithms for determination of myocardial infarction, time of onset, and other parameters were examined. A visit was made to the monitoring site where TEOM, CPC (particle number concentration), and Harvard impactor measurements were examined. All air pollution data were reviewed while on site including internally and externally generated data.
9/13–14/2004	An audit of the Final Report of the study was conducted. Data in the Report were audited against electronic files. The study file was audited to determine that satisfactory follow-up had occurred for previous audit findings.

B. Kristin Hoover, Audit Coordinator
Hoover Consultants

APPENDIX AVAILABLE ON REQUEST

The following document may be requested by contacting the Health Effects Institute at: Charlestown Navy Yard, 120 Second Avenue, Boston MA 02129-4533, +1-617-886-9330, fax +1-617-886-9335, or email (*pubs@healtheffects.org*). Please give (1) the first author, full title, and number of the Research Report and (2) title of the appendix requested.

APPENDIX D. German Version of Appendix A: Sample Questionnaire to Elicit Information About Symptoms and Activities on the Day of and for 3 Days Before the Subject's MI (original German version of Questionnaire in Appendix A).

ABOUT THE AUTHORS

Annette Peters is a senior scientist leading the working unit Air Pollution Health Effects at the Institute of Epidemiology of the GSF-National Research Center of Environment and Health in Neuherberg, Germany. In addition she is assistant professor (privatdozent) at the Ludwig-Maximilian University, Munich. She received her doctoral degree from the Ludwig-Maximilian University in Munich and a

master's degree in epidemiology from the Harvard School of Public Health. Her research focus is on the health effects of ambient air pollution. She has pioneered work on the cardiovascular health effects of particles and the health effects of ultrafine particles. She has received the American Thoracic Society David Bates award for outstanding young scientists.

Stephanie von Klot is a scientist at the Institute of Epidemiology of the GSF-National Research Center for Environment and Health, Neuherberg, Germany. She received her master's degree in public health from the Ludwig-Maximilian University, Munich. Her research focus is on individual and environmental risk factors for MIs.

Margit Heier is a scientist at the Institute of Epidemiology of the GSF-National Research Center for Environment and Health, Neuherberg, Germany. She received her medical degree from the Ludwig-Maximilian University, Munich. Her research focus is the impact of medication intake on cardiovascular disease development.

Ines Trentinaglia is a senior health data manager at the Institute of Epidemiology of the GSF-National Research Center for Environment and Health, Neuherberg, Germany. She received her training at the Academy for Health Data Management at the University of Ulm. Her interest is complex data programming and statistical analyses.

Josef Cyrys is a scientist at the Institute of Epidemiology of the GSF-National Research Center for Environment and Health, Neuherberg, Germany. He finished the study of chemistry at the Ludwig-Maximilian University, Munich and got his PhD from the agriculture faculty of the Technical University of Munich. At the GSF Institute of Epidemiology, he is responsible for exposure assessment; for example, for developing and validating sampling strategies for determining short- and long-term exposure of study populations to different gaseous and particulate air pollutants. Since 1998, he has supervised the GSF air pollution measurement station in Erfurt and, since 2001, the measurement site in Augsburg.

Allmut Hörmann is a senior scientist and deputy of the working unit Quantitative Methods for Evaluation Research at the Institute of Health Economics and Health Care Management at the GSF-National Research Center for Environment and Health, Neuherberg, Germany. She received her diploma in physics from the Technical University in Munich. For 29 years she has been managing editor of the Statistical Software Newsletter, now a section of Computational Statistics and Data Analysis. Since 2001, she is a member of the International Statistical Institute (ISI).

Michael Hauptmann is a principal investigator in the Biostatistics Branch of the Division of Cancer Epidemiology and Genetics at the US National Cancer Institute in Bethesda, MD. He received his PhD in statistics from the University of Dortmund, Germany. His research interests include statistical methods for assessing the effects of timing of exposure, methods for epidemiologic studies with missing information in exposure histories, polymorphisms in DNA repair genes and susceptibility to cancer of the lung and the breast, risk of cancer and other diseases from exposure to ionizing radiation, and the health effects of exposure to formaldehyde.

H Erich Wichmann is professor and chairmen of the Department of Epidemiology at the Ludwig-Maximilian University and the director of the Institute of Epidemiology at the GSF-National Research Center for Environment and Health. He received his doctoral degree in physics and his medical degree from the University of Düsseldorf. His research has focussed on environmental and occupational agents; currently, it spans from allergy development in newborn infants and children to chronic diseases in older persons. Major focuses are the application of molecular and genetic tools in epidemiologic studies.

Hannelore Löwel is a senior scientist leading the working unit Epidemiology of Chronic Diseases at the Institute of Epidemiology of the GSF-National Research Center of Environment and Health in Neuherberg, Germany. In addition she is head of the population-based register of acute MI of the study region of Augsburg, which was part of the WHO MONICA project (1985–1995), and then continued in the frame of the Cooperative Health Research in the Region Augsburg (GSF-KORA). She received her doctoral degree and a master's degree in social medicine (facharzt für sozialhygiene) from the Humboldt University in Berlin. Her research focus is on time trends and determinants in cardiovascular and metabolic diseases.

OTHER PUBLICATIONS RESULTING FROM THIS RESEARCH

Peters A, von Klot S, Heier M, Trentinaglia I, Hörmann A, Wichmann HE, Löwel H. 2004. Exposure to traffic and the onset of myocardial infarction. N Engl J Med 351:1721–1730.

ABBREVIATIONS AND OTHER TERMS

AIC	Akaike information criterion
APHEA	Air Pollution and Health: A European Approach [study]
CI	confidence interval
CO	carbon monoxide
CPC	condensation particle counter
df	degrees of freedom
ECG	electrocardiogram
HI	Harvard impactor
IQR	interquartile range
LOESS	locally weighted smoothing scatterplots
MET	metabolic equivalent unit
MI	myocardial infarction
MONICA	MONItoring of trends and determinants in CArdiovascular disease [study]
NO	nitric oxide
NO_2	nitrogen dioxide
O_3	ozone
OR	odds ratio
PM_{10}	particles with an aerodynamic diameter less than 10 μm
$PM_{2.5}$	particles with an aerodynamic diameter less than 2.5 μm
RR	relative risk
SO_2	sulfur dioxide
TEOM	tapered element oscillating microbalance
TNC	total number concentration [of particles]
TSP	total suspended particles
ULTRA	Exposure and Risk Assessment for Fine and Ultrafine Particles in Ambient Air [study]

COMMENTARY ON PART I
Health Review Committee

INTRODUCTION

Ambient (outdoor) particulate matter (PM*) is a complex mixture of solid and liquid particles suspended in air. The size (ranging from approximately 0.005 to 100 µm in aerodynamic diameter), chemical composition, and other physical and biological properties of these particles vary spatially and temporally. This variability in PM characteristics derives largely from differences in the sources of pollution. These sources may be natural or the result of human activities, such as driving vehicles and operating manufacturing or power plants. In addition, reactive species in the atmosphere combine to generate secondary particles such as sulfates that may comprise a significant fraction of total PM at a given site. Ambient PM levels in any particular location are also affected by local geography, weather, and seasonal patterns.

Although the characteristics of PM differ from place to place, epidemiologic studies in diverse locations have reported associations between increases in levels of PM and short-term increases in morbidity and mortality (reviewed in Health Effects Institute 2001, 2002). Exposure to PM over several years has also been associated with increased mortality from cardiopulmonary causes (Dockery et al 1993; Pope et al 1995, 2002). On the basis of these and other results, many governmental agencies have set regulatory standards or guidelines for levels of ambient PM. To protect the general population and groups considered most vulnerable to adverse effects from PM in the United States, the US Environmental Protection Agency 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 PM_{10} (the size considered respirable in humans); the EPA monitors levels of both particle sizes.

Among the most critical questions in PM research are the size and chemical composition of particles that have the potential to cause harmful human health effects (National Research Council 2004). A key related issue is the toxicity of ultrafine particles, which are less than 100 nm in diameter. Some scientists believe that this particle fraction may be particularly toxic (see Scientific Background). Also critical are the biologic mechanisms of PM effects that may underlie the epidemiologic associations reported between exposure to PM and morbidity and mortality. Because people with compromised cardiac or airway function are considered particularly susceptible to the effects of PM (reviewed in US Environmental Protection Agency 1996), much current PM research is focused on evaluating PM effects on the respiratory and cardiovascular systems (reviewed in Health Effects Institute 2002).

In 1998, HEI issued Request for Applications (RFA) 98-1, "Characterization of Exposure to and Health Effects of Particulate Matter," to address these topics. A key component of RFA 98-1 was to evaluate the health effects of exposure to ambient particles in people particularly sensitive to PM. In response to the RFA, Dr Annette Peters and colleagues proposed an epidemiologic study to assess the association between exposure to particulate air pollution and the onset of nonfatal myocardial infarction (MI). Specifically, Peters and colleagues proposed to use data from a registry of patients who had experienced coronary events to assess whether exposure to ultrafine particles, $PM_{2.5}$, or gaseous pollutants had been associated with MI onset up to 2 hours later. The HEI Research Committee recommended Peters' study for funding. The Committee thought that Peters' approach, a case–crossover design in which each individual acts as his or her own control, had the potential to provide important information about the association of exposure to air pollutants, and ultrafine particles in particular, with the induction of a nonfatal MI.†

SCIENTIFIC BACKGROUND

CARDIOVASCULAR EFFECTS OF PM

Before the current study began, epidemiologic studies had found associations between cardiopulmonary mortality and exposure to $PM_{2.5}$ over several years (Dockery et al 1993; Pope et al 1995). In addition, other studies had reported associations between increases in daily hospital admissions for cardiovascular diseases and levels of different types of PM or its components: PM_{10} (Schwartz and

* A list of abbreviations and other terms appears at the end of the Investigators' Report.

This document has not been reviewed by public or private party institutions, including those that support the Health Effects Institute; therefore, it may not reflect the views of these parties, and no endorsements by them should be inferred.

† Dr Peters' 3-year study, "Particulate Air Pollution and the Onset of Non-Fatal Myocardial Infarction—a Case–Crossover Study," began in October 1998. Total expenditures were $757,000. The draft Investigators' Report from Peters and colleagues was received for review in September 2002. A revised report, received in September 2003, was accepted for publication in June 2004. During the review process, the HEI Health Review Committee and the investigators had the opportunity to exchange comments and to clarify issues in both the Investigators' Report and in the Review Committee's Commentary.

Morris 1995; Schwartz 1997), black smoke (Poloniecki et al 1997), and sulfates (Burnett et al 1995). Studies had also linked exposure to carbon monoxide (CO) with hospitalization for congestive heart failure and other cardiovascular diseases (Morris et al 1995; Schwartz 1997). After the current study was funded, Peters and colleagues reported results from a case–crossover study of patients in Boston, Massachusetts, in which they found an increased risk of MI associated with exposure to $PM_{2.5}$ during both a 2-hour and 24-hour period before MI onset (Peters et al 2001).

The mechanism by which exposure to air pollutants, and PM in particular, might affect cardiovascular function is not clear (Brook et al 2004). Seaton and colleagues (1995) proposed that particle deposition in the airways would lead to a systematic inflammatory response that would induce an acute-phase response. The acute-phase response, part of the body's defenses to infectious and other noxious agents, is characterized by the production, within hours of exposure, of proteins in the circulation that include fibrinogen and C-reactive protein. Because fibrinogen binds to platelets and contributes to their aggregation, Seaton and colleagues proposed that particle deposition in the airways would subsequently lead to a transient increase in the coagulability of blood. This would in turn result in an increased risk of thrombus formation and possible cardiovascular consequences. In support of this hypothesis, Peters and colleagues (Peters et al 1997a) found an increase in plasma viscosity associated with exposure to PM during an air pollution episode in Augsburg, Germany.

In addition, at the time the current study was funded, preliminary results of controlled exposures in nonhuman species suggested that PM could affect cardiovascular responses: Healthy dogs exposed to concentrated ambient particles in Boston showed changes in normal cardiac rhythm (Godleski et al 1997). Furthermore, in a study with rats that had been treated with monocrotaline to produce pulmonary hypertension and right-heart hypertrophy, instilling high concentrations of residual oil fly ash (a highly toxic, combustion-generated, urban particulate that is rich in metals) induced sometimes fatal arrhythmias (Campen et al 1997; Watkinson et al 1998).

TOXICITY OF ULTRAFINE PARTICLES

Ultrafine particles are the dominant contributors of particle numbers in the $PM_{2.5}$ particulate fraction; for example, a particle mass concentration of 10 $\mu g/m^3$ would contain only one fine particle of diameter 2.5 µm, but more than two million ultrafine particles of diameter 0.02 µm (Oberdörster et al 1995). Ultrafine particles are emitted in high numbers by combustion engines, but are short-lived because they combine with each other or with larger particles to form particles in a larger size range. Thus, the concentration of ultrafine particles decreases with distance from highways.

Although particles of several different size ranges have been associated with health effects, some scientists have hypothesized that ultrafine particles may be especially toxic. This hypothesis is derived from suggestions based on initial results in several studies (reviewed in Utell and Frampton [2000]; Frampton [2001]; and Oberdörster [2001]):

- Smaller particles have a greater total surface area per unit of mass than larger particles. Thus, for a given mass, smaller particles may present a larger surface area for interacting with airway tissue or for transporting toxic material associated with the particle surface into the airways.
- In vitro studies suggest that ultrafine particles may not be as effectively phagocytosed (ie, ingested for removal) as larger particles by cells of the innate immune response.
- On the basis of size, models predict that a higher proportion of ultrafine particles of ~ 20 nm than of larger particles reach the air-exchanging alveolar region of the lung. On the basis of mass, however, more larger particles than smaller particles reach this lung region.
- When particles have been instilled intratracheally into animals, on the basis of mass, ultrafine particles were more effective than fine particles in inducing airway inflammatory responses.
- In some recent studies ultrafine particles appeared to move rapidly out of the airways and into the circulation (Nemmar et al 2001, 2002).

Few studies have compared the effects of exposure to ultrafine particles and to fine particles via inhalation, the normal physiologic route. The results of recent studies suggest that properties other than size, such as solubility, are likely to play an important role in particle effects (Leikauf et al 2001; Hahn et al 2005).

Before the current study began, some epidemiologic studies had described associations between increases in respiratory effects and exposure to ultrafine particles in children with asthma (Pekkanen et al 1997; Peters et al 1997b). However, these studies found no greater effect for ultrafine particles than for fine particles, so they did not establish whether ultrafine particles had a larger independent effect. In addition, during the early stages of the current study, Wichmann and colleagues (2000) reported that mortality was associated with ultrafine particle levels in Erfurt, Germany. The association between ultrafine particles and mortality, however, was not greater than associations for other components of the PM mix. Few studies have evaluated the effects of controlled human inhalation

exposure to ultrafine particles: Anderson and colleagues (1992) found little or no effect on respiratory function or symptoms immediately after 15 healthy and 15 asthmatic volunteers inhaled 100 μg/m^3 ultrafine sulfuric acid aerosol for 2 hours with intermittent exercise. Kuschner and colleagues (1997) found little or no effect on cell numbers and cytokine concentrations in bronchoalveolar lavage fluid, pulmonary function, or peripheral blood neutrophil concentrations of 6 healthy volunteers 18 to 20 hours after they had inhaled a high concentration of fine and ultrafine magnesium oxide particles. A more recent study (Frampton et al 2004) found little or no effect on respiratory or cardiovascular function of healthy and asthmatic volunteers exposed to ultrafine carbon particles (10 or 25 μg/m^3) for 2 hours with intermittent exercise.

The current study was intended to address whether acute exposure to ultrafine particles and $PM_{2.5}$ was associated with the induction of a nonfatal MI. In addition, the study planned to evaluate an association between MI onset and exposure to other ambient pollutants and to other possible activity-related triggers, such as exercise or time spent traveling by various modes of transportation.

AIMS AND STUDY DESIGN

Peters and colleagues hypothesized that MI onset is (1) associated with acute exposures to particulate air pollution up to 2 hours before the event, and (2) specifically associated with the number of ultrafine particles rather than the mass of fine particles. They reasoned that a 2-hour time frame would average out local fluctuations in particle concentrations but still capture short-term variation in exposure. This was reasonable because earlier studies had found an increase in MIs associated with triggers such as strenuous physical exertion, anger, and sexual activity up to 2 hours before the event (Willich et al 1993; Mittleman et al 1993, 1995; Muller et al 1996). In addition, as we describe under Scientific Background and more fully in the Discussion, Peters and colleagues' reported results from a study in Boston in which exposure to fine particles was associated with the induction of MI within 2 hours (Peters et al 2001).

To assess the onset of nonfatal MI, Peters and colleagues studied people in Augsburg, Germany who had survived an MI and had provided information to the local Coronary Events Registry. This Registry had been set up in 1985 as part of the World Health Organization's multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) Project.

Participants were interviewed about their activities up to 4 days before MI onset, thus providing information about possible triggers of an MI and the impact of time spent in different microenvironments, such as being in traffic or outdoors. To evaluate the effects of exposure to air pollutants on MI onset, the investigators measured levels of particulate pollutants in outdoor air in Augsburg. They also obtained information about levels of gaseous pollutants and weather conditions from a local agency, the Bavarian Air Monitoring Network.

The major approach Peters and colleagues used to determine whether exposure to pollutants was associated with MI onset was a case–crossover analysis. In this approach, each person who had had a nonfatal MI acted as his or her own control; exposures to pollutants during a specified time period relevant to the occurrence of MI onset (the case period) were compared with exposures during an event-free, different time period (the control period). As described in the accompanying sidebar, by appropriately selecting control periods, rather than a control population, this approach controls for many possible confounders that do not vary with time. The strengths and weaknesses of this approach are discussed fully in the sidebar and by Janes and colleagues (2004b).

STUDY PARTICIPANTS

The study participants were patients in 11 hospitals in the Augsburg region who survived at least 24 hours after an MI and were entered in the Coronary Events Registry during the period February 1999 through July 2001. The diagnosis of MI for entering patients into the Registry was based on the MONICA Project definition: chest pain for 20 minutes or more; changes in electrocardiogram (ECG) readings; and increases above the normal range of enzymes in plasma associated with myocardial ischemia. These patients completed an interview about their smoking habits, medical history, and other factors.

For 851 such patients, the date and time of MI onset could be validated. The time of onset of the MI was defined as the time when angina pectoris (chest pain or tightness) that persisted for more than 20 minutes had begun. For a portion of these 851 subjects, the Registry nurses continued the interview to acquire more information for this study: they completed a questionnaire about the subject's exposure to environmental tobacco smoke, respiratory infections, their presence in the study area, activities (eg, time spent indoors, driving, strenuous exertion), emotions, possible symptoms during each hour of the 4 days leading up to the onset of MI, and the date and time of the MI. Of the 851 subjects, 691 provided information complete enough to be used in analyses of case and control periods. The median time between MI onset and interview was 9 days (see Table 8 in the Investigators' Report).

CASE–CROSSOVER DESIGN

The study by Peters and colleagues illustrates the advantages and challenges of using the case–crossover design in combination with Poisson regression analyses of time-series data.

In a conventional case–control study, the experiences of one group of subjects with an illness (the case group) are compared with a those of another group of subjects without the illness (the control group). A case–crossover analysis is in many ways similar to a case–control study except the case subject and the control subject are the same person, as in a crossover experiment. Conventional case–control studies (and most cohort studies) usually address the question: "Why did these people become ill although other people did not?"; a case–crossover study addresses the question: "Why did these people become ill now and not before?"

The Peters study combined these two questions when it asked "Do peaks of air pollutants trigger heart attacks in people who are already susceptible?" In other words, "Is air pollution part of why the heart attack occurred now rather than yesterday, especially in people who are susceptible rather than in people who are not."

ADVANTAGES

The first test of any epidemiologic hypothesis is whether an association is observable. One advantage of a case–crossover design is that it can make a weak association more observable than other study designs by defining time zero as the onset of the outcome rather than as an exposure episode. In the Peters case–crossover study, time zero was the onset of pain that led to a diagnosis of MI. Scaling events relative to time zero can help investigators detect patterns, such as the induction time between pollutant exposure and outcome. Peters' finding that the concentration of $PM_{2.5}$ 2 days earlier was associated with a 4% to 17% increase in the relative risk of MI onset illustrates this well. Whether it is causal or a chance association, it might have been obscured in analyses that synchronize exposure times (eg, peaks of air pollutants) rather than outcome times (eg, onset of MI pain).

The second test of an epidemiologic hypothesis is whether the observed association can be explained by confounding. Confounding factors are those that are associated with both the exposure and the outcome, but are not part of the causal pathway between the exposure and outcome.

Here a second advantage of the case–crossover design comes into play: clarity of comparisons because of self-matching. When the case period and the control periods are related to the same person, the study avoids bias from many immeasurable potential confounders because they are constant characteristics of each subject. (Individuals in a control group are not perfectly matched with individuals in the case group, whereas individuals are perfectly matched with themselves.)

Confounding is further controlled when considering exposures that change over time; this requires selecting an appropriately matched control period. After setting time zero to be the onset of MI pain, the period (eg, 1 hour) before MI onset is designated as the case time-window (or case period) when possible triggering factors are examined. Then the question arises "With what other time interval or intervals should the case period be compared?" The investigator must select one or more control time-windows (or control periods) carefully to avoid confounding.

The need for good selection of control periods is illustrated in the Peters study by the fact that traffic density, air pollution concentrations, and MI onset all have circadian patterns. Therefore, the control periods should be selected at the same time of day as the case period. If the control period is obviously a good match for the case period, as in this example, it is easy for readers to understand the analysis and to have confidence that confounding has been controlled. Simple crude analyses from case–crossover studies are fairly easy to understand, despite the fact that they control for many confounders by self-matching the participants. Even presenting the raw counts of subjects in case and control periods, as in Figures 6 and 7 of the Investigators' Report, often gives a good overall impression of the results.

MEASUREMENTS OF POLLUTANTS

The investigators obtained hourly information about particle number concentration and mass by using continuous measurement devices at a residential site, the cloister of a monastery approximately a half-mile outside central Augsburg. They used a condensation particle counter to measure total number concentration of ultrafine particles and a tapered element oscillating microbalance to measure $PM_{2.5}$ mass. For comparison, $PM_{2.5}$ mass measurements were also obtained every second day using a Harvard impactor at the same site. PM_{10} levels were measured at a different location in central Augsburg. Peters and colleagues obtained hourly information on mean levels of gaseous pollutants—ozone (O_3), CO, sulfur dioxide (SO_2), nitric oxide (NO), and nitrogen dioxide (NO_2)—and of meteorologic variables (temperature, relative humidity, and air pressure) from the Bavarian Air Monitoring Network.

METHODS OF DATA ANALYSIS

The data analysis plan evolved, in part, as a result of discussions between the investigators and the HEI Research Committee. For the case–crossover analysis, Peters and colleagues estimated the effects of ambient concentrations of individual pollutants measured before the onset of MI. In unidirectional analyses (that is, the control periods were selected before, but not after, onset of MI), the case period was determined as an hourly interval (up to 6 hours) or as 24-hour intervals up to 5 days preceding MI onset. For control

Poisson regression analyses of time-series data also use methods to control for time of day, day of the week, and season. However, making adjustments for possible confounding factors by adding terms to a multivariate model in a Poisson regression requires many readers to make a leap of faith in the statistical model and the investigators. If possible, it is best to use a case–crossover analysis for clarity and Poisson regression analyses for their greater statistical power. If the case–crossover analyses produce the same results as the Poisson regression analyses of time-series data, researchers and readers are reassured.

Perhaps the biggest advantage of a case–crossover study is the opportunity to collect rich data on possible confounders from the subjects being studied. For example, Peters evaluated self-reported information about subjects' activities before MI onset, and found that strenuous exertion was much more frequent than usual in the hour before MI onset. Also, time spent traveling by bicycle, public transport, or car occurred more than twice as often as expected in the hour before MI onset. One can imagine that transport-related physical exertion could produce an association between peaks of transport-related air pollution and onset of MIs; this association might be deemed spurious when it is not. The data needed to rule out this possibility are often missing from other types of air pollution studies because collecting experiential data from subjects is usually expensive. If the decision has been made to collect experiential data, then a case–crossover study can be economical compared with case–control or cohort studies because one interview with a subject provides information about both case and control periods.

After an epidemiologic association has been shown to exist and not to disappear when potential confounders are controlled, the third stage of testing is the assessing modifications of the association. The self-reported data available to Peters helped to identify possible modifiers of their susceptibility (for example, possible interactions between strenuous exertion and exposure to outdoor $PM_{2.5}$ concentrations may have increased susceptibility to MI onset). Of course, analyzing such modifiers in any epidemiologic study involves subdividing the data. In case–crossover studies the problem seems to be greater because attention is focused on rare events that modify susceptibility. For example, at the peak of air pollution (or any other time of the day) only a tiny fraction of the population is busy doing strenuous physical exertion. This means the subgroups are often too small for rigorous statistical tests of hypotheses about modification. Consequently, in the current study's analysis of interactions between PM concentrations and various levels of strenuous activity, although some point estimates of effects were large, the corresponding confidence intervals were very wide. Such wide confidence intervals, which indicate large statistical uncertainty, were the direct result of the small number of people strenuously exerting themselves at any one moment.

A unique feature of the present study is the complete history gathered about the subjects' locations and movements in the 4 days before the MI. This information was linked to the local air quality monitoring data to produce a better estimate of the subjects' exposures to pollutants. Not only did this improve the precision of exposure measurements, it may also provide clues on possible mechanisms (intermediate steps between cause and effect) by which the pollutants might exert their influence. For example, in other studies of triggers of MI unrelated to air pollution, clues about a mechanism came from observing that the relative risk of physical exertion appeared to be lower among people taking aspirin. In other words, aspirin appeared to modify susceptibility to MI brought on by exertion.

The same applies to a pollutant's effect being transiently modified by an episode of exertion. More accurate measurement of the timing and locations of exposure to pollutants increases the investigators' ability to detect when transient modifiers happen to coincide with pollution. A hypothetical example is if for bicyclists the risk of MI onset from exposure to pollution was greater in slowly moving congested traffic than when cars are moving fast. Such differences between relative risks in different microenvironments could help generate hypotheses about aspects of those microenvironments that might increase susceptibility.

(*Continued*)

periods, the investigators selected hourly intervals at a comparable time of day, 1, 2, or 3 days before the onset of MI. For 24-hour intervals, control periods were selected 1, 2, or 3 days before the case period. They chose time-matched periods because they recognized that crucial factors such as traffic density, air pollution, and MI onset have circadian patterns. The investigators conducted conditional regression analyses. They reported estimates of effects (per interquartile range increase in air pollutant concentration) as the odds ratio (OR) from the case–crossover or relative risk (RR) from other analyses with 95% confidence intervals (CIs) expressing the precision of the estimate of the effect. They also presented *P* values for specific hypothesis tests of significance.

To evaluate the effects of specific activities on risk of MI onset, the investigators conducted only unidirectional case–crossover analyses because the symptoms and occurrence of the MI would have affected activities after the event. For other variables that would not be affected by MI onset, such as pollutant concentrations, the investigators compared results from unidirectional analyses with results from bidirectional analyses, in which control periods are selected both before and after the outcome of interest. In addition, they conducted stratified analyses choosing the same weekdays of the same month as control periods.

Peters and colleagues also conducted Poisson regression analyses to evaluate effects for pollutant concentrations lagged 1, 2, 3, 4, or 5 days; for 5-day and 15-day mean concentrations; and for 30-day and 45-day moving averages of concentrations. Analyses were adjusted for trends, season,

CHALLENGES

The advantages of case–crossover studies are not without a price. New possibilities for bias are introduced by how subjects are recruited, control periods are selected, and subjects recall events.

Subject-selection bias usually results from the recruitment process; for example, study subjects are recruited from several hospitals in a certain area. At one centrally located hospital, patients who qualify for the study may be recruited every day, whereas at hospitals closer to rural areas, subjects may be identified and recruited only once a week. Some eligible subjects could be lost at the more rural hospitals because of the infrequent identification and recruitment process. Usually this would not be a problem. But if a study with this recruitment plan should also find a strong relation between the outcome of interest and a particular day of the week, then it might produce a selection bias. For example, $PM_{2.5}$ concentrations might be associated with MI onset if patients are recruited only on Mondays and pollution is worse on Mondays than Sundays. Control periods might need to be selected more carefully to compensate for subjects having been recruited more widely on certain days of the week.

Another source of subject-selection bias could be excluding subjects with poor prognosis; for example, subjects who suffered fatal MIs are unavailable for interviews and thus excluded. If more fatal MIs occur on weekends when hospital staff are reduced or, conversely, more occur on weekdays when ambulances take longer to get patients to the hospital, these factors could result in some subject-selection bias. This example shows why it would be better to have data available on all MIs, both fatal and nonfatal, to be analyzed by Poisson regression in a time-series approach. If similar associations are seen in both the Poisson regression and case–crossover analyses, the likelihood is low that a subject-selection bias explains the association.

Control period–selection bias has been a major problem in some case–crossover studies. For example, if MIs are found to be more frequent on a weekday (the case period), the control periods may need to be selected from the same day of the week. This is problematic if the study relies on interviews because a person's memory of events one week before is much poorer than the day before. Matching case and control periods is not an issue with air pollution data, however, because pollutant concentrations are recorded when monitored.

Another limitation of a case–crossover study investigating behavioral triggers of MI is that control periods can be selected only before the MI. Periods after the MI cannot be used as control periods because MIs cause large changes of individual behavior. When control periods are selected only before the outcome, it is called a unidirectional case–crossover design. A problem with this design arises if a strong constant trend upward (or downward) is observed in the frequency or intensity of a pollutant exposure. Then an earlier control day will always have a lower (or higher) exposure intensity. This is a special kind of control period–selection bias, but it is not a major problem in air pollution studies if the case and control time periods are close. Therefore, a unidirectional design with a control period only 4 days before the MI would have essentially no control period–selection bias attributable to the choice of a unidirectional design.

In a bidirectional case–crossover design, each control period before the outcome event is balanced with a comparable control period after the event. Such a control period could be used in a study of a milder type of illness, such as recurrent episodes of asthma. The patient's behavior pattern immediately after an asthma episode would probably differ from their normal pattern, but as the days pass, the patient is likely to return to usual habits. Then it would be possible to select control periods equally before and after the outcome, and to collect additional data by interviewing the subjects again after the later control period. Thus, the effect of exposure could be estimated by comparing the data from the case period with the data collected on control periods both before and after the case period.

Of course, for a study of MIs, a bidirectional case–crossover analysis based on interviews before and after the MI would be seriously biased by reverse causation. That is, the patient's MI would probably cause a change in their future exposure to pollutants and certainly limit their episodes of strenuous exertion.

In contrast, a bidirectional analysis of the effects of air pollution is likely to be unbiased because the patient's MI cannot influence concentrations of pollutants. When comparing results from the

temperature, relative humidity, barometric pressure, and day of the week.

In addition, they conducted spline regression analyses to assess the effect of varying the induction time (ie, the time between exposure to the pollutant and MI onset), from 1 hour to up to 6 hours before the event (based on 1-hour average pollutant concentrations); and for periods of up to 5 days preceding the event (using 24-hour average pollutant concentrations). Placement of knots in the spline models was varied in the sensitivity analyses. To assess linearity of the association between the level of an air pollutant and the onset of an MI, the investigators used quartiles of observed pollutant concentrations as cut points.

The investigators also considered effects of confounding and evaluated effect modification. A confounder is a factor that is associated with both the exposure of interest (pollutant) and the outcome of interest (MI onset), but is not directly part of the causal pathway for the factor under investigation. For example, in this study, season was considered a possible confounder because particle concentrations in the area are higher in winter than in summer, and MI frequency is also higher in winter than in summer. An effect modifier is a factor, such as a chronic disease, that may alter the size or direction of the effect of air pollution on a patient's risk of developing an MI. In this study, exercise was considered as both a potential confounder and an effect modifier.

case–crossover and Poisson regression analyses of air pollutants, Peters used a bidirectional case–crossover design: Knowing that (1) the trends in pollutant concentrations were weak, (2) MIs showed no trends across the study period, and (3) MI frequency was not associated with day of the week, there was no reason to expect that unidirectional analyses would differ substantially from bidirectional analyses. Any differences would be due to chance.

Recall bias can result from several circumstances in gathering data from subjects. The timing of the interview, the questions asked, and the subject's ability to remember all affect the quality and precision of subject-related data.

Timing of an interview

Some subject interviews may happen within a few days of the event of interest, others within a week or two. Most people find it difficult to remember what happened, for example, 9 days ago, as in the Peters study. For many MI patients, the day of their heart attack is recalled and described repeatedly to family members and hospital staff. The same cannot be said for the day before or other days preceding the heart attack. The more time that elapses between the day of the MI and the interview, the less likely a patient is to remember accurately the activities or circumstances on the days before the event.

Data gathered during an interview

Regardless of when the interview takes place, some information fails to be reported or recorded. Individual interviewers may operate under different assumptions: A problem could arise from the data collection form or from an interviewer's interpretation of when the "4th day before the MI" begins and ends; does each "day" start at midnight or at increments of 24 hours before MI onset?

Subjects may fail to report some events because either they do not remember (selective recall) or they do not think them important. Another possibility is that a subject overemphasizes personal conditions or certain activities before the MI: Shortness of breath, a symptom of MI, may have made exercise seem (and be reported as) more strenuous than it actually was.

If subjects are asked to describe their activities in the first hour before the MI, and then the second through fifth hours before, they will probably provide fairly accurate information (for example, they may recount four activities that required strenuous or a higher degree of exertion). If they are asked to describe their activities during those same hours on the previous day, it is likely they will forget approximately half the activities that also called for strenuous exertion. When a case period 2–5 hours before MI onset is compared with a control period of the same hours on the day before, the result may appear to be a significantly increased risk of MI due to strenuous exertion. However, recall bias may not influence a comparison of the first hour before MI onset to the period 2 to 5 hours earlier. Fortunately case–crossover studies often provide data on multiple alternative control periods so that conclusions do not rest on only a single comparison, such as the event day and the preceding day.

Regularity of activities or events

Some patterns of activities are quite regular and therefore easier to recall: "It was a weekday at 9:30, so I must have arrived at my office half an hour earlier. I always climb stairs to my office, so I must have climbed stairs just before my heart attack." It is more difficult to recall episodes of such an activity that are not routine. Therefore, in case–crossover analyses using interview data, we must be more skeptical of any association found with self-reported behaviors that were unusual but uneventful.

Of course, biased self-reporting of exposure is not a problem with air pollution data because the pollutant concentrations are not self-reported. The only self-reported piece of information that could bias the main analysis is timing of MI pain onset. If the patient is aware that the main purpose is to study air pollution, their reported time of pain onset could conceivably be influenced by their memory of their last exposure to pollutants. But it is easy to avoid telling patients the primary hypothesis of a study.

The opportunity for recall bias means that case–crossover studies in which subjects are interviewed are not ideal for testing hypotheses concerning weak causal effects. But air pollution studies have the advantage of no recall bias for the primary exposure of interest. Therefore, a case–crossover design, with careful selection of case and control periods, can be a valuable complement to other conventional designs.

RESULTS

The main results of the case–crossover analyses presented in Tables 9, 11, 12, 16, and 19 of the Investigators' Report are summarized in the Commentary Table. These and other results are discussed below.

ASSOCIATION BETWEEN AIR POLLUTANTS AND ONSET OF NONFATAL MI

Ultrafine Particles

No statistically significant association was found between nonfatal MIs and ultrafine particle numbers either concurrently or 1 to 6 hours earlier (unidirectional analyses), or up to 5 days earlier (unidirectional and bidirectional analyses). When a unidirectional approach with a 3-day lag was used, the increase in relative risk of MI onset associated with the interquartile range increase of 7800 particles/cm^3 was 13% (OR 1.13 [95% CI 0.98, 1.31]; $P = 0.1$).

$PM_{2.5}$

No statistically significant association was found between nonfatal MI onset and $PM_{2.5}$ concentrations concurrently or 1 to 6 hours earlier (unidirectional analyses). $PM_{2.5}$ levels 2 days before the event were associated with

Commentary Table. Main Findings from Case–Crossover Analyses: Associations Between Nonfatal MI and Either Air Pollutants or Subject-Specific Triggers

Possible Trigger	Time Before MI Onset[a]	Association[b]		Type of Analysis[c]
		OR	95% CI	
Pollutant				
Ultrafine particles[d,e]	Concurrent or 1–6 hours	None		U
Ultrafine particles[d]	Same day, 1, 2, 4, or 5 days	None		U, B
	3 days	1.13	0.98 , 1.31	U
$PM_{2.5}$[e]	Concurrent or 1–6 hours	None		U
$PM_{2.5}$	Same day, 4, or 5 days	None		U, B
	1 day	1.10	0.96 , 1.25	U
		1.07	0.98 , 1.17	B
	2 days	1.18	1.03 , 1.34	U
		1.08	0.99 , 1.17	B
	3 days	1.07	0.94 , 1.22	U
		None		B
PM_{10}	Same day, 3, 4, or 5 days	None		B
	1 day	1.07	0.98 , 1.16	B
	2 days	1.09	1.00 , 1.18	B
Gases: NO_2, CO, SO_2, and O_3	Same day or 1–5 days	≤ 1.05, except:		B
	1 day	NO_2 1.07	0.97 , 1.18	
	2 or 3 days	CO 1.09 & 1.07		
	2 days	SO_2 1.06	1.01 , 1.11	
Activity				All U
Strenuous physical activity	Concurrent	5.52	2.8 , 10.9	
	1 hour	8.05	4.0 , 16.3	
	2 hours	3.41	1.7 , 6.9	
	6 hours	7.74	2.5 , 23.8	
Less strenuous physical activity	Concurrent	1.65	1.1 , 2.4	
	1 hour	2.84	2.0 , 4.1	
	2 hours	2.33	1.6 , 3.4	
Walking	Concurrent	None		
	1 hour	2.39	1.3 , 4.4	
	2 hours	2.66	1.5 , 4.9	
Time spent outdoors	Concurrent	1.59	1.0 , 2.5	
	1 hour	4.12	2.7 , 6.4	
	2 hours	2.67	1.8 , 4.1	
Bicycling	Concurrent	2.92	1.1 , 7.9	
	1 hour	3.77	1.5 , 9.6	
	2 hours	2.49	0.9 , 6.6	
Time spent in traffic				
Any mode of transport	Concurrent	2.06	1.3 , 3.2	
	1 hour	3.11	2.1 , 4.6	
	2 hours	1.91	1.2 , 2.9	
Public transport	Concurrent	6.46	0.6 , 67.7	
	1 hour	4.03	1.2 , 14.1	
	2 hours	7.11	0.8 , 67.6	
Car	Concurrent	1.69	1.0 , 2.9	
	1 hour	2.63	1.7 , 4.1	
	2 hours	1.76	1.1 , 2.9	

[a] Ranges (eg, 1–6) indicate an analysis was conducted for each of the hourly or daily time points before MI onset.

[b] For each particulate or gaseous pollutant, the OR is associated with an increase in the interquartile range. *None* indicates an OR between 0.95 and 1.05.

[c] U = unidirectional, B = bidirectional.

[d] Assessed as total number concentration of particles.

[e] Based on hourly average pollutant concentrations; all other pollutant estimates based on daily averages.

onset of MI; the increase in relative risk depended on the control selection method: 18% in unidirectional analyses and 8% in bidirectional analyses (based on an interquartile range increase in $PM_{2.5}$ level of 7.7 $\mu g/m^3$). 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 (unidirectional and bidirectional analyses).

PM_{10}

PM_{10} levels 1 and 2 days before onset of nonfatal MI were associated with increased relative risk (7% and 9%, respectively) in bidirectional analyses, but the associations were not statistically significant.

Gaseous Pollutants

With some time lags, effect estimates for NO_2, CO, and SO_2 were between 1.05 and 1.10 in bidirectional analyses (NO_2—same day, and up to 2 days earlier; CO—2 to 4 days earlier; and SO_2—2 days earlier). With other time lags, ORs were less than 1.05 for these gases. For O_3, levels lagged 1 to 5 days were negatively associated with MI onset (OR < 1).

ASSOCIATION BETWEEN SUBJECT-RELATED TRIGGERS AND ONSET OF NONFATAL MI

The main results of the case–crossover analyses using the unidirectional approach were that strenuous activity—such as playing tennis or soccer and dancing—concurrently or 1 to 6 hours before MI onset was strongly associated with MI induction (OR range 2.37 to a maximum OR 8.05, [95% CI 4.0, 16.3] 1 hour earlier). Less strenuous physical activity, walking, time spent in traffic, and time spent outdoors were also associated with increased relative risk of MI onset up to 6 hours later; maximum relative risk (highest OR) generally occurred 1 to 2 hours before the event. ORs were generally in the range of 1.5 to 4.1. For time spent in public transportation, the ORs were higher with wide 95% CIs (concurrent—OR 6.46 [95% CI 0.62, 67.7]; 1 hour—OR 4.03 [95% CI 1.15, 14.1]; 2 hours—OR 7.11 [95% CI 0.75, 67.6]). (Note that these estimates of effects in traffic are somewhat larger than Peters and colleagues reported recently for this group of MI subjects (Peters et al 2004); in that analysis, the investigators used a different control selection strategy and adjusted for time of day.) High temperature was associated with increased relative risk, but low temperature was not. Temperature effects were modeled using a nonparametric approach (locally weighted smoothers with a span of 0.8) that allows for a flexible relation (Figure 22).

OTHER ANALYSES

Sensitivity Analyses and Effect Modification

As described in the preceding section, estimates of effect were sensitive to the method of control period selection in the case–crossover approach. Similar sensitivity was also found using time-series or Poisson regression estimates. For $PM_{2.5}$ (Table 9 and Figure 21), the unidirectional selection method produced the highest estimate of effect for a 2-day lag (OR 1.18), whereas bidirectional selection methods and Poisson regression estimates were consistent and resulted in lower estimates (OR < 1.08). For the gaseous pollutants NO_2, CO, and SO_2, estimates of relative risk for individual gases derived from time-series analyses were generally lower than estimates of OR derived from bidirectional case–crossover analysis (Table 12 and Figure 23).

Previously diagnosed cardiovascular conditions such as angina, hypertension, and MI increased the relative risk of MI induction associated with $PM_{2.5}$; that is, these conditions modified the estimated effect of $PM_{2.5}$. Associations with $PM_{2.5}$ were strongest in subjects who noted symptoms during the 4 days before MI onset (OR 1.21, Table 14).

A statistically significant and potentially important interaction was found between the relative risk of MI induction associated with $PM_{2.5}$ levels 2 hours before MI onset and time spent in traffic (Table 23). The potential effect modification of other activities, such as strenuous physical activity and time spent outside, on the association with lagged $PM_{2.5}$ levels was not consistent.

Other Results

Increased Relative Risk Using Long-Term Assessments of Pollutant Levels For time-series analyses, Peters and colleagues used Poisson regression and generalized additive models with 30-day and 45-day averages of individual pollutants (Tables 11 and 12). For particles (total number concentration, $PM_{2.5}$, and PM_{10}) and gaseous pollutants (NO_2, CO, and SO_2), the increases in relative risk were between 6% and 13%. No increased risk was found for O_3.

Induction Time The investigators used several models to explore whether the risk of MI onset varied with PM exposure at different times up to 96 hours before MI onset (Table 10 and Figure 20). For $PM_{2.5}$ the best model fit was obtained with a linear spline model with one interior knot at 82 hours, as an indication of the induction time (Figure 20). Cubic spline models using hourly $PM_{2.5}$ levels suggested a shorter induction time of approximately 48 to 72 hours.

DISCUSSION

This study tested specific hypotheses about ambient pollutant levels and the induction of a major clinical endpoint, nonfatal MI. The investigators designed, conducted, analyzed, and reported the study with great care. In addition, the study provided valuable information about associations between the onset of MI and other possible triggers, such as time spent in traffic and levels of gaseous pollutants.

PARTICULATE POLLUTION AND CARDIOVASCULAR EFFECTS

Using a variety of analyses that addressed different threats to validity, the investigators found no association between nonfatal MI onset and exposure to $PM_{2.5}$ or ultrafine particles (ie, total number concentration) up to 2 hours before the event. Thus, these results do not support the two main hypotheses that Peters and colleagues put forward at the start of the study. In addition, the investigators found no associations between MI induction and ultrafine particle levels up to 5 days before MI onset, indicating that ultrafine particles are not associated with MI induction over this time period. In other studies that assessed different endpoints, however, Peters and collaborators have reported associations with ultrafine particle levels: In one study (Wichmann et al 2000), ultrafine particle levels in the previous 4 to 5 days were associated with increased mortality; and in another study (Pekkanen et al 2002), ultrafine (and fine) particle levels in the previous 2 days were associated with depression of the cardiac ST segment during exercise testing, a change characteristic of myocardial ischemia. Differences in results from these investigations may be explained by several factors including the clinical endpoints evaluated and the populations studied.

As the investigators note, the precise location of the ultrafine particle monitor used in each study may also be important. If ultrafine particle levels vary spatially, then this measurement will tend to reduce any observed association toward the null. The highest levels of ultrafine particles are found close to roadways (Zhu et al 2002), so it is possible that the monitor in the current study, located in a monastery cloister and away from traffic, did not measure these particles. Monitors in other studies in which effects of ultrafine particles were detected may 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.

The fact that the investigators found a small increased relative risk of MI onset associated with $PM_{2.5}$ levels on days preceding the MI suggests that exposure to particles could have some impact on the development of a first or subsequent MI. These $PM_{2.5}$ results should be considered with results of other studies of acute effects of pollutants on the induction of cardiovascular events, and in particular with Peters and colleagues' case–crossover study of MI patients conducted in Boston (Peters et al 2001). That study reported an increased risk of MI associated with exposure to $PM_{2.5}$ in a 1- to 2-hour period (ORs ~1.10 for an increase of 10 $\mu g/m^3$) and a 24- to 48-hour period (ORs ~1.11 for an increase of 10 $\mu g/m^3$) before MI onset. Thus, the results of the current study and those of Peters and colleagues' Boston study (2001) are similar in that both show associations between MI induction and $PM_{2.5}$ levels lagged 1 or 2 days; and those associations show similar magnitudes of increased relative risk per unit of increase in $PM_{2.5}$.

In contrast, the current study did not find an effect of $PM_{2.5}$ exposure within 2 hours of MI onset and the 95% CI for the OR is concentrated near 1.00. Thus, this study does not support the very-short–term or hyperacute $PM_{2.5}$ effect on MI reported from the Boston study (Peters et al 2001). The investigators amply discuss possible explanations for the differences between the results of the two studies. Both used similar criteria for MI induction and had a similar age distribution of subjects. Compared with the Boston study, however, the current study had a higher proportion of men and a substantially higher proportion of subjects with hypertension, but a lower proportion of subjects who had had previous infarctions. In addition, the subjects in the current study may have been taking more up-to-date and hence more protective medications for cardiovascular disease. (The investigators noted that subjects were recruited between 1995 and 1997 in Boston and 1999 and 2001 in Augsburg.) Peters and colleagues also comment that the characteristics of $PM_{2.5}$ may differ between the two locations: For example, transported secondary sulfate particles dominated $PM_{2.5}$ during the summer in which the Boston study was conducted, whereas $PM_{2.5}$ from local sources dominated pollutant levels in the current study. Their implication that the toxicity of $PM_{2.5}$ may vary at different study sites merits further, systematic study. An alternative explanation for differences in results between the two studies is that the associations reported in the Boston study were due to chance rather than to real associations between PM levels and MI onset; additional studies are needed to adjudicate the differences.

One recently published study addressed these issues: Sullivan and colleagues (2005) reported the results of a case–crossover study of the onset of MI in over 3000 patients living in the Seattle area. Their principal analytical approach was to use a case and control selection strategy similar to one used by Peters and associates in the

current study: Peters compared the same day of the week for each week within a 28-day time span; Sullivan used the same day of the week within the same month. In contrast to the results of Peters' Boston study (Peters et al 2001), Sullivan and colleagues found small but not significant increases in MI onset associated with levels of $PM_{2.5}$ at either 2 or 24 hours before onset, in individuals with or without preexisting cardiovascular disease. Furthermore, using the same statistical approach that Peters and colleagues took in the Boston study, Sullivan and colleagues found little evidence of an association between MI onset and $PM_{2.5}$ levels 2 or 24 hours earlier. One explanation Sullivan and colleagues suggest for the lack of consistency between the results of the two studies is a difference in the characteristics of the pollution mix in the two study areas. They also suggest that Peters and colleagues' Boston study might have used a biased control selection strategy (Janes et al 2004a).

Some other recent studies have reported results similar to those of the time-series studies (see the Scientific Background section) that found associations between particulate pollution levels and cardiovascular endpoints (Dockery et al 1993; Burnett et al 1995; Pope et al 1995; Schwartz and Morris 1995; Poloniecki et al 1997; Schwartz 1997; Peters et al 2001). (As discussed below, these studies also found associations with concentrations of gaseous pollutants.) The recent studies include hospital admissions for cardiovascular causes (Ballester et al 2001; Le Tertre et al 2002a; D'Ippoliti et al 2003; Metzger et al 2004) and deaths attributed to cardiovascular causes (Hoek et al 2001; Le Tertre et al 2002b). In contrast, Peters and colleagues (2000) found little or no association with $PM_{2.5}$ levels in a study that evaluated the association between air pollutant levels and arrhythmia (another acute cardiovascular outcome); subjects had cardiovascular disease and an implanted cardioverter defibrillator. However, in the subset of patients whose defibrillators fired multiple times during the study, and thus may be a potentially sensitive subgroup, $PM_{2.5}$ levels lagged by 2 days were significantly associated with defibrillator discharge (OR 1.64 [95% CI 1.03, 2.62]) (Peters et al 2000).

In a follow-up study of cardiac patients with these devices that HEI will publish shortly, however, Dockery and colleagues did not find a statistically significant association between the induction of arrhythmias and $PM_{2.5}$ levels (Dockery et al 2005). Some studies, notably using a case–crossover approach to address whether PM is associated with sudden cardiac death in Seattle, Washington, have not found such associations (Checkoway et al 2000; Levy et al 2001; Sullivan et al 2003).

GASEOUS POLLUTANTS AND CARDIOVASCULAR EFFECTS

For the relations of the gaseous pollutants NO_2, CO, and SO_2 with MI onset, the investigators associations similar to those found for $PM_{2.5}$. These results may be important because most of the NO_2 and CO in cities is attributable to automobile traffic (Hirsch et al 1999). As with ultrafine particle levels, NO_2 levels are spatially variable, so a monitor sited away from traffic may not measure the full extent of NO_2 exposure. At the same time, although SO_2 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 O_3 levels were not associated with MI onset suggests that exposure to this pollutant in the time frame examined has no effect on the onset of nonfatal MI.

The results reported in the current study between the levels of gases and MI induction parallel those of Peters and colleagues' Boston MI induction study (2001); some analyses showed positive, but not statistically significant, associations between NO_2 and CO concentrations lagged by 2 days with the onset of MI. In addition, in Peters and colleagues' (2000) arrhythmia study, NO_2 showed the strongest association of any pollutant with defibrillator discharge (5-day mean—OR 3.13; 2-day lag—OR 2.79; previous day—OR 2.45). In a study of hospital admissions for cardiovascular disease, the increases in risk associated with CO and PM_{10} were small and comparable (OR 1.03) (Schwartz 1997). Eilstein and colleagues (2001) found that winter NO_2 concentrations lagged by 5 days were positively associated with MI induction in Strasbourg, France.

POSSIBLE SUBJECT-RELATED TRIGGERS OF MI ONSET

This study has provided valuable data on factors other than pollutants that may be associated with MI onset. The associations that Peters and colleagues found between MI onset and time spent in traffic are novel and potentially important. Data from the same subjects, but with a different control-selection strategy applied, were published and commented on in the New England Journal of Medicine (Peters et al 2004; Stone 2004). Further study is necessary to determine whether time spent in traffic is a stressor to the heart akin to strenuous activity or is a surrogate for increased exposure to PM or other pollutants; traffic is also associated with noise that may produce stress. Future studies of how activities may modify pollutant effects will need to formally test for interaction effects, rather than merely assessing a trend in effects across subgroups of possible effect-modifying factors (as was done in the current

study). Measurements of time spent outside may be a more accurate reflection of personal exposure to pollution, and thus a more accurate reflection of the association between PM exposure and cardiovascular outcome, than measurements of pollutant levels at a central monitor. Nonetheless, time spent outdoors is likely to be a very nonspecific measure of PM exposure.

The association that Peters and colleagues found between strenuous physical activity and rapid induction of MI confirms previous results (Mittleman et al 1993). They also found that elevated temperatures were associated with increased risk of MI onset; however, several—but not all—studies have suggested that cold weather, particularly during the winter, is associated with increased occurrences of MI (eg, Marchant et al 1993; Spencer et al 1998; Sheth et al 1999).

The investigators found that 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. Because the level or type of activity did not change the observed associations between $PM_{2.5}$ and MI onset, these results indicate that the effect of PM was not due to people changing their activities when PM levels increased.

One concern about the interpretation of these results is whether individuals in the study more accurately or more completely recalled activities immediately before being hospitalized with an MI than those on preceding days, especially given that histories were obtained a median of 9 days after the event. The effect of this differential recall might have been to overestimate the effect of these activities. To assess the impact of recall bias on the results, the investigators could have included a control group of hospitalized patients who had not experienced an MI, or assessed the role of activities not expected to be increase the relative risk of MI.

STUDY DESIGN

The principal approach to analyzing data in the study was case–crossover. As discussed in the sidebar and in several reports (Lumley and Levy 2000; Bateson and Schwartz 2001; Navidi and Weinhandl 2002; Janes et al 2004b), however, this approach may introduce bias when either unidirectional or bidirectional control periods are selected. As the investigators appropriately note, the extent of the increased relative risk associated with $PM_{2.5}$ depended on the control selection method. The fact that the highest associations with air pollution were found using the unidirectional case–crossover approach is unlikely to be due to the possible biases inherent in this selection process in which control periods are selected only before the event. As the sidebar and Janes and colleagues (2004b) indicate, the unidirectional approach can be confounded by consistent trends in "exposure." Although long-term trends are apparent for air pollution, consistent short-term trends have not yet been found; the investigators reasonably infer that the biases in their results with this approach were not explained by confounding due to trend or season. The Review Committee concluded that Peters and colleagues had not uncovered the sources of bias in the unidirectional approach, should they exist.

SUMMARY AND CONCLUSIONS

This important study investigated specific hypotheses about exposure to particulate pollutants and the induction of a major clinical endpoint, 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 using transportation.

Peters and colleagues principally used a case–crossover approach with 851 subjects who had recently suffered a nonfatal MI in the Augsburg region of Germany. The investigators measured several air pollutants and administered a questionnaire to the participants. They found no support for their original hypotheses: that levels of ultrafine particles or $PM_{2.5}$ within 2 hours of a nonfatal MI would be associated with its induction. They also found no association between levels of ultrafine particles and induction of an MI up to 5 days later. Thus, the results do not support a role for ultrafine particles in the acute induction of a nonfatal MI. The investigators did find that levels of $PM_{2.5}$ 2 days before MI onset were associated with induction of the event.

The data from the current study extend information from a study of $PM_{2.5}$ effects that Peters and colleagues conducted in Boston. The two studies reported similar magnitudes of increased relative risk of MI per unit of increase in $PM_{2.5}$ levels 24–48 hours before MI onset; this suggests that exposure to $PM_{2.5}$ may play a role in the acute induction of MI. For reasons that are not clear, however, the current study did not confirm the association reported in the earlier study between $PM_{2.5}$ levels 2 hours before MI onset and the event.

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 is still open as to which pollutants—and sources of these pollutants—are responsible for the effects observed.

This study also found that strenuous activity, time spent outdoors, and time spent in traffic were associated with

increased relative risk of MI onset hours later. The magnitudes of these associations were much larger than those between MI onset and any of the air pollutants measured at a central site in Augsburg. The finding that time spent in traffic—in cars, on public transportation, or riding bicycles—was strongly associated with increased relative risk of nonfatal MI onset is important new information. 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 traffic may help to resolve this issue.

ACKNOWLEDGMENTS

The Health Review Committee thanks the ad hoc reviewers for their help in evaluating the scientific merit of the Investigators' Report. The Committee is also grateful to Aaron Cohen for his oversight of the study; to Cristina Cann and Joanne Sordillo for their assistance in preparing the initial draft of the Commentary; to Geoffrey Sunshine for revising and finalizing its Commentary; to Virgi Hepner for providing science editing on the Investigators' Report and the Commentary; and to Fred Howe, Genevieve MacLellan, Jenny Lamont, Kasey L Oliver, and Ruth E Shaw and for their roles in publishing this Research Report.

REFERENCES

Anderson KR, Avol EL, Edwards SA, Shamoo DA, Peng RC, Linn WS, Hackney JD. 1992. Controlled exposures of volunteers to respirable carbon and sulfuric acid aerosols. J Air Waste Manage Assoc 42:770–776.

Ballester F, Tenias JM, Perez-Hoyos S. 2001. Air pollution and emergency hospital admissions for cardiovascular diseases in Valencia, Spain. J Epidemiol Community Health 55:57–65.

Bateson TF, Schwartz J. 2001. Selection bias and confounding in case-crossover analyses of environmental time-series data. Epidemiology 12:654–661.

Brook RD, Franklin B, Cascio W, Hong Y, Howard G, Lipsett M, Luepker R, Mittleman M, Samet J, Smith SC Jr, Tager I; Expert Panel on Population and Prevention Science of the American Heart Association. 2004. Air pollution and cardiovascular disease: A statement for healthcare professionals from the Expert Panel on Population and Prevention Science of the American Heart Association. Circulation 109:2655–2671.

Burnett RT, Dales R, Krewski D, Vincent R, Dann T, Brook JR. 1995. Associations between ambient particulate sulfate and admissions to Ontario hospitals for cardiac and respiratory diseases. Am J Epidemiol 142:15–22.

Campen MJ, Watkinson WP, Dowd SM, Costa DL. 1997. Changes in electrocardiographic waveform parameters after exposure to residual oil fly ash particles in the cold-acclimated and cardiopulmonary-compromised rat. Am J Respir Crit Care Med 155:A247.

Checkoway H, Levy D, Sheppard L, Kaufman J, Koenig J, Siscovick D. 2000. A Case-Crossover Analysis of Fine Particulate Matter Air Pollution and Out-of-Hospital Sudden Cardiac Arrest. Research Report 99. Health Effects Institute, Cambridge MA.

D'Ippoliti D, Forastiere F, Ancona C, Agabiti N, Fusco D, Michelozzi P, Perucci CA. 2003. Air pollution and myocardial infarction in Rome: A case-crossover analysis. Epidemiology 14:528–535.

Dockery DW, Pope CA III, Xu X, Spengler JD, Ware JH, Fay ME, Ferris BG Jr, Speizer FE. 1993. An association between air pollution and mortality in six US cities. N Engl J Med 329:1753–1759.

Dockery DW, Luttmann-Gibson H, Rich DQ, Schwartz JD, Gold DR, Koutrakis P, Link MS, Verrier RL, Mittleman. MA. 2005. Particulate Air Pollution and Nonfatal Cardiac Events, Part II. Association of Air Pollution with Confirmed Arrhythmias Recorded by Implanted Defibrillators. Research Report 124. Health Effects Institute, Boston MA.

Eilstein D, Quenel P, Hedelin G, Kleinpeter J, Arveiler D, Schaffer P. 2001. [Air pollution and myocardial infarction: Strasbourg France, 1984–89.] Rev Epidemiol Santé Publique 49:13–25.

Environmental Protection Agency (US). 1996. Air Quality Criteria for PM. EPA/600/P-95/001. Office of Research and Development, Washington DC.

Frampton MW. 2001. Systemic and cardiovascular effects of airway injury and inflammation: Ultrafine particle exposure in humans. Environ Health Perspect 109:529–532.

Frampton MW, Utell MJ, Zareba W, Oberdörster G, Cox C, Huang L-S, Morrow PE, Lee FE-H, Chalupa D, Frasier LM, Speers DM, Stewart J. 2004. Effects of Exposure to Ultrafine Carbon Particles in Healthy Subjects and Subjects with Asthma. Research Report 126. Health Effects Institute, Boston MA.

Godleski JJ, Sioutas C, Verrier RL, Killingsworth CR, Lovett E, Murthy GGK, Hatch V, Wolfson JM, Ferguson ST, Koutrakis P. 1997. Inhalation exposure of canines to concentrated ambient air particles. Am J Respir Crit Care Med 155:A246.

Hahn FF, Barr EB, Ménache MG, Seagrave JC. 2005. Particle Size- and Composition-Related Adverse Health Effects in an Aged, Sensitive Population of Rats. Research Report. Health Effects Institute, Boston MA. In press.

Health Effects Institute. 2001. Airborne Particles and Health: HEI Epidemiologic Evidence. HEI Perspectives. Health Effects Institute, Cambridge MA.

Health Effects Institute. 2002. Understanding the Health Effects of Components of the Particulate Matter Mix: Progress and Next Steps. HEI Perspectives. Health Effects Institute, Boston MA.

Health Effects Institute. 2003. Revised Analyses of Time-Series Studies of Air Pollution and Health. Special Report. Health Effects Institute, Boston MA.

Hirsch T, Weiland SK, von Mutius E, Safeca AF, Grafe H, Csaplovics E, Duhme H, Keil U, Leupold W. 1999. Inner city air pollution and respiratory health and atopy in children. Eur Respir J 14:669–77.

Hoek G, Brunekreef B, Fischer P, van Wijnen J. 2001. The association between air pollution and heart failure, arrhythmia, embolism, thrombosis, and other cardiovascular causes of death in a time series study. Epidemiology 12:355–357.

Janes H, Sheppard L, Lumley T. 2004a. Overlap bias in the case-crossover design, with application to air pollution exposures. University of Washington Biostatistics Working Paper Series. Paper 213 (posted 1/13/04). The Berkeley Electronic Press, Berkeley CA. *www.bepress.com/uwbiostat/paper213* (accessed August 2004).

Janes H, Sheppard L, Lumley T. 2004b. Referent selection strategies in case-crossover analyses of air pollution exposure data: Implications for bias. University of Washington Biostatistics Working Paper Series. Paper 214 (posted 12/13/04). The Berkeley Electronic Press, Berkeley CA. *www.bepress.com/uwbiotat/paper214* (accessed 1/05).

Kuschner WG, Wong H, D'Alessandro A, Quinlan P, Blanc PD. 1997. Human pulmonary responses to experimental inhalation of high concentration fine and ultrafine magnesium oxide particles. Environ Health Perspect 105:1234–1237.

Leikauf GD, McDowell SA, Wesselkamper SC, Miller CR, Hardie WD, Gammon K, Biswas PP, Korfhagen TR, Bachurski CJ, Wiest JS, Willeke K, Bingham E, Leikauf JE, Aronow BJ, Prows DR. 2001. Pathogenomic Mechanisms for Particulate Matter Induction of Acute Lung Injury and Inflammation in Mice. Research Report 105. Health Effects Institute, Boston MA.

Le Tertre A, Medina S, Samoli E, Forsberg B, Michelozzi P, Boumghar A, Vonk JM, Bellini A, Atkinson R, Ayres JG, Sunyer J, Schwartz J, Katsouyanni K. 2002a. Short-term effects of particulate air pollution on cardiovascular diseases in eight European cities. J Epidemiol Community Health. 56: 773–779.

Le Tertre A, Quenel P, Eilstein D, Medina S, Prouvost H, Pascal L, Boumghar A, Saviuc P, Zeghnoun A, Filleul L, Declercq C, Cassadou S, Le Goaster C. 2002b. Short-term effects of air pollution on mortality in nine French cities: a quantitative summary. Arch Environ Health 57:311–319.

Levy D, Sheppard L, Checkoway H, Kaufman J, Lumley T, Koenig J, Siscovick D. 2001. A case-crossover analysis of particulate matter air pollution and out-of-hospital primary cardiac arrest. Epidemiology 12:193–199.

Lumley T, Levy D. 2000. Bias in the case-crossover design: Implications for studies of air pollution. Environmetrics 11:689–704.

Marchant B, Ranjadayalan K, Stevenson R, Wilkinson P, Timmis AD. 1993. Circadian and seasonal factors in the pathogenesis of acute myocardial infarction: The influence of environmental temperature. Br Heart J 69:385–387.

Metzger KB, Tolbert PE, Klein M, Peel JL, Flanders WD, Todd K, Mulholland JA, Ryan PB, Frumkin H. 2004. Ambient air pollution and cardiovascular emergency department visits. Epidemiology 15:46–56.

Mittleman MA, Maclure M, Sherwood JB, Mulry RP, Tofler GH, Jacobs SC, Friedman R, Benson H, Muller JE. 1995. Triggering of acute myocardial infarction onset by episodes of anger. Circulation 92:1720–1725.

Mittleman MA, Maclure M, Tofler GH, Sherwood JB, Goldberg RJ, Muller JE, for the Determinants of Myocardial Infarction Onset Study Investigators. 1993. Triggering of acute myocardial infarction by heavy physical exertion—protection against triggering by regular exertion. N Engl J Med 329:1677–1683.

Morris RD, Naumova EN, Munasinghe RL. 1995. Ambient air pollution and hospitalization for congestive heart

failure among elderly people in seven large US cities. Am J Public Health 85:1361–1365.

Muller JE, Mittleman A, Maclure M, Sherwood JB, Tofler GH. 1996. Triggering myocardial infarction by sexual activity. Low absolute risk and prevention by regular physical exertion. Determinants of Myocardial Infarction Onset Study Investigators. JAMA 275:1405–1409.

National Research Council 2004. Research Priorities for Airborne Particulate Matter. IV. Continuing Research Progress. National Academies Press, Washington DC.

Navidi W, Weinhandl E. 2002. Risk set sampling for case-crossover designs. Epidemiology 13:100–105.

Nemmar A, Hoet PH, Vanquickenborne B, Dinsdale D, Thomeer M, Hoylaerts MF, Vanbilloen H, Mortelmans L, Nemery B. 2002. Passage of inhaled particles into the blood circulation in humans. Circulation 105:411–414.

Nemmar A, Vanbilloen H, Hoylaerts MF, Hoet PHM, Verbruggen A, Nemery B. 2001. Passage of intratracheally instilled ultrafine particles from the lung into the systemic circulation in hamster. Am J Respir Crit Care Med 164:1665–1668.

Oberdörster G. 2001. Pulmonary effects of inhaled ultrafine particles. Int Arch Occup Environ Health 74:1–8.

Oberdörster G, Gelein RM, Ferin J, Weiss B.1995. Association of particulate air pollution and acute mortality: Involvement of ultra-fine particles? Inhal Toxicol 7:111B124.

Pekkanen J, Timonen KL, Ruuskanen J, Reponen A, Mirme A.1997. Effects of ultrafine and fine particles in urban air on peak expiratory flow among children with asthmatic symptoms. Environ Res 74:24–33.

Pekkanen J, Peters A, Hoek G, Tiittanen P, Brunekreef B, de Hartog J, Heinrich J, Ibald-Mulli A, Kreyling WG, Lanki T, Timonen KL, Vanninen E. 2002. Particulate air pollution and risk of ST-segment depression during repeated submaximal exercise tests among subjects with coronary heart disease: The Exposure and Risk Assessment for Fine and Ultrafine Particles in Ambient Air (ULTRA) study. Circulation 106:933–938.

Peters A, Dockery DW, Muller JE, Mittleman MA. 2001 Increased particulate air pollution and the triggering of myocardial infarction. Circulation 103:2810–2815.

Peters A, Döring A, Wichmann HE, Koenig W. 1997a. Increased plasma viscosity during air pollution episode: A link to mortality? Lancet 349:1582–1587.

Peters A, Wichmann HE, Tuch T, Heinrich J, Heyder J. 1997b. Respiratory effects are associated with the number of ultra-fine particles. Am J Respir Crit Care Med 155:1376–1383.

Peters A, Liu E, Verrier RL, Schwartz J, Gold DR, Mittleman M, Baliff J, Oh JA, Allen G, Monaham K, Dockery DW. 2000. Air pollution and incidence of cardiac arrhythmia. Epidemiology 11:11–17.

Peters A, von Klot S, Heier M, Trentinaglia I, Hörmann A, Wichmann HE, Löwel H. 2004. Exposure to traffic and the onset of myocardial infarction. N Engl J Med 351:1721–1730.

Poloniecki JD, Atkinson RW, de Leon AP, Anderson HR. 1997. Daily time series for cardiovascular hospital admissions and previous day's air pollution in London, UK. Occup Environ Med 54:535–540.

Pope CA III, Thun MJ, Namboodiri MM, Dockery DW, Evans JS, Speizer FE, Heath CW Jr. 1995. Particulate air pollution as a predictor of mortality in a prospective study of US adults. Am J Respir Crit Care Med 151:669–674.

Pope CA III, Burnett RT, Thun MJ, Calle EE, Krewski D, Ito K, Thurston GD. 2002. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. JAMA 287:1132–1141.

Schwartz J. 1997. Air pollution and hospital admissions for cardiovascular disease in Tucson. Epidemiology 8:371–377.

Schwartz J, Morris R. 1995. Air pollution and hospital admissions for cardiovascular disease in Detroit, Michigan. Am J Epidemiol 142:23–35.

Seaton A, MacNee W, Donaldson K, Godden D. 1995. Particulate air pollution and acute health effects. Lancet 345:176–178.

Sheth T, Nair C, Muller J, Yusuf S. 1999. Increased winter mortality from acute myocardial infarction and stroke: the effect of age. J Am Coll Cardiol 33:1916–1919.

Spencer FA, Goldberg RJ, Becker RC, Gore JM. 1998. Seasonal distribution of acute myocardial infarction in the second National Registry of Myocardial Infarction. J Am Coll Cardiol 31:1226–1233.

Stone P. 2004. Triggering myocardial infarction. N Engl J Med 351:1716–1718.

Sullivan J, Ishikawa N, Sheppard L, Siscovick D, Checkoway H, Kaufman J. 2003. Exposure to ambient fine particulate matter and primary cardiac arrest among persons

with and without clinically recognized heart disease. Am J Epidemiol 157:501–509.

Sullivan J, Sheppard L, Schreuder A, Ishikawa N, Siscovick D, Kaufman J. 2005. Relation between short-term fine-particulate matter exposure and onset of myocardial infarction. Epidemiology 16:41–48.

Utell MJ, Frampton MW. 2000. Acute health effects of ambient air pollution: The ultrafine particle hypothesis. J Aerosol Med 13:355–359.

Watkinson WP, Campen MJ, Costa DL. 1998. Cardiac arrhythmia induction after exposure to residual oil fly ash particles in a rodent model of pulmonary hypertension. Toxicol Sci 41:209–216.

Wichmann HE, Spix C, Tuch T, Woelke G, Peters A, Heinrich J, Kreyling WG, Heyder J. 2000. Daily mortality and fine and ultrafine particles in Erfurt, Germany. Part I: Role of particle number and particle mass. Research Report 98. Health Effects Institute, Cambridge MA.

Willich SN, Lewis M, Lowel H, Arntz HR, Schubert F, Schroder R, for the Triggers and Mechanisms of Myocardial Infarction Study Group. 1993. Physical exertion as a trigger of acute myocardial infarction. N Engl J Med 329:1684–1690.

Zhu Y, Hinda WC, Kim S, Sioutas C. 2002. Concentration and size distribution of ultrafine particles near a major highway. J Air Waste Manage Assoc 52:1032–1042.

INVESTIGATORS' REPORT

Particulate Air Pollution and Nonfatal Cardiac Events

Part II. Association of Air Pollution with Confirmed Arrhythmias Recorded by Implanted Defibrillators

Douglas W Dockery, Heike Luttmann-Gibson, David Q Rich, Mark S Link, Joel D Schwartz, Diane R Gold, Petros Koutrakis, Richard L Verrier, and Murray A Mittleman

ABSTRACT

Implanted cardioverter defibrillators (ICDs*) monitor patients for episodes of cardiac arrhythmias and can initiate a therapeutic intervention to restore normal heart rhythm. These devices also record dates, times, and electrograms of these episodes. We examined the effects of air pollution on the incidence of arrhythmias in 195 cardiac patients with ICD devices in the Boston metropolitan area between July 1995 and July 2002. Gaseous air pollutant and meteorologic data were measured on essentially all days, fine particle mass on 80% of the days, and black carbon (BC) on 61% of the days. Date and time of detected arrhythmias, intracardiac electrograms, and therapeutic interventions were downloaded during the patients' regular follow-up visits every 3 months on average. A cardiac electrophysiologist reviewed electrograms recorded before, during, and after the arrhythmias and categorized them into ventricular and supraventricular events. Risk of arrhythmias associated with air pollution was estimated using logistic regression with adjustments for season, temperature, relative humidity, day of the week, and patient.

We found increased relative risks of ventricular arrhythmias (VAs) associated with an increase in 2-day mean concentrations for all air pollutants considered, although these associations were not statistically significant. The relative risks of supraventricular arrhythmias (SVAs) increased in association with 2-day mean concentrations for all air pollutants, and this association was significant only for sulfur dioxide (SO_2) at 4 ppb (odds ratio [OR] = 1.33; 95% confidence interval [CI] = 1.04, 1.70). The positive associations of VAs and SVAs with particulate matter less than 2.5 μm in aerodynamic diameter ($PM_{2.5}$; also referred to as fine particles), carbon monoxide (CO), nitrogen dioxide (NO_2), BC, and SO_2 suggest a link with motor vehicle pollutants. We explored patient characteristics that may have identified subjects susceptible to the effects of air pollution. The association of air pollution with SVAs was blunted by regularly prescribed β-blockers. We found stronger associations of air pollution with VAs for episodes within 3 days of a previous arrhythmia, suggesting that VAs were triggered by air pollution episodes in combination with other factors that raised the patient's underlying risk. Although ICDs are specifically designed to monitor and treat only VAs, these results suggest that air pollution may trigger both VAs and SVAs.

INTRODUCTION

Severe heart rhythm disorders (arrhythmias) are one of the leading causes of sudden cardiac death in the United States. Approximately 350,000 such deaths are recorded annually (Rapaport 1988; Gillum 1989; Myerburg et al 1992), accounting for approximately 50% of all cardiovascular mortality. For many people, sudden cardiac death is the first sign that heart disease was present (Doyle et al 1976; Kannel et al 1987). VAs, primarily ventricular tachycardia and ventricular fibrillation, are common precursors to sudden cardiac death (Bayes de Luna et al 1989; Myerburg et al 1992). The current study assessed the links between ambient (outdoor) air pollution and cardiac arrhythmias among subjects who live independently and have increased risk of such events.

* A list of abbreviations and other terms appears at the end of the Investigators' Report.

This Investigators' Report is Part II of Health Effects Institute Research Report 124. The Report also includes a Commentary by the Health Review Committee and an HEI Statement about the research project conducted by Dockery and associates; the Part I Investigators' Report for research conducted by Peters and colleagues, and the Health Review Committee's Commentary and the HEI Statement about the Peters research project; and an Integrative Discussion that compares and contrasts the two studies. Correspondence concerning this Investigators' Report may be addressed to Dr Douglas W Dockery, Environmental and Epidemiology Program, Harvard School of Public Health, Landmark Building, 401 Park Dr, Suite 415 West, Boston MA 02215. *ddockery@hsph.harvard.edu*

Although this document was produced with partial funding by the United States Environmental Protection Agency under Assistance Award R82811201 to the Health Effects Institute, it has not been subjected to the Agency's peer and administrative review and therefore may not necessarily reflect the views of the Agency, and no official endorsement by it should be inferred. The contents of this document also have not been reviewed by private party institutions, including those that support the Health Effects Institute; therefore, it may not reflect the views or policies of these parties, and no endorsement by them should be inferred.

AIR POLLUTION AND CARDIOVASCULAR MORBIDITY AND MORTALITY

Increases in daily mortality have been consistently associated with particulate air pollution episodes. Most deaths attributable to air pollution are cardiovascular rather than respiratory (Dockery and Pope 1994; Dockery 2001), and many studies have associated episodes of particulate air pollution with increased cardiovascular mortality (Fairley 1990; Pope et al 1992; Schwartz and Dockery 1992; Schwartz 1994a,b; Schwartz et al 1996; Katsouyanni et al 1997; Samet et al 2000a,b,c; Dominici et al 2003). Cardiovascular deaths outside a hospital in Philadelphia increased with particulate air pollutant concentrations (Schwartz 1994b), and this increase was largest among patients declared dead on arrival. In a study of 10 US cities, deaths (many of which were sudden) associated with inhalable particulate matter less than 10 μm in aerodynamic diameter (PM_{10}) were more likely to occur outside a hospital (Schwartz 2000a).

PM_{10} air pollution also has been associated with increased hospital admissions for cardiovascular disease (Peters 1990; Burnett et al 1995, 1997, 1999; Schwartz and Morris 1995; Schwartz 1997; Prescott et al 1998; Wong et al 1999; Zanobetti et al 2000; Ballester et al 2001; Linn and Gong 2001). Emergency department visits in Atlanta for cardiovascular conditions were significantly associated with PM_{10}, $PM_{2.5}$, NO_2, and CO concentrations (Metzger et al 2004).

Peters and colleagues (2001a) reported that increases in $PM_{2.5}$, NO_2, and BC each elevated the risk of myocardial infarction within 2 hours and within 2 days after exposure. Eilstein and colleagues (2001) found increased risk of myocardial infarction associated with air pollution episodes in France. However, a study in Seattle of patients with sudden cardiac arrest and no prior cardiovascular disease failed to find any association with ambient particulate air pollution as measured by nephelometry (Checkoway et al 2000; Levy et al 2001a,b; Sheppard et al 2001). In controlled exposures of rats with pharmacologically induced pulmonary hypertension, instillation of 250 μg of combustion particles into the lungs produced arrhythmia and doubled mortality (Watkinson et al 1998). The mechanisms for these observed associations with sudden cardiac events have not been identified, but studies of air pollution effects on several intermediate markers of cardiovascular function have provided some guidance. Blood pressure, for example, has been reported to increase after air pollution episodes (Ibald-Mulli et al 2001; Linn and Gong 2001).

Animal studies have suggested that cardiac responses are not mediated by hypoxia, but rather by autonomic control (Godleski et al 2000). Hypoxia was not associated with episodes of increased PM_{10} concentrations in a study of older subjects living at a high elevation in Utah (Dockery et al 1999; Pope et al 1999a). Pulse rate, however, was found to increase with air pollution exposure in the Utah study and in an analysis of data from heart patients in Germany (Peters et al 1999).

In a subset of subjects in the Utah study, heart rate variability decreased with increasing PM_{10} concentrations (Pope et al 1999b). Similar results have also been observed in panel studies of older subjects in Baltimore (Liao et al 1999; Creason et al 2001) and Boston (Gold et al 2000). In a semiexperimental study, Pope and colleagues (2001) found a reduction in heart rate variability among a panel of volunteers after 2 hours of environmental exposure to tobacco smoke particles. In a study of boilermakers, Magari and colleagues (2001, 2002a,b) reported decreased heart rate variability after occupational exposure and environmental exposure to particulate air pollution.

In studies with dogs, exposure to concentrated ambient particles resulted in increased heart rate variability and morphologic changes in electrocardiograms, indicating an increase in sympathetic activity (Nearing et al 1996; Godleski et al 1997, 2000). In a rat model of myocardial infarction, increased frequency of premature ventricular complexes and decreased heart rate variability were reported after inhalation exposure to residual oil fly ash particles (Wellenius et al 2002).

Increased heart rate and decreased heart rate variability are both indicators of altered autonomic control, specifically of increased sympathetic stress. Reduced heart rate variability is associated with an increased risk of mortality from all causes, specifically in middle-aged men (Dekker et al 1997) and older persons (Shaper et al 1993; Dekker et al 1997). In survivors of a myocardial infarction, reduced heart rate variability predicted arrhythmic events (Farrell et al 1991). Acutely reduced heart rate variability has been associated with increased risk of ventricular tachycardia (Meyerfeldt et al 2002), atrial fibrillation (Bettoni and Zimmermann 2002), myocardial infarction (Kop et al 2001), and sudden cardiac death (La Rovere et al 2003). Raised sympathetic activity has been shown to increase the risk of ventricular fibrillation leading to sudden death (Verrier et al 1996). Elevated risk of ventricular fibrillation was observed during ischemic events, which are responsible for approximately 75% of sudden cardiac deaths (Myerburg 1997).

The acute pulmonary effects of particle exposures include oxidative lung damage, inflammation, and release of cytokines (Clarke et al 1999). These pulmonary effects would be expected to lead to analogous acute systemic effects. Using data from a cohort study of cardiovascular function in German men aged 45 to 64 years, Peters and colleagues reported increased plasma viscosity (Peters et

al 1997) and increased C-reactive protein levels (a marker for cell damage and inflammation; Peters et al 2001b) during an air pollution episode. Increased fibrinogen levels have been reported in animals exposed to urban particles (Gardner et al 2000) and in human volunteers exposed to concentrated air particles (Ghio et al 2000). Fibrinogen levels measured in the Third National Health and Nutrition Examination Survey (NHANES III) were positively associated with ambient PM_{10} concentrations (Schwartz 2001). Among residents of London, increased levels of plasma fibrinogen were associated with exposure to NO_2, CO, black smoke, and PM_{10} (Pekkanen et al 2000). Controlled human exposure to diesel particles (300 $\mu g/m^3$ for 1 hour) resulted in increased levels of peripheral neutrophils (Salvi et al 1999). White cell counts were positively associated with PM_{10} in the NHANES III study (Schwartz 2001).

Godleski and colleagues (1996) hypothesized that inflammatory response to particles in the lungs might have direct effects on heart cells including increases in inflammatory cytokines. In a study of controlled exposures to concentrated ambient particles, dogs with coronary artery occlusion developed cardiac responses suggestive of excessive sympathetic tone (Godleski et al 2000). Normal dogs (without coronary artery occlusion) exposed to concentrated ambient particles exhibited apnea, increased heart rate variability, and arrhythmias suggestive of excess vagal control. On the basis of these observations, Stone and Godleski (1999) proposed a model of possible pathways by which inhaled particles may affect neural control of the heart or activate inflammatory pathways.

This study assesses the association between ambient air pollution and cardiac arrhythmias in a population at high risk for such arrhythmias: patients with ICDs.

MANAGEMENT OF CARDIAC ARRHYTHMIAS

Implanted Cardioverter Defibrillators

Conventionally, VAs have been treated with drug therapy. In 1985 the US Food and Drug Administration approved an alternative electrical device, the automatic ICD, for use with patients who had experienced cardiac arrest or recurrent VAs that were not suppressible by antiarrhythmic drugs in the electrophysiology laboratory (Cannom 1992).

In 1996 the Multicenter Automatic Defibrillator Implantation Trial (MADIT) (Moss et al 1996) demonstrated that the ICD was significantly more effective than other treatments at reducing the risk of sudden cardiac death among asymptomatic patients who had all of these conditions: (1) a history of a prior heart attack, (2) a left ventricular ejection fraction below 0.35, (3) episodes of an arrhythmia called nonsustained ventricular tachycardia, and (4) an abnormal set of electrophysiologic tests. In 1997 the Antiarrhythmics Versus Implantable Defibrillators (AVID) clinical trial showed that, when compared with medications alone, ICDs improved survival among patients with prior cardiac arrhythmias (AVID Investigators 1997).

In 1998 the American College of Cardiology and the American Heart Association published indications for ICD therapy (Gregoratos et al 1998). The indications for which there was evidence of (or general agreement regarding) benefit, usefulness, and effectiveness (class I indications) were:

1. Cardiac arrest due to ventricular fibrillation or ventricular tachycardia that was not stimulated by a transient or reversible cause.
2. Spontaneous sustained ventricular tachycardia.
3. Syncope of undetermined origin with clinically relevant, hemodynamically significant, sustained ventricular tachycardia or ventricular fibrillation induced by electrophysiologic testing when drug therapy is ineffective, not tolerated, or not preferred.
4. Nonsustained ventricular tachycardia with coronary disease, prior myocardial infarction, left ventricular dysfunction, and ventricular fibrillation or sustained ventricular tachycardia inducible by electrophysiologic testing that is not suppressible by an antiarrhythmic drug.

The indications for which there was conflicting evidence (or a divergence of opinion) regarding usefulness or effectiveness (class IIb indications) were:

1. Cardiac arrest presumed to be due to ventricular fibrillation when electrophysiologic testing is precluded by other medical conditions.
2. Severe symptoms attributable to sustained ventricular tachyarrhythmias while awaiting cardiac transplantation.
3. Familial or inherited conditions with a high risk of life-threatening ventricular tachyarrhythmias such as long QT syndrome or hypertrophic cardiomyopathy.
4. Nonsustained ventricular tachycardia with coronary artery disease, prior myocardial infarction, left ventricular dysfunction, and sustained ventricular tachycardia or ventricular fibrillation inducible by electrophysiologic testing.
5. Recurrent syncope of undetermined etiology in the presence of ventricular dysfunction and VAs inducible by electrophysiologic testing when other causes of syncope have been excluded.

These indication guidelines were updated in 2002 (Gregoratos et al 2002). For this analysis of ICDs implanted between 1995 and 1999, however, the indications for implantation defined earlier were applicable.

The ICD is implanted under the skin with electrodes and leads extending transvenously and attached to the heart. The ICD is programmed to identify a ventricular tachycardia or ventricular fibrillation above a certain number of beats per minute (bpm); if the ICD detects a heart rate faster than programmed values, it can initiate pacing or shock therapy or both to restore normal rhythm. The first and second generations of implantable defibrillators provided event counters that recorded only the delivery of shock therapy. Third-generation devices provide programmable tiered therapy for ventricular tachycardia or ventricular fibrillation, diagnostic information about the function of the cardiac electrical system and detected events, and backup ventricular pacing for bradyarrhythmias as required (Gillis 1996). Of most importance for the current study, third-generation ICDs record the date and time of each event, the beat-to-beat (R–R) intervals (the intervals between successive R waves in an ECG tracing), and electrograms before, during, and after each arrhythmia.

Adjustable settings within the device are used to categorize events as ventricular tachycardia, fast ventricular tachycardia, or ventricular fibrillation based on monitoring the R–R intervals. Among the patients in this study, the median setting for ventricular tachycardia was 160 bpm, with a 5th to 95th percentile range of 105 to 200 bpm; and the median setting for ventricular fibrillation was 200 bpm, with a 5th to 95th percentile range of 165 to 220 bpm. The interval settings can be modified during follow-up to optimize the detection and treatment of clinically significant VAs. The effect of adjusting these settings may be to reduce or increase the number of detected abnormalities. Screening the cardiac arrhythmias is optimized to avoid detecting too few ventricular tachyarrhythmias (Reiter and Mann 1996).

In the ICD, the detection algorithm based on R–R intervals is not specific and could classify any arrhythmia that exceeds the detection settings (eg, sinus tachycardia) as a ventricular tachycardia. Morphologic evaluation of the intracardiac electrograms is not automated in the ICD. Proper classification of each arrhythmic event requires that a trained cardiac electrophysiologist review each intracardiac electrogram tracing or R–R intervals.

For each patient, the ICD is programmed for a specified rate of R–R intervals and to recognize patterns that deviate from that number of beats per minute. The ICD can initiate a series of therapies in response to a detected abnormality. If the R–R interval is shorter than the triggering level for a specified number of beats (usually six or more), the device will prepare to administer a prescribed antiarrhythmic therapy. In response to a very rapid heart rate suggestive of ventricular fibrillation, the ICD can administer a low-energy defibrillation shock (less than 35 J) directly to the heart or a cardioversion shock (also less than 35 J) synchronized with the heart rhythm. Antitachycardic pacing is used to break reentry circuits and reestablish normal sinus rhythm. It can be administered as burst pacing (in which a specified number of pulses are given in an interval), or as ramp pacing (in which pulses are administered at an increasing or decreasing rate). If the arrhythmia is not resolved, then further therapeutic interventions are initiated. If the heart rhythm reverts to normal before therapy is initiated (a nonsustained event), then the therapy is diverted. Whether a therapeutic intervention is initiated or diverted, the data (including the R–R intervals and electrograms) for the arrhythmia are still recorded and stored on the ICD for later review.

This study was limited to patients with third-generation ICDs with the capability of storing electrograms. This allowed a cardiac electrophysiologist to review and characterize each ICD-detected arrhythmia. If a large number of events occur, the stored electrograms may completely fill the memory set aside for these data, and new electrograms will overwrite the oldest ones. However, the ICD maintains a separate record of R–R intervals and if the electrograms are overwritten, this record of R–R intervals can be used to assess the characteristics of the earlier arrhythmias.

ICDs are designed and programmed to detect and treat life-threatening cardiac arrhythmic events. Detecting such events is accomplished by identifying a series of consecutive beats with R–R intervals shorter than the minimum level that was programmed by the clinician caring for the patient. ICDs do not detect preclinical indicators of cardiovascular risk such as short runs of nonsustained ventricular tachycardia or premature ventricular contractions, both of which have been associated with air pollution exposures in animal studies (Wellenius et al 2003). The ICDs do identify clinically important life-threatening VAs.

Prescribed Cardiac Medications

ICD patients are commonly treated with medications to reduce the risk of VAs and SVAs and to treat underlying cardiac conditions such as coronary artery disease. Medications may blunt or otherwise modify the response to air pollution episodes by, for example, modifying autonomic responses to external triggers. It is important to keep in mind that, in addition to their antiarrhythmic characteristics, some of these drugs may have proarrhythmic effects in that they may initiate new arrhythmias or perpetuate

existing arrhythmias (Chaudhry and Haffajee 2000). Understanding how medications may influence a person's response to air pollution may provide new insights into the mechanisms of air pollution's effects.

Activation of the sympathetic nervous system may be associated with sudden cardiac death. Medications that lower sympathetic tone have been shown to reduce the risk of sudden cardiac death and to modify the sympathetic nervous system's response to external triggers. β-Blockers have been shown to reduce the morning peak in sudden cardiac deaths (Peters 1990), nonfatal myocardial infarctions (Muller et al 1985), and transient myocardial ischemia (Parker et al 1994). β-Blockers decrease the frequency of ventricular tachycardia and ventricular fibrillation by preventing reentrant supraventricular tachycardias dependent on the atrioventricular node and decrease the ventricular response to atrial fibrillation (Chaudhry and Haffajee 2000).

Because digoxin enhances vagal tone, and depresses atrioventricular conduction by decreasing the transmission of atrial impulses to the ventricle, it is useful for atrial fibrillation (Chaudhry and Haffajee 2000). However, digoxin also may decrease atrial refractoriness, thus increasing the atrial rate in atrial fibrillation. Digoxin may be effective in terminating reentrant arrhythmias involving the atrioventricular node, but it is considerably less effective than calcium channel blockers and β-blockers for controlling the ventricular rate in atrial fibrillation and in tachycardias dependent on the atrioventricular node (Chaudhry and Haffajee 2000).

Amiodarone, a potassium channel blocker, is considered one of the more effective treatments for VAs (Cairns et al 1991). Chronic amiodarone therapy has been shown to affect circadian rhythms and to bring about spectral changes of heart rate and the QT interval (Antimisiaris et al 1994). ICDs have been shown to be superior to amiodarone in preventing sudden arrhythmic death (Moss et al 1996; Buxton et al 1999). Treatment with amiodarone is recommended in conjunction with ICDs to decrease ventricular tachycardia and ventricular fibrillation episodes, to suppress nonsustained ventricular tachycardic episodes, to slow the rate of ventricular tachycardias, to allow effective ICD antitachycardic pacing, and to suppress SVAs (Hilleman and Bauman 2001).

AIR POLLUTION EPISODES AND CARDIAC ARRHYTHMIAS DETECTED BY ICDs: A PILOT STUDY

In a pilot study we evaluated the utility of ICD data as indicators of acute cardiovascular response to air pollution in Boston (Peters et al 2000; see the section Appendices Available on Request). We tested the hypothesis that patients with ICDs would experience potentially life-threatening arrhythmias associated with air pollution episodes.

We abstracted records of patients at the Beth Israel Deaconess Medical Center (BIDMC) Cardiac Device Clinic who had had an ICD implanted before September 1997, had survived until December 1997, had had more than 30 days of follow-up, and lived in eastern Massachusetts. The data from 2 months after the device was surgically implanted were excluded from analysis to avoid effects of implantation and initial adjustment of programmable device settings. Of the 120 patients seen at the clinic, 100 met the inclusion criteria.

From the ICD-generated Episode Summary Report printed at each clinical follow-up visit, we abstracted the date, time, type of arrhythmia defined by the ICD, and the ICD's therapeutic intervention for each detected arrhythmia. We restricted the analysis to defibrillator discharges precipitated by tachycardia or fibrillation. PM_{10}, $PM_{2.5}$, BC, ozone (O_3) and CO were measured continuously at a monitoring site in South Boston operated by the Harvard School of Public Health (HSPH) from January 1995 through December 1997. SO_2 and NO_2 were measured at a site in Chelsea (approximately 7.5 km north of South Boston) operated by the Massachusetts Department of Environmental Protection (DEP).

The probability of a therapeutic ICD discharge intervention on any given day was compared with the daily measures of air pollution by logistic regression models, using fixed effect models with individual intercepts and adjustments for possible confounding by trend, season, meteorologic conditions, and day of the week. Associations were reported based on an interquartile range (IQR) increase in each air pollutant concentration. (The IQR is the 75th percentile minus the 25th percentile.)

Of the 100 patients, 33 had at least one ICD discharge during the follow-up period. For those patients, a 26-ppb increase in daily NO_2 concentrations was associated with increased risk of an ICD discharge 2 days later (OR = 1.77; 95% CI = 1.06, 2.93). Positive but not statistically significant associations were found for BC and CO. Among the six patients with at least 10 ICD discharge events, we observed that an IQR increase of 13 $\mu g/m^3$ in the 5-day mean $PM_{2.5}$ concentration was associated with a relative risk of an ICD discharge of 1.22 (95% CI = 0.73, 2.01). Stronger associations were found with each IQR increase in 5-day mean BC particle mass (OR = 2.16; 95% CI = 0.96, 4.86) and NO_2 concentration (OR = 3.13; 95% CI = 1.76, 5.56).

This pilot study (Peters et al 2000) showed that ICD data could be used to assess the effects of short-term air pollution episodes on risk of acute cardiovascular events; and suggested that exposure to air pollution episodes could stimulate acute cardiovascular arrhythmias, which if not detected or corrected by the ICD, may have resulted in sudden death.

This pilot study also suggested that the small fraction of the patients who had repeated arrhythmias may have been more sensitive to the effects of air pollution. Patient characteristics such as underlying cardiac disease, other coexisting conditions, or medications may have modified their responses to air pollution. Unfortunately, no other clinical data were available on the participants in this pilot study.

The pilot study also highlighted the limitations of the ICD data. For instance, these ICDs monitored only R–R intervals. Therefore, it is possible that normally fast heart rhythms, and electrical noise or mechanical interference from the ICD (referred to as oversensing) could have been erroneously characterized as abnormal tachycardias. Newer ICDs store not only the dates and times of events but also R–R intervals and intracardiac electrograms for the periods before, during, and after the detected arrhythmias. Thus a cardiac electrophysiologist could review these records, identify erroneous arrhythmic events, and assign an appropriate clinical characterization.

To address these issues, we undertook a larger study of patients with ICDs: we evaluated each patient's specific clinical indications for implantation; the implanted ICDs included more sophisticated storage of characteristics and electrograms for arrhythmic events; we monitored patients' medications during follow-up; and we included only those ICD-recorded arrhythmic events that were confirmed by an electrophysiologist.

SPECIFIC OBJECTIVES

The study as originally designed would test the following hypotheses:

1. Patients subject to serious arrhythmias that require ICDs experience potentially life-threatening arrhythmias associated with particulate air pollution episodes.
2. Patients with ICDs that have specific preexisting and coexisting conditions, such as chronic or cardiovascular respiratory disease, have a higher risk of arrhythmias associated with particulate air pollution episodes than those without such conditions.
3. Cardiac arrhythmias are associated with fine particle mass concentrations, and specifically with the concentration of soluble metal cations in the fine particles.
4. Morphologic changes in electrocardiograms that have been observed in dogs exposed to particulate air pollution are also observed in the intracardiac electrograms of humans.

In the second specific aim, we proposed to consider coexisting noncardiovascular conditions as effect modifiers of the air pollution associations. Although ICD patient records included detailed information on cardiovascular indicators, because subjects were drawn from a referral center for patients who require cardiac pacing devices, their records did not necessarily include complete medical histories for noncardiovascular conditions. Thus we could not abstract complete information on respiratory disease and other coexisting conditions as anticipated in the original design, and focused on cardiovascular conditions documented within the available records.

In the third specific aim, we proposed to examine the associations with constituents of fine particle mass, specifically soluble cations. This study design took advantage of regular compliance monitoring by the Commonwealth of Massachusetts and other ongoing research projects to measure ambient air pollution. We were fortunate to have data on fine particle mass, number of particles (an indicator of ultrafine particles), particulate BC, and particulate sulfate (SO_4^{2-}) over long periods of the study. For other research projects, we had collected mass and composition data for fine particles in South Boston starting in 1995; and daily fine particle mass monitoring was started by the Massachusetts DEP in 1999. Measurements of particulate metal concentrations were episodic and did not continue over a substantial portion of this follow-up period. Funds had not been requested in our application for these measurements, and data were not sufficient to assess specific associations with metal constituents. However, we were able to assess associations with particulate BC and, to a limited extent, with SO_4^{2-} and number of particles.

In the fourth specific aim, a secondary objective, we proposed to examine morphologic changes in the ICD-recorded intracardiac electrograms of these patients and compare them with those seen in electrocardiograms of canines exposed to concentrated ambient particles in Boston (Godleski et al 2000). Because the ICD works by examining R–R intervals, the intracardiac electrograms are filtered to isolate the R wave, meaning that other components of the electrogram are suppressed. Thus we were not able to examine morphologic changes as proposed in this specific aim.

Although we were not able to address all of the specific aims as originally proposed, we were able to expand the length of follow-up. The study was originally designed to assess clinical follow-up only through mid 2000. Through a no-cost extension from the Health Effects Institute and additional funding through the National Institute of Environmental Health Sciences, we were able to extend follow-up for 2 more years through clinical visits in mid 2002.

METHODS

PATIENT AND ARRHYTHMIA DATA

Data on ICD-detected arrhythmias were abstracted from patients' clinical records at the New England Medical Center (NEMC) Cardiac Electrophysiology and Pacemaker Laboratory. Each patient was assigned a random study identification number. All identifiable patient information and the cross-link with the study identification numbers were kept in locked files within the NEMC laboratory. The abstracted ICD and patient data (identified only by the study ID) were transferred to the HSPH for processing and analysis. The HSPH Human Studies Committee and the NEMC Institutional Review Board approved this record review.

Sample Population

The source population consisted of patients with Ventak series third-generation ICDs implanted at the NEMC Cardiac Electrophysiology and Pacemaker Laboratory between June 1, 1995 and December 31, 1999. The medical records of these ICD patients included a 3½-inch floppy disk containing a complete record of all detected arrhythmias, including intracardiac electrograms, for each device. These electronic records greatly facilitated data abstraction for the ICD patients. We considered also including patients from the BIDMC Cardiac Device Clinic, the source of the pilot study data (Peters et al 2000). However, all the records at that clinic were on paper forms and thus incompatible with the electronic NEMC records, so they were not included in this study.

Patient characteristics before implantation were abstracted from patients' records by NEMC staff.

Follow-Up of Patients and ICD Data Retrieved

ICD patients visited the NEMC Cardiac Electrophysiology and Pacemaker Laboratory clinic for follow-up approximately every 3 months or whenever they experienced an antiarrhythmic shock. The mean interval between follow-up clinical visits was 89 days.

At each follow-up visit, the ICD was interrogated and data were retrieved by noninvasive radiofrequency transmission, printed, and stored on the floppy disk that was kept in the patient's file with the paper records. A nurse manager or cardiac physician checked the device by assessing the memory and charging circuitry, battery voltage and charging times, and lead impedance. A real-time intracardiac electrogram tracing was displayed to check the device's overall performance. Triggering levels and programmed therapies were downloaded. The device was then interrogated to obtain a list of detected episodes and therapeutic interventions. For each detected episode, the ICD had recorded the date and time along with an automated characterization of the type of event (ventricular tachycardia, fast ventricular tachycardia, or ventricular fibrillation range), the initiated therapy (eg, shock, antitachycardic pacing) or diverted therapy, and the results of the therapy. These data, along with R–R intervals and the electrogram of the heartbeats immediately before, during, and after the event, were recorded on the floppy disk. The nurse manager or cardiac physician recorded prescribed medications and any symptoms that the patient recalled from the time of each arrhythmia. The ICD memory was then cleared.

The NEMC Cardiac Electrophysiology and Pacemaker Laboratory clinic receives referrals from other hospitals throughout eastern New England. Patients implanted with an ICD could have follow-up by NEMC, their primary cardiologist, or both. Thus it was important that for each patient all follow-up visits at other clinics were identified, and their days of follow-up in the study were adjusted accordingly. A comprehensive tracking system for patients at the clinic was not available, and no active monitoring of patients' vital status was conducted. Deaths were recorded if the clinic was notified. However, the ICDs were not interrogated after the death of a patient. Thus we could not abstract data on arrhythmic events for the deceased patients comparable to data gathered on living patients being followed clinically.

Data Abstraction

NEMC staff abstracted baseline characteristics from the patient record; these included gender, ethnicity, date of birth, residential ZIP code, cardiovascular history, indications for ICD implantation, implant date, physiologic measures at implantation, and preimplantation left ventricular ejection fraction.

Each clinical follow-up visit was recorded on the visit data abstraction form (Appendix A). The date and time of the clinical visits were abstracted from the nurse's records, and compared with dates and times of the current and previous interrogations of the ICD device on printouts of the ICD records. These dates defined the periods during which the patient contributed person-time to the study. Prescribed uses (Yes or No) of β-blockers, antiarrhythmic drugs, and digoxin since the last visit were also abstracted from the nurse's notes.

For each patient in this study, an episode log of all ICD-detected events by episode number, date, and time was printed from the patient's computer disk. Arrhythmias reported in the nurse's notes were checked against the ICD episode log printout. For each arrhythmic event in the ICD episode log, we recorded the date and time, initial and

final heart rates, therapy, and the device's characterization of the arrhythmia on the event data abstraction form (Appendix A). The nurse's notes were copied and the patient's floppy disk record was printed for each ICD episode. Electrograms for each episode were printed from the patient's disk. All these records were compiled for review by the study's cardiac electrophysiologist.

Cardiac Electrophysiologist Review

The cardiac electrophysiologist used data from the clinical visit record, the ICD episode report (including a list of R–R intervals), and the recorded ICD intracardiac electrograms to classify each detected arrhythmic event. The onset interval, rate, and electrogram morphology of the arrhythmia were compared within each episode and compared with baseline electrograms (when available) to classify the arrhythmia. In a small number of cases, some of the earlier electrograms in the ICD memory had been overwritten because the patient had experienced a large number of episodes since the previous follow-up visit. In those cases, arrhythmic classification was based on the R–R interval records.

The criteria used to classify arrhythmias are summarized in Table 1. These criteria include not only the ventricular rate, but also characterization of the onset and regularity of the arrhythmia, changes in the morphology of the electrogram, and when available, response to therapy. For single-chamber ICDs (which record VAs only), the changes in electrogram morphology and the response to therapy are diagnostic data that we used to separate VAs from SVAs. For the dual-chamber (ventricular and atrial) ICDs, VAs are also characterized by dissociation of the atrial and ventricular beats.

Each episode was designated and categorized on the event form: ventricular fibrillation, nonsustained ventricular fibrillation, ventricular tachycardia, or nonsustained ventricular tachycardia as VAs; atrial fibrillation, atrial flutter, atrial tachycardia, or supraventricular tachycardia as SVAs; and sinus tachycardia or oversensing as normal rhythms.

Data Processing

Abstracted data were recorded on machine-readable forms identified only by the patient's study ID (Appendix A). The data abstraction forms were scanned (Canon 3020 Scanner), and images were interpreted and processed using Teleform data processing software (Cardiff Software, Vista CA). Positive responses in check boxes were identified. Character data were read using optical character recognition. Within each field on the form, range and consistency of responses were checked immediately during scanning. If a potential scanning error was detected, the image of the scanned form was displayed next to the data determined by the automated processing.

Table 1. Characteristics of Recorded Electrograms and Beat-to-Beat Intervals Used by the Reviewing Cardiac Electrophysiologist to Classify Arrhythmias

Arrhythmia	Onset	Regularity of Arrhythmia	Ventricular Rate (bpm)	QRS Morphology	Response to Antitachycardic Pacing[a]	Response to ICD Shock[a]
Normal Rhythm						
Sinus tachycardia	Gradual	Regular	100–180	No change	None	None
SVAs						
Atrial fibrillation	Gradual (occasionally acute)	Irregular	120–200	No change	None	Converts occasionally (especially if paroxysmal)
Atrial flutter	Gradual (occasionally acute)	Regular or irregular	140–160	No change	None	Converts occasionally (especially if paroxysmal)
Atrial tachycardia	Acute	Regular	140–200	No change	None	Rarely converts
VAs						
Ventricular tachycardia	Acute	Regular	140–250	Change in QRS complex	Terminates	Converts
Ventricular fibrillation	Acute	Irregular	>250	Change in QRS complex	Terminates	Converts

[a] If applied in response to a detected arrhythmia.

The operator then verified or corrected the recorded response. After all the data points on each form were reviewed and any necessary corrections were made, the data were exported to an Access (Microsoft, Belleview WA) database, which was backed up nightly.

The scanned data were subjected to further within-episode and between-episode consistency checks. A list of queries was generated for manual review against the original records. The corrected data were then rechecked for within-record and between-record consistency.

After completing our Final Report to HEI, an external audit (Appendix C) found that abstracted records for 14 subjects with follow-up visits had not been included in the analysis data. Because these subjects were omitted from analysis for clerical reasons independent of both air pollutant concentrations and the presence of arrhythmias, their exclusion would not be expected to introduce any bias in the analyses. The characteristics of these individuals and an assessment of their influence on the results when these observations were included are presented in Appendix B. After including the data for the missing patients, results for the primary analyses differed little, if at all.

AIR POLLUTION

Ambient air pollution measurements were obtained from multiple monitoring sites in the Boston area. To represent mean ambient concentrations across the metropolitan area, data reported from all monitoring sites, adjusted for missing observations, were used to calculate the hour-specific means. Daily mean concentrations were then calculated from the hourly means.

Particulate Monitoring

Hourly measurements of $PM_{2.5}$ concentrations were made at an ambient monitoring site in South Boston operated by the HSPH between January 15, 1995 and January 19, 1998. The same measurements were made at the HSPH main site in Boston starting on March 17, 1999. These monitors provided a unique data set of continuous fine particle measurements over almost the entire period of this 7-year study (July 11, 1995 through July 11, 2002; 2558 days).

$PM_{2.5}$ concentrations were measured continuously with a tapered element oscillating microbalance (TEOM; model 1400A, Rupprecht and Patashnick, East Greenbush NY). The TEOM measures mass concentrations by collecting particles on a heated (50°C) filter mounted on the end of a hollow tapered oscillating glass rod. The frequency of oscillation decreases as the mass on the filter increases. The US Environmental Protection Agency (1997) has designated the instrument as a correlated acceptable continuous monitor for $PM_{2.5}$.

Particle mass concentrations measured by the TEOM were usually lower than those determined gravimetrically owing to the loss of semivolatile particulate components in the heated sampler inlet (Allen et al 1997). To account for these losses, we applied a season-specific correction factor to the TEOM measurements that has been shown to produce good agreement between filter-based and TEOM measurements (Oh 2000).

The Massachusetts DEP began hourly monitoring of $PM_{2.5}$ at several locations in the greater Boston area in April 1999. These samplers provided only limited information for the last 3 of the 7 years of this study, and the data were therefore not included in this analysis.

Integrated 24-hour samples of inhalable PM_{10} were collected at the HSPH and Massachusetts DEP sites every third day. Because we were investigating only acute effects on cardiac arrhythmias, these intermittent PM_{10} measurements were not included in the analyses.

Particulate BC was measured hourly by an aethalometer (model 8021, McGee Scientific, Berkeley CA) at the South Boston site through March 29, 1997 and at the main HSPH site starting on October 15, 1999.

Daily particulate SO_4^{2-} was measured by ion chromatography (model 120, Dionex, Sunnyvale CA) on aqueous extract from integrated 24-hour $PM_{2.5}$ filter samples collected at the main HSPH monitoring site starting on September 25, 1999. On October 13, 1999 at the same site, we began operating a condensation particle counter (TSI, Shoreview MN) to record the number concentration of particles. Despite the relatively small sample sizes for both SO_4^{2-} and number of particles, data for these components were included in some analyses because of the specific interest in possible associations between indicators of particle composition and the sources of particles.

Pollutant Gas Monitoring

Hourly ambient concentrations of gaseous criteria pollutants were obtained from the Massachusetts DEP for the greater Boston area (Middlesex, Suffolk, Essex, Norfolk, and Plymouth counties). Continuous measurements of one or more gaseous criteria pollutants were available from 26 ambient monitoring stations between 1995 and 2002. However, air monitoring data for the full period of analysis were available from only a small number of sites. We extracted data from six sites with nearly complete air

pollutant measurements for O_3, NO_2, and SO_2: Lynn Water Treatment Plant in Essex County; Waltham Field Station in Middlesex County; and Chelsea Soldier's Home, Kenmore Square (Boston), Breman Street (East Boston), and Harrison Avenue (Boston) in Suffolk County. CO was measured at urban sites that had been selected to monitor violations of the National Ambient Air Quality Standards: Kenmore Square, Breman Street, Federal Post Office (Boston), and Harrison Avenue, all in Suffolk County. Table 2 lists the air monitoring sites in the greater Boston area and the number of days with measurements for each air pollutant during the study period.

Calculation of Mean Ambient Concentrations

We calculated hourly mean ambient air pollutant concentrations from data reported by all air pollution monitoring stations. Because mean concentrations can be influenced by the specific monitors that contribute data, we used a method to calculate means that was independent of the monitors and therefore did not introduce changes in mean exposure estimates from day to day. For each pollutant, the calculated hourly mean across monitors accounted for differences in the annual mean and the standardized deviations of each monitor (Schwartz 2000b). The annual mean for each pollutant also was calculated for each monitor for each year. These monitor- and year-specific means were subtracted from the hourly measurement for that monitor, and the difference was divided by the monitor-specific standard deviation to produce a standardized deviation. The standardized deviations for all reporting monitors were averaged for each hour. The average standardized deviation was then multiplied by the standard deviation of all the centered measurements for the year and added to the annual average of all the monitors to produce an average concentration for each hour. The daily mean was then calculated from the 24 hour–specific mean concentrations across the monitors.

WEATHER DATA

The hourly surface air observations from the National Weather Service First Order Station at Logan Airport in East Boston were extracted from climatic records (EarthInfo, Boulder CO). Daily means were calculated from the hourly observations of temperature and relative humidity.

ANALYTIC METHODS

We merged the patient-specific time-series data for days of follow-up and the ICD-detected arrhythmias with the time series of daily mean air pollutant and weather data. The association between arrhythmic episode-days and air pollution was analyzed by logistic regression models following the approach used in the pilot study (Peters et al

Table 2. Air Pollution Monitoring Sites and Number of Days of Observations[a] July 11, 1995 through July 11, 2002 (2558 Days)

Greater Boston Monitoring Site	$PM_{2.5}$	BC	NO_2	CO	SO_2	O_3	SO_4^{2-}	Number of Particles
Massachusetts DEP (AIRS Number[b])								
Lynn Water Treatment Plant, Lynn (25-0092-006)			2142			1675		
Waltham Field Station, Waltham (25-0174-003)					1423	1067		
Chelsea Soldier's Home, Chelsea (25-0251-003)			1529		1609	1471		
Kenmore Square, Boston (25-0250-002)			2338	2434	2460			
Breman St, East Boston (25-0250-021)			2410	2439	2555			
Federal Post Office, Boston (25-0250-038)				2469				
Harrison Ave, Boston (25-0250-042)			656	449	757	701		
Harvard School of Public Health								
South Boston	903	598						
Main Location, Boston	1144	957					971	806
Total Days for which one or more monitors contributed measurements	2047	1555	2557	2558	2558	2552	971	806

[a] Based on at least 18 hourly measurements.

[b] Compliance site number for the Aerometric Information Retrieval System, a nationwide database.

2000). We used fixed effect models with individual intercepts for each patient, except as noted below. We used multivariate analysis to evaluate confounding by trend, season, meteorologic conditions, and day of the week. The logistic model included a linear trend, sine and cosine terms with periods of one, one-half, one-third, and one-quarter year, quadratic functions of minimum temperature and humidity, and indicators for day of the week.

All data analyses were performed separately for VAs and SVAs. For comparison with the pilot study data, we assessed associations between air pollutant concentrations and all arrhythmias combined.

We considered mean air pollutant concentrations on the arrhythmic episode-day and on the previous 3 days. The lag structure of the data was estimated by evaluating each lag day (0 to 3) separately and also jointly in an unconstrained distributed lag model (Pope and Schwartz 1996). Examination of the day-specific data consistently showed associations between an arrhythmic episode-day and elevated air pollutant concentrations on the day of (lag 0) and the day before (lag 1) the arrhythmia. We therefore used the running mean concentrations of lag days 0 and 1 to evaluate the effects of air pollutants.

To assess the robustness of the logistic regression for the repeated observations from individual patients, we repeated analyses with the 2-day mean air pollution models using generalized estimating equations (GEEs) (Zeger et al 1988).

We conducted sensitivity analyses for subgroups of patients to explore the possible modifications of the air pollution associations by the following categories of patient characteristics. Patients were stratified in three ways: (1) by residential location (ie, inside and outside Route 128, the inner beltway around Boston) as a measure of distance from the primary monitors at the HSPH; (2) by diagnosis of coronary artery disease compared with other cardiac diagnoses before implantation (the limited number of patients with other cardiac diagnoses precluded diagnosis-specific analyses) and by reported left ventricular ejection fraction before implantation (≤ 0.35 versus > 0.35); and (3) by usual cardiac medications (reported at more than half of clinical follow-up visits) in three broad designations (β-blockers, antiarrhythmics, and digoxin). In addition we stratified VAs and SVAs by whether each episode had been preceded (or not) by an arrhythmia of the same type within the previous 3 days. Air pollutant effects and tests of effect modification by patient characteristics were estimated in multivariate logistic regression including interactions between air pollutants and categories of patient characteristics.

We present ORs and 95% CIs based on an IQR increase in each air pollutant concentration. The magnitude of estimates for different pollutants is therefore based on comparable increments of exposure for the study period. P values from the Wald χ^2 test are reported for the effects of air pollution and for the interactions of air pollution with posited effect modifiers. We highlight statistically significant associations ($P < 0.05$ for two-sided tests) and marginally significant associations ($P < 0.10$).

RESULTS

PATIENT POPULATION

A total of 293 patients had third-generation ICDs implanted at the NEMC between June 1, 1995 and the end of 1999. Of these, 277 lived in Massachusetts and had more than 14 days of follow-up. We limited our analysis to 195 patients with reported residential ZIP codes within 40 km (25 miles) of the main ambient air pollution monitoring site at the HSPH (Figure 1). The western half of this circle roughly follows the Boston area's outer beltway, Interstate 495. Of the 195 patients, 83 (43%) lived inside the inner beltway (Route 128), 10 to 25 km from the main HSPH monitoring site. The distribution of subjects by county of residence was Middlesex (40%), Norfolk (25%), Suffolk (14%), Plymouth (12%), Bristol (5%), and Essex (4%). Figure 1 shows the distribution of these patients by ZIP code area.

Table 3 summarizes the number of patients by ICD model and the reported date of the first implantation. Most of these devices (81%) were single-chamber, which sense activity only in the ventricle. Dual-chamber devices, which sense activity in both the atrium and ventricle, were first implanted in study patients in January 1997 (1.5 years after the study began).

Figure 2 shows the date of implant and the period of follow-up for each of the 195 patients in the analysis. Follow-up started on July 11, 1995 and continued through July 11, 2002, for a total of 2558 days (7 years). Data recorded during clinical follow-up were abstracted for 1912 ICD-detected arrhythmias. Upon review by the study cardiac electrophysiologist, 144 (8%) of these episodes were identified as due to oversensing, and 80 (4%) as sinus tachycardias. A total of 1342 (70%) of the episodes were identified as VAs (106 ventricular fibrillation, 31 nonsustained ventricular fibrillation, 1096 ventricular tachycardia, and 109 nonsustained ventricular tachycardia), and

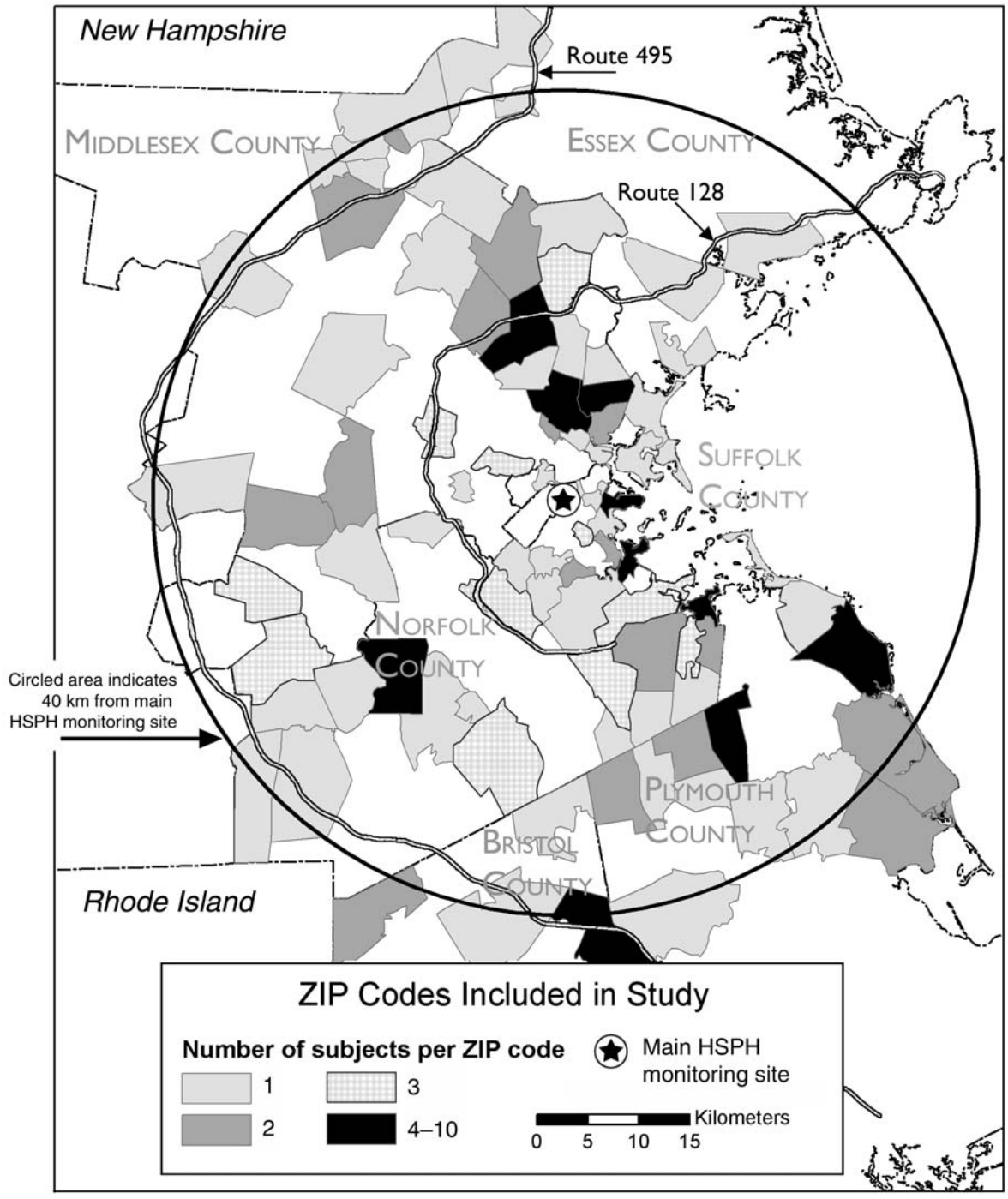

Figure 1. Distribution of patients by residential ZIP code within 40 km of the main HSPH air monitoring site. Sources: 2000 US Census and Harvard School of Public Health 10/17/2002.

346 (18%) as SVAs (306 atrial fibrillation, 12 atrial tachycardia, and 28 supraventricular tachycardia). For this analysis, an episode-day for a patient was defined as any calendar day on which one or more VAs or SVAs occurred. Episode-days are shown as dots on Figure 2. For data analysis, episode-days were identified separately for VAs, SVAs, and all arrhythmias combined. Analyses were restricted to the 772 episode-days for which the electrophysiologist confirmed the occurrence of a VA or an SVA or both. Some subjects (103) had no confirmed arrhythmias.

Table 3. Number of ICD Patients and Date of First Implant by Device Type and Model

Type and Model	Patients	First Recorded Implant
Single Chamber		
PRx III	23	01 June 1995
Ventak Mini	17	10 January 1996
Ventak Mini II	67	28 August 1996
Ventak Mini III	25	30 April 1998
Ventak Mini IV	26	05 March 1999
Dual Chambers		
Ventak AV	8	28 January 1997
Ventak AV II DR	5	20 February 1998
Ventak AV III DR	22	22 October 1998
Ventak VR	1	06 December 1999
Contak CD	1	04 April 1999

PATIENT CHARACTERISTICS

Detected Arrhythmias

The 195 ICD patients had a total of 225,567 person-days of follow-up (Table 4) or an average of 1157 days (3.2 years) of follow-up. Of the 195 patients, 92 (47%) had 772 arrhythmic episode-days confirmed by the electrophysiologist; this equaled an average of 1.3 episode-days per person-year of follow-up for all 195 patients.

Table 4 shows the breakdown of patients and follow-up as a function of the number of episode-days. Of the 92 patients with confirmed arrhythmias, 72 (78%) had episodes on 2 or more days, 46 (50%) had episodes on 5 or more days, and 26 (28%) had episodes on 10 or more days. The patients with multiple episodes tended to be older and had longer follow-up. The 92 patients with one or more arrhythmic episodes had an average of 2.4 episode-days per person-year of follow-up.

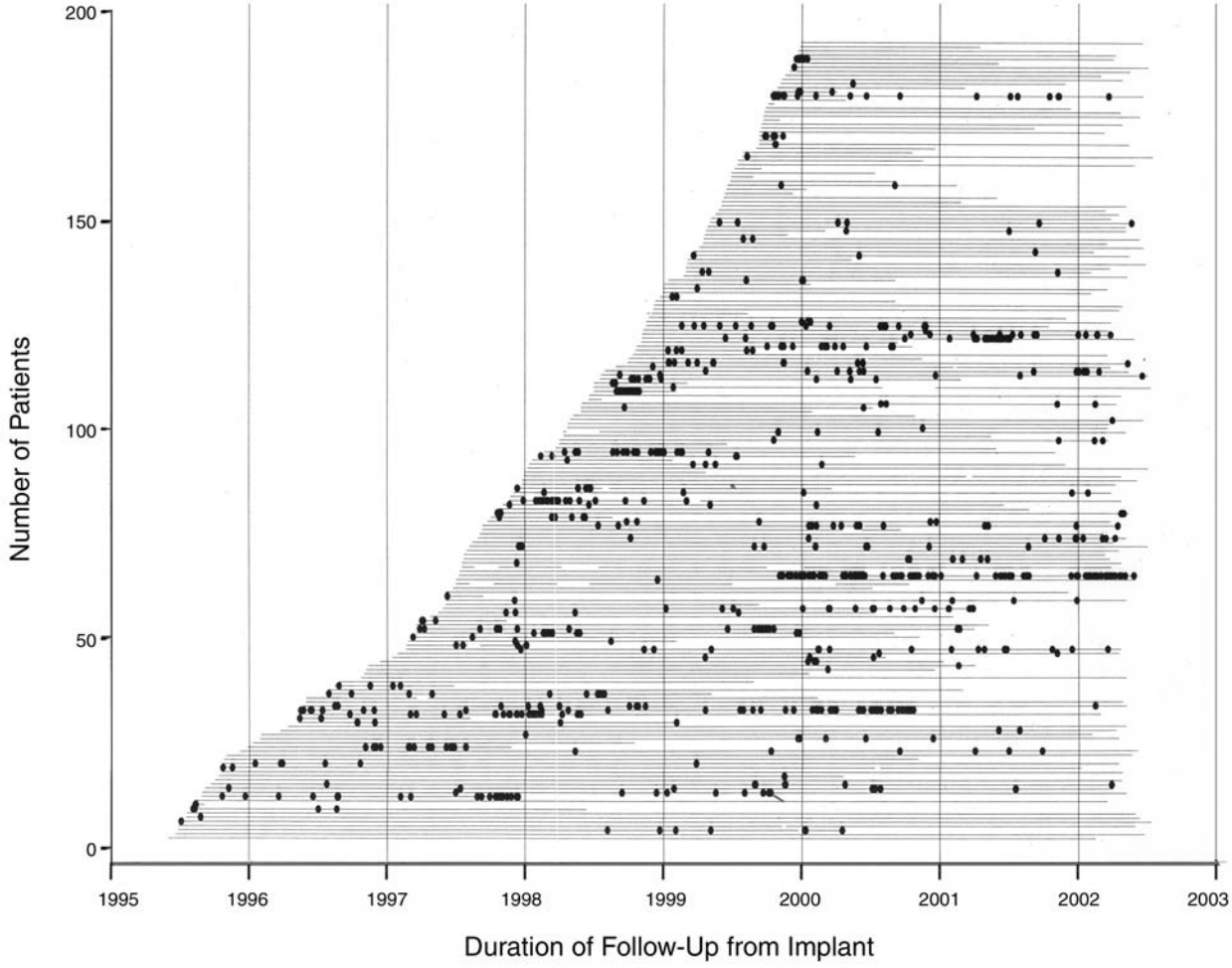

Figure 2. Plot of accumulated person-time for 195 patients during the study period (June 11, 1995 through December 31, 1999). Follow-up continued through clinical visits on July 11, 2002. Dots indicate detected arrhythmic episodes. Vertical lines show January 1 of each year.

Of the arrhythmias that occurred on the 772 episode-days, 659 (85%) were VAs and 114 (15%) were SVAs as defined by the reviewing electrophysiologist. One patient had both a VA and a separate SVA on the same day.

Demographics

Most of the 195 patients were men (74%) and the mean age at implantation was 63.6 years (range 19 to 90 years); 44 (22%) were less than 55 years old, and 44 (23%) were older than 75 years (Table 5). Based on the medical records, 83% of the patients were reported to be white, 5% Hispanic, 3% Afro-American, 3% Asian, and 7% of undetermined or unknown ethnicity.

The rate of ventricular episode-days per person-year was substantially higher in male than in female patients and increased with age at implantation (Table 5). The 6 Afro-American patients had a rate of 2.50 VA episode-days per year compared with 1.06 episode-days per year for the

Table 4. Follow-Up Days and Episode-Days Defined by Each Patient's Number of Episode-Days with Arrhythmias

Number of Episode-Days for Each Patient	Number of Patients	Age at Implant		Follow-Up Days		Episode-Days			Episode-Days per Person-Year		
		Mean	Range	Mean	Person-Days	All	VA	SVA	All	VA	SVA
0	103	62.4	19–89	1051	108,204	0	0	0	0	0	0
1	20	61.7	19–78	1393	27,861	20	14	6	0.3	0.2	0.1
2–4	26	64.4	42–81	1041	27,074	74	59	15	1.0	0.8	0.2
5–9	20	66.5	26–83	1340	26,806	118[a]	88	31	1.6	1.2	0.4
10 or more	26	66.9	43–90	1370	35,622	560	498	62	5.7	5.1	0.6
Total	195	63.6	19–90	1157	225,567	772[a]	659	114	1.3	1.1	0.2

[a] One subject had a VA and an SVA on the same day.

Table 5. VAs and SVAs by Gender, Age, And Ethnicity of Study Patients

Characteristic	Patients		VAs		SVAs	
	Number	% of Total	% of Patients by Characteristic	Days per Person-Year	% of Patients by Characteristic	Days per Person-Year
Gender						
Male	144	74	44	1.24	19	0.20
Female	51	26	35	0.62	22	0.15
Age (Years)						
< 45	16	8	31	0.31	13	0.09
45–54	28	14	39	0.59	18	0.23
55–64	40	21	48	1.07	25	0.13
65–74	66	34	44	1.42	17	0.11
75–84	41	21	39	1.10	27	0.42
85+	3	2	33	2.21	0	0
Unknown	1					
Ethnicity						
White	161	83	42	1.06	19	0.19
Hispanic	10	5	70	1.08	50	0.22
Afro-American	6	3	67	2.50	17	0.06
Asian	5	3	20	0.94	0	0
Unknown	13	7	15	0.29	15	0.08

161 white patients. For SVA episode-days, we found little difference in the rate by gender, age, or ethnicity.

Clinical Characteristics and Medications

Of the 195 patients, 158 (81%) had single-chamber devices, and 37 (19%) had dual-chamber devices (Table 6). The dual-chamber devices were more likely to detect VAs (1.45 episode-days per person-year) than the single-chamber devices (1.00 episode-day per person-year), but less likely to detect SVAs (0.07 episode-day per person-year) than the single-chamber devices (0.20 episode-day per person-year).

Among the 67 (34%) patients who were reported to have had a myocardial infarction before ICD implantation (Table 6), the rate of detected VAs was 1.89 per person-year, which is more than three times the rate among the 125 patients reported not to have had a myocardial infarction (0.61 per person-year). Little difference was detected in the rates of SVAs between those with and without a reported myocardial infarction before implantation.

Of the 195 patients, 122 (63%) had low ejection fractions (0.35 or less) before implantation. The number of ventricular episode-days (Table 6) was three times as large

Table 6. VAs and SVAs During Follow-Up Stratified by Patients' Clinical Characteristics

	Patients		VAs		SVAs	
Clinical Charistictic	Number	% of Total	% of Patients by Characteristic	Episode-Days per Person-Year	% of Patients by Characteristic	Episode-Days per Person-Year
ICD Type						
Single chamber	158	81	44	1.00	22	0.20
Dual chambers	37	19	32	1.45	11	0.07
Myocardial Infarction Before Implantation						
Yes	70	36	56	1.77	27	0.17
No	125	64	34	0.61	16	0.19
Ejection Fraction at Implantation						
⩽ 0.35	122	63	49	1.49	19	0.17
> 0.35	73	37	29	0.46	22	0.21
Diagnosis at Implantation						
Coronary artery disease	138	71	44	1.31	20	0.13
Idiopathic cardiomyopathy	29	15	38	0.57	28	0.58
Hypertrophic cardiomyopathy	5	2.6	0	0	0	0
Primary electrical disease	9	4.6	44	0.62	22	0.06
Long QT syndrome	4	2.1	25	0.83	0	0
Valve disease	4	2.1	50	0.48	25	0.12
Congenital heart disease	1	0.5	100	1.23	100	4.92
Arrhythmogenic right ventricular dysplasia	2	1.0	50	0.10	0	0
Brugada syndrome	1	0.5	0	0	0	0
Hypertensive heart disease	1	0.5	0	0	0	0
Sarcoidosis	1	0.5	0	0	0	0
Cardiac Medications (> 50% of follow-up)						
β-Blockers	127	65	40	0.95	19	0.17
Antiarrhythmics	66	34	48	1.52	17	0.12
Digoxin	85	44	51	1.69	24	0.19
None	23	12	39	0.88	22	0.12
All Patients	195	100	42	1.07	20	0.18

among those with low ejection fractions as among those with ejection fractions above 0.35 (1.49 versus 0.46 episode-days per person-year). The rates of SVAs were similar in these two groups of patients.

Coronary artery disease, reported for 138 (71%) patients, was the most common preimplantation diagnosis (Table 6). Patients with this diagnosis had the highest rate of detected VAs (1.31 per person-year). Cardiomyopathies were the second most frequent preimplantation diagnosis: 29 patients (15%) were diagnosed with idiopathic cardiomyopathy and 5 patients (3%) with hypertrophic cardiomyopathy. Primary electrical disease was diagnosed in 9 (5%) patients, and 4 of these had VAs during follow-up. Long QT syndrome was found in 4 patients (2%), but only 1 of these experienced an arrhythmic event during follow-up.

For each patient we assessed visit-specific reports of prescribed cardiac medications (β-blockers, antiarrhythmic medications, and digoxin). Approximately 80% of the patients had no change in their prescribed medications during their follow-up. We therefore divided patients into groups based on their usual medication, defined as the prescriptions reported on more than half of their clinical follow-up visits. Among the two-thirds of the patients regularly prescribed β-blockers, the rate of ventricular episode-days was 0.95 per person-year (Table 6) compared with 0.88 among those taking no medications. The one-third of patients regularly prescribed antiarrhythmics had 1.52 ventricular episode-days per person-year. Digoxin was regularly prescribed for 85 (44%) of the patients and they had 1.69 ventricular episode-days per person-year.

Most patients were prescribed more than one of these medications. We assessed the possible changes in the relative risks of VAs or SVAs for these three classes of drugs simultaneously in a logistic regression model. We found no statistically significant differences for VAs, but β-blockers were associated with decreased relative risk of VA (OR = 0.67; 95% CI = 0.37, 1.20; $P = 0.12$), whereas antiarrhythmics were associated with increased relative risk (OR = 1.58; 95% CI = 0.89, 2.80; $P = 0.12$), as was digoxin (OR = 1.38; 95% CI = 0.77, 2.45; $P = 0.28$; Table 7).

Underlying medical conditions may confound associations between prescribed drugs and relative risks of arrhythmias. We therefore simultaneously adjusted for two primary preimplantation patient characteristics: ejection fraction less than 0.35 and a diagnosis of coronary artery disease. For VAs, each of these conditions was associated with increased relative risk (Table 7). However, adjustment for low ejection fraction and diagnosis of coronary artery disease did not substantially change the estimated associations with β-blockers, antiarrhythmics, or digoxin (Table 7).

For SVAs, the three drug classes were each associated with a lower relative risk of SVAs, but only the association with antiarrhythmics approached statistical significance ($P = 0.12$). In the simultaneous model for prescribed medications and preimplantation conditions (Table 7), neither the drugs nor diagnoses were associated significantly with decreased risk of SVAs ($P > 0.20$).

AIR POLLUTION

Particulate and gaseous pollutant concentrations were averaged across the monitoring stations in the greater Boston area. $PM_{2.5}$ was measured for 2047 days; that is, 80% of follow-up days (Table 8). The mean daily $PM_{2.5}$ was 11.6 $\mu g/m^3$ with a maximum of 53.2 $\mu g/m^3$. Higher $PM_{2.5}$ concentrations were observed during the summer months (Figure 3). BC was measured on 1555 (61%) days (Figure 3) and had a mean concentration of 1.1 $\mu g/m^3$. Fine particle SO_4^{2-} and number of particles were measured starting in 1999. SO_4^{2-} was measured on 971 (38%) days and had a mean concentration of 3.1 $\mu g/m^3$; and number of particles was obtained on 806 (32%) days and had a mean of 30,700/cm^3 (Table 8). Daily $PM_{2.5}$ was most strongly correlated with SO_4^{2-} and BC, but was not correlated ($r = -0.13$) with daily numbers of particles (Table 9).

Daily concentrations of gaseous pollutants were reported on virtually all days. The mean NO_2 concentration was 23.1 ppb (Table 8) and the maximum was 61.8 ppb. NO_2 concentrations had little seasonal trend (Figure 3). NO_2 was positively correlated with the other motor vehicle pollutants (CO, $PM_{2.5}$, and BC) and with SO_2; it was negatively correlated with O_3 (Table 9).

Mean daily CO was 0.8 ppm (Table 8), and the maximum was 1.66 ppm. CO concentrations were highest in the winters and declined over the course of the study (Figure 3).

Table 7. Associations of Prescribed Cardiac Medications and Preimplantation Conditions with Relative Risk of VAs and SVAs Recorded by ICD[a]

	VAs	SVAs
β-Blocker	0.64 (0.35 , 1.17)	0.98 (0.40 , 2.37)
Antiarrhythmics	1.27 (0.71 , 2.28)	0.83 (0.30 , 2.29)
Digoxin	1.36 (0.75 , 2.47)	0.67 (0.28 , 1.60)
Coronary artery disease	1.43 (0.70 , 2.93)	0.54 (0.21 , 1.39)
Ejection fraction < 0.35	1.50 (0.75 , 3.00)	0.92 (0.40 , 2.14)

[a] Associations of medications and conditions were estimated simultaneously. Results are presented as ORs and 95% CIs.

Table 8. Distribution of Weather Variables and Daily Mean Air Pollutant Concentrations Across Multiple Sites in Boston for July 11, 1995 through July 11, 2002

Pollutant or Weather Variable	n[a]	Mean Concentration	Percentiles					IQR (75%−25%)
			5%	25%	50%	75%	95%	
$PM_{2.5}$ (μg/m^3)	2047	11.6	3.8	6.7	9.8	14.7	25.1	8.0
BC (μg/m^3)	1555	1.1	0.31	0.59	0.95	1.43	2.58	0.84
NO_2 (ppb)	2557	23.1	13.0	18.1	22.4	27.3	35.2	9.2
CO (ppm)	2558	0.8	0.3	0.5	0.8	1.0	1.4	0.5
SO_2 (ppb)	2558	5.8	1.7	3.2	4.7	7.2	13.7	4.1
O_3 (ppb)	2552	23.8	7.0	15.3	22.8	31.2	44.2	15.9
SO_4^{2-} (μg/m^3)	971	3.1	0.8	1.6	2.4	3.8	7.8	2.2
Number of particles (10^3/cm^3)	806	30.7	11.8	20.2	29.3	40.6	53.0	20.4
Mean temperature (°C)	2553	11.0	−3.3	3.7	10.9	18.7	24.8	15.0
Minimum temperature (°C)	2553	7.1	−7.2	0.6	7.2	14.4	20.6	13.8
Relative humidity (%)	2549	69.0	42.9	56.7	69.0	81.5	94.3	24.8

[a] Number of days for which measurements were obtained.

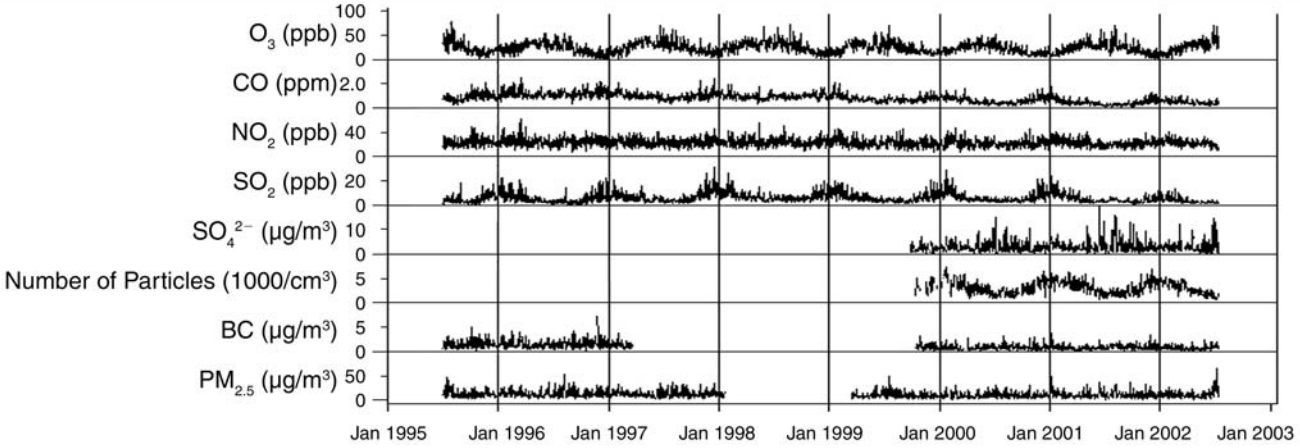

Figure 3. Daily mean air pollutant concentrations across monitoring sites in the greater Boston area for July 1995 through July 2002. Note that different scales are used for each pollutant.

Table 9. Day-to-Day Correlation Between Air Pollutant Concentrations[a]

Pollutant	$PM_{2.5}$	SO_4^{2-}	BC	NO_2	CO	SO_2	O_3	Number of Particles
$PM_{2.5}$	***1***	0.77	0.67	0.54	0.41	0.33	0.18	−0.13
SO_4^{2-}	0.77	***1***	0.45	0.35	0.13	0.13	0.30	−0.20
BC	0.69	0.44	***1***	0.65	0.71	0.38	−0.21	0.13
NO_2	0.57	0.42	0.70	***1***	0.61	0.57	−0.20	0.42
CO	0.51	0.32	0.70	0.73	***1***	0.54	−0.29	0.56
SO_2	0.40	0.27	0.45	0.58	0.50	***1***	−0.40	0.57
O_3	0.21	0.32	−0.22	−0.19	−0.26	−0.22	***1***	−0.53
Number of particles	−0.06	−0.10	0.36	0.30	0.24	0.35	−0.35	***1***

[a] Values above and to the right of the diagonal are unadjusted correlations; those below and to the left are partial correlations adjusted for season.

CO, an indicator of mobile-source emissions, was strongly correlated with BC, NO_2, $PM_{2.5}$, and SO_2 (Table 9).

Daily SO_2 concentrations were low in Boston and had a mean of 5.8 ppb (Table 8). Highest SO_2 concentrations were observed in the winter months (Figure 3). SO_2 was positively correlated with the indicators of the mobile-source pollutants $PM_{2.5}$, CO, NO_2, and BC, but negatively correlated with O_3 (Table 9).

Daily O_3 concentrations showed the expected seasonal pattern of the highest values during the warm months (Figure 3). The mean O_3 concentration across the entire analysis period was 23.8 ppb (Table 8). Daily O_3 was positively correlated with temperature ($r = 0.44$) and with $PM_{2.5}$ and SO_4^{2-}, but negatively correlated with CO, SO_2, and NO_2 (Table 9).

ASSOCIATION BETWEEN AIR POLLUTANTS AND ARRHYTHMIAS

All Arrhythmic Events Combined

In the pilot study (Peters et al 2000), we found positive associations between air pollutant concentrations and ICD discharge interventions. Table 10 presents the results of the current study obtained by multivariate logistic regression analyses of associations between air pollutant concentrations at lag times of 0, 1, 2, and 3 days (plus the 5-day mean) and all episode-days with a confirmed arrhythmia; each pollutant and lag time was estimated independently. The OR and 95% CI were estimated for an IQR increase in each pollutant. For comparison we have included the effect estimates from the pilot study for the same increments in air pollutants.

Positive associations were found between all confirmed arrhythmic episode-days and ambient concentrations of SO_2 (OR = 1.10; 95% CI = 1.01, 1.21; $P = 0.037$) on the same day (Table 10), O_3 concentrations on the day before exposure (1-day lag) (OR = 1.16; 95% CI = 1.00, 1.34; $P = 0.051$). All arrhythmias combined were positively but not significantly associated with $PM_{2.5}$, BC, NO_2, CO, and SO_2 ($P > 0.20$). For all pollutants except SO_2, the associations were weaker at 2 and 3 days after exposure.

Increases in 5-day mean concentrations in SO_2 were associated with a 23% increase in relative risk for all arrhythmias combined (95% CI = 1.07, 1.42), whereas comparable increases in CO were associated with an 11% increase (95% CI = 0.88, 1.40). IQR increases in concentrations of $PM_{2.5}$, BC, NO_2, or O_3 lagged 2 or 3 days and their 5-day mean concentrations had little or no association with arrhythmias (Table 10).

We estimated associations separately for VA and SVA episode-days (single lag day columns in Table 11). Positive associations were found between VA episode-days and

Table 10. Estimated Arrhythmic Effects per IQR Increase in Daily Mean of Air Pollutant Concentrations at Different Lag Times Compared with Effects on ICD Discharges in Pilot Study Patients[a]

Pollutant and Lag Time	Present Study[b] (NEMC patients; all arrhythmias combined)		Pilot Study[c] (BIDMC patients; ICD dischanges)	
$PM_{2.5}$ (8.0 μg/m^3) 84 patients, 562 episode-days				
0 Day	1.07	(0.94 , 1.21)	0.99	(0.86 , 1.12)
1 Day	1.06	(0.95 , 1.20)	1.00	(0.88 , 1.14)
2 Days	0.91	(0.81 , 1.02)	1.01	(0.90 , 1.14)
3 Days	0.95	(0.85 , 1.06)	0.96	(0.84 , 1.08)
5-Day mean	0.96	(0.84 , 1.10)	0.96	(0.83 , 1.11)
BC (0.84 μg/m^3) 69 patients, 429 episode-days				
0 Day	1.04	(0.86 , 1.26)	0.98	(0.79 , 1.22)
1 Day	1.12	(0.94 , 1.33)	1.01	(0.81 , 1.25)
2 Days	0.95	(0.80 , 1.13)	1.10	(0.90 , 1.35)
3 Days	0.97	(0.82 , 1.15)	1.03	(0.84 , 1.26)
5-Day mean	0.94	(0.73 , 1.20)	1.13	(0.83 , 1.48)
NO_2 (9.2 ppb) 92 patients, 764 episode-days				
0 Day	1.06	(0.96 , 1.18)	1.08	(0.90 , 1.29)
1 Day	1.06	(0.95 , 1.18)	1.22[d]	(1.02 , 1.47)
2 Days	0.99	(0.89 , 1.10)	1.15	(0.97 , 1.36)
3 Days	0.97	(0.87 , 1.08)	1.06	(0.89 , 1.26)
5-Day mean	1.00	(0.90 , 1.1)1	1.18[d]	(1.00 , 1.39)
CO (0.5 ppm) 92 patients, 765 episode-days				
0 Day	1.12	(0.96 , 1.32)	1.05	(0.69 , 1.60)
1 Day	1.09	(0.92 , 1.29)	1.05	(0.68 , 1.60)
2 Days	1.01	(0.86 , 1.19)	1.04	(0.69 , 1.56)
3 Days	1.04	(0.89 , 1.23)	1.07	(0.72 , 1.59)
5-Day mean	1.11	(0.88 , 1.40)	1.25	(0.69 , 2.29)
SO_2 (4.1 ppb) 92 patients, 765 episode-days				
0 Day	1.10[d]	(1.01 , 1.21)	0.94	(0.85 , 1.04)
1 Day	1.06	(0.96 , 1.16)	0.98	(0.89 , 1.08)
2 Days	1.14[e]	(1.04 , 1.24)	0.97	(0.89 , 1.07)
3 Days	1.12[d]	(1.02 , 1.22)	1.02	(0.94 , 1.10)
5-Day mean	1.23[e]	(1.07 , 1.42)	0.96	(0.84 , 1.10)
O_3 (16 ppb) 92 patients, 764 episode-days				
0 Day	1.02	(0.88 , 1.20)	0.98	(0.69 , 1.40)
1 Day	1.16[f]	(1.00 , 1.34)	1.04	(0.74 , 1.47)
2 Days	0.99	(0.86 , 1.14)	1.24	(0.89 , 1.71)
3 Days	0.93	(0.81 , 1.07)	0.81	(0.57 , 1.15)
5-Day mean	0.98	(0.79 , 1.22)	0.87	(0.51 , 1.50)

[a] Results are presented as ORs and 95% CIs for all arrhythmias combined in the present study compared with all ICD discharges in the pilot study.

[b] In this study, effects of each pollutant (per IQR increase in daily mean) and each lag time were estimated separately based on (1) the total number of days for which measurements of that pollutant were available (as shown in Table 2); (2) the number of episode-days; and (3) the corresponding number of patients.

[c] Estimated associations between pollutant concentrations and ICD discharges for all 100 patients from the pilot study (BIDMC cohort; Peters et al 2000). Concentration of each pollutant was scaled to the same increment of increase used in the current study.

[d] $P < 0.05$.

[e] $P < 0.01$.

[f] $P < 0.10$.

Table 11. Estimated Arrhythmic Effects per IQR Increase in Daily Mean of Air Pollutant Concentrations at Different Lag Times[a]

Pollutant, IQR Increase in Daily Mean, and Lag Time	VAs		SVAs	
	Single Lag Day	Distributed Lag	Single Lag Day	Distributed Lag
$PM_{2.5}$ (8.0 μg/m^3)[b]				
72 Patients, 494 episode-days			31 Patients, 69 episode-days	
0 Day	1.06 (0.93 , 1.21)	1.04 (0.90 , 1.20)	0 day 1.09 (0.77 , 1.54)	1.08 (0.73 , 1.59)
1 Day	1.05 (0.93 , 1.19)	1.08 (0.93 , 1.26)	1 day 1.21 (0.87 , 1.68)	1.42 (0.94 , 2.15)
2 Days	0.94 (0.83 , 1.06)	0.90 (0.77 , 1.05)	2 days 0.74 (0.52 , 1.06)	0.73 (0.45 , 1.17)
3 Days	0.98 (0.87 , 1.10)	0.98 (0.86 , 1.13)	3 days 0.71 (0.49 , 1.03)	0.72 (0.46 , 1.12)
BC (0.84 μg/m^3)				
60 Patients, 374 episode-days			23 Patients, 56 episode-days	
0 Day	1.03 (0.85 , 1.26)	1.01 (0.82 , 1.25)	0 day 0.99 (0.62 , 1.60)	0.81 (0.48 , 1.37)
1 Day	1.09 (0.90 , 1.32)	1.13 (0.92 , 1.38)	1 day 1.32 (0.86 , 2.02)	1.48 (0.92 , 2.38)
2 Days	0.99 (0.83 , 1.18)	0.91 (0.74 , 1.12)	2 days 0.75 (0.47 , 1.22)	0.70 (0.40 , 1.23)
3 Days	1.02 (0.85 , 1.22)	1.06 (0.88 , 1.28)	3 days 0.70 (0.43 , 1.16)	0.78 (0.47 , 1.31)
NO_2 (92 ppb)				
81 Patients, 653 episode-days			38 Patients, 112 episode-days	
0 Day	1.04 (0.93 , 1.17)	1.03 (0.91 , 1.17)	0 day 1.15 (0.89 , 1.49)	1.14 (0.86 , 1.51)
1 Day	1.05 (0.93 , 1.18)	1.04 (0.91 , 1.20)	1 day 1.11 (0.84 , 1.47)	1.06 (0.77 , 1.47)
2 Days	0.99 (0.88 , 1.12)	0.99 (0.86 , 1.13)	2 days 1.00 (0.77 , 1.31)	1.01 (0.74 , 1.38)
3 Days	0.98 (0.88 , 1.10)	0.99 (0.87 , 1.12)	3 days 0.91 (0.70 , 1.19)	0.90 (0.67 , 1.20)
CO (0.50 ppm)				
81 Patients, 654 episode-days			38 Patients, 112 episode-days	
0 Day	1.12 (0.94 , 1.34)	1.11 (0.91 , 1.35)	0 day 1.13 (0.75 , 1.70)	1.06 (0.68 , 1.66)
1 Day	1.07 (0.89 , 1.28)	1.01 (0.81 , 1.26)	1 day 1.24 (0.82 , 1.87)	1.31 (0.80 , 2.15)
2 Days	1.04 (0.87 , 1.24)	0.98 (0.79 , 1.21)	2 days 0.93 (0.61 , 1.41)	0.88 (0.53 , 1.46)
3 Days	1.09 (0.91 , 1.30)	1.08 (0.89 , 1.32)	3 days 0.85 (0.56 , 1.30)	0.85 (0.53 , 1.37)
SO_2 (4.1 ppb)				
81 Patients, 654 episode-days			38 Patients, 112 episode-days	
0 Day	1.08 (0.98 , 1.20)	1.08 (0.97 , 1.21)	0 day 1.20[c] (0.97 , 1.48)	1.11 (0.88 , 1.40)
1 Day	1.02 (0.92 , 1.13)	0.94 (0.83 , 1.06)	1 day 1.25[d] (1.02 , 1.55)	1.15 (0.89 , 1.48)
2 Days	1.13[d] (1.03 , 1.25)	1.12[d] (1.00 , 1.25)	2 days 1.21[c] (0.98 , 1.48)	1.11 (0.87 , 1.41)
3 Days	1.12[d] (1.01 , 1.23)	1.07 (0.96 , 1.19)	3 days 1.15 (0.93 , 1.42)	1.07 (0.84 , 1.37)
O_3 (16 ppb)				
81 Patients, 653 episode-days			38 Patients, 112 episode-days	
0 Day	1.00 (0.85 , 1.19)	0.94 (0.78 , 1.13)	0 day 1.18 (0.80 , 1.75)	1.14 (0.75 , 1.74)
1 Day	1.16[c] (0.99 , 1.36)	1.22[d] (1.01 , 1.47)	1 day 1.12 (0.77 , 1.63)	1.18 (0.75 , 1.85)
2 Days	1.02 (0.87 , 1.18)	0.96 (0.80 , 1.16)	2 days 0.84 (0.58 , 1.22)	0.83 (0.52 , 1.31)
3 Days	0.94 (0.81 , 1.10)	0.94 (0.79 , 1.12)	3 days 0.85 (0.58 , 1.23)	0.89 (0.58 , 1.35)

[a] Results are presented as ORs and 95% CIs.

[b] Effects of each pollutant and each lag time were estimated separately based on (1) the total number of days for which measurements of that pollutant were available (as shown in Table 2); (2) the number of episode-days; and (3) the corresponding number of patients. Distributed lag was estimated for all lag times simultaneously.

[c] $P < 0.10$.

[d] $P < 0.05$.

each of the pollutants considered on the same and previous days; the concentration of O_3 on only the previous day was associated with VAs; the SO_2 concentrations lagged 2 or 3 days were associated with a 12% to 13% increase in estimated OR for VAs (Table 11).

Although SVAs were only a small fraction of the total arrhythmias detected by the ICDs, positive nonsignificant associations were found on the same day for concentrations of NO_2 ($P = 0.29$) and SO_2 ($P = 0.087$); and on the previous day (1-day lag) for BC ($P = 0.20$), CO ($P = 0.31$), and SO_2 ($P = 0.36$) concentrations (Table 11).

Unconstrained Distributed Lag Models

To evaluate the lag structure in the associations between air pollutants and arrhythmias, and to estimate the net effect of acute air pollutant concentrations over the subsequent few days, we fit an unconstrained distributed lag model for air pollutant concentrations on the same day and for each of 3 lag days. In Table 11 the distributed lag columns present the estimated effect of each day and 95% CI when lags of 0 to 3 days were estimated simultaneously.

Although very few associations between VAs and air pollutant concentrations for specific lag times (Table 11) were statistically significant, the ORs were consistently elevated for air pollutant concentrations on the day of (lag 0) and the day before (lag 1) the arrhythmia. Consistently positive elevated risks for SVAs were found for lags 0 and 1 associated with each air pollutant (Table 11).

Two-Day Mean Air Pollutant Concentrations

The single-day lag model and the unconstrained distributed lag model suggested associations of days of arrhythmias with air pollutant concentrations on the episode-day and on the preceding day. We therefore fit episode-days for all arrhythmias combined, VAs, and SVAs separately to the running mean concentration of each pollutant over lag days 0 and 1. Estimated ORs were scaled to the IQR of these 2-day means (Table 12).

Positive associations were found between IQR increases in 2-day mean concentrations of each of the pollutants and all arrhythmias combined. The statistically strongest association was observed with SO_2, primarily because of its association with SVAs (OR = 1.33; 95% CI = 1.04, 1.70). Effect estimates for all pollutants were higher for SVAs than for VAs, except for number of particles; however, the limited number of available measurements (806) precluded a definite interpretation of this result (Table 12).

Adjustment for Repeated Measures

Although arrhythmias were rare events in these patients, clustering of events within patients was possible (Figure 1). To assess the influence of repeated measures in this analysis, we repeated the analysis of the associations between 2-day mean air pollutant concentrations and arrhythmic episode-days using GEEs. We specified an exchangeable covariance structure in which the correlation of risk between days for each patient is assumed to be the same for all days. Table 13 presents the results of this analysis adjusting for repeated measures for VAs and SVAs. Comparing these results with the simple logistic

Table 12. Estimated Arrhythmic Effects per IQR Increase in 2-Day Mean of Air Pollutant Concentrations Estimated with Logistic Regression Analysis[a]

Pollutant (IQR Increase in 2-Day Mean)	n[b]	All Arrhythmias	VAs	SVAs
$PM_{2.5}$ (7.0 μg/m^3)	2047	1.09 (0.96 , 1.24)	1.07 (0.94 , 1.23)	1.23 (0.86 , 1.77)
BC (0.74 μg/m^3)	1555	1.10 (0.90 , 1.36)	1.09 (0.87 , 1.36)	1.16 (0.68 , 1.99)
NO_2 (7.7 ppb)	2557	1.08 (0.96 , 1.20)	1.06 (0.94 , 1.20)	1.17 (0.89 , 1.53)
CO (0.48 ppm)	2558	1.15 (0.95 , 1.38)	1.13 (0.92 , 1.39)	1.25 (0.78 , 2.01)
SO_2 (4.0 ppb)	2558	1.11[c] (1.00 , 1.24)	1.07 (0.95 , 1.21)	1.33[d] (1.04 , 1.70)
O_3 (15 ppb)	2552	1.13 (0.95 , 1.35)	1.12 (0.93 , 1.35)	1.21 (0.79 , 1.87)
SO_4^{2-} (1.99 μg/m^3)	971	1.05 (0.92 , 1.20)	1.05 (0.91 , 1.20)	1.08 (0.74 , 1.59)
Number of particles (19,120/cm^3)	806	1.02 (0.69 , 1.50)	1.13 (0.76 , 1.70)	0.35 (0.10 , 1.27)

[a] Results are presented as ORs and 95% CIs.

[b] Number of days for which air pollutant measurements were obtained.

[c] $P < 0.10$.

[d] $P < 0.05$.

results (Table 12), we see that the estimated effects are slightly reduced and the CIs tighter for the GEE regression (Table 13). For example, consider the estimated association of VAs with CO, the pollutant with the largest estimate of effect obtained using logistic regression (Table 12). The estimated OR was 1.13 (95% CI = 0.92, 1.39); using GEE regression (Table 13), the estimated OR was 1.12 (95% CI = 0.94, 1.34). The GEE parameter estimate (log OR) for the association between CO and VAs was 92% of the logistic regression estimate, and the GEE estimate of the standard error was 88% of the logistic estimate. Similarly, for SVAs, the CO parameter estimate by GEE was 95% of the logistic regression estimate, and the GEE estimate of the standard error was 87% of the logistic estimate. We found the GEE regression to be computationally intensive and slow to converge compared with the logistic regression. Therefore, we elected to restrict our analyses to the logistic regression, recognizing that this method would generally give slightly larger estimates of the magnitude of associations and wider CIs compared with the GEE regression.

Multipollutant Models

To assess whether the association of each pollutant with arrhythmias was independent of the other pollutants, we fit two-pollutant models comparing the estimated OR for the 2-day mean single-pollutant model with those adjusting for the second pollutant. We did not include number of particles and SO_4^{2-} in these analyses because of the limited number of observations. In Table 14 the columns present the estimated OR (95% CI) for a VA episode-day associated with an IQR increase in each pollutant. The rows indicate the estimated association for the pollutant at the head of the column adjusted for the copollutant at the left of the row. The diagonals represent the single-pollutant estimates presented in Table 12. Looking down the columns, the change in the pollutant-specific associations in the rows compared with the single-pollutant associations in the diagonals provides an indication of the degree of confounding by the second pollutant. Thus for the association of VAs with an increase of 7.0 μg/m^3 in $PM_{2.5}$, the estimated OR was 1.07 (95% CI = 0.94, 1.23). When the association of $PM_{2.5}$ with VA was adjusted for BC, the estimated OR was 1.08 (95% CI = 0.83, 1.39). For $PM_{2.5}$ these pairwise comparisons of 2-day mean air pollutant concentrations were reduced after adjusting for NO_2, CO, and SO_2, suggesting that the association between $PM_{2.5}$ and VAs is confounded by these copollutants. Similarly the BC, NO_2, CO, and SO_2 associations were reduced after adjusting for each of these other pollutants. This suggests that these correlated pollutants (see Table 9) are all indicators of a common characteristic of the air pollution mixture that is associated with increased risk of VA. The data suggest a negative confounding by $PM_{2.5}$ with these same pollutants in that stronger associations were found for NO_2, CO, and SO_2 after adjusting for $PM_{2.5}$.

Similar results are presented for SVA episode-days (Table 14). Positive associations were found between SVAs and each of the pollutants evaluated individually (Table 12). All these associations (except for O_3) decreased substantially after adjusting for confounding by SO_2, whereas the SO_2 association was not affected by adjusting for other pollutants (Table 14).

SENSITIVITY TO AND EFFECT MODIFICATION BY PATIENT CHARACTERISTICS

We undertook a series of exploratory analyses to examine whether the associations between air pollutants and VAs or SVAs might be sensitive to or possibly modified by patient

Table 13. Estimated Arrhythmic Effects per IQR Increase in 2-Day Mean of Air Pollutant Concentrations Estimated with GEE[a]

Pollutant (IQR Increase in 2-Day Mean)	n[b]	VAs	SVAs
$PM_{2.5}$ (7.0 μg/m^3)	2047	1.07 (0.95 , 1.20)	1.21 (0.89 , 1.65)
BC (0.74 μg/m^3)	1555	1.07 (0.93 , 1.24)	1.17 (0.80 , 1.72)
NO_2 (7.7 ppb)	2557	1.06 (0.96 , 1.16)	1.14 (0.92 , 1.42)
CO (0.48 ppm)	2558	1.12 (0.94 , 1.34)	1.24 (0.82 , 1.87)
SO_2 (4.0 ppb)	2558	1.06 (0.96 , 1.17)	1.30[c] (1.07 , 1.57)
O_3 (15 ppb)	2552	1.09 (0.94 , 1.28)	1.18 (0.87 , 1.61)
SO_4^{2-} (1.99 μg/m^3)	971	1.04 (0.93 , 1.16)	1.08 (0.79 , 1.49)
Number of particles (19,120/cm^3)	806	1.10 (0.85 , 1.44)	0.33 (0.12 , 0.93)

[a] Results are presented as ORs and 95% CIs.

[b] Number of days for which air pollutant measurements were obtained.

[c] $P < 0.01$.

Table 14. Estimated Arrhythmic Effects of IQR Increase in 2-Day Mean of Air Pollutant Concentrations Obtained from One- and Two-Pollutant Analytic Models[a]

Pollutant	$PM_{2.5}$ (7.0 μg/m^3)	BC (0.74 μg/m^3)	NO_2 (7.7 ppb)	CO (0.48 ppm)	SO_2 (4.0 ppb)	O_3 (15 ppb)
VAs						
$PM_{2.5}$	***1.07 (0.94 , 1.23)***	1.08 (0.79 , 1.47)	1.12 (0.94 , 1.33)	1.37[b] (1.03 , 1.82)	1.13 (0.97 , 1.32)	1.00 (0.80 , 1.25)
BC	1.08 (0.83 , 1.39)	***1.09 (0.87 , 1.36)***	1.06 (0.85 , 1.32)	1.22 (0.83 , 1.79)	1.02 (0.86 , 1.22)	1.07 (0.81 , 1.39)
NO_2	1.01 (0.83 , 1.23)	1.05 (0.79 , 1.39)	***1.06 (0.94 , 1.20)***	1.11 (0.85 , 1.44)	1.05 (0.91 , 1.22)	1.14 (0.94 , 1.37)
CO	0.98 (0.82 , 1.18)	1.00 (0.76 , 1.33)	1.02 (0.88 , 1.19)	***1.13 (0.92 , 1.39)***	1.04 (0.91 , 1.19)	1.16 (0.96 , 1.40)
SO_2	1.02 (0.86 , 1.21)	1.08 (0.85 , 1.37)	1.03 (0.89 , 1.19)	1.09 (0.87 , 1.37)	***1.07 (0.95 , 1.21)***	1.14 (0.95 , 1.38)
O_3	1.08 (0.93 , 1.27)	1.09 (0.87 , 1.36)	1.07 (0.95 , 1.20)	1.17 (0.96 , 1.44)	1.08 (0.96 , 1.22)	***1.12 (0.93 , 1.35)***
SVAs						
$PM_{2.5}$	***1.23 (0.86 , 1.77)***	1.58 (0.72 , 3.48)	0.97 (0.61 , 1.56)	1.42 (0.67 , 3.01)	1.60[c] (1.12 , 2.28)	0.89 (0.48 , 1.66)
BC	0.78 (0.36 , 1.67)	***1.16 (0.68 , 1.99)***	0.78 (0.45 , 1.37)	0.73 (0.28 , 1.90)	1.47[d] (0.99 , 2.18)	0.87 (0.42 , 1.82)
NO_2	1.30 (0.78 , 2.18)	1.39 (0.71 , 2.74)	***1.17 (0.89 , 1.53)***	1.10 (0.59 , 2.03)	1.39[b] (1.01 , 1.93)	1.29 (0.83 , 2.01)
CO	1.13 (0.69 , 1.85)	1.34 (0.67 , 2.66)	1.13 (0.79 , 1.61)	***1.25 (0.78 , 2.01)***	1.37[b] (1.01 , 1.85)	1.30 (0.83 , 2.03)
SO_2	0.93 (0.56 , 1.55)	0.87 (0.47 , 1.64)	0.93 (0.65 , 1.32)	0.91 (0.52 , 1.59)	***1.33[b] (1.04 , 1.70)***	1.35 (0.87 , 2.08)
O_3	1.28 (0.84 , 1.96)	1.13 (0.65 , 1.95)	1.21 (0.92 , 1.60)	1.35 (0.83 , 2.18)	1.38[b] (1.08 , 1.77)	***1.21 (0.79 , 1.87)***

[a] Results in each column are presented as ORs and 95% CIs associated with the IQR increase listed at the top of the column for each pollutant; each OR is adjusted for the copollutant given at the left of each row in the two-pollutant model. Diagonal values (bold italic type) present the single-pollutant associations (based on the same results shown in Tables 11 and 12).

[b] $P < 0.05$.

[c] $P < 0.01$.

[d] $P < 0.10$.

characteristics. We present only the analyses for 2-day mean concentrations of $PM_{2.5}$, BC, NO_2, CO, SO_2, and O_3 because these are the pollutants for which the monitoring data were most complete.

Geographic Area of Residence

We divided the patients into areas based on town of residence at implantation as defined by postal ZIP codes. Route 128, the inner beltway around Boston, is 10 to 25 km from the main HSPH air pollution monitoring site (Figure 1). We expected that the air monitoring measurements would be more representative of exposure for those patients living inside Route 128 than for those outside Route 128.

Table 15 presents the estimated effects of 2-day mean air pollutant concentrations on VA and SVA episode-days stratified by location of residence. For VA episode-days, we found stronger but not significant associations with $PM_{2.5}$ and BC, but weaker associations with CO and O_3, among the patients living inside Route 128 compared with those outside Route 128.

For SVAs, positive associations were found for subjects living outside Route 128 with BC, NO_2, and CO, but little association with each of these same pollutants was found for those living inside Route 128. We found positive associations with SO_2 for those living outside 128 that were significantly larger than for those living inside 128; and a strong positive association for O_3 with SVAs among those living inside 128 and a negative association for those living outside 128.

Clinical Cardiovascular Characteristics

We stratified the patients by their clinical characteristics before implantation (high vs low ejection fraction; a history of myocardial infarction vs none; and CAD vs other cardiac conditions).

Ejection fraction was a strong modifier of the effect of some pollutants on arrhythmias (Table 16). Among those with ventricular ejection fractions greater than 0.35, IQR increases in 2-day mean concentrations of CO approximately doubled the relative risk of VAs (OR = 1.84; 95% CI = 1.34, 2.53) and SVAs (OR = 1.85; 95% CI = 1.04, 3.30) compared with the risks for those with low ejection fractions; and SO_2 increased the relative risk of VAs (OR = 1.23; 95% CI = 0.99, 1.52) and of SVAs (OR = 1.53; 95% CI = 1.11, 2.09). Patients were also at twice the relative risk of SVAs with a comparable increase in BC concentrations (OR = 2.14; 95% CI = 1.13, 4.05 for SVAs vs OR = 1.12; 95% CI = 0.67, 1.86 for

Table 15. Estimated Arrhythmic Effects per IQR Increase in 2-Day Mean Pollutant Concentrations Categorized by Residence Inside or Outside the Inner Beltway (Route 128)[a]

Pollutant (IQR Increase in 2-Day Mean)	VAs			SVAs		
	Inside 128	Outside 128	*P* Value for Interaction	Inside 128	Outside 128	*P* Value for Interaction
$PM_{2.5}$ (7.0 μg/m^3)	1.11 (0.95 , 1.30)	1.01 (0.82 , 1.25)	0.44	1.02 (0.58 , 1.80)	1.37 (0.91 , 2.05)	0.31
BC (0.74 μg/m^3)	1.15 (0.89 , 1.49)	1.00 (0.72 , 1.37)	0.43	0.74 (0.31 , 1.77)	1.47 (0.81 , 2.69)	0.16
NO_2 (7.7 ppb)	1.06 (0.92 , 1.22)	1.06 (0.88 , 1.28)	0.99	1.06 (0.74 , 1.51)	1.30 (0.90 , 1.87)	0.41
CO (0.48 ppm)	1.04 (0.83 , 1.30)	1.30[b] (1.00 , 1.69)	0.10	1.03 (0.59 , 1.80)	1.59 (0.90 , 2.82)	0.18
SO_2 (4.0 ppb)	1.07 (0.94 , 1.23)	1.06 (0.90 , 1.26)	0.93	1.09 (0.78 , 1.52)	1.61[c] (1.21 , 2.14)	0.039
O_3 (15 ppb)	1.07 (0.87 , 1.32)	1.21 (0.95 , 1.54)	0.33	1.79[b] (1.12 , 2.85)	0.64 (0.35 , 1.16)	0.001

[a] Results are presented as ORs and 95% CIs.

[b] $P < 0.05$.

[c] $P < 0.01$.

Table 16. Estimated Arrhythmic Effects per IQR Increase in 2-Day Mean Pollutant Concentrations Categorized by Ejection Fraction Before ICD Implantation[a]

Pollutant (IQR Increase in 2-Day Mean)	VAs			SVAs		
	≤ 0.35	> 0.35	*P* Value for Interaction	≤ 0.35	> 0.35	*P* Value for Interaction
$PM_{2.5}$ (7.0 μg/m^3)	1.09 (0.94 , 1.25)	0.99 (0.72 , 1.38)	0.60	1.00 (0.59 , 1.72)	1.43 (0.94 , 2.19)	0.27
BC (0.74 μg/m^3)	1.09 (0.86 , 1.37)	1.12 (0.67 , 1.86)	0.42	0.61 (0.27 , 1.36)	2.14[b] (1.13 , 4.05)	0.008
NO_2 (7.7 ppb)	1.05 (0.92 , 1.20)	1.10 (0.86 , 1.42)	0.72	1.18 (0.84 , 1.66)	1.15 (0.78 , 1.69)	0.92
CO (0.48 ppm)	1.01 (0.81 , 1.25)	1.84[c] (1.34 , 2.53)	0.0002	0.94 (0.53 , 1.64)	1.85[b] (1.04 , 3.30)	0.039
SO_2 (4.0 ppb)	1.04 (0.91 , 1.18)	1.23[d] (0.99 , 1.52)	0.13	1.21 (0.89 , 1.63)	1.53[c] (1.11 , 2.09)	0.21
O_3 (15 ppb)	1.22[b] (1.01 , 1.47)	0.68[b] (0.48 , 0.97)	0.001	1.31 (0.81 , 2.13)	1.09 (0.64 , 1.87)	0.51

[a] Results are presented as ORs and 95% CIs.

[b] $P < 0.05$.

[c] $P < 0.01$.

[d] $P < 0.10$.

VAs). $PM_{2.5}$ was associated with an increase in relative risk of SVAs only (OR = 1.43; 95% CI = 0.94, 2.19).

Previous myocardial infarction was a strong modifier of the effect of CO, SO_2, NO_2, and BC on relative risk of arrhythmias (Table 17). Patients who had had a myocardial infarction were at greater risk of VAs with increases in concentrations of NO_2 (OR = 1.17) and SO_2 (OR = 1.15); however, relative risk of SVAs was not increased among these patients. Those who had not had a myocardial infarction before ICD implantation were at higher relative risk of SVAs (OR between 1.40 and 1.82) from all pollutants except O_3; O_3 had a weak association with SVAs, but it was unrelated to previous myocardial infarction.

Patients who had been diagnosed with cardiac conditions other than coronary artery disease were at higher risk of SVAs associated with specific air pollutants than patients with coronary artery disease. These patients were also at nearly twice the relative risk of having a VA with IQR increases in CO (Table 18). A cardiac diagnosis other than coronary artery disease at the time of device implantation was a strong effect modifier for exposure to CO and NO_2.

Prescribed Cardiac Medications

In this sample of 195 patients, 172 (88%) were prescribed one or more medications to control arrhythmias in conjunction with their ICDs. We stratified the air pollution analyses by usual prescription (reported at more than 50% of follow-up visits) for each of three broad categories: β-blockers, antiarrhythmics, and digoxin.

Of the 195, 127 (65%) of the patients were regularly prescribed β-blockers (see Table 6). For VAs we found no significant differences (interaction P values > 0.30) in response to air pollution between ICD patients prescribed β-blockers compared with those not prescribed β-blockers (Table 19). In contrast, for SVAs the association with all pollutants except BC was weaker for those prescribed β-blockers.

The effect modification by β-blockers was most striking for the effects of NO_2, CO, and SO_2 on SVAs (interaction P values are given in Table 19), but was also evident for IQR increases in $PM_{2.5}$ and O_3 (Table 19). Patients who reported taking β-blockers were at lower relative risk of SVAs associated with air pollution, except for an increase in BC concentration.

The effects of regular use of other antiarrhythmic medications and digoxin were inconsistent, although their use was associated with increased relative risk of SVAs with increasing concentrations of most individual pollutants (Tables 20 and 21). The strongest effect on relative risk of SVAs was observed among those taking antiarrhythmics in association with increasing SO_2 (OR = 1.63; 95% CI = 1.16, 2.29; Table 20), and among those

Table 17. Estimated Arrhythmic Effects per IQR Increase in 2-Day Mean Pollutant Concentrations Categorized by Myocardial Infarction Before ICD Implantation[a]

Pollutant (IQR Increase in 2-Day Mean)	VAs			SVAs		
	Yes	No	*P* Value for Interaction	Yes	No	*P* Value for Interaction
$PM_{2.5}$ (7.0 μg/m^3)	1.07 (0.92 , 1.25)	1.08 (0.87 , 1.35)	0.96	0.93 (0.50 , 1.74)	1.40 (0.94 , 2.08)	0.27
BC (0.74 μg/m^3)	1.11 (0.87 , 1.41)	1.04 (0.72 , 1.51)	0.76	0.48 (0.16 , 1.45)	1.52 (0.86 , 2.67)	0.067
NO_2 (7.7 ppb)	1.17[b] (1.02 , 1.34)	0.86 (0.71 , 1.05)	0.007	0.83 (0.53 , 1.29)	1.40[b] (1.02 , 1.92)	0.045
CO (0.48 ppm)	1.07 (0.86 , 1.33)	1.28[c] (0.97 , 1.69)	0.20	0.61 (0.31 , 1.21)	1.82[b] (1.10 , 3.02)	0.002
SO_2 (4.0 ppb)	1.15[b] (1.01 , 1.30)	0.90 (0.74 , 1.09)	0.015	0.84 (0.54 , 1.31)	1.62[d] (1.25 , 2.11)	0.005
O_3 (15 ppb)	1.07 (0.87 , 1.31)	1.22 (0.96 , 1.55)	0.30	1.20 (0.69 , 2.09)	1.22 (0.76 , 1.96)	0.97

[a] Results are presented as ORs and 95% CIs.

[b] $P < 0.05$.

[c] $P < 0.10$.

[d] $P < 0.01$.

Table 18. Estimated Arrhythmic Effects per IQR Increase in 2-Day Mean Pollutant Concentrations Categorized by Cardiac Diagnosis Before ICD Implantation[a]

Pollutant (IQR Increase in 2-Day Mean)	VAs			SVAs		
	CAD	Other	*P* Value for Interaction	CAD	Other	*P* Value for Interaction
$PM_{2.5}$ (7.0 μg/m^3)	1.06 (0.87 , 1.30)	1.14 (0.83 , 1.57)	0.68	1.06 (0.65 , 1.73)	1.43 (0.92 , 2.24)	0.32
BC (0.74 μg/m^3)	1.08 (0.86 , 1.35)	1.28 (0.69 , 2.39)	0.59	0.77 (0.35 , 1.69)	1.61 (0.85 , 3.02)	0.11
NO_2 (7.7 ppb)	1.07 (0.94 , 1.21)	1.01 (0.76 , 1.34)	0.72	0.86 (0.59 , 1.27)	1.52[b] (1.08 , 2.14)	0.021
CO (0.48 ppm)	1.02 (0.83 , 1.26)	1.92[c] (1.36 , 2.69)	0.0003	0.82 (0.45 , 1.51)	1.80[b] (1.05 , 3.09)	0.017
SO_2 (4.0 ppb)	1.06 (0.93 , 1.20)	1.13 (0.89 , 1.44)	0.59	1.18 (0.85 , 1.63)	1.49[c] (1.11 , 2.00)	0.22
O_3 (15 ppb)	1.14 (0.94 , 1.38)	0.98 (0.69 , 1.40)	0.39	1.03 (0.61 , 1.73)	1.40 (0.86 , 2.28)	0.24

[a] Results are presented as ORs and 95% CIs.

[b] $P < 0.05$.

[c] $P < 0.01$.

Table 19. Estimated Arrhythmic Effects per IQR Increase in 2-Day Mean Pollutant Concentrations Categorized by Prescribed β-Blockers[a]

Pollutant (IQR Increase in 2-Day Mean)	VAs			SVAs		
	Yes	No	*P* Value for Interaction	Yes	No	*P* Value for Interaction
$PM_{2.5}$ (7.0 μg/m^3)	1.13 (0.96 , 1.34)	1.01 (0.83 , 1.22)	0.33	1.09 (0.71 , 1.69)	1.52[b] (0.93 , 2.48)	0.28
BC (0.74 μg/m^3)	1.17 (0.90 , 1.54)	1.00 (0.74 , 1.35)	0.38	1.31 (0.75 , 2.30)	0.64 (0.20 , 2.08)	0.26
NO_2 (7.7 ppb)	1.04 (0.90 , 1.21)	1.08 (0.91 , 1.28)	0.74	0.78 (0.54 , 1.12)	1.91[c] (1.33 , 2.74)	0.0002
CO (0.48 ppm)	1.22[b] (0.97 , 1.54)	1.03 (0.80 , 1.32)	0.21	0.88 (0.49 , 1.55)	1.88[d] (1.08 , 3.26)	0.019
SO_2 (4.0 ppb)	1.09 (0.95 , 1.26)	1.04 (0.89 , 1.22)	0.61	1.07 (0.77 , 1.48)	1.64[c] (1.24 , 2.17)	0.023
O_3 (15 ppb)	1.17 (0.96 , 1.44)	1.03 (0.81 , 1.31)	0.24	1.10 (0.67 , 1.80)	1.39 (0.82 , 2.34)	0.38

[a] Regular use of medications as reported by patients at more than half of their follow-up visits. Results are presented as ORs and 95% CIs.

[b] $P < 0.10$.

[c] $P < 0.01$.

[d] $P < 0.05$.

Table 20. Estimated Arrhythmic Effects per IQR Increase in 2-Day Mean Pollutant Concentrations Categorized by Prescribed Antiarrhythmics[a]

Pollutant (IQR Increase in 2-Day Mean)	VAs			SVAs		
	Yes	No	*P* Value for Interaction	Yes	No	*P* Value for Interaction
$PM_{2.5}$ (7.0 μg/m^3)	1.11 (0.93 , 1.32)	1.04 (0.87 , 1.25)	0.61	1.48 (0.86 , 2.54)	1.14 (0.75 , 1.73)	0.41
BC (0.74 μg/m^3)	1.11 (0.85 , 1.47)	1.07 (0.80 , 1.43)	0.81	0.66 (0.21 , 2.08)	1.32 (0.75 , 2.31)	0.25
NO_2 (7.7 ppb)	1.05 (0.89 , 1.23)	1.07 (0.92 , 1.25)	0.81	1.27 (0.77 , 2.08)	1.14 (0.84 , 1.54)	0.70
CO (0.48 ppm)	1.05 (0.82 , 1.34)	1.21 (0.96 , 1.52)	0.28	1.55 (0.78 , 3.09)	1.16 (0.70 , 1.93)	0.42
SO_2 (4.0 ppb)	1.03 (0.88 , 1.20)	1.11 (0.96 , 1.28)	0.39	1.63[b] (1.16 , 2.29)	1.21 (0.91 , 1.61)	0.14
O_3 (15 ppb)	1.15 (0.92 , 1.43)	1.09 (0.88 , 1.36)	0.68	1.27 (0.68 , 2.37)	1.19 (0.75 , 1.89)	0.84

[a] Regular use of medications as reported by patients at more than half of their follow-up visits. Results are presented as ORs and 95% CIs.

[b] $P < 0.01$.

Table 21. Estimated Arrhythmic Effects per IQR Increase in 2-Day Mean Pollutant Concentrations Categorized by Prescribed Digoxin[a]

Pollutant (IQR Increase in 2-Day Mean)	VAs			SVAs		
	Yes	No	*P* Value for Interaction	Yes	No	*P* Value for Interaction
$PM_{2.5}$ (7.0 μg/m^3)	1.06 (0.90 , 1.24)	1.11 (0.90 , 1.37)	0.70	1.12 (0.66 , 1.92)	1.31 (0.86 , 2.01)	0.63
BC (0.74 μg/m^3)	1.10 (0.86 , 1.41)	1.07 (0.75 , 1.52)	0.90	0.80 (0.37 , 1.71)	1.66 (0.86 , 3.21)	0.12
NO_2 (7.7 ppb)	1.09 (0.95 , 1.26)	0.99 (0.81 , 1.20)	0.36	1.42[b] (0.99 , 2.03)	0.97 (0.68 , 1.39)	0.11
CO (0.48 ppm)	1.08 (0.86 , 1.35)	1.25 (0.95 , 1.65)	0.30	1.10 (0.61 , 1.96)	1.41 (0.81 , 2.45)	0.43
SO_2 (4.0 ppb)	1.08 (0.94 , 1.23)	1.06 (0.88 , 1.26)	0.85	1.25 (0.90 , 1.74)	1.40[c] (1.05 , 1.87)	0.56
O_3 (15 ppb)	1.15 (0.94 , 1.40)	1.05 (0.81 , 1.37)	0.51	1.30 (0.78 , 2.15)	1.14 (0.69 , 1.89)	0.64

[a] Regular use of medications as reported by patients at more than half of their follow-up visits. Results are presented as ORs and 95% CIs.

[b] $P < 0.10$.

[c] $P < 0.05$.

taking digoxin in association with increased NO_2 (OR = 1.42; 95% CI = 0.99, 2.03; Table 21).

Many of the patients we studied were prescribed multiple drugs. We assessed the independent modifying effects of these three classes of prescribed medications on the air pollution associations in a multivariate mixed model of the 2-day mean air pollutant concentrations including interactions with indicators of regular prescriptions for β-blockers, antiarrhythmics, and digoxin as well as a random patient effect (Table 22). The results are presented as the estimated effects of 2-day mean air pollutant concentrations among patients taking no prescribed medications (the reference group) and the estimated modifying effects of each class of prescribed medication separately.

For VAs, we saw little evidence that any of the drugs modified the associations with individual air pollutants.

For SVAs, among patients with no regularly prescribed medications, we found a strong association of NO_2 with SVAs (OR = 1.99; 95% CI = 1.19, 3.33). Among patients regularly prescribed β-blockers, the estimated association of NO_2 with SVAs was reduced (OR = 0.38; 95% CI = 0.23, 0.64). Thus for the association of NO_2 with SVAs among those taking β-blockers, the estimated OR was 1.99 times 0.38, which is 0.76—that is, no association. Similarly, for the effect of NO_2 among those taking antiarrhythmics, the estimated OR was 1.39 (1.99 times 0.70), and among those taking digoxin, the estimated OR was 2.39 (1.99 times 1.20).

Also for SVAs, we saw stronger positive associations with CO and SO_2 among ICD patients without regular prescriptions for drugs in any of the three classes. There was little evidence of effect modification by digoxin or antiarrhythmics; however, patients with a regular prescription for β-blockers had a substantially reduced response to NO_2, CO, and SO_2, and only small changes in response to $PM_{2.5}$ and O_3 (Table 22).

Frequent and Recent Episodes of Arrhythmia

In the pilot study (Peters et al 2000) we found six patients who had 10 or more episode-days with ICD discharge interventions; the patients with that many episode-days had a stronger association with air pollution than those with fewer episode-days. In the current study 26 patients had 10 or more episode-days for either type of arrhythmia (see Table 4). Table 23 shows the estimated effects of 2-day mean air pollutant concentrations on all arrhythmias combined, VAs, and SVAs for the 26 patients with 10 or more episode-days compared with the effects

Table 22. Estimated Arrhythmic Effects per IQR Increase in 2-Day Mean Pollutant Concentrations Obtained from Multivariate Regression Analyses and Categorized by Use of Each Class of Cardiac Medication[a]

Pollutant (IQR Increase in 2-Day Mean)	No Prescribed Medications	Beta Blocker	Antiarrhythmic	Digoxin
VAs				
$PM_{2.5}$ (7.0 μg/m^3)	1.04 (0.81 , 1.34)	1.10 (0.85 , 1.41)	1.06 (0.84 , 1.33)	0.93 (0.73 , 1.19)
BC (0.74 μg/m^3)	1.00 (0.67 , 1.52)	1.11 (0.80 , 1.54)	1.03 (0.74 , 1.44)	1.00 (0.70 , 1.44)
NO_2 (7.7 ppb)	1.03 (0.82 , 1.29)	0.96 (0.79 , 1.17)	0.95 (0.78 , 1.16)	1.12 (0.90 , 1.40)
CO (0.48 ppm)	1.22 (0.90 , 1.66)	1.16 (0.90 , 1.49)	0.87 (0.68 , 1.12)	0.87 (0.67 , 1.14)
SO_2 (4.0 ppb)	1.06 (0.87 , 1.30)	1.05 (0.88 , 1.25)	0.91 (0.77 , 1.09)	1.03 (0.86 , 1.25)
O_3 (15 ppb)	0.98 (0.73 , 1.31)	1.13 (0.90 , 1.42)	1.02 (0.87 , 1.28)	1.08 (0.84 , 1.39)
SVAs				
$PM_{2.5}$ (7.0 μg/m^3)	1.49 (0.75 , 2.95)	0.76 (0.38 , 1.51)	1.12 (0.54 , 2.30)	0.90 (0.51 , 1.62)
BC (0.74 μg/m^3)	1.23 (0.24 , 6.42)	1.38 (0.28 , 6.68)	0.69 (0.15 , 3.16)	0.62 (0.25 , 1.49)
NO_2 (7.7 ppb)	1.99[b] (1.19 , 3.33)	0.38[b] (0.23 , 0.64)	0.70 (0.39 , 1.24)	1.20 (0.75 , 1.93)
CO (0.48 ppm)	2.34[c] (1.16 , 4.71)	0.43[c] (0.22 , 0.84)	0.96 (0.47 , 1.95)	0.71 (0.39 , 1.30)
SO_2 (4.0 ppb)	1.77[b] (1.20 , 2.59)	0.65[c] (0.44 , 0.96)	1.15 (0.77 , 1.73)	0.77 (0.54 , 1.12)
O_3 (15 ppb)	1.35 (0.70 , 2.63)	0.78 (0.44 , 1.39)	0.95 (0.50 , 1.80)	1.09 (0.64 , 1.83)

[a] Effect modification was evaluated for each patient by adjusting simultaneously for the use of other cardiac medication in a mixed random effects model. Results are presented as ORs and 95% CIs.

[b] $P < 0.01$.

[c] $P < 0.05$.

for patients with fewer than 10 episode-days of any type. In this study, among the patients with 10 or more episode-days, we did not find consistently stronger associations with any of the pollutants, either for all arrhythmias combined or for VAs (Table 23). For the same group and SVAs, we found a suggestion of stronger associations with concentrations of BC, NO_2, CO, and O_3.

The likelihood of having 10 or more episodes clearly depends on the length of follow-up. Therefore we examined possible effect modification by a recent previous event. We found that having had an arrhythmia within the previous 3 days was a strong predictor of subsequent arrhythmia: for another VA within 3 days, the estimated OR was 7.2 (95% CI = 5.9, 8.9); for another SVA within 3 days, the estimated OR was 19.7 (95% CI = 11.8, 32.7).

We stratified the patients by whether or not they had had an arrhythmia within the previous 3 days (Table 24). Patients who had had a VA within 3 days were at substantially higher risk of VA associated with air pollution than those who had not. A VA within the previous 3 days was a strong modifier of the effects of all individual pollutants, except for O_3, on risk of subsequent VA. For SVAs, we found no consistent pattern of air pollutant associations with or without a previous SVA within the previous 3 days (Table 24).

Table 23. Estimated Arrhythmic Effects per IQR Increase in 2-Day Mean Pollutant Concentrations Categorized by Total Number of Episode-Days[a]

Pollutant (IQR Increase in 2-Day Mean)	All Arrhythmias			VAs			SVAs		
	< 10 Episode-Days	≥ 10 Episode-Days	*P* Value for Interaction	< 10 Episode-Days	≥ 10 Episode-Days	*P* Value for Interaction	< 10 Episode-Days	≥ 10 Episode-Days	*P* Value for Interaction
$PM_{2.5}$ (7.0 μg/m^3)	1.04 (0.84 , 1.29)	1.11 (0.97 , 1.29)	0.59	0.99 (0.77 , 1.27)	1.10 (0.95 , 1.28)	0.45	1.24 (0.80 , 1.92)	1.22 (0.74 , 2.03)	0.96
BC (0.74 μg/m^3)	0.87 (0.62 , 1.23)	1.21[b] (0.97 , 1.52)	0.080	0.91 (0.62 , 1.34)	1.16 (0.91 , 1.48)	0.25	0.79 (0.38 , 1.63)	1.76[b] (0.92 , 3.37)	0.06
NO_2 (7.7 ppb)	0.98 (0.81 , 1.19)	1.11 (0.98 , 1.26)	0.26	0.99 (0.79 , 1.24)	1.08 (0.95 , 1.24)	0.47	0.95 (0.64 , 1.39)	1.38[b] (0.987 , 1.95)	0.12
CO (0.48 ppm)	1.28[b] (0.98 , 1.67)	1.09 (0.90 , 1.34)	0.25	1.38[c] (1.02 , 1.85)	1.06 (0.85 , 1.31)	0.087	0.88 (0.48 , 1.62)	1.65 (0.97 , 2.82)	0.05
SO_2 (4.0 ppb)	1.17 (0.99 , 1.37)	1.09 (0.97 , 1.23)	0.47	1.08 (0.88 , 1.31)	1.07 (0.94 , 1.22)	0.95	1.42[c] (1.05 , 1.90)	1.25 (0.91 , 1.71)	0.49
O_3 (15 ppb)	0.98 (0.76 , 1.26)	1.18[b] (0.99 , 1.42)	0.13	1.06 (0.80 , 1.41)	1.14 (0.94 , 1.38)	0.61	0.71 (0.40 , 1.26)	1.68[c] (1.06 , 2.66)	0.002

[a] Results are presented as ORs and 95% CIs.

[b] $P < 0.10$.

[c] $P < 0.05$.

Table 24. Estimated Arrhythmic Effects per IQR Increase in 2-Day Mean Pollutant Concentrations Categorized by an Arrhythmia Within the Previous 3 Days or Not[a]

Pollutant (IQR Increase in 2-Day Mean)	VAs			SVAs		
	Within 3 Days	More Than 3 Days	*P* Value for Interaction	Within 3 Days	More Than 3 Days	*P* Value for Interaction
$PM_{2.5}$ (7.0 g/m^3)	1.60[b] (1.25 , 2.04)	0.98 (0.84 , 1.14)	0.0003	1.18 (0.45 , 3.08)	1.27 (0.87 , 1.85)	0.94
BC (0.74 g/m^3)	1.74[b] (1.17 , 2.60)	1.02 (0.80 , 1.30)	0.010	1.41 (0.51 , 3.92)	1.12 (0.62 , 2.02)	0.67
NO_2 (7.7 ppb)	1.35[c] (1.07 , 1.69)	1.01 (0.89 , 1.16)	0.025	1.21 (0.71 , 2.05)	1.13 (0.83 , 1.53)	0.82
CO (0.48 ppm)	1.64[b] (1.21 , 2.22)	1.03 (0.82 , 1.28)	0.012	1.01 (0.47 , 2.20)	1.36 (0.83 , 2.24)	0.54
SO_2 (4.0 ppb)	1.28[c] (1.05 , 1.55)	0.98 (0.86 , 1.12)	0.0015	1.14 (0.66 , 1.95)	1.35[c] (1.04 , 1.76)	0.45
O_3 (15 ppb)	1.05 (0.77 , 1.44)	1.16 (0.95 , 1.41)	0.54	1.52 (0.71 , 3.22)	1.13 (0.71 , 1.79)	0.63

[a] Results are presented as ORs and 95% CIs.

[b] $P < 0.01$.

[c] $P < 0.05$.

DISCUSSION

The primary objective of this study was to assess associations between ICD-detected and confirmed cardiac arrhythmias and air pollution episodes, specifically associations with particulate air pollution. We had conducted a pilot study of ICD discharge interventions among 100 ICD patients from BIDMC in eastern Massachusetts with up to 3 years of follow-up (Peters et al 2000). In that pilot study, we found that the risk of an ICD-detected episode requiring a therapeutic intervention was significantly elevated in association with the ambient daily mean NO_2 concentration on the previous day and with the previous 5-day mean NO_2 concentration.

In this study of 195 NEMC ICD patients living in the Boston metropolitan area with up to 7 years of follow-up, we found that the risk of any ICD-detected and confirmed arrhythmia (VA or SVA) was positively associated with increased exposure to air pollution on the day of or the day before the arrhythmia (Table 10), although the only significant associations were with SO_2 on the same day (P = 0.037) and O_3 on the previous day (P = 0.051).

These results are broadly consistent with those of the pilot study; in this study, ICD interventions were more strongly associated with air pollution on the previous days. However, these results do not support specific air pollutant associations. This larger study provides insights into these associations on the basis of more precisely defined cardiac arrhythmias, more detailed characterization of the air pollution mixture, and more specific characterizations of patients who may be susceptible to the effects of air pollution exposure.

CLASSIFICATION OF ARRHYTHMIAS

ICDs have been shown to be effective in preventing sudden deaths by identifying life-threatening VAs and initiating cardioverter shocks or pacing to restore normal rhythm (Moss et al 1996; AVID Investigators 1997). ICD screening of arrhythmias is optimized to avoid underdetection of ventricular tachyarrhythmias (Reiter and Mann 1996). Because the ICD detection of arrhythmias is based on assessing R–R intervals, fast normal rates (sinus tachycardia) or fast ventricular rates that result from stimulation above the ventricle (supraventricular tachycardias) can be mistakenly identified as arrhythmias. In addition, mechanical or electrical interference (oversensing) can be identified as potentially life-threatening arrhythmias.

To specifically identify potentially life-threatening VAs in this study, we limited eligibility to patients with third-generation ICDs that record electrograms and R–R intervals before and during each detected arrhythmia. A cardiac electrophysiologist who was blinded to air pollution levels reviewed these records and classified the arrhythmias. Of almost 2000 arrhythmias identified and recorded by the ICDs, 8% were classified as oversensing, 4% were sinus tachycardias, 18% were confirmed SVAs, and 70% were confirmed VAs. Thus 30% of the ICD-detected arrhythmias were not the life-threatening VAs defined as the primary outcome for this study.

In the pilot study (Peters et al 2000), abstraction of clinical records did not include reviewing or classifying detected arrhythmias. Therefore all ICD-detected episodes, including oversensing and nonVAs, were classified as potentially life-threatening arrhythmias. If misclassification of ICD discharges is nondifferential (that is, independent of air pollution exposure), then we would expect a loss of power (wider CIs), but not any bias in the estimated associations. Thus we expected that analysis of VAs and confirmation by a cardiac electrophysiologist would improve the power to detect associations between air pollution and VAs.

As a secondary objective, we assessed air pollution associations with the detected SVAs. These SVAs were only a portion of the total SVAs these patients may have experienced; SVAs are detected only if they stimulate a ventricular rate fast enough to be classified as ventricular tachycardia or fibrillation. SVAs are of interest themselves as risk factors for stroke (Flegel et al 1987) and mortality (Kannel et al 1983; Krahn et al 1995). Moreover, understanding the specific associations of air pollution with VAs versus SVAs may provide insights into the mechanisms of air pollution's effects on cardiac arrhythmias.

ASSOCIATIONS WITH VAs VERSUS SVAs

In analyses that included all 195 patients, we found little evidence for associations between VAs and concentrations of most air pollutants on the same day or any of 3 previous (lagged) days; however, we did find a 16% increase in risk associated with O_3 concentration on the day before the episode and 13% and 12% increases associated with SO_2 concentrations 2 and 3 days before the event, respectively (Table 11).

For SVAs, we found positive associations with SO_2 concentrations on the day of, the day before, and 2 days before the event. NO_2 and O_3 concentrations on the day of the event, and $PM_{2.5}$, BC, and CO concentrations on the previous day were also positively associated with SVAs, but the results were less precise. These results suggest that in the pilot study (Peters et al 2000) the positive associations of air pollution with any ICD discharge intervention may have resulted from specific associations with SVAs.

In the current study, the air pollution associations with SVAs were unexpected given the small number of SVA episode-days compared with those for VAs. Although these SVAs represent only a subset of arrhythmias originating above the ventricle, they all are characterized by rapid ventricular heart rates that could lead to more serious arrhythmias. This study was not designed to evaluate associations with SVAs specifically; thus, these results are exploratory and require replication.

AIR POLLUTION CONSTITUENTS

One of the primary objectives of this study was to identify the specific components or characteristics of the air pollution mixture responsible for any observed association with cardiac arrhythmias. Over the 7 years (2558 days) of follow-up, we had measurements of the gaseous criteria air pollutants (NO_2, CO, SO_2, and O_3) on all but a few days (Table 8). We had more limited data on the particle concentrations, including $PM_{2.5}$ measurements on 2047 days (80%), BC on 1555 days (61%), SO_4^{2-} on 971 days (38%), and particle number on 806 days (32%). In assessing the relative importance of individual pollutants, one must keep in mind that the power to detect statistically significant associations increases with the number of days of observation. Thus we had the greatest power to detect statistically significant associations for the gases (NO_2, CO, SO_2, and O_3), less power for $PM_{2.5}$ and BC, and the least power for SO_4^{2-} and number of particles. This lack of power does not mean that the estimated associations for the air pollutants with fewer observations are biased, but only that these associations are measured with less precision and thus result in wider CIs. Thus, in interpreting these results, we have focused on the magnitude of the association for comparable increments (IQR) in air pollutant concentrations in addition to statistical significance.

An important question in these analyses is the appropriate exposure averaging time and the lag time between exposure and cardiac arrhythmia. In the pilot study (Peters et al 2000) we found associations with air pollutant concentrations 2 days before ICD interventions and with the 5-day mean air pollutant concentrations. In this study VAs and SVAs were positively associated with increased concentrations of most air pollutants on the same and the previous calendar days. Temporality would require that air pollution exposure precede the arrhythmia. This is clearly true for associations of arrhythmias with air pollution on the previous day, but 24-hour mean air pollutant concentrations on the same calendar day would include concentrations for hours after as well as before the detected arrhythmia. On the basis of these a priori expectations and our observations of positive associations with air pollution on the same and previous days, we focused our analyses on associations with mean ambient air pollution on the day of and the day before the arrhythmias (Table 12). For VAs, we found positive associations for all pollutants considered (from 2% to 12% increase in risk). For SVAs, we found a 20% to 25% increase in risk for SO_2 lagged 0 to 2 days and positive but less precise associations for $PM_{2.5}$, NO_2, CO, and O_3 lagged 0 and 1 days and for BC lagged 1 day.

These associations with CO, NO_2, and BC suggest that air pollutants from gasoline and diesel motor vehicles have a possible role. Other than the correlation between $PM_{2.5}$ and SO_4^{2-}, these three pollutants had the highest between-pollutant day-to-day correlations (Table 8). Thus it would be difficult to differentiate the independent effects of any one of these pollutants. In two-pollutant models of the risk of VAs (Table 14), we found evidence of confounding by NO_2, CO, and SO_2 as copollutants, although the associations were all weak. For SVAs, we found strong suggestions that each of the air pollutant associations was confounded by SO_2.

During the follow-up period, SO_2 concentrations in Boston were low (mean of 5.8 ppb). We were therefore surprised to find strong positive associations of 2-day mean SO_2 concentrations (Table 12) with all arrhythmias combined ($P = 0.055$) and with SVAs in particular ($P = 0.022$). Although SO_2 is generally considered a marker of fossil fuel combustion by stationary sources, in these data SO_2 was most strongly correlated with pollutants associated with mobile sources: that is, with NO_2, CO, BC, and number of particles (Table 9).

Animal studies in Boston have found specific associations between changes in cardiac function indicators and motor vehicle pollution (Clarke et al 2000). In epidemiologic studies, analysis of daily mortality in Boston and five other cities suggested that motor vehicle pollution was more strongly related to cardiovascular mortality than to respiratory mortality (Laden et al 2000). Cardiovascular emergency department visits in Atlanta were strongly associated with markers of motor vehicle air pollution: that is, with NO_2, CO, $PM_{2.5}$, elemental carbon, and fine-particle organic carbon (Metzger et al 2004). Only 26% of these Atlanta emergency department visits were for dysrhythmias, however, and the smaller number of events precluded obtaining precise estimates of effects. Nevertheless, positive associations were found for these motor vehicle pollutants.

Further analyses of the components of particles and the general air pollution mixture may provide additional insights into the effects of sources of particles, and specifically the role of particles from mobile sources.

SUSCEPTIBLE PATIENTS

A major advantage of ICD data is that they are obtained by passively monitoring cardiac arrhythmias. This group of patients is of special interest because their history of previous cardiovascular disease might make them particularly sensitive to the effects of air pollution episodes. Indeed, the observed associations between potentially fatal cardiac arrhythmias (VAs) and particulate air pollution for these subjects were large but unstable (ie, the CIs were wide) because of the relatively small number of events.

When compared with the general population, the susceptibility of this group is evident. In a time-series analysis of mortality in Boston and five other cities (Schwartz et al 1996), each increase of 10 $\mu g/m^3$ in the 2-day mean $PM_{2.5}$ concentration was associated with a 2% increase in the risk of cardiovascular mortality. When the observed associations for Boston ICD patients (Table 12) were calculated for the same 10-$\mu g/m^3$ increase in the 2-day mean $PM_{2.5}$ concentration, the increased relative risk of potentially fatal VAs was 11% (95% CI = −9, 35). Thus the relative risk of life-threatening cardiac events associated with exposure to fine particles for the ICD patients in Boston was more than five times greater than the relative risk of cardiovascular death from particle exposure for the general population. Because this group of patients clearly represents a highly selected cohort, these results may not be generalizable to the entire population.

To attempt to identify specific susceptible subgroups within this group of ICD patients and to understand the factors that might increase their responsiveness, we undertook a series of exploratory analyses to assess how patient characteristics might modify the air pollution associations. Because the main effects of air pollution we observed were weak, we had low statistical power to detect such effect modifications. However, identification of susceptible patients and the characteristics that may make them more susceptible would suggest hypotheses for future studies; such investigations could provide insight into possible pathways that would link air pollution exposure with cardiac arrhythmias.

EXPOSURE MISCLASSIFICATION

Misclassification of air pollution exposure is a potential source of bias in this study. When epidemiologic studies assume that associations are linear, random misclassification of exposure produces an attenuated estimate of associations (and wider CIs).

The day-to-day correlations of fine particle concentrations between sites are high across large regions in the eastern United States. Suh and colleagues (1997) reported correlations higher than 0.90 between fine particle monitoring stations across metropolitan Washington, DC, and a correlation of 0.76 between monitors in Philadelphia and Washington. For the patients in our study who live in eastern Massachusetts, our estimates of air pollution exposure were based on data from a single monitor or a small number of monitors in the Boston metropolitan area.

We considered proximity to the primary air pollution monitoring site as an indicator of the adequacy of the exposure estimates. Assuming that the air pollutant exposure estimates for those living closer to the monitors had less misclassification, we would expect stronger associations for patients living inside Route 128 than for patients living outside Route 128. For VAs, however, we found a suggestion of stronger associations only with $PM_{2.5}$ and BC for patients living inside 128 (see Table 15). For SVAs air pollutant associations were not consistently stronger, and were often weaker, for patients living inside 128. Thus we did not find consistently stronger associations among patients living closer to the exposure monitors. It still may be true that the observed weak associations are due to random exposure misclassification, and that studies with improved estimation of subject-specific air pollution exposures might find stronger associations.

CARDIOVASCULAR CONDITIONS AND PRESCRIBED MEDICATIONS

We examined indicators of cardiac function and cardiovascular disease before ICD implantation as possible modifiers of air pollutant associations with arrhythmias. For VAs we did not find consistent indications that the air pollutant associations were modified by a prior myocardial infarction, a diagnosis of coronary artery disease, or a left ventricular ejection fraction less than 0.35.

For SVAs there was a suggestion that associations were stronger for patients without a prior myocardial infarction, with better ejection fraction (> 0.35), or without a diagnosis of coronary artery disease. Given the relatively small number of SVAs, it was surprising that many of these interactions between the air pollution associations and patient characteristics showed statistically significant effect modification.

We also examined the possibility that prescribed medications might modify the air pollutant associations. In a multivariate analysis we simultaneously controlled for regular prescriptions of β-blockers, antiarrhythmics, and digoxin, and assessed modification of the air pollutant associations by these three drug classes. We found positive associations between air pollutants and SVAs among the small group of patients who were not regularly prescribed any of these drugs (Table 22). Prescribed β-blockers significantly blunted the associations of SVAs with NO_2, CO,

and SO_2. No such effect modification by β-blockers was found for VAs.

β-Blockers are prescribed for a wide range of cardiovascular conditions. Any observed modification of an air pollutant association by β-blockers may reflect characteristics of the patients who are prescribed β-blockers rather than the effect of β-blockers themselves. In this study, we had limited information on the clinical condition of the ICD patients. Although the observation that β-blockers blunted the risk of SVAs associated with air pollution in these patients is interesting, it should be replicated in studies that specifically consider the clinical characteristics of the patients in more detail than was possible in this analysis.

RECENT ARRHYTHMIAS

In the pilot study (Peters et al 2000) the strongest associations between air pollutant exposure and arrhythmic events were found among the small number of patients with 10 or more ICD discharges. In general, the number of events observed depends on the length of follow-up for each patient. We therefore examined the period between arrhythmic episode-days rather than the number of arrhythmic episode-days as an indicator of possible susceptibility. We found that having an arrhythmic event was highly predictive of a subsequent event. For these daily episodes, the OR was 7 for a VA within 3 days of a previous episode-day, and 20 for an SVA. We found a significantly increased risk of VAs associated with air pollution only in the case of a VA within the previous 3 days. We found no modification by previous events of the air pollution associations with SVAs.

It may be that air pollution only produces a potentially life-threatening arrhythmia in the presence of acutely predisposing conditions that increase ventricular electrical instability. In a recent analysis of the effects of long-term particle concentrations on cardiovascular mortality, Pope and colleagues (2004) found that $PM_{2.5}$ concentrations were significantly associated with deaths from ischemic heart disease and sudden deaths from dysrhythmias, heart failure, or cardiac arrest. For sudden cardiac deaths, the association with $PM_{2.5}$ was stronger for current smokers than for former smokers, and stronger for former smokers than for never smokers. This suggests that the risk of sudden cardiac death associated with particulate air pollution is enhanced in smokers, who presumably suffer from smoking-related changes in the cardiac substrate. Further studies are necessary to replicate this finding, and to determine if air pollution associations are modified by chronic and irreversible changes, or by acute and potentially reversible changes in cardiac substrate, or by both.

LESSONS

In principle, monitoring and recording cardiac arrhythmias by an ICD appears to be a simple and direct way to passively monitor a vulnerable population for potentially fatal arrhythmic events over an extended period of follow-up. In practice, abstracting and interpreting the ICD records and associated supporting data were hindered by unexpected problems.

- Even though ICD patients are a highly vulnerable population, cardiac arrhythmias were rare events. The ICDs of more than half of these patients did not record any arrhythmias, even though the patients were followed for an average of more than 3 years. Patients with no detected arrhythmia contributed no information to the analysis. Even among those with arrhythmias, the rate of events was only 2.4 per year. Thus to accumulate a large enough number of arrhythmias to provide adequate statistical power for an air pollution study requires a substantial number of patients followed over many years. Nevertheless, because of the life-saving therapeutic interventions of ICDs, this group of patients can contribute data about multiple potentially fatal cardiac events.
- Arrhythmic events were readily identified from the ICD records retrieved in clinical follow-up. Identifying periods when patients were free of arrhythmias was more difficult. It was possible that patients attended clinics other than the NEMC and therefore were not contributing person-time to the study. Thus it was necessary to compare in detail the computerized ICD records of interrogation and memory clearing with the clinic records of follow-up visits to define and verify periods when each subject was and was not contributing person-time.
- We would have preferred to identify and exclude any time periods when the patient was not within the defined study area (ie, within 40 km of the HSPH main monitoring site). Although information on trips or vacations might have been noted if the patient had had an ICD discharge, such data were never recorded otherwise. Thus it was not possible to differentiate the times the patient was in or out of the study area.
- We also would have been interested in information on activities, exercise, emotional states such as anger, and location (indoors or outdoors) immediately before a detected arrhythmia. Such information was sometimes reported when the clinic staff questioned a patient. However, the patient sometimes was unaware of the detected arrhythmias. Moreover, such data were never recorded for the nonevent periods. Thus we were not able to consider these factors as confounders or effect modifiers.

- The core arrhythmic data were automatically recorded by the ICD and retrieved from computer disks; however, some data were abstracted retrospectively from handwritten records, which is difficult to do and subject to uncertainties and inconsistencies. A structured data recording form completed prospectively would be preferable to ensure that all data of interest are collected consistently.
- ICDs are designed to be sensitive in detecting arrhythmias, but they are not specific. Upon review by a cardiac electrophysiologist, 8% of the ICD-detected arrhythmic episodes were classified as oversensing and another 4% as normal sinus tachycardias. Had we used all the ICD-detected arrhythmic episodes without an electrophysiologist's review, our analyses would have included many false-positive readings. Thus, review and classification of all ICD-detected events by a cardiac electrophysiologist is a necessary quality control step for these data.
- The recordings of the electrograms before detected arrhythmias appeared to provide the opportunity to assess subtle changes in the morphology of the electrocardiograms that have been observed in controlled exposure studies. However, we found that the recorded electrograms had been filtered to clearly define R–R intervals between beats, so that other details of the electrogram's morphology were not measurable.
- This study was designed as an anonymous retrospective review of records. Patient data were abstracted at the NEMC and all identifying information was removed before released for analysis. Some patient characteristics such as age and gender, or ICD characteristics such as manufacturer, type, and model were readily available. Patient characteristics such as residential street address were not available to protect confidentiality. To acquire other patient characteristics such as preimplantation medical conditions, coexisting illnesses or conditions, and prescribed medications required that a cardiologist review each patient's file. Data on some patient characteristics of interest such as smoking history were not recorded consistently. Prospective follow-up using a structured enrollment questionnaire would provide more complete data on patient characteristics and underlying medical conditions.
- It would be interesting to assess mortality (especially cardiovascular deaths) in these patients. Although deaths were recorded in the clinical records, vital status was not actively monitored and records were known to be incomplete. We found no cases in which the ICD device had been interrogated after death, and therefore we had no records of arrhythmias for the period between the last clinical visit and death. Thus, identifying deaths would help to track patients but would not contribute data about arrhythmias immediately before death.

Our experience with these data suggests some modifications for future study designs. To efficiently collect data on a patient's activities and characteristics immediately before ICD-detected arrhythmias, a prospective monitoring system is preferable to retrospective abstraction. Participants would be enrolled in the study with appropriate informed consent and permission to review their medical records. A structured questionnaire would obtain the required information for each episode by interview and medical record review.

Because arrhythmias are rare even in this highly susceptible population, it may be more efficient to design the study based on event (arrhythmia) ascertainment rather than following a cohort of ICD patients. Rather than enrolling all ICD patients meeting eligibility requirements into a follow-up study, it could be more efficient to enroll ICD patients only when they have had a cardiac arrhythmia detected by the ICD. The data would then be analyzed using case-crossover methods (Muller et al 1996) rather than logistic or time-series analyses.

SUMMARY

The primary objective of this study was to estimate the association of particulate air pollution episodes with increased risk of potentially life-threatening arrhythmias in patients with ICDs. We evaluated separately all confirmed ICD-detected arrhythmias according to diagnosis: VAs, which are acutely life-threatening, and SVAs, which are clinically significant but not necessarily life-threatening.

We found that VA episode-days among patients with ICDs were positively associated with air pollutant concentrations (but not fine particles specifically) on the same and previous days, but these associations did not reach statistical significance. For patients who had had a recent arrhythmia, however, VAs were significantly and strongly associated with air pollution. These observations suggest that air pollution may act in combination with an electrically unstable ventricular substrate to increase the risk of cardiac arrhythmias.

For SVAs, we found a statistically significant increase in relative risk associated with SO_2 concentrations on the same and previous day. Risk of SVAs was positively but not significantly associated with CO, NO_2, BC, and SO_2. The associations with CO, NO_2, and BC suggest that mobile-source air pollution is specifically associated with these cardiac arrhythmias.

The strong associations with SVAs were unexpected given that these ICDs were designed and programmed to avoid detecting and treating these arrhythmias. Fast atrial impulses can lead to fast ventricular heart rates and increased risk of ventricular tachycardias. In fact these SVAs were detected because they induced ventricular heart rates above the device's settings for clinically significant events. Thus investigations to specifically assess the links between air pollution exposure and atrial tachycardia, atrial fibrillation, and other SVAs are warranted. Atrial tachycardias are much more common than ventricular tachycardias, and people with atrial tachycardias may constitute a large group within the population at risk of acute adverse effects of air pollution. The suggestion that β-blockers blunt the effect of air pollution exposure on SVAs should be verified and investigated further.

ICDs that monitor heart rhythm and can initiate therapeutic interventions are rapidly evolving. The current generation of dual-chamber ICDs monitor and respond to VAs and SVAs separately. Moreover, the number of patients in which these devices are being implanted is increasing, and the indications for implanting these devices are expanding. In this study, ICDs have provided important insights into nonfatal cardiovascular effects of air pollution, and the potential is great for further innovative studies of these devices.

ACKNOWLEDGMENTS

The Health Effects Institute (grant 98-14) and the National Institute of Environmental Health Sciences (grant ES-09825) funded this study. The pilot study (Peters et al 2000) had been funded in part by the Harvard Center for Environmental Health supported by the National Institute of Environmental Health Sciences (grant ES-00002). Particulate air pollution measurements at the HSPH main monitoring site in Boston were funded in part by the US Environmental Protection Agency (grant R827353) at the Harvard Center on Ambient Particle Health Effects and measurements in South Boston were supported by contracts from the Boston Edison and Gillette companies.

The authors particularly appreciate the work of the fellows and researchers who abstracted the ICD data, including Jeff Baliff, Emerson Liu, Lynn McClelland, Chris Freed, Chris Hu, and Robert Hulefeld. David Bush provided important guidance during the quality assurance review. George Allen was an important resource for the air pollution data. We appreciate the guidance and encouragement of Frank E Speizer and NA Mark Estes III and the contributions from Aaron Cohen and Cristina I Cann at HEI. Finally, we thank Annette Peters, whose analyses of the pilot study data were instrumental in the design and initiation of this study.

REFERENCES

Allen G, Sioutas C, Koutrakis P, Reiss R, Lurmann FW, Roberts PT. 1997. Evaluation of the TEOM method for measurement of ambient particulate mass in urban areas. J Air Waste Manage Assoc 47:682–689.

Antimisiaris M, Sarma JS, Schoenbaum MP, Sharma PP, Venkataraman K, Singh BN. 1994. Effects of amiodarone on the circadian rhythm and power spectral changes of heart rate and QT interval: Significance for the control of sudden cardiac death. Am Heart J 128:884–891.

AVID Investigators. 1997. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. N Engl J Med 337:1576–1583.

Ballester F, Tenias JM, Pérez-Hoyas S. 2001. Air pollution and emergency hospital admissions for cardiovascular diseases in Valencia, Spain. J Epidemiol Community Health 55:57–65.

Bayes de Luna A, Coumel P, Leclercq JF. 1989. Ambulatory sudden cardiac death: Mechanisms of production of fatal arrhythmia on the basis of data from 157 cases. Am Heart J 117:151–159.

Bettoni M, Zimmermann M. 2002. Autonomic tone variations before the onset of paroxysmal atrial fibrillation. Circulation 105:2753–2759.

Burnett RT, Cakmak S, Brook JR, Krewski D. 1997. The role of particulate size and chemistry in the association between summertime ambient air pollution and hospitalization for cardiorespiratory diseases. Environ Health Perspect 105:614–620.

Burnett RT, Dales R, Krewski D, Vincent R, Dann T, Brook JR. 1995. Associations between ambient particulate sulfate and admissions to Ontario hospitals for cardiac and respiratory diseases. Am J Epidemiol 142:15–22.

Burnett RT, Smith-Doiron M, Stieb D, Cakmak S, Brook JR. 1999. Effects of particulate and gaseous air pollution on cardiorespiratory hospitalizations. Arch Environ Health 54:130–139.

Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. 1999. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. N Engl J Med 341:1882–1890.

Cairns JA, Connolly SJ, Gent M, Roberts R. 1991. Post-myocardial infarction mortality in patients with ventricular premature depolarizations. Canadian Amiodarone Myocardial Infarction Arrhythmia Trial Pilot Study. Circulation 84:550–557.

Cannom DS. 1992. A critical appraisal of indications for the implantable cardioverter defibrillator (ICD). Clin Cardiol 15:369–372.

Chaudhry GM, Haffajee CI. 2000. Antiarrhythmic agents and proarrhythmia. Crit Care Med 28(Suppl 10):N158–N164.

Checkoway H, Levy D, Sheppard L, Kaufman J, Koenig J, Siscovick D. 2000. A Case-Crossover Analysis of Fine Particulate Matter Air Pollution and Out-of-Hospital Sudden Cardiac Arrest. Research Report 99. Health Effects Institute, Cambridge MA.

Clarke RW, Catalano PJ, Koutrakis P, Murthy GG, Sioutas C, Paulauskis J, Coull B, Ferguson S, Godleski JJ. 1999. Urban air particulate inhalation alters pulmonary function and induces pulmonary inflammation in a rodent model of chronic bronchitis. Inhalation Toxicol 11:637–656.

Clarke RW, Coull B, Reinisch U, Catalano P, Killingsworth CR, Koutrakis P, Kavouras I, Murthy GG, Lawrence J, Lovett E, Wolfson JM, Verrier RL, Godleski JJ. 2000. Inhaled concentrated ambient particles are associated with hematologic and bronchoalveolar lavage changes in canines. Environ Health Perspect 108:1179–1187.

Creason J, Neas L, Walsh D, Williams R, Sheldon L, Liao D, Shy C. 2001. Particulate matter and heart rate variability among elderly retirees: The Baltimore 1998 PM study. J Expos Anal Environ Epidemiol 11:116–122.

Dekker JM, Schouten EG, Klootwijk P, Pool J, Swenne CA, Kromhout D. 1997. Heart rate variability from short electrocardiographic recordings predicts mortality from all causes in middle-aged and elderly men. The Zutphen Study. Am J Epidemiol 145:899–908.

Dockery DW. 2001. Epidemiologic evidence of cardiovascular effects of particulate air pollution. Environ Health Perspect 109(Suppl 4):483–486.

Dockery DW, Pope CA III. 1994. Acute respiratory effects of particulate air pollution. Annu Rev Public Health 15:107–132.

Dockery DW, Pope CA III, Kanner RE, Villegas GM, Schwartz J. 1999. Daily Changes in Oxygen Saturation and Pulse Rate Associated with Particulate Air Pollution and Barometric Pressure. Research Report 83. Health Effects Institute, Cambridge MA.

Dominici F, McDermott A, Zeger SL, Samet JM. 2003. National maps of the effects of particulate matter on mortality: Exploring geographical variation. Environ Health Perspect 111:39–44.

Doyle JT, Kannel WB, McNamara PM, Quickenton P, Gordon T. 1976. Factors related to suddenness of death from coronary disease: Combined Albany-Framingham studies. Am J Cardiol 37:1073–1078.

Eilstein D, Quenel P, Hedelin G, Kleinpeter J, Arveiler D, Schaffer P. 2001. Air pollution and myocardial infarction. Strasbourg France, 1984–89 [in French]. Rev Epidemiol Santé Publique 49:13–25.

Environmental Protection Agency (US). 1997. Revised Requirements for Designation of Reference and Equivalent Methods for $PM_{2.5}$ and Ambient Air Quality Surveillance for Particulate Matter; Final Rule. 40 CFR, Parts 52, 58. Fed Regist 62:38763–38854.

Fairley D. 1990. The relationship of daily mortality to suspended particulates in Santa Clara County, 1980–1986. Environ Health Perspect 89:159–168.

Farrell TG, Bashir Y, Cripps T, Malik M, Poloniecki J, Bennett ED, Ward DE, Camm AJ. 1991. Risk stratification for arrhythmic events in postinfarction patients based on heart rate variability, ambulatory electrocardiographic variables and the signal-averaged electrocardiogram. J Am Coll Cardiol 18:687–697.

Flegel KM, Shipley MJ, Rose G. 1987. Risk of stroke in nonrheumatic atrial fibrillation. Lancet 1:526–529.

Gardner SY, Lehmann JR, Costa DL. 2000. Oil fly ash-induced elevation of plasma fibrinogen levels in rats. Toxicol Sci 56:175–180.

Ghio AJ, Kim C, Devlin RB. 2000. Concentrated ambient air particles induce mild pulmonary inflammation in healthy human volunteers. Am J Respir Crit Care Med 162:981–988.

Gillis AM. 1996. The current status of the implantable cardioverter defibrillator. Annu Rev Med 47:85–93.

Gillum RF. 1989. Sudden coronary death in the United States: 1980–1985. Circulation 79:756–765.

Godleski JJ, Sioutas C, et al. 1996. Death from inhalation of concentrated ambient particles in animal models of pulmonary disease. In: Proceedings of the Second Colloquium on Particulate Air Pollution & Human Health (Lee J, Phalen R, eds), pp 136–143. University of Utah/University of California, Salt Lake City UT/Irvine CA.

Godleski JJ, Sioutas C, Verrier RL, Killingsworth CR, Love HE, Murphy GG, Hatch V, Wolfson JM, Ferguson T, Koutrakis P. 1997. Inhalation exposure of canines to concentrated ambient air particles (abstract). Am J Respir Crit Care Med 155:A246.

Godleski JJ, Verrier RL, Koutrakis P, Catalano P. 2000. Mechanisms of Morbidity and Mortality from Exposure to Ambient Air Particles. Research Report 91. Health Effects Institute, Cambridge MA.

Gold DR, Litonjua A, Schwartz J, Lovett E, Larson A, Nearing B, Allen G, Verrier M, Cherry R, Verrier R. 2000. Ambient pollution and heart rate variability. Circulation 101:1267–1273.

Gregoratos G, Abrams J, Epstein AE, Freedman RA, Hayes DL, Hlatky MA, Kerber RE, Naccarelli GV, Schoenfeld MH, Silka MJ, Winters SL, Gibbons RJ, Antman EM, Alpert JS, Gregoratos G, Hiratzka LF, Faxon DP, Jacobs AK, Fuster V, Smith SC Jr. 2002. ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices: Summary article. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/NASPE Committee to Update the 1998 Pacemaker Guidelines). Circulation 106:2145–2161.

Gregoratos G, Cheitlin MD, Conill A, Epstein AE, Fellows C, Ferguson TB Jr, Freedman RA, Hlatky MA, Naccarelli GV, Saksena S, Schlant RC, Silka MJ. 1998. ACC/AHA guidelines for implantation of cardiac pacemakers and antiarrhythmia devices: Executive summary. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Pacemaker Implantation). Circulation 97:1325–1335.

Hilleman DE, Bauman AL. 2001. Role of antiarrhythmic therapy in patients at risk for sudden cardiac death: An evidence-based review. Pharmacotherapy 21:556–575.

Ibald-Mulli A, Stieber J, Wichmann HE, Koenig W, Peters A. 2001. Effects of air pollution on blood pressure: A population-based approach. Am J Public Health 91:571–577.

Kannel WB, Abbott RD, Savage DD, McNamara PM. 1983. Coronary heart disease and atrial fibrillation: The Framingham Study. Am Heart J 106:389–396.

Kannel WB, Cupples LA, D'Agostino RB. 1987. Sudden death risk in overt coronary heart disease: The Framingham Study. Am Heart J 113:799–804.

Katsouyanni K, Zmirou D, Spix C, Sunyer J, Schouten JP, Ponka A, Anderson HR, Le Moullec Y, Wojtyniak B, Vigotti MA, Bacharova L, Schwartz J. 1997. Short-term effects of air pollution on health: A European approach using epidemiologic time series data. The APHEA Project. Air Pollution Health Effects: A European Approach. Public Health Rev 25:7–28.

Kop WJ, Verdino RJ, Gottdiener JS, O'Leary ST, Bairey Merz CN, Krantz DS. 2001. Changes in heart rate and heart rate variability before ambulatory ischemic events(1). J Am Coll Cardiol 38:742–749.

Krahn AD, Manfreda J, Tate RB, Mathewson FA, Cuddy TE. 1995. The natural history of atrial fibrillation: Incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. Am J Med 98:476–484.

La Rovere MT, Pinna GD, Maestri R, Mortara A, Capomolla S, Febo O, Ferrari R, Franchini M, Gnemmi M, Opasich C, Riccardi PG, Traversi E, Cobelli F. 2003. Short-term heart rate variability strongly predicts sudden cardiac death in chronic heart failure patients. Circulation 107:565–570.

Laden F, Neas LM, Dockery DW, Schwartz J. 2000. Association of fine particulate matter from different sources with daily mortality in six US cities. Environ Health Perspect 108:941–947.

Levy D, Lumley T, Sheppard L, Kaufman J, Checkoway H. 2001a. Referent selection in case-crossover analyses of acute health effects of air pollution. Epidemiology 12:186–192.

Levy D, Sheppard L, Checkoway H, Kaufman J, Lumley T, Koenig J, Siscovick D. 2001b. A case-crossover analysis of particulate matter air pollution and out-of-hospital primary cardiac arrest. Epidemiology 12:193–199.

Liao D, Creason J, Shy C, Williams R, Watts R, Zweidinger R. 1999. Daily variation of particulate air pollution and poor cardiac autonomic control in the elderly. Environ Health Perspect 107:521–525.

Linn WS, Gong H Jr. 2001. Air pollution, weather stress, and blood pressure. Am J Public Health 91:1345–1346.

Magari SR, Hauser R, Schwartz J, Williams PL, Smith TJ, Christiani DC. 2001. Association of heart rate variability with occupational and environmental exposure to particulate air pollution. Circulation 104:986–991.

Magari SR, Schwartz J, Williams PL, Hauser R, Smith TJ, Christiani DC. 2002a. The association between personal measurements of environmental exposure to particulates and heart rate variability. Epidemiology 13:305–310.

Magari SR, Schwartz J, Williams PL, Hauser R, Smith TJ, Christiani DC. 2002b. The association of particulate air metal concentrations with heart rate variability. Environ Health Perspect 110:875–880.

Metzger KB, Tolbert PE, Klein M, Peel JL, Flanders WD, Todd K, Mulholland JA, Ryan PB, Frumkin H. 2004. Ambient air pollution and cardiovascular emergency department visits. Epidemiology 15:46–56.

Meyerfeldt U, Wessel N, Schutt H, Selbig D, Schumann A, Voss A, Kurths J, Ziehmann C, Dietz R, Schirdewan A. 2002. Heart rate variability before the onset of ventricular tachycardia: Differences between slow and fast arrhythmias. Int J Cardiol 84:141–151.

Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, Levine JH, Saksena S, Waldo AL, Wilber D, Brown MW, Heo M. 1996. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. N Engl J Med 335:1933–1940.

Muller JE, Mittleman A, Maclure M, Sherwood JB, Tofler GH. 1996. Triggering myocardial infarction by sexual activity. Low absolute risk and prevention by regular physical exertion. Determinants of Myocardial Infarction Onset Study Investigators. JAMA 275:1405–1409.

Muller JE, Stone PH, Turi ZG, Rutherford JD, Czeisler CA, Parker C, Poole WK, Passamani E, Roberts R, Robertson T, et al. 1985. Circadian variation in the frequency of onset of acute myocardial infarction. N Engl J Med 313:1315–1322.

Myerburg RJ. 1997. Sudden cardiac death in persons with normal (or near normal) hearts. Am J Cardiol 79:3–9.

Myerburg RJ, Kessler KM, Castellanos A. 1992. Sudden cardiac death. Structure, function, and time-dependence of risk. Circulation 85(Suppl 1):I2–I10.

Nearing BD, Verrier RL, Skornick WA, Gazulla G, Killingsworth CR, Oakberg K, Godleski J. 1996. Inhaled fly ash results in cardiac electrophysiologic function (abstract). Am J Respir Crit Care Med 153:A543.

Oh JA. 2000. Characterization and Source Apportionment of Air Pollution in Nashville, TN and Boston, MA. Department of Environmental Health, Harvard School of Public Health, Boston MA.

Parker JD, Testa MA, Jimenez AH, Tofler GH, Muller JE, Parker JO, Stone PH. 1994. Morning increase in ambulatory ischemia in patients with stable coronary artery disease. Importance of physical activity and increased cardiac demand. Circulation 89:604–614.

Pekkanen J, Brunner EJ, Anderson HR, Tiittanen P, Atkinson RW. 2000. Daily concentrations of air pollution and plasma fibrinogen in London. Occup Environ Med 57:818–822.

Peters A, Dockery DW, Muller JE, Mittleman MA. 2001a. Increased particulate air pollution and the triggering of myocardial infarction. Circulation 103:2810–2815.

Peters A, Doring A, Wichmann HE, Koenig W. 1997. Increased plasma viscosity during an air pollution episode: A link to mortality? Lancet 349:1582–1587.

Peters A, Frohlich M, Doring A, Immervoll T, Wichmann HE, Hutchinson WL, Pepys MB, Koenig W. 2001b. Particulate air pollution is associated with an acute phase response in men; results from the MONICA-Augsburg Study. Eur Heart J 22:1198–1204.

Peters A, Liu E, Verrier RL, Schwartz J, Gold DR, Mittleman M, Baliff J, Oh JA, Allen G, Monahan K, Dockery DW. 2000. Air pollution and incidence of cardiac arrhythmia. Epidemiology 11:11–17.

Peters A, Perz S, Doring A, Stieber J, Koenig W, Wichmann HE. 1999. Increases in heart rate during an air pollution episode. Am J Epidemiol 150:1094–1098.

Peters RW. 1990. Propranolol and the morning increase in sudden cardiac death: (The beta-blocker heart attack trial experience). Am J Cardiol 66:57G–59G.

Pope CA III, Burnett RT, Thurston GD, Thun MJ, Calle EE, Krewski D, Godleski JJ. 2004. Cardiovascular mortality and long-term exposure to particulate air pollution: Epidemiological evidence of general pathophysiological pathways of disease. Circulation 109:71–77.

Pope CA III, Dockery DW, Kanner RE, Villegas GM, Schwartz J. 1999a. Oxygen saturation, pulse rate, and particulate air pollution: A daily time-series panel study. Am J Respir Crit Care Med 159:365–372.

Pope CA III, Eatough DJ, Gold DR, Pang Y, Nielsen KR, Nath P, Verrier RL, Kanner RE. 2001. Acute exposure to environmental tobacco smoke and heart rate variability. Environ Health Perspect 109:711–716.

Pope CA III, Schwartz J. 1996. Time series for the analysis of pulmonary health data. Am J Respir Crit Care Med 154:S229–S233.

Pope CA III, Schwartz J, Ransom MR. 1992. Daily mortality and PM_{10} pollution in Utah Valley. Arch Environ Health 47:211–217.

Pope CA III, Verrier RL, Lovett EG, Larson AC, Raizenne ME, Kanner RE, Schwartz J, Villegas GM, Gold DR, Dockery DW. 1999b. Heart rate variability associated with particulate air pollution. Am Heart J 138:890–899.

Prescott GJ, Cohen GR, Elton RA, Fowkes FG, Agius RM. 1998. Urban air pollution and cardiopulmonary ill health: A 14.5 year time series study. Occup Environ Med 55:697–704.

Rapaport E. 1988. Sudden cardiac death. Am J Cardiol 62:3I–6I.

Reiter MJ, Mann DE. 1996. Sensing and tachyarrhythmia detection problems in implantable cardioverter defibrillators. J Cardiovasc Electrophysiol 7:542–558.

Salvi S, Blomberg A, Rudell B, Kelly F, Sandström T, Holgate ST, Frew A. 1999. Acute inflammatory responses in the airways and peripheral blood after short-term exposure to diesel exhaust in healthy human volunteers. Am J Respir Crit Care Med 159:702–709.

Samet JM, Dominici F, Curriero FC, Coursac I, Zeger SL. 2000a. Fine particulate air pollution and mortality in 20 US cities, 1987–1994. N Engl J Med 343:1742–1749.

Samet JM, Dominici F, Zeger SL, Schwartz J, Dockery DW. 2000b. The National Morbidity, Mortality, and Air Pollution Study, Part I: Methods and Methodologic Issues. Research Report 94. Health Effects Institute, Cambridge MA.

Samet JM, Zeger SL, Dominici F, Curriero F, Coursac I, Dockery DW, Schwartz J, Zanobetti A. 2000c. The National Morbidity, Mortality, and Air Pollution Study, Part II: Morbidity and Mortality from Air Pollution in the United States. Research Report 94. Health Effects Institute, Cambridge MA.

Schwartz J. 1994a. Total suspended particulate matter and daily mortality in Cincinnati, Ohio. Environ Health Perspect 102:186–189.

Schwartz J. 1994b. What are people dying of on high air pollution days? Environ Res 64:26–35.

Schwartz J. 1997. Air pollution and hospital admissions for cardiovascular disease in Tucson. Epidemiology 8:371–377.

Schwartz J. 2000a. Assessing confounding, effect modification, and thresholds in the association between ambient particles and daily deaths. Environ Health Perspect 108:563–568.

Schwartz J. 2000b. The distributed lag between air pollution and daily deaths. Epidemiology 11:320–326.

Schwartz J. 2001. Air pollution and blood markers of cardiovascular risk. Environ Health Perspect 109(Suppl 3):405–409.

Schwartz J, Dockery DW. 1992. Increased mortality in Philadelphia associated with daily air pollution concentrations. Am Rev Respir Dis 145:600–604.

Schwartz J, Dockery DW, Neas LM. 1996. Is daily mortality associated specifically with fine particles? J Air Waste Manage Assoc 46:927–939.

Schwartz J, Morris R. 1995. Air pollution and hospital admissions for cardiovascular disease in Detroit, Michigan. Am J Epidemiol 142:23–35.

Shaper AG, Wannamethee G, Macfarlane PW, Walker M. 1993. Heart rate, ischaemic heart disease, and sudden cardiac death in middle-aged British men. Br Heart J 70:49–55.

Sheppard L, Levy D, Checkoway H. 2001. Correcting for the effects of location and atmospheric conditions on air pollution exposures in a case-crossover study. J Expos Anal Environ Epidemiol 11:86–96.

Stone PH, Godleski JJ. 1999. First steps toward understanding the pathophysiologic link between air pollution and cardiac mortality. Am Heart J 138:804–807.

Suh HH, Nishioka Y, Allen GA, Koutrakis P, Burton RM. 1997. The metropolitan acid aerosol characterization study: Results from the summer 1994 Washington, DC field study. Environ Health Perspect 105:826–834.

Verrier RL, Muller JE, Hobson JA. 1996. Sleep, dreams, and sudden death: The case for sleep as an autonomic stress test for the heart. Cardiovasc Res 31:181–211.

Watkinson WP, Campen MJ, Costa DL. 1998. Cardiac arrhythmia induction after exposure to residual oil fly ash particles in a rodent model of pulmonary hypertension. Toxicol Sci 41:209–216.

Wellenius GA, Coull BA, Godleski JJ, Koutrakis P, Okabe K, Savage ST, Lawrence JE, Murthy GG, Verrier RL. 2003. Inhalation of concentrated ambient air particles exacerbates myocardial ischemia in conscious dogs. Environ Health Perspect 111:402–408.

Wellenius GA, Saldiva PH, Batalha JR, Krishna Murthy GG, Coull BA, Verrier RL, Godleski JJ. 2002. Electrocardiographic changes during exposure to residual oil fly ash (ROFA) particles in a rat model of myocardial infarction. Toxicol Sci 66:327–335.

Wong TW, Lau TS, Yu TS, Neller A, Wong SL, Tam W, Pang SW. 1999. Air pollution and hospital admissions for respiratory and cardiovascular diseases in Hong Kong. Occup Environ Med 56:679–683.

Zanobetti A, Schwartz J, Dockery DW. 2000. Airborne particles are a risk factor for hospital admissions for heart and lung disease. Environ Health Perspect 108:1071–1077.

Zeger SL, Liang KY, Albert PS. 1988. Models for longitudinal data: A generalized estimating equation approach. Biometrics 44:1049–1060.

APPENDIX A. Data Abstraction Forms

VISIT Data Abstraction Form. Version 3.

Study ID

Zip Code

Date of Birth __ / __ / __

Please fill out an EVENT Abstraction Form for every individual visit, even if there were no events for that visit.

Date of abstract __ / __ / __

Abstractor initials

Visit Date	Nurse's Form	Beta Blocker	Digoxin	AA Drugs	Was patient out of N.E. between this and prior visit?	Between this and prior visit, were there any arrhythmic hosp's?
__ / __ / __	☐ Y ☐ N	☐ Y ☐ N ☐ N/R	☐ Y ☐ N ☐ N/R	☐ Amiodarone ☐ Mexilitine ☐ Quinidine ☐ None ☐ Sotalol ☐ Other (specify)	☐ N ☐ Y ☐ N/R	☐ Y ☐ N ☐ N/R
__ / __ / __	☐ Y ☐ N	☐ Y ☐ N ☐ N/R	☐ Y ☐ N ☐ N/R	☐ Amiodarone ☐ Mexilitine ☐ Quinidine ☐ None ☐ Sotalol ☐ Other (specify)	☐ N ☐ Y ☐ N/R	☐ Y ☐ N ☐ N/R
__ / __ / __	☐ Y ☐ N	☐ Y ☐ N ☐ N/R	☐ Y ☐ N ☐ N/R	☐ Amiodarone ☐ Mexilitine ☐ Quinidine ☐ None ☐ Sotalol ☐ Other (specify)	☐ N ☐ Y ☐ N/R	☐ Y ☐ N ☐ N/R
__ / __ / __	☐ Y ☐ N	☐ Y ☐ N ☐ N/R	☐ Y ☐ N ☐ N/R	☐ Amiodarone ☐ Mexilitine ☐ Quinidine ☐ None ☐ Sotalol ☐ Other (specify)	☐ N ☐ Y ☐ N/R	☐ Y ☐ N ☐ N/R
__ / __ / __	☐ Y ☐ N	☐ Y ☐ N ☐ N/R	☐ Y ☐ N ☐ N/R	☐ Amiodarone ☐ Mexilitine ☐ Quinidine ☐ None ☐ Sotalol ☐ Other (specify)	☐ N ☐ Y ☐ N/R	☐ Y ☐ N ☐ N/R
__ / __ / __	☐ Y ☐ N	☐ Y ☐ N ☐ N/R	☐ Y ☐ N ☐ N/R	☐ Amiodarone ☐ Mexilitine ☐ Quinidine ☐ None ☐ Sotalol ☐ Other (specify)	☐ N ☐ Y ☐ N/R	☐ Y ☐ N ☐ N/R
__ / __ / __	☐ Y ☐ N	☐ Y ☐ N ☐ N/R	☐ Y ☐ N ☐ N/R	☐ Amiodarone ☐ Mexilitine ☐ Quinidine ☐ None ☐ Sotalol ☐ Other (specify)	☐ N ☐ Y ☐ N/R	☐ Y ☐ N ☐ N/R

Comments

8116528247

Continued

EVENT Data Abstraction Form. Version 3

Study ID ___ Form # ___

Abstractor Initials ___

Visit Date ___/___/___

Last Visit Date ___/___/___

(If Last Visit Date is missing, please code as 99/99/9999)

Date of Abstract ___/___/___

☐ Single Zone

☐ Double Zone

VT Rate Cut-off ___

VF Rate Cut-off ___

Device type

☐ CPI ☐ Med

☐ Vent ☐ Other

Events since last visit ___

From the Nurse's Form, are there any events? ☐ YES ☐ NO

From the Abstractor, are there any events? ☐ YES ☐ NO

From MD review, are there any events? ☐ YES ☐ NO

Event Date	Time	Episode #	Device Rhythm	MD Rhythm	Review Rhythm	Cycle Length	BPM	Patient in N.E?
___/___/___	___:___	___	☐ VT ☐ VF					N Y N/R

Therapy (check all that apply): ☐ ATP ☐ Diverted ☐ Shock

Symptoms (check all that apply): ☐ Syncope ☐ Light Headed ☐ Palpitations ☐ Shortness of breath ☐ Asymptomatic ☐ Not Reported ☐ Other (specify) ___

Comments

Event Date	Time	Episode #	Device Rhythm	MD Rhythm	Review Rhythm	Cycle Length	BPM	Patient in N.E?
___/___/___	___:___	___	☐ VT ☐ VF					N Y N/R

Therapy (check all that apply): ☐ ATP ☐ Diverted ☐ Shock

Symptoms (check all that apply): ☐ Syncope ☐ Light Headed ☐ Palpitations ☐ Shortness of breath ☐ Asymptomatic ☐ Not Reported ☐ Other (specify) ___

Comments

Event Date	Time	Episode #	Device Rhythm	MD Rhythm	Review Rhythm	Cycle Length	BPM	Patient in N.E?
___/___/___	___:___	___	☐ VT ☐ VF					N Y N/R

Therapy (check all that apply): ☐ ATP ☐ Diverted ☐ Shock

Symptoms (check all that apply): ☐ Syncope ☐ Light Headed ☐ Palpitations ☐ Shortness of breath ☐ Asymptomatic ☐ Not Reported ☐ Other (specify) ___

Comments

2111526716

APPENDIX B. Abstracted Patient Records Not Included in Analyses

After the Final Report had been completed, and was under review at HEI, the final Quality Assurance Audit of this study revealed that the records of 14 patients with follow-up had been abstracted but had not been included in the analytic database because of clerical oversight. The individual characteristics of these 14 subjects are listed in Table B.1.

Eight of these subjects met the inclusion criterion of having residential ZIP codes within 40 km of the HSPH main air monitoring site. Three of these patients had a total of 11 VAs, and one patient had five SVAs.

Because these subjects were missed for reasons independent of both air pollutant concentrations and the presence of arrhythmias, their exclusion would not be expected to introduce any bias in the analyses. To assess the influence that inclusion of these eight subjects would have had on the results, we used the complete data set and reran several of the primary analyses for the associations with 2-day mean concentrations of $PM_{2.5}$, NO_2, and SO_2 (Table 12). Table B.2 presents the comparison of these analyses. We found minimal or undetectable differences between the results of the complete dataset (after including the missing observations) and the results as presented in Table 12.

Table B.1. Demographic and Clinical Characteristics of 14 Patients Found to Have Not Been Included in the Analysis Dataset

Implant Date	Age	Sex	Ethnicity	< 40 km[a]	Diagnosis[b]	Previous MI	Ejection Fraction	Device	Chamber	β- Blocker	Antiarrhythmics	Digoxin	During Follow-Up		
													VAs	SVAs	Person-Years
6 Sep 1995	35	M	White	Yes	HCM	No	0.60	PRx III	Single	Yes	Yes	No	1	No	4.60
27 Feb 1996	61	M	White	Yes	CAD	Yes	0.30	Mini	Single	Yes	Yes	No	No	No	4.24
24 Oct 1996	63	M	White	Yes	CAD	Yes	0.20	Mini II HC	Single	No	Yes	Yes	7	No	2.97
29 Jan 1998	59	M	White	Yes	IDCM	No	0.14	AV	Dual	No	Yes	Yes	3	5	2.01
27 Jul 1998	62	M	White	Yes	CAD	Yes	0.50	AV II DR	Dual	Yes	Yes	Yes	No	No	1.71
8 Jun 1999	75	M	White	Yes	CAD	Yes	0.30	Mini IV+	Single	No	Yes	Yes	No	No	0.04
1 Jul 1999	54	M	White	Yes	CAD	No	0.20	Mini IV+	Single	Yes	Yes	Yes	No	No	0.86
17 Sep 1999	82	M	White	Yes	ICDM	No	0.15	AV III DR	Dual	Yes	Yes	No	No	No	0.57
15 Dec 1995	59	M	White	No	IDCM	No	0.35	PRx III	Single	Yes	Yes	No	No	3	4.40
21 May 1997	35	M	Hispanic	No	IDCM	No	0.15	Mini II+	Single	Yes	Yes	Yes	No	No	3.10
13 Jun 1997	65	F	Hispanic	No	NL	No	0.60	Mini II	Single	No	Yes	No	No	No	2.25
8 Jul 1999	81	M	Unknown	No	CAD	No	0.20	AV III DR	Dual	No	Yes	Yes	No	No	0.09
3 Sep 1999	75	M	White	No	CAD	No	0.35	Mini IV+	Single	Yes	Yes	Yes	No	No	0.57
1 Mar 1999	70	M	White	No	CAD	No	0.30	Mini II	Single	Yes	Yes	No	No	No	1.20

[a] From the HSPH main monitoring site (see Figure 1); the inclusion criterion.

[b] HCM = hypertrophic cardiomyopathy; CAD = coronary artery disease; IDCM = idiopathic cardiomyopathy; and NL = not listed.

Table B.2. Estimated Arrhythmic Effects per IQR Increase in 2-Day Mean Pollutant Concentrations Obtained from Logarithmic Regression Analysis Comparing Results Presented in Table 12 and Results from Including the 8 Eligible but Omitted Patients

Pollutant (IQR Increase in 2-Day Mean) and Dataset Analyzed	All Arrhythmias				VAs				SVAs			
	Number of Patients	Number of Events	OR	95% CI	Number of Patients	Number of Events	OR	95% CI	Number of Patients	Number of Events	OR	95% CI
$PM_{2.5}$ (7.0 μg/m^3)												
Presented	84	547	1.09	(0.96 , 1.24)	72	483	1.07	(0.94 , 1.23)	30	65	1.23	(0.86 , 1.77)
Complete	87	556	1.09	(0.96 , 1.24)	75	490	1.07	(0.94 , 1.23)	31	67	1.22	0.85 , 1.75)
BC (0.74 μg/m^3)												
Presented	69	420	1.10	(0.90 , 1.36)	60	367	1.09	(0.87 , 1.36)	22	54	1.16	(0.68 , 1.99)
Complete	69	420	1.10	(0.90 , 1.36)	60	367	1.09	(0.87 , 1.36)	22	54	1.16	(0.68 , 1.99)
NO_2 (7.7 ppb)												
Presented	92	763	1.08	(0.96 , 1.20)	81	652	1.06	(0.94 , 1.20)	38	112	1.17	(0.89 , 1.53)
Complete	95	779	1.08	(0.97 , 1.20)	84	663	1.06	(0.94 , 1.20)	39	117	1.16	(0.89 , 1.52)
CO (0.48 ppm)												
Presented	92	765	1.15	(0.95 , 1.38)	81	654	1.13	(0.92 , 1.39)	38	112	1.25	(0.78 , 2.01)
Complete	95	781	1.15	(0.96 , 1.39)	84	665	1.14	(0.93 , 1.40)	39	117	1.26	(0.80 , 2.00)
SO_2 (4.0 ppb)												
Presented	92	765	1.11[a]	(1.00 , 1.24)	81	654	1.07	(0.95 , 1.21)	38	112	1.33[b]	(1.04 , 1.70)
Complete	95	781	1.12[b]	(1.00 , 1.24)	84	665	1.07	(0.95 , 1.21)	39	117	1.33[b]	(1.04 , 1.70)
O_3 (15 ppb)												
Presented	92	762	1.13	(0.95 , 1.35)	81	652	1.12	(0.93 , 1.35)	37	111	1.21	(0.79 , 1.87)
Complete	95	778	1.12	(0.94 , 1.33)	84	663	1.09	(0.91 , 1.31)	38	116	1.25	(0.82 , 1.91)

[a] $P < 0.10$.

[b] $P < 0.05$.

APPENDIX C. HEI Quality Assurance Audit Statement

The conduct of this study was subjected to independent audits by Mr David Bush of Technical & Business Systems, Inc. Mr Bush is an expert in quality assurance for air quality monitoring studies and data management. The audits included on-site reviews of study activities for conformance to the study protocol and operating procedures. The dates of the audits are listed in the table below with the phase of the study examined.

Written reports of each inspection were provided to the HEI project manager, who transmitted the findings to the Principal Investigator. These quality assurance audits demonstrated that the study was conducted by an experienced team with a high concern for data quality. Study personnel were very responsive to audit recommendations. The Final Report appears to be an accurate representation of the study.

Date	Phase of Study
October 27–28, 1999	The auditor conducted an on-site audit at HSPH and NEMC. Staffing and internal quality control procedures were considered. During this audit, significant issues were noted regarding the consistency and accuracy of the medical data abstracted at NEMC. Abstraction of the data was suspended until protocols were developed to address the noted issues.
February 10–11, 2000	On the basis of the results from the first audit, study personnel significantly revised the abstraction protocol and repeated the abstraction process. The auditor visited HSPH to verify the conduct of the new protocols. In addition, an audit of air quality monitoring performed by HSPH was conducted.
January 7–9, 2004	The auditor reviewed the study's Final Report. An on-site audit at the study facilities was conducted to verify the integrity of the reported data. Several data points for each parameter were traced through the entire data processing sequence to verify that the described procedures were being followed and to verify the integrity of the database. No errors were noted, although a small percentage of subjects were found to have been accidentally, although randomly, excluded from the analysis. Rerunning some key analyses by study personnel demonstrated that the reported results were not significantly affected by the exclusions.

David H Bush, Quality Assurance Officer

APPENDIX AVAILABLE ON REQUEST

The following materials may be requested by contacting the Health Effects Institute at Charlestown Navy Yard, 120 Second Avenue, Boston MA 02129-4533, +1-617-886-9330, fax +1-617-886-9335, or email (*pubs@healtheffects.org*). Please give (1) the first author, full title, and number of the Research Report and (2) the title of the appendix requested.

D. Air Pollution and Incidence of Cardiac Arrhythmia

This article reports the results from the pilot study referenced in this Investigators' Report: Peters A, Liu E, Verrier RL, Schwartz J, Gold DR, Mittleman M, Baliff J, Oh JA, Allen G, Monahan K, Dockery DW. 2000. Air pollution and incidence of cardiac arrhythmia. Epidemiology 11:11–17. Made available with permission from Epidemiology and Lippincott Williams & Wilkins.

ABOUT THE AUTHORS

Douglas W Dockery, ScD, is professor of environmental epidemiology at HSPH and associate professor of medicine (epidemiology) at Harvard Medical School. Dr Dockery has been one of the leaders in epidemiologic investigations of the health effects of air pollution, specifically particulate air pollution, for more than 25 years.

Heike Luttmann-Gibson, PhD, is a biostatistician in the Environmental Epidemiology Program at HSPH. Her research has focused on the respiratory health effects of chronic and acute air pollution exposures on children. More recently she has been investigating the cardiovascular effects of air pollution in adults.

David Q Rich, MPH**,** ScD, was a doctoral student in the Departments of Epidemiology and Environmental Health at HSPH when this research was under way; he is now a postdoctoral fellow in the Department of Environmental Health. He investigates acute air pollution and other triggers of cardiac arrhythmias. His previous research focused on environmental exposures of children to lead dust, the cognitive effects of lead exposures, and methods to reduce these exposures.

Mark S Link, MD, is codirector of the Cardiac Electrophysiology and Pacemaker Laboratory and director of the Center for the Evaluation of Heart Disease in Athletes in the Department of Medicine at Tufts–NEMC. Dr Link is also associate professor of medicine at Tufts University School of Medicine. His research interests are electrophysiology, arrhythmias, heart disease in athletes, and sudden death.

Joel D Schwartz, PhD, is professor of environmental epidemiology at HSPH and associate epidemiologist in the Department of Medicine at Brigham and Women's Hospital. Dr Schwartz has been a leader in epidemiologic assessment of the health effects of air pollution. His recent work has focused on the cardiovascular effects of air pollution and on factors that modify the response to air pollution.

Diane R Gold, MD, MPH, DTM&H, is associate professor of medicine at Harvard Medical School, associate professor of environmental health at HSPH, and associate physician at Brigham and Women's Hospital. Dr Gold's research focuses on the cardiopulmonary effects of particles on older persons. She also is studying the relations between environmental exposures, early life immune responses, and the development of allergy and asthma.

Petros Koutrakis, PhD, is professor of environmental sciences in the Department of Environmental Health and director of the Exposure, Epidemiology and Risk Program at HSPH. Dr Koutrakis' research activities focus on the development of human exposure measurement techniques and the investigation of sources, transport, and the fate of air pollutants.

Richard L Verrier, PhD, is associate professor in the Department of Environmental Health at HSPH and associate professor of medicine at Harvard Medical School, Beth Israel Deaconess Medical Center. His research is focused on neural, behavioral, and environmental triggers of sudden cardiac death and arrhythmias.

Murray A Mittleman, MD, DrPH, is associate professor in the Department of Epidemiology at HSPH and associate professor of medicine at Harvard Medical School. Dr Mittleman is also director of cardiovascular epidemiology at the Beth Israel Deaconess Medical Center. His primary research interest lies in identifying and understanding factors that trigger acute cardiovascular disease events (including acute myocardial infarction, sudden cardiac death, VAs, and stroke).

OTHER PUBLICATIONS RESULTING FROM THIS RESEARCH

Dockery DW, Luttmann-Gibson H, Rich DQ, Link MS, Mittleman MA, Gold DR, Koutrakis P, Schwartz JD, Verrier RL. 2005. Association of air pollution with increased incidence of ventricular tachyarrhythmias recorded by implanted cardioverter defibrillators. Environ Health Perspect 113(6):670–674.

Rich DQ, Schwartz J, Dockery DW, Mittleman MA, Link MS, Luttmann-Gibson H, Catalano PJ, Speizer FE, Dockery DW. 2005. Association of short-term ambient air pollution concentrations and ventricular arrhythmias. Am J Epidemiol 161(12):1123–1132.

ABBREVIATIONS AND OTHER TERMS

AVID	Antiarrhythmics Versus Implantable Defibrillators [clinical trial]
BC	black carbon
BIDMC	Beth Israel Deaconess Medical Center
bpm	beats per minute
CI	confidence interval
CO	carbon monoxide
DEP	Department of Environmental Protection (Massachusetts)
GEE	generalized estimating equation
HSPH	Harvard School of Public Health
ICD	implanted cardioverter defibrillator
IQR	interquartile range
MI	myocardial infarction
NEMC	New England Medical Center
NO_2	nitrogen dioxide
O_3	ozone
OR	odds ratio
PM_{10}	particulate matter less than 10 μm in aerodynamic diameter
$PM_{2.5}$	particulate matter less than 2.5 μm in aerodynamic diameter

QT interval	interval between Q and T waves in an ECG tracing
r	correlation coefficient for bivariate analysis
R–R interval	interval between successive R waves in an ECG tracing (beat-to-beat interval)
SO_2	sulfur dioxide
SO_4^{2-}	sulfate
SVA	supraventricular arrhythmia
TEOM	tapered element oscillating microbalance
VA	ventricular arrhythmia

INTRODUCTION

Before the current study began, epidemiologic studies had reported associations between increases in daily hospital admissions for cardiovascular diseases and concentrations of different types of particulate matter (PM*) or its components (Burnett et al 1995; Schwartz and Morris 1995; Poloniecki et al 1997; Schwartz 1997). How exposure to PM might be linked to exacerbation of cardiovascular disease was not well understood. In 1998 the HEI issued Request for Application 98-1, "Characterization of Exposure to and Health Effects of Particulate Matter." A key component of the RFA was to evaluate the effects of exposure to ambient (outdoor) particles in people who might be more susceptible than healthy individuals; people with cardiovascular conditions were considered one such population.

In response to RFA 98-1, Douglas Dockery and his colleagues at the Harvard School of Public Health (HSPH) submitted an application to assess the effects of air pollutants on patients who had an implanted cardioverter defibrillator (ICD). These patients are at risk of developing potentially fatal cardiac arrhythmias (described in more detail in the Scientific Background section). An ICD is programmed to respond when the heart rate exceeds a preset number of beats per minute; such changes in heart rhythm are recorded and stored. (If necessary, the ICD delivers an electrical stimulus to return the heart rate to normal.) By evaluating the patients' ICD electrogram tracings, the investigators would be able to assess whether pollutant concentrations were associated with arrhythmias recorded by the ICD.

The proposed study followed up on results from an earlier smaller study by Dockery and colleagues, also with patients who had ICDs; that study showed reported associations between ambient concentrations of certain air pollutants and ICD discharges (Peters et al 2000). The HEI Health Research Committee recommended the current study for funding because it provided an opportunity to evaluate the effects of ambient air pollutants on a larger group of patients with ICDs.†

* A list of abbreviations and other terms appears at the end of the Investigators' Report.

This document has not been reviewed by public or private party institutions, including those that support the Health Effects Institute; therefore, it may not reflect the views of these parties, and no endorsements by them should be inferred.

† Dr Dockery's 2-year study, "Association of Particulate Air Pollution with Arrhythmias Recorded by Implanted Cardioverter Defibrillators", began in September 1998. Total expenditures were $411,000. The draft Investigators' Report from Dockery and colleagues was received for review in April 2002. A revised report, received in March 2004, was accepted for publication in June 2004. During the review process, the HEI Health Review Committee and the investigators had the opportunity to exchange comments and to clarify issues in both the Investigators' Report and in the Review Committee's Commentary.

SCIENTIFIC BACKGROUND

CARDIAC ARRHYTHMIAS

A cardiac arrhythmia is a disturbance in the normal rhythm of the heart, which usually beats 60 to 100 times per minute. Most arrhythmias are temporary and benign (eg, a skipped beat), but some may be very serious, particularly if they persist, because they compromise, or even prevent, the ability of the heart to pump blood. Two important types of arrhythmias are tachycardia, an abnormally rapid heart beat (faster than approximately 140 bpm), and fibrillation, an even faster heart rate (faster than about 250 bpm) that also involves uncoordinated contractions of the heart.

Cardiac arrhythmias are also classified by their site of origin: the ventricles (the lower chambers) or the atria (the upper chambers) of the heart. Ventricular arrhythmias (VAs) cause most sudden cardiac deaths. Ventricular tachycardia can degenerate into ventricular fibrillation, an extremely rapid, chaotic rhythm that prevents the heart from pumping blood to the rest of the body. Without effective and immediate treatment of ventricular fibrillation, death occurs rapidly. Heart attack (myocardial infarction; MI) is one of the many cardiac disorders associated with VAs. In patients prone to arrhythmias, factors that can trigger VAs include stress, exercise, tobacco, alcohol, and some pharmaceuticals—such as amphetamines, tricyclic antidepressants, and diuretic and digitalis preparations used to treat various heart conditions.

The most common type of atrial arrhythmia (also known as supraventricular arrhythmia [SVA] because it originates from the area of the heart above the ventricles) is atrial fibrillation, which affects 3% to 5% of cardiac patients older than 60 (Levy 1998). Although atrial fibrillation itself does not directly threaten life, it is associated with increased risk of stroke: Blood clots that develop in the atria may move to the brain. Thus, the mortality rate for stroke in patients with atrial fibrillation is approximately twice as high as the rate in patients without this abnormality (Pritchett 1992). Most risk factors for atrial fibrillation are associated with heart disease, such as hypertension, left ventricular hypertrophy, and coronary artery disease, but they also include chronic obstructive pulmonary disease.

TREATMENT OF ARRHYTHMIAS: ICDs AND MEDICATIONS

Most frequently, an ICD is implanted in a person who has experienced at least one episode of ventricular tachycardia,

ventricular fibrillation, or cardiac arrest. It is also used in selected patients with other conditions: those who have had an MI; those who have had an arrhythmic condition that did not respond to drug therapy; and those who have a low ejection fraction (the fraction of blood ejected from the left ventricle into the arteries with each beat of the heart; normally this is around 55%, but is frequently 35% or less for people with cardiovascular disease; Gregoratos et al 2002).

The ICD is implanted just under the skin, usually in the left shoulder area. Leads connected to the defibrillator are inserted into the heart through a vein. These leads have electrodes on the ends that constantly monitor the rhythm of the heart, looking for rapid arrhythmias that can cause sudden cardiac death. ICDs are preprogrammed to deliver different therapies, such as an electrical shock to restore normal rhythm, depending on the beat rate and duration of the arrhythmia. ICDs are designed to detect and treat life-threatening arrhythmias, which are generally ventricular rather than supraventricular in origin. However, if an arrhythmia that originates in the atria leads to a ventricular rate faster than the preset detection level, the ICD discharges.

Single-chamber ICDs have one lead, placed in or on the right ventricle, to defibrillate and pace the ventricle. More recent dual-chamber ICDs also monitor rhythms in the atrium, but pace or defibrillate the ventricle when needed. Both devices respond to an increase in heart rate above a preprogrammed number. The electrogram (a tracing of the heart beat) recorded by the dual-chamber device is more informative than that from the single-chamber device because it provides atrial as well as ventricular tracings.

CARDIOVASCULAR EFFECTS OF PM AND GASEOUS POLLUTANTS

Before the current study began, cohort studies had found associations between cardiopulmonary mortality and long-term concentrations of $PM_{2.5}$ ($PM \leq 2.5$ µm in aerodynamic diameter; also referred to as fine particles) (Dockery et al 1993; Pope et al 1995). In addition, time-series studies had reported associations between daily hospital admissions for cardiovascular diseases and short-term changes in concentrations of different sizes of PM or its components: PM_{10} (Schwartz and Morris 1995; Schwartz 1997), $PM_{2.5}$ and black smoke (Poloniecki et al 1997), and sulfate (SO_4^{2-}; Burnett et al 1995). Studies had also reported associations between exposure to carbon monoxide (CO) and hospitalization for congestive heart failure as well as other cardiovascular diseases (Morris et al 1995; Schwartz 1997). Subsequently a number of studies have explored potential pathways for these effects; the mechanism or mechanisms by which exposure to air pollutants, and PM in particular, might affect cardiovascular function is still not clear, however (Brook et al 2004).

Evaluating the effects of particulate air pollution on possibly life-threatening cardiac arrhythmias has been of particular interest because it is one possible mechanism that would link PM exposure and death. Patients with ICDs are one population in whom this question may be addressed. Dockery and colleagues conducted a pilot study (Peters et al 2000) that reported that increases in ambient concentrations of certain air pollutants were associated with an increased number of ICD discharges in a group of 100 patients. The increased relative risk associated with changes in the concentrations of either $PM_{2.5}$ or most gaseous pollutants was small and not statistically significant; nitrogen dioxide (NO_2) was the only pollutant to have a statistically significant association with ICD discharges (on the day before an event [a lag time of 1 day] and with the 5-day mean concentration). The effects of $PM_{2.5}$, and NO_2 especially, were larger and statistically significant in the small group of patients who experienced multiple arrhythmic episodes.

The current study provided Dockery and colleagues an opportunity to assess the association between air pollutants and arrhythmias in a larger group of patients with ICDs for whom they intended to collect detailed clinical information to compare with pollutant measurements.

AIMS AND STUDY DESIGN

The primary study objectives were to evaluate (1) whether short-term increases in ambient concentrations of PM increased relative risk of potentially life-threatening arrhythmias in patients with ICDs; and (2) whether relative risk was higher in patients with ICDs who also had preexisting cardiovascular disease.

The investigators proposed two further objectives:

1. to evaluate whether concentrations of soluble metal cations in the fine particles were associated with increased relative risk of arrhythmias. Dockery and colleagues did not have sufficient data on metal concentrations and so did not complete this part of the study.
2. to compare electrocardiographic changes observed in dogs exposed to particulate air pollution with changes observed in the electrograms (tracings similar to electrocardiograms) recorded by ICDs in patients in this study. This objective could not be accomplished because the ICD electrogram tracings did not show all the information needed to compare them with electrocardiogram tracings; specifically, the T-wave portion of a typical pattern of heart beats is filtered out of an electrogram to

avoid miscalculating the beat-to-beat (R–R) interval, one of the criteria used to identify arrhythmias.

The investigators proposed to evaluate the particulate pollutants $PM_{2.5}$, PM_{10}, black carbon (BC), SO_4^{2-}, and total number of particles (a measure of ultrafine particles). PM_{10} was not included in the data analysis, however; measurements had been made every third day and the investigators did not want to use these measurements to estimate 2-day mean pollutant concentrations, which were the basis for many of their primary analyses. In addition, because information about SO_4^{2-} levels and total number of particles was available for less than 3 years of the 7-year study period, these pollutants were included in only a few of the analyses. Although not part of the original proposal, the investigators also obtained daily concentrations of the gaseous pollutants NO_2, CO, sulfur dioxide (SO_2), and ozone (O_3).

The initial study design was intended to include patients with ICDs treated at two Boston medical centers, the New England Medical Center (NEMC) and Beth Israel Deaconess Medical Center (the source of data for the 100 patients included in the pilot study; Peters et al 2000). However, when Dockery and colleagues started collecting data for the current study, they found that clinical data at Beth Israel Deaconess were recorded on paper forms and thus incompatible with the electronic NEMC records; thus the Beth Israel Deaconess patients were not included in this study.

STUDY POPULATION

Dockery and colleagues evaluated ICD data collected between August 1995 and July 2002 from 195 Boston area patients treated at the NEMC Cardiac Electrophysiology and Pacemaker Laboratory. The patients were Massachusetts residents who lived within 40 km (25 miles) of the study's main monitoring site at the HSPH and who had been followed for more than 60 days (average follow-up 3.2 years).

CLINICAL CHARACTERISTICS

Patients had ICDs implanted at the NEMC Cardiac Electrophysiology and Pacemaker Laboratory between June 1995 and December 1999; 81% (158/195) of the patients had single-chamber ICDs and 19% had dual-chamber ICDs (see Tables 5 and 6 in the Investigators' Report). The average age at implantation was 63.6 years; 74% of the participants were male and 83% were white. The most common diagnoses at the time of ICD implantation were coronary artery disease (71%), low ejection fraction (defined as $\leq$ 35%; 63%), and previous MI (36%). For their cardiac conditions, the majority of the patients were prescribed multiple medications, predominantly β-blockers, antiarrhythmics, and digoxin; 12% of the patients were not prescribed any cardiac medications. Approximately 80% of patients reported taking the same medications throughout the study.

EVALUATION OF ICD ELECTROGRAMS

All ICDs recorded the time, date, and an electrogram of each arrhythmic event, as well as the ICD's response. The study's cardiologist evaluated all the ICD-detected arrhythmias using multiple criteria (shown in Table 1). These included the ventricular rate, characteristics of the onset and regularity of arrhythmias, changes evident from the electrogram tracings, and when available, responses to the ICD-initiated therapy. For a small number of patients who had had several episodes since the previous follow-up visit, one or more of the earliest electrograms had been overwritten due to limitations in the ICD storage capacity; however, even though the electrograms were unavailable, all of the other ICD records, especially R–R intervals, were intact. For these patients, the earlier episodes were classified from the remaining data. The cardiologist had no knowledge of pollutant concentrations at the time the events were recorded.

Patients were followed at NEMC approximately every 3 months or if they experienced an antiarrhythmic shock (some ICD interventions were not felt by the patient). If a patient died during the follow-up period, all the ICD recordings between the last follow-up visit and death were unavailable. Thus, only recordings of nonfatal arrhythmias were included in the study.

AIR POLLUTANT AND WEATHER MONITORING DATA

Using a tapered element oscillating microbalance (TEOM), the investigators measured $PM_{2.5}$ concentrations continuously at one monitoring site, either in South Boston (1995–1998) or at HSPH (1999–2002). Because the TEOM method of measuring PM is thought to produce lower mass concentrations than concentrations obtained from gravimetric methods, they applied a season-specific correction factor to bring the continuous measurements in line with concentrations obtained by the gravimetric approach (Oh 2000). Using an aethalometer, the investigators measured hourly BC concentrations at whichever $PM_{2.5}$ monitoring site was operating (1995–1997 or 1999–2002). Starting in late 1999, they used a condensation particle counter at the HSPH site to monitor total number of particles—a measure of ultrafine particles. Daily particulate SO_4^{2-} was measured

by ion chromatography on aqueous extracts of 24-hour $PM_{2.5}$ filter samples collected at the HSPH main monitoring site (late 1999–2002).

For the gaseous pollutants SO_2, NO_2, O_3, and CO, the investigators calculated 24-hour averages from hourly data collected over the entire study period at multiple sites around the Boston area operated by the Massachusetts Department of Environmental Protection. Temperature and relative humidity were measured at Logan Airport in Boston.

DATA ANALYSIS

Dockery and colleagues evaluated the association between arrhythmic episode-days (any day on which any patient had had an arrhythmia) and air pollutants by applying logistic regression models to the data. They performed all analyses separately for VAs and SVAs and some analyses for all arrhythmias combined. The investigators used fixed effect models with individual intercepts for each patient, except in the sensitivity analyses described later in this section. They used multivariate analysis to evaluate and account for potential confounding of the associations by time trends, season, meteorological conditions (temperature and relative humidity), and day of the week.

Dockery and colleagues presented each association as an odds ratio (OR) with 95% confidence intervals (CIs) based on an interquartile-range (IQR) increase in the concentration of each pollutant concentration. (The IQR is the 75th percentile minus the 25th percentile.) The magnitude of estimates for different pollutants is therefore based on comparable increments of exposure for the study period. They also reported *P* values for the effects of air pollutants on arrhythmias and for the interactions between those effects and possible modifiers (such as patient characteristics).

After the investigators' had submitted their Final Report and it was under review at HEI, they found that data from eight eligible patients had not been included in the analyses. When the investigators performed key analyses that included data from these eight patients, however, the results differed little from those that had not included them (see Appendix Tables B.1 and B.2). Thus, the investigators decided not to change the results already presented in the main portion of their report.

Effects of Pollutants Evaluated for Days 0 to 3 Before an Arrhythmic Event

The investigators considered mean air pollutant concentrations on the same day (lag 0) and lagged by 1, 2, or 3 days. They evaluated each lag day separately and also jointly in an unconstrained distributed lag model (Pope and Schwartz 1996). Because the results of these analyses showed elevated relative risk estimates associated with air pollutant concentrations on lag days 0 and 1, Dockery and colleagues also evaluated the effects of air pollutants based on the running 2-day mean concentration for those 2 days. This 2-day mean was used to analyze the possible effect modifications that are described later in this section. To assess the role of each pollutant in the presence of other pollutants, the investigators fit two-pollutant models that compared the effect estimates for the 2-day mean single-pollutant model with effect estimates adjusted for a second pollutant (ie, including a second pollutant in the analytic model).

To assess the robustness of the logistic regression for the repeated observations from individual patients, they reanalyzed the 2-day mean air pollutant associations using generalized estimating equations with a compound symmetric covariance structure (compatible with a random intercept in the logistic regression for each patient). (Compound symmetry produces a constant correlation of risk between days irrespective of their time separation [Zeger et al 1988].)

Pollutant Effects Possibly Modified by Patient Characteristics at the Time of ICD Implantation

To explore whether associations between air pollutants and arrhythmias were modified by patient characteristics, the investigators conducted stratum-specific and interaction analyses. These analyses sought to determine whether an air pollutant's effect on arrhythmias was modified by a specific patient characteristic. Patients were stratified by:

- distance of residence from the main HSPH monitoring site (ie, inside or outside Route 128, the inner beltway around Boston, which is approximately 10 to 25 km from the site);
- diagnosis at the time of ICD implantation (coronary artery disease compared with other cardiac diagnoses; ejection fraction $\leq$ 35% compared with > 35%; a previous MI or not); and
- cardiac medications prescribed: β-blockers, antiarrhythmics, and digoxin (on the basis of what patients reported at more than half of their clinical follow-up visits).

Because many of the patients were prescribed two or more cardiac medications, the investigators also assessed the modifying effects of all three classes of medications jointly on the associations between individual air pollutants and arrhythmias. They also examined interactions between an air pollutant and prescriptions for β-blockers, antiarrhythmics, and digoxin individually. They compared the estimated effects of the 2-day mean of an air pollutant among patients taking each type of cardiac medication (while adjusting for concurrent use of cardiac medications

in the other two classes) with the estimated effect obtained among patients who did not take any prescribed cardiac medications (the reference group).

Pollutant Effects Possibly Modified by Frequent and Recent Occurrence of Arrhythmic Episodes During Follow-Up

In their pilot study the investigators found that the small group of patients who had 10 or more episode-days had a stronger association with air pollutants than those with fewer episode-days (Peters et al 2000). Thus, the investigators used this criterion to stratify patients in the current study.

During the analysis of results from the current study, Dockery and colleagues found that having a recent arrhythmia was a strong predictor for having a subsequent arrhythmia of the same type. Thus, they stratified patients by whether or not a VA or SVA had been preceded by an arrhythmia of the same type within the previous 3 days.

RESULTS

CARDIAC EVENTS

ICDs recorded 1912 arrhythmic events among the 195 patients. The study cardiologist excluded 232 events as not meeting the criteria for an arrhythmia, and identified 1342 as VAs (most of which were ventricular tachycardia) and 346 as SVAs (most of which were atrial fibrillation). At least one VA or SVA was identified in 92 patients. Of these 92 patients, 72 (78%) had episodes on one or more days, 46 (50%) had episodes on five or more days, and 26 (28%) had episodes on 10 or more days.

The confirmed arrhythmias occurred on 772 episode-days out of a total possible 225,567 person-days in the study. Of these 772 episode-days, 659 (85%) were classified as days with VAs and 114 (15%) as days with SVAs (one patient was diagnosed with a VA and an SVA on the same day).

POLLUTANT-RELATED EFFECTS

The Commentary Table and the following paragraphs summarize the key results from the Investigators' Report of associations between specific pollutants and arrhythmias. The table shows associations between individual pollutants and arrhythmias from the principal analyses. In addition, from more exploratory analyses, possible modifications of the associations by the recent occurrence of an arrhythmic episode are also presented.

Particulate Pollutants

$PM_{2.5}$ For all arrhythmias combined and $PM_{2.5}$ concentrations in single-day lag analyses, effect estimates at lag days 0 and 1 were small and positive but not statistically

Commentary Table. Estimated Arrhythmic Effects per IQR Increase in 2-Day Mean of Pollutant Concentrations Plus Pollutant Effects as Modified by an Arrhythmia Within the Previous 3 Days[a]

Pollutant (IQR Increase in 2-Day Mean)	All Arrhythmias Combined	VAs	SVAs
$PM_{2.5}$ (7.0 μg/m^3)	1.09 (0.96 , 1.24)	1.07 (0.94 , 1.23)	1.23 (0.86 , 1.77)
$PM_{2.5}$ + arrhythmia within previous 3 days		1.60 (1.25 , 2.04)	1.18 (0.45 , 3.08)
BC (0.4 μg/m^3)	1.10 (0.90 , 1.36)	1.09 (0.87 , 1.36)	1.16 (0.68 , 1.99)
BC + arrhythmia within previous 3 days		1.74 (1.17 , 2.60)	1.41 (0.51 , 3.92)
NO_2 (7.7 ppb)	1.08 (0.96 , 1.20)	1.07 (0.95 , 1.21)	1.17 (0.89 , 1.53)
NO_2 + arrhythmia within previous 3 days		1.35 (1.07 , 1.69)	1.21 (0.71 , 2.05)
CO (0.48 ppm)	1.15 (0.95 , 1.38)	1.13 (0.92 , 1.39)	1.25 (0.78 , 2.01)
CO + arrhythmia within previous 3 days		1.64 (1.21 , 2.22)	1.01 (0.47 , 2.20)
SO_2 (4.0 ppb)	1.11 (1.00 , 1.24)	1.07 (0.95 , 1.21)	1.33 (1.04 , 1.70)
SO_2 + arrhythmia within previous 3 days		1.28 (1.05 , 1.55)	1.14 (0.66 , 1.95)
O_3 (15 ppb)	1.13 (0.95 , 1.35)	1.12 (0.93 , 1.35)	1.21 (0.79 , 1.87)
O_3 + arrhythmia within previous 3 days		1.05 (0.77 , 1.44)	1.52 (0.71 , 3.22)

[a] The day of and the day before the arrhythmia (lag days 0 and 1) were used to calculate the 2-day mean for each pollutant. The effect modification was estimated for a small subset of 26 patients who had had the same type of arrhythmia during the previous 3 days. Results are presented as ORs with 95% CIs in parentheses.

significant (OR = 1.07 with 95% CI = 0.94, 1.21 for lag day 0; and OR = 1.06 with 95% CI = 0.95, 1.20 for lag day 1; based on an IQR increase of 8.0 μg/m^3 $PM_{2.5}$; see Table 10). No positive associations were found with $PM_{2.5}$ concentrations lagged by 2 or 3 days.

For VAs and $PM_{2.5}$ concentrations, effect estimates at all lag times (both in single-day and distributed lag analyses) were similar to those reported for all arrhythmias combined (see Table 11).

The pattern was also similar for SVAs; however, estimates of $PM_{2.5}$ effects at lag days 0 and 1 in both the single-day and distributed lag analyses were, for the most part, slightly higher but had wider confidence intervals (ie, were less precise) than estimates reported for all arrhythmias or VAs. The largest estimates for SVAs were found for lag day 1 with both the single-day and distributed lag analyses, but again these were not statistically significant. No associations were found between $PM_{2.5}$ concentrations and SVAs at lag days 2 or 3.

Using the 2-day mean of lag days 0 and 1, estimates of $PM_{2.5}$ effects (based on an IQR increase of 7.0 μg/m^3) on all arrhythmias combined, VAs, or SVAs were similar to those reported for lag days 0 and 1 in the single-day analyses; that is, small and positive but not statistically significant for all arrhythmias and for VAs, but larger, positive, and also not significant for SVAs (Table 12).

BC Effect estimates for BC concentrations and all arrhythmias, VAs, and SVAs were similar in pattern and magnitude to estimates reported for $PM_{2.5}$ in the comparable analyses.

SO_4^{2-} and Ultrafine Particles Using the 2-day mean of lag days 0 and 1, estimates of SO_4^{2-} effects on all arrhythmias, VAs, and SVAs were small and positive but not statistically significant (Table 12). Estimates of ultrafine particle effects (ie, based on number of particles) were similar to those reported for SO_4^{2-}, except for a negative association between ultrafine particles and SVAs.

Gaseous Pollutants

SO_2 Considering all arrhythmias combined in single-day lag analyses (Table 10), estimates for SO_2 (IQR increase of 4.0 ppb) were positive for each lag day from 0 to 3 (OR range 1.06–1.14), with statistically significant associations for days 0, 2, and 3.

For SO_2 and VAs (Table 11), estimates were similar in magnitude to those found for all arrhythmias: Significant increases in VAs were associated with SO_2 concentrations lagged by 2 and 3 days (for single-day analyses) and on day 2 only (for distributed lag analyses).

For SO_2 and SVAs in single-day lag analyses (Table 11), estimates were larger (OR range 1.15–1.25) at all lag times than those for all arrhythmias and for VAs. In the single-day lag models, the effect estimate was statistically significant at lag day 1, and marginally significant for lag days 0 and 2. For SO_2 and SVAs in distributed lag analyses, estimates on individual days were smaller than those reported for the single-day lag analyses.

Using the 2-day mean of days 0 and 1 (Table 12), the SO_2 association was significant with SVAs (OR = 1.33; 95% CI = 1.04, 1.70) and marginally significant with all arrhythmias combined, but much weaker with VAs.

NO_2, CO, and O_3 Estimates of the effects of NO_2, CO, and O_3 (Table 10) on all arrhythmias combined were generally similar in single-day lag analyses to those reported for particulate pollutants; that is, weakly positive but not significant associations for lag days 0 and 1 (except for O_3), and no positive association at lag days 2 and 3. The increased relative risk associated with O_3 concentrations lagged by 1 day was marginally significant (OR = 1.16; 95% CI = 1.00, 1.34).

For NO_2, CO, and O_3 associations with VAs (Table 11), estimates were similar in magnitude to those found for all arrhythmias combined. For O_3 with VAs, the effect estimate for a 1-day lag time was marginally significant in single-day lag analyses (OR = 1.16; 95% CI = 0.99, 1.36) and significant in distributed lag analyses (OR = 1.22; 95% CI = 1.01, 1.47).

For NO_2, CO, and O_3 with SVAs (Table 11), estimates at lag days 0 and 1 were higher than estimates for all arrhythmias and for VAs.

Using the 2-day mean concentration of days 0 and 1, estimates of NO_2, CO, and O_3 associations with arrhythmias in every group were similar to those described for estimates at day 1 in the single-day lag analyses; estimates of effects on SVAs were higher than for other arrhythmias (Table 12).

OTHER ANALYTIC APPROACHES

The investigators used the 2-day running mean of pollutant concentrations at lag days 0 and 1 to estimate pollutant effects on VAs and SVAs in several additional analyses.

Generalized Estimating Equations

Accounting for repeated measures using generalized estimating equations (Table 13), estimates for all pollutants

with VAs and SVAs were more precise, but very similar to those derived from simple logistic analyses.

Multipollutant Models

Multipollutant regression models include as regressors (or explanatory variables) two or more indices of pollution (eg, O_3 and $PM_{2.5}$). The multipollutant models applied by Dockery and colleagues assume that each pollutant multiplies the risk by a constant amount, which is assumed not to vary across concentrations of the other pollutants in the model.

For VAs (Table 14), after adjusting for NO_2, CO, or SO_2, estimates for $PM_{2.5}$ were substantially lower. After adjusting for $PM_{2.5}$, the effect estimate for CO increased and was statistically significant (OR = 1.37; 95% CI = 1.03, 1.82). The effects of SO_2 were sensitive to including BC, and the effects of O_3 were sensitive to including $PM_{2.5}$.

For SVAs (Table 14), adjusting for $PM_{2.5}$ (also for BC) increased the statistically significant estimate for SO_2 found in the single-pollutant model (from OR = 1.33 [95% CI = 1.04, 1.70] to OR = 1.60 [95% CI = 1.12, 2.28]). The estimated effect of SO_2 was not sensitive to including any other pollutant in the model. After adjusting for SO_2, no associations were present for $PM_{2.5}$, CO, or NO_2, but the association with O_3 persisted. The effect of O_3 disappeared, however, when $PM_{2.5}$ was included in the model.

POLLUTANT EFFECTS MODIFIED BY PATIENT CHARACTERISTICS

To explore whether associations between air pollutants and VAs or SVAs were modified by patient characteristics, the investigators conducted evaluations of three possible diagnoses at the time of ICD implantation, cardiac medications prescribed, distance of residence from the main HSPH monitoring site, and having 10 or more episode-days. This last analysis they also conducted for all arrhythmias combined so they could compare the current results with those from their pilot study (Peters et al 2000); that study had shown that patients who had 10 or more episode-days had a stronger association with air pollutants than those with fewer episode-days.

The interaction statistical models applied by Dockery and colleagues estimate whether the effects of air pollutants would vary in magnitude according to other factors, such as patient characteristics. These interaction models assume that this variation is multiplicative; that is, that the joint effect on arrhythmias of air pollution exposure and, say, medication use is the product of the two individual estimates. The investigators present *P* values that quantify the compatibility of the observed results with this multiplicative assumption.

Frequent and Recent Occurrence of Arrhythmic Episodes

Frequent Days with Arrhythmic Episodes (Table 23) Frequent episodes was defined as 10 or more episode-days during the follow-up period. In addition to evaluating the frequency of VAs and SVAs separately, these analyses were performed for all arrhythmias combined in addition to VAs and SVAs so results could be compared with those from the pilot study (Peters et al 2000). For all arrhythmias combined, no strong differences were found between patients with more than and less than 10 episode-days for any pollutant except BC.

For VAs, among patients who had fewer than 10 episode-days, SO_2 and O_3 were only weakly associated with increased relative risks; CO was more strongly associated and indicated some multiplicative interaction. Among patients with more than 10 episode-days, weak associations with VAs were found for all pollutants.

For SVAs, SO_2 was the only pollutant with a substantially higher increase in relative risk among patients who had fewer than 10 episode-days but showed no interaction among patients with more than 10 episode-days. In contrast, BC, NO_2, CO, and O_3 (but not SO_2 or $PM_{2.5}$) showed stronger associations among those who had more than 10 episode-days; of these, multiplicative interactions were noted for BC, CO, and O_3.

Recent Arrhythmic Episodes (Table 24) A recent arrhythmia was defined as a patient having had the same type of an arrhythmia within the previous 3 days. For VAs in this time frame, strong interactions were noted; a VA within 3 days strongly and positively affected associations with all pollutants except O_3. For VAs earlier than 3 days, only O_3 showed a weakly positive effect. For SVAs, no consistent pattern of air pollutant associations was found whether or not an SVA had occurred within 3 days.

Distance of Residence from the Main HSPH Monitoring Site

As shown in Table 15, effect estimates of $PM_{2.5}$ and BC on VAs were greater for residents inside Route 128 than outside Route 128; for $PM_{2.5}$ and BC with SVAs, the opposite was found.

Effect estimates of O_3 and CO on VAs were greater for residents outside Route 128 than inside Route 128; estimates of NO_2 and SO_2 effects on VAs were very similar for those inside and outside Route 128.

For all pollutants except O_3, effect estimates for SVAs were larger for residents outside than inside Route 128; tests for interaction reached significance only for SO_2. Strong interaction was observed between O_3 and residence within or outside Route 128 for SVAs: the most positive association was estimated for those living inside Route 128, but a negative association was found for those living outside Route 128.

Diagnosis at ICD Implantation

Coronary Artery Disease Compared with Other Cardiac Diagnoses (Table 18) For VAs, these baseline diagnoses did not modify the effect of any air pollutant except CO, for which the relative risk doubled among those with diagnoses other than coronary artery disease.

For SVAs, relative risk estimates were higher for all pollutants among patients with diagnoses other than coronary artery disease, especially for CO and NO_2.

Previous MI (Table 17) NO_2 and SO_2 were positively associated with VAs among patients who had had an MI before ICD implantation; strong interactions were also noted for both NO_2 and SO_2. $PM_{2.5}$, BC, and O_3 were positively associated with VAs in both sets of patients (those who had had an MI and those who had not), but the associations were weak; no interactions were noted for any of these pollutants. CO had a weakly positive association with VAs among patients with a previous MI but this association was stronger among patients without a previous MI.

Every pollutant except O_3 was positively associated with SVAs among those without a previously reported MI; strong interaction was also noted with the associations for BC, NO_2, CO, and SO_2.

Low Ejection Fraction (Table 16) Ejection fraction was defined as low ($\leq$ 35%) or high (> 35%) as measured at the time of ICD implantation.

For VAs, among patients with high ejection fractions, a higher relative risk was associated with CO (and this interaction was strong) and with SO_2 (which showed no interaction effect). Low ejection fraction interacted strongly with O_3 only, which lead to an increased relative risk.

For SVAs, among patients with higher ejection fractions, significantly higher relative risks were associated with BC, CO, and SO_2, and nonsignificantly higher relative risks with $PM_{2.5}$. Strong interactions with ejection fraction were noted for BC and CO, and less pronounced interactions for $PM_{2.5}$; higher effect estimates were obtained for patients with higher ejection fractions. No interactions were observed for this diagnosis and other pollutants.

Prescribed Cardiac Medications

When evaluating whether taking cardiac medications influenced the effect of pollutants, the investigators first evaluated each category of cardiac medication separately, not taking into account other cardiac medications that patients were taking concurrently.

β-Blockers (Table 19) For VAs, increased relative risk estimates were noted with all pollutants among patients prescribed β-blockers; however no multiplicative interactions were noted.

For SVAs, all pollutants except BC were associated with increased relative risk estimates among patients not prescribed β-blockers. Interactions with these medications were strong for NO_2, SO_2, and CO.

Antiarrhythmic Drugs (Table 20) For VAs, effect modification by use of antiarrhythmics varied according to the pollutant, but no multiplicative interaction was noted.

For SVAs, of all pollutants only BC had a larger relative risk estimate among patients who did not report taking antiarrhythmics than among those who did. However, tests for interaction were negative.

Digoxin (Table 21) The use of digoxin produced no consistent pattern of effect modification for VAs in association with any air pollutant.

For SVAs, increased relative risks were observed for NO_2 among those prescribed digoxin, and with SO_2, CO, $PM_{2.5}$, and BC among those not taking digoxin; however, no multiplicative interaction was noted.

Prescribed Medications Taken Concurrently (Table 22) Most patients reported taking several types of cardiac medications. It is possible that an effect of one medication on the association between a pollutant and arrhythmias might be influenced by other types of medication taken concurrently. Therefore the investigators also evaluated how each category of medication might influence effects found with a single medication when evaluated simultaneously in the same analytic model.

In this combined analysis, results of pollutant effects among patients taking each cardiac medication were compared with the results obtained for patients who did not take any cardiac medications (Table 22). Comparisons can also be made with results presented in Tables 19 through 21, which present results for individual categories of medications without adjusting for the others.

For VAs, adjusting for medications prescribed concurrently with β-blockers produced little evidence that any association found between any air pollutant and β-blockers

was modified. Some suggestion of an effect was noted for antiarrhythmics and digoxin with CO; however, the estimates were imprecise.

For SVAs, among patients who reported taking no cardiac drugs, strong positive associations were found, especially for the effects of NO_2, CO, and SO_2. Compared with results from the group taking no drugs, results from patients who took medications indicated that, when adjusted for all other cardiac medications in the model, only β-blockers were associated with substantial decreases in the effects of all pollutants except BC.

When compared with results that did not adjust for other cardiac medications, digoxin was associated with decreased relative risks for BC, and with greater decreases in relative risks for $PM_{2.5}$, CO, and SO_2. In this same comparison, antiarrhythmics were associated with decreased relative risk estimates for BC, NO_2, CO, and O_3.

DISCUSSION

The study investigated specific hypotheses about ambient pollutant concentrations and the induction of a major clinical endpoint, nonfatal cardiac arrhythmia, among a population potentially susceptible to air pollution: patients with cardiac or cardiovascular disease who had had an ICD implanted. (The arrhythmias studied may have been fatal were it not for the interventions of the implanted ICDs.) The investigators were able to assess these associations by taking advantage of the fact that ICDs provide a dated and timed record of the type of arrhythmia and the therapy that occurred at each event.

The investigators designed, conducted, and reported the study with care. They obtained and evaluated data for several ambient pollutants, both particulate and gaseous. They adjusted the associations they reported for effects of different confounders (such as meteorologic conditions and other pollutants) and also evaluated the modifying effects of several patient characteristics (including preexisting clinical conditions and prescribed cardiac medications).

This is the first published study in which a cardiologist evaluated the ICD tracings to determine whether each recorded event was, in fact, an arrhythmia. It is also the first in which a cardiologist attempted to distinguish the origin of the verified arrhythmia as ventricular or supraventricular. Thus, the investigators were able to assess the effects of individual pollutants not only on all arrhythmic events, but also on arrhythmias that had originated in either the ventricles or the atria.

KEY RESULTS AND COMPARISONS WITH THE PILOT STUDY

Main Analyses of Particulate Pollutants and Arrhythmias

The principal pollutant analyses—single-day, mean 2-day, and distributed lag models—indicated that nonfatal arrhythmic events were weakly and not significantly associated with ambient concentrations of $PM_{2.5}$ or BC at any lag time up to 3 days before the event.

The weak associations reported for $PM_{2.5}$ in the current study are similar to those reported in Dockery and colleagues' pilot study (Peters et al 2000). Taken together the two studies suggest little or no association between arrhythmias and $PM_{2.5}$ concentrations on the same day or up to 3 days before the event. In addition, as we describe below in more detail, results from the current study do not support the pilot study's result of a stronger association between $PM_{2.5}$ and ICD discharges in the small subgroup of patients who had multiple arrhythmias (6 people with 10 or more events).

Because the investigators obtained only a limited amount of monitoring data on concentrations of SO_4^{2-} and ultrafine particles in the current study, it is difficult to draw conclusions about the associations between these PM components and arrhythmia induction in the limited set of analyses reported. In a subsequent analysis of the data that included additional patients and used distinct statistical approaches, Dockery and colleagues (2005) did report a marginally significant association between SO_4^{2-} and VAs that occurred within 3 days of a prior arrhythmia; they found no statistically significant association between the number of particles (an indicator of ultrafine particles) and VAs (Dockery et al 2005).

Main Analyses of Gaseous Pollutants and Arrhythmias

Of all of the pollutants evaluated, SO_2 showed the most statistically significant, robust, and generally strongest effects in that they were significantly associated with arrhythmias on the day of and 2 and 3 days before the event. This result differs from the results of the pilot study, in which the association between SO_2 and ICD discharges was not statistically significant (Peters et al 2000). It is not clear, however, whether the associations reported for SO_2 and arrhythmias are due to SO_2 per se or whether SO_2 may be a marker for some other pollutant, as has been suggested by studies of personal exposure to different pollutants (Sarnat et al 2000, 2005).

In addition, in the current study, NO_2 overall showed weak or no association with arrhythmias. In the pilot study NO_2 was the only pollutant, gaseous or particulate, to be

associated with ICD discharges (strongest association for a 1-day lag time and the 5-day mean).

The sources that emit the different pollutants are not clear. In the Boston area where the current study was conducted, NO_2, CO, and $PM_{2.5}$ are associated primarily with vehicular emissions, but SO_2 is associated primarily with stationary sources. Methods are needed to accurately identify the sources of emissions and to evaluate the relative contributions to health effects from stationary and mobile sources.

Differences in Design and Analysis Between the Current and Pilot Studies

In the current study, at least one arrhythmia was detected in 92 patients (of 195) during the period of observation (up to 7 years) compared with one ICD discharge in only 33 patients (100 patients followed for up to 3 years) in the pilot study. Therefore, the power to detect effects should have been substantially greater in the current study.

In addition to having more patients and more events to evaluate in the current study, the investigators also made improvements to the earlier study's design by verifying that ICD discharges were indeed associated with arrhythmias and excluding those that were not (12% of discharges). Given this percentage of false positive recordings, other studies of ICD events that have relied solely on ICD discharges have most likely included some events that were not arrhythmias. In the current study, inspecting all electrograms and R–R intervals recorded by the ICDs also allowed the investigators to include arrhythmias that had not stimulated ICD discharges and to attempt to distinguish VAs from SVAs; neither of these had been done in the pilot or other studies.

Interpretation of ICD Electrograms

Evaluating associations between pollutant concentrations and different types of arrhythmias was an important feature of this study. The majority of recorded events and arrhythmias (85%) were diagnosed as ventricular in origin. ICDs are designed to respond to life-threatening VAs, which are clinically significant; having had one is frequently a reason for implanting an ICD. One would therefore expect that the statistical power to detect an effect would be substantially greater for VAs than SVAs. However, in the main analyses the investigators performed, only weak associations were found between air pollutants and VAs. (As we discuss below, however, pollutants were more strongly associated with VAs among patients who had had an arrhythmia within the previous 3 days.) The statistically significant associations found for air pollutants in this study were predominantly with SVAs, which are considered less clinically important and are not the primary indicator for monitoring patients with ICDs.

ICDs are programmed to react to rapid heart rhythms; when these occur, they most frequently originate in the ventricles. Most SVAs, however, which originate in the atria, would not be expected to have a ventricular rhythm rapid enough to trigger an ICD discharge. Thus, most SVAs would have gone undetected in this study because they did not lead to a ventricular response rapid enough to be recorded by the ICD. Only the smaller subset of atrial arrhythmias with rapid ventricular responses, which are unlikely to be representative of all atrial events, were likely to have been evaluated in the current study. For these reasons, some caution should be used in extrapolating these results to SVAs in general.

The criteria the study cardiologist used to categorize arrhythmias were appropriate; for example, heart beat rates and patterns to identify ventricular tachycardias and fibrillations. However, identifying the heart chamber in which an arrhythmia originates is more straightforward in dual-chamber ICDs, which monitor both the ventricle and the atrium, than in single-chamber devices, which monitor only the ventricle. In this study, most of the patients (81%) had single-chamber ICDs, and yet were diagnosed with SVAs nearly three times as often as those with dual-chamber devices. This suggests that SVAs assessed from single-chamber tracings may have been more often misclassified than those from dual-chamber devices.

One factor in the ICD design further complicates interpreting ICD recordings. The storage capacity of the ICD limits the number of electrogram tracings that can be recorded. Thus if a patient had a large number of arrhythmias between clinical visits, the ICD may have overwritten the oldest electrograms. Although the R–R intervals remained in storage, the ability to distinguish VAs from SVAs from just the intervals is not possible.

Effect Modifications

Analyses to evaluate how patient characteristics might modify pollutant effects on arrhythmias yielded some interesting and unexpected suggestions that may merit pursuit in future studies. These subgroup analyses suggested that a recent arrhythmic event and the use of medications could significantly modify the reported associations between pollutants and arrhythmias. For $PM_{2.5}$ and BC in particular, but also for the gaseous pollutants except O_3, people who had had a VA within the previous 3 days had an increased relative risk of having another VA. This result suggests that the heart may be somehow primed to be more susceptible to air pollution

effects in the period shortly after a VA. No such effect was observed with SVAs.

The estimated relative risk of SVAs but not VAs was decreased for most pollutants among patients taking β-blockers. However, when interpreting the modifying effects of medications such as β-blockers, it is not clear whether these are attributable to the medication or to the condition for which the medication is prescribed.

Note, though, that in the current study medication use was recorded on the basis of whether the patient reported taking a particular medication at more than half of their follow-up visits. In future studies, an understanding of visit-specific medication use would be more informative. For example, patients taking a β-blocker for 9 of 10 visits may have had an arrhythmia during the one period when they were not taking the drug. Such an event may change the effect of β-blockers on the association between pollutants and arrhythmias.

In addition, records of medications in the current study did not include noncardiac medications that can affect arrhythmias. Some commonly prescribed medications such as tricyclic antidepressants, several antibiotics, and tamoxifen are known or suspected to be associated with arrhythmias (Liu and Juurlink 2004); others, such as statins used to lower serum cholesterol, are antiarrhythmic (Mitchell et al 2003). It is not clear how taking these medications might have affected the results of the current study.

One unexpected result was related to arrhythmias and the distance of residence from the main HSPH monitoring site. As is often done in this type of epidemiologic study, the investigators relied on a single central monitor for $PM_{2.5}$ and ultrafine particles to derive estimates of exposure for people living in a wide geographical area (thousands of square miles). It is not known how well pollutant concentrations at monitors represent exposure for the target population. Based on the results of Zeger and colleagues (2000) in the National Morbidity, Mortality, and Air Pollution Study, the typical outcome of this type of measurement error is to bias any estimate of effect of pollutants toward the null value of no effect. In the Dockery study, one might therefore have expected that pollutant concentrations recorded by the monitors would provide a more accurate estimate of exposure for those living closer to the monitoring site and a less accurate estimate with increasing distance away from it. This would mean a higher estimated effect from pollutants for those living closer and a lower estimated effect for those living furthest away. In accordance with this premise, results suggested positive associations for $PM_{2.5}$ and BC with VAs only among those living closer to the monitors. In contrast, however, analyses for all pollutants except O_3 with SVAs showed larger associations for those living further away. What underlies the increase in magnitude for the association among pollutants, arrhythmias, and distance from the central monitor is not clear.

Most other analyses of patient characteristics, such as frequency of arrhythmias or diagnosis at ICD implantation, did not find important modifications of effects; this suggests that these factors may not play a role in modifying air pollutant effects, or that an insufficient number of subjects did not allow unequivocal conclusions to be drawn. As we noted, the lack of association in the current study between pollutants and frequent arrhythmias (all arrhythmias combined, VAs, or SVAs among 26 patients who had 10 or more episode-days), differs from the result in the pilot study. In that study, the 6 patients who had 10 or more ICD discharges had stronger associations with $PM_{2.5}$ concentrations than the total study group (Peters et al 2000). The reasons for the differences in results between the studies are not clear: the studies did have different lengths of follow-up and the current study relied on confirmed arrhythmias rather than ICD discharges. Nevertheless, the differences between the studies' findings suggest caution in interpreting these results.

As noted in the Results section above, however, the one analysis of patient characteristics that did find increases in the size and statistical significance of the associations was that done for a particular subgroup of those individuals who had had a recent previous arrhythmia (ie, within 3 days).

RESULTS OF OTHER STUDIES OF AIR POLLUTANTS AND CARDIOVASCULAR OUTCOMES

Since this study started in 1998, some epidemiologic and cohort studies have found a positive association between PM or other air pollutants and cardiovascular health outcomes (eg, Liao et al 1999; Peters et al 2000, 2001; Hoek et al 2001; Hoek 2003; Magari et al 2001; Pope et al 2004), but others have not (Checkoway et al 2000; Levy et al 2001; Rich et al 2004; Vedal et al 2004; Peters et al 2005; Sullivan et al 2005). Many of these studies and toxicologic studies of PM effects on cardiovascular outcomes were discussed in a recent review (Brook et al 2004). Here, we focus on other epidemiologic studies of air pollutants and arrhythmia in patients with ICDs (Rich et al 2004; Vedal et al 2004).

Studies in Vancouver, Canada, that evaluated the effect of air pollutant concentrations on ICD-recorded discharges among 150 patients reported results similar to the overall results found in the current study (Rich et al 2004; Vedal et al 2004). Using logistic regression analysis in a subset of 50 patients with at least one recorded ICD discharge, Vedal and colleagues (2004) reported no positive associations

between ICD discharge and concentrations of PM_{10}, O_3, CO, NO_2, or SO_2. However, among 16 of the 50 patients with at least two ICD discharges per year and who had been followed for at least 6 months, an increase in SO_2 concentrations at lag day 2 during the winter was associated with a 20% increase in relative risk of ICD discharge; a less pronounced increase was observed at lag day 3. Positive but weaker and nonsignificant associations were also observed for O_3 at lag day 0, NO_2 at lag day 2, and PM_{10} at lag days 0 and 2. The results regarding SO_2 are therefore somewhat consistent with those of the current study.

Rich and associates (2004) used bidirectional case–crossover analyses with a subset of patients who had had at least one ICD discharge in 10 months of follow-up, during which time detailed particle composition data (including elemental carbon and organic carbon) were available. The study cardiologist excluded inappropriate events, such as a patient assault and an exogenous electrical shock. The investigators found no positive association with $PM_{2.5}$ concentrations at lag days 0 to 3, nor with SO_4^{2-}, CO, NO_2 or SO_2. Same-day increases in SO_2 and CO doubled the relative risk of ICD discharges only in the summer. O_3 concentrations were associated with arrhythmias only during the winter, whereas little or no positive association was observed for elemental carbon, organic carbon, SO_4^{2-}, and CO in the summer.

SUMMARY AND CONCLUSIONS

Overall, results of this study indicate that among patients who have an implanted ICD, ambient concentrations of $PM_{2.5}$ or BC on the day of or up to 3 days before the event are only weakly, if at all, associated with the induction of nonfatal arrhythmias. These results reported for particulate pollutants largely parallel those described in the investigators' earlier pilot study in the Boston area (Peters et al 2000). Thus, these results do not provide much support for one of the investigators' main hypotheses, that increased ambient concentrations of particulate air pollutants would be associated with increased incidence of arrhythmias. For SO_4^{2-} and ultrafine particles, fewer measurements were made and not many analyses were performed or reported; thus, conclusions are difficult to draw from the results in this report about associations between these particulate pollutants and arrhythmias.

Compared with all other pollutants, associations between arrhythmias and SO_2—a pollutant derived primarily from stationary sources in this study area—were more likely to be statistically significant and more robust, especially for SVAs. It is not clear, however, whether the associations reported for SO_2 and arrhythmias are due to SO_2 per se or reflect the activity of another pollutant associated with SO_2. NO_2, CO, and O_3 showed weak associations with all arrhythmias combined; these were similar to those reported for particulate pollutants. These results differ from the pilot study in which NO_2 was the only pollutant, gaseous or particulate, to be significantly associated with ICD discharges in the overall study population.

A strength of this study was the care taken to characterize the tracings recorded by the ICDs. This allowed nonarrhythmic events to be excluded from the analyses and VAs to be distinguished from SVAs. As expected, the majority of arrhythmias identified were ventricular in origin. Thus, effect estimates for particulate or gaseous pollutants and VAs were similar to those reported for all arrhythmias combined.

Overall, the estimated effects of particulate pollutants and SO_2 on SVAs were larger (statistically significant only for SO_2) than those reported for VAs and for all arrhythmias combined. These results are intriguing and suggest new avenues for research on the cardiovascular effects of air pollution.

The results about SVAs should be interpreted with caution, however. Of the tracings recorded, those identified as SVAs comprised only 15%; thus the statistical power to draw conclusions about associations between pollutant concentrations and this type of arrhythmia is somewhat low. In addition, the SVAs recorded by ICDs used in this study are only a small set of the total SVAs that actually occurred because most patients (81%) were fitted with single-chamber ICDs. These devices monitor only the ventricle and are triggered by arrhythmias that originate in the atrium only if the corresponding ventricular rate is fast enough to stimulate an ICD discharge. Thus, when reviewing the tracings recorded by a single-chamber ICD, only the SVAs that initiated a recording in advance of an ICD discharge (ie, those associated with a rapid ventricular response) could have been included. Rarely, SVAs may have been misclassified as VAs. Therefore, most SVAs in patients with single-chamber ICDs would not have been recognized and some might have been misclassified.

Another strength of this study was using information on the patients' cardiac histories, cardiac functions, and prescribed medications to explore whether these characteristics would modify the effects of pollutants. Possibly of most clinical significance, several pollutants—$PM_{2.5}$, BC, NO_2, CO, and SO_2—showed a significant positive association with VAs among patients who had also had a VA within the previous 3 days. In studies in which multiple subgroup analyses are performed, some results may be due to chance; thus, these associations should be interpreted

cautiously. Given that the results were similar for many of the pollutants, they also increase the challenge of determining whether a particular pollutant or source may be responsible for the observed associations or may vary simultaneously over time with the responsible pollutant or pollutants. Nonetheless, these results suggest that air pollutant effects may be most important for individuals in whom cardiac electrophysiology is most compromised.

Although the results of this study are not definitive, most likely due to the modest number of arrhythmias observed, they suggest avenues for further research that could be fruitful. Obviously, a study in which a substantially larger number of arrhythmias are recorded, through increasing the number of subjects involved, the length of follow-up, or both, is needed. The results also indicate that future studies need to pay careful attention to distinguishing SVAs from VAs. Newer generations of ICDs should facilitate making this distinction. Given the intriguing results related to SVAs, other methods for investigating the effects of exposure to pollution on this common subset of cardiac arrhythmias should be sought. At this point it is still not clear whether effects on cardiac arrhythmias is an important mechanism through which exposure to air pollution, and especially particulate pollutants, exerts an effect on cardiovascular conditions.

ACKNOWLEDGMENTS

The Health Review Committee thanks the ad hoc reviewers for their help in evaluating the scientific merit of the Investigators' Report. The Committee is also grateful to Aaron Cohen for his oversight of the study; to Joan Sordillo for help in preparing the initial draft of the Commentary; to Geoffrey Sunshine and Cristina I Cann for preparing and finalizing the Commentary; to Virgi Hepner for science editing of the Report and this Commentary; and to Melissa R Harke, Fred Howe, Jenny Lamont, Kasey Oliver, and Ruth E Shaw for their roles in publishing this Research Report.

REFERENCES

Brook RD, Franklin B, Cascio W, Hong Y, Howard G, Lipsett M, Luepker R, Mittleman M, Samet J, Smith SC Jr, Tager I. 2004. Air pollution and cardiovascular disease: A statement for healthcare professionals from the Expert Panel on Population and Prevention Science of the American Heart Association. Circulation 109(21):2655–2671.

Burnett RT, Dales R, Krewski D, Vincent R, Dann T, Brook JR. 1995. Associations between ambient particulate sulfate and admissions to Ontario hospitals for cardiac and respiratory diseases. Am J Epidemiol 142:15–22.

Checkoway H, Levy D, Sheppard L, Kaufman J, Koenig J, Siscovick D. 2000. A case-crossover analysis of fine particulate matter air pollution and out-of-hospital sudden cardiac arrest. Research Report 99. Health Effects Institute, Cambridge MA.

Dockery DW, Luttman-Gibson H, Rich DQ, Link MS, Mittleman MA, Gold DR, Koutrakis P, Schwartz JD, Verrier RL. 2005. Association of air pollution with increased incidence of ventricular tachyarrhythmias recorded by implanted cardioverter defibrillators. Environ Health Perspect 113:670–674.

Dockery DW, Pope CA III, Xu X, Spengler JD, Ware JH, Fay ME, Ferris BG Jr, Speizer FE. 1993. An association between air pollution and mortality in six US cities. N Engl J Med 329:1753–1759.

Gregoratos G, Abrams J, Epstein AE, Freedman RA, Hayes DL, Hlatky MA, Kerber RE, Naccarelli GV, Schoenfeld MH, Silka MJ, Winters SL, Gibbons RJ, Antman EM, Alpert JS, Gregoratos G, Hiratzka LF, Faxon DP, Jacobs AK, Fuster V, Smith SC Jr. 2002. ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices: Summary article (a report of the American College of Cardiology/American Heart Association / North American Society for Pacing and Electrophysiology Task Force on Practice Guidelines). Circulation 109:2655–2671.

Hoek G. 2003. Daily mortality and air pollution in the Netherlands. In: Revised Analyses of Time-Series Studies of Air Pollution and Health, pp 133–141. Special Report. Health Effects Institute, Boston MA.

Hoek G, Brunekreef B, Fischer P, van Wijnen J. 2001. The association between air pollution and heart failure, arrhythmia, embolism, thrombosis, and other cardiovascular causes of death in a time series study. Epidemiology 12:355–357.

Levy S. 1998. Epidemiology and classification of atrial fibrillation. J Cardiovasc Electrophysiol 9(Suppl 8): S78–82.

Levy D, Sheppard L, Checkoway H, Kaufman J, Lumley T, Koenig J, Siscovick D. 2001. A case-crossover analysis of particulate matter air pollution and out-of-hospital primary cardiac arrest. Epidemiology 12:193–199.

Liao D, Creason J, Shy C, Williams R, Watts R, Zweidinger R. 1999. Daily variation of particulate air pollution and

poor cardiac autonomic control in the elderly. Environ Health Perspect 107:521–525.

Liu BA, Juurlink DN. 2004. Drugs and the QT interval—Caveat doctor. N Engl J Med 351:1053–1056.

Magari SR, Hauser R, Schwartz J, Williams PL, Smith TJ, Christiani DC. 2001. Association of heart rate variability with occupational and environmental exposure to particulate air pollution. Circulation 104:986–991.

Mitchell LB, Powell JL, Gillis AM, Kehl V, Hallstrom AP, and the AVID investigators. 2003. Are lipid-lowering drugs also antiarrhythmic drugs? An analysis of the antiarrythmias versus implantable defibrillators (AVID) trial. Am J Coll Cardiol 42:88–92.

Morris RD, Naumova EN, Munasinghe RL. 1995. Ambient air pollution and hospitalization for congestive heart failure among elderly people in seven large US cities. Am J Public Health 85:1361–1365.

Oh JA. 2000. Characterization and Source Apportionment of Air Pollution in Nashville, TN and Boston, MA [dissertation]. Harvard School of Public Health, Boston MA.

Peters A, Dockery DW, Muller JE, Mittleman MA. 2001. Increased particulate air pollution and the triggering of myocardial infarction. Circulation 103:2810–2815.

Peters A, Liu E, Verrier RL, Schwartz J, Gold DR, Mittleman M, Baliff J, Oh JA, Allen G, Monaham K, Dockery DW. 2000. Air pollution and incidence of cardiac arrhythmia. Epidemiology 11:11–17.

Peters A, von Klot S, Heier M, Trentinaglia I, Cyrys J, Hörmann A, Hauptmann M, Wichmann HE, Löwel H. 2005. *Particulate Air Pollution and Nonfatal Cardiac Events, Part I. Air Pollution, Personal Activities, and Onset of Myocardial Infarction in a Case–Crossover Study.* Research Report 124. Health Effects Institute, Boston MA.

Poloniecki JD, Atkinson RW, de Leon AP, Anderson HR. 1997. Daily time series for cardiovascular hospital admissions and previous day's air pollution in London, UK. Occup Environ Med 54:535–540.

Pope CA III, Burnett RT, Thurston GD, Thun MJ, Calle EE, Krewski D, Godleski JJ. 2004. Cardiovascular mortality and long-term exposure to particulate air pollution: Epidemiological evidence of general pathophysiological pathways of disease. Circulation 109:71–77.

Pope CA III, Schwartz J. 1996. Time series for the analysis of pulmonary health data. Am J Respir Crit Care Med 154:S229–233.

Pope CA III, Thun MJ, Namboodiri MM, Dockery DW, Evans JS, Speizer FE, Heath CW Jr. 1995. Particulate air pollution as a predictor of mortality in a prospective study of US adults. Am J Respir Crit Care Med 151(3 Pt 1):669–674.

Pritchett EL. 1992. Management of atrial fibrillation. N Engl J Med 326:1264–1271.

Rich KE, Petkau J, Vedal S, Brauer M. 2004. A case-crossover analysis of particulate air pollution and cardiac arrhythmia in patients with implantable cardioverter defibrillators. Inhal Toxicol 16(6–7):363–372.

Sarnat JA, Brown KW, Schwartz J, Coull BA, Koutrakis P. 2005. Ambient gas concentrations and personal particulate matter exposures: Implications for studying the health effects of particles. Epidemiology 16:385–395.

Sarnat JA, Koutrakis P, Suh HH. 2000. Assessing the relationship between personal particulate and gaseous exposures of senior citizens living in Baltimore, MD. J Air Waste Manag Assoc 50:1184–1198.

Schwartz J. 1997. Air pollution and hospital admissions for cardiovascular disease in Tucson. Epidemiology 8:371–377.

Schwartz J, Morris R. 1995. Air pollution and hospital admissions for cardiovascular disease in Detroit, Michigan. Am J Epidemiol 142:23–35.

Sullivan J, Sheppard L, Schreuder A, Ishikawa N, Siscovick D, Kaufman J. 2005. Relation between short-term fine-particulate matter exposure and onset of myocardial infarction. Epidemiology 16:41–48.

Vedal S, Rich K, Brauer M, White R, Petkau J. 2004. Air pollution and cardiac arrhythmias in patients with implantable cardioverter defibrillators. Inhal Toxicol 16:353–362.

Zeger SL, Liang KY, Albert PS. 1988. Models for longitudinal data: A generalized estimating equation approach. Biometrics 44:1049–1060.

Zeger SL, Thomas D, Dominici F, Samet JM, Schwartz J, Dockery DW, Cohen A. 2000. Section I: Exposure Measurement Error in Time-Series Studies of Air Pollution. In: The National Morbidity, Mortality, and Air Pollution Study, Part I: Methods and Methodologic Issues, pp 15–27. Research Report 94. Health Effects Institute, Cambridge MA.

Integrative Discussion of the Peters and Dockery Studies

Health Review Committee

STUDIES OF POLLUTANT EFFECTS ON CARDIOVASCULAR FUNCTION

The HEI studies by Drs Annette Peters and Douglas Dockery (HEI Research Report 124 Parts I and II) were conducted amid growing interest about the possible effects of air pollutants on mortality and morbidity due to cardiovascular disease. Much of the research conducted since the middle of the twentieth century on the health effects of air pollution had focused on the respiratory system. By the late 1990s, however, when HEI funded this research, a number of studies had reported associations between short-term exposure to air pollution and cardiovascular disease; these associations had been found for both daily mortality and hospital admissions (eg, Schwartz and Morris 1995; Poloniecki et al 1997; Pope and Dockery 1999). Cohort studies had also reported associations between long-term average exposure and mortality from chronic cardiorespiratory diseases (Dockery et al 1993; Pope et al 1995). Toxicologic studies, some funded by HEI (eg, Godleski et al 1997), had begun to explore the biologic plausibility of the epidemiologic results and to suggest possible mechanisms through which short-term exposure to particulate air pollution might increase the risk of mortality from cardiovascular disease.

HEI funded epidemiologic studies such as those led by Drs Dockery and Peters to undertake more rigorous assessments of the effects of short-term exposure to air pollutants by using detailed information about individuals with specific forms of cardiovascular disease (Request for Applications 98-1; Health Effects Institute 1998). In addition, HEI hoped that continuing research might further illuminate the possible pathophysiologic pathways that might be initiated by exposure to particulate matter (PM*).

In recent years, two reviews of current literature have described the range of epidemiologic and controlled exposure studies with humans and other species that have evaluated the effects of PM, especially on cardiovascular responses (World Health Organization 2003; Brook et al 2004). Many of the studies described in those reviews are also referenced in the Peters and Dockery Investigators' Reports and the accompanying Health Review Committee's Commentaries. The Commentaries also refer to more recent studies that have evaluated associations between short-term exposure to air pollutants and the rapid onset of arrhythmias and myocardial infarctions (MIs) (the cardiac conditions investigated by Dockery and Peters; Rich et al 2004; Vedal et al 2004; Sullivan et al 2005).

Other recent studies have started to assess directly the cardiovascular effects of exposure to known traffic-related emissions. These studies have evaluated effects in laboratory animals exposed to particles close to major roadways (Kleinman et al 2003; Hamade et al 2005) and have measured personal pollutant exposures and electrocardiographic and inflammatory changes among police patrolmen before, during, and after long driving shifts (Riediker et al 2004a,b).

The results from studies of pollutants, cardiovascular events, and possible pathophysiologic mechanisms for specific outcomes are inconsistent. Thus, summarizing all the related information is challenging. Differences among study findings can result from the characteristics of the study populations (eg, level of health or underlying conditions, age, and gender); the composition and concentration of the pollutant mixture and its sources in different study locations; the cardiovascular endpoints measured; the sensitivities of assays for different indicators measured in vivo and in vitro; and the statistical analyses performed.

The intent of this brief Integrated Discussion is to place the Peters and Dockery studies in the context of ongoing research, to indicate how they have contributed information to this field of inquiry, and to describe potentially informative avenues of research suggested by their results.

DESIGN AND CONDUCT OF THE PETERS AND DOCKERY STUDIES

KEY FEATURES

The key features are summarized in the Integrative Discussion Table. Both studies hypothesized that exposure to specific size fractions of PM would induce within hours an important nonfatal cardiovascular event (MI in the Peters

* List of abbreviations and other terms appear at the end of the Investigators' Reports.

Integrative Discussion Table. Comparison of the Peters and Dockery Studies

	Peters	Dockery
Principal hypothesis	Exposure to PM—particularly ultrafine particles—induces a nonfatal MI within a few hours	Exposure to $PM_{2.5}$ acutely induces arrhythmia in patients with ICDs
Clinical endpoint	Induction of nonfatal MI	Confirmed arrhythmia
Study population	Patients in Augsburg, Germany, who had a nonfatal MI recorded in one of the area hospitals; part of a prospective Cardiac Registry study	Patients with ICDs treated at a cardiac center in Boston MA
Study design	Case–crossover as main analysis	Time-series analysis
Pollutants measured	Ultrafine particles, $PM_{2.5}$, and PM_{10}; NO_2, CO, SO_2, and O_3	$PM_{2.5}$ and BC; NO_2, CO, SO_2, and O_3; few measurements of ultrafine particles and sulfate
Other key points	• Interviews after MIs assessed the possible association between MI induction and activities shortly before the event	• Study cardiologist evaluated ICD electrogram tracings to confirm arrhythmic events and categorize them as SVAs or VAs according to origin • Evaluated multiplicative interactions between pollutant effects and important clinical factors, such as cardiac function at ICD implantation and cardiac medications prescribed during follow-up
Main results	• No positive association between MI onset and ultrafine particle number up to 6 hours and up to 5 days earlier • No positive association between MI onset and $PM_{2.5}$ concurrently (0 hour) or up to 6 hours earlier; positive associations (OR 1.05–1.18) with $PM_{2.5}$ at lag day 2 (effect estimates varied depending on the analytic method) • Weak associations (OR < 1.10) between MI onset and CO, SO_2, and NO_2 on different lag days, but not with O_3 • ORs given below for 1 hour before MI onset: Strong associations between MI onset and engaging in strenuous activities in the hours before MI onset (OR 8.1); consistent but less pronounced associations for engaging in less strenuous activities (OR 2.8), for time spent outdoors (OR 4.1), and for time spent in traffic (OR 3.1); magnitude of effect estimates for these activities were much greater than the magnitude of effect estimates for $PM_{2.5}$	• Weak positive nonsignificant associations (OR < 1.10) for $PM_{2.5}$ or BC at lag days 0, 1, 2, or 3 with all arrhythmias combined and with VAs; larger positive nonsignificant associations for $PM_{2.5}$ or BC with SVAs; similar findings for CO, NO_2, and SO_2 • Weak positive associations (OR range 1.06–1.14) for SO_2 at lag days 0, 1, 2, and 3 with all arrhythmias combined or with VAs—statistically significant for lag days 2 and 3; somewhat larger associations (OR range 1.15–1.25) for SO_2 with SVAs • Stronger associations (OR range 1.28–1.74 depending on the pollutant) for $PM_{2.5}$, BC, SO_2, CO, and NO_2 with VAs among patients who had had an arrhythmia of the same type within the previous 3 days

study; arrhythmia in the Dockery study). Both groups studied associations between acute induction of the cardiovascular event and concentrations of gaseous pollutants and of different size fractions and components of PM; they examined these associations in a range of specified times before the event. The data from each study, however, provided little or no support for the main hypotheses.

STRENGTHS AND LIMITATIONS OF THE STUDIES

Both studies were appropriately designed and conducted to test specific well-defined hypotheses. They both gained insight into the associations between air pollutant concentrations measured in the community and the induction of two clinically important cardiac events. MIs and arrhythmias are clinically relevant because they are

responsible for the majority of all cardiovascular deaths; even when not fatal, they are generally manifestations of severe underlying chronic cardiovascular conditions.

However, the studies also shared some limitations that may have hampered the ability to detect possible associations between pollutant concentrations and the cardiac events of interest and therefore to draw conclusions on the basis of the results.

Exposure Measurement Error

Both studies were limited by the method used to measure exposure; each relied on a single central monitor for concentrations of $PM_{2.5}$ ($PM \leq 2.5$ µm in aerodynamic diameter; fine particles) and ultrafine particles to derive estimates of exposure for a wide geographical area (several hundred square miles in each study). It is not known how well central-site monitors represent the actual exposure of individuals and therefore may introduce measurement error. Based on the results of Zeger and colleagues (2000) in the National Morbidity and Mortality Air Pollution Study, the typical result of this type of measurement error is to bias any estimate of effect toward the null value of no effect.

In the Dockery study, one might therefore have expected more measurement error with increasing distance from the monitoring site and, hence, a lower estimated effect for those living furthest away. This was indeed the case for $PM_{2.5}$ and ventricular arrhythmias (VAs), but for supraventricular arrhythmias (SVAs) and several other pollutants, including carbon monoxide, Dockery and colleagues found that distance from the monitor was associated with an increase in relative risk of arrhythmias. What underlies these increased magnitudes of association among pollutants, SVAs, and distance from the central monitor is not clear.

In the Peters study, the location of the ultrafine particle monitor may not have been the best place to evaluate the exposure of the study participants. It was situated in the cloister of a monastery, which can be characterized as an urban background site. Measurements of pollutants at that site, however, did correlate with daily pollutant patterns recorded at a site in the city that was influenced by traffic; but the measurements at the cloister had lower maximum values than at the traffic site. Other studies that have found associations between different types of health effects and concentrations of ultrafine particles measured in the community (eg, Peters et al 1997; Wichmann et al 2000; Pekkanen et al 2002) might have had monitors better located to represent the exposure of the target population; or those populations might have been exposed to a more toxic type of ultrafine mixture.

Mobile and some stationary sources are major contributors of ultrafine particles in urban air. Recent studies suggest that the spatial distribution of these particles is highly variable: Concentrations tend to be higher in proximity to the source, but they also depend on factors such as wind direction and photochemical activity (eg, Zhu et al 2002). If future epidemiologic studies are to be designed and thus interpreted appropriately, more information is needed about the spatial distribution of ultrafine particles emitted by all possible sources.

Lack of Statistical Power

In the Dockery study, the planned sample size was not achieved due to problems in obtaining data from a main medical center that had patients with implanted cardioverter defibrillators (ICDs). In addition, measurements of some particle components were not available for all of the study days: $PM_{2.5}$ measurements were missing for 20% of days, black carbon for 39%, and ultrafine particles and sulfate for about 70%. Thus, for events such as cardiac arrhythmias that occurred with low frequency in the study population, data on a particular PM fraction or component might have been unavailable for too many days to draw conclusions.

Completeness of pollutant data was not a problem in the Peters study. However, the comparatively small number of MI occurrences during the study period lessened the power of the study; this might have prevented some small effects of pollutants from being estimated with enough precision to support or exclude an association.

Correct Diagnosis of the Cardiovascular Events

Misclassification of events could affect the estimate of relative risk. Thus, the accuracy of diagnoses is important to the validity of the results from both studies. In the Peters study, this is unlikely to have been a serious issue because criteria for MI induction had been established by a long-term health study of cardiovascular events (the MONICA Project sponsored by the World Health Organization; Lewis et al 1990).

In the Dockery study, however, classification of arrhythmias was more difficult. ICDs respond when a preprogrammed heart rate is exceeded. The program is intended to detect and treat VAs (the more clinically relevant of the two types), but the ICD is also triggered by SVAs if they stimulate a rapid enough ventricular rate. Thus, because only these SVAs are recorded by the ICD, they represent a small percentage of the SVAs that actually occur.

In addition, some SVAs are most likely misclassified as VAs. Single-chamber devices (used in over 80% of patients in the Dockery study) monitor only the ventricle (lower heart chamber) and are thus not designed to record the point of origin of the arrhythmia. Dual-chamber devices have separate leads in the atrium (upper heart chamber)

and ventricle and can distinguish between points of origin. However, as described above, most SVAs are not recorded by the ICD at all.

The origin of arrhythmias also can be distinguished by cardiologic assessment of the electrogram tracings recorded by the ICD. Differentiation is more difficult in tracings from single-chamber ICDs because the electrograms are less informative than those generated by dual-chamber devices. Thus, SVAs may be misclassified as VAs through this method as well. (Misclassification by either method can occur in the reverse direction, but this is rare.)

In the Dockery study, all of these factors were likely to lead to inaccurate assessments of the numbers of VAs and SVAs used to analyze the associations between air pollutant concentrations and arrhythmias. Thus the estimated relative risks associated with air pollution may be spuriously low, even though these factors are unrelated to air pollution exposure.

Fatal MIs and Arrhythmias Not Included in the Study Designs

Pollutant effects may differ among individuals for whom a cardiac event is fatal or not. Both arrhythmia and MI might lead to sudden cardiac death, but the underlying pathophysiology and the relative contributions of potential risk factors might differ. Nevertheless, by design both studies evaluated only survivors of the cardiac events of interest. In the Dockery study, it is likely that some of the VAs recorded might have been fatal if not for the treatment by the ICD. It is more likely that fatality is related to the severity of the underlying disease, the intensity of the acute event, access to medical care, or all three. Access to care may be of particular importance, and an individual's ability to receive emergency services when they are stricken by a severe cardiac event may depend on where they are within the large area encompassed by a study. Geographic location, however, may correlate with personal factors such as social class as well as with differences in exposure. Thus, reasons to believe that air pollutants would affect fatal and nonfatal events differently are not apparent.

In the Dockery study, including fatal arrhythmias was not an option. If a patient died, the ICD was unavailable for extracting the final data and the electrogram recordings stored since the last clinical visit. Thus, if exposure to pollutants influenced in any way the fatal event, those associations were impossible to assess.

Peters and colleagues could, in a future study, compare results of pollutant effects on the onset of nonfatal and fatal MIs fairly easily. They could obtain data on mortality due to MIs in the Augsburg region during the same timeframe used for this study of MI survivors, which could then be analyzed in combination with the pollutant information from the current study. Including data about fatal MIs may add information about possible associations between pollutants and MI onset. However, an important aspect of the Peters study was gathering information directly from the patients about their activities and whereabouts just before the MI. Thus, future studies that want to include data on fatal MIs would need to have this information provided by third parties, who may not know or remember the activities of the deceased. This could add to bias or measurement error in the analyses.

MECHANISMS BY WHICH AIR POLLUTANTS COULD INDUCE CARDIOVASCULAR EVENTS

Both studies investigated the acute effects (that is, within hours to days) of air pollution on triggering or increasing the incidence of a cardiovascular event. Some analyses found associations between the cardiac event studied and pollutant concentrations 1 to 2 days earlier (lag days 1 and 2), but not in the hours immediately preceding an event. In addition, the Dockery study found larger effects (albeit less precise) on the subset of SVAs. Because the mechanisms underlying SVAs and VAs are different, these findings may provide insight into the mechanisms by which PM could trigger acute cardiac effects.

How short-term exposure to PM might precipitate such events is still a topic for speculation. The Health Review Committee's Commentary about the Peters Investigators' Report and an HEI Perspectives (Health Effects Institute 2002) describe how exposure to particles may affect vascular responses and result in an increased tendency to form blood clots and thrombi (the aggregation of platelets and other blood components that cause vascular obstruction). Short-term exposure studies of humans and other species have shown such vascular changes (eg, Clarke et al 2000; Ghio and Devlin 2001). Exposure to particles may also activate pulmonary neural reflexes, which can then lead to changes in the autonomic nervous system's control of the heart rate (heart rate variability; Creason et al 2001; Pope et al 2004b).

Clots or thrombi induced in individuals with damaged cardiac or vascular systems are likely to have more serious consequences than in persons with no preexisting disease. Individuals with atherosclerosis, a condition that involves thickening and hardening of the arteries, are particularly vulnerable. In atherosclerosis, the build-up of plaque (deposits of cholesterol and other fats, plus fibrin, inflammatory cells, and cytokines) narrows the arteries and hinders blood flow; the function of the endothelial cells that

line the blood vessels is also impaired. If a blood clot is formed after plaque rupture or erosion, the entire artery may become blocked. If this occurs in a coronary artery, the supply of oxygen to the heart muscle is reduced. This condition, myocardial ischemia, may lead to the rapid onset of heart damage (that is MIs and arrhythmias, both of which can be fatal). Even after surviving an MI, an individual is susceptible to further MIs, other ischemic events, or heart failure. Similarly, changes in heart rate variability and autonomic tone as a result of exposure to PM might have more serious consequences in susceptible persons than in healthy individuals.

Because atherosclerosis develops over several years, exposure to air pollution during this timeframe may be a factor that influences the development of the condition. (This possible long-term effect was not addressed in either the Peters or Dockery studies; however, mechanistic and epidemiologic studies are under way.) A study with rabbits bred to have features of human atherosclerosis found that PM_{10} instilled into the lungs promoted atherosclerotic plaques to progress into more vulnerable states (Suwa et al 2002; Tranfield et al 2004b). Exposure to PM_{10} in this animal model (by methods that do not necessarily parallel inhalation) also resulted in the accumulation of lipids under the endothelium, increased expression of endothelial adhesion molecules that are important for monocyte recruitment, and endothelial dysfunction in cells cultivated in vitro (Quinlan et al 2003; Tranfield et al 2004a; van Eeden et al 2004). Recent observations also suggest that ambient $PM_{2.5}$ concentrations are associated with subclinical indicators of atherosclerosis (Künzli et al 2005).

This emerging examination of potential mechanisms for cardiovascular effects from longer-term exposure is increasingly important. Reanalyses and extended analyses of earlier cohort studies have continued to report increased relative risks of mortality from cardiovascular disease associated with long-term average exposure to $PM_{2.5}$ or other indices of air pollution (Krewski et al 2000; Pope et al 2002, 2004a).

Thus, considering the available evidence, both short-term and long-term exposure to air pollution may affect cardiovascular events. Depending on the duration of exposure, the characteristics of PM and the pathophysiologic pathways that could be involved in inducing these effects may differ. Both of these factors may also differ among persons with normal cardiovascular systems compared with those whose systems are compromised by preexisting conditions.

EFFECTS OF GASEOUS POLLUTANTS ON THE HEART

Although most recent attention has focused on the cardiovascular effects of PM, effects of the gaseous pollutants also need to be considered. The effects of carbon monoxide exposure on cardiovascular disease have been studied for a long time (eg, Allred et al 1989). However, only limited information is available about the possible cardiac effects of gaseous pollutants at concentrations close to those in ambient air. Experimental studies have demonstrated mild cardiac effects from both sulfur dioxide (Tunnicliffe et al 2001) and ozone (Gong et al 1998); and results from recent epidemiologic studies have suggested that ozone might have serious cardiovascular effects (Bell et al 2004; Park et al 2005; Ruidavets et al 2005). Estimated effects of the gaseous pollutants in the studies by Peters and Dockery were at least as substantial as those of PM.

In other studies, researchers who have investigated personal exposure to different pollutants have suggested that the estimated cardiac effects attributed to gases, including sulfur dioxide, are actually effects of other pollutants, specifically PM (Sarnat et al 2000, 2005). Currently, however, we have no plausible explanation for the associations with sulfur dioxide at the very low concentrations encountered in those studies—apart from the conjecture that it is closely related to some other toxic exposure. At this stage of our knowledge it is difficult to differentiate between the effects of PM and those of gases because people are normally exposed at the same time to both types of pollutants.

Because of these uncertainties, it seems prudent to investigate further both the effects that low concentrations of gaseous pollutants, alone or in combination with PM, might have on cardiovascular disease, and the possibility that the associations with gaseous pollutants may actually reflect the effects of PM or some component that is not currently being measured.

FUTURE STUDIES

The Peters and Dockery studies have provided important insights into the relation between exposure to air pollutants and the acute induction of cardiovascular events. The results point the way to further avenues of research.

- Study other distinct cardiovascular endpoints.
- Evaluate different induction times between pollutant effects and the events of interest.
- Incorporate detailed information on an individual's clinical history, medication status, activities, and other

types of stressors (especially the activities and stressors that occur within hours preceding a cardiac event).

- Acquire information about individual exposure concentrations rather than estimating exposure from a central monitor (this would be ideal, although not practical for large population studies).
- Consider specific particles and their components derived from an individual source, such as wood smoke or traffic.
- In the same study, compare the impact of pollutants on both fatal and nonfatal cardiovascular events such as MIs or arrhythmias; although ICDs may be effective in treating most arrhythmias, the etiology of fatal and nonfatal events may vary. Such studies would provide useful information about possible pollutant effects, even though they would not be as able to relate prior activities to the cardiovascular events in all groups of patients.
- Given the intriguing results in the Dockery study about SVAs, future work on arrhythmias needs to distinguish clearly between the types of arrhythmias, possibly by restricting the study to dual-chamber or more advanced ICDs.
- The ability of any new study to address definitively a number of the issues above may be limited by the small numbers of events in any single study. For example, arrhythmias detected by ICDs may occur predominantly in small subgroups of susceptible individuals, such as those who had recent or multiple events, as was reported in the current Dockery study and in their earlier pilot study (Peters et al 2000). Opportunities to combine the results of multiple studies, through meta-analysis or pooling, could be explored.

CONCLUSIONS

Recent findings on the associations between short-term changes in PM concentrations and cardiovascular outcomes have prompted researchers to consider previously unsuspected effects and mechanisms. Some of these findings were derived from pilot studies, which tend to be more exploratory in nature. Those results motivated larger and more precisely defined studies to address suggested hypotheses. Two such hypotheses pursued by Peters and Dockery were that short-term PM exposure can cause (1) adverse effects (MIs) within just a few hours, and (2) cardiac arrhythmias in susceptible persons. Both of these hypotheses had been suggested by earlier studies conducted by these HEI investigators (Peters et al 2000, 2001), who then set out to address them more definitively. However, using different study designs and analytic methods, the Peters study found no evidence to support the first hypothesis and the Dockery study found only very limited evidence to support the second.

Nonetheless, some important or potentially important results have been derived from these studies. The association between MI onset and PM concentrations 24 to 48 hours earlier confirmed a similar finding in the pilot study (Peters et al 2001). (The pathophysiologic pathways that may explain these associations are the subject of intense current research.) The Peters study also identified activities that may increase the risk of MI onset. The possibility that, among patients with ICDs, $PM_{2.5}$ exposure may play a role in SVAs as well as VAs is an original finding, as is the result that the effects of $PM_{2.5}$ and most gaseous pollutants were more clearly observed among patients who had experienced a recent arrhythmia than among those who had not. Finally, the results from both studies show that associations with gaseous pollutants (and in particular sulfur dioxide) are at least as strong as those for PM in these two susceptible populations.

REFERENCES

Allred EN, Bleecker ER, Chaitman BR, Dahms TE, Gottlieb SO, Hackney JD, Pagano M, Selvester RH, Walden SM, Warren J. 1989. Short-term effects of carbon monoxide exposure on the exercise performance of subjects with coronary artery disease. New Engl J Med 321:1426–1432.

Bell ML, McDermott A, Zeger SL, Samet JM, Dominici F. 2004. Ozone and short-term mortality in 95 US urban communities, 1987–2000. JAMA 292:2372–2378.

Brook RD, Franklin B, Cascio W, Hong Y, Howard G, Lipsett M, Luepker R, Mittleman M, Samet J, Smith SC Jr, Tager I (Expert Panel on Population and Prevention Science of the American Hearth Association). 2004. Air pollution and cardiovascular disease: A statement for healthcare professionals from the Expert Panel on Population and Prevention Science of the American Heart Association. Circulation 109:2655–2671.

Clarke RW, Coull B, Reinisch U, Catalano P, Killingsworth CR, Koutrakis P, Kavouras I, Krishna Murthy GG, Lawrence J, Lovett E, Wolfson JM, Verrier RL, Godleski JJ. 2000. Inhaled concentrated ambient particles are associated with hematologic and bronchoalveolar lavage changes in canines. Environ Health Perspect 108:1179–1187.

Creason J, Neas L, Walsh D, Williams R, Sheldon L, Liao D, Shy C. 2001. Particulate matter and heart rate variability

among elderly retirees: The Baltimore 1998 PM study. J Expo Anal Environ Epidemiol 11:116–122.

Dockery DW, Pope CA III, Xu X, Spengler JD, Ware JH, Fay ME, Ferris BG Jr, Speizer FE. 1993. An association between air pollution and mortality in six US cities. N Engl J Med 329:1753–1759.

Ghio AJ, Devlin RB. 2001. Inflammatory lung injury after bronchial instillation of air pollution particles. Am J Respir Crit Care Med 164:704–708.

Godleski JJ, Sioutas C, Verrier RL, Killingsworth CR, Lovett E, Murthy GGK, Hatch V, Wolfson JM, Ferguson ST, Koutrakis P. 1997. Inhalation exposure of canines to concentrated ambient air particles (abstract). Am J Respir Crit Care Med 155:A246.

Gong H Jr, Wong R, Sarma RJ, Linn WS, Sullivan ED, Shamoo DA, Anderson KR, Prasad SB. 1998. Cardiovascular effects of ozone exposure in human volunteers. Am J Respir Crit Care Med 158:538–546.

Hamade AK, Lam T, Kleinman MT. 2005. Heart rate changes in 24-month old Fisher 344 rats exposed to concentrated particulate matter ($PM_{2.5}$) close to a freeway in Diamond Bar, GA. Toxicol Sci 84(S-1):90.

Health Effects Institute. 1998. RFA 98-1: Characterization of exposure to and health effects of particulate matter. In: Request for Applications Winter 1998 Research Agenda, pp 5–14. Health Effects Institute, Cambridge MA.

Health Effects Institute. 2002. Understanding the Health Effects of Components of the Particulate Matter Mix: Progress and Next Steps. HEI Perspectives. Health Effects Institute, Boston MA.

Kleinman MT, Meacher D, Oldham M, Sioutas C, Misra C, Cho A, Froines J. 2003. Exposure to concentrated fine and ultrafine ambient particles near heavily trafficked roads induces allergic reactions in mice (abstract OR03-04). In: Particulate Matter: Atmospheric Sciences, Exposure and the Fourth Colloquium on PM and Human Health. March–April 2003. American Assoc for Aerosol Research, Mt Laurel NJ. Available from *www.abstracts2view.com/aaarpm*.

Krewski D, Burnett RT, Goldberg MS, Hoover K, Siemiatycki J, Jerrett M, Abrahamowicz M, White WH. 2000. Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of Particulate Air Pollution and Mortality. A Special Report of the Institute's Particle Epidemiology Reanalysis Project. Health Effects Institute, Cambridge MA.

Künzli N, Jerrett M, Mack WJ, Beckerman B, LaBree L, Gilliland F, Thomas D, Peters J, Hodis HN. 2005. Ambient air pollution and atherosclerosis in Los Angeles. Environ Health Perspect 113:201–206.

Lewis M, Löwel H, Winter C, Zimmermann G, Pitschi P, Göpfert E, Luktisch D, Schwartzwälder I, Koenig W, Bolte H-D, Hörmann A, Schneider A, Janku D, Kaup W, Keil U. 1990. MONICA-Augsburg Coronary Event Registry: Handbook for the Registration of Hospitalized Events. GSF-Institut für Medizinische Informatik und Systemforschung Arbeitsgruppe Epidemiologie, Neuherberg, Germany. Available from *www.ktl.fi/monica*.

Park SK, O'Neill MS, Vokonas PS, Sparrow D, Schwartz J. 2005. Effects of air pollution on heart rate variability: The VA normative aging study. Environ Health Perspect 113:304–309.

Pekkanen J, Peters A, Hoek G, Tiittanen P, Brunekreef B, de Hartog J, Heinrich J, Ibald-Mulli A, Kreyling WG, Lanki T, Timonen KL, Vanninen E. 2002. Particulate air pollution and risk of ST-segment depression during repeated submaximal exercise tests among subjects with coronary heart disease: The Exposure and Risk Assessment for Fine and Ultrafine Particles in Ambient Air (ULTRA) study. Circulation 106:933–938.

Peters A, Dockery DW, Muller JE, Mittleman MA. 2001. Increased particulate air pollution and the triggering of myocardial infarction. Circulation 103:2810–2815.

Peters A, Liu E, Verrier RL, Schwartz J, Gold DR, Mittleman M, Baliff J, Oh JA, Allen G, Monaham K, Dockery DW. 2000. Air pollution and incidence of cardiac arrhythmia. Epidemiology 11:11–17.

Peters A, Wichmann HE, Tuch T, Heinrich J, Heyder J. 1997. Respiratory effects are associated with the number of ultrafine particles. Am J Respir Crit Care Med 155:1376–1383.

Poloniecki JD, Atkinson RW, de Leon AP, Anderson HR. 1997. Daily time series for cardiovascular hospital admissions and previous day's air pollution in London, UK. Occup Environ Med 54:535–540.

Pope CA III, Burnett RT, Thun MJ, Calle EE, Krewski D, Ito K, Thurston GD. 2002. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. JAMA 287:1132–1141.

Pope CA III, Burnett RT, Thurston GD, Thun MJ, Calle EE, Krewski D, Godleski JJ. 2004a. Cardiovascular mortality and long-term exposure to particulate air pollution: Epidemiological evidence of general pathophysiological pathways of disease. Circulation 109:71–77.

Pope CA III, Dockery DW. 1999. Epidemiology of particle effects. In: Air Pollution and Health (Holgate ST, Samet JM,

Koren HS, Maynard RL, eds), pp 673–705. Academic Press, Orlando FL.

Pope CA III, Hansen ML, Long RW, Nielsen KR, Eatough NL, Wilson WE, Eatough DJ. 2004b. Ambient particulate air pollution, heart rate variability, and blood markers of inflammation in a panel of elderly subjects. Environ Health Perspect 112:339–345.

Pope CA III, Thun MJ, Namboodiri MM, Dockery DW, Evans JS, Speizer FE, Heath CW Jr. 1995. Particulate air pollution as a predictor of mortality in a prospective study of US adults. Am J Respir Crit Care Med 151(3 Pt 1):669–674.

Quinlan KB, van Eeden SF, Suwa T, Vincent R, Hogg JC. 2003. Particulate matter air pollution (PM_{10}) exposure activates endothelium (abstract). Am J Respir Crit Care Med 167: A108.

Rich KE, Petkau J, Vedal S, Brauer M. 2004. A case-crossover analysis of particulate air pollution and cardiac arrhythmia in patients with implantable cardioverter defibrillators. Inhal Toxicol 16:363–372.

Riediker M, Cascio WE, Griggs TR, Herbst MC, Bromberg PA, Neas L, Williams RW, Devlin RB. 2004a. Particulate matter exposure in cars is associated with cardiovascular effects in healthy young men. Am J Respir Crit Care Med 169:934–940.

Riediker M, Devlin RB, Griggs TR, Herbst MC, Bromberg PA, Williams RW, Cascio WE. 2004b. Cardiovascular effects in patrol officers are associated with fine particulate matter from brake wear and engine emissions. Part Fibre Toxicol 1:2.

Rothman KJ, Greenland S. 1998. Modern Epidemiology, Second Edition. Lippincott-Raven Publishers, Philadelphia PA. pp 130–131.

Ruidavets JB, Cournot M, Cassadou S, Giroux M, Meybeck M, Ferrieres J. 2005. Ozone air pollution is associated with acute myocardial infarction. Circulation 111:563–569.

Sarnat JA, Brown KW, Schwartz J, Coull BA, Koutrakis P. 2005. Ambient gas concentrations and personal particulate matter exposures: Implications for studying the health effects of particles. Epidemiology 16:385–395.

Sarnat JA, Koutrakis P, Suh HH. 2000. Assessing the relationship between personal particulate and gaseous exposures of senior citizens living in Baltimore, MD. J Air Waste Manag Assoc 50:1184–1198.

Schwartz J, Morris R. 1995. Air pollution and hospital admissions for cardiovascular disease in Detroit, Michigan. Am J Epidemiol 142:23–35.

Sullivan J, Sheppard L, Schreuder A, Ishikawa N, Siscovick D, Kaufman J. 2005. Relation between short-term fine-particulate matter exposure and onset of myocardial infarction. Epidemiology 16:41–48.

Suwa T, Hogg JC, Quinlan KB, Ohgami A, Vincent R, van Eeden SF. 2002. Particulate air pollution induces progression of atherosclerosis. J Am Coll Cardiol 39:935–942.

Tranfield EM, van Eeden SF, Hogg JC, Walker DC. 2004a. Accumulation of macrophage foam cells below the endothelium in atherosclerotic plaques exposed to fine particulate air pollution (PM_{10}) (abstract). Exp Clin Cardiol 9:A185.

Tranfield EM, van Eeden SF, Hogg JC, Walker DC. 2004b. Alterations in atherosclerotic plaque architecture following exposure to fine particulate air pollution (PM_{10}) (abstract). FASEB J 18:A11.

Tunnicliffe WS, Hilton MF, Harrison RM, Ayres JG. 2001. The effects of sulphur dioxide on indices of heart rate variability in normal and asthmatic adults. Europ Respir J 17:604–608.

van Eeden SF, Holman C, Yatera K, Vincent R, Laher I. 2004. Exposure to atmospheric air pollution particles induces endothelial dysfunction (abstract). Am J Respir Crit Care Med 169:A885.

Vedal S, Rich K, Brauer M, White R, Petkau J. 2004. Air pollution and cardiac arrhythmias in patients with implantable cardioverter defibrillators. Inhal Toxicol 16:353–362.

Wichmann H-E, Spix C, Tuch T, Wölke G, Peters A, Heinrich J, Kreyling WG, Heyder J. 2000. Daily Mortality and Fine and Ultrafine Particles in Erfurt, Germany, Part I: Role of Particle Number and Particle Mass. Research Report 98. Health Effects Institute, Cambridge MA.

World Health Organization. 2003. Health Effects of Air Pollution with Particulate Matter, Ozone and Nitrogen Dioxide. Report on a WHO Working Group. Bonn, Germany. Available from *www.euro.who.int/air/activities/ 20030612_1*.

Zeger SL, Thomas D, Dominici F, Samet JM, Schwartz J, Dockery DW, Cohen A. 2000. Section 1: Exposure measurement error in time-series studies of air pollution. In: The National Morbidity, Mortality, and Air Pollution Study, Part I: Methods and Methodologic Issues, pp 15–27. Research Report 94. Health Effects Institute, Cambridge MA.

Zhu Y, Hinda WC, Kim S, Sioutas C. 2002. Concentration and size distribution of ultrafine particles near a major highway. J Air Waste Manage Assoc 52:1032–1042.

RELATED HEI PUBLICATIONS: PARTICULATE MATTER AND DIESEL EXHAUST

Number	Title	Principal Investigator	Date*
Research Reports			
127	Personal, Indoor, and Outdoor Exposures to $PM_{2.5}$ and Its Components for Groups of Cardiovascular Patients in Amsterdam and Helsinki	B Brunekreef	2005
126	Effects of Exposure to Ultrafine Carbon Particles in Healthy Subjects and Subjects with Asthma	MW Frampton	2004
120	Effects of Concentrated Ambient Particles on Normal and Hypersecretory Airways in Rats	JR Harkema	2004
118	Controlled Exposures of Healthy and Asthmatic Volunteers to Concentrated Ambient Particles in Metropolitan Los Angeles	H Gong Jr	2003
112	Health Effects of Acute Exposure to Air Pollution *Part I.* Healthy and Asthmatic Subjects Exposed to Diesel Exhaust *Part II.* Healthy Subjects Exposed to Concentrated Ambient Particles	ST Holgate	2003
110	Particle Characteristics Responsible for Effects on Human Lung Epithelial Cells	AE Aust	2002
104	Inhalation Toxicology of Urban Ambient Particulate Matter: Acute Cardiovascular Effects in Rats	R Vincent	2001
99	A Case-Crossover Analysis of Fine Particulate Matter Air Pollution and Out-of-Hospital Sudden Cardiac Arrest	H Checkaway	2000
98	Daily Mortality and Fine and Ultrafine Particles in Erfurt, Germany *Part I.* Role of Particle Number and Particle Mass	H-E Wichmann	2000
97	Identifying Subgroups of the General Population That May Be Susceptible to Short-Term Increases in Particulate Air Pollution: A Time-Series Study in Montreal, Quebec	MS Goldberg	2000
96	Acute Pulmonary Effects of Ultrafine Particles in Rats and Mice	G Oberdörster	2000
95	Association of Particulate Matter Components with Daily Mortality and Morbidity in Urban Populations	M Lippmann	2000
91	Mechanisms of Morbidity and Mortality from Exposure to Ambient Air Particles	JJ Godleski	2000

Continued

** Reports published since 1990.*
Copies of these reports can be obtained from the Health Effects Institute and many are available at www.healtheffects.org.

RELATED HEI PUBLICATIONS: PARTICULATE MATTER AND DIESEL EXHAUST

Number	Title	Principal Investigator	Date*
Special Reports			
	Revised Analyses of Time-Series Studies of Air Pollution and Health		2003
	Research Directions to Improve Estimates of Human Exposure and Risk from Diesel Exhaust		2002
	Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of Particulate Air Pollution and Mortality: A Special Report of the Institute's Particle Epidemiology Reanalysis Project		2000
	Diesel Emissions and Lung Cancer: Epidemiology and Quantitative Risk Assessment		1999
	Particulate Air Pollution and Daily Mortality: The Phase I Report of the Particle Epidemiology Evaluation Project		
	Phase I.A. Replication and Validation of Selected Studies		1995
	Phase I.B. Analyses of the Effects of Weather and Multiple Air Pollutants		1997
	Diesel Exhaust: A Critical Analysis of Emissions, Exposure and Health Effects		1995
HEI Communications			
8	The Health Effects of Fine Particles: Key Questions and the 2003 Review (Report of the Joint Meeting of the EC and HEI)		1999
HEI Research Program Summaries			
	Research on Particulate Matter		1999
HEI Perspectives			
	Understanding the Health Effects of Components of the Particulate Matter Mix: Progress and Next Steps		2002
	Airborne Particles and Health: HEI Epidemiologic Evidence		2001

** Reports published since 1990.*
Copies of these reports can be obtained from the Health Effects Institute and many are available at www.healtheffects.org.

HEALTH
EFFECTS
INSTITUTE

Charlestown Navy Yard
120 Second Avenue
Boston MA 02129-4533 USA
+1-617-886-9330
www.healtheffects.org

RESEARCH
REPORT

Number 124
June 2005