RESEARCH REPORT

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A Case-Crossover Analysis of Fine Particulate Matter Air Pollution and Out-of-Hospital Sudden Cardiac Arrest

Harvey Checkoway, Drew Levy, Lianne Sheppard,
Joel Kaufman, Jane Koenig, and David Siscovick

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HEI STATEMENT

Synopsis of Research Report 99

A Case-Crossover Analysis of Fine Particulate Matter Air Pollution and Out-of-Hospital Sudden Cardiac Arrest

BACKGROUND

Epidemiologic studies have reported associations between short-term increases in particulate matter (PM) air pollution and increased daily mortality and morbidity from respiratory and cardiovascular diseases. Although these studies suggest that persons with preexisting disease are most susceptible to the effects of small increases in PM, the specific clinical conditions that confer increased risk have been unclear. Because most studies use mortality data from death certificates, clinical conditions at the time of death have not been known. Dr Checkoway and his colleagues proposed to investigate a previously uninvestigated association between sudden cardiac arrest and fine particulate air pollution. Such an association would have important public health implications because sudden cardiac arrest is most often observed as sudden cardiac death, responsible for almost 10% of total US mortality.

APPROACH

The primary hypothesis that Dr Checkoway and colleagues tested was that increases in daily fine particle levels were related to increased risk of out-of-hospital sudden cardiac arrest. Sudden cardiac arrest and questionnaire data collected for a different purpose were used for this study in conjunction with exposure data available from the Puget Sound Clean Air Agency (Seattle WA).

The investigators used a case-crossover study design in which only case subjects were studied (rather than cases and control subjects); their exposure at the time when the health outcome of interest (sudden cardiac arrest) occurred was compared with some estimate of their typical level of exposure measured at another time. The case-crossover method can be used to investigate whether a recent exposure has triggered or is related to the occurrence of an event—here, whether levels of PM are related to sudden cardiac arrest.

In this study, for each case of sudden cardiac arrest, a time period when the person was disease free was selected as a matched "referent" period. The exposure status at the time of disease onset, the "hazard" period, was compared with exposure during the referent period for that subject. (The authors also examined potential sources of bias in case-crossover studies of air pollution [Appendix A].)

RESULTS AND IMPLICATIONS

Analyses were conducted for models that included a single pollutant (one of two sizes of PM) and multiple pollutants (in which SO_2, CO, or both were added). The relative risk estimates for sudden cardiac arrest, which considered exposure to pollutants on the day of the outcome event and up to 5 days before the event, showed no evidence of an increase in risk. Furthermore, these results did not change when either SO_2 or CO exposure were included in the analyses. The investigators also examined several factors that might modify the results, including season, time of entry into the study, age, and risk factors for sudden cardiac arrest, such as diet, education, and smoking. These analyses showed no modification of the results; in addition, stratifying the subjects by age and other cardiovascular disease risk factors did not identify possible susceptible subgroups of the population studied.

Dr Checkoway and his colleagues made good use of a unique but small dataset, collected for a different purpose, to examine the association between PM and sudden cardiac arrest, a well-defined and specific health outcome. This outcome is of interest because of the associations between cardiovascular deaths and PM levels reported in other studies. The study results are sufficiently precise to rule out a 50% increase in risk of sudden cardiac arrest from exposure to PM in Seattle residents with no prior history of heart disease. It should be understood, however, that a lack of association between sudden cardiac arrest and PM in this study does not rule out an association between other cardiac or cardiovascular disease outcomes and PM. Epidemiologic and laboratory studies currently under way will add to our current knowledge about the possible PM effects on potentially susceptible individuals.

This Statement, prepared by the Health Effects Institute, summarizes a research project funded by HEI from 1997 to 1999 and conducted by Dr Harvey Checkoway of the University of Washington, Seattle WA. The following Research Report contains both the detailed Investigators' Report and a Critique on the study prepared by the Institute's Health Review Committee.

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HEI STATEMENT

This Statement is a nontechnical summary of the Investigators' Report and the Health Review Committee's Commentary.

PREFACE

INVESTIGATORS' REPORT

When an HEI-funded study is completed, the investigators submit a final report. The Investigators' Report is first examined by three outside 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.

CRITIQUE Health Review Committee

The Critique 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 the remaining uncertainties and the implications of the findings for public health.

RELATED HEI PUBLICATIONS

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PREFACE

In 1994, HEI initiated a research program to investigate the complex issues associated with the health effects of exposure to particulate matter (PM)* in the air. This program was developed in response to growing concern about the potential public health significance of reported associations between daily fluctuations in levels of PM and changes in daily morbidity and mortality in time-series epidemiology studies. These results were questioned for a variety of reasons, including the lack of support from experimental studies and the lack of a mechanism to explain how such effects would occur. To address these issues HEI undertook two research initiatives in 1994: (1) the Particle Epidemiology Evaluation Project (Samet et al 1995, 1997), which evaluated six of the time-series epidemiology studies that had reported effects of PM on mortality; and (2) a program of toxicologic and epidemiologic studies (funded from RFA 94-2, "Particulate Air Pollution and Daily Mortality: Identification of Populations at Risk and Underlying Mechanisms"), which aimed to understand better how PM might cause toxicity and what factors might affect susceptibility. In all, HEI has issued five requests for research on PM and funded 34 studies or reanalyses over the last five years.

This Preface provides general regulatory and scientific background information relevant to studies funded from RFA 94-2 (or from the preliminary application process during the same period), including the study by Harvey Checkoway that is described in the accompanying Report and Critique. All of the studies from RFA 94-2 have been published. The *HEI Program Summary: Research on Particulate Matter* (Health Effects Institute 1999) provides information on studies funded since 1996.

BACKGROUND

Particulate matter is the term used to define a complex mixture of anthropogenic and naturally occurring airborne particles. The size, chemical composition, and other physical and biological properties of PM depend on the sources of the particles and the changes the particles undergo in the atmosphere. In urban environments, these particles derive mainly from combustion, including mobile sources such as motor vehicles and stationary sources such as power plants. The most commonly used descriptor of particle size is *aerodynamic diameter.* Based on this parameter, ambient particles tend to fall into three size classes (often defined as modes): ultrafine or nuclei mode (particles less than 0.1 μm in diameter); fine or accumulation mode (particles between 0.1 and 2.5 μm in diameter), and coarse (particles larger than 2.5 μm in diameter). Fine and ultrafine particles are dominated by emissions from combustion processes while coarse particles are mostly generated by mechanical processes from a variety of noncombustion sources. Generally, the ultrafine and fine fractions are composed of carbonaceous material, metals, sulfate, nitrate and ammonium ions. The coarse fraction is composed mostly of mechanically generated particles and consists of insoluble minerals and biologic aerosols, with smaller contributions from primary and secondary aerosols and sea salts (US Environmental Protection Agency [EPA] 1996).

A number of early epidemiologic studies indicated that human exposure to high concentrations of PM, such as London fog, had deleterious effects (such as increased number of deaths), particularly in children, the elderly, and those with cardiopulmonary conditions (Firket 1931; Ciocco and Thompson 1961; Logan 1953; Gore and Shaddick 1968). Because of this apparent relation to increased mortality, the EPA has regulated the levels of ambient PM since 1971, when the Clean Air Act was first promulgated. This act authorized the EPA to set National Ambient Air Quality Standards (NAAQSs) for a number of potentially harmful air pollutants (including PM) in order to protect the health of the population, particularly those thought to be sensitive.

The first NAAQS for PM was based on controlling total suspended PM or particles up to 40 μm in diameter. In 1978, the standard was revised to regulate inhalable particles, or particles than can deposit in the respiratory tract and therefore have greater potential for causing adverse health effects. These are particles with an aerodynamic diameter of 10 μm or less (PM_{10}). More recent epidemiologic studies, published in the early 1990s, indicated a relatively consistent association between small short-term increases in PM levels and increases in both mortality and morbidity from respiratory and cardiovascular diseases (reviewed by the Committee of the Environmental and Occupational Health Assembly, American Thoracic Society [Bascom et al 1996]).

Some studies also suggested that long-term exposure to low levels of PM is associated with adverse effects (Dockery et al 1993; Pope et al 1995). These latter studies

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

Table 1. Current NAAQSs for PM (set in 1997)

	PM_{10}	$PM_{2.5}$
Daily Standard	150 μg/m^3	65 μg/m^3
Annual Standard	50 μg/m^3	15 μg/m^3

also pointed to a possible role of fine particles (less than 2.5 μm in aerodynamic diameter [$PM_{2.5}$]). In 1997, the EPA considered the evidence for the effects of fine particles sufficient to promulgate a fine particle standard while retaining the PM_{10} standard (US Environmental Protection Agency 1997) (see Table 1). The next review of the PM NAAQS is scheduled to be completed by the year 2002.

RESEARCH PROGRAM FROM HEI RFA 94-2

The wealth of epidemiologic data published in the early 1990s suggested an association between PM and health effects, but aspects of these findings were not well understood. Problems involved uncertainties in the exposure estimates, confounding by weather or other factors, the role of copollutants, and the mechanisms by which particles may cause effects. Moreover, although the epidemiologic findings were consistent across different communities exposed to distinct mixes and levels of pollutants, they were not well supported by either human chamber studies or animal inhalation studies aimed at delineating pathologic changes that might result in death. Failure of the experimental studies to provide support for the epidemiologic findings was attributed to insufficient statistical power, use of particles not representative of ambient particles, or use of animals not representative of the individuals susceptible to increased mortality.

By the mid 1990s, it became apparent that the research to advance our understanding of the association between exposure to particles and daily mortality found in the epidemiologic studies needed to focus on identifying (1) susceptible populations, (2) mechanisms by which particles may lead to increased mortality, and (3) characteristics of the particles responsible for the effects. It was recognized that both epidemiologic and experimental studies would be required.

The HEI program initiated in 1994 was aimed at addressing these research needs. Six epidemiologic and toxicologic studies were funded through RFA 94-2, and three additional studies were added through the preliminary application process. As a group, the five epidemiologic studies investigated: (1) social and medical factors that might increase the risk of mortality when particulate pollution increases (Mark Goldberg of the National Institute of Scientific Research, University of Quebec [see Goldberg et al 2000]); (2) components of particulate pollution that might account for its effect on mortality (Morton Lippmann of the New York University School of Medicine [see Lippmann et al 2000] and Erich Wichmann of the GSF Insitute of Epidemiology and Ludwig Maximilian University [see Wichmann et al 2000]); and (3) cause of death (Harvey Checkoway), presented in this report, or possible pathophysiologic mechanisms that might lead to death in people exposed to particulate air pollution (Douglas Dockery of Harvard School of Public Health [see Dockery et al 1999]).

The four experimental studies tested the hypothesis that older animals or animals with preexisting lung or heart disease or respiratory infections are more sensitive to the acute effects of particles than healthy animals. They investigated possible mechanisms leading to mortality such as inflammation, changes in immune response, or changes in cardiac and respiratory function. Three of these studies used for the first time concentrated ambient particles (CAPs) (John Godleski of Harvard School of Public Health [see Godleski et al 2000], and Terry Gordon [see Gordon et al 2000] and Judith Zelikoff of New York University School of Medicine). In these CAPs studies, particles in the range of about 0.1 to 2.5 μm are concentrated while those greater than 2.5 μm are removed and those under 0.1 μm remain at the ambient concentration. CAPs exposures represent a significant fraction of ambient PM and provide a reasonable approach to mimicking the exposure to PM in epidemiology studies. The fourth experimental study (Günter Oberdörster of the University of Rochester School of Medicine [see Oberdörster et al 2000]) focused on evaluating the effects of different ultrafine particles that have been hypothesized to be more toxic than fine particles.

CONTINUING RESEARCH

Many of the key questions identified in the early 1990s are still relevant and much research is ongoing to address them. The research strategies have evolved, however, as results from previous studies have provided insights into which animal models and which endpoints may be the most helpful to evaluate. In addition, advances in exposure assessment and statistical methods have pointed to new approaches for conducting epidemiologic studies. Since RFA 94-2, HEI has funded a number of research projects that build on the new findings and approaches. These studies will be completed by the end of 2002.

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INVESTIGATORS' REPORT

A Case-Crossover Analysis of Fine Particulate Matter Air Pollution and Out-of-Hospital Sudden Cardiac Arrest

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ABSTRACT

Numerous recent epidemiologic studies report increases in the daily incidence of cardiovascular disease mortality and morbidity related to increases in daily levels of fine particulate matter (PM)* air pollution. This study sought to evaluate the possible association between the occurrence of out-of-hospital sudden cardiac arrest (SCA) and daily PM levels in the Seattle metropolitan area. The underlying hypothesis was that PM exposure may act as a cardiovascular trigger for SCA. A case-crossover study was conducted among 362 SCA cases identified by paramedics from October 1988 through June 1994. Cases were King County WA residents who were married, aged 25 to 74 years at the time of their SCA, with no prior history of clinically recognized heart disease or other life-threatening comorbid conditions. Daily averages of regional PM monitoring data for nephelometry measures of PM (reported in units of bsp, referred to as coefficient of light scattering) and PM_{10} (particulate matter 10 μm or smaller in aerodynamic diameter) from three monitoring sites were used as indicators of exposure. In the case-crossover analysis, PM levels during index times of cases within the five days preceding an SCA were compared with PM levels at referent days, defined as the same days of the week during the month of SCA occurrence. Lag periods for index days of 0 to 5 days were investigated. The estimated relative risk (RR) at a lag of 1 day for an interquartile range (IQR) change in nephelometry (0.51 bsp) was 0.893 (95% confidence interval [CI] 0.779–1.024). Varying the lag period had only minimal change on the observed association. The estimated relative risk at a lag of 1 day for an IQR change of PM_{10} (19.3 $\mu g/m^3$) was 0.868 (95% CI 0.744–1.012). There was no evidence of confounding by ambient daily exposures to carbon monoxide or sulfur dioxide. Analysis of effect modification by individual-level variables, including age, cigarette smoke exposure, physical activity, and other risk or protective factors for cardiovascular disease did not reveal any susceptible subgroups. The null results of this study may be due to several factors; these include: the highly selected nature of this SCA case series; the fact that cases were free of prior clinically recognized heart disease or major life-threatening comorbidity; and the possibility that PM exposures at the relatively low levels seen in the Seattle metropolitan area do not trigger cardiovascular toxic mechanisms that culminate in SCA.

INTRODUCTION

Increasing epidemiologic evidence indicates that elevated levels of ambient PM air pollution are associated with elevated daily nonaccidental mortality counts. The majority of this evidence is from time-series analyses, largely from North America and Western Europe (Pope et al 1992, 1995; Dockery et al 1993; Schwartz 1993; Verhoeff et al 1996; Zmirou et al 1998; Fairley 1999). On average, daily total mortality increases by roughly 1% per 10 $\mu g/m^3$ increase in PM_{10} (Schwartz 1994b). Several studies provide time-series data separately for mortality from two major disease categories, respiratory and cardiovascular diseases, and indicate summary estimates of 3.5% and 1.4% per 10 $\mu g/m^3$, respectively (Pope et al 1992; Schwartz and Dockery 1992; Schwartz 1993). Corroborative evidence for cardiovascular disease effects has been obtained from analyses of hospital admissions (Burnett et al 1995; Schwartz and Morris 1995; Schwartz 1997, 1999).

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

This Investigators' Report is one part of Health Effects Institute Research Report Number 99, which also includes a Preface, a Critique by the Institute's Health Review Committee, and an HEI Statement about the research project. Correspondence concerning the Investigators' Report may be addressed to Dr Harvey Checkoway, University of Washington, Department of Environmental Health, Seattle WA 98195–7234 USA.

Although this document was produced with partial funding by the United States Environmental Protection Agency under Assistance Award R828112 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.

Cardiovascular disease accounts for a sizable proportion of total mortality and is thus an appropriate research focus for PM-related health effects. Moreover, possible effects on the cardiovascular system from transient (daily) changes in PM levels should be most readily detected in studies of acute-onset events, such as SCA—the abrupt, unexpected loss of cardiac function that is usually fatal. Sudden cardiac arrest was the focus of this project. Death from SCA accounts for roughly 10% of mortality in US adults (Kannel and Schatzkin 1985). The proximate cause of fatal SCA is typically ventricular tachyarrhythmia, which may be provoked by a series of triggering events acting on the myocardium (Goldstein et al 1994). The biological mechanisms whereby PM air pollution potentially increases SCA risk have not been elucidated, although some candidate models have been proposed. Transient toxic insults that induce inflammatory responses with accompanying electrophysiological disturbances may be relevant triggers (Oberdörster et al 1995; Killingsworth et al 1997). Supportive findings for cardiac event triggers have been obtained from experiments on bronchitic dogs treated with PM from urban air (Godleski et al 1996). Seaton and colleagues (1995) posit that ultrafine particles (< 0.1 μm) reaching the deep lung may release mediators that increase blood coagulation. A study in Germany (Peters et al 1997) demonstrates increased blood viscosity subsequent to an acute air pollution episode, although specific attribution of this effect to particulates was not possible. Some evidence suggests associations of elevated PM with transient reductions in heart rate variability (Liao et al 1999) and reduced blood oxygenation (Pope et al 1999), both of which may contribute to cardiovascular disease triggers. Additionally, elevations of various air pollutants, including PM_{10}, are associated with multiple occurrences of cardiac arrhythmia in a recent study of Massachusetts patients with implanted cardiac defibrillators (Peters et al 2000).

Despite the general consistency of the epidemiologic findings for PM effects on daily cardiovascular disease mortality, several important unresolved issues remain that limit causal interpretation. These include: (1) the nonspecificity of disease outcomes analyzed in most time-series studies; (2) uncertainties regarding the most toxic components of PM; (3) the frequently noted problems of exposure misclassification; (4) potential confounding by climatic factors, copollutants, and other putative disease risk factors. The ecological time-series design, wherein exposures and health outcomes are investigated in the aggregate (population) rather than at the individual level, is a major contributor to the limitations of existing evidence. The absence of personal-level risk factor data, apart from basic demographic variables, also limits the ability to assess effect modification by other risk factors. Characterization of effect modification, which can assist in identifying susceptible subgroups in the population, becomes especially important in epidemiologic studies of PM because of the small population-wide relative risks that are usually observed.

The case-crossover design is suited to the study of a transient effect of an intermittent exposure on the subsequent occurrence of a rare, acute-onset disease such as SCA, hypothesized to occur a short time after exposure. Used in this investigation, this design may reduce biases of confounding due to secular trends in exposure and disease occurrence that are limitations of conventional time-series analyses. Additionally, the case group available for our analysis was well characterized in regard to potential confounders and effect modifiers that included diet, smoking, and comorbid conditions.

SPECIFIC AIMS

In this report, we present findings from a case-crossover study of SCA among Seattle-area residents. The primary objective of the research was to test the hypothesis that increases in daily, fine PM levels, measured by nephelometry and PM_{10}, were related to increased risk of out-of-hospital SCA. A related goal was to determine the influence on effect estimates of exposure variations explained by urban/suburban and elevation gradients. This was accomplished by means of a parallel environmental nephelometry sampling survey at selected locations. A secondary objective was to compare observed effect estimates among three measures of PM exposure: nephelometry (which measures particulates less than 1 μm in aerodynamic diameter), $PM_{2.5}$ (particles smaller than 2.5 μm), and PM_{10}. As we will describe in the Methods section, available $PM_{2.5}$ data were not sufficiently complete for analysis. Consequently, we limited our analyses to examining relations of nephelometry and PM_{10} measures with risk of SCA.

METHODS

STUDY SUBJECTS

The case series for this study included SCA cases identified in an earlier case-control study by Siscovick and coworkers (1995). Study subjects were SCA cases from among King County WA residents whose cardiac arrests occurred out of hospital and were attended by paramedics

from October 1988 through June 1994. At the time of case identification, these individuals had a sudden pulseless condition that could not be explained by a noncardiac cause, based on review of emergency medical service reports, death certificates, and, when available, medical examiner and autopsy reports. SCA cases were excluded if they had prior histories of clinically recognized heart disease, including angina, myocardial infarction, coronary bypass surgery or angioplasty, congestive heart failure, arrhythmias, cardiomyopathy, congenital heart disease, or valvular disease. Also excluded were cases with other life-threatening conditions, such as cancer or end-stage lung, liver, or kidney disease. Cases were further restricted to persons aged 25 to 75 who were married and whose spouses participated in an in-person interview (83% of eligible cases). In total, 362 cases were available for analysis. The original case-control study (Siscovick et al 1995) also provided data on education, diet, smoking, hypercholesterolemia, diabetes, and family history of myocardial infarction. Characteristics of the cases are summarized in Table 1.

Table 1. Characteristics of Cases

Risk Factor	Percentage of Total (N = 362)
Age[a]	61 (29,74)
Men	80
White	94
Education (high school graduate)	62
Employed	48
Current smoker	35
Former smoker	37
Hypertension	38
Diabetes mellitus	12
Hypercholesterolemia	24
Family history of myocardial infarction or sudden death	54
Early family history of same	25
Perceived health (excellent, very good, or good)	78

[a] Age given in median years (min, max).

AIR QUALITY DATA

The primary exposure metric used in this study was PM measured by nephelometry; these values are reported in units of bsp (where *b* is the coefficient of extinction, *s* is for scattering as opposed to absorption, and *p* is for particles as opposed to gases) and referred to simply as the *coefficient of light scattering.* Nephelometry data correlate well with gravimetric measurements for particles in the range of 0.2 to 1.2 µm aerodynamic diameter (Ruby et al 1989; Thomas and Gebhart 1994). Since 1985, the Puget Sound Clean Air Agency (PSCAA) has operated three King County monitoring sites: Duwamish, Lake Forest Park, and Kent (see Figure 1). Daily averages of nephelometry data for each monitoring site were obtained from PSCAA for the 2,161 days of the study (October 1988 through June 1994). PM_{10} data for 2,106 days were also obtained from PSCAA. For both bsp and PM_{10}, we computed daily values as the mean of the three sites. We were only able to obtain $PM_{2.5}$ data for 579 days, and thus decided not to perform exposure-response analyses using this metric. Daily average data for sulfur dioxide (SO_2) were available for 2,024 days from one monitor that was colocated with the Duwamish PM monitor. Carbon monoxide (CO) air levels from various locations were combined into single daily averages for 2,161 days. Ozone data were collected only during summer months from one site 30 miles east of the population center of King County. We elected not to use ozone data because of the irregular nature of the data collection and the remoteness of the collection site. Distributions of the air pollutant data are summarized in Table 2; correlations among the air pollutants are shown in Table 3. As expected, relatively high correlations were found among bsp, $PM_{2.5}$, and PM_{10}. CO was also strongly correlated with PM measures, with Pearson correlation coefficients of 0.75 to 0.82.

EXPOSURE SUBSTUDY

Particulate air pollution variability is likely to be influenced by temperature, air stagnation, and topographic factors such as elevation. Accordingly, we conducted an additional nephelometry measurement survey to generate data to examine the effects of topographic and atmospheric conditions on exposure estimates and, ultimately, on the results of the case-crossover analysis. Previous work in the Seattle metropolitan area has established woodburning as a major source of PM during periods of highest exposures, ie, cold winter-season days with stagnant air. During periods of stagnation, atmospheric inversions develop in which cold air is trapped close to the ground and particulates from woodsmoke accumulate at lower elevations. Also, woodburning is more common in nonurban than in urban areas; thus, urban/rural gradients were considered as predictors of PM levels. Because the observed associations between PM and SCA were not materially altered when adjustments were made for these climatic and topographic variables, we will emphasize results not adjusted for those factors. The methods and findings from the substudy are available from HEI on request.

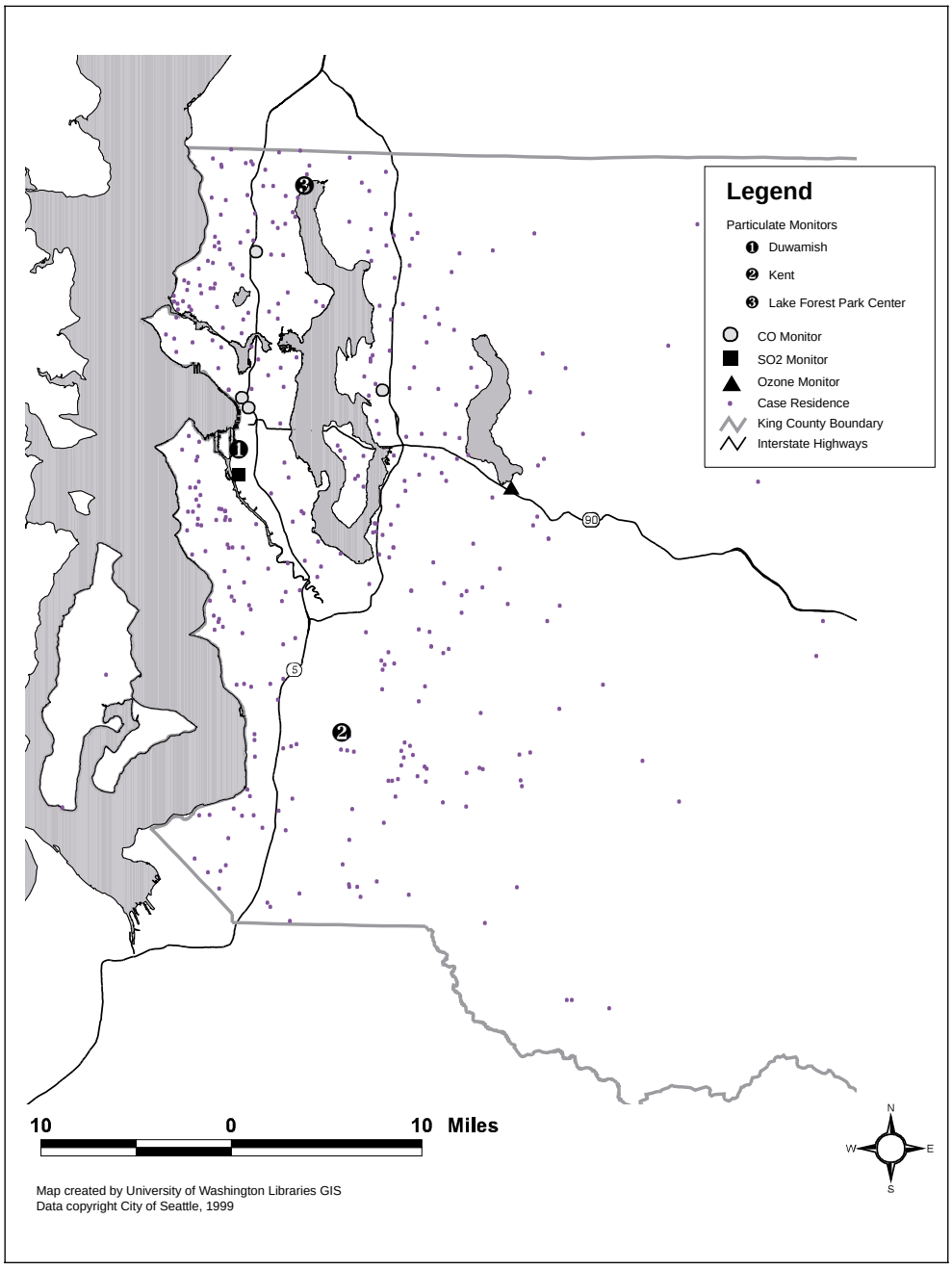

Figure 1. Map of air quality monitors and case residences. Reprinted with permission from the University of Washington Libraries and the City of Seattle.

STATISTICAL METHODS

The case-crossover design was originally devised by Maclure (1991) to study the effects of transient changes in exposure on health events that occur in close temporal proximity to exposure. This design only requires exposure data for cases but can be regarded as a special type of case-control study in which each case serves as his/her referent. As originally formulated, exposures close in time to the event (index period) are contrasted with exposures at a previous, presumably typical, time when an event did not occur (referent period) (Maclure 1991; Mittleman et al 1995). Selection of the index period (usually a single day in

Table 2. Distributions of Daily Means of Air Pollution Variables and Temperature

Variable	Units	*n*	Minimum	10%	25%	50%	75%	90%	Maximum	Mean
Nephelometer measures of PM	bsp	2,161	0.09	0.22	0.30	0.47	0.80	1.32	3.70	0.65
$PM_{2.5}$	$\mu g/m^3$	579	1.0	7.5	10.0	15.5	23.0	33.0	96.0	18.4
PM_{10}	$\mu g/m^3$	2,106	6.0	15.0	19.7	27.7	39.0	54.7	178.0	31.9
SO_2	ppm	2,024	0.000	0.004	0.006	0.008	0.010	0.013	0.029	0.008
CO	ppm	2,161	0.52	1.03	1.28	1.65	2.17	2.68	5.92	1.79
Ozone[a]	ppm	1,331	0.000	0.006	0.010	0.016	0.021	0.026	0.044	0.016
Temperature	˚F	2,161	15	40	45	53	62	66	83	53.03

[a] April to October monitoring only.

Table 3. Pearson Correlation Coefficients Among Air Pollutants

Variable	Nephelometer	$PM_{2.5}$	PM_{10}	SO_2	CO	Ozone	Temperature
Nephelometer	1	0.936	0.864	0.247	0.750	–0.465	–0.383
$PM_{2.5}$		1	0.907	0.350	0.821	–0.514	–0.271
PM_{10}			1	0.375	0.812	–0.325	–0.259
SO_2				1	0.290	0.039	–0.047
CO					1	–0.473	–0.267
Ozone						1	0.322
Temperature							1

studies of air pollution) follows similar logic to conventional time-series analyses; the index day may be the day of the event or some previous day, allowing for a lag between exposure and the manifestation of the event. However, as discussed in the literature (Greenland 1996; Navidi 1998; Bateson and Schwartz 1999; Lee and Schwartz 1999; Neas et al 1999), the choice of referent days in air pollution research poses greater methodologic challenges than selection of the index period because several potential biases need to be avoided or minimized: (1) selection bias from long-term or seasonal patterns of exposure and disease events, as might occur when index and referent periods are spaced too far apart; (2) autocorrelation among daily exposure levels, which would occur when index and referent periods are too closely spaced; and (3) confounding by day-of-week effects, when the day of week is a predictor of both exposure and health outcome. Navidi (1998) proposes a bidirectional approach to referent time selection, in which referents may be chosen from times before as well as after the case event times. This scheme reduces bias from time trends of exposure, provided that case occurrences do not influence subsequent exposure (a very reasonable assumption for studies of air pollution.)

Despite some methodological guidance regarding referent day selection from others' work, no optimal referent sampling strategy for case-crossover designs in general or for air pollution studies has been identified. Moreover, recent work by Levy (1999) and Lumley and Levy (2000b) demonstrates that the necessary statistical assumptions for conditional logistic regression, which is the standard method for case-crossover analysis, may be violated by prevailing referent sampling schemes. In order to examine these methodological issues, we conducted a simulation study that contrasted the direction and magnitude of bias in estimated relative risks from conditional logistic regression analyses of case-crossover data under a variety of referent sampling schemes. The simulation study is described in detail in Appendix A and elsewhere (Levy 1999). A brief summary follows.

Simulations were performed in which referent days were selected within 30 days, before and after, of the index days; 30 days was chosen to avoid potential bias related to seasonal trends. The influences on bias associated with directionality (retrospective vs bidirectional), imposition of an exclusion period between index and referent days to minimize short-term autocorrelation of exposure, and number of

referents per index day were examined. The results indicate that the least biased referent selection scheme is one in which referent days are matched to index days on day of the week within the month and year of the index day. This is bidirectional referent sampling that is not constrained to be symmetrical around the index day. This sampling strategy has the desirable characteristic of controlling for day of week, which is often related to both exposure and acute disease outcomes. This scheme also satisfies the principle of independence of exposures among index and referent days, thus permitting valid application of conditional logistic regression (Lumley and Levy 2000b).

Relative risks and 95% confidence intervals associated with interquartile ranges of daily nephelometry (51 bsp) and PM_{10} (19.3 μg/m^3) exposures were estimated by conditional logistic regression from comparisons between index and referent days, using the referent sampling scheme described above. Separate analyses were performed allowing for lags of 0 to 5 days between SCA event and index days. Analyses were performed for single pollutant models (bsp, PM_{10}), and for multiple pollutant models that included CO and SO_2. Effect modification was examined by stratified analysis according to season, time period of the study (early, late), age, and other known risk factors for SCA: cigarette smoke exposure, aspirin use, alcohol consumption, physical activity, consumption of long chain *N*-3 polyunsaturated fatty acids, as well as a composite index of coronary heart disease risk factors. The composite index was defined as the presence of any of the following: diabetes mellitus, hypercholesterolemia, hypertension, and history of myocardial infarction or sudden death in a first-degree relative.

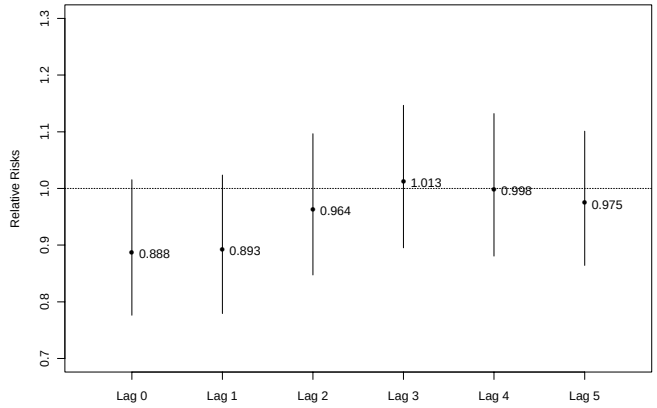

Figure 2. Unadjusted interquartile range relative risks and 95% confidence intervals for nephelometry measures of fine PM by lag days.

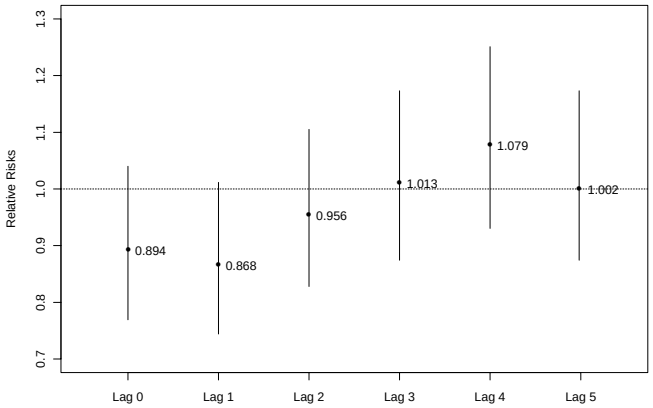

Figure 3. Unadjusted interquartile range relative risks and 95% confidence intervals for PM_{10} by lag days.

RESULTS

Interquartile range relative risks (IQR-RR) for nephelometry of PM exposure are shown for lag times ranging from 0 to 5 days in Figure 2. The only instance of an elevated interquartile range relative risk was for a lag of 3 days, although this was a very small excess (IQR-RR = 1.013). Relative risk estimates of less than 1.0 were observed for all other lag intervals, and all effect estimate confidence intervals included the null value. The corresponding findings for PM_{10}, displayed in Figure 3, follow a generally similar pattern of association that is neither strong nor consistent with SCA. Analysis of bsp with a 1-day lag is presented by season and time period of study in Table 4. Adjustments for copollutants SO_2 and CO had, at most, slight effects on the results. For example, the crude and copollutant-adjusted interquartile range relative risk for bsp with a 1-day lag were, respectively, 0.893 and 0.902. Thus,

Table 4. Interquartile Range Relative Risk Estimates for Nephelometry Measures of PM (bsp), PM_{10}, CO, and SO_2 at 1-Day Lag

Pollutant	IQR-RR	95% CI
bsp, unadjusted	0.893	0.779 – 1.024
PM_{10}, unadjusted	0.868	0.744 – 1.012
CO, unadjusted	0.990	0.828 – 1.183
SO_2, unadjusted	0.872	0.762 – 0.999
bsp, adjusted for CO	0.887	0.725 – 1.085
bsp, adjusted for SO_2	0.916	0.794 – 1.056
bsp, adjusted for CO, SO_2	0.902	0.735 – 1.106
PM_{10}, adjusted for CO	0.795	0.621 – 1.017
PM_{10}, adjusted for SO_2	0.881	0.742 – 1.045
PM_{10}, adjusted for CO, SO_2	0.802	0.612 – 1.051

confounding by copollutants did not mask associations with SCA.

Table 5 summarizes results of stratified analyses according to levels of potential effect modifiers, including age, cigarette smoke exposure, other cardiovascular disease risk or protective factors, and season. The observed interquartile range relative risks fluctuated somewhat by season, but the results were essentially null. The strongest effect (IQR-RR = 1.20) was observed for autumn (September to November). However, the largest risks would have been anticipated for the winter (December to February) when PM levels in Seattle are greatest due to woodburning activity. The relative risk estimate for the winter months (0.88) was not elevated. No pattern of association by time of study was noted. Stratified analyses by age and other cardiovascular disease risk factors did not reveal evidence of effect modification. Thus, we did not identify any apparent susceptible subgroups in this case series. We also performed stratified analyses examining main effects and effect modification with lag intervals other than 1 day for bsp and for PM_{10}, with lags of 0 to 5 days. The results of these analyses (data not shown) were not materially different from those presented for bsp with a 1-day lag.

Table 5. Interquartile Relative Risks for Nephelometry (bsp) at 1-Day Lag, Stratified by Potential Effect Modifiers[a]

Potential Modifier	IQR-RR	95% CI
Age		
< 55 Years	0.80	0.67–0.95
≥ 55 Years	1.08	0.87–1.35
Current Smoker or ETS Exposure		
No	0.84	0.68–1.03
Yes	0.98	0.81–1.19
Aspirin Use		
< 2 Tablets/week	0.91	0.78–1.06
≥ 2 Tablets/week	0.83	0.62–1.12
Alcohol Consumption		
< 1 Alcoholic beverage/day	0.84	0.71–0.99
≥ 1 Alcoholic beverage/day	1.03	0.82–1.31
Long-Chain *N*-3 Polyunsaturated Fatty Acids		
≤ Median and no supplements	0.80	0.66–0.99
> Median or fish oil supplements	0.98	0.82–1.19
Physical Activity		
Inactive	0.90	0.63–1.27
Active	0.89	0.77–1.03
Composite of Indicators for Coronary Artery Disease		
Any DM, Chol, Htn, FHx	0.84	0.71–0.99
None	1.04	0.81–1.33
Any Susceptibility Risk Factor (Absence of Any Previous 6)		
Yes	0.90	0.78–0.99
No	0.76	0.36–1.63
Season		
Winter (Dec, Jan, Feb)	0.88	0.74–1.04
Spring (Mar, Apr, May)	0.57	0.36–0.91
Summer (Jun, Jul, Aug)	0.34	0.10–1.13
Autumn (Sep, Oct, Nov)	1.20	0.91–1.58
Time Period		
Early	0.94	0.79–1.11
Late	0.82	0.65–1.03

[a] ETS, environmental tobacco smoke; DM, history of treatment for diabetes mellitus; Chol, history of treatment for high cholesterol; Htn, history of treatment for hypertension; FHx, family history of early myocardial infarction or sudden death.

DISCUSSION

Considerable uncertainty remains about the types and magnitudes of deleterious effects to the cardiovascular system that might be attributable to daily PM air pollution. Most prior epidemiologic research on this topic has been limited to time-series studies of mortality and hospital admission rates. The literature indicates a generally consistent pattern of excess risk, albeit small in magnitude. In view of the nonspecific cardiovascular disease outcomes assessed in prior studies, detection of much stronger effects for particular subtypes of cardiovascular disease might have been anticipated. In this study, we investigated a well-defined manifestation of cardiovascular disease—out-of-hospital SCA—to explore the hypothesis that increases in PM might act as a trigger for SCA events. We found no evidence that elevated PM exposure was associated with risk in this case series. Moreover, we did not observe effect modification in the association between PM with SCA by season, age, smoking, or a composite of cardiovascular disease risk factors; no susceptible subgroups were identified. Our findings were consistent when either nephelometry or PM_{10} was regarded as the PM exposure metric.

Interpretation of these null results should be made in light of the study's strengths and limitations. One notable strength of this study was the availability of personal risk factor information, which enabled examination of effect modification. This is an improvement over most prior research, which has relied on anonymous mortality or hospital admissions data. Also, parallel analyses were

possible for nephelometry data (particles < 1 μm in aerodynamic diameter) and PM_{10}. There were too few $PM_{2.5}$ data to support a third analysis, although given the strong correlation between bsp and $PM_{2.5}$ seen here and previously in Seattle (Koenig et al 1993), it is unlikely that a qualitatively different association with SCA would have been seen for $PM_{2.5}$.

Our study did, however, suffer from potential exposure misclassification because we were forced to rely on daily city-wide exposure measurements. Environmental PM monitoring of this type cannot take into account interindividual exposure variability due to personal mobility, indoor PM exposures, and other factors. This methodological problem pervades much of the research on PM-related health effects. Unfortunately, no practical solution for this problem is currently available for epidemiologic studies of acute-onset, life-threatening diseases. Nonetheless, masking of an important exposure-response relation by exposure misclassification is highly unlikely. Our study had adequate statistical power to detect modest relative risks of roughly 1.5, although this series of 362 cases was too small to detect smaller magnitude effects (eg, RR = 1.1) commonly reported in the PM and cardiovascular disease literature.

Several plausible explanations can be offered for the absence of an observed effect of daily PM on SCA risk in this case series. One possible explanation for our results relates to the highly selective nature of the SCA case series. In the original study by Siscovick and coworkers (1995), cases were intentionally selected to be events that occurred out of hospital in persons with no history of previously identified clinical heart disease. The case group was further limited to persons without known life-threatening comorbid conditions (eg, cancer). Consequently, this case group probably had a lower prevalence of compromised cardiovascular or general health than would be expected in a typical, unselected SCA case series. The possibility thus exists that cases in our study were resistant to the cardiotoxic effects of PM, if indeed such effects do occur. Studies of larger case series that include both persons with and without prior cardiovascular disease would certainly be indicated. Another explanation might be that the mechanisms of PM cardiovascular toxicity do not involve short-term triggers that culminate in SCA. For example, an effect of PM on cardiac function might involve cumulative damage over periods of months or years that ultimately increases risk of cardiac arrest. A study such as ours, which considered only exposures close in time to case occurrence, would not be suitable to detect adverse effects from long-term cumulative exposure. Better understanding of the underlying mechanisms of PM-related toxicity to the cardiovascular system obtained from suitably designed animal experiments and studies of preclinical physiological functional changes in humans should help guide further epidemiologic investigations.

Another possible reason for our results is that exposures in the Seattle area are too low to cause an effect. The case-crossover findings reported here agree with results from time-series analyses of daily mortality data in Seattle from 1985 to 1995 in which no elevated risks related to PM were detected for either all cardiovascular diseases combined or ischemic heart disease (Levy 1999). The mean PM_{10} level for study days in this analysis was 32 $\mu g/m^3$, which is lower than levels found in other metropolitan areas in which positive associations were found (see Table 6). Hospital admissions for cardiovascular disease in Seattle were related to daily PM_{10} increases in the analysis by Schwartz (1999); however, among the eight metropolitan areas studied, the relation was weakest for Seattle. Epidemiologic studies of cardiovascular disease in other settings with low PM and copollutant ambient levels would help clarify whether our findings are anomolous or are truly consistent with null effects.

Table 6. Comparison of Distributions of PM_{10} from Published Analyses

	PM_{10} ($\mu g/m^3$)							
	10%	25%	Median	75%	90%	Mean	Years	Interquartile Value
Seattle (present study)	15	20	28	39	55	33	88–94	19
Detroit (Schwartz and Morris 1995)	22	30	43	62	82	48	86–89	32
Tuscon (Schwartz 1997)	21	28	39	51	63	42	88–90	23
Spokane (Schwartz 1996)	—[a]	24	37	57	—	46	88–90	33
Minneapolis-St Paul (Moolgavkar et al 1997)	17	22	30	41	55	34	86–91	19
Birmingham (Moolgavkar et al 1997)	19	26	39	56	74	43	86–91	30
Utah Valley (Pope et al 1992)	—	29	38	51	—	47	85–89	22

[a] A dash (—) indicates data not provided.

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APPENDIX A. Referent Selection in Case-Crossover Analyses of Acute Health Effects of Air Pollution*

INTRODUCTION

The case-crossover design is suited to the study of a transient effect of an intermittent exposure on the subsequent

* The authors of Appendix A are Drew Levy, Lianne Sheppard, and Harvey Checkoway.

risk of a rare acute-onset disease hypothesized to occur a short time after exposure. In the original development of the method (Maclure 1991; Mittleman et al 1995), risk estimates were based on within-subject comparisons of exposures associated with incident disease events and exposures at times prior to the occurrence of disease, using matched case-control methods. The principle of the analysis is that exposure of cases just prior to the event are compared to the distribution of exposure estimated from some separate time period. This separate referent time period represents the expected distribution of exposure for follow-up time at risk.

The health effects of fine PM is a topical epidemiologic issue for which the case-crossover design may be especially useful. Fine particulate air pollution is an exposure that varies over time, and it raises concern regarding its effect on the incidence of acute cardiovascular and respiratory disease events (Dockery and Pope 1994; Schwartz 1994a,b). Extensive time series of daily air pollution measures for metropolitan regions are often available for air pollution research. Previous studies of the relation of air pollution and health events have taken advantage of these data in Poisson regression time-series analyses of health events (Samet et al 1995; Schwartz et al 1996; Vedal 1997). The use of alternative analytic approaches and statistical models is indicated in attempting to make causal inferences about air pollution effects. When detailed data are available on an individual level, the case-crossover design may have advantages over ecologic Poisson regression studies in being able to evaluate effect measure modification by individual level factors.

A disadvantage of the case-crossover design is the potential for bias due to time trends in the exposure time series. Since case-crossover comparisons are made between different points in time, the case-crossover analysis implicitly depends on the assumption that the distribution of the study exposure is stable over time. Consistency over time in the measure of location and variance for a distribution of a variable is referred to in statistics as "stationarity." If the exposure time series is nonstationary and case exposures are compared with referent exposures systematically selected from a different period in time, a bias may be introduced into estimates of the measure of association for the exposure and disease.

In the original descriptions of the case-crossover method, time is completely associated with selection of referents: the cases in the case-crossover pairs come only from later periods; the referents come only from earlier periods. Greenland (1996) identifies the effects on estimation of measures of association when the distribution of exposure is nonstationary as a form of selection bias. This time-selection bias is of particular concern for those undertaking case-crossover analyses of acute health effects of air pollution because of the temporal patterns in PM time-series data.

In PM data, the average PM level is not stationary over time in two ways and, thereby, there are two ways in which the case-crossover analysis could be vulnerable to time-selection bias. Long-term, or secular, time trend occurs as pollution levels change gradually from year to year (Figure A.1 provides an example of a declining long-term trend in the Seattle PM data). If PM levels gradually increase over time, due, for instance, to population pressures and increased traffic in a region, systematically selecting historical referents from an earlier period, when pollution levels tend to be lower, can yield a bias that will exaggerate the relative risk.

In addition, distinct seasonal differences in PM levels can induce a time-selection bias (Figure A.1). In this intermediate-scale time frame, some historical referent selection strategies may introduce a bias. Selecting referents from other seasons misrepresents the expected distribution of exposure for the season that gave rise to the case. For instance, systematically selecting referents from other seasons for cases that occur in winter may induce a bias away from the null.

Navidi (1998) proposes an approach for addressing time-selection bias in case-crossover analyses—the bidirectional case-crossover design—for exposures with time trends. When the occurrence of disease events does not affect subsequent exposure, as is the case with time series of environmental exposures such as air pollution, Navidi proposes that referent exposures sampled after the event are also suitable for estimating the distribution of exposures not associated with a case event. In the bidirectional case-crossover design, exposures associated with disease

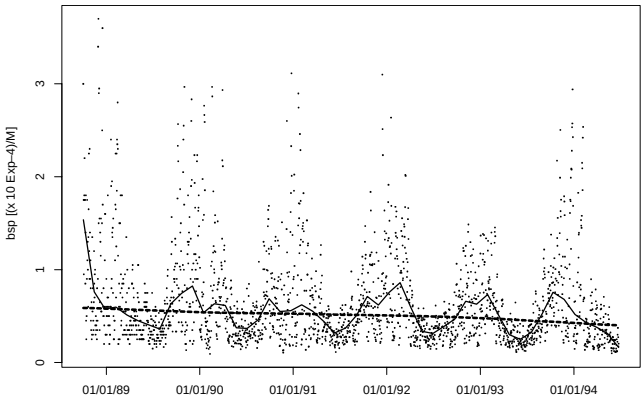


Figure A.1. PM for study period showing long-term trend and seasonal patterns.

events are compared with exposures occurring both before and after the event. By balancing referent exposures prior to the event with referent exposures that occur subsequent to the event, the time-selection bias due to linear time trend that occurs with unidirectional sampling is canceled out. Navidi provides a series of simulations showing that relative risk estimates from the bidirectional referent sampling strategy are resistant to the time-selection bias.

Seasonal and secular patterns in PM levels represent ways in which independence among observations assumed in most statistical models used in analysis does not hold in analyses of PM data. Seasonal patterns of correlation in PM time series are evident (Figure A.2). Another form of dependence occurs with short-term (6 days or less) autocorrelation in PM time series (Figure A.3). This short-term autocorrelation is likely due to synoptic weather patterns that affect ambient PM concentration through source generation and accumulation in the atmosphere. Selecting referents from time adjacent to the case event exposure may be thought of as being analogous to overmatching in conventional case-control studies, and the likelihood that short-term autocorrelation in the time series contributes a bias toward the null is anticipated.

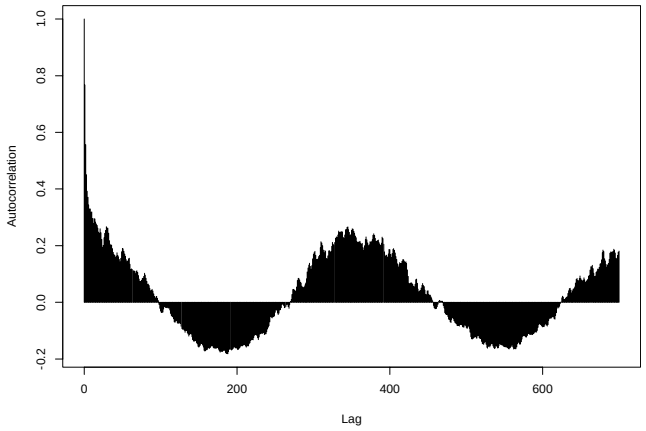


Figure A.2. Autocorrelation as a function of lag.

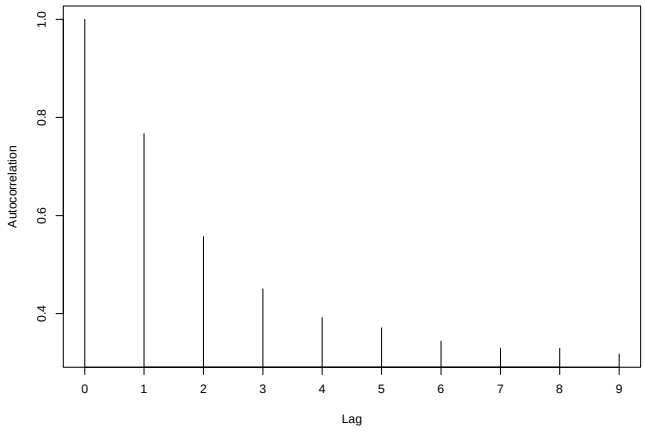


Figure A.3. Short-term autocorrelation as a function of lag.

Awareness of the potential for biases due to long-term time trend, seasonality, and autocorrelation in a case-crossover analysis of acute health effects of PM prompts consideration of various design strategies for sampling referents that might avoid substantial bias. Bidirectional referent sampling would, in principle, control for linear long-term time trend. The problem of seasonality (and secular trend) in the PM time series might be dealt with by restricting the sample frame for referents to a period short enough to be free of significant seasonal transitions. If the influence of season is relatively homogeneous within a window of ± 30 days of a case event, restricting referent selection to a window of this period might minimize the problem posed by seasonal time-selection bias. Autocorrelation in the time series might be dealt with by further restricting the referent sampling window. Excluding from the referent sample frame a period in which substantial autocorrelation in the time series is found would mitigate this source of time-selection bias.

The following simulations were undertaken to (1) explore the nature and degree of time-selection bias and (2) examine the ability of the strategies proposed above to counter biases in a case-crossover analysis of the association of fine PM and out-of-hospital SCA. The main strategy tested in our simulations is use of a bidirectional referent sampling window restricted to 30 days before and after the occurrence of a case event (Figure A.4 panel C). Additionally, a 6-day window around the case event day, excluding potential referent days (Figure A.4 panel D), is defined to address potential bias from short-term autocorrelation in the exposure time series.

An alternative strategy was devised to address the concern that short-term autocorrelation between the referents themselves may also be a source of bias in the estimates. The original strategy was further elaborated by requiring a 6-day autocorrelation exclusion period between all observations used in the analysis. The reason was that this would allow for the necessary independence among all observations. The alternative fixed interval strategies (Figure A.4 panels E and F) select referents only among lags and leads of 7, 14, 21, and 28 days.

Statistical precision is important for analyses of health effects of air pollution that characteristically have small relative risks and a limited number of cases. Multiple referents may allow us to extract the maximum amount of information from the data. Since preexisting exposure time-series data are used, referents are inexpensive and

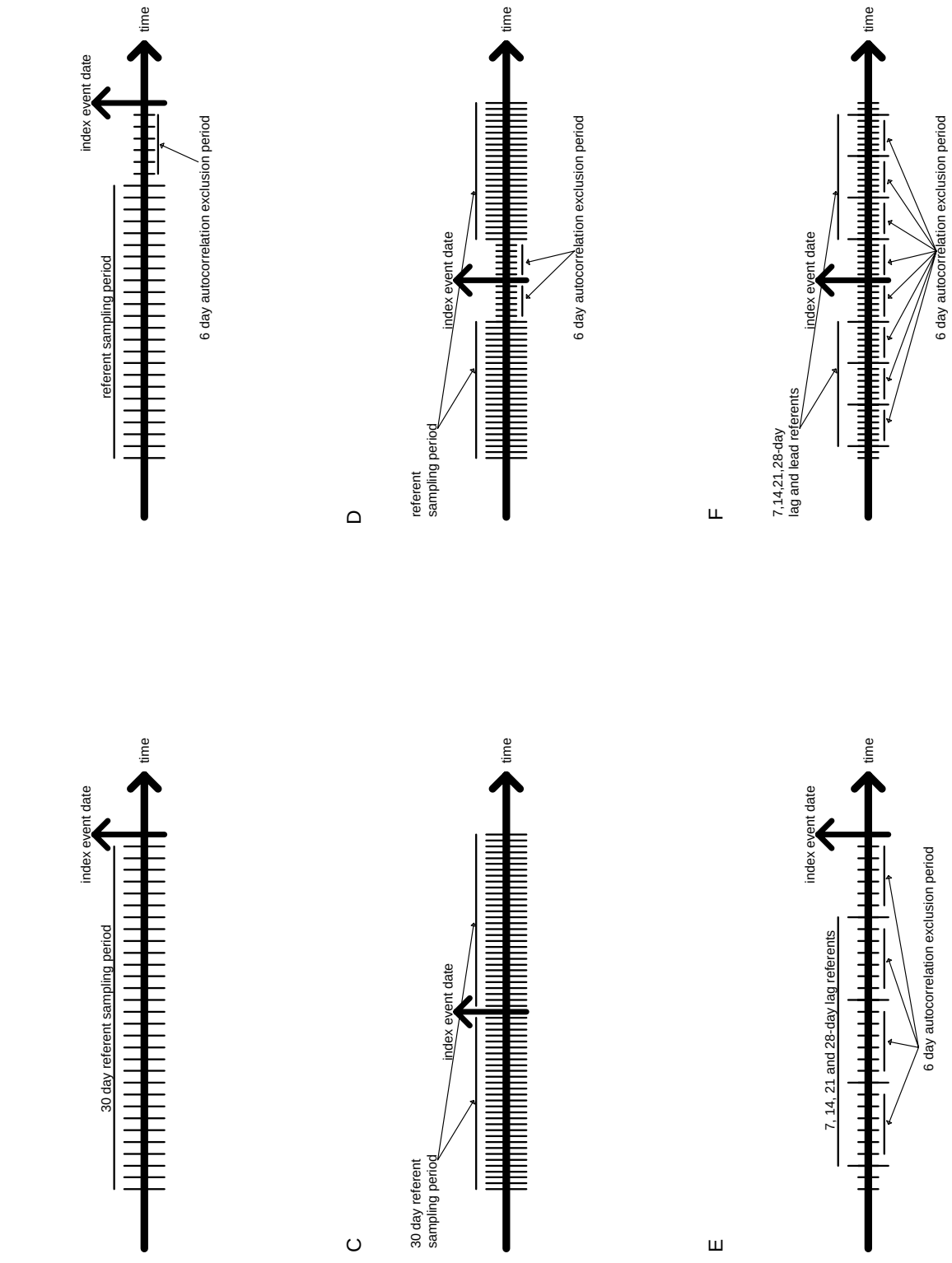


Figure A.4. Referent selection strategies. A: Set 2; retrospective referent selection within the prior 30 days of the case event without the 6-day autocorrelation exclusion period. B: Set 3; same as panel A, but with the 6-day autocorrelation exclusion period. C: Set 4; bidirectional referent selection without the 6-day exclusion period. D: Set 5; same as panel C but with the 6-day exclusion period. E: Set 8; retrospective fixed-interval strategy. F: Set 9; bidirectional fixed-interval strategy.

the issue is one of optimal statistical efficiency rather than cost. Examining the variation in statistical precision that occurs as a function of the number of referents used was also of interest in exploring various analysis strategies.

This series of simulations had two objectives: (1) to assess the nature of time-selection bias in the PM data series used in the analysis of the study data by examining the effect of various fixed retrospective lags on the measure of association; and (2) to assess the ability of the proposed referent selection strategies to counter the bias anticipated from secular trends, seasonal patterns, and short-term autocorrelation in the PM time series. The design of the simulations concerning the proposed referent selection strategies had four aims: (1) to compare use of retrospective referents with bidirectional referents; (2) to evaluate the effect of varying the number of referents on precision of estimation; (3) to consider the inclusion of the 6-day exclusion period (initially between cases and their referents and subsequently between all referents in a stratum as well) intended to mitigate the influence of short-term autocorrelation. The simulations were extended: (4) to evaluate the effect of serial correlation in the proposed bidirectional sampling design by using permuted PM time-series data to remove serial correlation from the data.

METHODS

"Real" ambient air pollution measurements were used for the exposure time-series portion in this simulation study. Data for PM were obtained from the PSCAA. Daily averages of fine PM as measured by nephelometer were used. The particle light-scattering extinction coefficient (given in bsp units) measured by a nephelometer is proportional to the particle mass concentration (Assembly of Life Sciences 1979). The serial correlation between $PM_{2.5}$ and bsp at individual monitoring sites in the Seattle area was 0.94–0.95, indicating that nephelometry was an excellent proxy for daily variation in gravimetric measures of PM. Data from three sites in King County—Lake Forest Park, Duwamish, and Kent—were averaged to provide daily measures of exposure for the region. For a total of 2,092 observations, the range of PM (in bsp) was 0.09–3.7 and the mean value was 0.65; the 25% quartile was 0.3, the median was 0.47, and the 75% quartile was 0.81.

In these simulations, the occurrence of events was simulated. Reflecting the actual case series to be used in the analysis, 362 events were distributed over the 2,092-day study period as a function of exposure on day j. The probability that an event occurred at time t_j is given by the proportional hazards model,

$$\lambda = h(t, x) = h_0(t) \bullet e^{\beta x}, \qquad (1)$$

where the coefficient β, was specified based on an incidence density ratio, $\exp(\beta)$, of 1.5 per interquartile range change in bsp:

$$\beta = \ln(1.5)/IQR.$$

The interquartile range for the Cardiac Arrest Blood Study period is 0.51 bsp, giving a $\beta = 0.795$.

Furthermore, let $h_0(t) = \alpha$ represent the baseline incidence rate. The sum of the mean daily incidence rate over the study period, which yields a cumulative incidence of 362 cases, is expressed as:

$$\sum_{t=1}^{n=2092} \lambda = 362.$$

Based on the proportional hazards model:

$$\sum_{t=1}^{n} (\alpha \bullet e^{\beta x}) = 362,$$

$$\alpha \bullet \sum_{1}^{n} e^{\beta x} = 362,$$

$$\alpha = 362/\sum_{1}^{n} e^{\beta x},$$

where α is the baseline incidence for model (1), which supplies the Poisson random number generator with the hazard that is a function of exposure at time t_j.

Nine sets of simulations were performed. The first set, to assess the nature of time-selection bias, used fixed retrospective single-day lags: 365, 180, 90, 60, 30, 21, 14, 7, and 1 day prior to case events. Subsequent sets were designed to assess the ability of various referent selection strategies to counter bias. The second set (Figure A.4 panel A) involved retrospective referent selection within the prior 30 days of the case event using 1, 2, 4, and 10 randomly selected (with replacement) days, and all 30 days in the referent selection sampling frame. The third set (Figure A.4 panel B) involved retrospective referent selection with the 6-day exclusion period using 1, 2, 4, and 10 randomly selected days, and all 24 days in the referent selection sampling frame. The fourth set (Figure A.4 panel C) involved bidirectional referent selection without 6-day exclusion period using 1, 2, 4, and 10 randomly selected days, and all 60 days in the referent selection sampling frame. The fifth set (Figure A.4 panel D) involved bidirectional referent selection with the 6-day exclusion period using 1, 2, 4, and 10 randomly selected days, and all 48 (61 minus 13) days in the referent selection sampling frame. The sixth and seventh set repeated the fourth and fifth set with permuted data.

The eighth and ninth set involved a referent selection strategy in which all cases and referents were required to be separated by 6 days within the ± 30-day window. The eighth set (Figure A.4 panel E) retrospectively selected referents at these lag periods: 7 days; 7 and 14 days; 7, 14, and 21 days; and 7, 14, 21, and 28 days. The ninth set (Figure A.4 panel F) bidirectionally selected referents at identical lead and lag periods: 7 days; 7 and 14 days; 7, 14, and 21 days; and 7, 14, 21, and 28 days.

All analyses were performed in S-PLUS (MathSoft, Seattle WA). Conditional logistic regression was performed with the Cox proportional-hazards function, with a dummy variable for *time* = 1, and the method option set to "exact." For simulations of retrospective referent sampling at fixed lags, 10,000 iterations were performed; all other simulations were iterated 1,000 times. Standard errors and confidence intervals for the mean of the individual estimated coefficients are based on the number of iterations. Coverage statistics are calculated as the proportion of the time that confidence intervals for individual estimates in each iteration include the true parameter.

RESULTS

Figure A.1 illustrates the small but discernible long-term time trend in the PM time series over the course of the study period. Seasonality is evident in the scatterplot of the data, and a locally weighted smoother (LOESS) (span = 90/2,092) fit to the data demonstrates the nonstationarity of the average PM level, which follows a seasonal pattern over time. A strong seasonal pattern of serial correlation in the time-series data is evident in the autocorrelation function graph in Figure A.2. Short-term autocorrelation, more appreciable in Figure A.3, ranges from 0.75 at immediately adjacent days to 0.35 at the 6-day lag when the pattern begins to plateau to a level consistent with anniversary and seasonal correlations.

The pattern of bias in the estimation of the association of PM and the incidence of events that occurs when various single, specific fixed lags are chosen as the referent exposure (set 1) is shown in Figure A.5. A 1-year lag is associated with a negative bias of 24%, with only 67% of the 95% confidence intervals for each of the estimates in the 10,000 iterations containing the value of the true coefficient (Table A.1). Lags of half a year through one month are biased in the range of 2.7% to 0.7%. A 21-day lag for referents is negatively biased by 2% to 3%, while 7-day and 14-day lags have biases of less than 1%. The 1-day lag is positively biased by 2.6% to 3.8%, and the average standard error is relatively inflated.

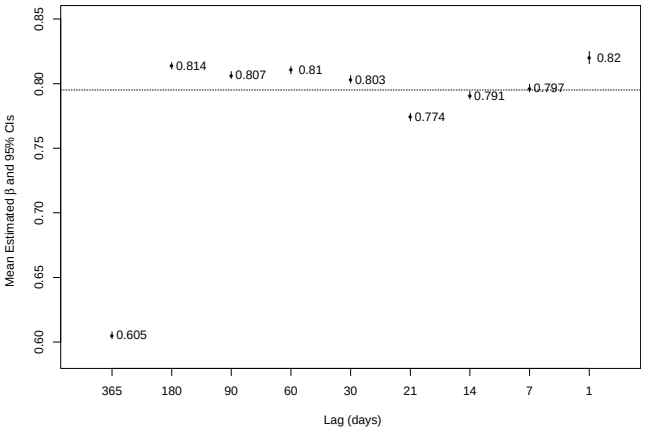


Figure A.5. Simulation set 1: Historical referent selection.

The strategy of randomly choosing retrospective referent exposures from within a 30-day window (set 2, Figure A.6) shows a pattern of bias that is a function of the number of referents chosen. A single referent is relatively unbiased. Choosing 10 referents randomly within the 30-day window improves the precision by one-third but is associated with a bias of 5% to 6%. Using all 30 days in the sample frame is associated with a bias of 3% to 4%. This pattern of increasing bias with the number of referents is exacerbated when the 6-day autocorrelation exclusion period is included in the definition of the sample frame (set 3, Figure A.7). With the 6-day exclusion, using 10 referents is associated with a positive bias of 12% to 14%.

Bidirectional random sampling of referents within the ± 30-day window results in a positive bias of 4% or less for all referents without the 6-day exclusion period (set 4, Figure A.8). For the bidirectional series with the 6-day exclusion period (set 5, Figure A.9) the bias begins in the range of 2% and increases with the number of referents to 9% to 10% with 10 referents. With the 6-day exclusion period, use of all available days in the sampling frame as referents results in a bias of 6% to 7% and yields coverage of only 88%.

Using permuted data to remove serial correlation from the time series results in biases in the range of 0.6% to 3% for 4 referents or less, regardless of whether the 6-day exclusion period pertains. For 10 referents, the bias is 1.4% to 2.6% without the ± 6-day exclusion (set 6, Figure A.10), and 2.1% to 3.3% with the ± 6-day exclusion (set 7, Figure A.11). Using all days in the window as referents in the permuted data yields an unbiased estimate with or without the ± 6-day exclusion.

Both of the fixed-interval referent selection strategies show a monotonically changing pattern of bias. For the

strategy limited to retrospective referents (set 8, Figure A.12) the single 7-day lag is unbiased, but an increasing negative bias as large as –2.0% to –3.7% is evident as the 14-day, 21-day, and 28-day lags are included. For the strategy with bidirectional referents (set 9, Figure A.13), the 7-day lead and lag is biased by 1.5% to 3.4%, and this bias progressively disappears as 14-day, 21-day, and 28-day leads and lags are added.

Table A.1. Simulation Results

Lag Period, Number of Referents, or Strategy	95% CI[a]	Percentage of Bias	Coverage[b]	SE[c]
Set 1. Retrospective Referent Selection with Selected Single-Day Lags (Lag Period)				
365	0.603, 0.608	–24.2, –23.5	0.670	0.134
180	0.811, 0.816	2.0, 2.7	0.953	0.129
90	0.804, 0.809	1.1, 1.8	0.948	0.139
60	0.808, 0.813	1.6, 2.3	0.944	0.144
30	0.800, 0.806	0.7, 1.4	0.949	0.149
21	0.771, 0.777	–3.0, –2.3	0.945	0.146
14	0.788, 0.794	–0.9, –0.1	0.948	0.150
7	0.794, 0.799	–0.2, 0.6	0.950	0.151
1	0.815, 0.825	2.6, 3.8	0.942	0.243
Set 2. Retrospective Referent Selection with 6-Day Exclusion (Number of Referents)				
1	0.780, 0.799	–1.8, 0.5	0.938	0.152
2	0.791, 0.807	–0.5, 1.5	0.948	0.124
4	0.812, 0.825	2.1, 3.8	0.940	0.108
10	0.832, 0.844	4.7, 6.1	0.916	0.096
30	0.816, 0.827	2.7, 4.0	0.927	0.088
Set 3. Retrospective Referent Selection with 6-Day Exclusion (Number of Referents)				
1	0.782, 0.800	–1.7, 0.6	0.939	0.148
2	0.810, 0.826	1.9, 3.8	0.953	0.123
4	0.847, 0.861	6.6, 8.3	0.912	0.107
10	0.893, 0.905	12.3, 13.8	0.782	0.097
30	0.888, 0.899	11.6, 13.0	0.781	0.090
Set 4. Bidirectional Referent Selection Without ± 6-Day Exclusion (Number of Referents)				
1	0.808, 0.827	1.7, 4.1	0.953	0.154
2	0.802, 0.817	0.9, 2.8	0.955	0.124
4	0.805, 0.818	1.3, 2.9	0.939	0.106
10	0.811, 0.822	2.0, 3.4	0.950	0.093
60	0.797, 0.807	0.2, 1.5	0.958	0.084

Table continues next page

[a] 95% CI for the mean of estimated β in each iteration.

[b] Coverage indicates the proportion of 95% CIs for individual estimates in each iteration that include the true parameter.

[c] Standard errors of the estimated relative risk parameters (β).

Table A.1. ***(Continued)*** Simulation Results

Lag Period, Number of Referents, or Strategy	95% CI[a]	Percentage of Bias	Coverage[b]	SE[c]
Set 5. Bidirectional Referent Selection With ± 6-Day Exclusion (Number of Referents)				
1	0.808, 0.826	1.6, 3.9	0.947	0.150
2	0.821, 0.836	3.3, 5.2	0.943	0.122
4	0.832, 0.845	4.7, 6.3	0.931	0.105
10	0.865, 0.876	8.8, 10.2	0.862	0.093
48	0.844, 0.854	6.1, 7.4	0.882	0.084
Set 6. Bidirectional Referent Selection Using Permuted Data Without ± 6-Day Exclusion (Number of Referents)				
1	0.802, 0.819	0.9, 3.0	0.952	0.137
2	0.805, 0.818	1.2, 2.9	0.947	0.109
4	0.803, 0.814	1.0, 2.4	0.947	0.091
10	0.806, 0.816	1.4, 2.6	0.941	0.078
60	0.789, 0.798	–0.7, 0.3	0.951	0.068
Set 7. Bidirectional Referent Selection Using Permuted Data With ± 6-Day Exclusion (Number of Referents)				
1	0.800, 0.814	0.6, 2.4	0.940	0.114
2	0.802, 0.816	0.9, 2.6	0.963	0.109
4	0.804, 0.815	1.1, 2.5	0.942	0.091
10	0.812, 0.821	2.1, 3.3	0.930	0.079
48	0.793, 0.801	–0.3, 0.8	0.954	0.068
Set 8. Retrospective Fixed-Interval Referent Selection Strategies (Strategy)				
7-Day	0.785, 0.803	–1.3, 1.1	0.947	0.150
7- and 14-Day	0.784, 0.799	–1.4, 0.4	0.955	0.120
7-, 14-, and 21-Day	0.779, 0.792	–2.0, –0.4	0.955	0.107
7-, 14-, 21-, and 28-Day	0.766, 0.778	–3.7, –2.1	0.948	0.100
Set 9. Bidirectional Fixed-Interval Referent Selection Strategies (Strategy)				
7-Day	0.807, 0.822	1.5, 3.4	0.957	0.121
7- and 14-Day	0.797, 0.809	0.2, 1.8	0.961	0.102
7-, 14-, and 21-Day	0.798, 0.810	0.3, 1.8	0.954	0.095
7-, 14-, 21-, and 28-Day	0.787, 0.798	–1.0, 0.4	0.955	0.091

[a] 95% CI for the mean of estimated β in each iteration.

[b] Coverage indicates the proportion of 95% CIs for individual estimates in each iteration that include the true parameter.

[c] Standard errors of the estimated relative risk parameters (β).

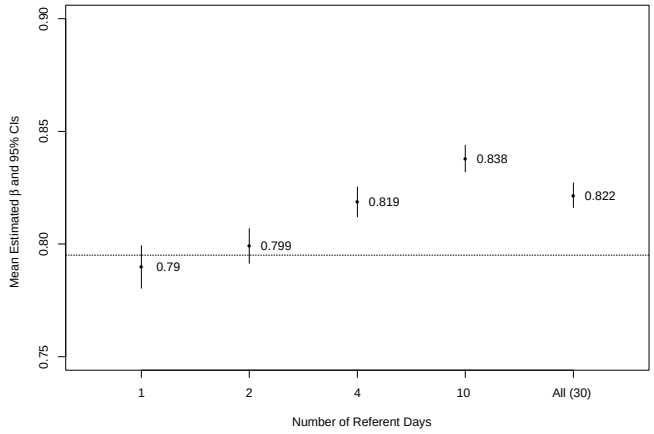


Figure A.6. Simulation set 2: Retrospective referent selection with 30-day window.

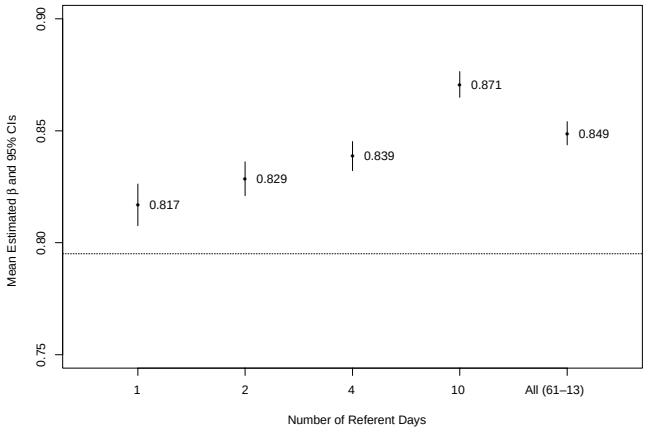


Figure A.9. Simulation set 5: Bidirectional referent selection with 6-day exclusion.

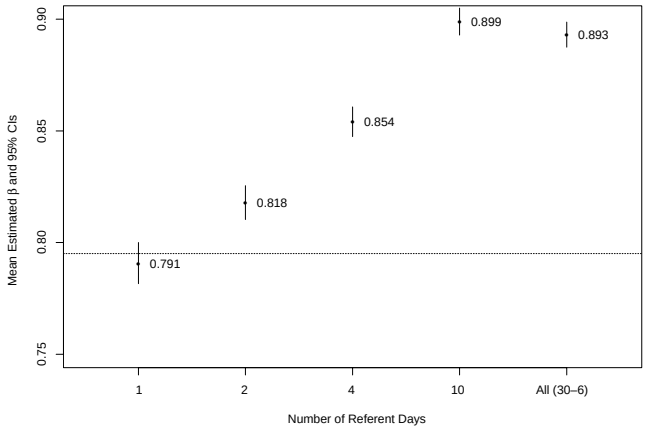


Figure A.7. Simulation set 3: Retrospective referent selection using 30-day window with 6-day exclusion.

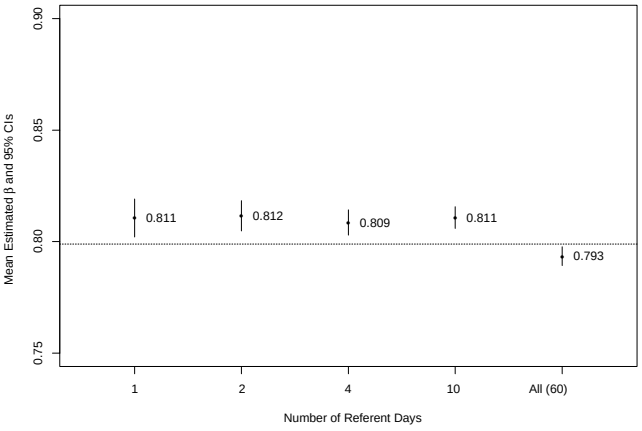


Figure A.10. Simulation set 6: Bidirectional referent selection with no 6-day exclusion and permuted data.

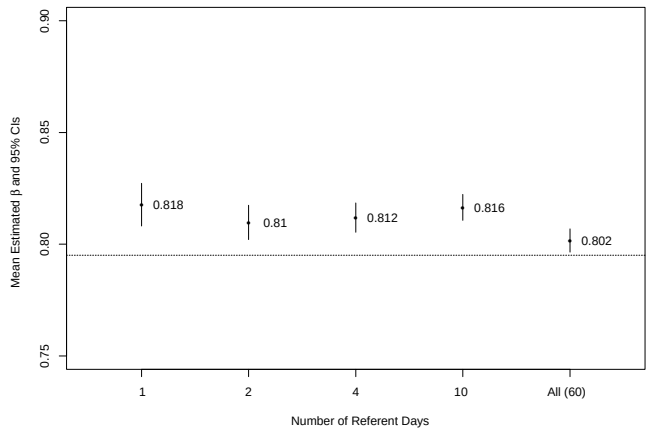


Figure A.8. Simulation set 4: Bidirectional referent selection with no 6-day exclusion.

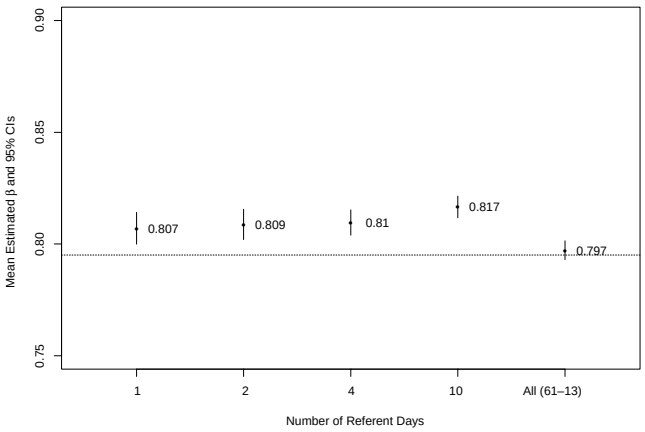


Figure A.11. Simulation set 7: Bidirectional referent selection with 6-day exclusion and permuted data.

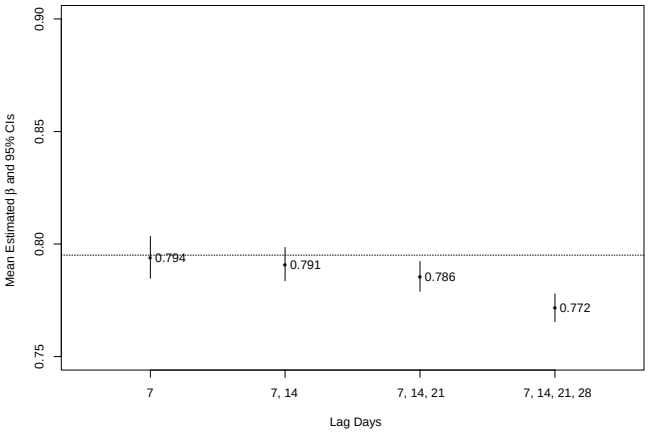


Figure A.12. Simulation set 8: Fixed-interval retrospective referent strategy.

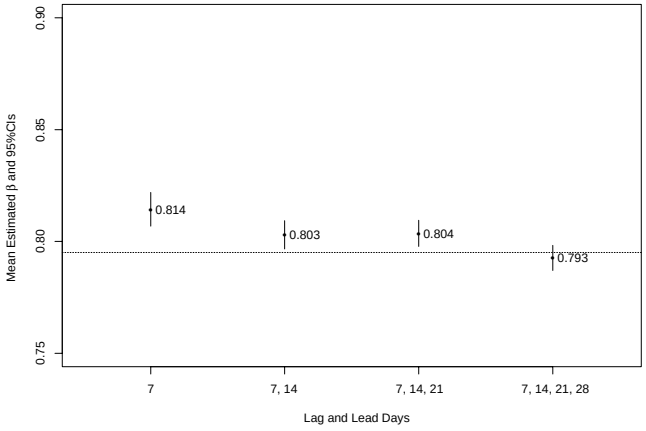


Figure A.13. Simulation set 9: Fixed-interval bidirectional referent strategy.

DISCUSSION

In these simulations of case-crossover analyses of air pollution time-series data, distinct and sometimes substantial bias is present in most of the referent sampling strategies studied. The approach based on restrictions designed to mitigate the various forms of bias anticipated in analysis of PM time-series data (simulation set 5), might have led to bias in the range of 6% to 10% with 10 or more referents if employed in a naive analysis. Given the small relative risks characteristic of the epidemiology studies of PM, this could easily have led to spurious conclusions. An analysis of the simulation results that leads to an understanding of the nature and cause of the biases observed can facilitate future application of the case-crossover design to air pollution problems.

These simulations attempt to elucidate the nature of time selection bias and the effect of various schemes for referent selection in case-crossover analyses involving PM time-series data by contrasting a number of factors: (1) retrospective versus bidirectional sampling, (2) the use of an exclusion to minimize short-term autocorrelation, and (3) the number of referents used. Simulations were extended to evaluate the influence of time-series patterns and serial correlation by permuting the data series. Complex patterns of bias are observed in these simulations. A possible explanation is that these complex patterns are the result of interaction of multiple competing sources of bias.

Time-Selection Bias Patterns

The retrospective single, fixed referent lag day series (simulation set 1) reveals a nonmonotonic pattern of bias. The extreme bias at the 365-day lag is qualitatively consistent with the expectation for the effect of a declining long-term time trend. If referents are systematically chosen from a period of time that tends to have higher exposure, then a bias toward the null is expected, as was observed. The positive bias of 2% to 3% seen for referent lags of 180, 90, and 60 days is qualitatively consistent with what might be expected for seasonal influences on referent exposure values, confounded to an unknown extent by the negative effect of long-term time trend. If cases tend to occur during the high air pollution seasons, choosing lags large enough to place referents in other seasons should make the referent exposures relatively lower. This selection bias would lead to the observed exaggeration of the estimated measure of association. The positive bias seen at the 30-day referent lag suggests that there may be some small seasonal influence even at that proximity to the case event. The negative bias seen at the 21-day referent lag and, to a lesser extent, at the 14-day lag, indicates that for some unknown reason the referent exposures at those lags systematically tend to be greater than expected. This may be related to cyclical weather patterns that drive local air pollution levels. Periodic signals consistent with these frequencies are apparent in the autocorrelation function. The 7-day referent lag (seen also in simulation set 8) seems to be unbiased. The 1-day referent lag shows a substantial positive bias. This conflicts with the expectation that a selection bias similar to “overmatching” in case-control studies leads to a bias toward the null. The reason for this positive bias is unknown. Overall, this complex pattern of biases indicates that there may be many patterns in the time series data that can influence effect estimation in various ways.

Bidirectional Versus Retrospective Sampling

The original conception of the case-crossover design was retrospective in that referents could only be chosen from time that preceded the event. The reason was that the original applications of the design involved outcomes that were likely to affect subsequent exposures. In these situations, sampling referent time post-failure could result in reverse-causation bias. For example, if exposure tended to decrease as a consequence of an event, using post-failure referent information could tend to bias risk estimates upward. Studying the effects of environmental rather than behavioral exposures has an advantage: Levels of exposure subsequent to the event are unaffected by the event. Therefore, it is possible to determine at times post-failure what the level of exposure would have been had a subject not failed. The case-crossover approach can be adapted to take advantage of the independence of the process generating the exposure by assessing referent information from times both before and after failure. In addition to redressing the influence of linear time trend, bidirectional sampling provides for doubling the number of referents available, thereby improving precision in estimates of measures of effect.

In the contrasts of bidirectional versus retrospective referent sampling—simulation sets 4 and 5 versus sets 2 and 3 as well as in the contrast of set 9 with set 8—the bias associated with bidirectional sampling is, in part, a function of the number of referents. The bias associated with bidirectional sampling is attenuated among four or more referents and exacerbated for one or two referents. The reason for this is not apparent.

With the limitations of sampling within a narrow time interval a tension exists between precision and bias. Restriction to a sampling window of 30 days limits the bias due to seasonality and coincidentally limits the influence of long-term time trend, which should be negligible in this relatively small window. Therefore, the main potential benefit of bidirectional referent sampling in this context is to double the size of the sampling frame and permit a greater number of referents to be chosen. In the absence of bias, the greater number of referents provides a small but possibly valuable improvement in precision.

Autocorrelation Exclusion Period

Among the bidirectional models (sets 4 and 5), the ± 6-day autocorrelation exclusion period, rather than simply protecting against a presumed bias toward the null due to overmatching, induces a positive bias which increases as a function of the number of referents. Among the retrospective models (sets 2 and 3) the 6-day autocorrelation exclusion period exacerbates the trend of increasing bias with the number of referents. The autocorrelation exclusion period produces a positive bias perhaps because it omits days which are likely high PM days. Since cases are distributed conditional on exposure, adjacent days would tend to be high PM days due to autocorrelation. Excluding these days alters the distribution of PM on referent days, that is, the distribution is biased low. This may inflate the estimated coefficient. When all serial correlation is eliminated by permuting the data series, the biasing effect of the 6-day autocorrelation exclusion period is essentially absent.

Residual Bias in the Estimating Procedure

Eliminating the serial correlation by permuting the time-series data attenuates the positive bias associated with the autocorrelation exclusion period and, moreover, proportionately attenuates bias among models that do not have an exclusion period. This improvement indicates that the majority of the bias observed is attributable to temporal patterns and autocorrelation. But even when all serial correlation and temporal patterns have been removed from the data by permutation, a small positive bias persists. The implication is that some bias is introduced by the estimation procedure being used. Lumley and Levy (2000a) identified two principal ways in which the analogy between case-crossover and matched case-control designs fails. These discrepancies point to problems in the use of the conditional logistic regression likelihoods in analysis of case-crossover designs, and suggests a modification of the case-crossover referent sampling strategy that permits correct estimation with conditional logistic regression.

The issues raised by Lumley and Levy (2000a) can be best understood in the context of a description of the conditional logistic regression estimation methods typically employed. The conditional likelihood (Breslow et al 1978; Kleinbaum 1994) used in maximum likelihood estimation of regression parameters is an extension of the unconditional likelihood, L_U:

$$L_U = \prod_{l=1}^{m} P(X_l) \prod_{l=m+1}^{n} [1 - P(X_l)];$$

where l indexes the number of m cases in each stratum, and $P(X)$ is the logistic model formula for individual X:

$$P(X) = \frac{1}{1 + e^{-(\alpha + \Sigma\beta_i X_i)}}.$$

The unconditional likelihood formula directly describes the joint probability of the study data as the product of the joint probability for the cases and the joint probability for referents. *Joint probability* refers to a

probability that combines the contributions of all the subjects in the study. The probability of obtaining the data for the lth case is given by $P(X_l)$ where $P(X)$ is the logistic model formula for the individual X_l. The probability for the data for the lth referent is given by $1 - P(X_l)$. We can use these products by assuming that the observations on all subjects are independent (uncorrelated).

The conditional likelihood formula (L_C) reflects the probability of the observed data configuration relative to the probability of all possible permutations of the data configuration, that is, the total probability of observing m cases in n subjects.

$$L_C = \frac{Pr(observed\ data)}{Pr(all\ possible\ configurations\ of\ the\ data)}.$$

We describe the observed data configuration as a collection of m cases and $n - m$ referents. We denote the cases by the X exposure vectors X_1, X_2, and so on through X_m and the referents by X_{m+1}, X_{m+2}, through X_n. This configuration assumes that we have arranged the observed data so that the m cases are listed first and are then followed in listing by the $n - m$ referents. Using this configuration, the conditional likelihood function gives the probability that the first m of the observed vectors of independent variables actually go with cases, given all possible permutations of configurations of the above n observations into a set of m cases and a set of $n - m$ referents. The total number of permutations of configurations is n choose m combinations.

The formula for the conditional likelihood for the kth stratum, where $k = 1,2,3, ..., K$, is then given by the expression:

$$L_C = \frac{\prod_{l=1}^{m} P(X_l) \prod_{l=m+1}^{n} [1 - P(X_l)]}{\sum_u \left\{ \prod_{l=1}^{m} P(X_{ul}) \prod_{l=m+1}^{n} [1 - P(X_{ul})] \right\}}.$$

The numerator is exactly the same as the likelihood for the unconditional method. The denominator sums the joint probabilities for all possible permutations of the n observations into m cases and $n - m$ referents. Each permutation is indicated by the u in the L_C formula. The full conditional likelihood is the product of L_C over the K strata.

An important feature of the matched case-control study is that the numbers of cases and controls sampled from each stratum formed by the matching variables are fixed in advance (at the design stage). In order to account for this fact in the statistical model it is appropriate to consider the conditional probability of the observed case-control data given the $m + (n - m)$ vectors of independent variables (X) in each stratum. This is achieved by conditioning L_U on the permutation of all possible exposure sequences. For this conditioning to work all exposures must be independent, that is, uncorrelated.

Analogies Between Case-Crossover and Case-Control Designs

The first problem with the analogy between case-crossover and matched case-control designs involves the expectation of independence in exposures for the conditional likelihood. In a matched case-control study the exposure observations for individual subjects in each stratum are independent (given an absence of selection bias). In contrast, the nature of time-series data and intra-individual comparisons in a case-crossover study will typically involve autocorrelation in the exposure over time. A consequence of this is that parameter estimation methods using the conditional likelihood are inappropriate. Such likelihoods do not represent the true likelihood for the process generating the data. The resulting bias will, in part, be a function of the degree of autocorrelation in the time-series data.

In many case-crossover referent sampling strategies, autocorrelation may exist between the case exposure and the referent as well as between all referents. This may help to explain the paradoxical effect of the autocorrelation exclusion period, evident in simulation sets 2 through 5, which exacerbated bias. While the exclusion period may have minimized autocorrelation between the case exposure and the referent, it contracted the period from which referents could be chosen, thereby increasing autocorrelation among the referents selected. Imposing the additional restriction that all subjects be far enough apart in time to minimize autocorrelation among them, as in simulation sets 8 and 9, results in relatively little or no bias. This also may explain why the bidirectional referent selection strategy with no autocorrelation exclusion period (set 4) is the least biased of simulation sets 2 through 5. It provides the largest window among which to choose a given number of referents, thereby reducing the probability that proximal, highly autocorrelated referents will be selected. This also suggests why bias tended to worsen with increasing number of referents. The more referents selected in a limited time interval, the greater the autocorrelation between them.

A second problem with the analogy between case-crossover and case-control designs involves the definition of strata and its implications for the conditional likelihood. In a matched case-control study, the division of the population into strata depends only on covariates and not on the response. The definition of strata typically occurs in advance of collecting the data. In contrast, for the

case-crossover design, referent sampling strategies considered in this study strata were defined on the basis of occurrence of each case. The window for selecting referents (± 30 days) was determined on the basis of occurrence of the case at time t_i. What the design does, in effect, is sample referent windows from the fixed exposure series from the study period with probability at t_i proportional to the case risk function at the window center $\exp(\beta z_{t_i} + \gamma_{t_i})$, where z_{t_i} are the covariates of interest and γ_t represents the season and trend effects that we wish to exclude by restriction (using a narrow referent window means that γ_t is roughly constant throughout the window).

This functional relation between the definition of the referent window and the intensity of exposure via the case risk function violates one of the fundamental principles of case-control methods, which requires that controls not be selected conditional on exposure. Moreover, since the referent window is determined based on the case time t_i, then, ipso facto, t_i is at a fixed place in the referent window. The important implication of the fixed relation between the referent window and t_i is that the conditional likelihood then contains no information. As described above, the likelihood formula for the conditional logistic regression reflects the probability of the observed data configuration relative to the probability of all possible configurations of the given data. This probability of all possible configurations of the given data assumes independence of the observations, that is, that any one of the observations, including the case, is equally likely to be at any position in the possible configurations of cases and referents in the given data. This cannot hold true if the position of the case event in the window is fixed by design.

In a matched case-control analysis, the stratum is fixed and the ordering within the stratum is random. In the case-crossover design, the position of the stratum (the referent sampling window) is random but the ordering of days within the window is fixed. If within each window the ordering of days is fixed, the true conditional likelihood, which relies on all possible orderings of the exposures, cannot provide a valid estimate. The conditional logistic regression then does not maximize a true likelihood and the estimates will be biased. The bias may be small, but not zero.

A third problem with the analogy between case-crossover and case-control designs also involves the definition of strata. In a matched case-control study, the population is divided a priori into mutually exclusive strata depending only on covariates completely independent of the response. In the case-crossover designs studied, the observation period is divided into overlapping potential strata, and the actual choice of strata depends on the observed responses. Austin and colleagues (1989) demonstrate that selection of controls from categories that overlap can lead to bias in case-control studies. Selection of controls from categories that are not mutually exclusive can lead to a situation in which the exposure of control subjects does not reflect that of members of the source population, which leads to bias because exposed individuals are either more or less likely than unexposed individuals to be included in multiple categories. Austin and colleagues provide as an example the use of friends, or siblings closest in age as controls, or caliper matching on age.

The bias observed in this simulation study is predominantly positive, suggesting that relatively low exposures are being overrepresented in the referent sampling. This could occur if the case events are sufficiently infrequent and far enough apart that the parts of the windows where the case risk function is lower (the tails) overlap, and thus relatively low exposures are tending to occur in overlapping portions of referent selection windows. The nature of the bias may be different in other studies in which autocorrelation in the time series, disease risk, correlation of events in time, and sampling designs may be different.

For practical purposes, this bias is relatively unimportant, and choosing the referent days far enough apart to remove local autocorrelation should be practically sufficient, as demonstrated by the fixed interval strategy (simulation set 9). Modifying the design by partitioning the data a priori into mutually exclusive categories or true strata, rather than selecting potentially overlapping referent windows, removes the bias completely, providing a valid and elegant design. For example, time could be stratified by the joint categories of year, month, and day of week—a stratification with the same robustness to trend in exposure as the bidirectional designs examined in this study.

Our simulation results show that the following design features are important for unbiased estimation:

1. Seasonality and long-term time trend in the PM time series may be dealt with by restricting the sample frame for referents to a period short enough to be free of significant seasonal transitions.
2. Short-term autocorrelation in the time series may be dealt with by further restricting the referent sampling window. Requiring a 6-day interval between all observations used in the analysis allows for the necessary independence among observations (and coincidentally, controls for day-of-week effects).
3. Unbiased estimation with conditional logistic regression requires dividing time into strata defined a priori and using the remainder of eligible days in each stratum as the referents for a case in that stratum, rather than selecting potentially overlapping referent windows centered at the time of each case event.

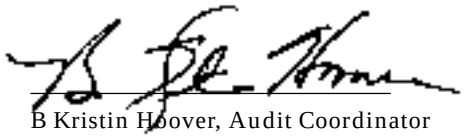
APPENDIX B. HEI Quality Assurance Report

The conduct of this study was subjected to periodic, independent audits by a team from Hoover Consultants. This team consisted of an auditor with experience in toxicology and epidemiology, a practicing board certified physician epidemiologist, and an expert in air monitoring. 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 in the table below with the phase of the study examined.

Quality Assurance Audits

Date	Phase of Study Audited
Nov 18–19, 1997	The auditors reviewed the Standard Operating Procedures/Manual of Operations, the original proposal, Institutional Review Board documentation, publication of earlier studies using a similar cohort, operation procedures for the nephelometer, sample SAS printout from the air quality data base, information used for geocoding addresses, and the study organization chart. Procedures for data processing and archiving were audited. Staffing, adequacy of equipment and facilities, and internal quality assurance procedures were considered.
Feb 22–23, 1999	The auditors reviewed the Year 1 five-month and ten-month progress reports, a description of project status dated 2/21/99, information regarding the nephelometer colocation test results, abstracted portions of the original tracking database for 14 cases, abstracted portions of the Cardiac Disease Registry Index survey database for 50 cases, summary of abstracted portions of the original Cardiac Disease Registry Index questionnaires of 14 cases, draft of the initial analysis, printout of the analysis data set for all 362 cases, and the Cardiac Arrest Blood Study Data Dictionary. A sample of CO data in the analytical database was audited against the original Aerometric Information Retrieval System data. Four days of nephelometer data were audited against the original data source. Procedures for data storage and maintenance of confidentiality were considered. Equipment and facilities considered in the first audit were reviewed.

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 the study was conducted by a well-coordinated, experienced team according to the study protocol and standard operating procedures. The report appears to be an accurate representation of the study.



B Kristin Hoover, Audit Coordinator

APPENDICES AVAILABLE ON REQUEST

Appendix C, Identifying the Effects of Location and the Atmospheric Conditions on Air Pollution Exposures for Health Effects Analyses, may be obtained by contacting the Health Effects Institute at 955 Massachusetts Avenue, Cambridge MA 02139, by phone (617-876-6700), fax (617-876-6709), or e-mail (*pubs@healtheffects.org*). Please give the full title of the Research Report, the first author's name, and the title of the appendix you wish to request.

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ABBREVIATIONS AND OTHER TERMS

bsp	coefficient of extinction for light scattering by particles
CI	confidence interval
CO	carbon monoxide
IQR	interquartile range
IQR-RR	interquartile range relative risk
LOESS	locally weighted smoother
PM	particulate matter
PM_{10}	particles 10 µm or smaller in aerodynamic diameter
$PM_{2.5}$	particles 2.5 µm or smaller in aerodynamic diameter
ppm	parts per million
PSCAA	Puget Sound Clean Air Agency
RR	relative risk
SCA	sudden cardiac arrest
SO_2	sulfur dioxide

CRITIQUE
Health Review Committee

INTRODUCTION

Epidemiologic studies have reported associations between short-term increases in particulate matter (PM)* air pollution and increased daily mortality and morbidity from respiratory and cardiovascular diseases (Ostro 1993; Dockery and Pope 1994; US Environmental Protection Agency [EPA] 1996). Although the results of these studies suggest that persons with preexisting disease are most susceptible to the effects of small increases in PM (Schwartz 1994; Utell and Samet 1993), the specific clinical conditions that confer increased risk have been unclear. Because most studies use mortality data from death certificates, clinical conditions at the time of death have not been known.

Schwartz (1994) observed that PM was most strongly associated with mortality among persons who were not residents of health care facilities and who were pronounced "dead on arrival" at the hospital. Others had observed that hospital admissions for cardiac disease were associated with ambient concentrations of respirable PM and sulfate, which are generally made up of fine particles ($PM_{2.5}$ or smaller) (Burnett et al 1995; Schwartz and Morris 1995). A study by Goldberg and colleagues (2000) used mortality data in conjunction with Quebec provincial insurance data to identify population groups who might be at increased risk of dying from PM exposure. They found that three indices of PM (coefficient of haze, sulfate, and a mathematically predicted $PM_{2.5}$ measure) were associated with acute lower respiratory disease, congestive heart failure, and cardiovascular diseases as a group. Coefficient of haze and predicted $PM_{2.5}$ were associated with cancer and chronic coronary artery disease. Effects of sulfate were reported for acute and chronic upper respiratory disease.

SCIENTIFIC BACKGROUND

Dr Checkoway and his colleagues proposed to investigate a previously uninvestigated association between sudden cardiac arrest and fine particulate air pollution. Such an association would have important public health implications because sudden cardiac arrest is most often observed as sudden cardiac death, which is responsible for almost 10% of total US mortality (Kannel and Schatzkin 1985). Over half of sudden cardiac deaths occur among persons with no previously diagnosed heart disease or major symptoms of coronary heart disease (Kannel and Schatzkin 1985).

The primary hypothesis that Dr Checkoway and colleagues tested was that increases in daily fine PM levels were related to increased risk of out-of-hospital sudden cardiac arrest. Questionnaire and sudden cardiac arrest data collected for a different purpose were used for this study in conjunction with exposure data available from the Puget Sound Clean Air Agency (Seattle WA).†

Nephelometry measures light scattering by aerosols integrated over a wide range of angles and on a time scale that is essentially continuous; nephelometric values are reported in bsp units (where *b* is the coefficient of extinction, *s* is for scattering as opposed to absorption, and *p* is for particles as opposed to gases) and referred to simply as the *coefficient of light scattering.* They represent measurements of particles in the fine range (≤ 2.5 μm), which are efficient scatterers of light. There is a strong relationship between fine particle mass and bsp. These exposure data were available from three monitoring locations in the Seattle WA area during the study period. At each of the three sampling sites, nephelometric and daily 24-hour gravimetric measurements for PM_{10} were obtained, and the mean of the three sites was used in the analysis. Gravimetric $PM_{2.5}$ 24-hour data were available for only about 25% of the days, and therefore were not used except for comparison with nephelometry measures. The authors conducted a substudy (reported in Appendix C, which is available on request from HEI) to determine whether a spatial gradient of fine particles existed across the region, to assess other factors that might effect the measures, and to determine whether better individual exposure information based on the spatial gradient would modify the health outcome.

Data on other pollutants were available. Average daily (24-hour) SO_2 levels were monitored throughout the study period at one location and average daily CO levels were

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

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† Dr Harvey Checkoway's 2-year study, *Extended Case-Crossover Study of Fine Particulate Air Pollution and Sudden Cardiac Arrest,* began in June 1997 and had total expenditures of $186,044. The draft Investigators' Report from Checkoway and colleagues was received for review in September 1999. A revised report, received in January 2000, was accepted for publication in February 2000. 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 Critique.

calculated from measurements at several monitoring sites. Daily temperature was obtained from a local airport. The investigators chose not to include ozone measures in the analysis because the monitoring station was located 30 miles from the study area and provided incomplete data, which might not be representative of concentrations in Seattle.

The investigators used a case-crossover study design (Maclure 1991) to examine the association between sudden cardiac arrest and PM. The case-crossover design is used in epidemiologic studies in which only case subjects (and no control subjects) are included; each subject's exposure at the time the health outcome of interest occurs is compared with some estimate of the typical level of the subject's exposure measured at another time. The case-crossover method can be used to investigate whether a recent exposure has triggered or is related to the occurrence of an event—here, whether levels of PM are related to sudden cardiac arrest. This design is a blend of the case-control and crossover study designs. In a case-control study, cases (for example, subjects with sudden cardiac arrest) are compared with controls (for example, subjects without sudden cardiac arrest). In a crossover study, subjects are compared with themselves under at least two conditions (eg, after two experimental interventions or treatments have been administered in a random sequence).

In the case-crossover study design, for each case the investigator selects a time period when the subject is disease free as a control or referent period. The investigator also specifies a period preceding the occurrence of the health outcome during which the exposure is hypothesized to have increased the subject's risk (the "hazard" period). From these data, an exposure odds ratio is calculated as an estimate of the relative risk. The validity of this estimate assumes that neither the exposure nor any potential confounders change over time in any systematic way that might bias the results. Dr Checkoway and his colleagues examined potential sources of bias in case-control studies of air pollution (reported in Appendix A).

FINDINGS

The authors used an existing dataset of sudden cardiac arrest deaths and next-of-kin interviews to investigate the association between sudden cardiac arrest and PM in Seattle WA. The data came from a study of the value of enhanced medical emergency services to sudden cardiac arrest victims. Dr Checkoway and associates limited their study to apparently healthy people who had no prior history of heart problems as indicated by questionnaire responses from next of kin. Analyses were conducted for single-pollutant (fine PM or PM_{10}) and multiple-pollutant (in which SO_2, CO, or both were added to the analyses) models. Results for lag periods from 0 to 5 days were reported for PM_{10} and fine PM. All effect estimates had confidence intervals that included the null value of no association, that is, a relative risk of 1.0. Results appeared not to be confounded by either SO_2 or CO exposure. The investigators also examined several possible effect modifiers including season, time of entry into the study, age, and risk factors for sudden cardiac arrest, such as diet, education, and smoking. No modification of association was seen in these analyses, and the stratification by age and other cardiovascular disease risk factors did not identify possible susceptible subgroups of the population studied.

TECHNICAL REVIEW

The study design used by Dr Checkoway and his colleagues is an innovative and appropriate application of the case-crossover approach, using an existing dataset to examine a possible association between PM and a specific cause of death. Appendix A contributes to the understanding of potential sources of bias using the case-crossover study design. The investigators also conducted an extensive quality control program for exposure measurements to ensure a high level of data quality.

STUDY DESIGN

This case-crossover study compared pollutant exposure at the time of sudden cardiac arrest to exposure at a time either before or after the event occurred. As a general rule, the referent period selected should avoid introducing any of a number of serious problems and biases. The authors pointed out that short-term and long-term time trends in pollutant levels pose an important threat to the validity of case-crossover studies of air pollution. In Appendix A, several simulation studies explored how the choice of referent exposure periods might affect the study outcomes. As a result of these simulation studies, the authors noted that if the referent periods are too remote from the case hazard period, an incorrect association with the longer-term seasonal patterns in particulate levels might actually be observed. On the other hand, if the referent periods chosen are too close to the hazard period or to each other, then their correlation will reduce the likelihood of finding a real effect. Finally, the authors also explored whether the use of symmetric referent periods taken both before and after the case hazard period would reduce bias due to short-term time trends. In the end, the authors decided to use symmetric time periods matched to the "hazard

period" by year, month, and day of the week (in this study, the day of the health outcome event). The investigators supported this choice of referent period with information reported in Appendix A that shows minimal introduction of bias with this choice.

Although the choice of referent periods appears to be appropriate, there is a strong possibility that the width of the hazard period (time of disease onset) was inappropriate. The authors assumed that for each lag period (0 days to 5 days), a 24-hour time window was appropriate for the induction of out-of-hospital sudden cardiac arrest. The underlying pathophysiologic processes in this event are typically split between primary arrhythmia and arrhythmia secondary to the myocardial ischemia that follows disruption of an atherosclerotic plaque in an epicardial coronary artery and intracoronary thrombosis. The authors cite data indicating that in the subgroup of sudden cardiac death victims who have an out-of-hospital sudden cardiac arrest, up to 80% appear to be due to a primary arrhythmia. This key piece of information shows that the induction time for the occurrence of primary arrhythmia may be much shorter than the 24-hour time window assumed. If this were the case, the daily variations in particulate concentration would lead to exposure mismeasurement and could bias findings toward the null.

Given the essentially real-time measurements that the nephelometers provided, the authors might have explored variations in exposure for time scales shorter than the 24-hour averaging period they used. This would have allowed them to evaluate additional hazard periods (ie, 1-, 2-, or 4-hour concentrations) that might be of interest for sudden cardiac arrest. The disadvantage of using a shorter averaging period, however, would be that the considerable spatial and temporal variations in PM concentrations within the study region might result in poor correlations among monitoring stations. Three sites might not be adequate to capture these variations.

ANALYSIS

Dr Checkoway and his colleagues made good use of a dataset that was collected by others for a different purpose. The analysis was appropriate and used all the available data. The point estimates of relative risks at lags of 0 to 5 days were, for all lags, either below the null value or included the null in the 95% confidence interval. These data do not support a finding of any major effect from either PM_{10} or fine PM in this dataset. Several analyses that examined possible effect-modifying variables did not change the null findings. However, the authors reported from their power calculations that the sample size (362 subjects) was not large enough to either find or rule out a relative risk less than 1.5. Looking for risk in defined demographic segments of Seattle was difficult because statistical power in subgroups was even more limited.

PARTICULATE MATTER EXPOSURE MEASUREMENTS

Because nephelometry measures the light scattering by aerosols, the moisture content and chemical composition of the aerosol can affect the relation between the bsp and fine particle mass. However, the authors report a correlation of 0.94 between 24-hour averaged bsp and gravimetric $PM_{2.5}$ measurements. This suggests that bsp measurements are, in fact, a strong proxy for the fine particle mass found in the Seattle area, where particles from wood combustion make up a significant portion of the ambient aerosol.

The authors acknowledged that using data from only three nephelometer sites to represent daily regional average concentrations was a limitation in their exposure assessment design. Limited central-site monitoring cannot capture differences in individual exposures related to regional outdoor spatial gradients, indoor concentration levels, or individual time-activity patterns. In an effort to address this issue, Checkoway and associates conducted a substudy (reported in Appendix C, which is available on request from HEI) to characterize the spatial variability of fine particle mass, measured by bsp at seven locations in the Seattle area, and to examine topographic and atmospheric conditions that might be associated with any observed spatial variability. The substudy did indicate a spatial gradient in bsp with regional differences by space and time. However, the analysis using site-specific estimates of exposure did not produce meaningful differences from the analyses using regional averages.

This is one of few epidemiologic studies that has addressed the potential for bias associated with not accounting for spatial variability of pollutant concentrations within a region when assigning exposure levels. Although the substudy has limitations, it highlights the variability of pollutants in space and time within a region and the need to assess the extent of that variability. The authors are correct in indicating that more attention needs to be directed toward improved assessment of individual exposures in epidemiologic studies of air pollution.

CONCLUSION

Dr Checkoway and his colleagues have made good use of a unique but small dataset, collected for a different purpose, to examine the association between PM and sudden cardiac arrest, a well-defined specific health outcome.

This outcome is of interest because of the associations between cardiovascular deaths and PM levels reported in other studies. Had Checkoway and colleagues found that sudden cardiac arrest was affected by PM exposure, this would have been an important result. The lack of positive findings indicates that any effect of PM on sudden cardiac arrest is unlikely to have a relative risk of 1.5 or more for Seattle residents with no prior history of heart problems. This study found no association between PM and one very specific health outcome in this population. A new study of sudden cardiac arrest might seek to include persons with a history of heart disease as a possible susceptible population at risk. It should be understood, as well, that a lack of association with PM in this study does not imply that other cardiac or cardiovascular disease outcomes are not associated with PM. Epidemiologic and laboratory studies currently under way will add to our current knowledge about the possible PM effects on potentially susceptible individuals.

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