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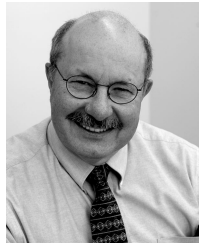

Douglas W. Dockery

Health Effects of Fine Particulate Air Pollution: Lines that Connect

C. Arden Pope III
Department of Economics, Brigham Young University, Provo, UT

Douglas W. Dockery
Department of Environmental Health, Harvard School of Public Health, Boston, MA

ABSTRACT

Efforts to understand and mitigate the health effects of particulate matter (PM) air pollution have a rich and interesting history. This review focuses on six substantial lines of research that have been pursued since 1997 that have helped elucidate our understanding about the effects of PM on human health. There has been substantial progress in the evaluation of PM health effects at different time-scales of exposure and in the exploration of the shape of the concentration-response function. There has also been emerging evidence of PM-related cardiovascular health effects and growing knowledge regarding interconnected general pathophysiological pathways that link PM exposure with cardiopulmonary morbidity and mortality. Despite important gaps in scientific knowledge and continued reasons for some skepticism, a comprehensive evaluation of the research findings provides persuasive evidence that exposure to fine particulate air pollution has adverse effects on cardiopulmonary health. Although much of this research has been motivated by environmental public health policy, these results have important scientific, medical, and public health implications that are broader than debates over legally mandated air quality standards.

INTRODUCTION

Efforts to understand and mitigate the effects of air pollution on human health and welfare have a rich and interesting history.[1–3] By the 1970s and 1980s, attributed largely to earlier well-documented increases in morbidity and mortality from extreme air pollution episodes,[4–12] the link between cardiopulmonary disease and very high concentrations of particulate matter (PM) air pollution was generally accepted. There remained, however, disagreement about what levels of PM exposures and what type of PM affected human health. Several prominent scientists concluded that there was not compelling evidence of substantive health effects at low-to-moderate particulate pollution levels.[13,14] Others disagreed and argued that particulate air pollution may adversely affect human health even at relatively low concentrations.[15,16]

The early to mid 1990s was a galvanizing period in the history of particulate air pollution and health research. During this relatively short time period, several loosely connected epidemiologic research efforts from the United States reported apparent health effects at unexpectedly low concentrations of ambient PM. These efforts included: (1) a series of studies that reported associations between daily changes in PM and daily mortality in several cities[17–24]; (2) the Harvard Six Cities and American Cancer Society (ACS) prospective cohort studies that reported long-term PM exposure was associated with respiratory illness in children[25] and cardiopulmonary mortality in adults[26,27]; and (3) a series of studies in Utah Valley that reported particulate pollution was associated with a wide range of health end points, including respiratory hospitalizations,[28,29] lung function and respiratory symptoms,[30–32] school absences,[33] and mortality.[20,34] Comparable results were also reported in studies from the United States,[35–37] Germany,[38] Canada,[39] Finland,[40] and the Czech Republic.[41] Although controversial, the convergence of these reported findings resulted in a critical mass of evidence that prompted serious reconsideration of the health effects of PM pollution at low-to-moderate exposures and motivated much additional research that continues to this day. Since the early 1990s, numerous reviews and critiques of the particulate air pollution and health literature have been published.[2,42–79]

The year 1997 began another benchmark period for several reasons. Vedal[80] published a thoughtful, insightful critical review of the previously published literature dealing with PM health effects. His review focused largely on lines of division that characterized much of the discussion on particle health effects at that time. A 1997 article in the journal *Science,* titled "Showdown over Clean Air Science,"[81] reported that "industry and environmental researchers are squaring off over studies linking air pollution and illness in what some are calling the biggest environmental fight of the decade."[81] Several other discussions of these controversies were also published during this time period.[82–84] Much of the divisiveness was because of the public policy implications of finding substantive adverse health effects at low-to-moderate particle concentrations that were common to many communities throughout the United States.[85–88]

After a lawsuit by the American Lung Association and a comprehensive review of the scientific literature,[89] in 1997, U.S. Environmental Protection Agency (EPA) promulgated National Ambient Air Quality Standards (NAAQS) designed to impose new regulatory limits on

fine particulate pollution.[90] Legal challenges relating to the promulgation of these standards were filed by a large number of parties. Various related legal issues were addressed in an initial Court of Appeals opinion[91] and a subsequent 2001 ruling by the U.S. Supreme Court.[92] Regarding the fine PM ($PM_{2.5}$) standards, these legal challenges were largely resolved in 2002 when the Court of Appeals found that the $PM_{2.5}$ standards were not "arbitrary or capricious."[93] After these rulings, EPA began implementing the standards by designating nonattainment areas.[94]

In January 2006, after another review of the scientific literature,[95] new NAAQS for fine and coarse particles were proposed.[96] In the wake of the substantial resistance to the initial fine particulate standards, the proposed new standards were criticized for ignoring relevant scientific evidence and the advice of EPA's own clean air science advisory committee[97,98] and for being too lax, with allowable pollution levels well above the recent World Health Organization (WHO) air quality guidelines.[99] The polarized response to this proposal illustrates that lines of division that troubled Vedal[80] in 1997, especially the problem of setting ambient PM air quality standards in the absence of clearly defined health effect thresholds, remain today.

This review is not intended to be a point-by-point discussion of the lines that divide as discussed by Vedal,[80] although various divisive issues, controversies, and contentious debates about air quality standards and related public policy issues have yet to be fully resolved. This review focuses on important lines of research that have helped connect the dots with regard to our understanding of the effects of ambient PM exposure on human health. Much has been learned and accomplished since 1997. This review will focus primarily on scientific literature published since 1997, although some earlier studies will be referenced to help provide context. Although there have been many important findings from toxicology and related studies,[100–104] this review will rely primarily on epidemiologic or human studies. Of course, unresolved scientific and public policy issues dealing with the health effects of PM must be recognized. These unresolved issues need not serve only as sources of division but also as opportunities for cooperation and increased collaboration among epidemiologists, toxicologists, exposure assessment researchers, public policy experts, and others.

In this review, the characteristics of particulate air pollution and the most substantial lines of research that have been pursued since 1997 that have helped connect or elucidate our understanding about human health effects of particulate air pollution are described. First, the recent meta-analyses (systematic quantitative reviews) of the single-city time series studies and several recent multicity time series studies that have focused on short-term exposure and mortality are described. Second, the reanalysis, extended analysis, and new analysis of cohort and related studies that have focused on mortality effects of long-term exposure are explored. Third, the recent studies that have attempted to explore different time scales of exposure are reviewed. Fourth, recent progress in formally analyzing the shape of the PM concentration or exposure-response function is presented and discussed. Fifth, an overview of the recent rapid growth and interest in research regarding the impact of PM on cardiovascular disease is given. Sixth, the growing number of studies that have focused on more specific physiologic or other innovative health outcomes and that provide information on biological plausibility and potential pathophysiological or mechanistic pathways that link exposure with disease and death are reviewed. Finally, several of the most important gaps in scientific knowledge and reasons for skepticism are discussed.

Characteristics of PM Air Pollution

PM air pollution is an air-suspended mixture of solid and liquid particles that vary in number, size, shape, surface area, chemical composition, solubility, and origin. The size distribution of total suspended particles (TSPs) in the ambient air is trimodal, including coarse particles, fine particles, and ultrafine particles. Size-selective sampling of PM refers to collecting particles below, above, or within a specified aerodynamic size range usually selected to have special relevance to inhalation and deposition, sources, or toxicity.[105] Because samplers are incapable of a precise size differentiation, particle size is usually defined relative to a 50% cut point at a specific aerodynamic diameter (such as 2.5 or 10 μm) and a slope of the sampling-effectiveness curve.[105]

Coarse particles are derived primarily from suspension or resuspension of dust, soil, or other crustal materials from roads, farming, mining, windstorms, volcanos, and so forth. Coarse particles also include sea salts, pollen, mold, spores, and other plant parts. Coarse particles are often indicated by mass concentrations of particles greater than a 2.5-μm cut point.

Fine particles are derived primarily from direct emissions from combustion processes, such as vehicle use of gasoline and diesel, wood burning, coal burning for power generation, and industrial processes, such as smelters, cement plants, paper mills, and steel mills. Fine particles also consist of transformation products, including sulfate and nitrate particles, which are generated by conversion from primary sulfur and nitrogen oxide emissions and secondary organic aerosol from volatile organic compound emissions. The most common indicator of fine PM is $PM_{2.5}$, consisting of particles with an aerodynamic diameter less than or equal to a 2.5-μm cut point (although some have argued that a better indicator of fine particles would be PM_1, particles with a diameter less than or equal to a 1-μm cut point).

Ultrafine particles are typically defined as particles with an aerodynamic diameter <0.1 μm.[95,106] Ambient air in urban and industrial environments is constantly receiving fresh emissions of ultrafine particles from combustion-related sources, such as vehicle exhaust and atmospheric photochemical reactions.[107,108] These primary ultrafine particles, however, have a very short life (minutes to hours) and rapidly grow (through coagulation and/or condensation) to form larger complex aggregates but typically remain as part of $PM_{2.5}$. There has been more interest recently in ultrafine particles, because they serve as a primary source of fine particle exposure and because poorly soluble ultrafine particles may be more likely than

larger particles to translocate from the lung to the blood and other parts of the body.[106]

Public health policy, in terms of establishing guidelines or standards for acceptable levels of ambient PM pollution,[96,99] have focused primarily on indicators of fine particles ($PM_{2.5}$), inhalable or thoracic particles (PM_{10}), and thoracic coarse particles ($PM_{10-2.5}$). With regard to $PM_{2.5,}$ various toxicological and physiological considerations suggest that fine particles may play the largest role in effecting human health. For example, they may be more toxic because they include sulfates, nitrates, acids, metals, and particles with various chemicals adsorbed onto their surfaces. Furthermore, relative to larger particles, particles indicated by $PM_{2.5}$ can be breathed more deeply into the lungs, remain suspended for longer periods of time, penetrate more readily into indoor environments, and are transported over much longer distances.[109] PM_{10}, an indicator for inhalable particles that can penetrate the thoracic region of the lung, consists of particles with an aerodynamic diameter less than or equal to a 10-μm cut point and includes fine particles and a subset of coarse particles. $PM_{10-2.5}$ consists of the PM_{10} coarse fraction defined as the difference between PM_{10} and $PM_{2.5}$ mass concentrations and, for regulatory purposes, serves as an indicator for thoracic coarse particles.[96]

SHORT-TERM EXPOSURE AND MORTALITY

The earliest and most methodologically simple studies that evaluated short-term changes in exposure to air pollution focused on severe air pollution episodes.[4–12] Death counts for several days or weeks were compared before, during, and after the episodes. By the early 1990s, the results of several daily time series studies were reported.[17–24,110] These studies did not rely on extreme pollution episodes but evaluated changes in daily mortality counts associated with daily changes in air pollution at relatively low, more common levels of pollution. The primary statistical approach was formal time series modeling of count data using Poisson regression. Because these studies suggested measurable mortality effects of particulate air pollution at relatively low concentrations, there were various questions and concerns that reflected legitimate skepticism about these studies. One question regarding these early daily time series mortality studies was whether or not they could be replicated by other researchers and in other study areas. The original research has been independently replicated,[111] and, more importantly, comparable associations have been observed in many other cities with different climates, weather conditions, pollution mixes, and demographics.[112–114]

A lingering concern regarding these daily time series mortality studies has been whether the observed pollution-mortality associations are attributable, at least in part, to biased analytic approaches or statistical modeling. Dominici et al.[115,116] have provided useful reviews and discussion of the statistical techniques that have been used in these time series studies. Over time, increasingly rigorous modeling techniques have been used in attempts to better estimate pollution-mortality associations while controlling for other time-dependent covariables that serve as potential confounders. By the mid-to-late 1990s, generalized additive models (GAMs) using nonparametric smoothing[117] were being applied in these time series studies. GAMs allowed for relatively flexible fitting of seasonality and long-term time trends, as well as nonlinear associations with weather variables, such as temperature and relative humidity (RH).[116,118] However, in 2002 it was learned that the default settings for the iterative estimation procedure in the most commonly used software package used to estimate these models were sometimes inadequate.[119] Subsequent reanalyses were conducted on many of the potentially affected studies using more rigorous convergence criteria or using alternative parametric smoothing approaches.[120] Statistical evidence that increased concentrations of particulate air pollution were associated with increased mortality remained. Not all of the studies were affected, but in the affected studies, effect estimates were generally smaller. Daily time series studies since 2002 have generally avoided this potential problem by using the more rigorous convergence criteria or by using alternative parametric smoothing or fitting approaches.

Another methodological innovation, the case-crossover study design,[121] has been applied to studying mortality effects of daily changes in particulate air pollution.[122–124] Rather than using time series analysis, the case-crossover design is an adaptation of the common retrospective case-control design. Basically, exposures at the time of death (case period) are matched with one or more periods when the death did not occur (control periods), and potential excess risks are estimated using conditional logistic regression. Deceased individuals essentially serve as their own controls. By carefully and strategically choosing control periods, this approach restructures the analysis such that day of week, seasonality, and long-term time trends are controlled for by design rather than by statistical modeling.[125,126] Because this approach focuses on individual deaths rather than death counts in a population, this approach facilitates evaluation of individual-level effect modification or susceptibility. The case-crossover design has some drawbacks. The results can be sensitive to the selection of control periods, especially when clear time trends exist.[125–133] Also, relative to the time series approach, the case-crossover approach has lower statistical power largely because of the loss of information from control periods not included in the analysis.

Meta-Analyses of Short-Term Exposure and Mortality Studies

Since the early 1990s, there have been >100 published research articles that report results on analyses of short-term exposure to particulate air pollution and mortality. Most of these studies are single-city daily time series mortality studies. Over time there have also been many quantitative reviews or meta-analyses of these single-city time series studies,[52,64,71,134–137] many of which provide pooled effect estimates. In addition, several of these meta-analyses have attempted to understand the differences in the city-specific response functions. Levy et al.[134] selected 29 PM_{10} mortality estimates from 21 published studies and applied empirical Bayes meta-analysis to provide pooled estimates and to evaluate whether various study-specific

Table 1. Comparison of pooled estimated percentage increase (and 95% confidence or posterior interval, CI, or *t* value) in relative risk of mortality estimated across meta-analyses and multicity studies of short-term (daily) changes in exposure.

Study	Primary Sources	Exposure Increment	Percent Increases in Relative Risk of Mortality (95% CI)		
			All Cause	Cardiovascular	Respiratory
Meta-analysis of 29 studies	Levy et al. 2000[134]	20 $\mu g/m^3$ PM_{10}	1.5 (1.2, 1.75)[a]	–	–
Meta-analysis: GAM-based studies	Stieb et al. 2002, 2003[135,136]	20 $\mu g/m^3$ PM_{10}	1.4 (1.0, 1.8)[a]	–	–
Non GAM-based studies			0.8 (0.5, 1.2)	–	–
Metaestimate from single-city studies,	Anderson et al. 2005[137]	20 $\mu g/m^3$ PM_{10}	1.2 (1.0, 1.4)[a]	–	–
adjusted for publication bias			1.0 (0.8, 1.2)[a]	–	–
Metaestimates from COMEAP report to the	COMEAP 2006[138]	20 $\mu g/m^3$ PM_{10}	–	1.8 (1.4, 2.4)	
U.K. Department of Health on		10 $\mu g/m^3$ $PM_{2.5}$	–	1.4 (0.7, 2.2)	–
Cardiovascular Disease and Air Pollution					
U.S. 6 cities	Klemm and Mason 2003[142]	10 $\mu g/m^3$ $PM_{2.5}$	1.2 (0.8, 1.6)	1.3 (0.3, 2.4)[b]	0.6 (−2.9, 4.2)[c]
Canadian 8 cities	Burnett and Goldberg 2003[144]	10 $\mu g/m^3$ $PM_{2.5}$	1.1 (t = 3.4)	–	–
Californian 9 cities	Ostro et al. 2006[145]	10 $\mu g/m^3$ $PM_{2.5}$	0.6 (0.2, 1.0)	0.6 (0.0, 1.1)	2.2 (0.6, 3.9)
U.S. 10 cities	Schwartz 2000, 2003[146,148]	20 $\mu g/m^3$ PM_{10}	1.3 (1.0, 1.6)	–	–
U.S. 14-city case-crossover	Schwartz 2004[149]	20 $\mu g/m^3$ PM_{10}	0.7 (0.4, 1.0)	–	–
NMMAPS 20–100 U.S. cities	Dominici et al. 2003[153]	20 $\mu g/m^3$ PM_{10}	0.4 (0.2, 0.8)	0.6 (0.3, 1.0)[d]	–
APHEA-2 15–29 European cities	Katsouyanni et al. 2003[162]	20 $\mu g/m^3$ PM_{10}	1.2 (0.8, 1.4)	–	–
APHEA-2 29 European cities	Analitis et al. 2006[163]	20 $\mu g/m^3$ PM_{10}	–	1.5 (0.9, 2.1)	1.2 (0.4, 1.9)
Australia 3-cities	Simpson et al. 2005[165]	10 $\mu g/m^3$ $PM_{2.5}$	0.9 (−0.7, 2.5)	–	–
French 9 cities	Le Tertre et al. 2002[164]	20 $\mu g/m^3$ BS	1.2 (0.5, 1.8)[a]	1.2 (0.2, 2.2)[a]	1.1 (−1.4, 3.2)[a]
Korean 7 cities	Lee et al. 2000[166]	40 $\mu g/m^3$ TSP	0.9 (0.5, 1.2)[a]	–	–
Japanese 13-cities, age >65 yr	Omori et al. 2003[167]	20 $\mu g/m^3$ SPM	1.0 (.8, 1.3)	1.1 (0.7, 1.5)	1.4 (0.9, 2.1)

[a]Includes GAM-based analyses with potentially inadequate convergence; [b]Ischemic heart disease deaths; [c]Chronic obstructive pulmonary disease deaths; [d]Cardiovascular and respiratory deaths combined.

factors explained some of the variability in effect estimates across the studies. Based on their pooled estimates, elevated concentrations of PM_{10} were associated with increased mortality counts (see Table 1). Across the studies, locations with higher $PM_{2.5}/PM_{10}$ ratios had stronger associations, suggesting that fine particles may be most responsible for the observed associations.

In another large meta-analysis, Steib et al.[135] extracted air pollution-related health effect estimates from 109 time series studies (although estimates for PM effects were only available from a subset of these studies). Random effects pooled estimates of excess mortality were calculated. Statistically significant positive associations were observed between daily mortality counts and various measures of air pollution, including PM_{10}. They concluded that "this synthesis leaves little doubt that acute air pollution exposure is a significant contributor to mortality."[135] In a latter publication[136] and in response to the concerns about the use of GAM-based models discussed above, the authors provided pooled estimates of PM mortality effects for studies where the primary estimates were based on models that used GAM versus studies where the primary estimates were not GAM based. As summarized in Table 1, the GAM-based estimates were larger than the non-GAM-based estimates. However, pooled estimates indicated that statistically significant adverse PM-mortality associations remained.

Because there are no clearly defined or uniform criteria for selecting study cities, a fundamental concern regarding PM-mortality estimates from published single-city studies is the potential for city selection and publication bias. In a formal meta-analysis of 74 single-city daily time series mortality studies, Anderson et al.[137] found evidence for publication bias; however, effect estimates were not substantially altered after statistical correction for this bias (see Table 1). Another similar meta-analysis was conducted as part of a report on cardiovascular disease and air pollution for the U.K. Department of Health.[138] Although this report focused on cardiovascular disease and mortality, as can be seen in Table 1, the effect estimates were comparable to estimates for total mortality.

Multicity Studies of Short-Term Exposure and Mortality

In 1997, multicity time series studies were nearly nonexistent. A notable exception was a study of six U.S. cities.[139] Daily mortality counts were found to be associated with PM_{10}, $PM_{2.5}$, and sulfate particles, but the strongest associations were found with $PM_{2.5}$. Several subsequent analyses of these data have been conducted.[140–142] Klemm and Mason,[142] responding to the concerns about the early use of GAM-based models, estimated the PM-mortality effects using alternative modeling approaches including a more stringent GAM convergence criteria (see Table 1).

Burnett et al.[143] analyzed daily mortality counts and various measures of air pollution in eight of Canada's largest cities and reported statistically significant PM-mortality associations. Because the original analysis used GAM modeling, a reanalysis of these data[144] was conducted using strict GAM convergence criteria. Although somewhat diminished, statistically significant $PM_{2.5}$-mortality associations remained (see Table 1). As part of the reanalysis, it was observed that PM-mortality associations were somewhat sensitive to parametric smoothing (natural spline models) with various fitting criteria.

Ostro et al.[145] conducted a daily mortality time series study of nine California cities using data from 1999 through 2002. They avoided the use of GAM models by using Poisson regression models that incorporated natural or penalized splines to control for time, seasonality, temperature, humidity, and day of week. Random-effects meta-analysis was used to make pooled estimates. Relatively small but statistically significant $PM_{2.5}$-mortality associations were observed (see Table 1). Several analyses have been conducted[146,147] using data from 10 U.S. cities with daily PM_{10} monitoring. Statistically significant PM_{10}-mortality associations were consistently observed, including a reanalysis[148] using more stringent GAM convergence criteria (see Table 1).

A study evaluated daily mortality and air pollution in 14 U.S. cities[149] using the case-crossover study design rather than daily time series. The exposure of each mortality case was compared with exposure on a nearby day. Potential confounding factors, such as seasonal patterns and other slowly varying covariates, were controlled for by matching (rather than statistical modeling as in the time series approach). Statistically significant PM_{10}-mortality associations were observed (Table 1). When the data were also analyzed using daily time series analysis, for comparison purposes, estimated PM_{10} mortality associations were similar.

One of the largest and most ambitious multicity daily time series studies is the National Morbidity, Mortality, and Air Pollution Study (NMMAPS). This study grew out of efforts to replicate several early single-city time series studies[150] and was designed to address concerns about city selection bias, publication bias, and influence of copollutants. A succession of analyses included as few as 20 U.S. cities[151,152] and as many as 100 cities.[153–155] Although the PM-mortality effect estimates were somewhat sensitive to various modeling and city selection choices, there was "consistent evidence that the levels of fine particulate matter in the air are associated with the risk of death from all causes and from cardiovascular and respiratory illnesses."[151] Excess risk estimates are presented in Table 1. Because the NMMAPS analysis included many cities with substantially different levels of copollutants, the influence of copollutants could be directly evaluated. The PM-mortality effect was not attributable to any of the copollutants studied (NO_2, CO, SO_2, or O_3).

A parallel research effort, the Air Pollution and Health: A European Approach (APHEA) project, examined the short-term PM-mortality effects in multiple European cities. Initially, this research effort analyzed daily mortality data from ≤15 European cities, including 5 from Central-Eastern Europe, using a common protocol.[156] Daily mortality was found to be significantly associated with PM and sulfur oxide concentrations,[157,158] although the effect estimates were sensitive to approaches to controlling for long-term time trends and seasonality.[159,160] A continuation and extension of the APHEA project, often referred to a APHEA-2, included analyses of daily mortality and pollution data for ≤29 European cities.[161,162] APHEA-2 also found that PM air pollution was significantly associated with daily mortality counts (see Table 1). Furthermore, the use of GAMs with strict convergent criteria or parametric smoothing approaches did not substantially alter the estimated PM-mortality effects.[162] Subsequent analysis of APHEA-2 data found PM-mortality effects with both cardiovascular and respiratory mortality (see Table 1).[163]

Mortality associations with PM were also observed for nine French cities[164] and three Australian cities.[165] Two Asian multicity studies have reported daily mortality associations with measures of PM (see Table 1). The first was a study of seven major Korean cities.[166] Measures of PM_{10} or $PM_{2.5}$ were not available, and PM was measured only as TSP. Although it was suggested that SO_2 may have functioned better as a surrogate for $PM_{2.5}$ in Korea's ambient air than TSP, mortality associations were observed with TSP, as well as with SO_2. The second analyzed data from the 13 largest Japanese cities[167] with mortality data for the elderly (aged ≥65 years) and suspended PM (special purpose monitoring, approximately PM_7; i.e., PM with a 50% cutoff diameter of ~7 μm). GAM and generalized linear models were used (estimated using SAS rather than S plus software).

Summary and Discussion

It seems unlikely that relatively small elevations in exposure to particulate air pollution over short periods of only 1 or a few days could be responsible for very large increases in death. In fact, these studies of mortality and short-term daily changes in PM are observing small effects. For example, assume that a short-term elevation of $PM_{2.5}$ of 10 $\mu g/m^3$ results in an ~1% increase in mortality (based on the effect estimates summarized in Table 1). Based on the year 2000 average death rate for the United States (8.54 deaths/1000 per year), a 50-$\mu g/m^3$ short-term increase in $PM_{2.5}$ would result in an average of only 1.2 deaths per day in a population of 1 million (compared with an expected rate of ~23.5/day). That is, on any given day, the number of people dying because of PM exposure in a population is small.

It is remarkable that these studies of mortality and short-term changes in PM are capable of observing such small effects. Uncertainties in estimating such small effects legitimately create some doubts or concerns regarding the validity or accuracy of these estimates. Nevertheless, associations between daily changes in PM concentrations and daily mortality counts continue to be observed in many different cities and, more importantly, in large multicity studies, which have much less opportunity for selection or publication bias. The estimated size of these associations is influenced by the methods used to control for potential confounding by long-term time trends, seasonality, weather, and other time-dependent covariates. However, numerous researchers using various methods, including alternative time series analytic approaches and case-crossover designs, continue to fairly consistently observe adverse mortality associations with short-term elevations in ambient PM.

LONG-TERM EXPOSURE AND MORTALITY

Although daily time series studies of acute exposures continue to suggest short-term acute PM effects, they provide little information about the degree of life shortening, pollution effects on longer-term mortality rates, or the

Table 2. Comparison of percentage increase (and 95% CI) in relative risk of mortality associated with long-term particulate exposure.

Study	Primary Sources	Exposure Increment	Percent Increases in Relative Risk of Mortality (95% CI)		
			All Cause	Cardiopulmonary	Lung Cancer
Harvard Six Cities, original	Dockery et al. 1993[26]	10 $\mu g/m^3$ $PM_{2.5}$	13 (4.2, 23)	18 (6.0, 32)	18 (−11, 57)
Harvard Six Cities, HEI reanalysis	Krewski et al. 2000[177]	10 $\mu g/m^3$ $PM_{2.5}$	14 (5.4, 23)	19 (6.5, 33)	21 (−8.4, 60)
Harvard Six Cities, extended analysis	Laden et al. 2006[184]	10 $\mu g/m^3$ $PM_{2.5}$	16 (7, 26)	28 (13, 44)[a]	27 (−4, 69)
ACS, original	Pope et al. 1995[27]	10 $\mu g/m^3$ $PM_{2.5}$	6.6 (3.5, 9.8)	12 (6.7,17)	1.2 (−8.7, 12)
ACS, HEI reanalysis	Krewski et al. 2000[177]	10 $\mu g/m^3$ $PM_{2.5}$	7.0 (3.9, 10)	12 (7.4, 17)	0.8 (−8.7, 11)
ACS, extended analysis	Pope et al. 2002[179]	10 $\mu g/m^3$ $PM_{2.5}$	6.2 (1.6, 11)	9.3 (3.3, 16)	13.5 (4.4, 23)
	Pope et al. 2004[180]			12 (8, 15)[a]	
ACS adjusted using various education weighting schemes	Dockery et al. 1993[26]	10 $\mu g/m^3$ $PM_{2.5}$	8–11	12–14	3–24
	Pope et al. 2002[179]				
	Krewski et al. 2000[177]				
ACS intrametro Los Angeles	Jerrett et al. 2005[181]	10 $\mu g/m^3$ $PM_{2.5}$	17 (5, 30)	12 (−3, 30)	44 (−2, 211)
Postneonatal infant mortality, U.S.	Woodruff et al. 1997[185]	20 $\mu g/m^3$ PM_{10}	8.0 (4, 14)	–	–
Postneonatal infant mortality, CA	Woodruff et al. 2006[186]	10 $\mu g/m^3$ $PM_{2.5}$	7.0 (−7, 24)	113 (12, 305)[c]	–
AHSMOG[b]	Abbey et al. 1999[187]	20 $\mu g/m^3$ PM_{10}	2.1 (−4.5, 9.2)	0.6 (−7.8, 10)	81 (14, 186)
AHSMOG, males only	McDonnell et al. 2000[188]	10 $\mu g/m^3$ $PM_{2.5}$	8.5 (−2.3, 21)	23 (−3, 55)	39 (−21, 150)
AHSMOG, females only	Chen et al. 2005[189]	10 $\mu g/m^3$ $PM_{2.5}$	–	42 (6, 90)[a]	–
Women's Health Initiative	Miller et al. 2004[190]	10 $\mu g/m^3$ $PM_{2.5}$	–	32 (1, 73)[a]	
VA, preliminary	Lipfert et al. 2000, 2003[190,192]	10 $\mu g/m^3$ $PM_{2.5}$	0.3 (NS)[d]	–	–
VA, extended	Lipfert et al. 2006[193]	10 $\mu g/m^3$ $PM_{2.5}$	15 (5, 26)[e]	–	–
11 CA counties, elderly	Enstrom 2005[194]	10 $\mu g/m^3$ $PM_{2.5}$	1 (−0.6, 2.6)	–	–
Netherlands	Hoek et al. 2002[195]	10 $\mu g/m^3$ BS	17 (−24, 78)	34 (−32, 164)	–
Netherlands	Hoek et al. 2002[195]	Near major road	41 (−6, 112)	95 (9, 251)	–
Hamilton, Ontario, Canada	Finkelstein et al. 2004[197]	Near major road	18 (2, 38)	–	–
French PAARC	Filleul et al. 2005[198]	10 $\mu g/m^3$ BS	7 (3, 10)[f]	5 (−2,12)[f]	3 (−8,15)[f]
Cystic fibrosis	Goss et al. 2004[200]	10 $\mu g/m^3$ $PM_{2.5}$	32 (−9, 93)	–	–

[a]Cardiovascular only; [b]Pooled estimates for males and females; pollution associations were observed primarily in males and not females; [c]Respiratory only; [d]Reported to be nonsignificant by author; overall, effect estimates to various measure of particulate air pollution were highly unstable and not robust to selection of model and time windows; [e]Estimates from the single pollutant model and for 1989–1996 follow-up; effect estimates are much smaller and statistically insignificant in an analysis restricted to counties with nitrogen dioxide data and for the 1997–2001 follow-up; furthermore, county-level traffic density is a strong predictor of survival and stronger than $PM_{2.5}$ when included with $PM_{2.5}$ in joint regressions; [f]Estimates when six monitors that were heavily influenced by local traffic sources were excluded; when data from all 24 monitors in all areas were used, no statistically significant associations between mortality and pollution were observed.

role of pollution in inducing or accelerating the progress of chronic disease.[168] Several analyses of pollution and mortality data, as early as 1970, reported that long-term average concentrations of $PM_{2.5}$ or sulfate are associated with annual mortality rates across U.S. metropolitan areas.[169–175] These population-based cross-sectional mortality rate studies were largely discounted by 1997 because of concern that they could not control for individual risk factors, such as cigarette smoking, which could potentially confound the air pollution effects. With regard to the mortality effects of long-term PM exposure, recent emphasis has been on prospective cohort studies[176] that can control for individual differences in age, sex, smoking history, and other risk factors. However, because these studies require collecting information on large numbers of people and following them prospectively for long periods of time, they are costly, time consuming, and, therefore, much less common. A brief summary of results from these studies is presented in Table 2.

Original Harvard Six Cities and ACS Studies

By 1997, two cohort-based mortality studies had reported evidence of mortality effects of chronic exposure to fine particulate air pollution. The first study, often referred to as the Harvard Six Cities Study,[26] reported on a 14- to 16-yr prospective follow-up of >8000 adults living in six U.S. cities, representing a wide range of pollution exposure. The second study, referred to as the ACS study, linked individual risk factor data from the ACS, Cancer Prevention Study II with national ambient air pollution data.[27] The analysis included data from >500,000 adults who lived in ≤151 metropolitan areas and were followed prospectively from 1982 through 1989. Both the Harvard Six Cities and the ACS cohort studies used Cox proportional hazard regression modeling to analyze survival times and to control for individual differences in age, sex, cigarette smoking, education levels, body mass index, and other individual risk factors. In both studies, cardiopulmonary mortality was significantly and most strongly associated with sulfate and $PM_{2.5}$ concentrations.

Although both the Harvard Six Cities and ACS studies used similar study designs and methods, these two studies had different strengths and limitations. The strengths of the Harvard Six Cities Study were its elegant and relatively balanced study design, the prospective collection of study-specific air pollution data, and the ability to present the core results in a straightforward graphical format. The primary limitations of the Harvard Six Cities Study were

the small number of subjects from a small number of study areas (that is exposures) in the Eastern United States. In contrast, the major strength of the ACS study was the large number of participants and cities distributed across the whole United States. The primary limitation of the ACS was the lack of planned, prospective collection of study-specific air pollution and health data and the reliance on limited, separately collected subject and pollution data. However, the ACS study provided a test of the hypotheses generated from the Harvard Six Cities Study in an independently collected dataset. These two studies, therefore, were complementary.

Reanalyses and Extended Analyses of Harvard Six Cities and ACS Studies

In the mid-1990s, the Harvard Six Cities and the ACS prospective cohort studies provided compelling evidence of mortality effects from long-term fine particulate air pollution. Nevertheless, these two studies were controversial, and the data quality, accessibility, analytic methods, and validity of these studies came under intense scrutiny.[81] There were calls from political leaders, industry representatives, interested scientists, and others to make the data available for further scrutiny and analyses. There were also serious constraints and concerns regarding the dissemination of confidential information and the intellectual property rights of the original investigators and their supporting institutions. In 1997, the investigators of the two studies agreed to provide the data for a intensive reanalysis by an independent research team under Health Effects Institute (HEI) oversight, management, sponsorship, and under conditions that assured the confidentiality of the information on individual study participants. The reanalysis included: (1) a quality assurance audit of the data, (2) a replication and validation of the originally reported results, and (3) sensitivity analyses to evaluate the robustness of the original findings. The reanalysis[177,178] reported that the data were "generally of high quality" and that the results originally reported could be reproduced and validated. The data audit and validation efforts revealed some data and analytic issues that required some tuning, but the adjusted results did not differ substantively from the original findings. The reanalysis demonstrated the robustness of the PM-mortality risk estimates to many alternative model specifications. The reanalysis team also made a number of innovative methodological contributions that not only demonstrated the robustness of the PM-mortality results but substantially contributed to subsequent analyses. In the reanalysis, persons with higher educational attainment were found to have lower relative risks of mortality associated with $PM_{2.5}$ in both studies.

Further extended analyses of the ACS cohort[179,180] included more than twice the follow-up time (>16 years) and approximately triple the number of deaths. The mortality associations with fine particulate and sulfur oxide pollution persisted and were robust to control for individual risk factors including age, sex, race, smoking, education, marital status, body mass index, alcohol use, occupational exposures, and diet and the incorporation of both random effects and nonparametric spatial smoothing components. There was no evidence that the PM-mortality associations were because of regional or other spatial differences that were not controlled in the analysis. These analyses also evaluated associations with expanded pollution data, including gaseous copollutant data and new $PM_{2.5}$ data. Elevated mortality risks were most strongly associated with measures of $PM_{2.5}$ and sulfur oxide pollution. Coarse particles and gaseous pollutants, except for sulfur dioxide (SO_2), were generally not significantly associated with elevated mortality risk.

Jerret et al.[181] assessed air pollution associations of the ~23,000 subjects in the ACS cohort who lived in the metropolitan Los Angeles area. PM-mortality associations were estimated based on $PM_{2.5}$ measures from 23 monitoring sites interpolated to 267 residential zip code centroids for the period between 1982 and 2000. Cox proportional hazards regression models controlled for age, sex, race, smoking, education, marital status, diet, alcohol use, occupational exposures, and body mass.[179] In addition, because variations in exposure to air pollution within a city may correlate with socioeconomic gradients that influence health and susceptibility to environmental exposures, zip code-level ecological variables were used to control for potential "contextual neighborhood confounding."[182,183] The mortality associations with the intrametropolitan $PM_{2.5}$ concentrations were generally larger than those observed previously in the ACS cohort across metropolitan areas.

A recent analysis of the Harvard Six Cities cohort[184] extended the mortality follow-up for 8 more years with approximately twice the number of deaths. $PM_{2.5}$ concentrations for the extended follow-up years were estimated from PM_{10} and visibility measures. $PM_{2.5}$-mortality associations, similar to those found in the original analysis, were observed for all-cause, cardiovascular, and lung cancer mortality. However, $PM_{2.5}$ concentrations were substantially lower for the extended follow-up period than they were for the original analysis, especially for two of the most polluted cities. Reductions in $PM_{2.5}$ concentrations were associated with reduced mortality risk and were largest in the cities with the largest declines in $PM_{2.5}$ concentrations. The authors note that, "these findings suggest that mortality effects of long-term air pollution may be at least partially reversible over periods of a decade."[184]

Other Independent Studies

Woodruff et al.[185] reported the results of an analysis of postneonatal infant mortality (deaths after 2 months following birth determined from the U.S. National Center for Health Statistics birth and death records) for ~4 million infants in 86 U.S. metropolitan areas between 1989 and 1991 linked with EPA-collected PM_{10}. Postneonatal infant mortality was compared with levels of PM_{10} concentrations during the 2 months after birth controlling for maternal race, maternal education, marital status, month of birth, maternal smoking during pregnancy, and ambient temperatures. Postneonatal infant mortality for all causes, respiratory causes and sudden infant death syndrome (SIDS) were associated with particulate air pollution. Woodruff et al.[186] also linked monitored $PM_{2.5}$ to

infants who were born in California in 1999 and 2000 and who lived within 5 mi of a monitor, matching 788 postneonatal deaths to 3089 survivors. Each 10-$\mu g/m^3$ increase in $PM_{2.5}$ was associated with a near doubling of the risk of postneonatal death because of respiratory causes and a statistically insignificant increase of ~7% for death from all causes (Table 2).

The Adventist Health Study of Smog (AHSMOG) cohort study related air pollution to 1977–1992 mortality in >6000 nonsmoking adults living in California, predominantly from San Diego, Los Angeles, and San Francisco.[187] All-cause mortality, nonmalignant respiratory mortality, and lung cancer mortality were significantly associated with ambient PM_{10} concentrations in males but not in females. Cardiopulmonary disease mortality was not significantly associated with PM_{10} in either males or females. This study did not have direct measures of $PM_{2.5}$ but relied on TSP and PM_{10} data. In a follow-up analysis,[188] visibility data were used to estimate $PM_{2.5}$ exposures of a subset of males who lived near an airport. All-cause, lung cancer, and nonmalignant respiratory disease (either as the underlying or a contributing cause) were more strongly associated with $PM_{2.5}$ than with PM_{10}. In a recent analysis of the AHSMOG cohort, fatal coronary heart disease was significantly associated with PM among females but not among males.[189]

The association between long-term $PM_{2.5}$ exposure and cardiovascular events (fatal and nonfatal) were explored in the Women's Health Initiative Observational Study.[190] Based on measurements from the nearest monitor, air pollution exposures were estimated for ~66,000 postmenopausal women without prior cardiovascular disease. After adjusting for age, smoking, and various other risk factors, an incremental difference of 10 $\mu g/m^3$ of $PM_{2.5}$ was associated with a 14% (95% confidence interval [CI], 3–26%) increase in nonfatal cardiovascular events and with a 32% (95% CI, 1–73%) increase in fatal cardiovascular events.

Lipfert et al.[191,192] assessed the association of total mortality and air pollution in a prospective cohort of ~50,000 middle-aged, hypertensive, male patients from 32 Veterans Administration (VA) clinics followed for ~21 years. The cohort had a disproportionately large number of current or former smokers (81%) and African-Americans (35%) relative to the U.S. population or to other cohorts that have been used to study air pollution. Air pollution exposures were estimated by averaging air pollution data for participants' county of residence at the time of entrance into the cohort. Only analyses of total mortality were reported. In addition to considering mortality and average exposures over the entire follow-up period, three sequential mortality periods and four exposure periods were defined and included in various analyses. Lipfert et al.[193] extended the follow-up of the VA cohort and focused on traffic density as the measure of environmental exposure. It was suggested that traffic density was a more "significant and robust predictor of survival in this cohort" than $PM_{2.5}$. However, of the various measures of ambient air pollution, $PM_{2.5}$ was most strongly correlated with traffic density ($r = 0.50$). In single pollutant models, $PM_{2.5}$ was associated with mortality risk resulting in risk estimates comparable to other cohorts (see Table 2). Overall in the VA analyses, effect estimates to various measures of PM were unstable and not robust to model selection, time windows used, or various other analytic decisions. It was difficult, based on the preliminary results presented, to make conclusive statistical inferences regarding PM-mortality associations.

Enstrom[194] reported an analysis of ~36,000 elderly males and females in 11 California counties followed between 1973 and 2002. Countywide $PM_{2.5}$ concentrations were estimated from outdoor ambient monitoring for the time period 1979–1983. For approximately the first half of the follow-up period (1973–1983) and for the time period approximately concurrent with $PM_{2.5}$ monitoring, a small $PM_{2.5}$-mortality association was observed (10 $\mu g/m^3$ of $PM_{2.5}$ was associated with a 4% [95% CI, 1- 7%] increase risk of mortality). No $PM_{2.5}$-mortality risk associations were observed for the later followup (1983–2002). For the entire follow-up period, only a small statistically insignificant association was observed (Table 2).

In a pilot study, Hoek et al.[195] evaluated the associations between mortality and PM based on a random sample of 5000 participants in the Netherlands Cohort Study on Diet and Cancer, originally 55–69 yr of age and followed for >8 yr. Although the effect estimates were not very precise, the adjusted risk of cardiopulmonary mortality was nearly double for individuals who lived within 100 m of a freeway or within 50 m of a major urban road. Based on residential location of participants and interpolation of pollution data from the Netherlands' national air pollution monitoring network, average background concentrations of black smoke ([BS] or British smoke measured by optical densities or light absorbance of filters used to gather PM from the air[196]) for the first 4 yr of follow-up were estimated. Background plus local traffic-related BS exposures were estimated by adding to the background concentration a quantitative estimate of living near a major road. Cardiopulmonary mortality was associated with estimates of exposure to BS, and the association was nearly doubled when local traffic-related sources of BS in addition to background concentrations were modeled.

In an exploration of the relationship between proximity to traffic air pollution and mortality observed in the Netherlands study, an analysis using a cohort of 5228 persons >40 yr of age living in Hamilton, Ontario, Canada, was conducted.[197] Somewhat higher mortality risks were observed for individuals who lived within 100 m of a highway or within 50 m of a major road.

Filleul et al.[198] reported an analysis of ~14,000 adults who resided in 24 areas from seven French cities as part of the Air Pollution and Chronic Respiratory Diseases (PAARC) survey. Participants were enrolled in 1974, and a 25-year mortality follow-up was conducted. Ambient air pollution monitoring for TSP, BS, nitrogen dioxide, and NO was conducted for 3 yr in each of the 24 study areas. When survival analysis was conducted using data from all 24 monitors in all of the areas, no statistically significant associations between mortality and pollution were observed. However, when the six monitors that were heavily

influenced by local traffic sources were excluded, nonaccidental mortality was significantly associated with all four measures of pollution, including BS (Table 2). In addition to PM, mortality was associated with nitrogen oxides. Nitrogen oxide concentrations were also significantly associated with mortality risk in a cohort of Norwegian men,[199] but no measure of PM was available.

Finally, a unique study of the effects of ambient air pollution was conducted utilizing a cohort of ~20,000 patients >6 yr old who were enrolled in the U.S.-based Cystic Fibrosis Foundation National Patient Registry in 1999 and 2000.[200] Annual average air pollution exposures were estimated by linking fixed-site ambient monitoring data with resident zip code. A positive, but not statistically significant, association between $PM_{2.5}$ and mortality was observed. $PM_{2.5}$ was associated with statistically significant declines in lung function (FEV_1) and an increase in the odds of two or more pulmonary exacerbations.

Summary and Discussion

As can be seen in Table 2, for both the Harvard Six Cities and the ACS prospective cohort studies, the estimated effects for all-cause and cardiopulmonary mortality were relatively stable across different analyses. The Harvard Six Cities estimates, however, were approximately twice as large as the ACS estimates. Two main factors may explain these differences in estimated PM-mortality effects.

First, both the reanalysis and extended analyses have found that persons with higher educational attainment had lower relative risk of PM-related mortality. The ACS cohort overrepresented relatively well-educated individuals relative to the Harvard Six Cities study. To provide a tentative estimate of how this overrepresentation may have influenced the pooled-effect estimates from the ACS study, various schemes for adjusting the ACS effect estimates by reweighting the regression coefficients were tried. A relatively conservative approach was to calculate a pooled ACS estimate by weighting the effect estimates by education level from the ACS cohort with the proportions of participants from each education level from the Harvard Six Cities cohort based on the Krewski et al.[177] reanalysis (Part II, Table 52). A more aggressive approach was to use the Cox proportional hazard regression coefficients for the ACS extended analysis[179] that were estimated for each of the three education levels. Pooled, weighted estimates were then calculated using weights (proportion of sample within each of the three education levels from Krewski et al.[177], Part II, Table 52) for both the Harvard Six Cities study and the ACS study, and then the ratio of the pooled, weighted estimates was used to adjust the originally reported ACS effect estimates. As can be seen in Table 2, reweighting to account for the overrepresentation of relatively well-educated individuals in the ACS cohort explains part, but not all, of the difference in effect estimates between the Harvard Six Cities and ACS studies.

Second, the geographical areas that defined the communities studied in the Harvard Six Cities study were, on average, substantially smaller than the metropolitan areas included in the ACS study. Indeed, an analysis of the Los Angeles metropolitan area ACS participants showed that interpolated $PM_{2.5}$ air pollution concentrations resulted in effect estimates comparable with estimates from the Harvard Six Cities Study. Similarly, in the Netherlands study, when local sources of particulate pollution exposure in addition to community-wide background concentrations were modeled, the elevated relative risk estimates also approximately doubled. These results suggest that PM-mortality effect estimates based on analysis that only uses metropolitan-wide average background concentrations may underestimate the true pollution-related health burden and suggests the importance of analyses with more focused spatial resolution.

In 1997, Vedal[80] argued that the evidence for substantive health effects because of chronic or long-term exposure to particulate air pollution was weak. Since then, the HEI reanalysis of the Harvard Six Cities and ACS prospective cohort studies and the subsequent extended analyses of these cohort studies have strengthened the evidence of long-term, chronic health effects. Reanalyses are not as convincing as new, independent cohort studies. The results from the independent Women's Health Initiative Study[190] add to the evidence that long-term exposure increases the risk of cardiovascular disease in women. The evidence is further bolstered by results from the infant mortality studies,[185,186] the Netherlands study,[195] and the Hamilton study[197] but less so by the mixed results from the AHSMOG studies,[187–189] the French PAARC study,[198] the VA analyses,[191–193] and the 11 California counties study.[194] With regard to the infant mortality findings,[185,186] although the analyses are based on cross-sectional or long-term differences in air pollution, the time frame of exposure for the infants was clearly shorter than for adults (a few months vs. years). The relevant time scales of exposure for different age groups, levels of susceptibility, and causes of death need further exploration.

TIME SCALES OF EXPOSURE

The PM-mortality effect estimates from the long-term prospective cohort studies (Table 2) are substantially larger than those from the daily time series and case-crossover studies (Table 1). The much larger PM-mortality effect estimates from the prospective cohort studies are inconsistent with the supposition that they are due to short-term harvesting or mortality displacement. If pollution-related excess deaths are only because of deaths of the very frail who have heightened susceptibility and who would have died within a few days anyway, then the appropriate time scale of exposure would be only a few days, and impacts on long-term mortality rates would be minimal.

Mortality effects of short-term exposure, however, may not be attributed primarily to harvesting. Long-term repeated exposures to pollution may have more broad-based impacts on long-term health and susceptibility. Much of the difference in PM-mortality associations observed between the daily time series and the prospective cohort studies may be because of the dramatically different time scales of exposure (a few days vs. decades). Effective dose, in terms of impact on risk of adverse health effects, is almost certainly dependent on both exposure concentrations and length of exposure. It is reasonable to expect that effect estimates could be different for different

time scales of exposure, that long-term repeated exposures could have larger, more persistent effects than short-term transient exposures, and that long-term average exposures could be different from the cumulative effect of short-term transient exposures.

Neither the daily time series studies nor the prospective cohort studies were designed to evaluate the alternative time scales of exposure. These studies were designed primarily to exploit obvious, observable sources of exposure variability. Short-term temporal variability is examined in the daily time series studies. In most of these studies, various approaches are used to focus only on short-term variability while taking out or controlling for longer-term temporal variability, such as seasonality and time trends. Thus, by design, opportunities to evaluate effects of intermediate or long-term exposure are largely eliminated. The other important dimension of exposure variability is spatial (or cross-sectional) variability of long-term average concentrations. The major prospective cohort studies have been designed primarily to exploit this much longer-term spatial variability. Efforts to estimate the dynamic exposure-response relationship between $PM_{2.5}$ exposure and human mortality must integrate evidence from long-term, intermediate, and short-term time scales.[201]

Studies of Intermediate Time Scales of Exposure

Before 1997, there was hardly any reported research that evaluated intermediate time scales of exposure. One exception was research related to the operation of a steel mill in Utah Valley.[20,28,202] During the winter of 1986–1987, a labor dispute and change in ownership resulted in a 13-month closure of the largest single source of particulate air pollution in the valley, a local steel mill. During the 13-month closure period, average PM_{10} concentrations decreased by 15 $\mu g/m^3$, and mortality decreased by 3.2%.

A more recent evaluation of PM-related changes in mortality using an intermediate time scale was conducted in Dublin, Ireland.[203] During the 1980s, a dominant source of Dublin's ambient PM was coal smoke from domestic fires. In September of 1990, the sale of coal was banned, resulting in a 36-$\mu g/m^3$ decrease in average ambient PM as measured by BS. After adjusting in Poisson regression for temperature, RH, day of week, respiratory epidemics, and standardized cause-specific death rate in the rest of Ireland, statistically significant drops in all of the nontrauma deaths (−5.7%; 95% CI, −7.2% to −4.1%), cardiovascular deaths (−10.3%; 95% CI, −12.6% to −8%), and respiratory deaths (−15.5%; 95% CI, −19.1% to −11.6%) were observed.

As noted above, in the extended analysis of the Harvard Six Cities cohort,[184] fine particulate concentrations were substantially lower for the 8-yr extended follow-up period than they were for the original analysis, especially for two of the most polluted cities. These reductions in $PM_{2.5}$ concentrations were associated with reduced mortality risk, suggesting that the mortality effects were at least partially reversible within a time scale of just a few years. Furthermore, the reductions in $PM_{2.5}$ in the extended follow-up compared with the original study period were associated with improved survival, that is, a relative risk of −27% (95% CI, −43% to −5%) for each 10-$\mu g/m^3$ reduction in $PM_{2.5}$.

Daily Time Series Studies with Longer Time Scales or Extended Distributed Lags

Several researchers have developed methods to analyze daily time series data for time scales of exposure substantially longer than just a few days. A primary motivation of this effort was to explore the "harvesting," or mortality displacement hypothesis. If pollution-related excess deaths occur only among the very frail, then the excess deaths during and immediately after days of high pollution should be followed by a short-term compensatory reduction in deaths. To explore whether or not this phenomena could be observed, Zeger et al.[204] proposed frequency decompositions of both the mortality counts and air pollution data. They applied frequency domain log-linear regression[205] to mortality data from a single city (Philadelphia, PA) and found larger PM effects on the relatively longer time scales, a finding inconsistent with harvesting. This work was extended by Dominici et al.[206] to a two-stage model that allowed for combining evidence across four U.S. cities with daily PM_{10} levels. They found the PM-mortality associations were larger at longer time scales (10 days to 2 months) than at time scales of just a few days. Schwartz[207–209] applied a related approach using smoothing techniques to decompose the data into different time scales in two separate analyses using data from Chicago, IL, and Boston, MA, and also found that the PM-mortality associations were much larger for the longer time scales.

An alternative approach to evaluate longer time scales is the use of extended distributed lags in time series analyses. Distributed lag models have long been used in econometrics[210,211] and have more recently been applied in air pollution epidemiology.[31,212] Studies using distributed lag models to evaluate associations from 5 to ≤60 days after exposure have been conducted using data from 10 U.S. cities,[213,214] European cities from the APHEA-2 project,[215,216] and Dublin.[217] In all of these analyses, the net PM-mortality effect was larger when time scales longer than a few days were used.

Summary and Discussion

For comparison purposes, Table 3 provides a simple summary of estimated excess risk of mortality estimates for different studies with different time scales of exposure. These results do not provide the complete picture, but they suggest that the short-term, daily time series air pollution studies are not observing only harvesting or mortality displacement. These results also suggest that daily time series studies capture only a small amount of the overall health effects of long-term repeated exposure to particulate air pollution. Because the adverse health effects of particulate air pollution are likely dependent on both exposure concentrations and length of exposure, it is expected that long-term repeated exposures would have larger, more persistent cumulative effects than short-term transient exposures. PM-mortality effect estimates for intermediate time intervals provide evidence that the difference in PM-mortality associations observed between the daily time series and the prospective cohort studies

Table 3. Comparison of estimated excess risk of mortality estimates for different time scales of exposure.

Study	Primary Sources	Time Scale of Exposure	% Change in Risk of Mortality Associated with an Increment of 10 $\mu g/m^3$ $PM_{2.5}$ or 20 $\mu g/m^3$ PM_{10} or BS			
			All Cause	Cardiovascular/ cardiopulmonary	Respiratory	Lung Cancer
Daily time series	Table 1	1–3 days	0.4–1.4	0.6–1.1	0.6–1.4	–
10 U.S. cities, time series, extended distributed lag	Schwartz 2000[213]	1 day	1.3	–	–	–
		2 days	2.1	–	–	–
		5 days	2.6	–	–	–
10 European cities, time series, extended distributed lag	Zanobetti et al. 2002[215]	2 days	1.4	–	–	–
		40 days	3.3	–	–	–
10 European cities, time series, extended distributed lag	Zanobetti et al. 2003[216]	2 days	–	1.4	1.5	–
		20 days	–	2.7	3.4	–
		30 days	–	3.5	5.3	–
		40 days	–	4.0	8.6	–
Dublin daily time series, extended distributed lag	Goodman et al. 2004[217]	1 day	0.8	0.8	1.8	–
		40 days	2.2	2.2	7.2	–
Dublin intervention	Clancy et al. 2002[203]	months to year	3.2	5.7	8.7	–
Utah Valley, time series and intervention	Pope et al. 1992[20]	5 days	3.1	3.6	7.5	–
		13 months	4.3	–	–	–
Harvard Six Cities, extended analysis	Laden et al. 2006[184]	1–8 yr	14	–	–	–
Prospective cohort studies	Dockery et al. 1993[26] Pope et al. 2002[179]	10+ yr	6–17	9–28	–	14–44

are at least partially because of the substantially different time scales of exposure.

SHAPE OF CONCENTRATION-RESPONSE FUNCTION

Understanding the shape of the concentration-response function and the existence of a no-effects threshold level has played a critical role in efforts to establish and evaluate ambient air quality standards and related public health policy. This information is also vital in economic and public policy analyses that require estimating the marginal health costs of pollution. An early analysis by Ostro[110] evaluated the shape of the concentration-response function and the existence of a no-effects threshold in London mortality and air pollution data for 14 winters (1958–1972). Linear spline functions that allowed for different response relationships below and above 150 $\mu g/m^3$ were estimated. Mortality effects were observed even in winters without historically severe pollution episodes, and there was no evidence of a threshold. Schwartz and Marcus[17] plotted the same London data after sorting the observations in order of increasing pollution levels and taking the means of adjacent observations. No threshold was observed; in fact, the slope of the concentration-response function was steeper at lower concentrations than at higher concentrations.

In the early 1990s, various approaches were used to evaluate the shape of the concentration-response function. For example, researchers often divided pollution concentrations into quintiles (or quartiles) and included indicator variables for different ranges of air pollution in the time series regression models. This allowed for the estimated adjusted relative risk of death to be plotted over various levels of pollution.[19–23] The associations generally appeared to be near linear with no clear threshold.[218] The development and use of various parametric and nonparametric smoothing approaches not only allowed for more flexible handling of long-term time trends, seasonality, and various weather variables, but they also allowed for direct exploration of the shape of the concentration-response function.[219] Such analyses were conducted in numerous single-city daily time series studies.[24,71,112,220] Generally the shapes of the estimated concentration-response function were not significantly different from linear and were not consistent with well-defined thresholds.[218] However, the lack of statistical power to make strong statistical inferences regarding function shape, and the generalizability of single-city estimates of the concentration-response relationships were questioned.

Multicity Daily Time Series Mortality

Since 1997, methods have been developed to explore the shape of the PM-mortality concentration-response functions in daily time series studies of multiple cities, which enhance statistical power and generalizability. Schwartz and Zanobetti[221] estimated a pooled or combined concentration-response function for 10 U.S. cities. The combined or "meta-smoothed" concentration-response function was estimated using Poisson regression models fitting nonparametric smoothed functions for PM_{10} and calculating the inverse variance weighted average across the 10 cities for each 2-$\mu g/m^3$ increment of PM_{10}. The estimated combined 10-city concentration-response function was near linear with no evidence of a threshold (see Figure 1a). Schwartz et al.[222] applied essentially the same approach on daily mortality and BS data from eight Spanish cities, finding a near linear concentration-response function with no evidence of a threshold (see Figure 1b).

An alternative approach to estimating multicity PM-mortality combined concentration-response functions was proposed by Daniels et al.[223] and Dominici et al.[224] They developed flexible modeling strategies for daily time series analyses that included spline and threshold

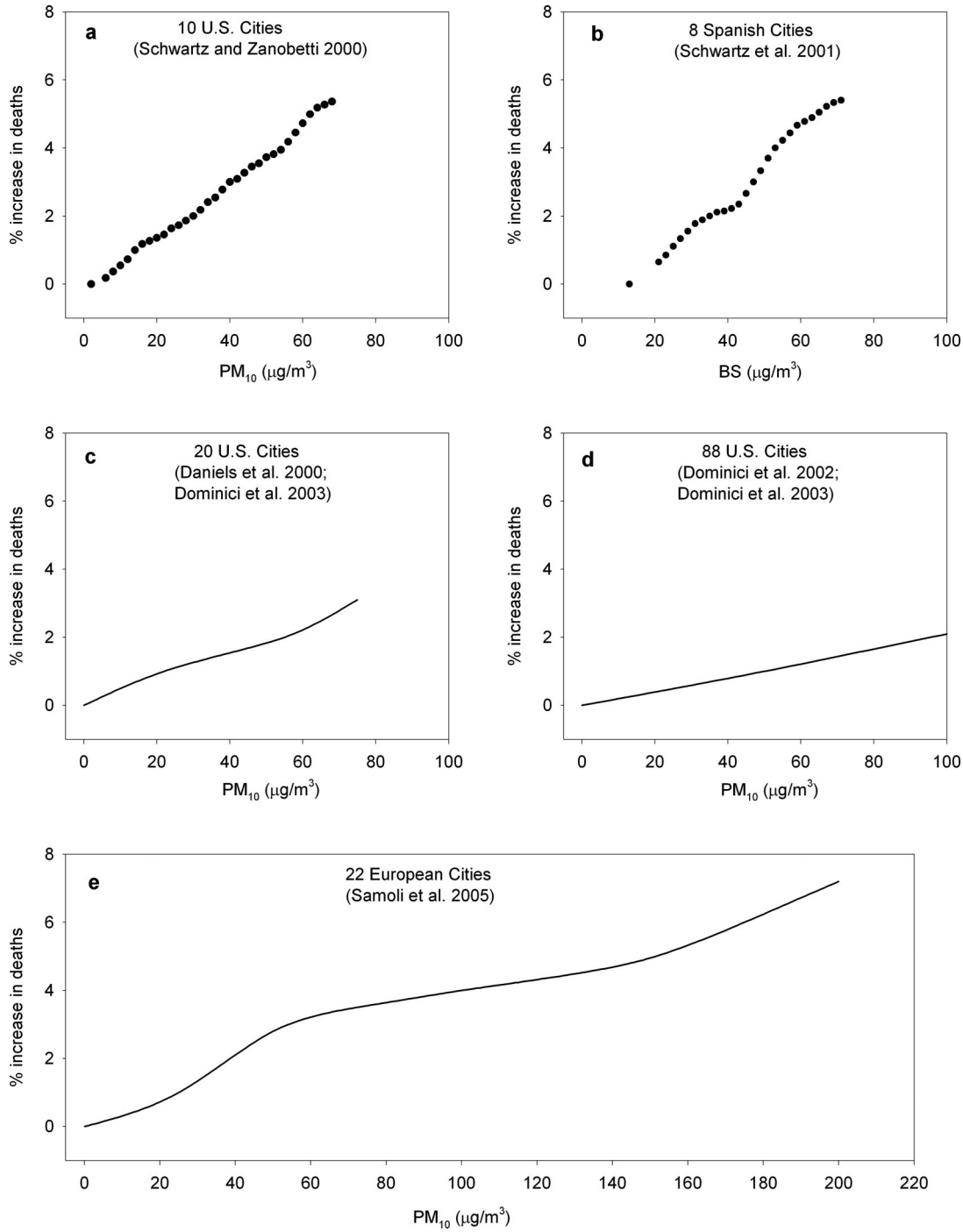

Figure 1. Selected concentration-response relationships estimated from various multicity daily time series mortality studies (approximate adaptations from original publications rescaled for comparison purposes).

concentration-response functions and applied these methods to data from the 20 largest U.S. cities from the NMMAPS project. PM-mortality concentration-response functions were estimated using three different modeling approaches: (1) models with log-linear functions for PM, (2) flexible smoothed functions, and (3) models that assumed or allowed for specific PM threshold levels. For all-cause mortality and for cardiopulmonary mortality, linear models without thresholds fit the PM-mortality association better than threshold models or even flexible cubic spline models (see Figure 1c). The researchers[225,226] extended these analyses to the 88 largest cities in the United States. Although they found regional differences, the overall pooled concentration-response function for the nation was nearly linear (see Figure 1d).

Samoli et al.[227] applied regression spline models to flexibly estimate the PM-mortality association to data from 22 European cities participating in the APHEA project. They observed some heterogeneity in effect estimates across the different cities, but the pooled estimated PM-mortality association was not significantly different from linear (see Figure 1e).

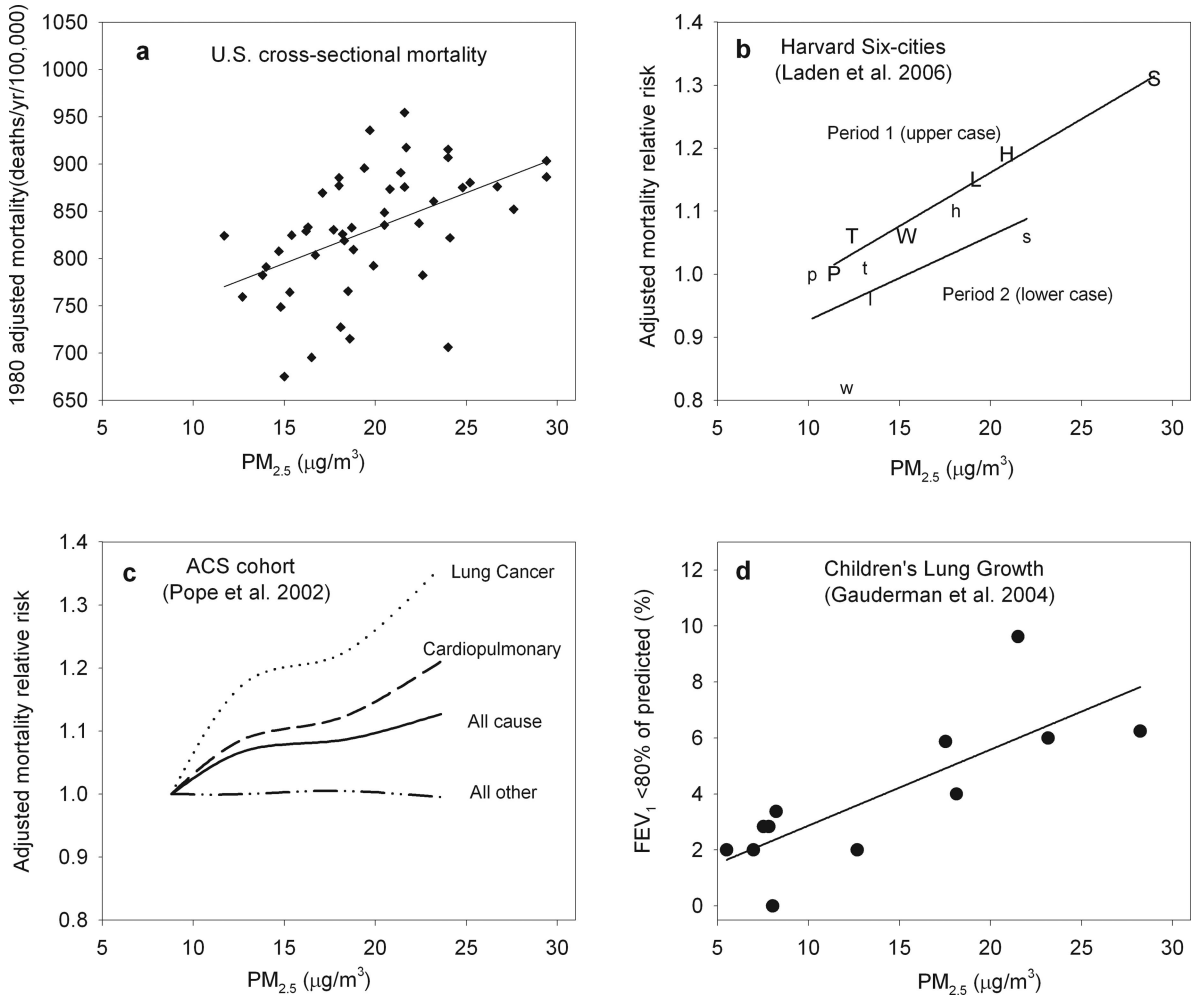

Figure 2. Selected concentration-response relationships estimated from various studies of long-term exposure (approximate adaptations from original publications rescaled for comparison purposes).

Cross-Sectional and Prospective Cohort Mortality Studies

Given the small number of cross-sectional and prospective cohort studies, the shape of the concentration-response function with long-term chronic exposure has not been as carefully explored as with the daily time series studies. It has long been observed that long-term average sulfate and/or fine particulate air pollution concentrations are associated with mortality rates across U.S. urban areas (especially after adjusting for age, sex, and race).[169–175] Figure 2a presents U.S. metropolitan area mortality rates for 1980[228] adjusted based on 1980 census[229] age-sex-race-specific population counts plotted over mean $PM_{2.5}$ concentrations as compiled and reported by Krewski et al.[177] Figure 2b presents adjusted mortality rates or rate ratios for U.S. cities plotted over corresponding $PM_{2.5}$ concentrations based on the extended analysis of the Harvard Six Cities Study.[184] The mortality effects can reasonably be modeled as linear or log linear.

The extended follow-up analysis of the ACS study more fully evaluated the shape of the concentration response function by using a robust locally weighted regression smoother.[179] The nonparametric smoothed exposure-response relationships between cause-specific mortality and long-term exposure to $PM_{2.5}$ are also presented in Figure 2c. Relative risks for all-cause, cardiopulmonary, and lung cancer mortality increased across the gradient of $PM_{2.5}$. Although some inevitable nonlinearity is observable, goodness-of-fit tests indicated that the associations were not significantly different from linear ($P > 0.20$). The shape of the exposure-response function at concentrations above the range of pollution observed in this analysis remains poorly estimated. Because concentrations above this range of pollution occur in many other parts of the world, an attempt to quantify the global burden of disease attributable to exposure to air pollution required projected effect estimates at higher concentrations.[230] A log-linear fit of $PM_{2.5}$, where the slope of the concentration-response function decreases at higher concentrations, also fit the data.[230]

The concentration-response function for long-term exposure to particulate air pollution and other health end points has not been systematically explored. However, various studies are suggestive. For example, Gauderman et al.[231] reported results from the Children's Health Study that prospectively monitored the growth in lung function of school children ages 10–18 yr who lived in 12 Southern California communities with a relatively wide range of air pollution. Over the 8-yr period, deficits in lung function

growth were associated with $PM_{2.5}$ and accompanying combustion-related air pollutants. As can be seen in Figure 2d, the concentration-response relationship between $PM_{2.5}$ and the proportion of 18-yr-olds with FEV_1 <80% of predicted appears to be near linear, without a discernible threshold.

Summary and Discussion

Recent empirical evidence about the shape of the PM concentration-response function is not consistent with a well-defined no-effects threshold. Concentration-response functions estimated from various multicity time series studies are illustrated in Figure 1 and concentration-response functions for long-term exposure studies are illustrated in Figure 2. These concentration-response functions have been adapted from the original publications and put on common scales for easy comparison. The best empirical evidence suggests that, across the range of particulate pollution observed in most recent studies, the concentration-response relationship can reasonably be modeled as linear. From a public policy perspective, at least with regard to ambient air quality standard setting, a linear concentration-response function without a well-defined safe threshold level might be inconvenient. As argued elsewhere,[218,232] from at least one perspective, these results are good news, because they suggest that even at common levels of air pollution, further improvements in air quality are likely to result in corresponding improvements in public health.

CARDIOVASCULAR DISEASE

Before the mid-1990s there was evidence of cardiovascular effects of PM air pollution. Deaths associated with the severe pollution episodes of Meuse Valley, Belgium,[4] Donora, PA,[9] and London[10] were due to both respiratory and cardiovascular disorders, often in combination.[6,7] Analyses of a less severe episode[38] observed stronger pollution-related associations with cardiovascular than with respiratory deaths. As noted earlier, many daily time series mortality studies and the early prospective cohort studies[26,27] also observed that pollution was associated with both respiratory and cardiovascular deaths (see Tables 1 and 2). Because it was unclear how these findings were influenced by diagnostic misclassification or cross-coding on death certificates, cardiovascular and respiratory deaths were often pooled together as cardiopulmonary deaths in the analyses.[26,27] Beginning in the mid-1990s, several daily time series studies reported pollution-related associations with hospitalizations for cardiovascular disease.[233–237]

Although there was evidence of cardiovascular health effects of PM air pollution, early research focused largely on respiratory disease, including research dealing with effects on asthma, obstructive pulmonary disease, respiratory symptoms, and lung function.[52] Furthermore, before 1997, studies of ambient particulate air pollution and health were rarely published or discussed in cardiovascular journals. Beginning in the late 1990s, studies dealing with air pollution and cardiovascular disease were being published, including in journals of cardiovascular medicine, where they were receiving useful editorial discussion[238–241] and reviews.[138,242–249] In 2004, the American Heart Association published a Scientific Statement that concluded that "studies have demonstrated a consistent increase risk for cardiovascular events in relation to both short- and long-term exposure to present-day concentrations of ambient particulate matter."[250]

Long-Term Exposure and Cardiovascular Disease

Table 4 provides a brief overview of recent evidence of cardiovascular and related effects associated with PM air pollution. Several studies provide evidence that long-term PM exposure contributes to cardiovascular morbidity and mortality. As illustrated in Figure 3, initial and extended analyses of the Harvard Six Cities and ACS cohorts consistently observed $PM_{2.5}$ associations with cardiovascular mortality. An extended analysis of the ACS cohort that focused on cardiopulmonary mortality found that long-term $PM_{2.5}$ exposures were strongly associated with ischemic heart disease, dysrhythmias, heart failure, and cardiac arrest mortality.[180] Relatively strong associations between $PM_{2.5}$ and ischemic heart disease mortality were observed in the metropolitan Los Angeles subcohort.[181]

There are three interesting studies that have evaluated the impact of long-term exposure to PM air pollution and the development and progression of cardiovascular disease. The first[251] explored associations between air pollution and blood markers of cardiovascular risk, specifically fibrinogen levels and counts of platelets and white blood cells. Data from the Third National Health and Nutrition Examination Survey were linked with air pollution data. After controlling for age, race, sex, body mass index, and smoking, elevated fibrinogen levels and platelet and white blood cell counts were all associated with exposure to PM_{10}. A second study[252] collected lung tissue samples during necropsies of individuals who died because of violent causes and who lived in relatively clean and polluted areas near Sao Paulo, Brazil. Individuals who lived in more polluted areas had histopathologic evidence of subclinical chronic inflammatory lung injury. A third study used data on 798 participants from two clinical trials conducted in the Los Angeles metro area.[253] $PM_{2.5}$ was associated with increased carotid intima-media thickness (CIMT), a measure of subclinical atherosclerosis. A cross-sectional contrast in exposure of 10-$\mu g/m^3$ of $PM_{2.5}$ was associated with an ~4% increase in CIMT.

Short-Term Exposure and Cardiovascular Disease

As noted above, there have been many studies that have reported associations between short-term exposures to particulate air pollution and cardiovascular mortality (see Table 1). Studies reporting PM associations with cardiovascular hospitalizations have been more recent, but there are now dozens of such studies. Table 5 presents a comparison of pooled estimates of percentage increase in relative risk of hospital admission for cardiovascular disease estimated across meta-analyses and multicity studies of short-term changes in PM exposures. In addition, there have been several recent studies that have reported associations between PM exposure and stroke mortality and hospitalizations. Several of these studies have been from Asian countries with relatively high stroke mortality.[254–257] However, a recent case-crossover study of

Table 4. Recent evidence of cardiovascular and related effects associated with particulate matter exposure.

Health End Points	Direction of Effect[a]	Primary Sources
Long-term exposures		
Cardiovascular mortality	↗	See Table 2 and Figure 3
Blood markers of cardiovascular risk (fibrinogen, platelets, white blood cells)	↗	Schwartz 2001[251]
Histopathologic markers of sub-clinical chronic inflammatory lung injury	↗	Souza et al. 1998[252]
Subclinical atherosclerosis (CIMT)	↗	Kunzli et al. 2005[253]
Short-term exposures		
Cardiovascular mortality	↗	See Table 1
Cardiovascular hospital admissions	↗	See Table 5
Stroke mortality and hospital admissions	↗	Hong et al. 2002, 2002[254,255]; Kan et al. 2003[256]; Tsai et al. 2003[257]; Welleninus et al. 2005[258] (also see Cerebrovascular estimates in Table 5)
MI	↗→	Peters et al. 2001, 2004[259,260]; D'Ippoliti et al. 2003[261]; Sullivan et al. 2005[262]; Zanobetti and Schwartz 2005[263]; von Klot et al. 2005[264]
Hypoxemia (SpO_2)	→↘	Pope et al. 1999[265]; DeMeo et al. 2004[266]; Gong et al. 2005[267]
HR	↗	See Table 6
HRV	↘	See Table 6
Inflammatory and related markers	↗→	See Table 7
Cardiac arrhythmia/cardiac arrest/sudden out-of-hospital coronary deaths	↗→	Peters et al. 2000[268]; Levy et al. 2001[269]; Sullivan et al. 2003[270]; Vedal et al. 2004[271]; Rich et al. 2004[272]; Dockery et al. 2005[273]; Forastiere et al. 2005[274]
ST-segment depression	↗	Pekkanen et al. 2002[275]; Gold et al. 2005[276]
Cardiac repolarization changes	↗	Henneberger et al. 2005[277]
Blood pressure/arterial vasoconstriction/vascular reactivity and endothelial function	↗	Ibald-Mulli et al. 2001[278]; Linn and Gong 2001[279]; Brook et al. 2002[280]; Zanobetti et al. 2004[281]; Urch et al. 2004[282]; Urch et al. 2005[283]; O'Neill et al. 2005[284]

[a]Positive PM-effect estimates are indicated by ↗, negative PM-effect estimates are indicated by ↘, no effects indicated by →, multiple arrows indicate inconsistent mixed effects from different studies.

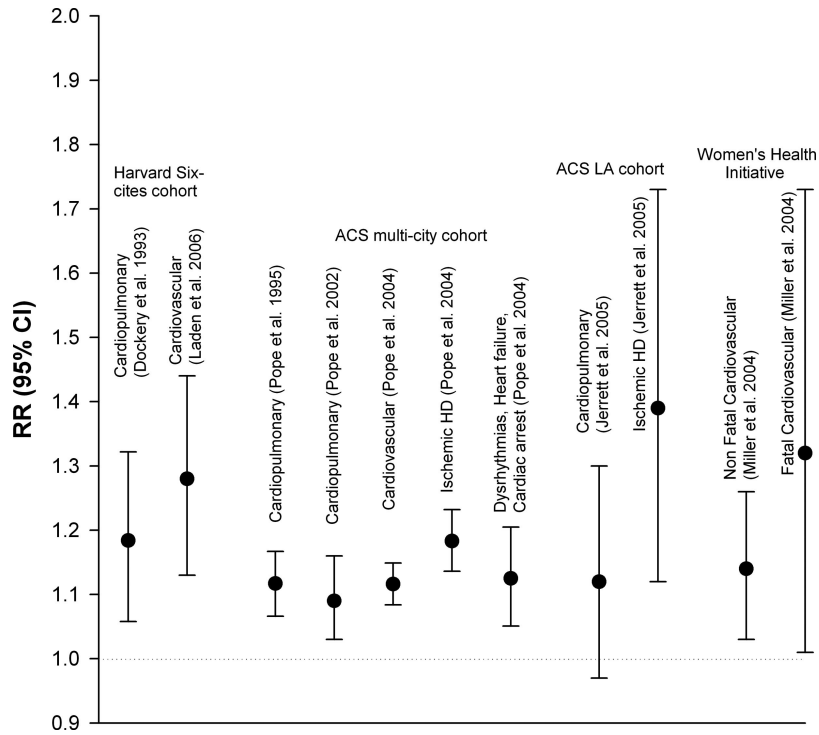

Figure 3. Adjusted relative risk ratios for cardiovascular-related mortality associated with a 10-$\mu g/m^3$ contrast in $PM_{2.5}$ for selected long-term exposure studies.

Table 5. Comparison of pooled estimated percentage increase (and 95% CI) in relative risk of hospital admission for cardiovascular disease estimated across meta-analyses and multicity studies of short-term (daily) changes in exposure.

Study	Primary Sources	Exposure Increment	% Increase (95% CI)
Cardiac admissions, meta-analysis of 51 estimates	COMEAP 2006[138]	20 $\mu g/m^3$ PM_{10}	1.8 (1.4, 1.2)
Ischemic heart disease admissions, meta-analysis of 19 estimates	COMEAP 2006[138]	20 $\mu g/m^3$ PM_{10}	1.6 (1.2, 2.2)
Admission for dysrhythmias, meta-analysis of 7 estimates	COMEAP 2006[138]	20 $\mu g/m^3$ PM_{10}	1.6 (0.2, 2.8)
Admission for heart failure, meta-analysis of 7 estimates	COMEAP 2006[138]	20 $\mu g/m^3$ PM_{10}	2.8 (1.0, 4.8)
Cerebrovascular admissions, meta-analysis of 9 estimates	COMEAP 2006[138]	20 $\mu g/m^3$ PM_{10}	0.8 (0.0, 1.6)
Cardiac admissions, 8 U.S. cities, 65+	Schwartz 1999[285]	20 $\mu g/m^3$ PM_{10}	2.0 (1.5, 2.5)
Cardiac admissions, 10 U.S. cities, 65+	Zanobetti et al. 2000[286]	20 $\mu g/m^3$ PM_{10}	2.6 (2.0, 3.0)
Cardiac admissions, 14 U.S. cities, 65+	Samet et al. 2000[287] Schwartz et al. 2003[288]	20 $\mu g/m^3$ PM_{10}	2.0 (1.5, 2.5)
8 European cities, 65+, cardiac admissions:	Le Tertre et al. 2002[289]	20 $\mu g/m^3$ PM_{10}	1.4 (0.8, 2.0)
Ischemic heart admissions			1.6 (0.6, 2.4)
204 U.S. counties, 65+, CVD admissions	Dominici et al. 2006[290]	10 $\mu g/m^3$ $PM_{2.5}$	
Heart failure			1.2 (0.8, 1.8)
Heart rhythm			0.6 (0.0, 1.2)
Ischemic heart			0.4 (0.0, 0.9)
Peripheral vascular			0.9 (−0.1, 1.8)
Cerebrovascular			0.8 (0.3, 1.3)

Notes: We acknowledge Dr. Ross Anderson and Joanna Carrington at the Department of Community Health Sciences, St. George's Hospital Medical School, London, United Kingdom, for help in providing meta-analyses and reviews of the cardiovascular hospitalizations studies.

elderly medicare recipients in nine U.S. cities reported small but statistically significant associations between PM_{10} and ischemic stroke but not hemorrhagic stroke.[258]

There are several studies that have reported that short-term PM exposure is also associated with ischemic heart disease, especially the triggering of myocardial infarction (MI). Peters et al.,[259] in a case-crossover study of 772 Boston area patients with MI, reported that elevated concentrations of $PM_{2.5}$ increased the risk of MI within a few hours and 1 day after exposure. Similarly, Peters et al.,[260] using data from 691 subjects with MI in the Augsburg area of Southern Germany, observed that the risk of MI was elevated within 1 hr after exposure to traffic. Two additional single-city case-crossover studies of air pollution and MI had inconsistent results. A study from Rome, Italy, reported increased risk of MI associated with PM pollution, especially during warm periods,[261] but a study from King County, WA, observed no PM-MI associations.[262] In a much larger case-crossover study using data from 21 U.S. cities with >300,000 MI events, a 20-$\mu g/m^3$ increase in PM_{10} ambient concentration was associated with a 1.3% (95% CI, 0.6%–2%) increased risk of MI.[263,264]

Short-Term Exposure and Various Physiologic Measures of Cardiac Risk

Recently, there has been a variety of studies that have explored an assortment of various subclinical physiologic measures in human subjects that may be related to risk of cardiovascular disease and death (see Table 4). These represent an assortment of studies with miscellaneous and mixed results that are not easy to interpret. The studies, nevertheless, have often been motivated by hypotheses concerning general pathophysiological pathways or mechanisms (to be discussed below), and they contribute to the overall epidemiological evidence pertaining to PM-related cardiopulmonary health effects. Several studies, for example, have hypothesized that exposure to PM may be associated with mild hypoxemia or declines in blood oxygen saturation.[265–267] Although there is only weak evidence of PM-related deficits in blood oxygen saturation, there is stronger evidence of PM-related changes in cardiac rhythm or cardiac autonomic function as measured by heart rate (HR) and HR variability (HRV). A stylized summary of studies that explored PM associations with HR and HRV is presented in Table 6. The results are not entirely consistent across the studies, but the general pattern suggests that PM exposure is associated with increased HR and reductions in most measures of HRV suggesting adverse effects on cardiac autonomic function.

Various other researchers have explored PM associations with markers of pulmonary and/or systemic inflammation. Table 7 presents a summary of studies of PM effects on various pulmonary or systemic inflammation and related markers of cardiovascular risk. Again, the results are not entirely consistent, but they suggest pollution-related inflammatory responses. PM-related associations also have been observed with cardiac arrhythmia, ST-segment depression, changes in cardiac repolarization, arterial vasoconstriction, and blood pressure changes (see Table 4). A more integrated discussion and interpretation of these results is presented below as part of the discussion of biological plausibility.

BIOLOGICAL PLAUSIBILITY

In 1997, there was substantial uncertainty with regard to the biological plausibility of causal associations between cardiopulmonary morbidity and mortality and PM air pollution at relatively low concentrations. In his review,

Table 6. HR and HRV and particulate air pollution associations summarized from recent studies.

Primary Sources	Type and Duration of Particulate Exposure	Study Subjects (Total observations or study time), Study Area	Length of Analyzed Recordings	Direction of Effect				
				HR	Total, SDNN	ULF, SDANN	VLF, LF	HF, r-MSSD
Pope et al. 1999[291]	24-hr PM_{10}	90 elderly (8760 obs), Utah Valley	3-min	↗				
Peters et al. 1999, 2000[292,293]	Pollution episode	2681 adults, Augsburg, Germany	20-sec	↗				
Liao et al. 1999[294]	24-hr $PM_{2.5}$	26 elderly (wk), Baltimore	6-min		↘		↘	↘
Pope et al. 1999[295]	1- or 2-day PM_{10}	7 elderly (29 person days), Utah Valley	24-hr	↗	↘	↘		↗
Gold et al. 2000[296]	4- and 24-hr $PM_{2.5}$	21 aged 53–81(163 obs), Boston	25-min	↘	↘			↘
Pope et al. 2001[297]	2-hr $PM_{2.5}$, ETS	16 adults (64 2-hr periods) Salt Lake City, UT, airport	2-hr	↘	↘	↘	↘	↘
Creason et al. 2001[298]	24-hr $PM_{2.5}$	65 elderly (4 weeks), Baltimore	6-min				↘	↘
Magari et al. 2001[299]	Up to 9hr $PM_{2.5}$	40 boilermakers, primarily occupational exposure	5-min	↗	↘			
Magari et al. 2002[300]	3-hr $PM_{2.5}$	20 boilermakers, nonworkday exposures	5-min	→	↘			
Devlin et al. 2003[301]	2-hr $PM_{2.5}$, CAPS	10 elderly, 60–80 yr (20 2-hr periods), Chamber	10-min		↘		→	↘
Devlin et al. 2003[301]	2-hr $PM_{2.5}$, CAPS	22 young, 29 yr (20 2-hr periods), Chamber	10-min		→		→	→
Holguin et al. 2003[302]	24-hr $PM_{2.5}$	34 mean age 79 yr (384 obs), Mexico City	5-min				↘	↘
Chan et al. 2004[303]	1- to 4-hr $NC_{0.02-1}$	19 adults (16-hr per subject), Teipei, Taiwan	5-min		↘		↘	↘
Riediker et al. 2004[304]	9-hr $PM_{2.5}$	9 young healthy North Carolina patrol troopers	10-min		↗		→	↗
Pope et al. 2004[305]	24-hr $PM_{2.5}$	88 elderly (250 person days), Utah Valley	24-hr	↘	↘	↘		↘
Liao et al. 2004[306]	24-hr PM_{10}	4899 adults, mean age 62 yr, ARIC study	5-min	↗	↘		→	↘
Park et al. 2005[307] Schwartz et al. 2005[308]	24-hr $PM_{2.5}$	497 adult male, mean age 73 yr, normative aging study in Boston	4-min				↘	↘
Romieu et al. 2005[309]	24-hr $PM_{2.5}$	50 elderly nursing home residents, Mexico City	6-min		↘		↘	↘
Chuang et al. 2005[310]	1- to 4-hr $PM_{0.3-1}$	26 CHD/hypertensive patients in Taipei, Taiwan	5-min		↘			↘

Notes: Positive PM-effect estimates are indicated by ↗, negative PM-effect estimates are indicated by ↘, no effects indicated by →, multiple arrows indicate inconsistent mixed effects from different studies; CHD = coronary heart disease.

Vedal[80] argued that "weak biological plausibility has been the single largest stumbling block to accepting the association as causal. There is no known mechanism whereby exposure to very low concentrations of inhaled particles would produce such severe outcomes as death, even from respiratory disease, and certainly not from cardiovascular disease."[80] Others suggested that biological plausibility was enhanced by the observation of a coherent cascade of cardiopulmonary health effects and by the fact that noncardiopulmonary health end points were not typically associated with the pollution.[52] Nevertheless, research studies that focused on pathophysiological pathways linking PM and cardiopulmonary disease and death were extremely limited, and biological plausibility was much in doubt. Since 1997, however, there has been substantial research exploring potential mechanisms and growing discussion pertaining to potential pathophysiological pathways.[138,180,242,248,250,326–331]

Biological Effects of Oil Fly Ash and Utah Valley PM

The biological effects of well-defined high acute exposure to specific combustion-source PM was described in a case study of a 42-yr-old, unemployed, male, never-smoker, who had an 8-yr history of diabetes mellitus.[332] During and after the cleaning of an oil-burning stove in the living room of his home, this man was exposed to high levels of aerosolized oil fly ash particles. Within 24 hr, this man developed shortness of breath, a nonproductive cough, and wheezing that progressed over 2 weeks to hypoxic respiratory failure and the need for mechanical ventilation. In addition to abnormal blood indices, particle-laden macrophages and diffuse alveolar damage were observed by thoracoscopic biopsy, and later anginal symptoms were experienced. It is rarely possible to attribute adverse health effects of a specific individual to a specific PM exposure. However, the authors of this case report note that this patient presented "with the aggregate of potential injuries described by epidemiological methods to be associated with air pollution particle exposure"[332] and suggest that this case serves as evidence that adverse cardiorespiratory effects from PM exposure are biologically plausible.

Biological effects of PM were examined in a series of studies from Utah Valley.[333–343] This valley, located in Central Utah with a 1990 population of ~265,000 people, had a very low smoking rate (6%) and often experienced substantial pollution episodes because of local emissions and low-level temperature inversions that were common to winter months. An early study observed that the shutdown of the steel mill was associated with large reductions in PM pollution with accompanying large reductions in pediatric respiratory hospital admissions.[28] Although there was some controversy and debate regarding the interpretation of this study,[202,344] subsequent epidemiologic studies in the valley continued to observe PM associations with hospitalizations,[29] lung function and respiratory symptoms,[30–32] school absences,[33] and mortality.[20,34,202,345]

Table 7. Summary of human studies of particulate air pollution effect on various pulmonary or systemic inflammation and related markers of cardiovascular risk.

Primary Sources	Exposure Type, Place, Subjects	PM Associations
Peters et al. 1997[311] Peters et at. 2001[312]	1985 pollution episode, Augsburg, Germany, adults	Increased blood plasma viscosity and CRP
Seaton et al. 1999[313]	Estimated personal exposure to PM_{10}, Belfast and Edinburgh, United Kingdom, elderly adults	Increased CRP, reduced red blood cells
Tan et al. 2000[314]	Elevated PM_{10} levels during forest fire episodes, Singapore, 19–24-yr-old healthy men	Elevated PMN band cells
Salvi et al. 1999[315] Salvi et al. 2000[316]	Diesel exhaust, exposure chambers, healthy nonsmoking young adults	Elevated neutrophils, lymphocytes, mast cells, endothelial adhesion molecules, IL-8, GRO-α in airway lavage, bronchial tissue, and/or bronchial epithelium; also increased neutrophils and platelets in peripheral blood.
Pekkanen et al. 2000[317]	Ambient air pollution including PM_{10}, London, male and female office workers	Higher plasma fibrinogen concentrations
Ghio et al. 2000[318] Harder et al. 2001[319] Gong et al. 2003[320] Ghio et al. 2003[321] Huang et al. 2003[322] Ghio and Huang 2004[103]	Exposure to concentrated ambient particles (CAPs) in exposure chambers, volunteer adults	Somewhat mixed results, but small increases in neutrophils and fibrinogen consistent with mild inflammatory responses to PM.
Sorensen et al. 2003[323]	Personal monitoring of $PM_{2.5}$ and carbon black, Copenhagen, young adults	Small increases in markers of oxidative stress
Adamkiewicz et al. 2003[324]	Ambient $PM_{2.5,}$ Steubenville, OH, elderly adults	Increase in airway inflammation as measured by exhaled nitric oxide
Pope et al. 2004[305]	Ambient $PM_{2.5,}$ Utah, elderly adults	Elevated CRP
Ruckerl et al. 2006[325]	Ambient PM, Erfurt, Germany, 57 males with CHD	Elevated CRP

CHD = coronary heart disease; CRP = C-reactive protein; PMN = polymorphonuclear leukocytes.

Almost 10 years after the initial epidemiologic studies, archived air monitoring filters from the valley were recovered, and PM was extracted from samples collected in the years before, during, and after the closure of the steel mill. This extracted PM was found to elicit acute airway injury and inflammation in experimentally exposed rats[339] and humans.[337] Inflammatory lung injury, in vitro oxidative stress, and release of proinflammatory mediators by cultured respiratory epithelial cells were all substantially more elevated when using extracts from filters collected during periods when the steel mill was operating versus when it was not, suggesting differential toxicities of PM not fully explained by differences in mass.[343] These studies generally observed that differences in the content and mixtures of metals seemed to play an important role in the biological effects of PM exposure.[333–343] They also demonstrated clearly relevant biological effects of controlled PM exposures consistent with specific epidemiological findings contributing to our understanding regarding biological plausibility and mechanisms.

Accelerated Progression and Exacerbation of Chronic Obstructive Pulmonary Disease

One of the earliest hypotheses regarding a general mechanistic pathway that links PM exposure with cardiopulmonary mortality suggests that long-term or chronic PM exposure results in more rapid progression of chronic obstructive pulmonary disease (COPD) and that acute PM exposure exacerbates existing pulmonary disease. Studies of the natural history of chronic airflow obstruction have observed that measures of lung function (such as forced vital capacity or FEV_1) increase until early adulthood and then decline during the rest of life. It has long been known that smoking contributes to more rapid progression of airflow obstruction as measured by deficits in FEV_1,[346] and it is also hypothesized that PM air pollution may have similar but smaller effects.[347] There is evidence, even in nonsmokers, that long-term exposure to PM air pollution results in pulmonary retention of fine particles and small airway remodeling and contributes to COPD.[348,349]

Epidemiologic evidence that supports this hypothesis includes various studies that have observed that long-term PM exposures are associated with deficits in lung function[350–354] and increased symptoms of obstructive airway disease, such as chronic cough, bronchitis, and chest illness.[25,355–359] Recently published results from the Southern California Children's Health Study indicate that exposure to $PM_{2.5}$ and other combustion-related air pollutants were significantly associated with deficits in the rate of lung function growth in children (see Figure 2d).[231,360]

MacNee and Donaldson[361,362] note that air pollution has long been recognized as a trigger for exacerbations of COPD and argue that inhaled combustion-related PM pollution increases oxidative stress and aggravates background inflammation in COPD, leading to acute exacerbations. There have also been many short-term exposure studies that have observed PM-related exacerbation of respiratory symptoms and transient declines in lung function.[30–32,363–369] Although there is evidence that supports the accelerated progression and exacerbation of the COPD hypothesis, it does not necessarily follow that air

pollution would only be associated with respiratory morbidity and mortality. van Eeden et al.[347] noted that systemic inflammation associated with COPD contributes to cardiovascular risk. Various studies have also demonstrated that COPD, indicated either by symptoms of chronic bronchitis or deficits in FEV_1, is a substantial risk factor for cardiovascular morbidity and mortality independent of age, gender, and smoking history.[370,371] For example, it is estimated that having chronic bronchitis symptoms increases the risk of coronary deaths by 50% and, for every 10% decrease in FEV_1, the risk of cardiovascular mortality increases by 28%.[370] Large deficits in FEV_1 are estimated to have a remarkably large impact on the risk of cardiovascular death. For example, one estimate indicates that individuals with FEV_1 in the lowest quintile compared with those in the highest quintile had approximately a 5-fold increase in death from ischemic heart disease.[370]

Pulmonary/Systemic Oxidative Stress/Inflammation/Accelerated Atherosclerosis

Another hypothesized general pathophysiological pathway involves pulmonary and systemic oxidative stress, inflammation, atherosclerosis, and related cardiovascular disease. Over the last few decades, research has linked inflammation along with blood lipid levels to initiation and progression of atherosclerosis.[372] This hypothesis proposes that low-to-moderate-grade inflammation induced by long-term chronic PM exposure may initiate and accelerate atherosclerosis. Short-term elevated PM exposures and related inflammation may also contribute to acute thrombotic complications of atherosclerosis increasing the risk of making atherosclerotic plaques more vulnerable to rupture, clotting, and precipitating acute cardiovascular or cerebrovascular events (MI or ischemic stroke). This hypothesis is not independent of the previous COPD hypothesis, because, as noted above, systemic inflammation associated with COPD may contribute to cardiovascular risk.[347] Seaton et al.[373] (including MacNee and Donaldson,[361,362] who outlined the evidence that inhaled combustion-related particulate pollution exacerbates COPD discussed above) were among the first to suggest this hypothesis. They suggested that particles may "provoke alveolar inflammation, with release of mediators capable, in susceptible individuals, of causing exacerbations of lung disease and of increasing blood coagulability, thus also explaining the observed increases in cardiovascular deaths associated with urban pollution episodes."[373]

There is growing evidence supporting this general pathophysiological pathway. The extended analysis of the ACS cohort that focused on cardiopulmonary mortality[180] found that long-term PM exposures were robustly associated with ischemic heart disease and suggested that the empirical pattern of PM mortality associations were consistent with the inflammation/accelerated atherosclerosis hypothesis (see Figure 3). Relatively strong associations between long-term PM and ischemic heart disease mortality were also observed in the metropolitan Los Angeles subcohort (see Figure 3).[181] Further evidence is provided by observations that long-term exposures to PM pollution are also associated with blood markers of cardiovascular risk (fibrinogen levels and counts of platelets and white blood cells),[251] subclinical chronic inflammatory lung injury,[252] and subclinical atherosclerosis (CIMT).[253] Additionally, findings that short-term elevations in PM exposure are associated with increased markers of pulmonary and systemic inflammation (Table 7), arterial vasoconstriction and increased blood pressure (Table 4), increased MI and ischemic stroke events, and ST-segment depression (Tables 4 and 5 and discussion above) are consistent with the proposition that PM exposure contributes to inflammation and subsequent acute thrombotic complications of atherosclerotic-related disease.

Although the focus of this review is on human studies, there have been many relevant toxicology studies using animals that have observed pro-oxidant- and proinflammatory-related effects of ambient PM pollution.[374] For example, Nemmar et al.[375–378] have demonstrated in hamsters that intratracheal instillation of diesel exhaust particles or silica particles leads to pulmonary inflammation, rapid activation of circulating blood platelets, and peripheral thrombosis. Wellenius et al.[379] reported that PM exposures exacerbated myocardial ischemia in dogs. Recent research that involved exposing ApoE-deficient (hyperlipidemic) mice to environmentally relevant concentrations of $PM_{2.5}$ particles (mean concentration: 85–110 $\mu g/m^3$) observed evidence of PM-potentiated vascular inflammation and atherosclerosis.[380,381]

van Eeden, Hogg, et al.[314,382–389] conducted an especially ambitious series of research studies using human subjects and *in vitro* and *in vivo* toxicology studies that explored this general pathophysiological pathway. PM exposure contributes to pulmonary inflammation, systemic inflammatory responses including the release of inflammatory mediators, bone marrow stimulation and the release of leukocytes and platelets, and ultimately the progression of and destabilization of atherosclerotic plaques.[382] PM exposure to humans during forest fire episodes resulted in stimulated bone marrow and the release of neutrophils, band cells, and monocytes into the circulation.[314] It was demonstrated that PM exposure can stimulate alveolar macrophages to produce proinflammatory cytokines and that these cytokines are elevated in the circulating blood of PM exposed humans.[383] They reported evidence that PM exposure increased circulating band cell counts, accelerated neutrophil bone marrow transit time, and expanded the leukocyte pool size.[384–388] In rabbits naturally prone to develop atherosclerosis, PM exposure caused accelerated progression of atherosclerotic plaques with greater vulnerability to plaque rupture.[389]

With regard to biological plausibility, it has also been shown that low-level PM exposure from secondhand smoke increases platelet activation[390,391] and promotes an inflammatory response and atherosclerosis, even at exposure to secondhand smoke as low as one cigarette per day.[392] These findings suggest that urban ambient PM and PM from cigarette smoke may invoke similar pathophysiological mechanisms related to pulmonary and systemic inflammation and atherosclerosis.

Altered Cardiac Autonomic Function

A third hypothesized pathway involves PM-induced adverse changes in cardiac autonomic function as indicated by various measures of HRV. The physiologic importance of changes in HRV is not fully understood, but there is growing recognition of the role of autonomic dysfunction in cardiovascular mortality, and HRV measures provide quantitative, well-defined indicators of cardiac autonomic function.[393] Various studies have observed that decreases in HRV are strong predictors of mortality.[394–396] Furthermore, as presented in Table 6, numerous studies have explored PM associations with HRV. PM exposure has generally been found to be associated with declines in most of the measures of HRV, suggesting adverse effects on cardiac autonomic function. Observed PM-related changes in cardiac repolarization, cardiac arrhythmia, and cardiac arrest (Table 4) are also suggestive. Several animal studies have also observed PM exposure-related changes in cardiac rhythm or function.[326,397–399]

There is evidence that PM-related changes in cardiac autonomic function are not independent of pathways that involve pulmonary and systemic oxidative stress. Schwartz et al.[308] provide evidence that the $PM_{2.5}$ associations with HRV (the high-frequency component) are at least partially mediated by reactive oxygen species. They observed negative $PM_{2.5}$-HRV associations in individuals without the allele for glutathione S-transferase M1 (GSTM1), encoding an enzyme that scavenges oxygen-free radicals, but no such association for individuals with the allele. The effects of $PM_{2.5}$ on HRV were mitigated by the use of statin drugs, which have antioxidant and anti-inflammatory properties.[308] In a study of elderly nursing home residents in Mexico City, Mexico, Romieu et al.[309] demonstrated that dietary supplementation of omega-3 polyunsaturated fatty acid significantly reduced the $PM_{2.5}$-related decline in HRV.

Vasculature Alterations

There is evidence that PM-induced pulmonary inflammation can play a role in activating the vascular endothelium and that alterations in vascular tone and endothelial function are important PM-related mechanisms. PM and O_3 exposure induced arterial vasoconstriction in healthy adults as measured by brachial artery diameter,[280] and various measures of PM were associated with impaired vascular reactivity and endothelial function in diabetic subjects.[284] PM exposure has also been associated with increased blood pressure in cardiac rehabilitation patients[281] and in adults with lung disease,[279] increased vasoconstriction in the pulmonary vessels of rats,[400] increased circulating levels of the vasoactive peptide endothelin in rats,[401] and elevated levels of endothelin in animals for 2 hr to up to 2 days after urban PM pollution.[402] Brook et al.[250] argue that arterial vasoconstriction is a likely explanation for the PM and exercise induced ischemia (as measured by ST-Segment depression in Pekkanen et al.[275]) and enhanced cardiac ischemia in dogs exposed to concentrated PM air pollution.[379] van Eeden et al.[347] note that the time course of elevated endothelin observed in animals[402] is consistent with the time course observed in recent studies of PM exposure and MI events.[259,260] Because they are so closely linked to pulmonary and systemic inflammation, mechanisms related to vasculature alterations cannot be considered independent of previously discussed COPD and inflammation/atherosclerosis-related pathways.

Translocation of Particles

Another possible mechanism of the cardiovascular effects of inhaled particles includes systemic translocation and prothrombotic effects. Extrapulmonary translocation has been observed primarily for ultrafine particles. PM in the blood may increase vascular inflammation, clotting, and the risk of MI.[403] Oberdorster et al.[404,405] have observed extrapulmonary translocation of ultrafine particles in rats. Nemmar et al.[406,407] demonstrated that ultrafine particles translocate from the lungs into the systemic circulation in hamsters[406] and in humans[407] and that exposure to diesel exhaust particles, in a hamster model of peripheral vascular thrombosis, induced inflammation, including increased neutrophils in bronchoalveolar lavage and evidence of enhanced platelet activation in the blood.[403,408,409] Extrapulmonary translocation of inhaled metals to the brain via olfactory pathways have also been reported.[410]

Modulated Host Defenses and Immunity

There is substantial toxicological evidence that breathing particulate air pollution can result in modulated host defenses and immunity.[411] Early studies that observed pollution associations with pediatric respiratory hospitalizations and bronchitis and pneumonia-related symptoms[28,52] were suggestive that modulated host defenses and immunity may be part of the biological mechanisms linking PM and cardiopulmonary disease. The increase in pneumonia and influenza deaths, but not COPD deaths, associated with long-term PM exposure[180] is also suggestive. Recent animal studies suggest that PM or its constituents play a role in affecting host defenses and increase susceptibility to pulmonary infections.[411–413]

Hypoxemia

Another mechanistic pathway involves PM-induced lung damage (potentially including oxidative lung damage and inflammation), declines in lung function, respiratory distress, and hypoxemia. In the case report discussed above,[332] exposure to high levels of aerosolized oil fly ash particles eventually led to the experiencing of hypoxic respiratory failure. However, in epidemiologic panel studies that evaluated ambient PM-related changes in blood oxygen saturation, the results are mixed. In the first study that explored this hypothesis, no PM-related hypoxemia was observed.[265] Small changes in blood oxygen saturation were observed in two later studies.[266,267]

Summary and Discussion

Demonstrating conclusively that the associations between PM and various adverse health effects are "real" or "causal" has proven to be difficult and somewhat elusive. Recent research, however, has increased confidence that the PM-cardiopulmonary health effects observed in the epidemiology are "biologically plausible." Clear biological

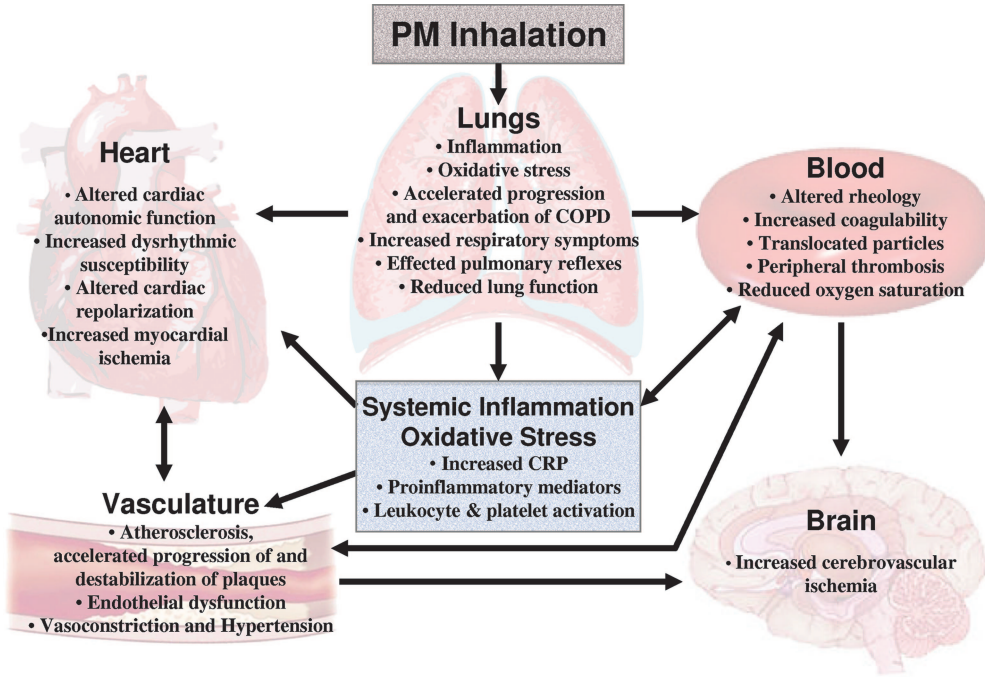

Figure 4. Potential general pathophysiological pathways linking PM exposure with cardiopulmonary morbidity and mortality.

effects of PM exposure have been observed, and various pathophysiological or mechanistic pathways have been explored. None of these pathways are definitively demonstrated to be the pathway that clearly and directly links exposure of ambient PM pollution to cardiopulmonary morbidity and mortality. In fact, it is unlikely that any single pathway is responsible. There are almost certainly multiple mechanistic pathways with complex interactions and interdependencies. Figure 4 provides a schema of some of the hypothetical mechanistic pathways linking PM with cardiopulmonary disease. Similar stylized attempts to illustrate these mechanistic pathways and their interactions have been presented elsewhere.[138,244,250] Although much remains to be learned, it is no longer true that there are no known pathophysiological or mechanistic pathways that could plausibly link PM exposure with cardiopulmonary disease and death.

GAPS IN KNOWLEDGE AND REASONS FOR SKEPTICISM

There has been an enormous amount of research dealing with the health effects of PM reported since 1997. Although much has been learned, much remains to be learned, and there are important gaps in our knowledge. Also, there are legitimate reasons for at least some skepticism regarding our interpretation of these overall results and our possibly naive application of these findings for public health and environmental public policy.

Who's Most at Risk or Susceptible?

One of the most important gaps in our current knowledge regarding PM-related health effects is an understanding of who is most at risk or most susceptible. As has been discussed elsewhere,[70] who is susceptible is dependent on the specific health end point being evaluated and the level and length of exposure. For example, with respect to acute or short-term exposures to only moderately elevated PM concentrations, it seems evident that persons with chronic cardiopulmonary disease, influenza, and asthma, especially those who are elderly or very young, are most likely to be susceptible. As noted earlier, the increased risk of mortality because of acutely elevated PM exposure is very small, and on any given day there may only be a very small fraction of the population at serious risk of dying or being hospitalized because of this exposure. However, the number of those susceptible to less serious health effects may be larger, and, for most people, those effects are likely to be small, transient, and largely unnoticed. As noted above, long-term repeated PM exposure has been associated with increased risk of mortality in broad-based cohorts of adults and children. Although there may be broad susceptibility to long-term repeated exposure, the cumulative effects are most likely to be observed in older age groups with longer exposures and higher baseline risks of mortality.

Various characteristics have been shown to influence susceptibility including: pre-existing respiratory or cardiovascular disease;[414,415] diabetes;[416,417] medication use;[308,418] age;[419–421] gender, race, socioeconomic status, and healthcare availability;[422–426] educational attainment;[177,179] and housing characteristics.[427] Genetic differences also play an important role regarding susceptibility. For example, Kelly's[428] assertion that an individual's sensitivity to PM may depend in part to their pulmonary antioxidant defenses is partially supported by the observation of negative $PM_{2.5}$-HRV associations in individuals without the allele for GSTM1, encoding an enzyme that scavenges oxygen-free radicals, but no such associations for individuals with the allele.[308] PM-potentiated atherosclerosis observed in both ApoE-deficient mice[380] and heritable

hyperlipidemic rabbits[389] was also clearly influenced by the genetic propensity of these animals to develop the disease.

Infant/Birth Outcomes

There is ample evidence that PM exposure impacts the health of children. PM exposure in children has been associated with deficits in lung function,[30,31,353,363–369] lung function growth,[231,360] increased respiratory illness and symptoms,[25,358,359] increased school absences,[33] and hospitalizations for respiratory disease.[28,29] There is also substantial and growing evidence that air pollution is a risk factor for increased mortality in infants and young children. Relatively large increases in infant mortality were observed during the London smog episode of 1952.[6,7] Contemporary studies have observed PM-infant mortality associations.[41,185,186,429–437] There have also been several recent reviews of these studies that generally conclude that PM exposure is most strongly and consistently associated with postneonatal respiratory mortality with less compelling evidence of a link between PM and SIDS.[438–444]

The effects of air pollution on various other birth outcomes are substantially less well established and understood. Nevertheless, there are a growing number of contemporary studies that have evaluated potential links between air pollution and birth weight,[445–456] premature birth,[449,456–458] fetal growth,[459–461] intrauterine mortality,[462] birth defects,[463] and lymphocyte immunophenotypes in cord and maternal blood at delivery.[464] Recent reviews of the literature dealing with air pollution and these various birth outcomes[441,442,444] generally suggest that there may be effects of ambient PM air pollution on these outcomes but that these effects are not well understood. Although the evidence is reasonably compelling that PM exposure increases the risk of infant mortality, especially postneonatal respiratory mortality, there remain serious gaps in our knowledge regarding the potential effects of ambient PM on fetal growth, premature birth, and related birth outcomes.

Lung Cancer

Substantial uncertainty remains regarding the effect of ambient PM pollution on the risk of lung cancer. Reviews of the literature suggest that combustion-related ambient PM air pollution may result in small increases in lung cancer risk,[465,466] but there remain substantial gaps in our knowledge.[467] There are several factors that make it relatively difficult to evaluate the effects of air pollution on lung cancer. Cigarette smoking is by far the largest risk factor. Any study that attempts to evaluate the effects of air pollution on lung cancer must aggressively control for exposure to tobacco smoke (both from active smoking and environmental exposure), and, even then, concerns about residual confounding by tobacco smoke remain. Furthermore, because of the latency period required to develop lung cancer, daily time series, case-crossover, and related studies of short-term exposure are not appropriate methodological tools to study the effects of PM pollution on lung cancer.

Population-based cross-sectional studies have observed ecological associations between PM pollution and lung cancer.[34,468] Several case-control studies have also observed similar PM-lung cancer associations.[469–472] Early prospective cohort studies that attempted to evaluate long-term PM exposure observed relatively weak PM-lung cancer associations.[26,27,187] In the extended follow-up of the much larger ACS cohort, similar but statistically significant PM-lung cancer associations were observed.[179] The recent extended follow-up analysis of the Harvard Six Cities cohort observed comparably increased risk of lung cancer mortality associated with $PM_{2.5}$, which was not statistically significant.[184] Currently, the available evidence suggests a small (certainly compared with active cigarette smoking) increased lung cancer risk because of air pollution. The evidence of a PM-lung cancer association is not nearly as compelling as is the association for nonmalignant cardiopulmonary disease, and further study is needed.

Relative Toxicity and Role of Sources and Copollutants

One of the biggest gaps in our knowledge relates to what specific air pollutants, combination of pollutants, sources of pollutants, and characteristics of pollutants are most responsible for the observed health effects. Although the literature provides little evidence that a single major or trace component of PM is responsible for the observed health effects,[473] various general characteristics may affect the relative toxicity of PM pollution. For example, with regard to particle size, the epidemiological, physiological, and toxicological evidence suggests that fine particles (indicated by $PM_{2.5}$) play a substantial role in affecting human health. These fine particles can be breathed deeply into the lungs, penetrate into indoor environments, remain suspended in the air for long periods of time, and are transported over long distances, resulting in relatively ubiquitous exposures. Furthermore, fine particles are largely generated, directly or indirectly, by combustion processes and are relatively complex mixtures that include sulfates, nitrates, acids, metals, and carbon particles with various chemicals adsorbed onto their surfaces. Fairly consistent associations between $PM_{2.5}$ and various cardiopulmonary health end points have been observed, yet the roles of coarse particles and ultrafine particles are yet to be fully resolved,[474–477] as are the roles of atmospheric secondary inorganic PM.[102] Other characteristics of PM pollution that likely relate to relative toxicity include solubility,[478,479] metal content,[343,480–485] and surface area and reactivity.[106,486] These characteristics need further study.

Highly related to understanding the role of various characteristics and constituents of PM is understanding the relative importance of various sources and related copollutants. For example, PM exposure to pollution from the burning of coal typically includes substantial secondary sulfates and coexposure to SO_2. PM exposure to pollution from traffic sources often includes substantial secondary nitrates and coexposure to nitrogen dioxide and CO. Of course in most real-world environments, ambient PM pollution comes from many sources, including local and regional sources. Although the literature provides little evidence that a single source or well-defined combination of sources are responsible for the health effects, the relative importance of PM from various sources and the

additive or synergistic effects of related copollutants remains a matter of debate[487,488] and will require substantial additional research.

Continued Skepticism

Beyond simply recognizing gaps in knowledge, there remains a need for a healthy skepticism regarding what we may think we know about the health effects of PM exposure. Although there has been a growing consensus that PM exposure can contribute to cardiopulmonary morbidity and mortality, there continues to be concerns that the evidence is inadequate to establish costly health-based air quality standards for $PM_{2.5}$. Some of this skepticism seems to be motivated at least in part by pro forma opposition to recent public policy efforts to regulate $PM_{2.5}$.[489–491] Nevertheless, there are important scientific issues that are not fully resolved. For example, Moolgavkar[492,493] argues that potential confounding, measurement error, model building and selection, and related issues remain concerns, especially when the estimated risks are small. Lumley and Sheppard[494] point out what contemporary air pollution epidemiologists know well: "estimation of very weak associations in the presence of measurement error and strong confounding is inherently challenging."[494]

As discussed above, it is the judgment of the authors that recent research has provided increased evidence that the PM-cardiopulmonary health effects observed in epidemiologic studies are biologically plausible. However, some reviewers of the literature remain troubled by the issue of biological plausibility and argue that there is inadequate consistency across the toxicological and epidemiologic evidence.[495–499] Toxicology is playing a crucial role in understanding the health effects of PM,[500] but there are substantial challenges, especially when it comes to dealing with exposures to complex mixtures.[104,501,502]

Another reason for skepticism is at least implied by Phalen[88] in his book dealing with the particulate air pollution controversy. Scientific efforts to understand the health effects of air pollution have taken place within the context of contentious and controversial debate about public health policy, environmental regulations, the relative costs of pollution versus its abatement, and who pays these costs. Such conditions present both challenges and opportunities to researchers, but these conditions are not always most conducive to deliberate, objective, scientific inquiry. The extent to which politics, pressure groups, special interests, and funding opportunities and sources influence the science and how it is interpreted is unknown, but these influences may contribute to our skepticism.

CONCLUSIONS

Since 1997, there has been a substantial amount of research that added to the evidence that breathing combustion-related fine particulate air pollution is harmful to human health. Various lines of research have helped connect some of the important gaps in our knowledge. Different research teams using various analytic methods, including alternative time series approaches and case-crossover designs, continue to observe reasonably consistent associations between cardiopulmonary mortality and daily changes in PM. The associations are observed, not only in many single-city studies, but also in various large multicity studies with less opportunity for city selection or publication bias. The evidence of long-term chronic health effects has been strengthened by various reanalyses and extended analyses of the Harvard Six Cities and ACS cohorts and by results from several other independent studies of long-term PM exposure.

The PM-mortality effect estimates from the studies of long-term exposure are substantially larger than those from the daily time series or case-crossover studies that evaluated daily changes in exposure. Time series studies with longer time scales or extended distributed lags generally observed larger PM-mortality effects, suggesting that the daily time series studies that use only short-term day-to-day variability are observing more than just a phenomenon of short-term harvesting or mortality displacement. Studies of intermediate time scales of exposure typically observed PM-mortality associations that are larger than those observed in the time series studies but smaller than those observed in the long-term prospective cohort studies. Overall, the results suggest that PM health effects are dependent on both exposure concentrations and length of exposure and that the short-term studies only capture a small amount of the overall health effects of PM exposure. Long-term repeated exposures have larger, more persistent cumulative effects than short-term transient exposures.

Several methodological enhancements have been developed to further explore the shape of the PM health effects concentration-response functions. Daily time series data from multiple cities have been pooled to enhance statistical power and generalizability. Combined, or "meta-smoothed," concentration-response functions were estimated using flexible smoothing strategies. Estimated concentration-response functions are near linear, with no evidence of safe threshold levels. The PM concentration-response function for long-term exposure has also been explored. Again, across the range of PM concentrations observed, the concentration-response relationships were generally near linear.

There has been substantial growth in studies dealing with PM exposure and cardiovascular disease. Long-term PM exposure has been associated with increased cardiovascular mortality, various blood markers of cardiovascular risk, histopathological markers of subclinical chronic inflammatory lung injury, and subclinical atherosclerosis. Short-term exposures have been associated with cardiovascular mortality and hospital admissions, stroke mortality and hospital admissions, MIs, evidence of pulmonary and systemic inflammation and oxidative stress, altered cardiac autonomic function, arterial vasoconstriction, and more. There has also been substantial research exploring potential biological mechanisms or pathophysiological pathways that link PM exposure and cardiopulmonary disease and death.

Biological effects of PM have been observed, and various general mechanistic pathways are proposed, including: (1) long-term exposure results in more rapid progression of COPD, and acute exposure exacerbates existing pulmonary disease; (2) pulmonary and systemic oxidative

stress, inflammation, atherosclerosis, and related cardiovascular disease; (3) adverse changes in cardiac autonomic function; (4) vasculature alterations, including vascular tone and endothelial function; (5) systemic translocation of PM and prothrombotic effects; (6) modulated host defenses and immunity; and (7) PM-induced lung damage, declines in lung function, respiratory distress, and hypoxemia. None of these pathways have been adequately or fully explored. Furthermore, as illustrated in Figure 4, there are almost certainly multiple mechanistic pathways with complex interactions and interdependencies. Incomplete but intriguing evidence now provides several hypothetical and interdependent mechanistic pathways that could plausibly link PM exposure with cardiopulmonary morbidity and mortality.

The various lines of research explored in this review have certainly helped connect some of the gaps in our knowledge regarding PM pollution and health. Other gaps remain unresolved, including: (1) an understanding of who is most at risk or most susceptible; (2) the impacts of PM exposure on infant mortality and various birth outcomes, including fetal growth, premature birth, intrauterine mortality, and birth defects; (3) effect of ambient PM on the risk of lung cancer; and (4) the role of various characteristics and constituents of PM, and what is the relative importance of various sources and related copollutants. Additional research is needed to resolve these and related issues. Although there is growing evidence that the epidemiologically observed links between PM and cardiopulmonary disease and death may be plausible, there remains a need to further elucidate the biological mechanisms. Despite some unresolved issues, there have been several important lines of research that have been pursued since 1997 that have substantially helped connect the gaps and elucidate our understanding about human health effects of particulate air pollution. Unresolved scientific issues dealing with the health effects of PM air pollution need not serve as sources of division but as opportunities for cooperation and increased collaboration among epidemiology, toxicology, exposure assessment, and related disciplines.

New national ambient air quality standards for PM were proposed by EPA[96] at about the time a draft paper of this critical review was being completed for peer evaluation and comments. As noted earlier, the polarized response to the proposed NAAQS demonstrated that lines of division that troubled Vedal[80] in 1997 continue, especially the problem of setting standards in the absence of clearly defined health effect thresholds. Some reviewers of this critical review opined that "the big question is: how valid is the EPA NAAQS proposal." A comprehensive evaluation of the literature provides compelling evidence that continued reductions in exposure to combustion-related fine particulate air pollution as indicated by $PM_{2.5}$ will result in improvements in cardiopulmonary health. The recommendations by the Clean Air Scientific Advisory Committee[98] provide for responsible standards given current knowledge. The more stringent WHO[99] guidelines for PM_{10} and $PM_{2.5}$ provide reasonable goals for most urban environments. Although research on the health effects of PM has been motivated largely by environmental health policy, in this review, the progress of the science has been of more interest than debates over legally mandated standards. There has been substantial progress in the evaluation of the health effects of PM at different time scales of exposure and in the exploration of the shape of the concentration-response function. The emerging evidence of PM-related cardiovascular health effects and the growing knowledge regarding interconnected general pathophysiological pathways that link PM exposure with cardiopulmonary morbidity and mortality are fascinating results. These results have important scientific, medical, and public health implications that are much broader than debates over air quality standards.

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REFERENCES

1. Brimblecombe, P. *The Big Smoke: A History of Air Pollution in London since Medieval Times*. Methuen: London, United Kingdom, 1987.
2. Lipfert, F.W. *Air Pollution and Community Health: A Critical Review and Data Sourcebook*. Van Nostrand Reinhold: New York, NY, 1994.
3. Davis, D. *When Smoke Ran Like Water*. Basic Books, New York, NY, 2002.
4. Firket, J. The Cause of the Symptoms Found in the Meuse Valley during the Fog of December, 1930; *Bull. Acad. R. Med. Belg.* **1931**, *11,* 683-741.
5. Schrenk, H.H.; Heimann, H.; Clayton, G.D.; Gafafer, W.M.; Wexler, H. *Air Pollution in Donora, Pa.: Epidemiology of the Unusual Smog Episode of October 1948*. Public Health Service: Washington, DC, 1949.
6. U.K. Ministry of Health. *The Report of the Chief Medical Officer on the State of Public Health*. Her Majesty's Stationery Office: London, United Kingdom, 1953.
7. U.K. Ministry of Health. *Mortality and Morbidity during the London Fog of December 1952. Reports on Public Health and Medical Subjects No. 95*. Ministry of Health: London, United Kingdom, 1954.
8. Nemery, B.; Hoet, P.H.M.; Nemmar, A. The Meuse Valley Fog of 1930: An Air Pollution Disaster; *Lancet* **2001,** *357,* 704-08.
9. Ciocco, A.; Thompson, D.J. A Follow-Up of Donora Ten Years After: Methodology and Findings; *Am. J. Public Health* **1961**, *51,* 155-164.
10. Logan, W.P.D. Mortality in London Fog Incident, 1952; *Lancet* **1953**, *1,* 336-338.
11. Bell, M.L.; Davis, D.L. Reassessment of the Lethal London Fog of 1952: Novel Indicators of Acute and Chronic Consequences of Acute Exposure to Air Pollution; *Environ. Health Perspect.* **2001**, *109,* 389-394.
12. Bell, M.L.; Davis, D.L.; Fletcher, T. A Retrospective Assessment of Mortality from the London Smog Episode of 1952: The Role of Influenza and Pollution; *Environ. Health Perspect.* **2004**, *112,* 6-8.
13. Ellison, J.M.; Waller, R.E. A Review of Sulphur Oxides and Particulate Matter as Air Pollutants with Particular Reference to Effects on Health in the United Kingdom; *Environ. Res.* **1978**, *16,* 302-325.
14. Holland, W.W.; Bennett, A.E.; Cameron, I.R.; Florey, C.V.; Leeder, S.R.; Schilling, R.S.F., Swan, A.V.; Waller, R.E. Health Effects of Particulate Pollution: Reappraising the Evidence; *Am. J. Epidemiol.* **1979**, *110,* 527-659.
15. Shy, C.M. Epidemiologic Evidence and the United States Air Quality Standards. *Am. J. Epidemiol.* **1979,** *110,* 661-671.
16. Ware, J.H.; Thibodeau, L.A.; Speizer, F.E.; Colome, S.; Ferris, B.G., Jr. Assessment of the Health Effects of Atmospheric Sulfur Oxides and Particulate Matter: Evidence from Observational Studies; *Environ. Health Perspect.* **1981**, *41,* 255-276.

17. Schwartz, J.; Marcus, A. Mortality and Air Pollution in London: A Time Series Analysis; *Am. J. Epidemiol.* **1990**, *131,* 185-194.
18. Fairley, D. The Relationship of Daily Mortality to Suspended Particulates in Santa Clara County, 1980–1986; *Environ. Health Perspect.* **1990**, *89,* 159-168.
19. Schwartz, J. Particulate Air Pollution and Daily Mortality in Detroit; *Environ. Res.* **1991**, *56,* 204-213.
20. Pope, C.A., III; Schwartz, J.; Ransom, M.R. Daily Mortality and PM_{10} Pollution in Utah Valley; *Arch. Environ. Health* **1992**, *47,* 211-217.
21. Schwartz, J.; Dockery, D.W. Particulate Air Pollution and Daily Mortality in Steubenville, Ohio; *Am. J. Epidemiol.* **1992**, *135,* 12-19.
22. Schwartz, J.; Dockery, D.W. Increased Mortality in Philadelphia Associated with Daily Air Pollution Concentrations; *Am. Rev. Respir. Dis.* **1992**, *145,* 600-604.
23. Dockery, D.W.; Schwartz, J.; Spengler, J.D. Air Pollution and Daily Mortality: Associations with Particulates and Acid Aerosols; *Environ. Res.* **1992**, *59,* 362-373.
24. Schwartz, J. Air Pollution and Daily Mortality in Birmingham, Alabama; *Am. J. Epidemiol.* **1993**, *137,* 1136-1147.
25. Dockery, D.W.; Speizer, F.E.; Stram, D.O.; Ware, J.H.; Spengler, J.D.; Ferris, B.G. Effects of Inhalable Particles on Respiratory Health of Children; *Am. Rev. Respir. Dis.* **1989**, *139,* 587-594.
26. Dockery, D.W.; Pope, C.A., III; Xu, X.; Spengler, J.D.; Ware, J.H.; Fay, M.E.; Ferris, B.G.; Speizer, F.A. An Association between Air Pollution and Mortality in Six U.S. Cities; *N. Engl. J. Med.* **1993**, *329,* 1753-1759.
27. Pope, C.A., III; Thun, M.J.; Namboodiri, M.M.; Dockery, D.W.; Evans, J.S.; Speizer, F.E.; Heath, J.C.W. Particulate Air Pollution as a Predictor of Mortality in a Prospective Study of U.S. Adults; *Am. J. Respir. Crit. Care. Med.* **1995**, *151,* 669-674.
28. Pope, C.A., III. Respiratory Disease Associated with Community Air Pollution and a Steel Mill, Utah Valley; *Am. J. Public Health* **1989**, *79,* 623-628.
29. Pope, C.A., III. Respiratory Hospital Admissions Associated with PM_{10} Pollution in Utah, Salt Lake, and Cache Valleys; *Arch. Environ. Health* **1991**, *46,* 90-97.
30. Pope, C.A., III; Dockery, D.W. Acute Health Effects of PM_{10} Pollution on Symptomatic and Asymptomatic Children; *Am. Rev. Respir. Dis.* **1992**, *145,* 1123-1128.
31. Pope, C.A., III; Dockery, D.W.; Spengler, J.D;. Raizenne, M.E. Respiratory Health and PM_{10} Pollution: A Daily Time Series Analysis; *Am. Rev. Respir. Dis.* **1991**, *144,* 668-674.
32. Pope, C.A., III; Kanner, R.E. Acute Effects of PM_{10} Pollution on Pulmonary Function of Smokers with Mild to Moderate Chronic Obstructive Pulmonary Disease; *Am. Rev. Respir. Dis.* **1993**, *147,* 1336-1340.
33. Ransom, M.R.; Pope, C.A., III. Elementary School Absences and PM_{10} Pollution in Utah Valley; *Environ. Res.* **1992**, *58,* 204-219.
34. Archer, V.E. Air Pollution and Fatal Lung Disease in Three Utah Counties; *Arch. Environ. Health* **1990**, *45,* 325-334.
35. Ostro, B.D. Associations between Morbidity and Alternative Measures of Particulate Matter; *Risk Anal.* **1990**, *10,* 421-427.
36. Ostro, B.D.; Rothschild, S. Air Pollution and Acute Respiratory Morbidity: An Observational Study of Multiple Pollutants; *Environ. Res.* **1989**, *50,* 238-247.
37. Thurston, G.D.; Ito, K.; Kinney, P.L.; Lippmann, M. A Multi-Year Study of Air Pollution and Respiratory Hospital Admissions in Three New York State Metropolitan Areas: Results for 1988 and 1989 Summers; *J. Expos. Anal. Environ. Epidemiol.* **1992**, *2,* 429-450.
38. Wichmann, H.E.; Mueller, W.; Allhof, P.; Beckmann, M.; Bocter, N.; Csicsaky, M.J.; Jung, M.; Molik, B.; Schoeneberg, G. Health Effects during a Smog Episode in West Germany in 1985; *Environ. Health Perspect.* **1989**, *79,* 89-99.
39. Bates, D.V.; Sizto, R. The Ontario Air Pollution Study: Identification of the Causative Agent; *Environ. Health Perspect.* **1989**, *79,* 69-72.
40. Ponka, A. Asthma and Low Level Air Pollution in Helsinki; *Arch. Environ. Health* **1991**, *46,* 262-270.
41. Bobak, M.; Leon, D.A. Air Pollution and Infant Mortality in the Czech Republic, 1986–1988; *Lancet* **1992**, *340,* 1010-1014.
42. Anderson, H.R. Differential Epidemiology of Ambient Aerosols; *Phil. Trans. R. Soc. Lond. Series A* **2000**, *358,* 2771-2785.
43. Bates, D.V. Health Indices of the Adverse Effects of Air Pollution: The Question of Coherence; *Environ. Res.* **1992**, *59,* 336-349.
44. Bates, D.V. The Effects of Air Pollution on Children; *Environ. Health Perspect.* **1995**, *103,* 49-53.
45. Bates, D.V. Particulate Air Pollution; *Thorax* **1996,** *51,* S3-S8.
46. Brunekreef, B.; Dockery, D.W.; Krzyzanowski, M. Epidemiologic Studies on Short-Term Effects of Low Levels of Major Ambient Air Pollution Components; *Environ. Health Perspect.* **1995**, *103,* 3-13.
47. Brunekreef, B.; Holgate, S.T. Air Pollution and Health; *Lancet* **2002**, *360,* 1233-1242.
48. CEPA/FPAC. Working Group on Air Quality Objectives and Guidelines. *National Ambient Air Quality Objectives for Particulate Matter.* Minister, Public Works and Government Services: Ottawa, Ontario, Canada, 1998.
49. Committee of the Environmental and Occupational Health Assembly of the American Thoracic Society (CEOHA-ATS). Health Effects of Outdoor Air Pollution; *Am. J. Respir Crit. Care Med.* **1996**, *153,* 3-50.
50. Dab, W.; Ségala, C.; Dor, F.; Festy, B.; Lameloise, P.; Le Moullec, Y.; Le Tertre, A.; Médina, S.; Quénel, P.; Wallaert, B.; Zmirou, D. Air Pollution and Health: Correlation or Causality? The Case of the Relationship Between Exposure to Particles and Cardiopulmonary Mortality; *J. Air & Waste Manage. Assoc.* **2001**, *51,* 220-235.
51. Davidson, C.I.; Phalen, R.F.; Solomon, P.A. Airborne Particulate Matter and Human Health: A Review; *Aero. Sci. Technol.* **2005**, *39,* 737-749.
52. Dockery, D.W.; Pope, C.A., III. Acute Respiratory Effects of Particulate Air Pollution; *Annu. Rev. Public Health* **1994**, *15,* 107-132.
53. Dockery, D.W.; Pope, C.A., III. Epidemiology of Acute Health Effects: Summary of Time-Series Studies. In *Particles in Our Air: Concentrations and Health Effects*; Wilson, R., Spengler, J.D., Eds.; Harvard University Press: Cambridge, MA, 1996.
54. Dockery, D.W.; Pope, C.A., III. Outdoor Air I: Particulates. In *Topics in Environmental Epidemiology*; Steenland, K., Savitz D., Eds.; Oxford University Press: New York, NY, 1997.
55. Dockery, D.W.; Pope, C.A., III; Speizer, F. Effects of Particulate Air Pollution Exposures. In *Particle-Lung Interactions*; Gehr, P., Heyder, J., Eds.; Marcel Dekker: New York, NY, 2000; pp 671-703.
56. Englert, N. Fine Particles and Human Health—A Review of Epidemiological Studies. *Tox. Let.* **2004**, *149,* 235-242.
57. Gamble, J.F.; Lewis, R.J. Health and Respirable Particulate (PM_{10}) Air Pollution: A Causal or Statistical Association?; *Environ. Health Perspect.* **1996**, *104,* 838-850.
58. Katsouyanni, K. Ambient Air Pollution and Health; *Brit. Med. Bull.* **2003**, *68,* 143-156.
59. Kappos, A.D.; Bruckmann, P.; Eikmann, T.; Englert, N.; Heinrich, U.; Höppe, P.; Koch, E.; Krause, G.H.M., Kreyling, W.G.; Rauchfuss, K.; Rombout, P.; Schulz-Klemp, V.; Thiel, W.R.; Wichmann, H.-E. Health Effects of Particles in Ambient Air; *Int. J. Hyg. Environ. Health* **2004**, *207,* 399-407.
60. Lipfert, F.W.; Wyzga, R.E. Air Pollution and Mortality: Issues and Uncertainties; *J. Air & Waste Manage. Assoc.* **1995**, *45,* 949-966.
61. Lipfert, F.W. Air Pollution and Human Health: Perspectives for the '90s and Beyond; *Risk Anal.* **1997**, *17,* 137-146.
62. Moolgavkar, S.H.; Luebeck, E.G. A Critical Review of the Evidence on Particulate Air Pollution and Mortality; *Epidemiol.* **1996**, *7,* 420-428.
63. Nyberg, F.; Pershagen, G. Epidemiologic Studies on the Health Effects of Ambient Particulate Air Pollution; *Scand. J. Work Environ. Health* **2000**, *26,* 49-89.
64. Ostro, B. The Association of Air Pollution and Mortality: Examining the Case for Inference; *Arch. Environ. Health* **1993**, *48,* 336-342.
65. Pope, C.A., III; Dockery, D.W.; Schwartz, J. Review of Epidemiological Evidence of Health Effects of Particulate Air Pollution; *Inhal. Toxicol.* **1995**, *7,* 1-18.
66. Pope, C.A., III; Bates, D.; Raizenne, M. Health Effects of Particulate Air Pollution: Time for Reassessment?; *Environ. Health Perspect.* **1995**, *103,* 472-480.
67. Pope, C.A., III; Dockery, D.W. Epidemiology of Chronic Health Effects: Cross-Sectional Studies. In *Particles in Our Air: Concentrations and Health Effects*; Wilson, R.; Spengler, J.D., Eds; Harvard University Press: Cambridge, MA, 1996.
68. Pope, C.A., III; Dockery, D.W. Epidemiology of Particle Effects. In *Air Pollution and Health*; Holgate, S.T., Koren, H., Maynard, R., Samet, J., Eds.; Academic Press: San Diego, CA, 1999; pp 673-705.
69. Pope, C.A., III. Review: Epidemiological Basis for Particulate Air Pollution Health Standards; *Aerosol Sci. Tech.* **2000**, *32,* 4-14.
70. Pope, C.A., III. Epidemiology of Fine Particulate Air Pollution and Human Health: Biologic Mechanisms and Who's at Risk?; *Environ. Health. Perspect.* **2000**, *108,* 713-723.
71. Schwartz, J. Air Pollution and Daily Mortality: A Review and Meta Analysis; *Environ. Res.* **1994**, *64,* 36-52.
72. Schwartz, J. Health Effects of Air Pollution from Traffic: Ozone and Particulate Matter. In *Health at the Crossroads: Transport Policy and Urban Health*; Fletcher, T.; McMichael, A.J., Eds.; John Wiley and Sons: West Sussex, United Kingdom, 1997; pp 61-81.
73. Schwartz, J. Air Pollution and Children's Health; *Pediatrics* **2004**, *113,* 1037-43.
74. Schwela, D. Air Pollution and Health in Urban Areas; *Rev. Environ. Health* **2000**, *15,* 13-42.
75. Thurston, G.D. A Critical Review of pm_{10}-Mortality Time-Series Studies; *J. Expo. Anal. Environ. Epidemiol.* **1996**, *6,* 3-21.
76. U.K. Department of Health. Non-Biological Particles and Health. Comm. *On the Medical Effects of Air Pollutants*; HMSO: London, United Kingdom,1995.
77. Vedal, S. Update on the Health Effects of Outdoor Air Pollution; *Clin. Chest. Med.* **2002**, *23,* 763-775.
78. Update and Revision of the Air Quality Guidelines for Europe; EUR/ICP/EHAZ 94 05/PB01; World Health Organization-European Region: Copenhagen, Denmark, 1995.

79. Ward, D.J.; Ayres, J.G. Particulate Air Pollution and Panel Studies in Children: a Systematic Review; *Occup. Environ. Med.* **2004,** *61,* e13.
80. Vedal, S. Critical Review—Ambient Particles and Health: Lines that Divide; *J. Air & Waste Manage. Assoc.* **1997**, *47,* 551-581.
81. Kaiser, J. Showdown over Clean Air Science; *Science* **1997**, *277,* 466-469.
82. Reichhardt, T. Regulators Face Questioning on Particulate Rules; *Nature* **1996**, *380,* 11-12.
83. Corn, D. A Bad Air Day; *The Nation* **1997**, *15,* 16-20.
84. Fumento, M. *Polluted Science: The EPA's Campaign to Expand Clean Air Regulations;* AEI Press: Washington, DC, 1997.
85. Greenbaum, D.S.; Bachmann, J.D.; Krewski, D.; Samet, J.M.; White, R.; Wyzga, R.E. Particulate Air Pollution Standards and Morbidity and Mortality: Case Study; *Am. J. Epidemiol.* **2001**, *154,* S78-S90.
86. Maynard, R.; Krewski, D.; Burnett, R.T.; Samet, J.; Brook, J.R.; Granville, G.; Craig, L. Health and Air Quality: Directions for Policy-Relevant Research; *J. Tox. Environ. Health* **2003**, *66,* 1891-1903.
87. Samet, J.M. Epidemiology and Policy: The Pump Handle Meets the New Millennium; *Epidemiol. Rev.* **2000**, *22,* 145-154.
88. Phalen, R. F. *The Particulate Air Pollution Controversy: A Case Study and Lessons Learned;* Kluwer Academic Publishers: Norwell, MA, 2002.
89. Air Quality Criteria for Particulate Matter; EPA/600/P-95/001cF; U.S. Environmental Protection Agency: Washington, DC, 1996.
90. National Ambient Air Quality Standard for Particulate Matter. *Fed. Regist.* **1997**, 62, 38,652-38,752.
91. American Trucking Associations vs. Browner, 175F. 3d 1027, 1055–1056 (D.C. Cir. 1999a) Rehearing Granted in Part and Denied in Part 195F. 3d 4 (D.C. Cir 1999b).
92. Whitman vs. American Trucking Associations Inc., 531 US 457 (2001).
93. American Trucking Associations vs. EPA, 283F. 3d 355, 369–372 (D.C. Cir. 2002).
94. Air Quality Designations for the Fine Particles (PM25) National Ambient Air Quality Standards—Supplemental Amendments. *Fed. Regist.* **2005**, *70,* 19843-19856.
95. Air Quality Criteria for Particulate Matter; EPA/600/P-99/002aF; U.S. Environmental Protection Agency: Washington, DC, 2004.
96. National Ambient Air Quality Standards for Particulate Matter, Proposed Rule. *Fed. Regist.* **2006**, *71(10),* 2620-2708.
97. Moore, C.; Bates, D. An Inconvenient Reality; *Health Clean Air Newsletter* **2006**, *1,* 1-12.
98. Clean Air Scientific Advisory Committee Recommendation Concerning the Proposed National Ambient Air Quality Standards for Particulate Matter; EPA-CASAC-LTR-06-002; Letter to Stephen L. Johnson, March 21, 2006.
99. WHO Air Quality Guidelines Global Update 2005; Report on a Working Group Meeting, Bonn, Germany, October 18–20, 2005; World Health Organization, Regional Office for Europe: Copenhagen, Denmark, 2005.
100. Greim, H.; Borm, P.; Schins, R.; Donaldson, K.; Driscoll, K.; Hartwig, A.; Kuempel, E.; Oberdörster, G.; Speit, G. Toxicity of Fibers and Particles-Reprot of the Workshop Held in Munich, Germany, 26–27 October, 2000; *Inhal. Toxicol.* **2001**, *51,* 737-754.
101. Mauderly, J.L. Diesel Emissions: Is More Health Research Still Needed?; *Toxicol. Sci.* **2001**, *62,* 6-9.
102. Schlesinger, R.B.; Cassee, F. Atmospheric Secondary Inorganic Particulate Matter: The Toxicological Perspective as a Basis for Health Risk Assessment; *Inhal. Toxicol.* **2003**, *15,* 197-235.
103. Ghio, A.J.; Huang, Y.-C.T. Exposure to Concentrated Ambient Particles (CAPs): A Review; *Inhal. Toxicol.* **2004**, *16,* 53-59.
104. Schlesinger, R.B.; Künzli, N.; Hidy, G.M.; Gotschi, T.; Jerrett, M. The Health Relevance of Ambient Particulate Matter Characteristics: Coherence of Toxicological and Epidemiological Inferences; *Inhal. Toxicol.* **2006**, *18,* 95-125.
105. Chow, J.C. Measurment Methods to Determine Compliance with Ambient Air Quality Standards for Suspended Particles; *J. Air & Waste Manage. Assoc.* **1995**, *45,* 320-382.
106. Oberdorster, G.; Oberdorster, E.; Oberdorster, J. Nanotoxicology: An Emerging Discipline Evolving from Studies of Ultrafine Particles; *Environ. Health Perspect.* **2005**, *113,* 823-839.
107. Kulmala, M. How Particles Nucleate and Grow; *Science* **2003**, *302,* 1000-1001.
108. Watson, J.G.; Chow, J.C.; Lowenthal, D.H.; Kreisberg, N.M.; Hering, S.V.; Stolzenburg, M.R. Variations of Nanoparticle Concentrations at the Fresno Supersite; *Sci. Total Environ.* **2006,** *358,* 178-87.
109. Wilson, W.E.; Suh, H.H. Fine Particles and Coarse Particles: Concentration Relationships Relevant to Epidemiologic Studies; *J. Air & Waste Manage. Assoc.* **1997**, *47,* 1238-49.
110. Ostro, B. A Search for a Threshold in the Relationship of Air Pollution to Mortality: A Reanalysis of Data on London Winters; *Environ. Health Perspect.* **1984**, *58,* 397-9.
111. Samet, J.M.; Zeger, S.L.; Berhane, K. *Particulate Air Pollution and Daily Mortaltiy: Replication and Validation of Selected Studies. The Phase I Report of the Particulate Epidemiology Evaluation Project*; Health Effects Institute: Cambridge, MA, 1995.
112. Pope, C.A., III; Kalkstein, L.S. Synoptic Weather Modeling and Estimates of the Exposure-Response Relationship between Daily Mortality and Particulate Air Pollution; *Environ. Health Perspect.* **1996**, *104,* 414-420.
113. Samet, J.M.; Zeger, S.L.; Kelsall, J.E.; Xu, J;. Kalkstein, L.S. Does Weather Confound or Modify the Association of Particulate Air Pollution with Mortality? An Analysis of the Philadelphia Data, 1973–1980; *Environ. Res.* **1998**, *77,* 9-19.
114. Bell, M.L.; Samet, J.M.; Dominici, F. Time-Series Studies of Particulate Matter; *Annu. Rev. Pub. Health* **2004**, *24,* 247-280.
115. Dominici, F.; Sheppard, L.; Clyde, M. Health Effects of Air Pollution: A Statistical Review; *Internat. Stat. Rev.* **2003**, *71,* 243-276.
116. Dominici, F. Time-Series *Analysis of Air Pollution and Mortality: A Statistical Review. Research Report 123*; Health Effects Institute: Boston, MA, 2004.
117. Hastie, T.J.; Tibshirani, R.J. *Generalized Additive Models;* Chapman & Hall: London, United Kingdom, 1990.
118. Pope, C.A., III; Schwartz, J. Time Series for the Analysis of Pulmonary Health Data. *Am. J. Respir. Crit. Care Med.* **1996,** *154,* S229-S233.
119. Dominici, F.; McDermott, A.; Zeger, S.L.; Samet, J.M. On the Use of Generalized Additive Models in Time-Series Studies of Air Pollution and Health; *Am. J. Epidemiol.* **2002**, *156,* 193-203.
120. Health Effects Institute. *Revised Analyses of Time-Series of Air Pollution and Health. Special Report*; Health Effects Institute, Boston, MA, 2003.
121. Maclure, M. The Case-Crossover Design: A Method for Studying Transient Effects on the Risk of Acute Events; *Am. J. Epidemiol.* **1991**, *133,* 144-153.
122. Neas, L.M.; Schwartz, J.; Dockery, D. A Case-Crossover Analysis of Air Pollution and Mortality in Philadelphia; *Environ. Health Perspect.* **1999**, *107,* 629-631.
123. Lee, J.-T.; Schwartz, J. Reanalysis of the Effects of Air Pollution on Daily Mortality in Seoul, Korea: A Case-Crossover Design; *Environ. Health Perspect.* **1999**, *107,* 633-636.
124. Pope, C.A., III. Mortality and Air Pollution: Associations Persist with Continued Advances in Research Methodology; *Environ. Health Perspect.* **1999**, *107,* 613-614.
125. Janes, H.; Sheppard, L.; Lumley, T. Overlap Bias in the Case-Crossover Design, with Application to Air Pollution Exposures; *Statist. Med.* **2005**, *24,* 285-300.
126. Janes, H.; Sheppard, L.; Lumley, T. Case-Crossover Analyses of Air Pollution Exposure Data: Referent Selection Strategies and Their Implications for Bias; *Epidemiol.* **2005**, *16,* 717-726.
127. Bateson, T.F.; Schwartz, J. Control for Seasonal Variation and Time Trend in Case-Crossover Studies of Acute Effects of Environmental Exposure; *Epidemiol.* **1999**, *10,* 539-544.
128. Bateson, T.F.; Schwartz, J. Selection Bias and Confounding in Case-Crossover Analyses of Environmental Time-Series Data; *Epidemiology* **2001**, *12,* 654-661.
129. Lee, J.T.; Kim, H.; Schwartz, J. Bidirectional Case-Crossover Studies of Air Pollution: Bias From Skewed and Incomplete Waves; *Environ. Health Perspect.* **2000**, *108,* 1107-1111.
130. Levy, D.; Lumley, T.; Sheppard, L., Kaufman, J.; Checkoway, H. Referent Selection in Case-Crossover Analyses of Acute Health Effects of Air Pollution; *Epidemiol.* **2001**, *12,* 186-192.
131. Lumley, T.; Levy, D. Bias in the Case-Crossover Design: Implications from Studies of Air Pollution; *Environmetrics* **2000**, *11,* 689-704.
132. Lumley, T.; Sheppard, L. Assessing Seasonal Confounding and Model Selection Bias in Air Pollution Epidemiol Using Positive and Negative Control Analyses; *Environmetrics* **2000**, *11,* 705-718.
133. Mittleman, M.A. Optional Referent Selection Strategies in Case-Crossover Studies: A Settled Issue; *Epidemiol.* **2005**, *16,* 715-716.
134. Levy, J.I.; Hammitt, J.K.; Spengler, J.D. Estimating the Mortality Impacts of Particulate Matter: What Can Be Learned from Between-Study Variability?; *Environ. Health Perspect.* **2000**, *108,* 109-117.
135. Steib, D.M.; Judek, S.; Burnett, R.T. Meta-Analysis of Time-Series Studies of Air Pollution and Mortality: Effects of Gases and Particles and the Influence of Cause of Death, Age, and Season; *J. Air & Waste Manag. Assoc.* **2002**, *52,* 470-484.
136. Steib, D.M.; Judek, S.; Burnett, R.T. Meta-Analysis of Time-Series Studies of Air Pollution and Mortality: Update in Relation to the Use of Generalized Additive Models; *J. Air & Waste Manag. Assoc.* **2003**, *53,* 258-261.
137. Anderson, H.R.; Atkinson, R.W.; Peacock, J.L.; Sweeting, M.J.; Marston, L. Ambient Particulate Matter and Health Effects: Publication Bias in Studies of Short-Term Associations; *Epidemiol.* **2005**, *16,* 155-163.
138. COMEAP. *Cardiovascular Disease and Air Pollution. A Report by the Committee on the Medical Effects of Air Pollutant's Cardiovascular Sub-Group*; United Kingdom Department of Health: London, United Kingdom, 2006.
139. Schwartz, J.; Dockery, D.W.; Neas, L.M. Is Daily Mortality Associated Specifically with Fine Particles?; *J. Air & Waste Manag. Assoc.* **1996**, *46,* 927-936.

140. Klemm, R.J.; Mason, R.M.; Heilig, C.M.; Neas, L.M.; Dockery, D.W. Is Daily Mortality Associated Specifically with Fine Particles? Data Reconstruction and Replication of Analyses; *J. Air & Waste Manage. Assoc.* **2000**, *50,* 1215-1222.
141. Laden, F.; Neas, L.M.; Dockery, D.W.; Schwarts, J. Association of Fine Particulate Matter from Different Sources with Daily Mortality in Six U.S. Cities; *Environ. Health Perspect.* **2000**, *108,* 941-947.
142. Klemm, R.J.; Mason, R. Replication of Reanalysis of Harvard Six-City Mortality Study. In *Revised Analyses of Time-Series of Air Pollution and Health. Special Report*; Health Effects Institute: Boston, MA, 2003; pp 165–172.
143. Burnett, R.T.; Brook, J.; Dann, T.; Delocla, C.; Philips, O.; Cakmak, S.; Vincent, R.; Goldberg, M.S.; Krewski, D. Association between Particulate- and Gas-Phase Components of Urban Air Pollution and Daily Mortality in Eight Canadian Cities; *Inhal. Toxicol.* **2000**, *12,* 15-39.
144. Burnett, R.T.; Goldberg, M.S. Size-Fractionated Particulate Mass and Daily Mortality in Eight Canadian Cities. In *Revised Analyses of Time-Series of Air Pollution and Health. Special Report*; Health Effects Institute: Boston, MA, 2003; pp 85–90.
145. Ostro, B.; Broadwin, R.; Green, S.; Feng, W.-Y.; Lipsett, M. Fine Particulate Air Pollution and Mortality in Nine California Counties: Results from CALFINE; *Environ. Health Perspect.* **2006**, *114,* 29-33.
146. Schwartz, J. Assessing Confounding, Effect Modification, and Thresholds in the Association Between Ambient Particles and Daily Deaths; *Environ. Health Perspect.* **2000**, *108,* 563-568.
147. Braga, A.L.F., Zanobetti, A.; Schwartz, J. The Lag Structure between Particulate Air Pollution and Respiratory and Cardiovascular Deaths in Ten US Cities; *J. Occup. Environ. Med.* **2001**, *43,* 927-933.
148. Schwartz, J. Airborne Particles and Daily Deaths in 10 US Cities. In *Revised Analyses of Time-Series of Air Pollution and Health. Special Report*; Health Effects Institute: Boston, MA, 2003; pp 211–218.
149. Schwartz, J. The Effects of Particulate Air Pollution on Daily Deaths: A Multi-City Case-Crossover Analysis; *Occup. Environ. Med.* **2004**, *61,* 956-961.
150. Particulate Air Pollution and Daily Mortality: Replication and Validation of Selected Studies. Phase I Report of the Particle Epidemiology Evaluation Project; Health Effects Institute, Boston, MA, 1995.
151. Samet, J.M.; Dominici, F.; Curriero, F.C.; Coursac, I.; Zeger, S.L. Fine Particulate Air Pollution and Mortality in 20 U.S. Cities, 1987–1994; *N. Engl. J. Med.* **2000**, *343,* 1742-1749.
152. Dominici, F.; Samet, J.M.; Zeger, S.L. Combining Evidence on Air Pollution and Daily Mortality From the 20 Largest U.S. Cities: A Hierarchical Modeling Strategy; *J. Royal Stat. Soc.* **2000**, *163,* 263-302.
153. Dominici, F.; Daniels, M.; McDermott, A.; Zeger, S.L.; Samet, J. Shape of the Exposure-Response Relation and Mortality Displacement in the NMMAPS Database. In *Revised Analyses of Time-Series of Air Pollution and Health. Special Report*; Health Effects Institute: Boston, MA, 2003; pp 91–96.
154. Dominici, F.; McDermott, A.; Zeger, S.L.; Samet, J.M. National Maps of the Effects of Particulate Matter on Mortality: Exploring Geographical Variation; *Environ. Health Perspect.* **2003,** *111,* 39-43.
155. Peng, R.D.; Domonici, F.; Pastor-Barriuso, R.; Zeger, S.L.; Samet, J.M. Seasonal Analyses of Air Pollution and Mortality in 100 U.S. Cities; *Am. J. Epidemiol.* **2005**, *161,* 585-594.
156. Katsouyanni, K.; Schwartz, J.; Spix, C.; Touloumi, G.; Zmirou, D.; Zanobetti, A.; Wojtyniak, B.; Vonk, J.M.; Tobias, A.; Ponka, A.; Medina, S.; Bacharova, L.; Anderson, H.R. Short-Term Effects of Air Pollution on Health: a European Approach Using Epidemiologic Time-Series Data: The APHEA Protocol; *J. Epidemiol. Comm. Health* **1996,** *50,* S12-S18.
157. Katsouyanni, K.; Touloumi, G.; Spix, C.; Schwartz, J.; Balducci, F.; Medina, S.; Rossi, G.; Wojtyniak, B.; Sunyer, J.; Bacharova, L.; Schouten, J.P.; Ponka, A.; Anderson, H.R. Short-Term Effects of Ambient Sulfur Dioxide and Particulate Matter on Mortality in 12 European Cities: Results From Time-Series Data from the APHEA Project; *Br. Med. J.* **1997**, *314,* 1658-1663.
158. Zmirou, D.; Schwartz, J.; Saez, M.; Zanobetti, A.; Wojtyniak, B.; Touloumi, G.; Spix, C.; Ponce;. de León, A.; le Moullec, Y.; Bacharova, L.; Schouten, J.; Pönkä, A.; Katsouyanni, K. Time-Series Analysis of Air Pollution and Cause-Specific Mortality; *Epidemiol.* **1998**, *9,* 495-503.
159. Samoli, E.; Schwartz, J.; Wojtyniak, B.; Touloumi, G.; Spix, C.; Balducci, F.; Medina, S.; Rossi, G.; Sunyer, J.; Bacharova, L.; Anderson, H.R.; Katsouyanni, K. Investigating Regional Differences in Short-Term Effects of Air Pollution on Daily Mortality in the APHEA Project: A Sensitivity Analysis for Controlling Long-Term Trends and Seasonality; *Environ. Health Perspect.* **2001**, *109,* 349-353.
160. Samoli, E.; Schwartz, J.; Analitis, A.; Petasakis, Y.; Wojtyniak, B.; Touloumi, G.; Spix, C.; Balducci, F.; Medina, S.; Rossi, G.; Sunyer, J.; Anderson, H.R.; Katsouyanni, K. Sensitity Analyses of Regional Differences in Short-Term Effects of Air Pollution on Daily Mortality in APHEA Cities. In *Revised Analyses of Time-Series of Air Pollution and Health. Special Report*; Health Effects Institute: Boston, MA, 2003; pp 205–209.
161. Aga, E.; Samoli, E.; Touloumi, G.; Anderson, H.R.; Cadum, E.; Forsberg, B.; Goodman, P.; Gorgen, A.; Kotesovec, F.; Kriz, B.; Macarol-Hiti, M.; Medina, S.; Paldy, A.; Schindler, C.; Sunyer, J.; Tittanen, P.; Wojtyniak, B.; Zmirou, D.; Schwartz, J.; Katsouyanni, K. Short-Term Effects of Ambient Particles on Mortality in the Elderly: Results from 28 Cities in the APHEA2 Project. *Eur. Respir. J.* **2003**, *21,* 28s-33s.
162. Katsouyanni, K.; Touloumi, G.; Samolu, E.; Petasakis, Y.; Analitis, A.; Le Tertre, A.; Rossi, G.; Zmirou, D.; Ballester, F.; Boumghar, A.; Anderson, H.R.; Wojtyniak, B.; Paldy, A.; Braustein, R.; Pekkanen, J.; Schindler, C.; Schwartz, J. Sensitivity Analysis of Various Models of Short-Term Effects of Ambient Particles on Total Mortality in 29 Cities in APHEA2. In *Revised Analyses of Time-Series of Air Pollution and Health. Special Report*; Health Effects Institute: Boston, MA, 2003; pp 157–164.
163. Analitis, A.; Katsouyanni, K.; Dimakopoulou, K.; Samoli, E.; Nikoloulopoulos, A.K.; Petasakis, Y.; Touloumi, G.; Schwartz, J.; Anderson, H.R.; Cambra, K.; Forastiere, F.; Zmirou, D.; Vonk, J.M.; Clancy, L.; Kriz, B.; Bobvos, J.; Pekkanen, J. Short-Term Effects of Ambient Particles on Cardiovascular and Respiratory Mortality; *Epidemiol.* **2006**, *17,* 230-233.
164. Le Tertre, A.; Quénel, P.; Eilstein, D.; Medina, S.; Prouvost, H.; Pascal, L.; Boumghar, A.; Saviuc, P.; Zeghnoun, A.; Filleul, L.; Declercq, C.; Cassadou, S.; Goaster, C.L. Short-Term Effects of Air Pollution on Mortality in Nine French Cities: a Quantitative Summary; *Arch. Environ. Health* **2002**, *57,* 311-319.
165. Simpson, R.; Williams, G.; Petroeschevsky, A.; Best, T.; Morgan, G.; Denison, L.; Hinwood, A.; Neville, G.; Neller, A. The Short-Term Effects of Air Pollution on Daily Mortality in Four Australian Cities; *Aust. N. Z. J. Public Health* **2005**, *29,* 205-212.
166. Lee, J.-T.; Kim, H.; Hong, Y.-C.; Kwong, H.-J.; Schwartz, J.; Christiani, D.C. Air Pollution and Daily Mortality in Seven Major Cities of Korea, 1991–1997. *Environ. Res. Sect. A* **2000**, *84,* 247-254.
167. Omori, T.; Fujimoto, G.; Yoshimura, I.; Nitta, H.; Ono, M. Effects of Particulate Matter on Daily Mortality in 13 Japanese Cities; *J. Epidemiol.* **2003**, *13,* 314-322.
168. McMichael, A.J.; Anderson, H.R.; Brunekreef, B.; Cohen, A.J. Inappropriate Use of Daily Mortality Analyses to Estimate Longer-Term Mortality Effects of Air Pollution; *Int. J. Epidemiol.* **1998**, *27,* 450-453.
169. Lave, L.B.; Seskin, E.P. Air Pollution and Human Health; *Science* **1970**, *169,* 723-733.
170. Mendelsohn, R.; Orcutt, G. An Empirical Analysis of Air Pollution Dose-Response Curves; *J. Environ. Econ. Manag.* **1979**, *6,* 85-106.
171. Evans, J.S.; Tosteson, T.; Kinney, P.L. Cross-Sectional Mortality Studies and Air Pollution Risk Assessment; *Environ. Int.* **1984**, *10,* 55-83.
172. Lipfert, F.W. Air Pollution and Mortality: Specification Searches Using SMSA-Based Data; *J. Environ. Econ. Manag.* **1984**, *11,* 208-243.
173. Özkaynak, H.; Thurston, G.D. Associations between 1980 U.S. Mortality Rates and Alternative Measures of Airborne Particle Concentration; *Risk Anal.* **1987**, *7,* 449-461.
174. Lipfert, F.W.; Malone, R.G.; Daum, M.L.; Mendell, N.R.; Yang, C.-C. *A Statistical Study of the Macroepidemiology of Air Pollution and Total Mortality*; Report No. BNL 52122; U.S. Department of Energy: Washington, DC, 1988.
175. Lipfert, F.W.; Morris, S.C. Temporal and Spatial Relations between Age Specific Mortality and Ambient Air Quality in the United States: Regression Results for Counties, 1960–97; *Occup. Environ. Med.* **2002**, *59,* 147-8.
176. Brunekreef, B. Design of Cohort Studies for Air Pollution Health Effects; *J. Toxicol. Environ. Health, Part A* **2003**, *66,* 1723-1729.
177. Krewski, D.; Burnett, R.T.; Goldberg, M.S.; Hoover, K.; Siemiatycki, J.; Jarret, M.; Abrahamowicz, M.; White, W.H. *Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of Particulate Air Pollution and Mortality. Special Report*; Health Effects Institute: Cambridge MA, 2000.
178. Krewski, D.; Burnett, R.T.; Goldberg, M.S.; Hoover, K.; Siemiatycki, J.; Abrahamowicz, M.; White, W.H. Validation of the Harvard Six Cities Study of Particulate Air Pollution and Mortality; *N. Engl. J. Med.* **2004**, *350,* 198-199.
179. Pope, C.A.; III; Burnett, R.T.; Thun, M.J.; Calle, E.E.; Krewski, D.; Ito, K.; Thurston, G.D. Lung Cancer, Cardiopulmonary Mortality, and Long-Term Exposure to Fine Particulate Air Pollution; *J. Am. Med. Assoc.* **2002**, *287,* 1132-1141.
180. Pope, C.A.; III; Burnett, R.T.; Thurston, G.D.; Thun, M.J.; Calle, E.E.; Krewski, D.; Godleski, J.J. Cardiovascular Mortality and Long-Term Exposure to Particulate Air Pollution: Epidemiological Evidence of General Pathophysiological Pathways of Disease; *Circulation* **2004**, *109,* 71-77.
181. Jerrett, M.; Burnett, R.T.; Ma, R.; Pope, C.A., III; Krewski, D.; Newbold, K.B.; Thurston, G.; Shi, Y.; Finkelstein, N.; Calle, E.E.; Thun, M.J. Spatial Analysis of Air Pollution and Mortality in Los Angeles; *Epidemiol.* **2005**, *16,* 727-736.
182. Jerrett, M.; Burnett, R.T.; Willis, A.; Krewski, D.; Goldberg, M.S.; DeLuca, P.; Finkelstein, N. Spatial Analysis of the Air Pollution-Mortality Relationship in the Context of Ecologic Confounders; *J. Toxicol. Environ. Health* **2003**, *66,* 1735-1777.

183. Jerrett, M.; Finkelstein, M. Geographies of Risk in Studies Linking Chrionic Air Pollution Exposure to Health Outcomes. *J. Toxicol. Environ. Health A* **2005,** *68,* 13-14, 1207-1242.
184. Laden, F.; Schwartz, J.; Speizer, F.E.; Dockery, D.W. Reduction in Fine Particulate Air Pollution and Mortality: Extended Follow-Up of the Harvard Six Cities Study. *Am. J. Respir. Crit. Care Med.* **2006,** *173,* 667-672.
185. Woodruff, T.J.; Grillo, J.; Schoendorf, K.C. The Relationship between Selected Causes of Postneonatal Infant Mortality and Particulate Air Pollution in the United States; *Environ. Health Perspect.* **1997**, *105,* 608-612.
186. Woodruff, T.J.; Parker, J.D.; Schoendorf, K.C. Fine Particulate Matter ($PM_{2.5}$) Air Pollution and Selected Causes of Postneonatal Infant Mortality in California. *Environ. Health Perspect.* **2006**, *114,* 786-790.
187. Abbey, D.E.; Nishino, N.; McDonnell, W.F.; Burchette, R.J.; Knusten, S.F.; Beeson, W.L.; Yang, J.X. Long-Term Inhalable Particles and Other Air Pollutants Related to Mortality in Nonsmokers; *Am. J. Respir. Crit. Care Med.* **1999**, *159,* 373-382.
188. McDonnell, W.F.; Nishino-Ishikawa, N.; Petersen, F.F.; Chen, L.H.; Abbey, D.E. Relationships of Mortality with the Fine and Coarse Fraction of Long-Term Ambient PM_{10} Concentrations in Nonsmokers; *J. Expo. Anal. Environ. Epidemiol.* **2000**, *10,* 427-436.
189. Chen, L.H.; Knutsen, S.F.; Shavlik, D.; Beeson, W.L.; Petersen, F.; Ghamsary, M.; Abbey, D. The Association between Fatal Coronary Heart Disease and Ambient Particulate Air Pollution: Are Females at Greater Risk?; *Environ. Health Perspect.* **2005**, *113,* 1723-1729.
190. Miller, K.A.; Siscovick, D.S.; Sheppard, L.; Shepherd, K.; Anderson, G.; Kaufman, J.D. Air Pollution and Cardiovascular Disease Events in the Women's Health Initiative Observational (WHI-OS) Study. *Circulation* **2004**, 109, e71. (Abstract form the American Heart Association Conference on Cardiovascular Disease Epidemiology and Prevention. Full report currently in review).
191. Lipfert, F.W.; Perry, H.M., Jr.; Miller, J.P.; Baty, J.D.; Wyzga, R.E.; Carmody, S.E. The Washington University-EPRI Veterans' Cohort Mortality Study: Preliminary Results; *Inhal. Toxicol.* **2000**, *12,* 41-73.
192. Lipfert, F.W.; Perry, H.M., Jr.; Miller, J.P.; Baty, J.D.; Wyzga, R.E.; Carmody, S.E. Air Pollution, Blood Pressure, and Their Long-Term Associations with Mortality; *Inhal. Toxicol.* **2003**, *15,* 493-512.
193. Lipfert, F.W.; Wyzga, R.E.; Baty, J.D.; Miller, J.P. Traffic Density as a Surrogate Measure of Environmental Exposures in Studies of Air Pollution Health Effects: Long-Term Mortality in a Cohort of US Veterans; *Atmos. Environ.* **2006**, *40,* 154-169.
194. Enstrom, J.E. Fine Particulate Air Pollution and Total Mortality Among Elderly Californians, 1973–2002; *Inhal. Toxicol.* **2005**, *17,* 803-816.
195. Hoek, G.; Brunekreef, B.; Goldhohm, S.; Fischer, P.; van den Brandt, P.A. Association between Mortality and Indicators of Traffic-Related Air Pollution in the Netherlands: A Cohort Study; *Lancet* **2002**, *360,* 1203-1209.
196. Hill, A.S.G. Measurement of the Optical Densities of Smokestains of Filter Papers; *Trans. Faraday Soc.* **1936**, *32,* 1125-1131.
197. Finkelstein, M.M.; Jerrett, M.; Sears, M.R. Traffic Air Pollution and Mortality Rate Advancements Periods; *Am. J. Epidemiol.* **2004**, *160,* 173-177.
198. Filleul, L.; Rondeau, V.; Vandentorren, S.; Le Moual, N.; Cantagrel, A.; Annesi-Maesano, I.; Charpin, D.; Declercq, C.; Neukirch, F.; Paris, C.; Vervloet, D.; Brochard, P.; Tessier, J.F.; Kauffmann, F.; Baldi, I. Twenty-Five Year Mortality and Air Pollution: Results from the French PAARC Survey; *Occup. Environ. Med.* **2005**, *62,* 453-460.
199. Nafstad, P.; Håheim, L.L.; Wisløff, T.; Gram, F.; Oftedal, B.; Holme, I.; Hjermann, I.; Leren, P. Urban Air Pollution and Mortality in a Cohort of Norwegian Men; *Environ. Health Perspect.* **2004**, *112,* 610-615.
200. Goss, C.H.; Newsom, S.A.; Schildcrout, J.S.; Sheppard, L.; Kaufman, J.D. Effect of Ambient Air Pollution on Pulmonary Exacerbations and Lung Function in Cystic Fibrosis; *Am. J. Repir. Crit. Care Med.* **2004**, *169,* 816-821.
201. Röösli, M.; Künzli, N.; Braun-Fahrländer, C.; Egger, M. Years of Life Lost Attributed to Air Pollution in Switzerland: Dynamic Exposure-Response Model. *Inter. J. Epidemiol.* 2005; **34**, 1029-1035.
202. Pope, C.A., III. Particulate Pollution and Health: A Review of the Utah Valley Experience; *J. Expo. Analys. Environ. Epidemiol.* **1996**, *6,* 23-34.
203. Clancy, L.; Goodman, P.; Sinclair, H.; Dockery, D.W. Effect of Air-Pollution Control on Death Rates in Dublin, Ireland: An Intervention Study; *Lancet* **2002**, *360,* 1210-1214.
204. Zeger, S.L.; Dominici, F.; Samet, J. Harvesting-Resistant Estimates of Air Pollution Effects on Mortality; *Epidemiol.* **1999**, *10,* 171-175.
205. Kelsall, J.; Zeger, S.; Samet, J. Frequency Domain Log-Linear Models: Air Pollution and Mortality; *Appl. Stat.* **1999**, *48,* 331-344.
206. Dominici, F.; McDermott, A.; Zeger, S.L.; Samet, J.M. Airborne Particulate Matter and Mortality: Timescale Effects in Four U.S. Cities; *Am. J. Epidemiol.* **2003**, *157,* 1055-1065.
207. Schwartz, J. Is There Harvesting in the Association of Airborn Particles with Daily Deaths and Hospital Admissions?; *Epidemiol.* **2001**, *12,* 55-61.
208. Schwartz, J. Harvesting and Long Term Exposure Effects in the Relation between Air Pollution and Mortality; *Am. J. Epidemiol.* **2000**, *151,* 440-448.
209. Schwartz, J. Daily Deaths Associated with Air Pollution in Six U.S. Cities and Short-Term Mortality Displacement in Boston. In *Revised Analyses of Time-Series of Air Pollution and Health. Special Report*; Health Effects Institute: Boston, MA, 2003; pp 219-226.
210. Almon, S. The Distributed Lag between Capital Appropriations and Expenditures; *Econometrica* **1965**, *33,* 178-196.
211. Greene, W.H. *Econometric Analysis*, 5th ed.; Prentice Hall: New York, NY, 2003.
212. Pope, C.A., III; Schwartz, J. Time Series for the Analysis of Pulmonary Health Data; *Am. J. Respir. Crit. Care Med.* **1996,** *154,* S229-S233.
213. Schwartz, J. The Distributed Lag between Air Pollution and Daily Deaths; *Epidemiol.* **2000**, *11,* 320-326.
214. Braga, A.L.F., Zanobetti, A.; Schwartz, J. The Lag Structure between Particulate Air Pollution and Respiratory and Cardiovascular Deaths in 10 U.S. Cities; *J. Occup. Environ. Med.* **2001**, *43,* 927-933.
215. Zanobetti, A.; Schwartz, J.; Samoli, E.; Gryparis, A.; Touloumi, G.; Atkinson, R.; Le Tertre, A.; Bobros, J.; Celko, M.; Goren, A.; Forsberg, B.; Michelozzi, P.; Rabczenko, D.; Ruiz, E.A.; Katsouyanni, K. The Temporal Pattern of Mortality Responses to Air Pollution: A Multicity Assessment of Mortality Displacement; *Epidemiol.* **2002**, *13,* 87-93.
216. Zanobetti, A.; Schwartz, J.; Samoli, E.; Gryparis, A.; Touloumi, G.; Peacock, J.; Anderson, R.H.; Le Tertre, A.; Bobros, J.; Celko, M.; Goren, A.; Forsberg, B.; Michelozzi, P.; Rabczenko, D.; Hoyos, S.P.; Wichmann, H.E.; Katsouyanni, K. The Temporal Pattern of Respiratory and Heart Disease Mortality in Response to Air Pollution; *Environ. Health Perspect.* **2003**, *111,* 1188-1193.
217. Goodman, P.G.; Dockery, D.W.; Clancy, L. Cause-Specific Mortality and the Extended Effects of Particulate Pollution and Temperature Exposure; *Environ. Health Perspect.* **2004**, *112,* 179-185.
218. Pope, C.A., III. Invited Commentary: Particulate Matter-Mortality Exposure-Response Relations and Threshold; *Am. J. Epidemiol.* **2000**, *152,* 407-412.
219. Cakmak, S.; Burnett, R.T.; Krewski, D. Methods for Detecting and Estimating Population Threshold Concentrations for Air Pollution-Related Mortality with Exposure Measurement Error; *Risk Anal.* **1999**, *19,* 487-496.
220. Xu, Z.; Yu, D.; Jing, L.; Xu, X. Air Pollution and Daily Mortality in Shenyang, China; *Arch. Environ. Health* **2000**, *47,* 115-120.
221. Schwartz, J.; Zanobetti, A. Using Meta-Smoothing to Estimate Dose-Response Trends across Multiple Studies, with Application to Air Pollution and Daily Death; *Epidemiol.* **2000**, *11,* 666-672.
222. Schwartz, J.; Ballester, F.; Saez, M.; Pérez-Hoyos, S.; Bellido, J.; Cambra, K.; Arribas, F.; Cañada, A.; Pérez-Boillos, M.J.; Sunyer, J. The Concentration-Response Relation between Air Pollution and Daily Deaths; *Environ. Health Perspect.* **2001**, *109,* 1001-1006.
223. Daniels, M.J.; Dominici, F.; Samet, J.M.; Zeger, S.L. Estimating Particulate Matter-Mortality Dose-Response Curves and Threshold Levels: An Analysis of Daily Time-Series for the 20 Largest U.S. Cities; *Am. J. Epidemiol.* **2000**, *152,* 397-406.
224. Dominici, F.; Daniels, M.; McDermott, A.; Zeger, S.L.; Samet, J. Shape of the Exposure-Response Relation and Mortality Displacement in the NMMAPS Database. In *Revised Analyses of Time-Series of Air Pollution and Health. Special Report*; Health Effects Institute: Boston, MA, 2003; pp 91-96.
225. Dominici, F.; Daniels, M.; Zeger, S.L.; Samet, J. Air Pollution and Mortality: Estimating Regional and National Dose-Response Relationships; *J. Am. Stat. Assoc.* **2002**, *97,* 100-111.
226. Dominici, F.; Daniels, M.; McDermott, A.; Zeger, S.L.; Samet, J. Mortality among Residents of 90 Cities. In *Revised Analyses of Time-Series of Air Pollution and Health. Special Report*; Health Effects Institute: Boston, MA, 2003; pp 9-24.
227. Samoli, E.; Antonis, A.; Touloumi, G.; Schwartz, J.; Anderson, H.R.; Sunyer, J.; Bisanti, L.; Zmirou, D.; Vonk, J.M.; Pekkanen, J.; Goodman, P.; Paldy, A.; Schindler, C.; Katsouyanni, K. Estimating the Exposure-Response Relationships between Particulate Matter and Mortality within the APHEA Multicity Project; *Environ. Health. Perspect.* **2005**, *113,* 88-95.
228. National Center for Health Statistics. *Vital Statistics of the United States, 1980, Volume II, Annual Mortality, Part B*; U.S. Government Printing Office: Washington, DC, 1985.
229. U.S. Bureau of the Census. *1980 Census of Population*; U.S. Department of Commerce: Washington, DC, 1983.
230. Cohen, A.J.; Anderson, H.R.; Ostro, B.; Pandey, K.D.; Krzyzanowski, M.; Künzli, N.; Gutschmidt, K.; Pope, C.A., III; Romieu, I.; Samet, J.M.; Smith, K.R. Urban Air Pollution. In *Comparative Quantification of Health Risks: Global and Regional Burden of Disease Attributable to Selected Major Risk Favors, Vol. 2;* Ezzati, M.; Lopez, A.D.; Rodgers, A.; Murray, C.J.L., Eds.; World Health Organization: Geneva, Switzerland, 2004; pp 1353–1433.
231. Gauderman, W.J.; Avol, E.; Gilliland, F.; Vora, H.; Thomas, D.; Berhane, K.; McConnell, R.; Kuenzli, N.; Lurmann, F.; Rappaport, E.; Margolis, H.; Bates, D.; Peters, J. The Effect of Air Pollution on Lung

Development from 10 to 18 Years of Age; *N. Engl. J. Med.* **2004**, *351,* 1057-1067.
232. Pope, C.A., III. Air Pollution and Health—Good News and Bad; *N. Engl. J. Med.* **2004**, *351,* 1132-1134.
233. Burnett, R.T.; Dales, R.; Krewski, D.; Vincent, R.; Dann, T.; Brook, J.R. Associations between Ambient Particulate Sulfate and Admissions to Ontario Hospitals for Cardiac and Respiratory Diseases; *Am. J. Epidemiol.* **1995**, *142,* 15-22.
234. Schwartz, J.; Morris, R. Air Pollution and Hospital Admissions for Cardiovascular Disease in Detroit, Michigan; *Am. J. Epidemiol.* **1995**, *142,* 23-35.
235. Pantazopoulou, A.; Katsouyanni, K.; Kourea-Kremastinou, J.; Trichopoulos, D. Short-Term Effects of Air Pollution on Hospital Emergency Outpatient Visits and Admissions in the Greater Athens, Greece Area; *Environ. Res.* **1995**, *69,* 31-36.
236. Poloniecki, J.D.; Atkinson, R.W.; Ponce de Leon, A.; Anderson, H.R. Daily Time Series for Cardiovascular Hospital Admissions and Previous Day's Air Pollution in London, UK; *Occup. Environ. Med.* **1997**, *54,* 535-540.
237. Schwartz, J. Health Effects of Air Pollution from Traffic: Ozone and Particulate Matter. In *Health at the Crossroads: Transport Policy and Urban Health*; Fletcher, T.; McMichael, A.J., Eds.; John Wiley and Sons: West Sussex, U.K., 1997; pp 61-81.
238. Stone, P.H.; Godleski, J.J. First Steps toward Understanding the Pathophysiologic Link between Air Pollution and Cardiac Mortality; *Am. Heart J.* **1999**, *138,* 804-807.
239. Glantz, S.A. Air Pollution as a Cause of Heart Disease: Time for Action; *J. Am. Coll. Card.* **2002**, *39,* 943-945.
240. Verrier, R.L.; Mittleman, M.A.; Stone, P.H. Air Pollution: An Insidious and Pervasive Component of Cardiac Risk; *Circulation* **2002**, *106,* 890-892.
241. Johnson, R.L. Relative Effects of Air Pollution on Lung and Heart; *Circulation* **2004**, *109,* 5-7.
242. Dockery, D.W. Epidemiologic Evidence of Cardiovascular Effects of Particulate Air Pollution; *Environ. Health Perspect.* **2001**, *109,* 483-486.
243. Routledge, H.C.; Ayres, J.G.; Townend, J.N. Why Cardiologists Should Be Interested in Air Pollution; *Heart* **2003**, *89,* 1383-1388.
244. Brook, R.D.; Brook, J.R.; Rajagopalan, S. Air Pollution: The "Heart" of the Problem; *Curr. Hyperten. Rep.* **2003**, *5,* 32-39.
245. Weinhold, B. Environmental Cardiology: Getting to the Heart of the Matter; *Environ. Health Perspect.* **2004**, *112,* 881-887.
246. Bhatnagar, A. Cardiovascular Pathophysiology of Environmental Pollutants; *Am. J. Physiol. Heart Circ. Physiol.* **2004,** *286,* H479-H485.
247. Pope, C.A., III. Air Pollution. In *Coronary Heart Disease Epidemiology: From Aetiology to Public Health*; Marmot, M.; Elliot, P., Eds.; Oxford University Press: Oxford, United Kingdom, 2005; pp 480-494.
248. Schultz, H.; Volker, H.; Ibald-Mulli, A.; Khandoga, A.; Koenig, W.; Kromback, F.; Radykewicz, R.; Stampfl, A.; Thorand, B.; Peters, A. Cardiovascular Effects of Fine and Ultrafine Particles. *J. Aerosol Med.* **2005,** *18,* 1-22.
249. Künzli, N.; Tager, I.B. Air Pollution: From Lung to Heart; *Swiss Med. Wkly.* **2005**, *135,* 697-702.
250. Brook, R.D.; Franklin, B.; Cascio, W.; Hong, Y.; Howard, G.; Lipsett, M.; Luepker, R.; Mittleman, M.; Samet, J.; Smith, S.C., Jr.; Tager, I. Air Pollution and Cardiovascular Disease: A Statement for Healthcare Professionals from the Expert Panel on Population and Prevention Science of the American Heart Association; *Circulation* **2004**, *109,* 2655-2671.
251. Schwartz, J. Air Pollution and Blood Markers of Cardiovascular Risk; *Environ. Health Perspect.* **2001**, *109,* 405-409.
252. Souza, M.B.; Saldiva, P.H.N., Pope, C.A., III; Capelozzi, V.L. Respiratory Changes Due to Long-Term Exposure to Urban Levels of Air Pollution: A Histopatholigic Study in Humans; *Chest* **1998**, *113,* 1312-1318.
253. Künzli, N.; Jerret, M.; Mack, W.J.; Beckerman, B;. LaBree, L.; Gilliland, F.; Thomas, D.; Peters, J.; Hodis, H.N. Ambient Air Pollution and Atherosclerosis in Los Angeles; *Environ. Health Perspect.* **2005**, *113,* 201-206.
254. Hong, Y.-C.; Lee, J.-T.; Kim, H.; Kwon, H.-J. Air Pollution: A New Risk Factor in Ischemic Stroke Mortality; *Stroke* **2002**, *33,* 2165-2169.
255. Hong, Y.-C.; Lee, J.-T.; Kim, H.; Ha, E.-H.; Schwarz, J.; Christiani, D.C. Effects of Air Pollutants on Acute Stroke Mortality; *Environ. Health Perspect.* **2002**, *110,* 187-191.
256. Kan, H.; Jia, J.; Chen, B. Acute Stroke Mortality and Air Pollution: New Evidence from Shanghai, China; *J. Occup. Health* **2003**, *45,* 321-323.
257. Tsai, S.-S.; Goggins, W.B.; Chiu, H.-F.; Yang, C.-Y. Evidence for and Association between Air Pollution and Daily Stroke Admissions in Kaohsiung, Taiwan. *Stroke* **2003**, *34*, 2612.
258. Wellenius, G.A.; Schwartz, J.; Mittleman, M.A. Air Pollution and Hospital Admissions for Ischemic and Hemorrhagic Stroke among Medicare Beneficiaries; *Stroke* **2005**, *36,* 2549-2553.
259. Peters, A.; Dockery, D.W.; Muller, J.E.; Mittleman, M.A. Increased Particulate Air Pollution and the Triggering of Myocardial Infarction; *Circulation* **2001**, *103,* 2810-2815.
260. Peters, A.; von Klot, S.; Heier, M.; Trentinaglia, I.; Hörmann, A.; Wichmann, E.; Löwel, H. Exposure to Traffic and the Onset of Myocardial Infarction; *N. Engl. J. Med.* **2004**, *351,* 1721-30.
261. D'Ippoliti, D.; Forastiere, F.; Ancona, C.; Agabiti, N.; Fusco, D.; Michelozzi, P.; Perucci, C.A. Air Pollution and Myocardial Infarction in Rome: A Case-Crossover Analysis; *Epidemiol.* **2003**, *14,* 528-535.
262. Sullivan, J.; Sheppard, L.; Schreuder, A.; Ishikawa, N.; Siscovick, D.; Kaufman, J. Relation between Short-Term Fine-Particle Matter Exposure and Onset of Myocardial Infarction; *Epidemiol.* **2005**, *16,* 41-48.
263. Zanobetti, A.; Schwartz, J. The Effect of Particulate Air Pollution on Emergency Admissions for Myocardial Infarction: A Multicity Case-Crossover Analysis; *Environ. Health Perspect.* **2005**, *113,* 978-982.
264. von Klot, S.; Peters, A.; Aalto, P.; Bellander, T.; Berglind, N;. D'Ippoliti, D.; Elosua, R.; Hörmann, A.; Kulmala, M.; Lanki, T.; Löwel, H.; Pekkanen, J.; Picciotto, S.; Sunyer, J.; Forastiere, F. Ambient Air Pollution Is Associated with Increased Risk of Hospital Cardiac Readmissions of Myocardial Infarction Survivors in Five European Cities; *Circulation* **2005**, *112,* 3073-3079.
265. Pope, C.A.; III; Dockery, D.W.; Kanner, R.E.; Villegas, G.M.; Schwartz, J. Oxygen Saturation, Pulse Rate, and Particulate Air Pollution; *Am. J. Respir. Crit. Care Med.* **1999**, *159,* 365-372.
266. DeMeo, D.L.; Zanobetti, A.; Litonjua, A.A.; Coull, B.A.; Schwartz, J.; Gold, D.R. Ambient Air Pollution and Oxygen Saturation; *Am. J. Respir. Crit. Care Med.* **2004**, *170,* 383-387.
267. Gong, H., Jr.; Linn, W.S.; Clark, K.W.; Anderson, K.R.; Geller, M.D.; Sioutas, C. Respiratory Responses to Exposures with Fine Particulates and Nitrogen Dioxide in the Elderly with and without COPD; *Inhal. Toxicol.* **2005**, *17,* 123-132.
268. Peters, A.; Liu, E.; Verrier, R.L.; Schwartz, J.; Gold, D.R.; Mittleman, M.; Baliff, J.; Oh, J.A.; Allen, G.; Monahan, K.; Dockery, D.W. Air Pollution and Incidence of Cardiac Arrhythmia; *Epidemiol.* **2000**, *11,* 11-17.
269. Levy, D.; Sheppard, L.; Checkoway, H.; Kaufman, J.; Lumley, T.; Koenig, J.; Siscovick, D. A Case-Crossover Analysis of Particulate Matter Air Pollution and Out-of-Hospital Primary Cardiac Arrest; *Epidemiol.* **2001**, *12,* 193-199.
270. Sullivan, J.; Ishikawa, N.; Sheppard, L.; Siscovick, D.; Checkoway, H.; Kaufman, J. Exposure to Ambient Fine Particulate Matter and Primary Cardiac Arrest Among Persons with and without Clinically Recognized Heart Disease; *Am. J. Epidemiol.* **2003**, *157,* 501-509.
271. Vedal, S.; Rich, K.; Brauer, M.; White, R.; Petkau, J. Air Pollution and Cardiac Arrhythmias in Patients with Implantable Cardioverter Defibrillators; *Inhal. Tox.* **2004**, *16,* 353-362.
272. Rich, K.E.; Petkau, J.; Vedal, S.; Brauer, M. A Case-Crossover Analysis of Particulate Air Pollution and Cardiac Arrhythmia in Patients with Implantable Cardioverter Defibrillators; *Inhal. Toxicol.* **2004**, *16,* 363-372.
273. Dockery, D.W.; Luttmann-Gibson, H.; Rich, D.Q.; Link, M.S.; Mittleman, M.A.; Gold, D.R.; Koutrakis, P.; Schwartz, J.D.; Verrier, R.L. Association of Air Pollution with Increased Incidence of Ventricular Tachyarrhythmias Recorded by Implanted Cardioverter Defibrillators; *Environ. Health Perspect.* **2005**, *113,* 670-674.
274. Forastiere, F.; Strafoggia, M.; Piccioto, S.; Bellander, T;. D'Ippoliti, D.; Lanki, T.; von Klot, S.; Nyberg, F.; Paatero, P.; Peters, A.; Pekkanen, J.; Sunyer, J.; Perucci, C.A. A Case-Crossover Analysis of Out-of-Hospital Coronary Deaths and Air Pollution in Rome, Italy; *Am. J. Respir. Crit. Care Med.* **2005**, *172,* 1549-1555.
275. Pekkanen, J.; Peters, A.; Hoek, G.; Tiittanen, P.; Brunekreef, B.; de Hartog, J.; Heinrich, J.; Ibald-Mulli, A.; Kreyling, W.G.; Lanki, T.; Timonen, K.L.; Vanninen, E. Particulate Air Pollution and Risk of ST-Segment Depression during Repeated Submaximal Exercise Tests among Subjects with Coronary Heart Disease. *Circulation* **2002**, *106*, 933-938.
276. Gold, D.R.; Litonjua, A.A.; Zanobetti, A.; Coull, B.A.; Schwartz, J.; MacCallum, G.; Verrier, R.L.; Nearing, B.D.; Canner, M.J.; Suh, H.; Stone, P.H. Air Pollution and St-Segment Depression in Elderly Subjects; *Environ. Health Perspect.* **2005**, *113,* 883-887.
277. Henneberger, A.; Zareba, W.; Ibald-Mulli, A.; Rückerl, R.; Cyrys, J.; Couderc, J.-P.; Mykins, B.; Woelke, G.; Wichmann, H.-E.; Peters, A. Repolarization Changes Induced by Air Pollution in Ischemic Heart Disease Patients; *Environ. Health Perspect.* **2005**, *113,* 440-446.
278. Ibald-Mulli, A.; Stieber, J.; Wichmann, H.-E.; Koenig, W.; Peters, A. Effects of Air Pollution on Blood Pressure: A Population-Based Approach; *Am. J. Pub. Health* **2001**, *91,* 571-577.
279. Linn, W.S.; Gong, H. Air Pollution, Weather Stress, and Blood Pressure; *Am. J. Public Health* **2001**, *91,* 711-716.
280. Brook, R.D.; Brook, J.R.; Urch, B.; Vincent, R.; Rajagopalan, S.; Silverman, F. Inhalation of Fine Particles Air Pollution and Ozone Causes Acute Arterial Vasoconstriction in Healthy Adults; *Circulation* **2002**, *105,* 1534-1536.
281. Zanobetti, A.; Canner, M.J.; Stone, P.H.; Schwartz, J.; Sher, D.; Eagan-Bengston, E.; Gates, K.A.; Hartley, L.H.; Suh, H.; Gold, D.R. Ambient

Pollution and Blood Pressure in Cardiac Rehabilitation Patients; *Circulation* **2004**, *110,* 2184-2189.
282. Urch, B.; Brook, J.R.; Wasserstein, D.; Brook, R.D.; Rajagopalan, S.; Corey, P.; Silverman, F. Relative Contributions of $PM_{2.5}$ Chemical Constituents to Acute Arterial Vasoconstriction in Humans; *Inhal. Toxicol.* **2004**, *16,* 345-352.
283. Urch, B.; Silverman, F.; Corey, P.; Brook, J.R.; Lukic, K.Z.; Rajagopalan, S.; Brook, R.D. Acute Blood Pressure Responses in Healthy Adults during Controlled Air Pollution Exposures; *Environ. Health Perspect.* **2005**, *113,* 1052-1055.
284. O'Neill, M.S.; Veves, A.; Zanobetti, A.; Sarnat, J.A.; Gold, D.R.; Economides, P.A.; Horton, E.S.; Schwartz, J. Diabetes Enhances Vulnerability to Particulate Air Pollution-Associated Impairment in Vascular Reactivity and Endothelial Function; *Circulation* **2005**, *111,* 2913-2920.
285. Schwartz, J. Air Pollution and Hospital Admissions for Heart Disease in Eight U.S. Counties; *Epidemiol.* **1999**, *10,* 17-22.
286. Zanobetti, A.; Schwartz, J.; Dockery, D.W. Airborne Particles Are a Risk Factor for Hospital Admissions for Heart and Lung Disease; *Environ. Health Perspect.* **2000**, *108,* 1071-1077.
287. Samet, J.M.; Zeger, S.L.; Dominici, F.; Curriero, F.; Coursac, I.; Dockery, D.W.; Schwartz, J.; Zanobetti, A. The National Morbidity, Mortality, and Air Pollution Study. Part II: Morbidity and Mortality from Air Pollution in the United States; *Res. Rep. Health Eff. Inst.* **2000**, 94 (Part 2), 5-70.
288. Schwartz, J.; Zanobetti, A.; Bateson, T. Morbidity and Mortality Among Elderly Residents of Cities with Daily PM Measurements. In *Revised Analyses of Time-Series Studies of Air Pollution and Health. Special Report*; Health Effects Institute: Boston, MA, 2003; pp 25–58.
289. Le Tertre, A.; Medina, S.; Samoli, E.; Forsberg, B.; Michelozzi, P.; Boumghar, A.; Vonk, J.M.; Bellini, A.; Atkinson, R.; Ayres, J.G.; Sunyer, J.; Schwartz, J.; Katsouyanni, K. Short-Term Effects of Particulate Air Pollution on Cardiovascular Diseases in Eight European Cities; *J. Epidemiol. Comm. Health* **2002**, *56,* 773-779.
290. Dominici, F.; Peng, R.D.; Bell, M.L.; Pham, L;. McDermott, A.; Zeger, S.L.; Samet, J.M. Fine Particulate Air Pollution and Hospital Admission for Cardiovascular and Respiratory Disease; *J. Am. Med. Assoc.* **2006**, *295,* 1127-1134.
291. Dockery, D.W.; Pope, C.A., III; Kanner, R.E.; Villegas, G.M.; Schwartz, J. Daily Changes in Oxygen Saturation and Pulse Rate Associated with Particulate Air Pollution and Barometric Pressure. Research Report 83. Health Effects Institute: Cambridge, MA, 1999.
292. Peters, A.; Perz, S.; Döring, A.; Stieber, J.; Koenig, W.; Wichmann, H.-E. Increases in Heart Rate during an Air Pollution Episode; *Am. J. Epidemiol.* **1999**, *150,* 1094-1098.
293. Peters, A.; Perz, S.; Döring, A.; Stieber, J.; Koenig, W.; Wichmann, H.-E. Activation of the Autonomic Nervous System and Blood Coagulation in Association with an Air Pollution Episode; *Inhal. Toxicol.* **2000**, *12,* 51-61.
294. Liao, D.; Creason, J.; Shy, C.; Williams, R.; Watts, R.; Zweidinger, R. Daily Variation of Particulate Air Pollution and Poor Cardiac Autonomic Control in the Elderly; *Environ. Health Perspect.* **1999**, *107,* 521-525.
295. Pope, C.A.; III; Verrier, R.L.; Lovett, E.G.; Larson, A.C.; Raizenne, M.E.; Kanner, R.E.; Schwartz, J.; Villegas, G.M.; Gold, D.R.; Dockery, D.W. Heart Rate Variability Associated with Particulate Air Pollution; *Am. Heart J.* **1999**, *138,* 890-899.
296. Gold, D.R.; Litonjua, A.; Schwartz, J.; Lovett, E.; Larson, A.; Nearing, B.; Allen, G.; Verrier, M.; Cherry, R.; Verrier, R. Ambient Pollution and Heart Rate Variability; *Circulation* **2000**, *101,* 1267-1273.
297. Pope, C.A.; III; Eatough, D.J.; Gold, D.R.; Pang, Y.; Nielsen, K.R.; Nath, P.; Verrier, R.L.; Kanner, R.E. Acute Exposure to Environmental Tobacco Smoke and Heart Rate Variability; *Environ. Health Perspect.* **2001**, *109,* 711-716.
298. Creason, J.; Neas, L;. Walsh, D.; Williams, R.; Sheldon, L.; Liao, D.; Shy, C. Particulate Matter and Heart Rate Variability among Elderly Retirees: The Baltimore 1998 PM Study; *J. Expos. Anal. Environ. Epidemiol.* **2001**, *11,* 116-122.
299. Magari, S.R.; Hauser, R.; Schwartz, J.; Williams, P.L.; Smith, T.J.; Christiani, D.C. Association of Heart Rate Variability with Occupational and Environmental Exposure to Particulate Air Pollution; *Circulation* **2001**, *104,* 986-991.
300. Magari, S.R.; Schwartz, J.; Williams, P.L.; Hauser, R.; Smith, T.J.; Christiani, D.C. The Association between Personal Measurements of Environmental Exposure to Particulates and Heart Rate Variability; *Epidemiol.* **2002**, *13,* 305-310.
301. Devlin, R.B.; Ghio, A.J.; Kehrl, H.; Sanders, G.; Cascio, W. Elderly Humans Exposed to Concentrated Air Pollution Particles Have Decreased Heart Rate Variability. *Eur. Respir. J.* **2003,** *21*(Suppl. 40), 76s-80s.
302. Holguín, F.; Téllez-Rojo, M.M.; Hernández, M.; Cortez, M.; Chow, J.C.; Watson, J.G.; Mannino, D.; Romieu, I. Air Pollution and Heart Rate Variability among the Elderly in Mexico City; *Epidemiol.* **2003**, *14,* 521-527.
303. Chan, C.-C.; Chuang, K.-J.; Shiao, G.-M.; Lin, L.-Y. Personal Exposure to Submicrometer Particles and Heart Rate Variability in Human Subjects; *Environ. Health Perspect.* **2004**, *112,* 1063-1067.
304. Riediker, M.; Cascio, W.E.; Griggs, T.R.; Herbst, M.C.; Bromberg, P.A.; Neas, L.; Williams, R.W.; Devlin, R.B. Particulate Matter Exposure in Cars Is Associated with Cardiovascular Effects in Healthy Young Men; *Am. J. Respir. Crit. Care Med.* **2004**, *169,* 934-940.
305. Pope, C.A.; III; Hansen, M.L.; Long, R.W.; Nielsen, K.R.; Eatough, N.L.; Wilson, W.E.; Eatough, D.J. Ambient Particulate Air Pollution, Heart Rate Variability, and Blood Markers of Inflammation in a Panel of Elderly Subjects; *Environ. Health Perspect.* **2004**, *112,* 339-345.
306. Liao, D.; Duan, Y.; Whitsel, E.A.; Zheng, Z.-J.; Heiss, G.; Chinchilli, V.M.; Lin, H.-M. Association of Higher Levels of Ambient Criteria Pollutants with Impaired Cardiac Autonomic Control: A Population-Based Study; *Am. J. Epidemiol.* **2004**, *159,* 768-777.
307. Park, S.K.; O'Neill, M.S.; Vokonas, P.S.; Sparrow, D.; Schwartz, J. Effects of Air Pollution on Heart Rate Variability: The VA Normative Aging Study; *Environ. Health Perspect.* **2005**, *113,* 304-309.
308. Schwartz, J.; Park, S.K;. O'Neill, M.S.; Vokonas, P.S.; Sparrow, D.; Weiss, S.; Kelsey, K. Glutathione-S-Transferase M1, Obesity, Statins, and Autonomic Effects of Particles; *Am. J. Respir. Crit. Care Med.* **2005**, *172,* 1529-1533.
309. Romieu, I.; Téllez-Rojo, M.M.; Lazo, M.; Manzano-Patiño, A.; Cortez-Lugo, M.; Julien, P.; Bélanger, M.C.; Hernandez-Avila, M.; Holguin, F. Omega-3 Fatty Acid Prevents Heart Rate Variability Reductions Associated with Particulate Matter; *Am. J. Respir. Crit. Care Med.* **2005**, *172,* 1534-1540.
310. Chuang, K.-J.; Chan, C.-C.; Chen, N.-T.; Su, T.-C.; Lin, L.-Y. Effects of Particle Size Fractions on Reducing Heart Rate Variability in Cardiac and Hypertensive Patients; *Environ. Health Perspect.* **2005**, *113,* 1693-1697.
311. Peters, A.; Döring, A.; Wichmann, H.-E.; Koenig, W. Increased Plasma Viscosity during an Air Pollution Episode: A Link to Mortality?; *Lancet* **1997**, *349,* 1582-1587.
312. Peters, A.; Fröhlich, M.; Döring, A.; Immervoll, T.; Wichmann, H.-E.; Hutchinson, W.L.; Pepys, M.B.; Koenig, W. Particulate Air Pollution Is Associated with an Acute Phase Response in Men; *Euro. Heart J.* **2001**, *22,* 1198-1204.
313. Seaton, A.; Soutar, A.; Crawford, V.; Elton, R.; McNerlan, S.; Cherrie, J.; Watt, M.; Agius, R.; Stout, R. Particulate Air Pollution and the Blood; *Thorax* **1999**, *54,* 1027-1032.
314. Tan, W.C.; Qiu, D.; Liam, B.L.; Ng, T.P.; Lee, S.H.; van Eeden, S.F.; D'Yachkova, Y.; Hogg, J.C. The Human Bone Marrow Response to Acute Air Pollution Caused by Forest Fires; *Am. J. Respir. Crit. Care Med.* **2000**, *161,* 1213-1217.
315. Salvi, S.; Blomberg, A.; Rudell, B.; Kelly, F.; Sandström, T.; Holgate, S.T.; Frew, A. Acute Inflammatory Responses in the Airways and Peripheral Blood after Short-Term Exposure to Diesel Exhaust in Healthy Human Volunteers; *Am. J. Repir. Crit. Care Med.* **1999**, *159,* 702-709.
316. Salvi, S.S.; Nordenhall, C.; Blomberg, A.; Rudell, B.; Pourazar, J.; Kelly, F.J.; Wilson, S.; Sandström, T.; Holgate, S.T.; Frew, A.J. Acute Exposure to Diesel Exhaust Increases IL-8 and GRO-α Production in Healthy Human Airways; *Am. J. Respir. Crit. Care Med.* **2000**, *161,* 550-557.
317. Pekkanen, J.; Brunner, E.J.; Anderson, H.R.; Tiittanen, P.; Atkinson, R.W. Daily Concentrations of Air Pollution and Plasma Fibrinogen in London; *Occup. Environ. Med.* **2000**, *57,* 818-822.
318. Ghio, A.J.; Kim, C.; Devlin, R.B. Concentrated Ambient Air Particles Induce Mild Pulmonary Inflammation in Healthy Human Volunteers; *Am. J. Respir. Crit. Care Med.* **2000**, *162,* 981-988.
319. Harder, S.D.; Soukup, J.M.; Ghio, A.J.; Devlin, R.B.; Becker, S. Inhalation of $PM_{2.5}$ Does Not Modulate Host Defense or Immune Parameters in Blood or Lung of Normal Human Subjects; *Environ. Health Perspect.* **2001**, *109*(Suppl. 4), 599-604.
320. Gong, H., Jr.; Sioutas, C.; Linn, W.S. Controlled Exposures of Healthy and Asthmatic Volunteers to Concentrated Ambient Particles in Metropolitan Los Angeles; *Res. Rep. Health Eff. Inst.* **2003**, *118,* 1-36.
321. Ghio, A.J.; Hall, A.; Bassett, M.A.; Cascio, W.E.; Devlin, R.B. Exposure to Concentrated Ambient Air Particles Alters Hematologic Indices in Humans; *Inhal. Toxicol.* **2003**, *15,* 1465-1478.
322. Huang, Y.-C.T.; Ghio, A.J.; Stonehuerner, J.; McGee, J.; Carter, J.D.; Grambow, S.C.; Devlin, R.B. The Role of Soluble Components in Ambient Fine Particles-Induced Changes in Human Lungs and Blood; *Inhal. Toxicol.* **2003**, *15,* 327-342.
323. Sørensen, M.; Daneshvar, B.; Hansen, M.; Dragsted, L.O.; Hertel, O.; Knudsen, L.; Loft, S. Personal $PM_{2.5}$ Exposure and Markers of Oxidative Stress in Blood; *Environ. Health Perpect.* **2003**, *111,* 161-165.
324. Adamkiewicz, G.; Ebelt, S.; Syring, M.; Slater, J.; Speizer, F.E.; Schwartz, J.; Suh, H.; Gold, D.R. Association between Air Pollution Exposure and Exhaled Nitric Oxide in an Elderly Population; *Thorax* **2004**, *59,* 204-209.
325. Rückerl, R.; Ibald-Mulli, A.; Koenig, W.; Henneberger, A.; Woelke, G.; Cyrys, J.; Heinrich, J.; Marder, V.; Frampton, M.; Wichmann, H.E.;

Peters, A. Air Pollution and Markers of Inflammation and Coagulation in Patients with Coronary Heart Disease; *Am. J. Respir. Crit. Care Med.* **2006**, *173,* 432-441.
326. Godleski, J.J.; Verrier, R.L.; Koutrakis, P.; Catalano, P. *Mechanisms of Morbidity and Mortality from Exposure to Ambient Air Particles. Research Report*; Health Effects Institute: Cambridge, MA, 2000.
327. Donaldson, K.; Stone, V.; Seaton, A.; MacNee, W. Ambient Particle Inhalation and the Cardiovascular System: Potential Mechanisms; *Environ. Health Perspect.* **2001**, *109*(Suppl. 4), 523-527.
328. Frampton, M.W. Systemic and Cardiovascular Effects of Airway Injury and Inflammation: Ultrafine Particle Exposure in Humans; *Environ. Health Perspect.* **2001**, *109*(Suppl. 4), 529-532.
329. Utell, M.J.; Frampton, M.W.; Zareba, W.; Devlin, R.B.; Cascio, W.E. Cardiovascular Effects Associated with Air Pollution: Potential Mechanisms and Methods of Testing; *Inhal. Toxicol.* **2002**, *14,* 1231-1247.
330. Frank, R.; Tankersley, C. Air Pollution and Daily Mortality: A Hypothesis Concerning the Role of Impaired Homeostasis; *Environ. Health Pespect.* **2002**, *110,* 61-65.
331. Kreyling, W.G.; Semmler, M.; Möller, W. Dosimetry and Toxicology of Ultrafine Particles; *J. Aeros. Med.* **2004**, *17,* 140-152.
332. Ghio, A.J.; Gilbey, J.G.; Roggli, V.L.; Richards, J.H.; McGee, J.K.; Carson, J.L.; Devlin, R.B.; Cascio, W.E. Diffuse Alveolar Damage after Exposure to and Oil Fly Ash; *Am. J. Respir. Crit. Care Med.* **2001**, *164,* 1514-1518.
333. Kennedy, T.; Ghio, A.J.; Reed, W.; Samet, J.; Zagorski, J.; Quay, J.; Carter, J.; Dailey, L.; Hoidal, J.R.; Devlin, R.B. Copper-Dependent Inflammation and Nuclear Factor-κB Activation by Particulate Air Pollution; *Am. J. Respir. Cell Mol. Biol.* **1998**, *19,* 366-378.
334. Frampton, M.W.; Ghio, A.J.; Samet, J.M.; Carson, J.L.; Carter, J.D.; Devlin, R.B. Effects of Aqueous Extracts of PM_{10} Filters from the Utah Valley on Human Airway Epithelial Cells; *Am. J. Physiol.* **1999,** *277,* L960-L967.
335. Ghio, A.J.; Stonehuerner, J.; Dailey, L.A.; Carter, J.D. Metals Associated with Both the Water-Soluble and Insoluble Fractions of an Ambient Air Pollution Particle Catalyze an Oxidative Stress; *Inhal. Toxicol.* **1999**, *11,* 37-49.
336. Soukup, J.M.; Ghio, A.J.; Becker, S. Soluble Components of Utah Valley Particulate Pollution Alter Alveolar Macrophage Function in Vivo and in Vitro; *Inhal. Toxicol.* **2000**, *12,* 401-414.
337. Ghio, A.J.; Devlin, R.B. Inflammatory Lung Injury after Bronchial Instillation of Air Pollution Particles; *Am. J. Respir. Crit. Care Med.* **2001**, *164,* 704-708.
338. Beckett, W.S. The Air Pollution Detectives; *Am. J. Respir. Crit. Care Med.* **2001**, *164,* 515-516.
339. Dye, J.A.; Lehmann, J.R.; McGee, J.K.; Winsett, D.W.; Ledbetter, A.D.; Everitt, J.I.; Ghio, A.J.; Costa, D.L. Acute Pulmonary Toxicity of Particulate Matter Filter Extracts in Rats: Coherence with Epidemiologic Studies in Utah Valley Residents; *Environ. Health Perspect.* **2001**, *109*(Suppl. 3), 395-403.
340. Wu, W.; Samet, J.M.; Ghio, A.J.; Devlin, R.B. Activation of the EGF Receptor Signaling Pathway in Airway Epithelial Cells Exposed to Utah Valley PM; *Am. J. Physiol. Lung Cell Mol. Physiol.* **2001**, *281,* L483-L489.
341. Molinelli, A.R.; Madden, M.C.; McGee, J.K.; Stonehuerner, J.G.; Ghio, A.J. Effect of Metal Removal on the Toxicity of Airborne Particulate Matter from the Utah Valley; *Inhal. Toxicol.* **2002**, *14,* 1069-1086.
342. Pagan, I.; Costa, D.L.; McGee, J.K.; Richards, J.H.; Dye, J.A.; Dykstra, M.J. Metals Mimic Airway Epithelial Injury Induced by in Vitro Exposure to Utah Valley Ambient Particulate Matter Extracts; *J. Toxicol. Environ. Health Part A* **2003**, *66,* 1087-1112.
343. Ghio, A.J. Biological Effects of Utah Valley Ambient Air Particles in Humans: A Review; *J. Aeros. Med.* **2004**, *17,* 157-164.
344. Lamm, S.H.; Hall, T.A.; Engel, A.; Rueter, F.H.; White, L.D. PM_{10} Particulates: Are They the Major Determinant of Pediatric Respiratory Admissions in Utah County, Utah (1985–1989); *Ann. Occup. Hyg.* **1994**, *38*(Suppl. 1), 969-972.
345. Pope, C.A.; III; Hill, R.W.; Villegas, G.M. Particulate Air Pollution and Daily Mortality on Utah's Wasatch Front; *Environ. Health Perspect.* **1999**, *107,* 567-573.
346. Fletcher, C.; Peto, R. The Natural History of Chronic Airflow Obstruction; *Br. Med. J.* **1977**, *1,* 1645-1648.
347. van Eeden, S.F.; Yeung, A.; Quinlam, K.; Hogg, J.C. Systemic Response to Ambient Particulate Matter: Relevance to Chronic Obstructive Pulmonary Disease; *Proc. Am. Thorac. Soc.* **2005**, *2,* 61-67.
348. Brauer, M.; Avila-Casado, C.; Fortoul, T.I.; Vedal, S.; Stevens, B.; Churg, A. Air Pollution and Retained Particles in the Lung; *Environ. Health Perspect.* **2001**, *109,* 1039-1043.
349. Churg, A.; Brauer, M.; Avila-Casada, C.; Fortoul, T.I.; Wright, J.L. Chronic Exposure to High Levels of Particulate Air Pollution and Small Airway Remodeling; *Environ. Health Perspect.* **2003**, *111,* 714-718.
350. Schwartz, J. Lung Function and Chronic Exposure to Air Pollution: A Cross-Sectional Analysis of NHANES II; *Environ. Res.* **1989**, *50,* 309-321.
351. Chestnut, L.G.; Schwartz, J.; Savitz, D.A.; Burchfiel, C.M. Pulmonary Function and Ambient Particulate Matter: Epidemiological Evidence from NHANES I; *Arch. Environ. Health* **1991**, *46,* 135-144.
352. Tashkin, D.P.; Detels, R.; Simmons, M.; Liu, H.; Coulson, A.H.; Sayre, J.; Rokaw, S. The UCLA Population Studies of Chronic Obstructive Respiratory Disease: XI: Impact of Air Pollution and Smoking on Annual Change in Forced Expiratory Volume in One Second; *Am. J. Respir. Crit. Care Med.* **1994**, *149,* 1209-1217.
353. Raizenne, M.E.; Neas, L.M.; Damokosh, A.I.; Dockery, D.W.; Spengler, J.D.; Koutrakis, P.; Ware, J.H.; Speizer, F.E. Health Effects of Acid Aerosols on North American Children: Pulmonary Function; *Environ. Health Perspect.* **1996**, *104,* 506-514.
354. Ackermann-Liebrich, U.; Leuenberger, P.; Schwartz, J.; Schindler, C.; Monn, C.; Bolognini, G.; Bongard, J.P.; Brandli, O.; Domenighetti, G.; Elsasser, S., Grize, L.; Karrer, W.; Keller, R.; Keller-Wossidlo, H.; Kunzli, N.; Martin, B.W.; Medici, T.C.; Perruchoud, A.P.; Schoni, M.H.; Tschopp, J.M.; Villiger, B.; Wuthrich, B.; Zellweger, J.P.; Zemp, E. Lung Function and Long Term Exposure to Air Pollutants in Switzerland; *Am. J. Respir. Crit. Care Med.* **1997**, *155,* 122-129.
355. Portney, P.R.; Mullahy, J. Urban Air Quality and Chronic Respiratory Disease; *Regional Sci. Urban Econ.* **1990**, *20,* 407-418.
356. Schwartz, J. Particulate Air Pollution and Chronic Respiratory Disease; *Environ. Res.* **1993**, *62,* 7-13.
357. Abbey, D.E.; Hwang, B.L.; Burchette, R.L.; Vancuren, T.; Mills, P.K. Estimated Long-Term Ambient Concentrations of PM_{10} and Development of Respiratory Symptoms in a Nonsmoking Population; *Arch. Environ. Health* **1995**, *50,* 139-152.
358. Dockery, D.W.; Cunningham, J.; Damokosh, A.I.; Neas, L.M.; Spengler, J.D.; Koutrakis, P.; Ware, J.H.; Raizenne, M.; Speizer, F.E. Health Effects of Acid Aerosols on North American Children: Respiratory Symptoms; *Environ. Health Perspect.* **1996**, *104,* 500-505.
359. Peters, J.M.; Avol, E.; Navidi, W.; London, S.J.; Gauderman, W.J.; Lurmann, F.; Linn, W.S.; Margolis, H.; Rappaport, E.; Gong, H., Thomas, D.C. A Study of Twelve Southern California Communities with Differing Levels and Types of Air Pollution. I: Prevalence of Respiratory Morbidity; *Am. J. Respir. Crit. Care Med.* **1999**, *159,* 760-767.
360. Avol, E.L.; Gauderman, W.J.; Tan, S.M.; London, S.J.; Peters, J.M. Respiratory Effects of Relocating to Areas of Differing Air Pollution Levels; *Am. J. Respir. Crit. Care Med.* **2001**, *164,* 2067-2072.
361. MacNee, W.; Donaldson, K. Exacerbations of COPD: Environmental Mechanisms. *Chest* **2000,** 117, 390S-397S.
362. MacNee, W.; Donaldson, K. Mechanism of Lung Injury Caused by PM_{10} and Ultrafine Particles with Special Reference to COPD. *Eur. Respir. J.* **2003,** *21,* 47s-51s.
363. Dockery, D.W.; Ware, J.H.; Ferris, B.J.; Speizer, F.E.; Cook, N.R.; Herman, S.M. Change in Pulmonary Function in Children Associated with Air Pollution Episodes; *J. Air Pollut. Control Assoc.* **1982**, *32,* 937-942.
364. Roemer, W.; Hoek, G.; Brunekreef, B. Effect of Ambient Winter Air Pollution on Respiratory Health of Children with Chronic Respiratory Symptoms; *Am. Rev. Respir. Dis.* **1993**, *147,* 118-124.
365. Hoek, G.; Brunekreef, B. Acute Effects of a Winter Air Pollution Episode on Pulmonary Function and Respiratory Symptoms of Children; *Arch. Environ. Health* **1993**, *48,* 328-335.
366. Koenig, J.Q.; Larson, T.V.; Hanley, Q.S.; Rebolledo, V.; Dumler, K.; Checkoway, H.; Wang, S.Z.; Lin, D.; Pierson, W.E. Pulmonary Function Changes in Children Associated with Fine Particulate Matter; *Environ. Res.* **1993**, *63,* 26-38.
367. Neas, L.M.; Dockery, D.W.; Koutrakis, P.; Tollerud, D.J.; Speizer, F.E. The Association of Ambient Air Pollution with Twice Daily Peak Expiratory Flow Rate Measurements in Children; *Am. J. Epidemiol.* **1995**, *141,* 111-122.
368. Hoek, G.; Brunekreef, B. Effect of Photochemical Air Pollution on Acute Respiratory Symptoms in Children; *Am. J. Respir. Crit. Care Med.* **1995**, *151,* 27-32.
369. Hoek, G.; Dockery, D.W.; Pope, C.A., III; Neas, L.; Roemer, W.; Brunekreef, B. Association between PM_{10} and Decrements in Peak Expiratory Flow Rates in Children: Reanalysis of Data from Five Panel Studies; *Eur. Respir. J.* **1998**, *11,* 1307-1311.
370. Sin, D.D.; Man, S.F.P. Chronic Obstructive Pulmonary Disease as a Risk Factor for Cardiovascular Morbidity and Mortality; *Proc. Am. Thorac. Soc.* **2005**, *2,* 8-11.
371. Sin, D.D.; Wu, L.; Man, S.F.P. The Relationship between Reduced Lung Function and Cardiovascular Mortality: A Population-Based Study and a Systematic Review of the Literature; *Chest* **2005**, *127,* 1952-1959.
372. Libby, P.; Ridker, P.M.; Maseri, A. Inflammation and Atherosclerosis; *Circulation* **2002**, *105,* 1135-1143.
373. Seaton, A.; MacNee, W.; Donaldson, K.; Godden, D. Particulate Air Pollution and Acute Health Effects; *Lancet* **1995**, *345,* 176-178.
374. González-Flecha, B. Oxidant Mechanisms in Response to Ambient Air Particles; *Mol. Aspects Med.* **2004**, *25,* 169-182.

375. Nemmar, A.; Nemery, B.; Hoylaerts, M.F.; Vermylen, J. Air Pollution and Thrombosis: An Experimental Approach; *Pathophysiol. Haemost. Thromb.* **2002**, *32,* 349-350.
376. Nemmar, A.; Hoet, P.H.M., Dinsdale, D.; Vermylen, J.; Hoylaerts, M.F.; Nemery, B. Diesel Exhaust Particles in Lung Acutely Enhance Experimental Peripheral Thrombosis; *Circulation* **2003**, *107,* 1202-1208.
377. Nemmar, A.; Nemery, B.; Hoet, P.H.M., Vermylen, J.; Hoylaerts, M.F. Pulmonary Inflammation and Thrombogenicity Caused by Diesel Particles in Hamsters: Role of Histamine; *Am. J. Respir. Crit. Care Med.* **2003**, *168,* 1366-1372.
378. Nemmar, A.; Nemery, B.; Hoet, P.H.M., Van Rooijen, N.; Hoylaerts, M.F. Silica Particles Enhance Peripheral Thrombosis: Key Role of Lung Macrophage-Neutrophil Cross-Talk; *Am. J. Respir. Crit. Care Med.* **2005**, *171,* 872-879.
379. Wellenius, G.A.; Coull, B.A.; Godleski, J.J.; Koutrakis, P.; Okabe, K.; Savage, S.T.; Lawrence, J.E.; Murthy, G.G.K., Verrier, R.L. Inhalation of Concentrated Ambient Air Particles Exacerbates Myocardial Ischemia in Conscious Dogs; *Environ. Health Perspect.* **2003**, *111,* 402-408.
380. Sun, Q.; Wang, A.; Jin, X.; Natanzon, A.; Duquaine, D.; Brook, R.D.; Aguinaldo, J.-G.S.; Fayad, Z.A.; Fuster, V.; Lippmann, M.; Chen, L.C.; Rajagopalan, S. Long-Term Air Pollution Exposure and Acceleration of Atherosclerosis and Vascular Inflammation in an Animal Model; *J. Am. Med. Assoc.* **2005**, *294,* 3003-3010.
381. Chen, L.C.; Nadziejko, C. Effects of Subchronic Exposures to Concentrated Ambient Particles (CAPs) in Mice: V. CAPs Exacerbate Aortic Plaque Development in Hyperlipidemic Mice; *Inhal. Toxicol.* **2005**, *17,* 217-224.
382. van Eeden, S.F.; Hogg, J.C. Systemic Inflammatory Response Induced by Particulate Matter Air Pollution: The Importance of Bone-Marrow Stimulation; *J. Toxicol. Environ. Health* **2002**, *65,* 1597-1613.
383. van Eeden, S.F.; Tan, W.C.; Suwa, T.; Mukae, H.; Terashima, T.; Fujii, T.; Qui, D.; Vincent, R.; Hogg, J.C. Cytokines Involved in the Systemic Inflammatory Response Induced by Exposure to Particulate Matter Air Pollutants (PM_{10}); *Am. J. Respir. Crit. Care Med.* **2001**, *164,* 826-830.
384. Terashima, T.; Wiggs, B.; English, D.; Hogg, J.C.; van Eeden, S.F. Phagocytosis of Small Carbon Particles (PM_{10}) by Aveolar Marcrophages Stimulates the Release of Polymorphonuclear Leukocytes from Bone Marrow; *Am. J. Respir. Crit. Care Med.* **1997**, *155,* 1441-1447.
385. Mukae, H.; Hogg, J.C.; English, D.; Vincent, R.; van Eeden, S.F. Phagocytosis of Particulate Air Pollutants by Human Alveolar Macrophages Stimulates the Bone Marrow; *Am. J. Physiol. Lung Cell Mol. Physiol.* **2000,** *279,* L924-L931.
386. Mukae, H.; Vincent, R.; Quinlan, K.; English, D.; Hards, J.; Hogg, J.C.; van Eeden, S.F. The Effect of Repeated Exposure to Particulate Air Pollution (PM_{10}) on the Bone Marrow; *Am. J. Respir. Crit. Care Med.* **2001**, *163,* 201-209.
387. Fujii, T.; Hayashi, S.; Hogg, J.C.; Mukae, H.; Suwa, T.; Goto, Y.; Vincent, R.; van Eeden, S.F. Interaction of Alveolar Macrophages and Airway Epithelial Cells following Exposure to Particulate Matter Produces Mediators that Stimulate the Bone Marrow; *Am. J. Respir. Cell Mol. Biol.* **2002**, *27,* 34-41.
388. Goto, Y.; Ishii, H.; Hogg, J.C.; Shih, C.-H.; Yatera, K.; Vincent, R.; van Eeden, S.F. Particulate Matter Air Pollution Stimulates Monocyte Release from the Bone Marrow; *Am. J. Respir. Crit. Care Med.* **2004**, *170,* 891-897.
389. Suwa, T.; Hogg, J.C.; Quinlan, K.B.; Ohgami, A.; Vincent, R.; van Eeden, S.F. Particulate Air Pollution Induces Progression of Atherosclerosis; *J. Am. Coll. Cardiol.* **2002**, *39,* 935-942.
390. Glantz, S.A.; Parmley, W.W. Passive Smoking and Heart Disease. Epidemiology, Physiology, and Biochemistry; *Circulation* **1991**, *83,* 1-12.
391. Glantz, S.A.; Parmley, W.W. Passive Smoking and Heart Disease. Mechanisms and Risk; *J. Am. Med. Assoc.* **1995**, *273,* 1047-1053.
392. Penn, A.; Chen, L.C.; Snyder, C.A. Inhalation of Steady-State Sidestream Smoke from One Cigarette Promotes Arteriosclerotic Plaque Development; *Circulation* **1994**, *90,* 1363-1367.
393. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart Rate Variability: Standards of Measurement, Physiological Interpretation, and Clinical Use. *Circulation* **1996**, *93,* 1043-1065.
394. Kennedy, H.L. Beta Blockade, Ventricular Arrhythmias, and Sudden Cardiac Death. *Am. J. Cardiol.* **1997,** *80*(9b), 29J-34J.
395. Nolan, J.; Batin, P.D.; Andrews, R.; Lindsay, S.J.; Brooksby, P.; Mullen, M.; Baig, W.; Flapan, A.D.; Cowley, A.; Prescott, R.J.; Neilson, J.M.M., Fox, K.A.A. Prospective Study of Heart Rate Variability and Mortality in Chronic Heart Failure; *Circulation* **1998**, *98,* 1510-1516.
396. La Rovere, M.T.; Pinna, G.D.; Maestri, R.; Mortara, A.; Capomolla, S.; Febo, O.; Ferrari, R.; Franchini, M.; Gnemmi, M.; Opasich, C.; Riccardi, P.G.; Traversi, E.; Cobelli, F. Short-Term Heart Rate Variability Strongly Predicts Sudden Cardiac Death in Chronic Heart Failure Patients; *Circulation* **2003**, *107,* 565-570.
397. Watkinson, W.P.; Campen, M.J.; Nolan, J.P.; Costa, D.L. Cardiovascular and Systemic Responses to Inhaled Pollutants in Rodents: Effects of Ozone and Particulate Matter; *Environ. Health Perspect.* **2001**, *109*(Suppl. 4), 539-546.
398. Wellenius, G.A.; Saldiva, P.H.N., Batalha, J.R.F., Murthy, G.G.K., Coull, B.A.; Verrier, R.L.; Godleski, J.J. Electrocardiographic Changes during Exposure to Residual Oil Fly Ash (ROFA) Particles in a Rat Model of Myocardial Infarction; *Toxicol. Sci.* **2002**, *66,* 1-9.
399. Wichers, L.B.; Nolan, J.P.; Winsett, D.W.; Ledbetter, A.D.; Kodavanti, U.P.; Schladweiler, M.C.; Costa, D.L.; Watkinson, W.P. Effects of Instilled Combustion-Derived Particles in Spontaneously Hypertensive Rats. Part I: Cardiovascular Responses; *Inhal. Toxicol.* **2004,** *16,* 391-405.
400. Batalha, J.R.F., Saldiva, P.H.N., Clarke, R.W.; Coull, B.A.; Stearns, R.C.; Lawrence, J.; Murthy, G.G.; Koutrakis, P.; Godleski, J.J. Concentrated Ambient Air Particles Induce Vasoconstriction of Small Pulmonary Arteries in Rats; *Environ. Health Pespect.* **2002**, *110,* 1191-1197.
401. Vincent, R.; Kumarathasan, P.; Goegan, P.; Bjarnason, S.G.; Guenette, J.; Berube, D.; Adamson, I.Y.; Desjardins, S.; Burnett, R.T.; Miller, F.J., Baltistini, B. Inhalation Toxicology of Urban Ambient Particulate Matter: Acute Cardiovascular Effects in Rats; *Res. Rep. Health Eff. Inst.* **2001**, *104,* 5-54.
402. Bouthillier, L.; Vincent, R.; Goegan, P.; Adamson, I.Y.; Bjarnason, S.; Stewart, M.; Guenette, J.; Potvin, M.; Kumarathasan, P. Acute Effects of Inhaled Urban Particles and Ozone: Lung Morphology, Macrophage Activity, and Plasma Endothelin-1; *Am. J. Pathol.* **1998**, *153,* 1873-1884.
403. Nemmar, A.; Hoylaerts, M.F.; Hoet, P.H.M., Nemery, B. Possible Mechanisms of the Cardiovascular Effects of Inhaled Particles: Systemic Translocation and Prothrombotic Effects; *Toxicol. Lett.* **2004**, *149,* 243-253.
404. Oberdorster, G.; Sharp, Z.; Atudorei, V.; Elder, A.; Gelein, R.; Lunts, A.; Kreyling, W.; Cox, C. Extrapulmonary Translocation of Ultrafine Carbon Particles Following Whole-Body Inhalation Exposure of Rats; *J. Toxicol. Environ. Health* **2002**, *65,* 1531-1543.
405. Oberdorster, G.; Sharp, Z.; Atudorei, V.; Elder, A.; Gelein, R.; Kreyling, W.; Cox, C. Translocation of Inhaled Ultrafine Particles to the Brain; *Inhal. Toxicol.* **2004,** *16,* 437-445.
406. Nemmar, A.; Vanbilloen, H.; Hoylaerts, M.F.; Hoet, P.H.M., Verbruggen, A.; Nemery, B. Passage of Intratracheally Instilled Ultrafine Particles from the Lung into the Systemic Circulation in Hamster; *Am. J. Respir. Crit. Care Med.* **2001**, *164,* 1665-1668.
407. Nemmar, A.; Hoet, P.H.M., Vanquickenborne, B.; Dinsdale, D.; Thomeer, M.; Hoylaerts, M.F.; Vanbilloen, H.; Mortelmans, L.; Nemery, B. Passage of Inhaled Particles into the Blood Circulation in Humans; *Circulation* **2002**, *105,* 411-414.
408. Nemmar, A.; Nemery, B.; Hoylaerts, M.F.; Vermylen, J. Air Pollution and Thrombosis: an Experimental Approach; *Pathophysiol. Haemost. Thromb.* **2002,** *32,* 349-350.
409. Nemmar, A.; Nemery, B.; Hoet, P.H.M., Van Rooijen, N.; Hoylaerts, M.F. Silica Particles Enhance Peripheral Thrombosis: Key Role of Lung Macrophage-Neutrophil Cross-Talk; *Am. J. Respir. Crit. Care Med.* **2005**, *171,* 872-879.
410. Tjalve, H.; Henriksson, J. Uptake of Metals in the Brain via Olfactory Pathways; *Neurotoxicol.* **1999,** *20,* 181-195.
411. Thomas, P.T.; Zelikoff, J.T. Air Pollutants: Modulators of Pulmonary Host Resistance Against Infection. In *Air Pollution and Health*; Holgate, S.T.: Samet, J.M.; Koren, H.S.; Maynard, R.L., Eds.; Academic Press: London, United Kingdom, 1999; pp 357-379.
412. Zelikoff, J.T.; Schermerhorn, K.R.; Fang, K.; Cohen, M.D.; Schlesinger, R.B. A Role for Associated Transition Metals in the Immunotoxicity of Inhaled Ambient Particulate Matter; *Environ. Health Perspect.* **2002**, *110,* 871-875.
413. Zelikoff, J.T.; Chen, L.C.; Cohen, M.D.; Fang, K.; Gordon, T.; Li, Y.; Nadziejko, C.; Schlesinger, R.B. Effects of Inhaled Ambient Particulate Matter on Pulmonary Antimicrobial Immune Defense; *Inhal. Toxicol.* **2003**, *15,* 131-150.
414. Zanobetti, A.; Schwartz, J.; Gold, D. Are There Sensitive Subgroups for the Effects of Airborne Particles?; *Environ. Health Perspect.* **2000**, *108,* 841-845.
415. Goldberg, M.S.; Burnett, R.T.; Bailar, J.C., III; Tamblyn, R.; Ernst, P.; Flegel, K.; Brook, J.; Bonvalot, Y.; Singh, R.; Valois, M.-F.; Vincent, R. Identification of Persons with Cardiorespiratory Conditions Who Are at Risk of Dying from the Acute Effects of Ambient Air Particles; *Environ. Health Perspect.* **2001**, *109,* 487-494.
416. Zanobetti, A.; Schwartz, J. Are Diabetics More Susceptible to the Health Effects of Airborne Particles?; *Am. J. Respir. Crit. Care Med.* **2001**, *164,* 831-833.
417. Bateson, T.F.; Schwartz, J. Who is Sensitive to the Effects of Particulate Air Pollution on Mortality?: A Case-Crossover Analysis of Effect Modifiers; *Epidemiol.* **2004**, *15,* 143-149.
418. Peters, A.; Dockery, D.W.; Heinrich, J.; Wichmann, H.E. Medication use Modifies the Health Effects of Particulate Sulfate Air Pollution in Children with Asthma; *Environ. Health Perspect.* **1997**, *105,* 430-435.

419. Anderson, H.R.; Atkinson, R.W.; Bremner, S.A.; Marston, L. Particulate Air Pollution and Hospital Admissions for Cardiorespiratory Diseases: Are the Elderly at Greater Risk?; *Eur. Respir. J.* **2003**, *21,* 39S-46S.
420. Sandström, T.; Frew, A.J.; Svartengren, M.; Viegi, G. The Need for a Focus on Air Pollution Research in the Elderly; *Eur. Respir. J.* **2003**, *21*(Suppl. 40), 92S-95S.
421. Fischer, P.; Hoek, G.; Brunekreef, B.; Verhoeff, A.; van Wijnen, J. Air Pollution and Mortality in the Netherlands: Are the Elderly More at Risk?; *Eur. Respir. J.* **2003**, *21,* 34S-38S.
422. Zanobetti, A.; Schwartz, J. Race, Gender, and Social Status as Modifiers of the Effects of PM_{10} on Mortality; *J. Occup. Environ. Med.* **2000**, *42,* 469-474.
423. Gwynn, R.C.; Thurston, G.D. The Burden of Air Pollution: Impacts among Racial Minorities; *Environ. Health Perspect.* **2001**, *109,* 501-506.
424. Martins, M.C.H., Fatigati, F.L.; Véspoli, T.C.; Martins, L.C.; Pereira, L.A.A., Martins, M.A.; Saldiva, P.H.N., Braga, A.L.F. Influence of Socioeconomic Conditions on Air Pollution Adverse Health Effects in Elderly People: an Analysis of Six Regions in São Paulo, Brazil; *J. Epidemiol. Comm. Health* **2004**, *58,* 41-46.
425. O'Neill, M.S.; Jerrett, M.; Kawachi, I.; Levy, J.I.; Cohen, A.J.; Gouveia, N.; Wilkinson, P.; Fletcher, T.; Cifuentes, L.; Schwartz, J. Health, Wealth, and Air Pollution: Advancing Theory and Methods; *Environ. Health Perspect.* **2003**, *111,* 1861-1870.
426. Romieu, I.; Ramírez-Aguilar, M.; Moreno-Macias, H.; Barraza-Villarreal, A.; Miller, P.; Hernández-Cadena, L.; Carbajal-Arroyo, L.A.; Hernandez-Avila, M. Infant Mortality and Air Pollution: Modifying Effect by Social Class; *J. Occup. Environ. Med.* **2004**, *46,* 1210-1216.
427. Janssen, N.A.H., Schwartz, J.; Zanobetti, A.; Suh, H.H. Air Conditioning and Source-Specific Particles as Modifiers of the Effect of PM_{10} on Hospital Admissions for Heart and Lung Disease; *Environ. Health Perspect.* **2002**, *110,* 43-49.
428. Kelly, F.J. Oxidative Stress: Its Role in Air Pollution and Adverse Health Effects; *Occup. Environ. Med.* **2003**, *60,* 612-616.
429. Bobak, M.; Leon, D.A. The Effect of Air Pollution on Infant Mortality Appears Specific for Respiratory Causes in the Postneonatal Period; *Epidemiol.* **1999**, *10,* 666-670.
430. Loomis, D.; Castillejos, M.; Gold, D.R.; McDonnell, W.; Borja-Aburto, V.H. Air Pollution and Infant Mortality in Mexico City; *Epidemiol.* **1999**, *10,* 118-123.
431. Lipfert, F.W.; Zhang, J.; Wyzga, R.E. Infant Mortality and Air Pollution: A Comprehensive Analysis of U.S. Data for 1990; *J. Air & Waste Manage. Assoc.* **2000**, *50,* 1350-1366.
432. Conceição, G.M.S., Miraglia, S.G.E.K.; Kishi, H.S.; Saldiva, P.H.N., Singer, J.M. Air Pollution and Child Mortality: A Time-Series Study in São Paulo, Brazil; *Environ. Health Perspect.* **2001**, *109,* 347-350.
433. Braga, A.L.F., Saldiva, P.H.N., Pereira, L.A.A., Menezes, J.J.C., Conceição, G.M.S., Lin, C.A.; Zanobetti, A.; Schwartz, J.; Dockery, D.W. Health Effects of Air Pollution Exposure on Children and Adolescents in São Paulo, Brazil; *Pediatr. Pulmonol.* **2001**, *31,* 106-113.
434. Chay, K.Y.; Greenstone, M. *Air Quality, Infant Mortality, and the Clean Air Act of 1970*; Working Paper No. 42, Center for Labor Economics, University of California: Berkeley, CA; 2001.
435. Ha, E.-H.; Lee, J.-T.; Kim, H.; Hong, Y.-C.; Lee, B.-E.; Park, H.-S.; Christiani, D.C. Infant Susceptibility of Mortality to Air Pollution in Seoul, South Korea; *Pediatrics* **2003**, *111,* 284-290.
436. Chay, K.Y.; Greenstone, M. The Impact of Air Pollution on Infant Mortality: Evidence from Geographic Variation in Pollution Shocks Induced by a Recession; *Quart. J. Econ.* **2003**, *118,* 1121-1167.
437. Lin, C.A.; Pereira, L.A.A., Nishioka, D.C.; Conceição, G.M.S., Braga, A.L.F., Saldiva, P.H.N. Air Pollution and Neonatal Deaths in São Paulo, Brazil; *Braz. J. Med. Biol. Res.* **2004**, *37,* 765-770.
438. Glinianaia, S.V.; Rankin, J.; Bell, R.; Pless-Mulloli, T.; Howel, D. Does Particulate Air Pollution Contribute to Infant Death? A Systematic Review; *Environ. Health Perspect.* **2004**, *112,* 1365-1370.
439. Tong, S.; Colditz, P. Air Pollution and Sudden Infant Death Syndrome: A Literature Review; *Paediatric Perinatal Epidemiol.* **2004**, *18,* 327-335.
440. Lacasaña, M.; Esplugues, A.; Ballester, F. Exposure to Ambient Air Pollution and Prenatal and Early Childhood Health Effects; *Eur. J. Epidemiol.* **2005**, *20,* 183-199.
441. AAP Commitee on Environmental Health. Ambient Air Pollution: Health Hazards to Children. *Pediatrics* **2004**, *114,* 1699-1707.
442. Maisonet, M.; Correa, A.; Misra, D.; Jaakkola, J.J. A Review of the Literature on the Effects of Ambient Air Pollution on Fetal Growth; *Envrion. Res.* **2004**, *95,* 106-115.
443. Dales, R.; Burnett, R.T.; Smith-Doiron, M.; Stieb, D.M.; Brooks, J.R. Air Pollution and Sudden Infant Death Syndrome; *Pediatrics* **2004**, *113,* e628-e631.
444. Šrám, R.J.; Binková, B.; Dejmek, J.; Bobak, M. Ambient Air Pollution and Pregnancy Outcomes: A Review of the Literature; *Environ. Health Perspect.* **2005**, *113,* 375-382.
445. Wang, X.; Ding, H.; Ryan, L.; Xu, X. Association between Air Pollution and Low Birth Weight: A Community-Based Study; *Environ. Health Perspect.* **1997**, *105,* 514-520.
446. Bobak, M.; Leon, D.A. Pregnancy Outcomes and Outdoor Air Pollution: An Ecological Study in Districts of the Czech Republic 1986–8; *Occup. Environ. Med.* **1999**, *56,* 539-543.
447. Ritz, B.; Yu, F. The Effect of Ambient Carbon Monoxide on Low Birth Weight among Children Born in Southern California between 1989 and 1993; *Environ. Health Perspect.* **1999**, *107,* 17-25.
448. Rogers, J.F.; Thompson, S.J.; Addy, C.L.; McKeown, R.E.; Cowen, D.J.; Decoufle, P. Association of Very Low Birth Weight with Exposures to Environmental Sulfur Dioxide and Total Suspended Particulates; *Am. J. Epidemiol.* **2000**, *151,* 602-613.
449. Bobak, M. Outdoor Air Pollution, low Birth Weight, and Prematurity; *Environ. Health Perspect.* **2000**, *108,* 173-176.
450. Maisonet, M.; Bush, T.J.; Correa, A.; Jaakkola, J.J.K. Relation Between Ambient Air Pollution and Low Birth Weight in the Northeastern United States; *Environ. Health Perspect.* **2001**, *109,* 351-356.
451. Ha, E.-H.; Hong, Y.-C.; Lee, B.-E.; Woo, B.-H.; Schwartz, J.; Christiani, D.C. Is Air Pollution a Risk Factor for Low Birth Weight in Seoul?; *Epidemiol.* **2001**, *12,* 643-648.
452. Lee, B.E.; Ha, E.H.; Park, H.S.; Kim, Y.J.; Hong, Y.C.; Kim, H.; Lee, J.T. Exposure to Air Pollution during Different Gestational Phases Contributes to Risks of Low Birth Weight; *Hum. Reprod.* **2003**, *18,* 638-643.
453. Gouveia, N.; Bremner, S.A.; Novaes, H.M.D. Association between Ambient Air Pollution and Birth Weight in São Paulo, Brazil; *J. Epidemiol. Comm. Health* **2004**, *58,* 11-17.
454. Basu, R.; Woodruff, T.J.; Parker, J.D.; Saulnier, L.; Schoendorf, K.C. Comparing Exposure Metrics in the Relationship between $PM_{2.5}$ and Birth Weight in California; *J. Expo. Anal. Environ. Epidemiol.* **2004**, *14,* 391-396.
455. Parker, J.D.; Woodruff, T.J.; Basu, R.; Schoendorf, K.C. Air Pollution and Birth Weight among Term Infants in California; *Pediatrics* **2005**, *115,* 121-128.
456. Wilhelm, M.; Ritz, B. Local Variations in CO and Particulate Air Pollution and Adverse Birth Outcomes in Los Angeles County, California, USA; *Environ. Health Perspect.* **2005**, *113,* 1212-1221.
457. Ritz, B.; Yu, F.; Chapa, G.; Fruin, S. Effect of Air Pollution on Preterm Birth among Children Born in Southern California between 1989 and 1993; *Epidemiol.* **2000**, *11,* 502-511.
458. Sagiv, S.K.; Mendola, P.; Loomis, D.; Herring, A.H.; Neas, L.M.; Savitz, D.A.; Poole, C. A Time Series Analysis of Air Pollution and Preterm Birth in Pennsylvania, 1997–2001; *Environ. Health Perspect.* **2005**, *113,* 602-606.
459. Dejmek, J.; Selevan, S.G.; Beneš, I.; Solanský, I.; Šrám, R.J. Fetal Growth and Maternal Exposure to Particulate Matter During Pregnancy; *Environ. Health Perspect.* **1999**, *107,* 475-480.
460. Dejmek, J.; Solanský, I.; Beneš, I.; Lenicek, J.; Šrám, R.J. The Impact of Polycyclic Aromatic Hydrocarbons and Fine Particles on Pregnancy Outcome; *Environ. Health Perspect.* **2000**, *108,* 1159-1164.
461. Jedrychowski, W.; Bendkowska, I.; Flak, E.; Penar, A.; Jacek, R.; Kaim, I.; Spengler, J.D.; Camann, D.; Perera, F.P. Estimated Risk for Altered Fetal Growth Resulting from Exposure to Fine Particles during Pregnancy: An Epidemiologic Prospective Cohort Study in Poland; *Environ. Health Perspect.* **2004**, *112,* 1398-1402.
462. Pereira, L.A.A., Loomis, D.; Conceição, G.M.S., Braga, A.L.F., Arcas, R.M.; Kishi, H.S.; Singer, J.M.; Böhm, G.M.; Saldiva, P.H.N. Association between Air Pollution and Intrauterine Mortality in São Paulo, Brazil; *Environ. Health Perspect.* **1998**, *106,* 325-329.
463. Ritz, B.; Yu, F.; Fruin, S.; Chapa, G.; Shaw, G.M.; Harris, J.A. Ambient Air Pollution and Risk of Birth Defects in Southern California; *Am. J. Epidemiol.* **2002**, *155,* 17-25.
464. Hertz-Picciotto, I.; Dostál, M.; Dejmek, J.; Selevan, S.G.; Wegienka, G.; Gomez-Caminero, A.; Šrám, R.J. Air Pollution and Distributions of Lymphocyte Immunophenotypes in Cord and Maternal Blood at Delivery; *Epidemiol.* **2002**, *13,* 172-183.
465. Cohen, A.J.; Pope, C.A., III. Lung Cancer and Air Pollution; *Environ. Health Perspect.* **1995**, *103,* 219-224.
466. Samet, J.M.; Cohen, A.J. Air Pollution and Lung Cancer. In *Air Pollution and Health;* Holgate, S.T.; Samet, J.M.; Koren, H.S.; Maynard, R.L., Eds.; Academic Press: London, United Kingdom, 1999; pp 841-864.
467. Cohen, A.J. Air Pollution and Lung Cancer: What More Do We Need to Know?; *Thorax* **2003**, *58,* 1010-1012.
468. Buffler, P.A.; Cooper, S.P.; Stinnett, S.; Contant, C.; Shirts, S.; Hardy, R.J.; Agu, V.; Gehan, B.; Burau, K. Air Pollution and Lung Cancer Mortality in Harris County, Texas, 1979–1981; *Am. J. Epidemiol.* **1988**, *128,* 683-699.
469. Vena, J.E. Air Pollution as a Risk Factor in Lung Cancer; *Am. J. Epidemiol.* **1982**, *116,* 42-56.
470. Jedrychowski, W.; Becher, H.; Wahrendorf, J.; Basa-Cierpialek, Z. A Case-Control Study of Lung Cancer with Special Reference to the Effect of Air Pollution in Poland; *J. Epidemiol. Comm. Health* **1990**, *44,* 114-120.

471. Katsouyanni, K.; Trichopoulos, D.; Kalandidi, A.; Tomos, P.; Riboli, E. A Case-Control Study of Air Pollution and Tobacco Smoking in Lung Cancer Among Women in Athens; *Prev. Med.* **1991**, *20,* 271-278.
472. Barbone, F.; Bovenzi, M.; Cavallieri, F.; Stanta, G. Air Pollution and Lung Cancer in Trieste, Italy; *Am. J. Epidemiol.* **1995**, *141,* 1161-1169.
473. Harrison, R.M.; Yin, J. Particulate Matter in the Atmosphere: Which Particle Properties Are Important for Its Effects on Health?; *Sci. Total Environ.* **2000**, *249,* 85-101.
474. Brunekreef, B.; Forsberg, B. Epidemiological Evidence of Effects of Coarse Airborne Particles on Health; *Eur. Respir. J.* **2005**, *26,* 309-318.
475. Ostro, B.D.; Broadwin, R.; Lipsett, M.J. Coarse and Fine Particles and Daily Mortality in the Coachella Valley, California: A Follow-Up Study; *J. Expo. Anal. Environ. Epidemiol.* **2000**, *10,* 412-419.
476. Laden, F.; Neas, L.M.; Dockery, D.W.; Schwarts, J. Association of Fine Particulate Matter from Different Sources with Daily Mortality in Six U.S. Cities; *Environ. Health Perspect.* **2000**, *108,* 941-947.
477. Delfino, R.J.; Sioutas, C.; Malik, S. Potential Role of Ultrafine Particles in Associations between Airborne Particle Mass and Cardiovascular Health; *Environ. Health Perspect.* **2005**, *113,* 934-946.
478. Adamson, I.Y.; Prieditis, H.; Vincent, R. Soluble and Insoluble Air Particle Fractions Induce Differential Production of Tumor Necrosis Factor α in Rat Lung; *Exp. Lung. Res.* **2004**, *30,* 355-368.
479. Imrich, A.; Ning, Y.; Kobzik, L. Insoluble Components of Concentrated Air Particles Mediate Alveolar Macrophage Responses in Vitro; *Toxicol. Appl. Pharmacol.* **2000**, *167,* 140-150.
480. Ghio, A.J.; Cohen, M.D. Disruption of Iron Homeostasis as a Mechanism of Biologic Effect by Ambient Air Pollution Particles; *Inhal. Toxicol.* **2005**, *17,* 709-716.
481. Lubianova, I.P. Effects of Iron-Containing Welding Smoke on Pathological Changes in the Body (Review of the Literature); *Med. Tr. Prom. Ekol.* **1998**, *9,* 27-37.
482. Zhang, Q.; Kusaka, Y.; Sato, K.; Nakakuki, K.; Kohyama, N.; Donaldson, K. Differences in the Extent of Inflammation Caused by Intratracheal Exposure to Three Ultrafine Metals: Role of Free Radicals; *Toxicol. Environ. Health, Part A* **1998**, *53,* 423-438.
483. Zhang, Q.; Kusaka, Y.; Zhu, X.; Sato, K.; Mo, Y.; Kluz, T.; Donaldson, K. Comparative Toxicity of Standard Nickel and Ultrafine Nickel in Lung after Intratracheal Instillation; *J. Occup. Health* **2003**, *45,* 23-30.
484. Smith, K.R.; Aust, A.E. Mobilization of Iron from Urban Particulates Leads to Generation of Reactive Oxygen Species in Vitro and Induction of Ferritin Synthesis in Human Lung Epithelial Cells; *Chem. Res. Toxicol.* **1997**, *10,* 828-834.
485. Van Maanen, J.M.S., Borm, P.J.A., Knaapen, A.; Van Herwijen, M.; Schilderman, P.A.E.L.; Smith, K.R.; Aust, A.E.; Tomatis, M.; Fubini, B. In Vitro Effects of Coal Fly Ashes: Hydroxyl Radical Generation, Iron Release and DNA Damage and Toxicity in Rat Lung Epithelial Cells; *Inhal. Toxicol.* **1999**, *11,* 1123-1141.
486. Risom, L.; Moller, P.; Loft, S. Oxidative Stress-Induced DNA Damage by Particulate Air Pollution; *Mutat. Res.* **2005,** *592,* 119-137.
487. Grahame, T.J.; Schlesinger, R.B. Evaluating the Health Risk from Secondary Sulfates in Eastern North American Regional Ambient Air Particulate Matter; *Inhal. Toxicol.* **2005**, *17,* 15-27.
488. Thurston, G.D.; Ito, K.; Mar, T.; Christensen, W.F.; Eatough, D.J.; Henry, R.C.; Kim, E.; Laden, F.; Lall, R.; Larson, T.V., Liu, H.; Neas, L.; Pinto, J.; Stolzel, M.; Suh, H.; Hopke, P.K. Workgroup Report: Workshop on Source Apportionment of Particulate Matter Health Effects—Intercomparison of Results and Implications; *Environ. Health Perspect.* **2005**, *113,* 1768-1774.
489. Schwartz, J. Clearing the Air; *Regulation* **2003**, *26,* 22-29.
490. Schwartz, J. Particulate Air Pollution: Weighing the Risks. Competitive Enterprise Institute: 2003. Available at: http://www.cei.org/pdf/3452.pdf (accessed 2006).
491. Schwartz, J. EPA's Faith-Based Pollution Standards. American Enterprise Institute for Public Policy Research: 2006. Available at: http://www.aei.org/publications/pubID.23685,filter.all/pub_detail.asp (accessed 2006).
492. Moolgavkar, S.H. A Review and Critique of the EPA's Rationale for a Fine Particle Standard; *Regul. Toxicol. Pharmacol.* **2005**, *42,* 123-144.
493. Moolgavkar, S.H. Fine Particles and Mortality; *Inhal. Toxicol.* **2006**, *18,* 93-94.
494. Lumley, T.; Sheppard, L. Time Series Analyses of Air Pollution and Health: Straining at Gnats and Swallowing Camels?; *Epidemiol.* **2003**, *14,* 13-14.
495. Gamble, P.F. $PM_{2.5}$ and Mortality in Long-Term Prospective Cohort Studies: Cause-Effect or Statistical Associations; *Environ. Health Perspect.* **1998**, *106,* 535-549.
496. Gamble, P.F.; Nicolich, M.J. Comparison of Ambient PM Risk with Risks Estimated from PM Components of Smoking and Occupational Exposures; *J. Air & Waste Manag. Assoc.* **2000**, *50,* 1514-1531.
497. Green, L.C.; Crouch, E.A.C., Ames, M.R.; Lash, T.L. What' Wrong with the National Ambient Air Quality Standard (NAAQS) for Fine Particulate Matter ($PM_{2.5}$)?; *Reg. Toxicol. Pharmacol.* **2002**, *35,* 327-337.
498. Green, L.C.; Armstrong, S.R. Particulate Matter in Ambient Air and Mortality: Toxicologic Perspectives; *Reg. Toxicol. Pharmacol.* **2003**, *38,* 326-335.
499. Valberg, P.A. Is PM More Toxic than the Sum of Its Parts? Risk-Assessment Toxicity Factors Vs. PM-Moratality "Effect Functions"; *Inhal. Toxicol.* **2004,** *16*(Suppl. 1), 19-26.
500. Lippmann, M.; Schlesinger, R.B. Toxicological Bases for the Setting of Health-Related Air Pollution Standards; *Annu. Rev. Public Health* **2000**, *21,* 309-333.
501. Costa, D.L. Issues That Must Be Addressed for Risk Assessment of Mixed Exposures: the U.S. EPA Experience with Air Quality; *J. Toxicol. Environ. Health Part A* **2004**, *67,* 195-207.
502. Mauderly, J.L. Health Hazards of Complex Environmental Exposures: A Difficult Challenge to Inhalation Toxicology; *Inhal. Toxicol.* **2006**, *18,* 137-141.

About the Authors

C. Arden Pope III is a Mary Lou Fulton Professor at Brigham Young University. Douglas W. Dockery is a professor of environmental epidemiology at the Department of Environmental Health, Harvard School of Public Health. Address correspondence to: C. Arden Pope III, Brigham Young University, 142 FOB, P.O. Box 22363, Provo, UT 84602-2363; phone: +1-801-422-2157; fax: +1-801-422-0194; e-mail: cap3@byu.edu.

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