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Insights from HEI's research programs

Airborne Particles and Health: HEI Epidemiologic Evidence

HEI-funded epidemiologic research has addressed major issues concerning interpretation of previously reported associations between particulate matter (PM)[1] and adverse health effects. This essay reviews the key contributions of HEI's PM epidemiologic research program. To highlight these contributions, the text refers selectively to what is now a large epidemiologic literature on the health effects of PM, but this essay is not intended as a comprehensive review of either that literature or the evidence it provides on the health effects of PM. Specifically, the essay addresses the possibility that the widely reported associations between exposure to PM and adverse health effects could be interpreted as being due to other factors: environmental factors that vary with time in the same way as PM (eg, the weather, other air pollutants) or errors in measurement of exposure, for examples. The essay also considers the extent of life-shortening associated with exposure to PM and whether long-term exposure is associated with increased mortality from cardiac and/or pulmonary disease. The results of HEI-funded research strengthen the evidence for adverse effects of PM and help to define some remaining questions important for causal inference and public health decision-making.

Background

Striking increases in mortality and morbidity during several mid twentieth-century air pollution episodes demonstrated to both scientists and governments that air pollution from heavy industry and residential coal combustion were hazards to public health (Brimblecombe 2001). Where government introduced regulations to reduce emissions, the levels of ambient air pollution declined, and in 1979 Holland and colleagues concluded that, in areas with emission controls, air pollution was no longer a serious threat to human health. By the early 1990s, however, numerous epidemiologic studies were challenging that conclusion, and it was becoming increasingly clear that air pollution, even at the lower ambient concentrations prevalent in the US and Western Europe, was associated with increased mortality and other serious health effects (Pope and Dockery 1999). Many studies reported that these health effects were most strongly and consistently associated with small particles derived from combustion of fossil fuels.

The literature suggested that a range of health effects occurred at PM levels below US and European regulatory standards. Associations were reported between recent exposure and short-term increases in mortality and morbidity from cardiovascular and respiratory disease. Daily mortality rates, enumerated in most cities and easily accessible to researchers, were the most common endpoints evaluated in these studies, known as *time-series studies*. Daily rates of hospitalizations and visits to emergency rooms for exacerbations of cardiac or respiratory diseases, increased respiratory symptoms, and reductions in levels of pulmonary function, all were reported to be associated with PM. Some experts interpreted these results as consistent with a biologically plausible spectrum of adverse effects that increased in severity and culminated in premature mortality (Bates 1992). Others, however, disagreed on whether the results indicated that PM exposure had caused the serious health effects (Utell and Samet 1993). They found the associations implausible given the lack of documented pathophysiologic mechanisms. This latter perspective provided an impetus for both accelerated toxicologic

[1] Although we frequently refer to PM in general terms throughout this *HEI Perspectives*, ambient particulate matter in modern cities comes from many sources and varies in size, chemical, composition, and other physical and biological properties (see, for example, Hildemann et al 1991). The US Environmental Protection Agency (US EPA) currently regulates the ambient concentrations of particles less than 10 µm and less than 2.5 µm (aerodynamic diameter) because they are small enough to be inhaled and deposited in the lung.

research and additional epidemiologic work. An additional concern, however, was that most of the existing studies might share several methodologic weaknesses (HEI 1995, Commentary). These included:

- selective reporting of positive results due either to selective reporting of analyses or selective publication of results showing effects;
- inadequate statistical control for other risk factors that could cause increases in mortality and that might be correlated in time with PM (such as weather and influenza epidemics);
- inadequate statistical control of air pollutants whose ambient concentrations are correlated in space and time with PM; and
- the use of area-wide measurements of PM concentrations rather than estimates of exposure for each member of the study population.

Even if the reported associations of PM with daily mortality were causal, the extent of public health impact was unclear. If increases in daily mortality occurred mainly among the frail elderly or critically ill for whom exposure to PM might advance the time of death by days[2], then the public health impact might not be great. If these increases reflected larger reductions in life expectancy, however, the implications for public health would be more profound. Although time-series studies of daily mortality cannot determine the degree of lifespan reduction, cohort studies that follow people for longer time periods may be able to provide such estimates. Two prospective cohort studies, the Harvard Six Cities Study (Dockery et al 1993) and the American Cancer Society (ACS) Study (Pope et al 1995), followed large numbers of individuals over multiyear periods and observed their rates of mortality. They found that long-term average mortality rates were 17% to 26% higher among those living in communities with higher levels of fine PM ($PM_{2.5}$) even after accounting for the effects of risk factors such as cigarette smoking and medical history. The results of these studies have been used to quantify the shortening of lifespan associated with air pollution in the United States and Europe (Brunekreef 1997; US Environmental Protection Agency [EPA] 1999; UK Department of Health 2001).

Although these cohort studies might better quantify the mortality impact of exposure to PM than the time-series studies, they were open to criticism on other grounds. Their risk estimates were based on comparisons of mortality rates among geographically defined populations that not only differed in their levels of ambient air pollution but also differed in factors such as socioeconomic status and exposure to other air pollutants that might cause the reported associations between PM and mortality. Others noted that the study participants' risk factors for mortality (such as cigarette smoking, body build, medical history, and air pollution exposure itself) might have changed over time, a possibility not addressed in the original analyses.

The Six Cities and ACS Studies were published in peer-reviewed scientific journals and were reviewed by the EPA's Clean Air Scientific Advisory Committee (CASAC) prior to EPA's promulgation of new national ambient air quality standards for PM in 1997. Given the potential impact of the studies, however, representatives of industry, members

[2] Referred to as the *harvesting phenomenon* or *short-term mortality displacement*.

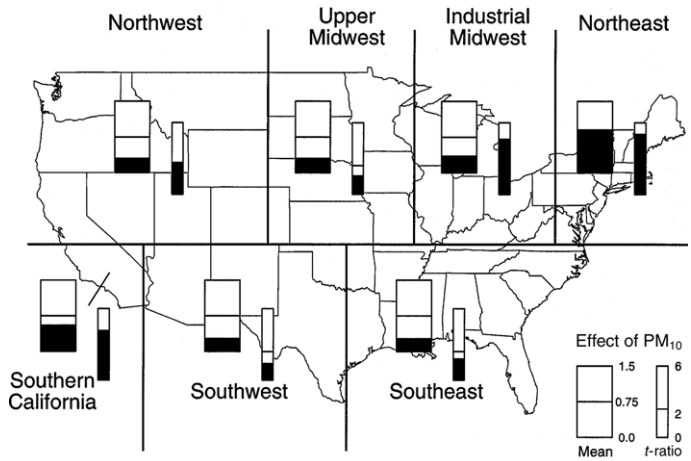

Figure 1. NMMAPS estimates of the means and standard errors (*t* ratio) of regional effects of PM_{10} on daily mortality.

of Congress, and other scientists urged the investigators and the EPA to make the original data from these studies available to other analysts. In response, Harvard University and the American Cancer Society requested that HEI organize an independent reanalysis of both studies and agreed to provide the original data to an independent team of analysts selected by HEI. The reanalysis team sought to replicate and validate the published results and to conduct sensitivity analyses to test the robustness of the original findings and interpretations to alternative analyses (HEI 2000).

Contributions of HEI-Funded Research

HEI's research program has addressed several of the uncertainties discussed here and provides a clearer indication of the health effects of PM than was available at the time of EPA's last review in 1997. HEI-sponsored research also has suggested directions for future research.

Were the apparently consistent associations between PM and daily morbidity and mortality reported in numerous studies due to selective reporting of study results? As of 1997, numerous time-series studies had reported associations between PM and daily mortality and morbidity. Reviews of US and Canadian studies reported that a 10-$\mu g/m^3$ increase in respirable particles (PM_{10}) was associated with an approximately 1% increase in daily mortality and with larger increases in daily hospital admissions (Dockery and Pope 1994; Schwartz 1994; US EPA 1996). These studies were largely conducted in single locations chosen for unspecified reasons, however, and were analyzed with a variety of statistical approaches. One notable exception was the 15-city European APHEA study, which used a standardized protocol for data management and analysis and published a complete report of its findings for all cities (Katsouyanni et al 1997). The cities themselves were not necessarily representative of all European cities, however; rather, they reflected the willingness and ability of local investigators to participate. The question remained: would a study of multiple locations, selected from a well-defined sampling frame and analyzed with uniform methods, find associations comparable to those already reported?

HEI's US-wide National Morbidity, Mortality and Air Pollution Study (NMMAPS) (Samet et al 2000a) was designed to answer this question. This study used explicit criteria to select cities from a well-defined sampling frame (the US EPA's Aerometic Information Retrieval System, or AIRS, database) and then analyzed them in a consistent and uniform fashion. Thus the study provides a systematic synthesis of the available evidence on the association of PM_{10} and daily mortality in the US—an analysis that, in effect, takes all comers without selecting only certain results. The NMMAPS investigators estimated a 0.5% increase in total nonaccidental mortality associated with a 10-$\mu g/m^3$ increase in PM_{10} in the 90 largest US cities where daily average PM_{10} ranged from 15 to 53 $\mu g/m^3$. This result agrees closely with that of the European APHEA study (0.6% per 10 $\mu g/m^3$)(Katsouyanni et al 1997) and with a recent meta-analysis of 29 studies in 23 locations in Europe and North and South America (0.7% per 10 $\mu g/m^3$) (Levy et al 2000).

The NMMAPS result is only half as large as the 1% increase in mortality reported in an earlier combined analysis of eight US studies (Dockery and Pope 1994; Samet et al 2000b). This difference may reflect methodologic differences among the studies themselves and/or the tendency of the scientific literature to preferentially attract and publish positive results.[3]

NMMAPS has also provided a clearer view of the extent to which the effect of PM on daily mortality might vary across the US. After taking into account the statistical uncertainty in the city-specific effects, PM_{10} was associated with increased mortality in most, but not all, locations[4] (Figure 1). Such heterogeneity invites a search for possible explanations: differences in the accuracy of exposure measurements, differences in the demographic and health characteristics of populations, and differences in the characteristics of PM and the air pollution mix itself. The NMMAPS investigators made an initial attempt to identify characteristics of individual cities related to the socioeconomic and health status of their populations that might explain the observed variation in

[3] This tendency, termed *publication bias*, is likely to be more pronounced when studies can be conducted relatively cheaply and easily (eg, with publicly available data) and when the cost to the investigator of discarding results that disagree with the published literature is small.

[4] Some relative risks may even be negative if the statistical model allows outlying or extreme results.

estimated PM effects but were not successful. Levy et al (2000) found some indication that among-city variation was related to characteristics of PM, with larger estimated effects observed in cities in which fine particles ($PM_{2.5}$) contributed a greater proportion of the PM_{10} mass.

Understanding why the effect of PM on daily mortality varies from place to place should be a focus of future research. Success will require, among other things, assembling data from locales that differ as widely as possible in the composition of ambient air pollution, demographics, and population health status. Ultimately, it may be possible to combine US, European, and Canadian data to address this issue, but assembling comparable data from sites around the world will present a formidable challenge.

Were the previously reported associations between PM and daily morbidity and mortality due to incomplete control of confounding by weather or other time-varying factors? Time-series estimates of the acute effects of PM exposure are based on the daily variation in ambient pollutant levels as related to the daily variation in mortality or morbidity rates. Some important causes of mortality (such as cigarette smoking or diet) would not be expected to vary with changes in daily PM levels, but factors such as seasonal changes, weather, influenza epidemics, and levels of other air pollutants, might. Unless the analysis accounts for such factors, their effects may become mixed with those of PM and produce an estimate of PM effect that is either too high or too low, a phenomenon epidemiologists term *confounding*.

Epidemiologists and statisticians have employed increasingly sophisticated and sensitive statistical tools to deal with potential confounding in time-series studies. These tools have allowed analysts to build statistical models that better describe the temporal variability of weather and other time-varying potential confounders, using fewer assumptions about their relation with mortality. As a result, a large body of work, including analyses conducted by the NMMAPS investigators in a precursor to that study (HEI 1997), has demonstrated that the associations of PM with daily mortality persist when weather and certain time-varying factors such as influenza epidemics are taken into account. NMMAPS has extended the use of these tools to multicity data.

Although we have a clearer understanding of the extent to which daily weather patterns and longer-term trends and seasonal patterns may have confounded current estimates of PM effects, additional analyses are needed to explore PM effects within seasons. Combined analyses of data from different climates, where seasonal weather patterns differ, will require development of new, more flexible seasonal indicators.

Were the previously reported associations between PM and daily morbidity and mortality due to incomplete control of confounding by other air pollutants? In cities, other air pollutants derive largely from the same sources as PM (ie, fossil fuel combustion for transportation and power generation), and therefore their ambient concentrations are often correlated over time and space with the ambient concentration of PM. Some gaseous pollutants, including sulfur dioxide (SO_2), nitrogen dioxide (NO_2), ozone (O_3), and carbon monoxide (CO), are also known to be associated with a variety of adverse health outcomes (Bascom et al 1996a,b), including increased daily mortality. Each is regulated separately, along with PM, by the EPA, although in the real world people breathe a mixture of particles and gases comprising thousands of individual substances. When evaluating associations between specific air pollutants and health, it is important to consider both the possible effects of the specific pollutant, and those of the mixture itself. The effect of the mixture may well not equal the sum of the effects of its individual constituents.

The possibility that observed associations between PM and mortality might be partially due to other pollutants has been a continuing concern. Epidemiologists have attempted to address this problem in two ways. First, they have tried to locate their studies in specific cities where levels of other pollutants are so low that they can be assumed to exert little or no effect. Under that assumption a single pollutant model that includes only PM and ignores other pollutants is fit to the mortality data. If an association with PM is observed, that association is interpreted as being independent of other pollutants. Second, epidemiologists have included data on PM and gaseous pollutants in a multipollutant statistical model in a given city, and compared the estimated effect of PM with and without consideration of other pollutants. Any association with PM remaining after such statistical control is interpreted as being independent of other pollutants.

Neither approach is entirely satisfactory. The single-pollutant approach depends critically on current knowledge about effects of low level exposure to other pollutants. In the case of SO_2, researchers continue to observe associations with daily mortality even at low ambient levels (eg, HEI 1997; Wichmann et al 2000). Although many experts would conclude, based on experimental toxicologic evidence that low ambient concentrations of SO_2 are unlikely to cause death (Bascom 1996), the persistence and strength of this association is notable. So ignoring SO_2 entirely, whatever it may represent, seems unwise. The challenge is to understand why these associations with SO_2 persist. The approach in which multiple pollutants are included in a single statistical model produces results that can be difficult to interpret when PM and gaseous pollutants are highly correlated (as they often are in single

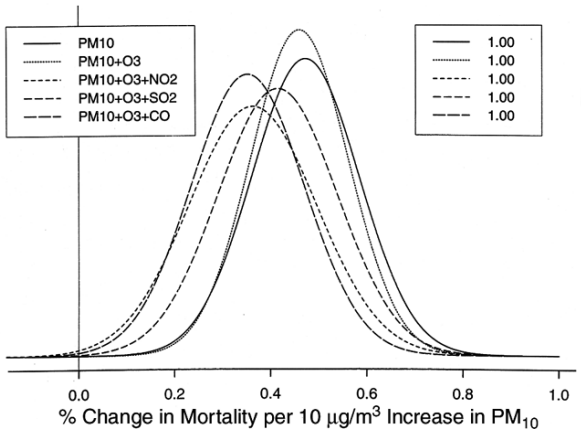

Figure 2. NMMAPS estimates of the distribution of estimated effects of PM_{10} on daily mortality with and without control for other pollutants, in 90 US cities. The box at the top right provides estimates of probabilities that the overall effects are greater than 0.

locations). HEI's earlier reanalysis (HEI 1997) of the Philadelphia time-series study of Schwartz and Dockery (1992) considered as many as 5 pollutants in the same model. Although the previous association of PM with daily mortality persisted, some other results (eg, apparently protective effects of NO_2) were difficult to explain except, perhaps, as indicating the limitations of multipollutant models when the pollutants are highly correlated with each other.

NMMAPS addressed the limitations of both approaches by estimating the association of PM_{10} with daily mortality and morbidity in a large number of US cities with varying ambient levels of gaseous pollutants. The NMMAPS design allowed a more effective use of multipollutant models (PM and as many as two other pollutants) than even the largest single-city study and allowed the effect of PM to be estimated in regions with different concentrations of copollutants and different degrees of spatial and temporal association among pollutants. Although several other pollutants (SO_2, CO, and O_3 in the summer) were weakly associated with daily mortality, none of the gaseous pollutants explained, or substantially changed, the association of PM_{10} with daily mortality (Figure 2) or hospital admissions. Different metrics (eg, peak levels of ozone) did not appear likely to explain these results.

NMMAPS strengthens the evidence that PM is associated with daily mortality and morbidity and that the association is not due to confounding effects of other, commonly measured, polluting gases. Other recent HEI-funded studies by Wichmann et al (2000) and Lippmann et al (2000), which also considered multiple pollutants, provide some support for this conclusion. While we can reasonably conclude that the PM association is valid, we should not ignore the persistent associations observed with other pollutants (SO_2, NO_2, CO, and O_3) in NMMAPS and other studies. Whether any of these associations reflects toxicity of the pollutant per se, or whether they represent the effects of a mixture of pollutants (including PM) from specific sources, is as yet unclear. We should, therefore, be careful in our interpretations of the output of even the most carefully designed statistical models.

Were the previously reported associations between PM and daily morbidity and mortality due to errors in the measurement of exposure to PM due to the use of area-wide measurements of PM concentrations rather than individual estimates of exposure for each member of the study population? For several decades governments in the US and Europe have monitored ambient levels of air pollutants to protect public health, to guide environmental regulation, and to monitor compliance. The measurement devices have generally been located so as to provide estimates of ambient concentrations of PM and other pollutants for broad geographic areas. One or a few monitors were sited to cover large urban areas. Epidemiologists have used these serial records of daily air pollution in major cities throughout the world to estimate the effects of exposure to air pollution. But they acknowledge that these measurements are crude substitutes for the data they would prefer: daily summaries of actual exposure of individual members of the population, which depends not just on the ambient levels but also on the activities of the individual (Zeger et al 2000b). For example, the frail elderly generally spend much of their time indoors, which would likely affect their exposure to ambient PM. Some suggest that use of exposure measurements from existing monitoring networks, rather than more personalized exposure estimates, overestimates the true effect of PM on daily mortality, while others argue that such measurements underestimate the true effect.

As part of NMMAPS, HEI-funded investigators examined the likely impact of exposure measurement error on the association of PM with daily mortality. First, they developed a conceptual framework, or model, that described the difference between PM measurements at central outdoor monitors and an individual's PM exposure (personal exposure) as the sum of several distinct components (including inaccuracies in the measuring equipment, and differences between a single individual's exposure and the average of the exposures of all individuals in the population). Based on this model and on the results of previous statistical research on measurement error, they concluded that under most realistic circumstances measurement error would cause an underestimate, rather than an overestimate, of the true association between PM and daily mortality. The results

of preliminary analyses using limited data from studies which measured the relationship over time between central monitor values for PM and personal exposure (including indoor exposure) support this conclusion. A more thorough assessment of the impact of measurement error using the models developed in NMMAPS would require more extensive data on measurement error for multiple pollutants (central versus personal measurements in groups at high risk of mortality such as the elderly) and in multiple cities collected over longer time periods. Ongoing research funded by HEI and others is seeking to provide these data.

What is the extent of life-shortening associated with increased daily mortality? NMMAPS investigators developed methods to determine whether the increased daily mortality associated with exposure to PM reflected only, or mainly, short-term displacement of mortality (ie, life-span reductions on the order of days (Schwartz 2000; Zeger et al 2000a). As a result, we now have a better understanding of the degree of mortality displacement due to short-term variation in air pollution. These assessments show that, after accounting for short-term mortality displacement, associations of daily mortality with PM persist and are in fact stronger at longer time scales on which the harvesting phenomenon would not be at play. This suggests some longer-term displacement, at the level of weeks or months, and implies that some individuals may have more substantial shortening of life due to air pollution. The extent of mortality displacement may differ according to cause of death (Schwartz et al 2000). These assessments are based on newly developed statistical models that have not been widely applied in air pollution epidemiology. Additional research is necessary to better understand their performance and limitations, and the sensitivity of the findings to alternative approaches.

Despite these advances in our understanding of the mortality impact of the association of PM with daily mortality, the full extent of life-span reduction associated with PM and other air pollutants cannot be estimated using the results of daily time-series studies (McMichael et al 1998). Cohort studies, in which the mortality and air pollution exposure of large populations are observed over many years, will be required. Estimates of the relative increase in mortality associated with air pollution for specific age groups can then be applied to specific populations to estimate average reductions in life-expectancy due to air pollution exposure (Brunekreef 1997; Nevalainen and Pekkanen 1998; US EPA 1999).

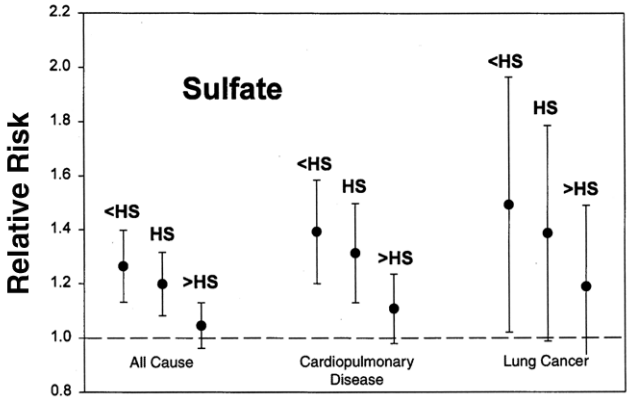

Figure 3. Relative risks of mortality by cause of death and educational attainment associated with sulfate or fine particles in the reanalysis of the ACS Study. HS = high school. Error bars represent ± SE.

Is long-term exposure to PM associated with increased mortality from chronic cardiac and/or respiratory disease? At present, only three studies, the Harvard Six Cities (Dockery et al 1993), ACS (Pope et al 1995), and Seventh Day Adventist (Abbey et al 1999) Studies have attempted to address this question directly.[5] Each reported that long-term averages (from 1 to approximately 20 years) of PM and other air pollutants were associated with increased mortality from cardiorespiratory diseases.

HEI's reanalysis of two of these studies, the Six Cities Study and the ACS Study, was intended to assess the validity of the original results. Overall, the reanalysis assured the quality of the original data and replicated the original results. In a comprehensive set of sensitivity analyses of the ACS Study data, the Reanalysis Team identified relatively robust associations of mortality with two indices of PM ($PM_{2.5}$, sulfate) and with SO_2, and they tested these associations in nearly every possible manner within the limitations of the data (HEI 2000).

Reanalysis of the Six Cities Study and the ACS Study extended and challenged our understanding of the original results in several important ways.

- In both studies the association of air pollution with mortality was greatest among those with less than a high school education (Figure 3).
- When the analyses were able to control for correlations in mortality rates among cities located near one another, the associations between mortality and PM remained but were diminished.
- In the ACS Study, an association between SO_2 and mortality persisted when other possible confounding

[5] A larger group of studies has addressed the relationship between long-term exposure to air pollution and lung cancer (Samet and Cohen 1999).

variables were included in the model; further, when SO_2 was included in models with various indices of PM, the associations between PM and mortality were reduced.

The HEI report concluded that the increased risk of "mortality may be attributed to more than one component of the complex mix of ambient air pollutants in urban areas in the United States."

There is a continuing question of how soon after exposure to pollution the effects on mortality occur. The answer will be important for determining the expected benefits of reducing air pollution. Some findings from reanalysis of the Six Cities Study are consistent with at least some of the effect being relatively short term: that is, related to air pollution levels in the previous few years. Others suggest effects of exposure 10 or more years in the past (HEI 2000). Unfortunately, neither of these studies may be capable of adequately addressing this issue due to deficiencies in the exposure data. Some reviewers, including the scientists who conducted the studies, have noted the difficulty in distinguishing between the effects of short term exposure and chronic effects that may result from long-term exposure in these studies (Dockery et al 1993; Vedal 1997). Clearer insight into these questions must await additional studies in which the temporal (as opposed to spatial) patterns of exposure can be better characterized.

Conclusions

The British biostatistician and epidemiologist AB Hill (Hill 1965), who described viewpoints[6] for causal interpretation of epidemiologic results, emphasized that the fundamental question is whether "… there [is] any other way of explaining the set of facts before us, … any other answer equally, or more, likely than cause and effect?" HEI's PM epidemiologic research program sought to address several key issues: for example, the confounding effects of other pollutants and errors in the measurement of exposure that argued against a causal interpretation of the prevailing evidence. The results are now available, and they indicate that epidemiologic evidence of PM's effects on morbidity and mortality persists even when the alternative explanations have been largely addressed.

But important questions do remain. Addressing alternative explanations for epidemiologic associations is necessary, but not sufficient, to explain them. As noted, understanding the factors responsible for variability in the estimated effects of PM among geographic regions in the US and European multicity studies is important. Much additional epidemiologic and toxicologic research is still needed to account for how both short-term and (especially) long-term exposure to PM and other pollutants affects the human cardiovascular and respiratory systems and to identify which physical and chemical features of PM are relevant to its toxicity. Finally, specific attention will need to be paid to how the results of epidemiologic and toxicologic studies should be used in health impact assessment and other public health and policy-related activities. HEI and others have begun to address some of these questions, and HEI's contributions to them are being summarized in an essay now being written.

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[6] *Viewpoints* is the term that Hill himself used to refer to the 9 aspects of epidemiologic associations that he discussed. They have been widely cited by others and frequently (ab)used as criteria for making causal judgements although Hill cautioned explicitly against this.

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This essay was prepared by the HEI Review Committee and Scientific Staff.

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