# Epidemiology of Fine Particulate Air Pollution and Human Health: Biologic Mechanisms and Who's at Risk?

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This article briefly summarizes the epidemiology of the health effects of fine particulate air pollution, provides an early, somewhat speculative, discussion of the contribution of epidemiology to evaluating biologic mechanisms, and evaluates who's at risk or is susceptible to adverse health effects. Based on preliminary epidemiologic evidence, it is speculated that a systemic response to fine particle-induced pulmonary inflammation, including cytokine release and altered cardiac autonomic function, may be part of the pathophysiologic mechanisms or pathways linking particulate pollution with cardiopulmonary disease. The elderly, infants, and persons with chronic cardiopulmonary disease, influenza, or asthma are most susceptible to mortality and serious morbidity effects from short-term acutely elevated exposures. Others are susceptible to less serious health effects such as transient increases in respiratory symptoms, decreased lung function, or other physiologic changes. Chronic exposure studies suggest relatively broad susceptibility to cumulative effects of long-term repeated exposure to fine particulate pollution, resulting in substantive estimates of population average loss of life expectancy in highly polluted environments. Additional knowledge is needed about the specific pollutants or mix of pollutants responsible for the adverse health effects and the biologic mechanisms involved. *Key words*: air pollution, cardiopulmonary disease, health effects, life expectancy, particulate pollution, review. — *Environ Health Perspect* 108(suppl 4):713–723 (2000).
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It has long been known, or at least suspected, that there are adverse health effects associated with ambient air pollution (*1*). Extreme air pollution episodes in the 1930s–1950s were associated with dramatically elevated cardiopulmonary morbidity and mortality. Evidence of serious health effects provided by these episodes spurred a growing concern about air pollution and in the United States during the 1950s through early 1970s, there was a series of legislative efforts related to trying to control air pollution. Current air pollution legislation is based largely on the 1970 Clean Air Act and 1990 Amendments to this act (*2*). The amended Clean Air Act mandated national ambient air quality standards for pollutants that are relatively common and widespread but may reasonably be anticipated to endanger public health. Six pollutants that met these basic criteria (criteria pollutants) were eventually selected, including particulate matter (PM), sulfur dioxide, nitrogen dioxide, carbon monoxide, ozone, and lead.

Since 1970 there have been hundreds of published studies that have evaluated the health effects of these air pollutants. A 1996 review of the health effects of these criteria pollutants (along with two other common pollutants) was prepared by the Committee of the Environmental and Occupational Health Assembly of the American Thoracic Society (ATS) (*2*). There have also been numerous recent reviews that have focused on health effects of particulate air pollution (*3–14*). This article does not attempt to replicate the excellent ATS review of all the criteria pollutants or previous general reviews of particulate air pollution. The overall plan of this article is to focus on three basic topics. First, the epidemiology of the health effects of fine particulate air pollution $PM_{2.5}$ (particles $\leq 2.5$ μm) will be briefly summarized, although recent, more comprehensive reviews are available. This summary relies heavily on updates of several previous reviews by Dockery and Pope (*6,8–11*). Second, a somewhat speculative discussion of the early but clearly incomplete contribution of epidemiology to evaluating the biologic mechanisms is provided. This discussion of biologic mechanisms is updated from papers originally prepared for presentation at international symposia (*10,11*). Finally, an original discussion of who risks adverse health effects due to exposure to fine particulate air pollution is presented.

## Characteristics of Fine Particles

Particulate air pollution refers to an air-suspended mixture of solid and liquid particles that vary in size, composition, and origin. The size distribution of total suspended particles (TSPs) in the atmosphere is trimodal and includes coarse particles, fine particles, and ultrafine particles. Coarse particles (often defined as those with an aerodynamic diameter $> 2.5$ μm) are often naturally occurring and derived primarily from soil and other crustal materials. Fine particles ($PM_{2.5}$) are derived chiefly from combustion processes in transportation, manufacturing, power generation, etc. Sulfate and nitrate particles are commonly generated by conversion from primary sulfur and nitrogen oxide emissions, and a varying portion of sulfate and nitrate particles may be acidic. Therefore, in most urban areas, $PM_{2.5}$ mostly comprises primary combustion-source particles as well as secondary combustion particles including sulfates and nitrates. Ultrafine particles are often defined as particles $< 0.1$ μm. These particles have relatively short residence times in the atmosphere because they accumulate or coagulate to form larger fine particles.

Various physiologic and toxicologic considerations suggest that exposure to fine particles may be a health concern. Their size is such that they can be breathed most deeply in the lungs. They include sulfates, nitrates, acids, metals, and carbon particles with various chemicals adsorbed onto their surfaces. Relative to coarse particles, they more readily penetrate indoors, are transported over longer distances, and are somewhat uniform within communities, resulting in highly ubiquitous exposure.

The initial reference method for measuring particle concentrations and establishing health standards in the United States was TSPs. In 1987 the U.S. Environmental Protection Agency (U.S. EPA) changed the reference method to include only inhalable particles. Inhalable particles refers to those particles that can penetrate the thoracic airways; for purposes of standard setting, inhalable particles were specifically defined as particles $\leq 10$ μm in aerodynamic diameter ($PM_{10}$). In 1997 the U.S. EPA promulgated new standards (*15*) for an even finer cut of particulate air pollution—particles $\leq 2.5$ μm in aerodynamic diameter ($PM_{2.5}$); however, in May 1999, a U.S. Court of Appeals blocked the implementation of these standards.

## Health Effects of Acute Exposure

The large majority of epidemiologic studies of particulate air pollution have been acute exposure studies that evaluated short-term

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(usually daily) variations in health end points such as mortality counts, hospitalizations, symptoms, and lung function associated with short-term variations in levels of pollution. A brief summary of the results of these acute exposure studies is presented in Table 1. Unfortunately, until recently (following the promulgation of the new $PM_{2.5}$ standards), there has been very little daily monitoring of fine particles, and most of the studies summarized in Table 1 used alternative measures of particulate concentrations.

## Episode Studies

The earliest and most methodologically simple epidemiologic studies are those that evaluate air pollution episodes. These studies compare mortality (and morbidity) before, during, and after pollution episodes. In December of 1930 in the Meuse Valley, Belgium, in October of 1948 in Donora, Pennsylvania, and in December of 1952 in London, England, stagnant air masses resulted in marked increases in the concentrations of air pollutants. Although the biologic mechanisms were not well understood, the large excess mortality and morbidity associated with the extreme episodes clearly demonstrated a link between mortality and morbidity and air pollution. During these episodes of highly stagnant air conditions, the PM pollution would have been primarily from combustion sources, and therefore PM mass would have been mostly fine particles. Two recent studies of less severe air pollution episodes (*16,21*) suggested smaller mortality and morbidity effects associated with less extreme pollution.

## Mortality Counts

Many recent daily time-series mortality studies have also observed changes in daily death counts associated with short-term changes in particulate air pollution, even at relatively low or moderate concentrations (Table 1). There have been more than 60 such studies conducted in at least 35 cities. The relative risk of mortality increased monotonically with particulate concentrations, usually in a linear or near-linear fashion. These studies did not observe a particulate pollution health effects threshold. In addition, these studies often observed a lead-lag relationship between air pollution and mortality. The results suggested that the increased mortality occurred concurrently or within 1–5 days following an increase in air pollution. Because various measurements of particulate pollution were used in the different studies, and because various modeling strategies were used, precise comparisons of effect estimates across all the studies were difficult. However, changes in daily mortality associated with particulate air pollution were typically estimated at approximately 0.5–1.5%/10 $\mu g/m^3$ increase in $PM_{10}$ concentrations, or per about 5 or 6 $\mu g/m^3$ increase in $PM_{2.5}$ concentrations.

Studies that provided a breakdown of mortality by broad cause-of-death categories observed that particulate air pollution generally had the largest effect on respiratory and cardiovascular disease mortality. Estimates of daily mortality effects of an increase in exposure to particulate air pollution by broad cause-of-death categories are summarized in Table 2. The estimated cause-specific increase in mortality risk is much larger for respiratory than for cardiovascular disease. However, the percent of excess deaths attributable to particulate exposure is mostly due to cardiovascular disease.

## Hospitalizations

Daily counts of hospital admissions can be analyzed in a manner similar to the assessment of daily counts of mortality. More than 50 daily time-series studies have reported associations between particulate air pollution and hospitalization or related health care end points (Table 1). Most of these studies have evaluated associations between respiratory hospital admissions and air pollution. Several studies have also analyzed emergency department visits for asthma, chronic obstructive pulmonary disease, and other respiratory ailments, and observed associations with particulate air pollution. More recent studies have observed associations between particulate air pollution and hospitalizations for cardiovascular disease (*73,74,87,98–100*).

## Symptoms/Lung Function

There are more than 40 published studies evaluating associations between daily respiratory symptoms and/or lung function and particulate air pollution (Table 1). Although many of these studies focused on asthmatics and exacerbation of asthma, others followed nonasthmatics and evaluated changes in acute respiratory health status more generally. Small, often statistically insignificant, associations between particulate pollution and upper respiratory symptoms were observed. Associations with lower respiratory symptoms and cough, however, were typically larger and usually statistically significant. Exacerbation of asthma, based on recorded asthma attacks or increased bronchodilator use, were also associated with particulate air pollution. Associations between more general measures

**Table 1.** Summary of epidemiologic evidence of health effects of acute exposure to particulate air pollution.

| Health end points | Basic study design | Observed associations with PM | References |
|---|---|---|---|
| Episodes of death and hospitalizations | Evaluate changes in mortality and morbidity before, during, and after pollution episodes. | Elevated respiratory and cardiovascular mortality and hospitalizations. | (*16–21*) |
| Mortality | Population-based time-series studies that include statistical time-series modeling to evaluate potential associations with daily mortality counts. | Elevated daily respiratory and cardiovascular mortality counts. Effects persisted with various approaches to control for time trends, seasonality, and weather. Near-linear associations with little evidence of a threshold. | (*22–66*) |
| Hospitalization and other health-care visits | Population-based time-series studies that evaluate associations between pollution and daily changes in hospitalization and related health-care end points. | Elevated hospitalizations, emergency visits, and clinic/outpatient visits for respiratory and cardiovascular disease. Effects generally persisted with various approaches to control for time trends, seasonality, and weather. | (*67–114*) |
| Symptoms/ lung function | Panel-based time-series studies of symptom and/or lung function data repeatedly collected from individuals in well-defined panels or cohorts. | Increased occurrence of lower respiratory symptoms, cough, and exacerbation of asthma. Only relatively weak associations with upper respiratory symptoms. Small, statistically significant declines in $FEV_{0.75}$, $FEV_1$, or PEF, and increased occurrence of clinically significant declines in lung function. | (*115–152*) |

Abbreviations: $FEV_{0.75}$, forced expiratory volume in 0.75 sec; $FEV_1$, forced expiratory volume in 1 sec; PEF, peak expiratory flow.

**Table 2.** Overall estimates of daily mortality effects of an increase in exposure to particulate air pollution by broad cause-of-death categories.

| Cause of death | Percent of total deaths[a] | Cause-specific percent increase per 50 $\mu g/m^3$ increase in $PM_{2.5}$[a] | Percent of excess deaths due to PM exposure |
|---|---|---|---|
| All causes[b] | 100 | 7.0 | 100 |
| Respiratory | 8 | 25.0 | 28 |
| Cardiovascular | 45 | 11.0 | 69 |
| Other disease | 47 | 0.4 | 3 |

[a]Based on updated summary estimates from previous reviews (*6,8,10*). [b]Excluding accidents, suicide, homicide, etc.

of acute disease have been studied, including evaluations of the timing of restricted activity days of U.S. adult workers due to illness (*131,132*) and school absences in grade school children (*141*).

Measures of lung function have also been used as an objective and potentially sensitive indicator of acute response to air pollution. Various studies have taken repeated measurements of the lung function of panels of children and/or adults. These studies have typically reported very small but often statistically significant decreases in lung function associated with elevated levels of particulate air pollution concentrations. Lagged effects of up to 7 days were observed.

## Effects of Chronic Exposure

The previously discussed acute exposure studies indicate that short-term exposures to elevated particulate air pollution are associated with short-term changes in cardiopulmonary health. These acute exposure studies provide little information about how much life is shortened, how pollution affects longer-term mortality rates, or pollution's potential role in the process of inducing chronic disease that may or may not be life threatening. Chronic exposure studies evaluate health end points across communities or neighborhoods with different levels of average pollution over longer time periods (usually 1 year or more). Chronic exposure studies attempt to evaluate the effects of low or moderate exposure that persists for long periods as well as the cumulative effects of repeated exposure to substantially elevated levels of pollution. A brief summary of the results of the chronic exposure studies is provided in Table 3.

### Mortality Rates

Several population-based, cross-sectional mortality studies have evaluated associations between annual mortality rates and particulate air pollution across U.S. metropolitan areas (Table 3). The basic conclusions from these population-based cross-sectional studies were that mortality rates were associated with air pollution, and they were most strongly associated with fine or sulfate PM. Such associations are illustrated in Figure 1. Age, sex, and race-adjusted population-based mortality rates for U.S. cities in 1980 are plotted over various indices of particulate air pollution [obtained from Lipfert et al. (*158*) and U.S. EPA (*163*)]. Although much apparently stochastic variability exists, adjusted mortality rates are positively correlated with fine ($PM_{2.5}$) and sulfate particles but not with TSPs. Multiple regression modeling techniques to evaluate cross-sectional differences in air pollution and mortality and to control for other ecologic variables have been used. Whereas the population-based cross-sectional studies from the United States dealt with total mortality, a study from the Czech Republic focused on infant mortality (*154*). Infant mortality, especially respiratory postneonatal infant mortality, was strongly associated with particulate air pollution. All of these population-based cross-sectional

**Table 3.** Summary of epidemiologic evidence of health effects of chronic exposure to particulate air pollution.

| Health end points | Basic study design | Observed associations with particulate pollution | References |
|---|---|---|---|
| Mortality rates | Population-based cross-sectional analysis of mortality rates across communities with different levels of pollution. | Higher mortality in areas with higher fine particulate and/or sulfate pollution levels. Pollution effect sensitive to model specification and choice of covariates included in the analysis. | (*153–160*) |
| Survival/life expectancy | Cohort-based cross-sectional studies that link community-based air pollution data with individual risk-factor and survival data. | Increased risk of respiratory and cardiovascular mortality in adults, and respiratory and sudden infant death syndrome mortality in infants, even after controlling for individual differences in cigarette smoking and various other risk factors. | (*161–164*) |
| Disease | Cross-sectional studies of community air pollution with individual symptom/disease data from surveys or collected cohorts. | Increased chronic cough, bronchitis, and chest illness (but not asthma). | (*165–170*) |
| Lung function | Cross-sectional studies of community ambient air pollution data with individual lung function data from national surveys or collected cohorts. | Particulate air pollution associated with small but often statistically significant declines in various measures of lung function in both children and adults. | (*171–176*) |

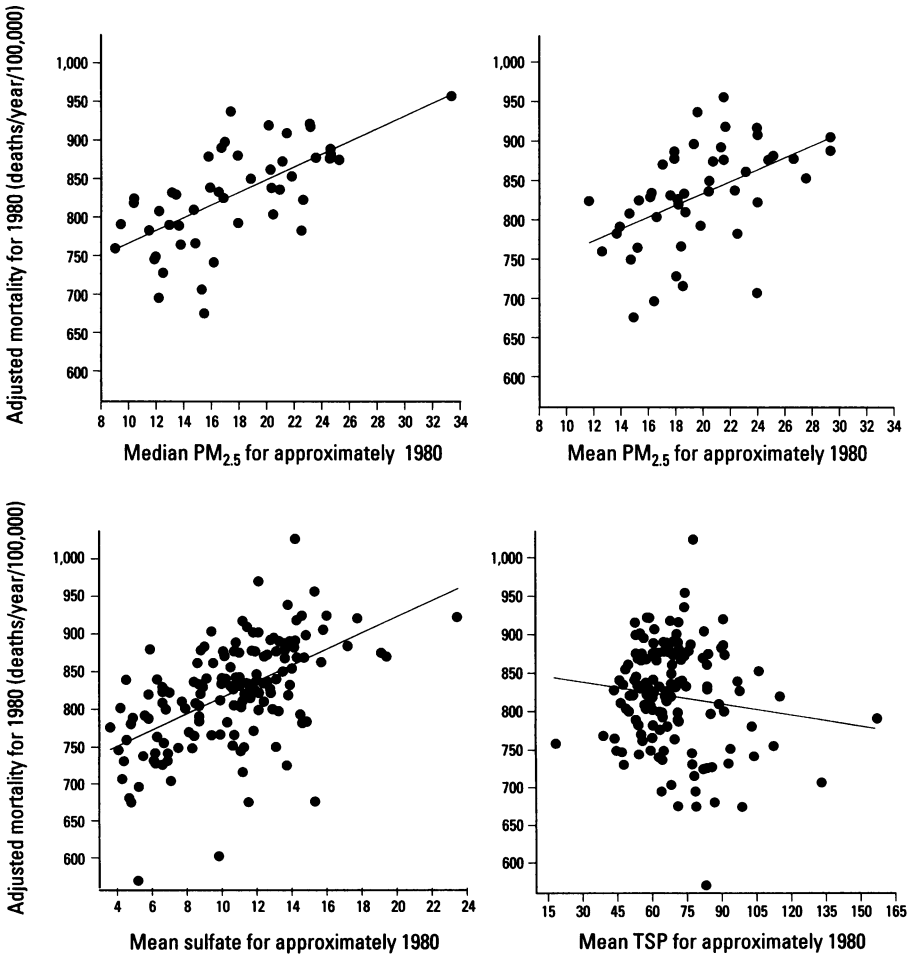


**Figure 1.** Age-, sex-, and race-adjusted population-based mortality rates in U.S. cities for 1980 plotted over various indices of particulate air pollution.

**Table 4.** Comparisons of mortality risk ratios (and 95% confidence interval) for air pollution from the Harvard Six-Cities, ACS, and postneonatal infant mortality studies.

| | Particulate air pollution (range of pollution) | | | | | |
|---|---|---|---|---|---|---|
| Cause of death | Six-Cities (18.6 μg/m$^3$ $PM_{2.5}$) | ACS (24.5 μg/m$^3$ $PM_{2.5}$) | ACS (19.9 μg/m$^3$ $SO_4$) | Infant (56.9 μg/m$^3$ $PM_{10}$) | AHSMOG (males) (24.1 μg/m$^3$ $PM_{10}$) | AHSMOG (females) (24.1 μg/m$^3$ $PM_{10}$) |
| All | 1.26 (1.08–1.47) | 1.17 (1.09–1.26) | 1.15 (1.09–1.22) | 1.25 (1.12–1.47) | 1.11 (0.98–1.26) | 0.94 (0.84–1.04) |
| Cardiopulmonary | 1.37 (1.11–1.68) | 1.31 (1.17–1.46) | 1.26 (1.16–1.37) | — | 1.10 (0.94–1.30) | 0.92 (0.80–1.05) |
| Respiratory mentioned[a] | — | — | — | — | 1.23 (0.94–1.61) | 1.10 (0.86–1.40) |
| SIDS, NBW | — | — | — | 1.91 (1.46–2.44) | — | — |
| Lung cancer | 1.37 (0.81–2.31) | 1.03 (0.80–1.33) | 1.36 (1.11–1.66) | — | 3.36 (1.57–7.19) | 1.33 (0.60–2.96) |
| All others | 1.01 (0.79–1.30) | 1.07 (0.92–1.24) | 1.01 (0.92–1.11) | 1.00[b] (0.94–1.06) | — | — |

Abbreviations: NBW, normal birth weight; PM, particulate matter; SIDS, sudden infant death syndrome.
[a]Any mention on the death certificate of nonmalignant respiratory disease as an underlying or contributing cause of death. [b]NBW.

mortality studies have severe limitations and have been discounted for several reasons. An overriding concern is that they cannot directly control for individual differences in other important risk factors including cigarette smoking.

## Survival/Life Expectancy

Several cohort-based mortality studies have evaluated effects of long-term pollution exposure. The first of these studies, often referred to as the Harvard Six-Cities study (*162*), involved a 14- to 16-year prospective follow-up of more than 8,000 adults living in six U.S. cities. It controlled for individual differences in age, sex, cigarette smoking, education levels, body mass index, and other risk factors. Cardiopulmonary mortality was significantly associated with mean sulfate and fine particulate concentrations over the years of the study period.

A second study, referred to as the ACS study, linked individual risk factor data from the American Cancer Society, Cancer Prevention Study II (CPS-II) with national ambient air pollution data (*163*). The analysis used data for more than 500,000 persons who lived in up to 151 different U.S. metropolitan areas and who were followed prospectively from 1982 through 1989. It controlled for individual differences in age, sex, race, cigarette smoking, and other risk factors, and evaluated the association of adjusted mortality with two indices of long-term exposure to combustion-source particulate air pollution, mean sulfate, and median fine particles. Both indices of combustion-source particulate air pollution were associated with overall mortality and especially with cardiopulmonary mortality.

In both the Harvard Six-Cities study (*162*) and the ACS study (*163*), the positive association between combustion-related air pollution and cardiopulmonary mortality was dominated by cardiovascular disease deaths. However, because of concerns about cause-of-death cross-coding on the death certificates, respiratory and cardiovascular deaths were grouped together and analyzed as cardiopulmonary deaths.

A study of postneonatal infant mortality in the U.S.-linked National Center for Health Statistics birth and death records for infants born between 1989 and 1991 with $PM_{10}$ data from the U.S. EPA's Aerometric Database (*164*). The full data set included approximately four million infants in 86 U.S. metropolitan areas. Because all infants in the study had $PM_{10}$ exposure for at least part of 2 months, the analysis compared postneonatal infant mortality across different levels of ambient $PM_{10}$ concentrations during the 2 months following birth. The analysis controlled for individual differences in maternal race, maternal education, marital status, month of birth, maternal smoking during pregnancy, and ambient temperatures. Particulate pollution exposure was associated with postneonatal infant mortality for all causes, respiratory causes, and sudden infant death syndrome.

A final cohort study, known as the Adventist Health Study of Smog (AHSMOG), related air pollution to 1977–1992 mortality in more than 6,000 nonsmoking adults living in California, predominantly from the three metropolitan areas of San Diego, Los Angeles, and San Francisco (*161*). All natural cause mortalities, nonmalignant respiratory mortalities, and lung cancer mortalities 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. Unfortunately, this study did not have direct measures of $PM_{2.5}$ but relied on TSP and $PM_{10}$ data. Furthermore, the cohort was relatively small and was predominantly from only three metropolitan areas, San Diego, Los Angeles, and San Francisco.

Comparisons of mortality risk ratios for air pollution from the Six-Cities, ACS, infant mortality, and AHSMOG studies are presented in Table 4. The estimated overall excess risk from the infant mortality study is similar to those estimated for adults in the Harvard Six-Cities and ACS studies, even though the time frame of exposure for the infants was clearly far shorter than for the adults. This observation suggests that the relevant time frame of exposure is short (a few months vs years) and/or that infants are at greater risk for exposure to air pollution.

## Disease/Lung Function

There have also been several studies evaluating associations between chronic exposure and particulate air pollution and respiratory symptoms and disease or lung function (Table 3). The effects of air pollution on respiratory disease or symptoms were often estimated while adjusting for individual differences in various other risk factors. Significant associations between particulate air pollution and various respiratory symptoms were often observed. Chronic cough, bronchitis, and chest illness (but not asthma) were associated with various measures of particulate air pollution. Studies that evaluated effects of air pollution on lung function adjusted for individual differences in age, race, sex, height, and weight, and controlled for smoking or restricted the analysis to never-smokers. These studies observed small associations between decreased lung function and particulate air pollution that were often statistically significant.

## Stylized Summary of Effects

The overall epidemiologic evidence is enhanced if adverse effects of exposure are reproducibly observed by different investigators in different settings. That is, there should be consistency of effects across independent studies. The evidence is further strengthened by a coherence of effects observed across a cascade of related health outcomes. Figure 2 presents a stylized summary of effect estimates of exposure to particulate air pollution. The effect estimates are not precise because different studies used various measures of pollution, different models, and differently defined health end points. In addition, the recent rapid growth of the literature in this area makes effect estimates a moving target. Figure 2, therefore, should be considered stylized but illustrative. The estimates for the

acute time-series studies are revised from recent reviews (*6,8*). The effect estimates for the cross-sectional and cohort studies are based on selected studies that are reasonably representative. The population-based mortality estimate is based on results presented by Evans et al. (*155*), Lipfert (*157*), Lipfert et al. (*158*), and Ozkaynak and Thurston (*160*). The cohort-based mortality estimates are based on Dockery et al. (*162*), Pope et al. (*163*), and Woodruff et al. (*164*), respectively. Bronchitis, children's lung function, and adult lung function estimates are based on results reported by Dockery et al. (*167*), Raizenne et al. (*173*), and Ackermann-Liebrich et al. (*171*), respectively.

As illustrated in Figure 2, a remarkable cascade of cardiopulmonary health end points has been observed. These include death from cardiac and pulmonary disease, emergency room and physician office visits for asthma and other cardiorespiratory disorders, hospital admissions for cardiopulmonary disease, increased reported respiratory symptoms, and decreased measured lung function. The overall epidemiologic evidence indicates a probable link between fine particulate air pollution and adverse effects on cardiopulmonary health. Nevertheless, there remains uncertainty about the role of chemistry versus size of the particles, the role of copollutants, and the use of central-site air quality monitoring to estimate the effects on individuals who spend most of their time indoors. In addition, there remains substantial uncertainty with regard to the biologic plausibility of these associations.

## What Are the Biologic Mechanisms?

Our knowledge about the underlying biologic mechanisms remains limited and requires much additional study. The results of the epidemiology outlined above, however, provide a pattern of effects that may be biologically germane. Biologic plausibility is enhanced by the observation of a coherent cascade of cardiopulmonary health effects and by the fact that noncardiopulmonary health end points are not typically associated with the pollution. In addition, as summarized in Table 5, very recent epidemiologic studies have attempted to look at specific physiologic end points, in addition to lung function, that may be part of the pathophysiologic pathway linking cardiopulmonary mortality and particulate air pollution.

One hypothesized general pathway includes pollution-induced lung damage (potentially including oxidative lung damage and inflammation), declines in lung function, respiratory distress, and cardiovascular disease potentially related to hypoxemia (*177*). Evidence of pollution-related inflammation has been observed (*183–185*) and, as indicated above, several studies have reported declines in lung function associated with elevated particulate pollution exposures. However, a study of potential PM-related hypoxemia did not observe declines in blood oxygen saturation associated with elevated exposures to particulate air pollution (*177*).

Alternatively, the autonomic nervous system may play an important role in the pathophysiologic pathway between particulate exposure and cardiopulmonary disease. Seaton et al. (*186*) hypothesized that fine particulate air pollution may provoke alveolar inflammation, resulting in the release of potentially harmful cytokines and increased blood coagulability. Autonomic nervous system-activated changes in blood viscosity, heart rate (HR), and heart rate variability (HRV) may increase the likelihood of cardiac death (*187*). A few recent epidemiologic studies (*177–183*) have evaluated such autonomic nervous system-related physiologic measures and air pollution, although they have been extremely limited and mostly exploratory pilot studies.

Peters et al. (*178*) evaluated blood plasma viscosity from a random sample of men and women living in Augsburg, Germany, during the winter of 1984–1985. Between January 4 and 7, 1985, there was a pollution episode with marked increases in sulfur oxide and particulate pollution concentrations. During this episode a significant increase in the risk of elevated plasma viscosity was observed. The odds ratios (and 95% confidence intervals [CIs]) for plasma viscosity were above the 95th percentile of the sample distribution; they were 3.6 (1.6–8.1) and 2.3 (1.0–5.3) for men and women, respectively.

A daily time-series panel study of elderly subjects with repeated measures of blood oxygenation did not observe pollution-related hypoxemia but did observe that elevated particulate air pollution levels were associated with increased pulse rate (*177*). A 100-mg/m$^3$

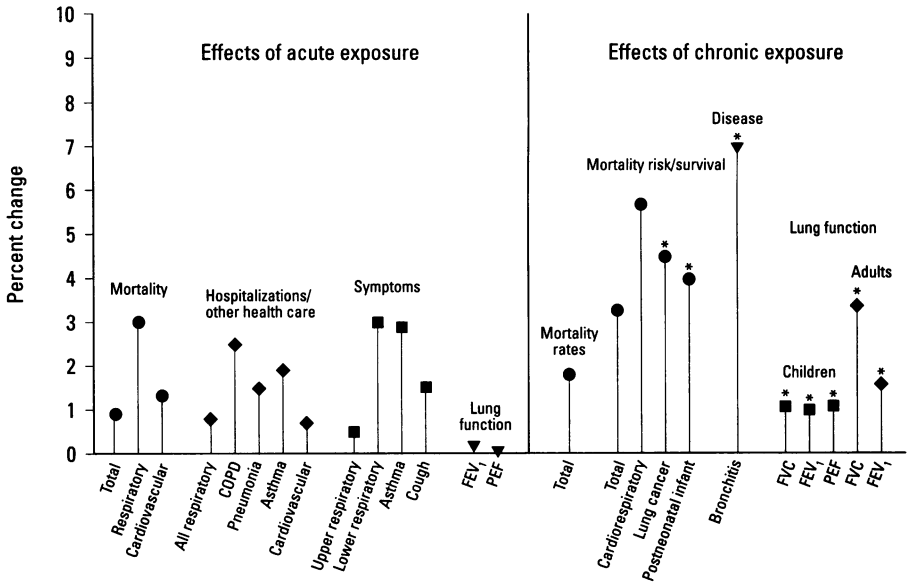


**Figure 2.** Stylized summary of observed health effects, presented as approximate percent changes in health end points per 5 μg/m$^3$ increase in $PM_{2.5}$. Abbreviations: COPD, chronic obstructive pulmonary disease; FVC, forced vital capacity; PEF, peak expiratory flow. Asterisk (*) indicates estimate based on very limited or inconsistent evidence.

**Table 5.** Brief summary of several recent epidemiologic studies of specific physiologic end points.

| Physiologic end points | Observed associations with elevated particulate matter exposure | Authors/year (reference) |
|---|---|---|
| Lung function | Small declines in lung function; large risk of substantial decrements | Hoek et al. 1999 (*125*) |
| Hypoxemia | No clear associations with blood oxygen saturation | Pope et al. 1999 (*177*) |
| Plasma viscosity | Increased risk of elevated blood plasma viscosity | Peters et al. 1997 (*178*) |
| Heart rate | Increased mean HR and odds of a substantially elevated HR. | Pope et al. 1999 (*177*)<br>Peters et al.1999 (*179*) |
| Heart rate variability | Changes in cardiac rhythm. Decrease in overall HRV. | Liao et al. 1999 (*180*)<br>Pope et al. 1999 (*181*)<br>Gold et al. 2000 (*182*) |
| Pulmonary inflammation | Elevated white blood cell counts, band cells expressed as percentage of polymorphonuclear leukocytes, platelets, lymphocytes, and eosinophils | Tan et al. 2000 (*183*)<br>Salvi et al. 1999 (*184*)[a] |

[a]This is actually a controlled human exposure study.

increase in $PM_{10}$ on the previous 1–5 days was associated with an average increase in the pulse rate of 0.8 beats/min and a 29% and 95% increase in the odds of the pulse rate being elevated by 5 or 10 beats/min, respectively.

In a related study (*181*), repeated 24-hr ambulatory electrocardiograph (ECG) monitoring was conducted on seven subjects for a total of 29 days during episodes of high pollution and during periods of relatively low pollution. HR was positively associated with particulate air pollution. Additionally, beat-to-beat (R-R) HRV was analyzed to assess cardiac autonomic control. Particulate air pollution was associated with changes in HRV including: reduced 24-hr SDNN (the standard deviation of all normal R-R intervals and an estimate of overall HRV); reduced SDANN (standard deviation of the averages of R-R intervals in all 5-min segments of the 24-hr ECG recording and an estimate of long-term components of HRV); and increased r-MSSD (the square root of the mean of squared differences between adjacent R-R intervals and an estimate of the short-term components of HRV). The associations between HRV and particulate pollution persisted even after controlling for mean HR, suggesting a possible link between elevated exposure to PM and lower cardiac autonomic control.

A prospective study of HRV and mortality in subjects with chronic heart failure was recently reported (*187*). Survival analysis conducted in this study included a Cox Proportional Hazards regression model to control for multiple risk factors. Based on this model the estimated risk ratio for a 41.2-ms decrease in SDNN (from 24-hr ambulatory ECG monitoring) was 1.62 (95% CI, 1.16–2.44). As an interesting but highly speculative look at plausibility, the 24-hr SDNN mortality relationship from this study can be combined with the decline in 24-hr SDNN associated with $PM_{10}$ from the above HRV study (*181*). The expected increase in mortality risk can then be estimated and compared with the PM-related cardiovascular mortality risk directly estimated from the PM mortality epidemiology studies. For example, the estimated decline in 24-hr SDNN associated with 100 $\mu g/m^3$ $PM_{10}$ was approximately 18 ms (SE = 4.9). Using the coefficients reported in these two studies (*181,187*), the estimated mortality risk ratio of an 18-ms decline in 24-hr SDNN can be calculated as 1.23 ($e^{[18*(\ln 1.62)/41.2]}$). This risk ratio seems somewhat plausible. It is larger than risk ratios for total or cardiovascular disease mortality that are generally estimated from daily time-series studies but smaller than risk ratios estimated from the prospective cohort mortality studies of long-term chronic exposure.

Two additional studies have also recently evaluated associations between particulate air pollution and HRV. One of these studies explored daily changes in HRV associated with daily changes in fine particulate air pollution with a panel of elderly subjects living in metropolitan Baltimore (*180*). Daily ECG monitoring was conducted with resting, supine, 6-min R-R interval data collected each day. The second study involved subjects 53–87 years of age living in Boston, Massachusetts (*182*). Weekly ECG monitoring was conducted using ambulatory (Holter) monitors continuously for 25 min, including 5 min of rest, 5 min of standing, 5 min of outdoor exercise, 5 min of recovery, and 20 cycles of slow breathing. Although the pollution levels were relatively low during the study periods in both of these studies, lower HRV was associated with elevated concentrations of fine particulate pollution, and the association was stronger for subjects with pre-existing cardiovascular conditions.

In the three currently available studies of particulate air pollution and HRV (*180–182*), a negative association with particulate exposure and overall HRV was observed. The results, however, are not entirely consistent, especially with measures of the short-term (or high-frequency) components of HRV. To what degree these inconsistencies across studies can be explained by differences in ECG monitoring time frames, make-up of subjects, differences in pollution levels, or other differences needs to be explored.

A study of rabbits found that alveolar macrophage phagocytosis of small carbon particles < 10 μm in aerodynamic diameter resulted in the release of cytokines that led to stimulation of the bone marrow to release young polymorphonuclear leukocytes (PMNs). The authors postulated that these PMNs caused the health effects noted in epidemiologic studies (*188*). A follow-up study was conducted of an air pollution episode due to fires in Southeast Asia in 1997 (*183*). Blood samples from 30 healthy male military personnel were collected during and after the episode. The pollution episode was associated with significant increases in total white blood cell counts, band cells expressed as a percentage of PMNs, platelets, lymphocytes, and eosinophils. The authors suggest that these results imply a systemic response to PM-related pulmonary inflammation. A recent controlled human study of exposure to diesel exhaust also observed a well-defined and marked systemic and pulmonary inflammatory response in healthy human volunteers (*184*).

The physiologic relevance of no PM-related hypoxemia but PM-related changes in blood plasma viscosity, HR, HRV, and pulmonary inflammation is not well understood. Recent animal studies have observed somewhat complementary results (*188–194*), but the epidemiologic observations are preliminary and based on only a few studies, most of which were exploratory pilot studies. These changes may reflect PM-induced pulmonary inflammation, cytokine release, and altered cardiac autonomic function as part of the pathophysiologic mechanisms or pathways linking PM and cardiovascular mortality. In general, it is speculated that interactions between inflammation, abnormal hemostatic function, and altered cardiac rhythm may play an important role in the pathogenesis of cardiopulmonary diseases related to air pollution. An adequate understanding of these relationships clearly requires further research.

## Who's at Risk?

The question of who is at risk or who is susceptible to adverse health effects of fine PM pollution does not have an easy answer. It seems evident that the elderly, young children, and persons with chronic cardiopulmonary disease, influenza, and asthma are most likely to be susceptible. However, this answer is far too simplistic. For example, assume a large population of nonsmokers. Require all in the population to smoke a pack of cigarettes for a day and then stop. Who will be susceptible to this relatively short-term exposure to cigarette smoking? Mortality and serious morbidity effects would most likely affect the very old, young, and those with asthma or chronic cardiopulmonary disease. This does not mean that others are unaffected. For healthy, middle-aged adults, the effects are unlikely to be immediately life threatening, but short-term adverse effects such as coughing, throat and eye irritation, or even mild or moderate cigarette smoke-induced pulmonary inflammation may be experienced. Further suppose smoking does not stop after 1 day but continues throughout the lives of all in the population. Now who is susceptible to exposure to cigarette smoke? Over a lifetime, the chronic exposure has the potential to eventually effect all. Although the exposures and effects for active cigarette smoking are much larger, cigarette smoking has been associated with a spectrum of cardiopulmonary diseases similar to those associated with fine PM. Interestingly, a decrease in HR and an increase in HRV have also been observed following smoking cessation (*195*). Clearly, the answer to the question of who is susceptible is not simple but is dependent on the health effects being evaluated and the level and length of exposure.

### At Risk from Short-Term, Acute Exposure

A summary of who may be susceptible to various adverse health effects from PM

exposure and overall health relevance is presented in Table 6. With respect to acutely elevated exposures, reflected by day-to-day changes in PM, those susceptible to dying are the elderly, the very young, and persons with chronic cardiopulmonary disease, influenza, or asthma. During the London episode of 1952, for example, approximately 80–90% of the excess deaths were in adults with respiratory and/or cardiovascular disease that was generally chronic in nature. There was also an approximate doubling of deaths in children less than 1 year of age (*20*). As summarized in Table 2, more recent daily time-series studies also observe that most of the excess mortality from PM exposure is from respiratory and cardiovascular disease deaths.

How much life shortening is due to acutely elevated levels of PM and how much of the mortality is due to short-term mortality displacement (harvesting) remains uncertain. If the increased mortality is only in the most frail persons with little remaining life expectancy, then death may be advanced by only a few days or weeks. However, recent research using data from Philadelphia, Pennsylvania observed that the increase in mortality was inconsistent with only short-term mortality displacement and suggests that mortality for many may be substantially advanced (*196*). These results also suggest that those who are susceptible to increased risk of mortality from acutely elevated PM may include more than just the most old and frail who are already very near death.

On any given day, the number dying due to PM exposure is extremely small. Based on the 1996 average death rate for the United States (8.8/1000/year) and the summary estimates presented in Table 2, a 50-$\mu g/m^3$ increase in $PM_{2.5}$ would result in an average of only 1.7 deaths per day per one million people (compared to an expected rate of approximately 24/day). This minimal excess deaths per day reflects the fact that the increased risk of mortality due to acutely elevated PM exposure is small, and on any given day there may only be a very small fraction of the population at serious risk of dying due to this acute exposure.

As summarized in Table 6, the number of those susceptible to being hospitalized because of acute PM exposure is probably also quite limited and similar to the number of those at risk of dying. However, the number of those susceptible to less serious health effects such as increased respiratory symptoms, decreased lung function, or other physiologic changes may be quite broad. For most people, these effects are likely small, transient, and maybe even unnoticed. For a few, the decline in lung function may be clinically relevant (*125*), or the effects may be result in short-term absence from work (*131,132*) or school (*141*).

## At Risk from Long-Term Chronic Exposure

Long-term, repeated PM exposure has been associated with increased population-based mortality rates (*155–160*) as well as increased risk of mortality in broad-based cohorts or samples of adults (*162,163*) and children (*164*) (Table 4). Chronic exposure studies of PM suggest rather broad susceptibility to cumulative effects of long-term repeated exposure. There is no evidence that increased mortality risk is unique to any well-defined susceptible subgroup. All who are chronically exposed may ultimately be affected. However, because the relative risk is small, the long-term cumulative effects are most likely to be observed in older age groups with relatively higher baseline risks of mortality.

To illustrate the potential cumulative mortality effects of PM, survival curves and life expectancies have been estimated under six different scenarios illustrated in Figure 3. The first curve is a baseline survival curve based on projected U.S. life tables prepared by the Office of the Chief Actuary in the Social Security Administration and obtained from the Berkeley Mortality Database (*197*). Although a survival curve for never-smokers and for persons not exposed to urban air pollution was not directly calculated, this projected baseline curve is used to represent a reasonable baseline estimate for the total U.S. population. The life expectancy of this baseline curve is equal to 76.4 years.

The second, third, and fourth survival curves are calculated from the baseline curve assuming an additional relative risk of mortality from PM exposure equal to 1.25. This is approximately the relative risk estimated in both the Harvard Six-Cities study (*162*) and the postneonatal infant mortality study (*164*) for the relevant range of PM air pollution that exists in U.S. urban areas (Table 4). The only difference between the second, third, and fourth curves is the age at which people begin to be susceptible to the effects of pollution. Curves two, three, and four assume that susceptibility begins at age 45 years, age 1 year, and at birth, respectively. As can be seen in Figure 3, these three survival curves appear to be nearly identical. The close concurrence between these three curves is because the baseline mortality risk for infants, children, and young adults is so low compared to the baseline mortality risks for older adults. The estimated life expectancy for curves two, three, and four equal 73.9, 73.5, and 73.4 years, respectively. This suggests an average loss of life expectancy equal to 2.5, 2.9, and 3.1 years, respectively. Obviously, earlier onset ages of susceptibility result in greater

**Table 6.** Summary of who's susceptible to adverse health effects from PM exposure and overall health relevance.

| Health effects | Who's susceptible? | Overall health relevance |
|---|---|---|
| Acute exposure | | |
| Mortality | Elderly, infants, persons with chronic cardiopulmonary disease, influenza, or asthma | Obviously relevant. How much life shortening is involved and how much is due to short-term mortality displacement (harvesting) is uncertain. |
| Hospitalization/ other health care visits | Elderly, infants, persons with chronic cardiopulmonary disease, pneumonia, influenza, or asthma | Reflects substantive health impacts in terms of illness, discomfort, treatment costs, work or school time lost, etc. |
| Increased respiratory symptoms | Most consistently observed in people with asthma and children | Mostly transient effects with minimal overall health consequence, although for a few there may be short-term absence from work or school due to illness. |
| Decreased lung function | Observed in both children and adults | For most, effects seem to be small and transient. For a few, lung function losses may be clinically relevant. |
| Plasma viscosity, heart rate, heart rate variability, pulmonary inflammation | Observed in both healthy and unhealthy adults. No studies of children | Effects seem to be small and transient. Overall health relevance is unclear, but may be part of pathophysiologic pathway linking PM with cardiopulmonary mortality. |
| Chronic exposure | | |
| Increased mortality rates, reduced survival times, chronic cardiopulmonary disease, reduced lung function | Observed in broad-based cohorts or samples of adults and children (including infants). All chronically exposed potentially are affected | Long-term, repeated exposure appears to increase the risk of cardiopulmonary disease and mortality. May result in lower lung function. Population average loss of life expectancy in highly polluted cities may be as much as a few years. |

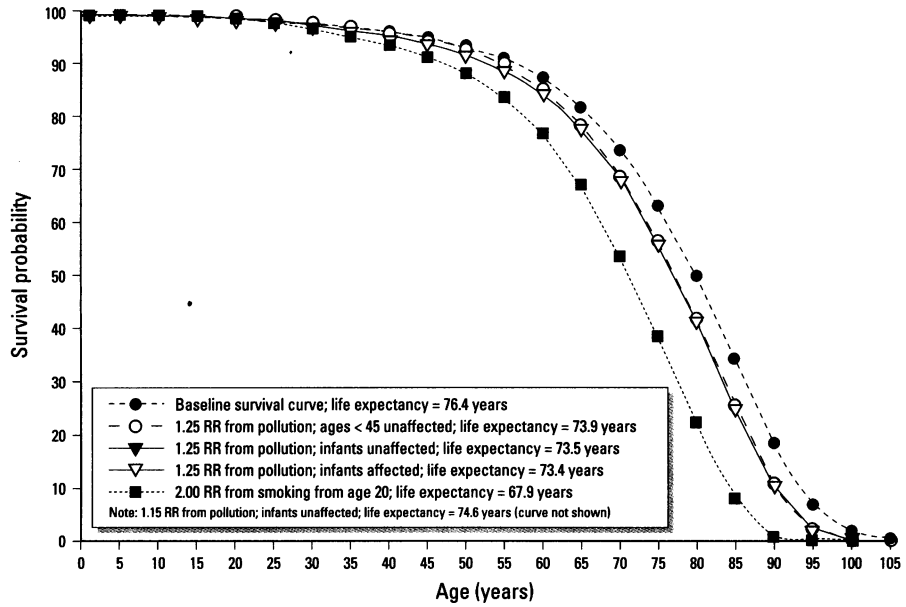


**Figure 3.** Survival curves based on projected U.S. life tables and alternative excess risk assumptions. Abbreviation: RR, relative risk.

overall loss of life. Differences in assumptions about the age when susceptibility begins, however, make only small differences for the younger ages because of the relatively low baseline mortality risks.

Survival curve five in Figure 3 was calculated from the baseline curve assuming an additional relative risk of mortality from cigarette smoking from age 20 equal to 2.00. This is approximately the average relative risk of approximately average levels of smoking versus never smoking that was estimated in both the Harvard Six-Cities study (*162*) and the ACS study (*163*). The estimated average life expectancy for smokers was 67.9, a loss of life expectancy equal to 8.6 years. Clearly, cigarette smoking has a much larger impact on mortality than ambient air pollution. However, this estimate of loss of life expectancy is not a population average, but the average loss to smokers only.

The sixth curve was calculated from the baseline curve assuming an additional relative risk of mortality from PM exposure equal to only 1.15. This is approximately the relative risk that was estimated from the ACS study (*163*) for the relevant range of PM air pollution in the United States (Table 4). Susceptibility was assumed to begin after infancy at age 1 year. The estimated life expectancy was 74.6, a loss of life expectancy equal to 1.8 years. These results are comparable to those obtained from two similar analyses (*198,199*).

Although the elevated risk associated with particulate air pollution exposure is relatively small compared with cigarette smoking, the public health significance of fine particulate air pollution, at least as measured in population average loss of life, is substantial for two basic reasons. Exposure is ubiquitous. Because fine particles are often generated indoors and ambient fine particles penetrate many indoor environments, essentially everyone is exposed. Furthermore, exposure is not a voluntary decision made as a teenager or in adulthood but occurs throughout life.

The above estimates of population average life lost from the pollution are probably a worst-case scenario for the United States. They use relatively large estimates of excess risk from chronic exposure to pollution from the recent prospective cohort studies of adults and the postneonatal infant mortality study. They assume that the risk effects are cumulative for all or a large part of persons' lives, and they assume lifelong residency in one of the most polluted U.S. cities. Loss of life estimates due to pollution exposure of 1–3 years for lifelong residents of highly polluted cities, however, is not unreasonable, especially in some of the more polluted cities in the world.

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