AHA Scientific Statement

Air Pollution and Cardiovascular Disease

A Statement for Healthcare Professionals From the Expert Panel on Population and Prevention Science of the American Heart Association

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Abstract—Air pollution is a heterogeneous, complex mixture of gases, liquids, and particulate matter. Epidemiological studies have demonstrated a consistent increased risk for cardiovascular events in relation to both short- and long-term exposure to present-day concentrations of ambient particulate matter. Several plausible mechanistic pathways have been described, including enhanced coagulation/thrombosis, a propensity for arrhythmias, acute arterial vasoconstriction, systemic inflammatory responses, and the chronic promotion of atherosclerosis. The purpose of this statement is to provide healthcare professionals and regulatory agencies with a comprehensive review of the literature on air pollution and cardiovascular disease. In addition, the implications of these findings in relation to public health and regulatory policies are addressed. Practical recommendations for healthcare providers and their patients are outlined. In the final section, suggestions for future research are made to address a number of remaining scientific questions. **(*Circulation*. 2004;109:2655-2671.)**

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Recently, the American Heart Association (AHA) published "Guidelines for Primary Prevention of Cardiovascular Disease and Stroke" as an aid to healthcare professionals and their patients without established coronary artery disease or other atherosclerotic diseases.[1] The statement was intended to complement the AHA/American College of Cardiology (ACC) "Guidelines for Preventing Heart Attack and Death in Patients with Atherosclerotic Cardiovascular Disease."[2] Both sets of recommendations emphasized multifactorial interventions, especially more intensive measures/goals to modify individual cardiovascular risk factors with diet, drugs, exercise, weight management, complete smoking cessation, and avoidance of secondhand smoke (SHS), or combinations thereof.

Over the last decade, however, a growing body of epidemiological and clinical evidence has led to a heightened concern about the potential deleterious effects of ambient air pollution on health and its relation to heart disease and stroke. Of special interest are several environmental air pollutants that include carbon monoxide, oxides of nitrogen, sulfur dioxide, ozone, lead, and particulate matter ("thoracic particles" [PM_{10}] <10 μm in aerodynamic diameter, "fine particles" [$PM_{2.5}$] <2.5 μm, and "coarse particles" [$PM_{10\ to\ 2.5}$]). These pollutants are associated with increased hospitalization[3] and mortality due to cardiovascular disease,[4–6] especially in persons with congestive heart failure, frequent arrhythmias, or both.[7] The well-established causal associations between active and passive smoking with heart disease and stroke support the plausibility of an adverse effect of PM on the cardiovascular system.

The most recent analysis of the National Mortality and Morbidity Air Pollution Study (NMMAPS), based on data from 90 of the largest cities in the United States, estimated that daily total and cardiopulmonary mortality increased in the short term by 0.21% ($\pm$0.06 standard error [SE]) and 0.31% ($\pm$0.09 SE), respectively, for each 10-μg/m^3 increase in PM_{10} (measured over a 24-hour period).[8] To give some context to a 24-hour PM_{10} increment of 10 μg/m^3, the US Environmental Protection Agency (EPA) reported a range of maximum city-specific 24-hour PM_{10} concentrations from 26 to 534 μg/m^3.[9] Data from the American Cancer Society (ACS) cohort[5] estimated that for each 10-μg/m^3 increase in annual average exposure to $PM_{2.5}$, long-term all-cause, cardiopulmonary, and lung cancer mortality were increased by

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approximately 4%, 6%, and 8%, respectively. On the basis of a job exposure matrix, Gustavsson et al[10] reported increasing risks of myocardial infarction among ≈3000 Swedish workers with increasing cumulative exposure to products from nonvehicular combustion processes.

To evaluate whether high concentrations of ambient particles can trigger the onset of acute myocardial infarction (AMI), Peters and associates,[11] using a case-crossover approach, interviewed 772 patients with AMI as part of the Determinants of Myocardial Infarction Onset Study. Elevated concentrations of $PM_{2.5}$ were associated with a transient risk of AMI onset during 2 separate time periods (within 2 hours and 1 day after exposure). On the other hand, investigators in Seattle, Wash, did not find an association between high levels of PM_{10} and the occurrence of primary cardiac arrest that occurred outside of the hospital in presumably healthy adults[12] or in subjects with known underlying heart disease.[13] A recent report by Suwa et al[14] provides experimental evidence to support the hypothesis that these epidemiological data truly reflect the deleterious effects of particulate pollution on the cardiovascular system. Compared with their control counterparts, hyperlipidemic rabbits exposed to PM_{10} showed more advanced coronary lesions, increased plaque size, more extensive atherosclerosis in the aorta, and an increase in the volume fraction of lesions composed of lipids (ie, plaques more likely to rupture).[15] Other contemporary studies suggest that possible links between acute and/or chronic exposure to PM and cardiovascular events may be related to increases in heart rate and blood pressure, fibrinogen, and blood coagulation factors; arterial vasoconstriction; inflammatory mediators (eg, C-reactive protein [CRP]); endothelial injury/dysfunction; and decreases in heart rate variability (HRV).[16] Consequences of these effects may include myocardial ischemia (manifested as significant ST-segment depression during exercise testing,[17] angina pectoris, or both), malignant ventricular arrhythmias,[18] increased plaque vulnerability, and enhanced potential for acute thrombosis triggering acute coronary syndromes. Further support that these changes can be attributed to air pollution comes from studies of the effects of SHS, which is the single largest contributor to indoor PM[19] when a smoker is present. Exposure to SHS increases platelet activation,[20] causes rapid deterioration in endothelial function,[21,22] promotes atherosclerotic plaque development,[23] and abets infarct expansion in experimental animals.[24] Because exposure to the SHS of just 1 cigarette per day accelerates the progression of atherosclerosis,[25] it is plausible that even low doses of air pollution could have negative effects on coronary morphology and circulation.

Collectively, these and other studies (described herein) suggest that air pollution may accelerate the development of coronary atherosclerosis and worsen its sequelae. Some of these effects may occur over time, as with acceleration of the progression of atherosclerosis, or rather abruptly, as with the triggering of an arrhythmia or myocardial infarction by acute inflammatory responses, altered platelet adhesiveness, or perhaps vascular endothelial dysfunction. This AHA scientific statement provides healthcare professionals and regulatory agencies with a comprehensive review of the relationship between air pollution and cardiovascular disease. A brief description of the different types of air pollutants is provided first for background. In the remaining sections, the focus of this statement is on PM, with occasional references to the health effects of other pollutants, alone or in combination. The link between SHS and heart disease is outlined next, which provides a relevant model for the cardiovascular effects of air pollution. In the following sections, many of the pertinent epidemiological studies and the potential pathophysiological mechanisms underlying the increased risk of cardiovascular events due to PM are discussed. In the summary and conclusion sections, the implications of these data regarding public health policy and unanswered (future) research questions are addressed.

Ambient Air Pollutants

A brief description of several individual air pollutants is provided first for background. A complete discussion is beyond the scope of this statement, and interested readers may find a more comprehensive review on this subject elsewhere.[26]

Particulate Matter

Airborne PM consists of a heterogeneous mixture of solid and liquid particles suspended in air, continually varying in size and chemical composition in space and time (Figure 1). Primary particles are emitted directly into the atmosphere, such as diesel soot, whereas secondary particles are created through physicochemical transformation of gases, such as nitrate and sulfate formation from gaseous nitric acid and sulfur dioxide (SO_2), respectively. The numerous natural and anthropogenic sources of PM include motor vehicle emissions, tire fragmentation and resuspension of road dust, power generation and other industrial combustion, smelting and other metal processing, agriculture, construction and demolition activities, residential wood burning, windblown soil, pollens and molds, forest fires and combustion of agricultural debris, volcanic emissions, and sea spray. Although there are thousands of chemicals that have been detected in PM in different locations, some of the more common constituents include nitrates, sulfates, elemental and organic carbon, organic compounds (eg, polycyclic aromatic hydrocarbons), biological compounds (eg, endotoxin, cell fragments), and a variety of metals (eg, iron, copper, nickel, zinc, and vanadium).

Largely because of the complex nature of PM, it has been measured and regulated based primarily on mass within defined size ranges. In 1987, the regulatory focus shifted from total suspended particles to particles that could readily penetrate and deposit in the tracheobronchial tree, or PM_{10} (PM with a median aerodynamic diameter of <10 μm). In 1997, the US EPA promulgated 24-hour and annual average standards for $PM_{2.5}$ (PM with median aerodynamic diameter <2.5 μm), comprising the size fraction that can reach the small airways and alveoli. The existing federal PM_{10} standards were retained, however, to address health effects that could be related to the "coarse fraction" ($PM_{10\ to\ 2.5}$). Currently, a separate $PM_{10\ to\ 2.5}$ standard is under consideration. In general, $PM_{2.5}$ originates mostly from combustion sources and

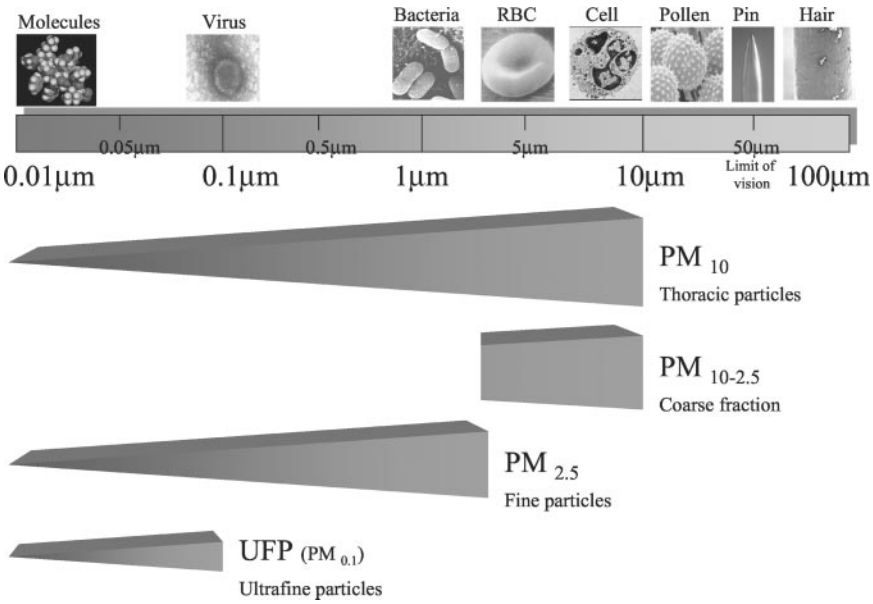

Figure 1. Particulate matter air pollution size distribution.

includes primary and secondary particles, whereas the coarse fraction derives predominantly from natural sources, especially crustal material (including windblown soil) and grinding processes. Important bioaerosols (eg, endotoxin, pollen grains, and fungal spores) are found mostly in the coarse fraction (and larger particles), although both endotoxin (an essential component of the cell wall of Gram-negative bacteria) and the antigenic protein content of pollen grains can also adsorb onto the surface of fine PM. Generally, larger particles demonstrate a greater fractional deposition in the extrathoracic and upper tracheobronchial regions, whereas smaller particles (eg, $PM_{2.5}$) show greater deposition in the deep lung. Although $PM_{2.5}$ generally behaves as a regional pollutant, there can be considerable small-scale spatial variability due to point source emissions (eg, a smelter) or features such as street canyons in large cities. In addition, prevailing wind patterns can affect human exposures.

More recently, considerable research attention has been devoted to ultrafine particles (UFPs) $<$100 nm (0.1 μm) in diameter, which result from combustion processes. UFPs tend to be short-lived, because they agglomerate and coalesce into larger particles. However, they demonstrate very high deposition in human alveoli,[27] account for a major portion of the actual numbers of particles within PM, and have a high surface area-to-mass ratio, potentially leading to enhanced biological toxicity. UFPs may even be able to pass directly into the circulatory system, which could allow them to be disseminated systemically.[28–30]

Nitrogen Oxides

Nitrogen oxides are reactive substances commonly understood to encompass nitric oxide (NO), nitrogen dioxide (NO_2), nitrogen trioxide, nitrogen tetroxide (N_2O_4), and dinitrogen pentoxide (N_2O_5). These compounds are referred to collectively as "NO_X." Gaseous nitric acid (HNO_3), a major source of particulate nitrate, is formed when NO_2 reacts with hydroxyl radicals during the day and when N_2O_5 reacts with water vapor at night.[31] Other members of the larger family of nitrogen oxides include nitrous acid, nitrous oxide, peroxyacetyl nitrate (responsible for some of the irritant effects of photochemical smog), nitrites, nitroso compounds, and other nitrogen-containing acids. Most toxicological and epidemiological research has focused on NO_2, because of the fact that (1) NO_2 is one of the regulated air pollutants for which standards are available worldwide; (2) NO from vehicular exhaust and power plants is largely converted to NO_2; and (3) NO_2 plays a primary role in the formation of tropospheric ozone (O_3).

The main anthropogenic source of NO_X in ambient air is fossil fuel combustion in motor vehicles and industrial processes, particularly in power generation. High-temperature combustion results in the oxidation of atmospheric N_2, first to NO and then to NO_2. Motor vehicle emissions near busy streets can result in high local NO_X concentrations. The typical diurnal NO_X pattern consists of a low background concentration, with morning and late afternoon peaks resulting from rush-hour traffic. Nitrogen in fossil fuels such as coal can be oxidized to NO_2 under oxygen-rich combustion conditions. NO_2 and NO are both formed naturally as a result of bacterial metabolism of nitrogenous compounds and, to a lesser extent, from fires, volcanoes, and fixation by lightning. The generation of tropospheric ozone and other photochemical oxidants is initiated with photolysis of NO_2, whereas NO acts as an ozone scavenger.[32]

Significant human exposure can occur in nonoccupational indoor settings.[33,34] Gas-burning appliances, such as unvented furnaces and stoves, are the principal sources of indoor NO_X, although kerosene space heaters and tobacco smoke may also play a role.[35,36] In urban areas, infiltration of ambient NO_2 from vehicular emissions may also influence indoor exposures.[33] Several reports have also documented toxic concentrations of NO_2 in ice-skating rinks.[37,38]

Carbon Monoxide

Carbon monoxide (CO) is a nearly ubiquitous product of incomplete combustion of carbon-containing fuels. Outdoor

sources include motor vehicles; engines on motorboats, lawnmowers, chain saws, and other devices that require fossil fuel combustion; residential wood burning; improperly adjusted gas-burning and oil appliances; coal combustion; and tobacco smoking.[39,40] In urban areas, the contributions of diesel and stationary source combustion are relatively small in relation to gasoline-powered engines.[41]

CO is an odorless, colorless, and tasteless gas that binds to hemoglobin with an affinity 250 times that of oxygen, thereby interfering with the systemic delivery of oxygen to tissues. In addition, binding of CO to hemoglobin causes an allosteric change in the conformation of the oxyhemoglobin complex that increases the oxygen affinity of the remaining binding sites and interferes with the release of O_2 at the tissue level. In addition, CO binds to cytochrome oxidase, exacerbates cellular hypoxia, and binds to other extravascular proteins that include myoglobin, cytochrome P-450, catalase, and peroxidases.[42] Given current ambient CO concentrations in the United States, it is likely that in most circumstances, this pollutant serves more as an indicator of combustion-related pollution than as a direct toxicant. However, in some situations (eg, insufficiently ventilated parking structures), CO could attain concentrations sufficient to lead to physiologically meaningful increases in carboxyhemoglobin in persons with significant atherosclerotic disease or other cardiac conditions.

Sulfur Dioxide

Sulfur dioxide (SO_2) is a highly irritating, colorless, soluble gas with a pungent odor and taste. In contact with water, it forms sulfurous acid, which accounts for its strong irritant effects on eyes, mucous membranes, and skin.[43] SO_2 is efficiently scrubbed from inhaled air in the upper airway.

In the absence of human activities, background concentrations of ambient SO_2 are very low, in the range of 1 ppb. In ambient air, the principal sources of SO_2 include combustion of sulfur-containing fuels, especially in power plants and diesel engines (prior to the reformulation of diesel fuels), and roasting of metal sulfide ores. Sulfur dioxide is oxidized to sulfur trioxide, which, because of its strong affinity for water, can be rapidly hydrated to form sulfuric acid.[44] Elevated levels of SO_2 have been associated with widespread illness in several 20th century air pollution catastrophes; however, much of the morbidity and mortality in these episodes may have been due to its role in the formation of particulate sulfates. In nonoccupational settings, SO_2 is generally found at substantially lower concentrations indoors than outside; however, the use of kerosene space heaters can generate significant indoor concentrations.[35]

Ozone

Ozone (O_3) is a highly reactive, colorless-to-bluish gas with a characteristic odor associated with electrical discharges.[43] Low-level exposure is ubiquitous, because O_3 is formed by natural processes and by human activities. Ozone is formed in the stratosphere by the action of solar radiation on molecular oxygen (O_2). Because stratospheric O_3 prevents high-energy UV radiation from penetrating the atmosphere, many terrestrial life forms would be unable to survive without this O_3 "shield."

O_3 has been recognized since the 1950s as the principal component of photochemical smog. In the troposphere, it is formed by the action of solar UV radiation on nitrogen oxides and reactive hydrocarbons, both of which are emitted by motor vehicles and many industrial sources. The reaction sequence involves photolysis of NO_2 into NO and oxygen atoms. The latter react with molecular oxygen to form O_3. NO, however, rapidly scavenges O_3, regenerating NO_2 and O_2, as summarized below:

$$NO_2 + h\nu\ (295 < \nu < 430\ \text{nm}) \rightarrow NO + O$$

$$O + O_2 + M \rightarrow O_3 + M$$

$$NO + O_3 \rightarrow NO_2 + O_2,$$

where M represents any nearby molecule that can absorb the energy of the reaction. Under steady-state conditions, there is little accumulation of O_3. However, many reactive organic compounds can facilitate the oxidation of NO to NO_2 by alternative mechanisms. These reactions reduce NO scavenging, which allows O_3 concentrations to increase.[45]

Photochemical O_3 formation tends to be greatest on warm, sunny days. The typical profile of tropospheric O_3 formation in populated areas is characterized by a broad peak that lasts from the late morning until the late afternoon or early evening. However, large-scale transport may result in elevated O_3 concentrations that extend over thousands of square miles to include rural areas far removed from the precursor sources. Thermal inversion height, wind speed and direction, addition of other O_3 precursors along an air mass trajectory, and other factors affect the temporal O_3 patterns downwind, so that peak concentrations may occur anytime from noon until late in the evening.[46] Human activities are major sources of O_3 precursors, although the latter are also generated by nonanthropogenic processes that include the intrusion of stratospheric O_3, the action of lightning on molecular oxygen, and chemical reactions involving naturally occurring nitrogen oxides and organic compounds, such as biogenic methane and other volatile organic compounds.[45]

Secondhand Smoke

The national awareness of SHS as a major risk factor for chronic disease was substantially heightened with the 1986 Report of the Surgeon General, "The Health Consequences of Involuntary Smoking,"[47] and the 1992 EPA report on the respiratory health effects of SHS.[48] The primary focus of the Surgeon General's report was on lung cancer and other respiratory diseases,[47] although evidence linking passive smoking to heart disease was just beginning to emerge.[49] Similarly, the EPA report focused primarily on the impact of SHS on lung cancer and asthma[50] by reporting that an estimated annual 3000 lung cancer deaths could be attributed to SHS.[48]

There is also clear evidence of an association of SHS and cardiovascular diseases. Several reports, including 2 recent separate meta-analyses of 17 and 18 individual studies, assessed the association of SHS with heart disease.[20,51–53]

Both estimated that nonsmoking spouses of smoking partners experience an approximately 25% (95% confidence interval [CI] 17% to 32%) increased risk of heart disease.[52,53] A review of 6 studies examining the association between SHS in the workplace and cardiovascular disease noted that although none of the studies individually reached the level of a significant association ($P<0.05$), there was a positive association in 5 of the 6 studies and a significant exposure-response relation between the intensity of SHS (measured by the number of cigarettes smoked by coworkers) and coronary risk in 2 of 3 studies that examined the trend.[54]

It is likely that SHS acts to increase cardiac risk through both chronic (atherogenic) and acute pathways. A review of the association of SHS and subclinical measures of atherosclerosis reported a consistent association of significantly increased intima-medial thickness of the carotid artery in 8 reports.[55] In addition, exposure to SHS has been shown experimentally to have effects on endothelium-dependent arterial dilatation[21,22] and coronary flow reserve in humans.[56]

Initial reports on an association between SHS and stroke support the observed association with heart disease. Two case-control studies have shown significantly increased odds ratios of clinical stroke with exposure to SHS: 1.72 (95% CI 1.07 to 2.77) and 2.59 (95% CI 1.51 to 4.47) for exposure to a spouse smoking 1 to 20 cigarettes a day and ≥21 cigarettes per day,[57] respectively, and 1.82 (95% CI 1.34 to 2.49) for SHS exposure at home or work for at least 1 year during the decade preceding the event.[58] There was a 6% (95% CI 0.64 to 1.75) increased odds of silent cerebral infarction in a population-based cohort study of nonsmokers exposed to SHS in relation to those not exposed; however, this difference did not reach statistical significance.[59]

The impact of SHS on heart disease and stroke is also supported by the remarkable "natural experiment" observed when Helena, Mont, banned public smoking beginning June 5, 2002. During the 6-month period of the ban, admissions to the local hospital for acute myocardial infarction dropped by 40%, a decline that was not observed in any of the other hospitals from surrounding communities.[60] The study investigators hypothesized that the reduction in hospital admissions was due to acute coagulation changes associated with reduced SHS exposure.

A recent review of the studies concluded that it is unlikely that experimental biases can invalidate the general conclusions of the epidemiological studies.[61] Moreover, the review cites the strong experimental evidence that provides a biological basis for the observed associations between SHS exposure and increased risk of cardiovascular disease.[61]

The importance of SHS as a public health issue comes from the high prevalence of SHS exposure in the general population. On the basis of the most recent data from the National Health Interview Survey, the prevalence of active cigarette smoking was 21.4% (95% CI 20.2% to 22.5%) in 2003.[62] NHANES III (1988–1991) found that ≈90% of tobacco nonusers have detectable levels of serum cotinine,[63] which suggests that as much as 65% of the entire population are nonsmokers exposed to SHS. This arises primarily from exposures at home or at the workplace. Between 1988 and 1991, among adult nonsmokers, 37% reported living in a home with at least 1 smoker or being exposed to SHS at work.[63] Forty-three percent of children lived in a home with at least 1 smoker, higher than the percentage observed among adults, which is due in part to children's opportunity to be exposed to SHS by either a smoking mother or father.[63] More recent reports available at the CDC website suggest that there may be substantial decreased exposure to SHS over the interval from 1991–1994 to 1999–2000, with decreased levels of cotinine in children (−58%), adolescents (−55%), and adults (−75%).[63a]

Exposure to SHS in workplace settings is also surprisingly high. Nineteen states participating in the Centers for Disease Control and Prevention's Behavioral Risk Factor Surveillance System included questions related to working in a smoke-free workplace during 1999. The survey reports a prevalence range of exposure to cigarette smoke at work from 18% (District of Columbia) to 38% (Mississippi).[64] Some other studies reported even higher rates.[65,66]

SHS exposure is associated with well-established increases in relative risks for circulatory diseases. It directly affects, at some level, perhaps as much as two thirds of the population, with some suggestion that the proportion exposed may be decreasing. Although the increased risk for cardiovascular diseases associated with SHS exposure (relative risk [RR] 1.25) has not drawn attention to it as a "major" cardiovascular risk factor, the high prevalence of exposure does make it a major public health issue. Given past patterns of exposure, it has been estimated that between 35 000 and 65 000 ischemic heart disease deaths result from SHS annually.[67,68] This is an order of magnitude greater than the estimated 3000 annual deaths from lung cancer. As such, SHS "pollution" represents a substantial public health burden, ranking it as one of the most important preventable causes of cardiovascular death.

Epidemiology of Ambient Air Pollution and Cardiovascular Disease

An association between high levels of anthropogenic air pollutants and human illnesses has been known for more than half a century. A few episodes of markedly increased mortality rates during extreme elevations in urban pollution, such as in the Meuse Valley, Belgium, in December 1930[69] and during the London fog incident of 1952,[70] sparked the initial epidemiological research. As a result, a several-decades-long effort to reduce air pollution ensued and culminated in the Clean Air Act legislation of 1970. Despite improvements in air quality over the past few decades, associations between current ambient pollution levels and excess morbidity and mortality have been consistently detected.[71–76]

There are several hundred published epidemiological studies linking air pollution with human illnesses. A number of extensive reviews on this topic are available.[77–79] Although many pollutants may cause disease individually or in combination (eg, O_3, SO_2, and NO_2),[80] over the past decade, PM has become a major focus of research. During the past 15 years, the magnitude of evidence and number of studies linking air pollution to cardiovascular diseases has grown substantially.[77,78]

In broad terms, studies can be separated into those that have investigated the health effects of acute or chronic air

pollution exposure. Observations related to the adverse health effects of short-term exposure are more numerous. In these studies, population-wide changes in acute outcomes (mortality, symptomatology, hospitalizations, and healthcare visits) are linked to short-term variations in ambient pollutant concentrations, most frequently through the use of population-based time-series analysis. More recently, case-crossover designs have been added to the analytical repertoire. Publications on the health effects of long-term exposure are few. These studies have involved analysis of data (eg, total mortality and in some circumstances cardiovascular events) from a few large cohorts from multiple geographic locations that differ in the average chronic ambient concentrations and mixtures of air pollutants.

Long-Term Health Effects Studies

The first large, prospective cohort study that demonstrated an adverse health impact of long-term air pollution exposure was the Harvard Six Cities study by Dockery et al.[81] This study demonstrated that chronic exposure to air pollutants is independently related to cardiovascular mortality. In a cohort of 8111 adults with 14 to 16 years of follow-up, the adjusted overall mortality rate ratio for the most-polluted city versus the least-polluted city was 1.26 (95% CI 1.08 to 1.47). Further adjustment for a variety of individual-level risk factors that included tobacco smoking, gender, body mass index, educational attainment, occupational exposures, hypertension, and diabetes did not significantly alter the relationship. Cardiovascular deaths accounted for the largest single category of the increased mortality. Of the 1401 validated deaths, 646 were due to cardiovascular causes (International Classification of Diseases, 9th Revision [ICD-9] codes 400 to 440). The risk ratios for lung cancer and overall cardiopulmonary mortality were increased by similar magnitudes. Among air pollutants, elevations of $PM_{2.5}$ and sulfates showed the strongest associations with disease.

These findings were complemented by similar observations from the first analysis of air pollution in relation to mortality in the ACS Cancer Prevention II study population.[82] Recently, a follow-up of the original ACS cohort by Pope et al,[5] based on additional subject mortality and ambient pollutant data, has provided the largest study of the long-term health effects of air pollution. In approximately 500 000 adults who resided in all 50 states, chronic exposure to multiple air pollutants was linked to mortality statistics for a 16-year period. The ACS follow-up study increased the degree of control for confounding variables, such as diet and gaseous copollutants. The primary results showed that each 10-μg/m^3 increase in annual $PM_{2.5}$ mean concentration, based on a number of different averaging periods, was associated with increases in all-cause, cardiopulmonary, and lung cancer mortality of 4%, 6%, and 8%, respectively. The relationship between $PM_{2.5}$ and adverse health effects was linear and without a discernible lower "safe" threshold. Mortality was most strongly associated with $PM_{2.5}$, sulfate particles, and SO_2. There also appeared to be an association between cardiopulmonary mortality and summertime O_3, when based on mean summer O_3 levels from 1982 to 1998. Educational level was a modifier of the risks estimated for PM-associated mortality. The increased risks were limited to those with no more than a high school education. This suggests that 1 or more unaccounted-for factors, such as intraurban geographic location or socioeconomic status, may be important determinants of health risk.

Hoek et al[83] confirmed the importance of within-city residential variations as a risk factor for mortality due to air pollution. In a cohort of 5000 adults followed up for 8 years, exposure to traffic-related air pollutants was more highly related to mortality than were citywide background levels. Of the various pollutant metrics, an indicator variable for living near a major road was most strongly associated with cardiopulmonary mortality in this cohort (RR 1.95, 95% CI 1.09 to 3.52). This study suggests that an individual's exposure to the "toxic" components of air pollution may vary as much within a single city as across different cities. Furthermore, it demonstrates that emissions from motor vehicles, a common source of urban air pollution, may be associated with an increased risk of mortality.

Until recently, the specific causes of the increased cardiovascular mortality due to long-term air pollution exposure have remained unclear. In an analysis of the ACS study published this year, the investigators reported PM-mortality associations with the specific cause of death.[4] A statistically robust association between $PM_{2.5}$ and overall cardiovascular mortality was confirmed for a 10-μg/m^3 increase in long-term exposure (RR 1.12, 95% CI 1.08 to 1.15). The single largest increase in risk was for ischemic heart disease (RR 1.18, 95% CI 1.14 to 1.23), which also accounted for the largest proportion of deaths. In addition, the risk for arrhythmia, heart failure, or cardiac arrest mortality was also increased (RR 1.13, 95% CI 1.05 to 1.21). There was no evidence for excess mortality in the entire cohort due to other reasons (eg, aortic aneurysms, stroke, diabetes, hypertensive disease, or any respiratory illness). These findings suggest that air pollution promotes both ischemic and nonischemic cardiovascular events.

Short-Term Health Effects Studies

The Six Cities[81] and ACS[4,5,82] studies provide strong evidence for the occurrence of adverse cardiovascular effects due to long-term air pollution exposure. However, many more studies have focused on short-term relationships between pollution exposure and adverse outcomes. The acute effects of air pollution are generally investigated by time-series analyses of changes in health outcomes (eg, mortality) in relation to day-to-day variations in ambient air pollution concentrations. The 2 largest studies to date are the NMMAPS in the United States[6,8] and the Air Pollution and Health: a European Approach (APHEA-2) project.[84] These studies produced remarkably consistent results.

The NMMAPS observed outcomes in 50 million people in the 20 largest cities in the United States. Average mortality rates were independently associated with particle concentrations the day before death. Each 10-μg/m^3 elevation in PM_{10} was associated with an increase of 0.21% ($\pm$0.06 SE) and 0.31% ($\pm$0.09 SE) for daily all-cause and cardiopulmonary mortality, respectively.[8]

The APHEA-2 study demonstrated slightly more robust associations between adverse health outcomes and air pollution.[84] For 43 million people in 29 European cities, the estimated increase in daily mortality was 0.6% (95% CI 0.4% to 0.8%) for each 10-μg/m^3 increase in PM_{10}. Cardiovascular deaths were increased by 0.69% (95% CI 0.31% to 1.08%).[85] APHEA-2 based calculations on average particle concentrations the day of and 1 day before observed health outcomes (a 2-day exposure time window). The NMMAPS investigators reported no differences among various lag time periods from 0 to 2 days and therefore based their estimates solely on the prior 24-hour period (1-day lag). The size of the observed health effect in a study is known to vary slightly depending on exposure metric and lag periods used in analyses. This may have contributed to the stronger associations found in the European study. Additional analyses of the APHEA-2 mortality data, based on lag periods up to 40 days, found that the risk of adverse health effects associated with air pollution more than doubled (eg, 1.97% increase in cardiovascular mortality [95% CI 1.38% to 2.55%] per 10-μg/m^3 elevation in PM_{10}).[85] This finding indicated that the increase in cardiopulmonary mortality was not simply the result of "harvesting" (also called mortality displacement, which refers to the advancement of death by no more than a few days for severely ill individuals). Analyses of data from other locations also have indicated that the increased risks cannot be explained solely by harvesting and that longer lags are associated with higher relative risks of cardiopulmonary mortality.[86–88] The higher relative risks demonstrated by using this statistical modeling may reflect the accumulation of both acute and subacute health effects over the longer lag periods.

APHEA-2 found that cities with higher levels of the copollutant NO_2 exhibited larger associations between changes in PM concentrations and mortality. In the United States, this modifying effect of NO_2 was not demonstrated. The APHEA-2 investigators speculated that this might reflect a higher proportion of NO_2 that is derived from diesel exhaust in Europe. Outcome differences by geographical region were also noted in both studies. In Europe, cities with warmer climates demonstrated stronger mortality associations with air pollutants. The NMMAPS study in the United States reported stronger relationships in the Northeast than the Southeast. It is plausible that differences in the underlying susceptibility of the populations, time spent outdoors, commute times, and ambient meteorology, as well as differences in the overall ambient pollutant mixtures, underlie the observed regional variability in risk estimates for both studies.

Hundreds of smaller, short-term studies have been published over the last few decades on the effects of acute air pollution exposure, as reviewed by Brunekreef and Holgate[77] and Pope.[78] Typically, short-term mortality rates[73,88] hospital admissions,[89–91] emergency room visits,[92,93] and symptom exacerbations[94,95] have been shown to increase in relation to variations in air pollution levels (time-series studies). Observations from across North America[96,97] and Europe[3,98] have demonstrated higher rates of hospitalizations for all cardiovascular causes. Direct associations have also been identified with respect to incidence of ischemic heart disease, arrhythmias, and heart failure.[98] A pooled analysis of hospital admissions studies showed significant increases in admission rates of 0.8% and 0.7% for heart failure and ischemic heart disease, respectively, for each 10-μg/m^3 elevation in PM_{10}.[99] More focused investigations have demonstrated elevated risks for AMI,[11] implantable cardioverter defibrillator discharges,[18] and myocardial ischemia during stress testing.[17] Extreme elevations in air pollution have also been associated with increased blood pressure during a prolonged air stagnation episode in Europe.[100] Finally, recent studies from Seoul, South Korea[101] and Taiwan[102] have reported higher incidences of ischemic strokes in direct relation to changes in ambient particle concentrations. In summary, these findings imply that short-term elevations in ambient particle levels are capable of evoking cardiac arrhythmias, worsening heart failure, and triggering acute atherosclerotic/ischemic cardiovascular complications.

Populations at Elevated Risk

It is now reasonably well established that both short-term and chronic air pollution exposures are related to cardiovascular diseases. Whether there are specific individuals or subsets of patients at increased relative risk is less well documented. A few observations have suggested that the elderly[5,81,84,103] and those with less than a high school education (low socioeconomic status) may be particularly susceptible populations.[5] Whether increased age per se or the high prevalence of underlying cardiovascular disease and other risk factors explains the enhanced risk observed in elderly populations is unclear. The presence of preexisting chronic lung disease, coronary heart disease, and heart failure may also elevate short-term cardiovascular mortality risk.[103] Most recently, publications from 2 separate groups provide evidence that the acute risk for cardiovascular events in patients with diabetes mellitus may be 2-fold higher than for nondiabetics.[104,105] It is plausible that both diabetes itself and the high incidence of concomitant cardiovascular disease may explain this relationship. There is no convincing evidence that gender, race, and other preexisting coronary risk factors (eg, obesity, dyslipidemia, and hypertension) increase the risk of cardiovascular events due to air pollution.

The effect of tobacco smoking on the cardiovascular risk due to long-term air pollution exposure was recently investigated in the large ACS study.[4] The risks for specific cardiovascular causes of death for each 10-μg/m^3 increase in the long-term exposure to $PM_{2.5}$ were stratified by smoking status. Ischemic heart disease mortality was consistently elevated, with RRs of 1.22 (95% CI 1.14 to 1.29), 1.15 (95% CI 1.07 to 1.23), and 1.16 (95% CI 1.07 to 1.27) for never-smokers, former smokers, and current smokers, respectively. Interestingly, smoking status clearly affected the risk associated with several other causes of death. The risk due to arrhythmias, heart failure, and cardiac arrest was not significantly elevated for those who never smoked (RR 1.04 [95% CI 0.95 to 1.15]). However, among former and current smokers, the risk increased substantially, with RRs of 1.14 (95% CI 1.00 to 1.29) and 1.31 (95% CI 1.12 to 2.19), respectively. Mortality risk due to hypertensive disease was also only increased in patients who actively smoked (RR

1.57, 95% CI 1.12 to 2.19). These findings show that smoking, while not affecting the PM-associated risk from ischemic heart disease, appeared to interact with air pollution to increase the risk of death from other circulatory diseases.

Environmental Pollution and Congenital Heart Disease

Malformations of the cardiovascular system are among the more frequently occurring congenital defects. The incidence of congenital heart disease is estimated at 8.1 per 1000 births.[106] The actual rate may be underestimated, because some cases may be lethal in utero and result in spontaneous abortion and stillbirths. Congenital heart disease is associated with genetic defects, infections (eg, rubella), radiation, medications, and environmental exposures.[106–111] Recent data from Eastern Europe in areas with high levels of industrial pollution suggest the possibility of increased heart defects.[112–114] More recently, a study of birth records in Los Angeles, Calif, found that odds ratios (ORs) for cardiac ventricular septal defects increased in a dose-response fashion with increasing carbon monoxide exposure (OR for second quartile 1.62 [95% CI 1.05 to 2.48], OR for third quartile 2.09 [95% CI 1.19 to 3.67], and OR for fourth quartile 2.95 [95% CI 1.44 to 6.05]).[115] Also observed were valvular, aortic, and truncal defects associated with O_3 levels. PM and other measured air pollutants showed no association. Although some animal data also suggest a relationship between air pollutants and congenital cardiac defects, these epidemiological data can only be considered suggestive at this time.

Significance of Epidemiological Findings

Epidemiological research has served to drive major governmental regulations and thus has been the subject of intense scrutiny. Two of the largest studies of the health effects of long-term air pollution exposure[81,82] that have served as the basis for the setting of annual average $PM_{2.5}$ standards have undergone complete reanalyses by independent investigators to ensure reproducibility.[116] The reanalyses validated the quality of the data and replicated the original results without any substantial alteration in findings. Although exposure to ambient air pollution poses smaller relative risks for incident cardiovascular disease than obesity or tobacco smoking, because it is ubiquitous, the absolute number of people affected is enormous, and exposure occurs over an entire lifetime. The adverse effects on the public health are clearly not limited to a harvesting effect as described earlier. Rather, Pope[78] has estimated an average loss of life expectancy directly related to chronic air pollution exposure from between 1.8 and 3.1 years for those living in the most polluted cities in the United States. Cardiovascular causes account for the majority (69%) of the overall excess in morbidity and mortality.[78]

Present Controversies

Given the continuous spatial and temporal variability of air pollution, combined with individuals' movements through numerous microenvironments every day, it is not surprising that exposure assessment in air pollution studies has always been subject to varying degrees of measurement error. Generally, in the epidemiological studies, an individual subject's exposure level has been estimated from citywide pollution measurement averages obtained from at most a few central locations. Past studies have also been limited by the fact that the numerous gaseous and particulate pollutants tend to covary in time and space. This has limited the ability to confidently link health outcomes with any given pollutant, although this may be an unrealistic goal given the complexity of the ambient pollutant mixture and the potential for combined toxic effects from many different combinations of constituents. Use of new tools such as geographic information systems and personal monitoring devices and better measures of the full toxic air pollution mix (eg, individual chemical and physical constituents or measurements of total oxidant capacity) may provide more refined estimates of the adverse health effects that can be related to specific (mixtures of) components.

Despite many past limitations, there has been a strong consistency in the findings among the array of assorted studies. A reasonable argument can now be made that the "real" effects are likely to be even stronger than previously estimated. Indeed, a recent study suggests a more robust linkage. In a recent "natural experiment," Clancy et al[117] were able to demonstrate a decrease in health effects after the intentional lowering of air pollutant levels. These investigators compared 72 months of mortality data before and after a ban on burning coal within the city of Dublin, Ireland, went into effect. Nontraumatic deaths decreased by 5.7% (95% CI 4.0% to 7.0%) and cardiovascular mortality by 10.3% (95% CI 8.0% to 13.0%). The authors estimated that the ban resulted in 243 fewer cardiovascular deaths per year. The decrease in the mortality rate in this "natural experiment" is more than twice what would be predicted by the short-term time-series analyses.

Potential Biological Mechanisms

The putative biological mechanisms linking air pollution to heart disease involve direct effects of pollutants on the cardiovascular system, blood, and lung receptors, and/or indirect effects mediated through pulmonary oxidative stress and inflammatory responses. Direct effects may occur via agents that readily cross the pulmonary epithelium into the circulation, such as gases, and possibly UFPs[28–30] along with soluble constituents of $PM_{2.5}$ (eg, transition metals). In addition, activation of pulmonary neural reflexes secondary to PM interactions with lung receptors may play a role. Ensuing alterations in autonomic tone, under appropriate circumstances, might contribute to the instability of a vascular plaque or initiate cardiac arrhythmias. These direct effects of air pollution represent a plausible explanation for the occurrence of rapid (within a few hours) cardiovascular responses, such as increased myocardial infarctions.[11] Less acute (several hours to days) and chronic indirect effects may occur via pulmonary oxidative stress/inflammation induced by inhaled pollutants. This subsequently may contribute to a systemic inflammatory state, which may in turn be capable of activating hemostatic pathways, impairing vascular function, and accelerating atherosclerosis. A general scheme illustrating potential mechanisms of the effects of PM on the cardiovascular system is shown in Figure 2.

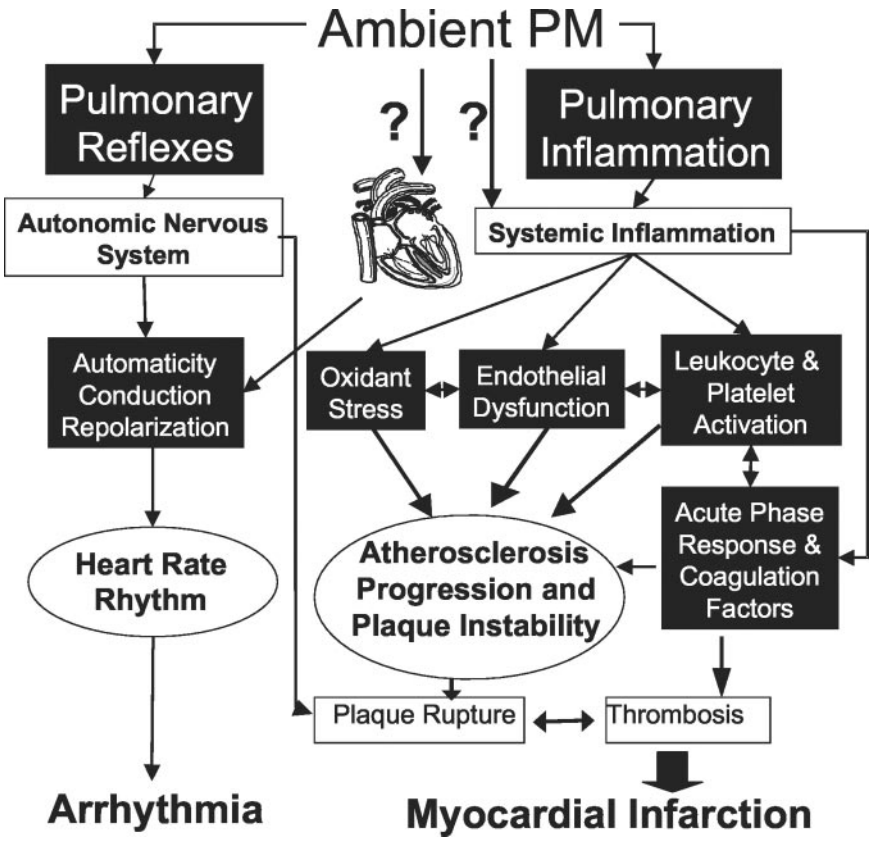

Figure 2. Possible biological mechanisms linking PM with cardiovascular disease.

Pulmonary and Systemic Oxidative Stress and Inflammation

Inhalation of air pollutants induces pulmonary oxidative stress and inflammation.[118] Exposure of human lungs to concentrated PM[119] and O_3[120] produces an inflammatory response consistent with in vivo animal models[121] and in vitro cellular models.[122–125] The presence of soluble transition metals in PM enhances the inflammatory responses[126] via increased oxidative stress.[127,128] However, lung inflammation may also occur via direct UFP effects independent of transition metals or soluble components.[129] Similarly, O_3 mediates a pulmonary inflammatory response via oxidative stress[118,130] and an impairment in lung function that can be attenuated by antioxidants.[131]

Oxidative stress occurs after exposure to ultrafine carbon black and diesel exhaust particles (DEPs),[129,132] ambient $PM_{2.5}$,[133] and cigarette smoke. A recent in vivo experiment using in situ chemiluminescence demonstrated the rapid occurrence of oxidative stress even in tissues beyond the lung. After exposure to concentrated ambient $PM_{2.5}$ for 2 hours, there was a doubling in reactive oxygen species generation in the hearts and lungs of rats.[134] This may occur in response to a variety of transition metals[134] or free radical components known to exist within $PM_{2.5}$ as a result of atmospheric chemical reactions.[135] Personal exposure to ambient concentrations of $PM_{2.5}$ is also associated with increased levels of markers of lipid and protein oxidation in human blood.[133] Pulmonary inflammation results at least in part because of the increased production of free radicals.[118] Oxidative stress activates specific transcription factors, including nuclear factor-κB and activator protein-1, which upregulate the expression of genes for cytokines, chemokines, and other proinflammatory mediators.[132] DEPs or organic extracts of DEPs can, through oxidant effects on mitochondria, induce apoptosis or necrosis of macrophages and respiratory epithelial cells, possibly decreasing the host defenses to respiratory infection or increasing airway reactivity.[136]

Endotoxin, usually associated with coarse particles, has also been shown to induce proinflammatory cytokine production[137,138]; increase lung inflammation, airway responsiveness, and systemic immune cell populations; and decrease lung function.[139,140] Endotoxin has been found to account for in vitro cytotoxicity and cytokine production related to $PM_{2.5}$ and coarse PM exposures[141,142]; however, its role in the overall toxicity of ambient PM remains to be clarified.

The intrapulmonary responses elicited by PM may also be due in part to neurogenic inflammation. Sensory neurons in contact with irritant particles (eg, within the conducting airways) can be stimulated to release neuropeptides (eg, substance P, calcitonin gene related peptide, and neurokinin A), which can initiate airway inflammatory events, including release of cytokines, vasodilation, and mucus secretion. Neuropeptides act on a variety of cell types within the lung, including epithelial and smooth muscle cells (resulting in modulation of inflammation and increased airway responsiveness), as well as immune cells (polymorphonuclear leukocytes [PMNs], lymphocytes, eosinophils, and others), thus amplifying the inflammatory response. Recent in vitro experiments indicate that specific irritant (capsaicin or vanilloid)

receptors on neurons mediate PM-related neurogenic inflammation, as evidenced by responses to particles originating from diverse sources.[143]

Several controlled-exposure studies demonstrate that inhalation of particles[119,144,145] and O_3[120] evokes both a pulmonary and a systemic inflammatory response in humans. One hour of exposure to very high concentrations of diesel exhaust has been shown to induce an inflammatory reaction in the lungs of healthy adults. This response included increased numbers of PMNs, T- and B-lymphocytes, mast cells, and inflammatory mediators.[144] One of these studies showed an increase in adhesion molecules that facilitate the passage of inflammatory cells from the circulation into the airways. In the blood, platelets and PMNs increased, which suggests that exposure to DEPs stimulated the bone marrow to release these cells into the circulation.

Exposure to DEP has been shown to increase intra-airway transcription of mRNA for interleukin (IL)-8 (a protein that attracts PMNs to sites of injury)[146] and increased production of IL-8 and growth-regulating oncogene-α (GRO)-promoting airway inflammation. Exposure of healthy adults to concentrated ambient particles (CAP) for 2 hours can increase airway inflammation without concomitant lung injury.[119] Nevertheless, plasma fibrinogen was elevated by the CAP exposure relative to filtered air. This controlled exposure study suggests that exposure to ambient particles in healthy humans can result in a mild pulmonary inflammatory response and increased blood factors that effect coagulation, even without lung damage. A similar human study also demonstrated an increase in blood fibrinogen after short-term exposure to CAP.[147] However, no other changes in inflammatory mediators or other coagulation factors were found.

Additional studies support the existence of a systemic inflammatory response beyond the lungs after air pollution exposure. In humans, exposure to forest fire smoke (measured as PM_{10} and SO_2) at levels that did not result in changes in lung function nevertheless resulted in stimulation of bone marrow to release immature PMNs into the circulation.[148]

In an animal experiment, rabbits that received 5 mg of PM_{10} intrapharyngeally twice per week for 3 weeks exhibited increased production of PMNs in the bone marrow and accelerated release into the circulation.[149] The PM_{10} exposure resulted in diffuse inflammation of the lungs, with particles present in alveolar macrophages, lung epithelial cells, and airway walls. The effects on PMN production in bone marrow and release of immature cells into the blood were associated with the numbers of particles ingested by alveolar macrophages.

Effects of Inflammation, Oxidative Stress, and Alterations in Blood-Borne Factors on the Cardiovascular System

Changes in the composition of the blood may result from air pollution exposure, with potentially serious effects on individuals with cardiovascular disease. Nearly a decade ago, Seaton et al[150] proposed a general hypothesis that exposure to inhaled particles induces alveolar inflammation, leading to exacerbation of preexisting lung disease, increased blood coagulability, and an associated increased risk of cardiovascular events. Subsequently, evidence supporting this hypothesis has slowly been accumulating. As described above, several studies of controlled exposures to particles demonstrate increases in both cellular and biochemical markers of pulmonary and systemic inflammation.

Exposure to PM increases fibrinogen,[119,147] a key component in blood coagulation and platelet thrombosis and a major determinant of blood viscosity. Blood viscosity has been associated with severity of cardiovascular disease[151] and has been found to increase in association with increased levels of ambient total suspended particles and SO_2.[152] Fibrinogen is also well established as an important independent risk factor for myocardial infarction and stroke. Epidemiological data suggest potential effects of particulate air pollution on blood coagulation.[152–154] Of note is that the strength of plasma level of fibrinogen to predict cardiac events and death in middle-aged men is modified by the presence of other inflammation-sensitive proteins,[155] which suggests that inflammation has a significant role in the determination of cardiovascular risk. In addition, enhanced platelet aggregation may further promote acute thrombosis formation after exposure to diesel exhaust[156] and UFPs.[157] The mechanisms responsible for platelet activation and fibrinogen elevation remain to be fully elucidated. Nevertheless, these findings support the notion that air pollution can acutely increase the risk of thrombosis, thus promoting ischemic events.

Increased concentrations of IL-6 are associated with an increased risk of cardiovascular events[158,159] and mortality.[160] Serum Il-6, IL-1β, and granulocyte macrophage colony-stimulating factor are increased in healthy male subjects after exposures to increased air pollution due to forest fires and are increased in vitro with exposure of human lung macrophages to urban PM_{10}.[161] Il-6 is directly involved in regulation of the synthesis of C-reactive protein in the liver. CRP is a sensitive indicator of infection, injury, and inflammation and is linked to increased risk of cardiovascular disease.[162,163] CRP concentration has been shown to be positively associated with exposure to total suspended particles[164] and PM_{10}.[153]

The mechanisms by which CRP increases the risk of cardiovascular events is the subject of intense research. One possibility is that CRP impairs endothelial vasoreactivity in individuals with preexisting coronary artery disease.[165] In addition, CRP may contribute directly to the development and progression of atherosclerosis via a number of mechanisms that involve enhanced formation of foam cells, recruitment of monocytes into the arterial wall, stimulation of prothrombotic tissue factors, decreased NO synthase activity, and expression of adhesion molecules.[166] Inflammation (proinflammatory cytokines, CRP, and components of innate immunity) plays a significant role in the genesis of atherosclerosis and in plaque instability.[167] It is possible, therefore, that air pollution–mediated systemic inflammation both promotes atherosclerosis formation over the long term[14] and instigates acute plaque instability and sudden cardiovascular events in the short term. Indeed, in hyperlipidemic rabbits exposed to PM, the progression of coronary atherosclerosis and extracellular lipid pools increased after 4 weeks.[14] The degree of plaque formation correlated with the number of alveolar macrophages that phagocytosed PM. These effects are likely to be

superimposed on the effects of age, hypertension, hyperlipidemia, diabetes, and other conditions associated with underlying inflammation.

Alterations in vascular tone due to air pollution exposure have also been demonstrated. The inhalation of high urban levels of CAP and ozone for 2 hours caused conduit arterial vasoconstriction in healthy adults.[168] Similarly, small pulmonary arteries were shown to constrict after short-term exposure to CAP in rats.[169] It is possible that the acute systemic inflammation and oxidative stress[133,134] are responsible for triggering endothelial dysfunction leading to vasoconstriction.[170] In support of this hypothesis, impaired arterial endothelial relaxation and decreased NO formation have been shown to occur in vessels exposed to DEPs owing to excess reactive oxygen species generation.[171] Alternatively, increased production of endothelins may play a role in the acute vasoconstriction.[172]

At present, the precise mechanisms underlying the rapid alterations in vascular tone remain to be resolved. However, a few published reports support the relevance of these findings by demonstrating an effect of air pollution on cardiovascular hemodynamics.[100,172] Ambient air pollution increases blood pressure in cardiac rehabilitation patients[173] and in adults with lung disease.[174] Indeed, arterial vasoconstriction is a likely explanation for the findings of the ULTRA study (The Exposure and Risk Assessment for Fine and Ultrafine Particles in Ambient Air). Ambient levels of PM 2 days before submaximal exercise testing were significantly associated with increased ST-segment depression during the test.[17] This finding suggests that air pollution exposure conveys a greater susceptibility to myocardial ischemia, as demonstrated in an experimental study of dogs exposed to CAP.[175] These results also offer insight regarding the relationship between exposure to PM and the timing of AMI.[11] Significant associations were identified between symptom onset and both acute (levels within 2 hours before symptoms) and subacute (previous-day average concentration) exposures to $PM_{2.5}$. Sudden arterial vasoconstriction (and/or possibly endothelial dysfunction) could conceivably instigate acute coronary syndromes by triggering plaque instability or by decreasing myocardial perfusion in patients with existing atherosclerosis.

Disturbances of the Cardiac Autonomic Nervous System

Mortality associated with air pollution might be further explained, at least in part, by alterations in the autonomic input to the heart. HRV, resting heart rate, and blood pressure are modulated by a balance between the 2 determinants of autonomic tone (the sympathetic and parasympathetic nervous systems). Decreased HRV predicts an increased risk of cardiovascular morbidity and mortality in the elderly and those with significant heart disease.[176] This is generally determined by analyses of time (eg, standard deviation of normal RR intervals [SDNN]) and frequency domains (eg, low frequency/high frequency ratio by power spectral analysis, reflecting autonomic balance) measured during 24 hours of electrocardiography. Because overall HRV (SDNN) decreases in response to ambient PM exposure,[177–181] decreased parasympathetic input to the heart may provide an important mechanistic link between air pollution and cardiovascular mortality by promoting fatal tachyarrhythmias. A recent study of controlled exposure to CAP provides further support to the notion that PM is capable of reducing HRV.[182] In general, the decrease of HRV occurs rapidly and is inversely proportional to the increase in the concentration of PM. However, in one study,[177] short-term measures of parasympathetic tone (r-MSSD) were increased in a group of individuals with preexisting heart disease. It is conceivable that in certain populations, air pollution–mediated bradyarrhythmias may also contribute to sudden death.

The relevance that these observed short-term changes in HRV have in relation to the worsening of cardiovascular outcomes and the triggering of significant arrhythmias over the long term remains unclear. However, some evidence suggests that PM exposure does promote clinically meaningful changes in cardiac electrophysiology. The incidence of cardiac arrhythmias has been associated with exposure to $PM_{2.5}$ in high-risk individuals (eg, individuals having an implanted cardioverter defibrillator). In 100 patients monitored for $\approx$3 years, NO_2 and CO concentrations were most strongly related to implanted cardioverter defibrillator discharges, whereas particulate black carbon showed a slightly lesser degree of association with such events.[18] Although this study is limited by the small number of high-risk patients and by the lack of individual clinical data beyond implanted cardioverter defibrillator discharges, it does suggest a potential for adverse effects of PM and gaseous pollutants on cardiac autonomic balance. A recent mortality time-series study[98] further supports this observation. The risks of mortality from threatening arrhythmias were shown to increase in relation to 7-day mean levels of black smoke and PM_{10}.

These clinical observations are consistent with several studies reporting the induction of cardiac arrhythmias in compromised animals (ie, with pulmonary and systemic hypertension) exposed to PM.[183] Dogs exposed to CAP for 6 hours on 3 consecutive days showed increases in low- and high-frequency HRV, as well as an elevated low frequency/high frequency ratio.[184] In addition, exposure to residual oil fly ash, a component of PM, decreased HRV and increased arrhythmia frequency in a myocardial infarction model of rats.[185] These animal exposure findings support the notion that air pollution is capable of altering autonomic balance in a manner that favors significant tachyarrhythmias. The underlying mechanisms responsible remain unclear but may involve activation of pulmonary neural reflex arcs, direct effects of pollutants on cardiac ion channels, or consequences of the heightened systemic inflammatory state.

Summary

Air pollution consists of a complex mixture of compounds in gaseous (eg, NO_2, SO_2, CO, O_3), liquid, and solid phases. PM itself is a heterogeneous mixture of suspended particles that vary in chemical composition and size, ranging from clusters of molecules (with diameters of several nanometers) to coarse PM (up to 10 μm and beyond). Among the many natural and anthropogenic sources of air pollution, the combustion of fossil fuels is a major contributor in urban and industrialized societies.

Numerous epidemiological studies conducted worldwide have demonstrated consistent associations between short-term elevations in PM and increases in daily cardiovascular morbidity and mortality. Several studies have also reported adverse cardiovascular outcomes in relation to long-term PM exposure. Elderly patients, those with underlying coronary or pulmonary disease, lower socioeconomic populations, and diabetics may be at particularly increased risk. At present, the constituent PM responsible for mediating these effects, along with the roles of the various gaseous copollutants, remain to be clarified.

Experimental evidence has revealed plausible biological mechanisms whereby PM has the potential to cause and exacerbate cardiovascular disease. One pathway involves the initiation of pulmonary and systemic oxidative stress and inflammation by components within PM. Subsequently, a cascade of physiological responses may follow that are capable of instigating cardiovascular events. These include alterations in blood rheology that favor thrombosis, cardiac dysrhythmias, acute vascular dysfunction, plaque instability, and the long-term development of atherosclerosis. Additional pathways may also be involved, such as changes in autonomic balance via lung neural reflex arcs and/or by PM (or certain components) reaching the circulation and beyond.

Potential for Prevention/Public Policy

The increase in relative risk for cardiovascular disease due to air pollution for an individual is small compared with the impact of the established cardiovascular risk factors. However, because of the enormous number of people affected, even conservative risk estimates translate into a substantial increase in total mortality within the population. The impact on cardiovascular disease therefore represents a serious public health problem. The latest draft of the US EPA Air Quality Criteria for Particulate Matter has confirmed the presence of an apparent linear dose-response relationship between PM and adverse events.[186] Data from all North American studies demonstrate that this curve is without a discernible threshold below which PM concentrations pose no health risk to the general population.[186] At present-day levels, ≈40 000 deaths per year in Austria, France, and Switzerland combined have been attributed to PM.[187] Estimates based on time-series studies suggest that ≈5000 excess deaths per year in Canada[188] and 6000 cardiovascular events in the United Kingdom[189] can be attributed to poor air quality. Approximately 1 in 50 myocardial infarctions were thought to be triggered by outdoor air pollution in a London, England, study.[3] On a global scale, the World Health Organization has estimated that 800 000 deaths occur per year and 7.9 million disability-adjusted life-years are lost annually due to PM exposure.[189a]

Given the burden of epidemiological evidence, the US EPA updated the National Ambient Air Quality Standards in 1997 to specifically include $PM_{2.5}$ (Table).[190] The most current estimates by the EPA suggest that attainment of these standards would reduce total mortality by 23 000 deaths annually and cardiovascular hospital admissions by 42 000 per year in the United States.[191] Nevertheless, 19% of all US counties with air-quality monitoring systems are presently not meeting these standards.[192] This percentage is substantially greater in regions such as the industrial Midwest (41%) and southern California (60%). In light of these data, there is a clear potential to improve the national public health and to substantially reduce cardiovascular morbidity and mortality by reducing PM levels to current EPA standards. The potential cardiovascular health effect of reducing the gaseous copollutants remains less certain.

Current US EPA National Ambient Air Quality Standards for PM (1997 NAAQS)

Time Period	PM_{10}, $\mu g/m^3$	$PM_{2.5}$, $\mu g/m^3$
Annual	50	15
Daily	150	65

The annual standard is satisfied when the 3-year average of the mean PM levels measured in a community is less than or equal to the indicated number. The daily standard is met when the 3-year average of the 98th or 99th percentile of 24-hour PM levels in each community is less than or equal to the indicated number.

Conclusions and Recommendations

Most[3–8,81] but not all[12,13] studies have found positive associations between several different air pollutants and adverse health outcomes. The results of observational studies are influenced by numerous factors, including characteristics of the air pollution, the population studied, and methodological issues, such as control of relevant confounders. The lack of complete uniformity is not surprising given that numerous variables (atmospheric conditions, geographic locations, cohort characteristics, sample sizes, exposure estimates, and statistical modeling) can affect the results. Our understanding of the relevant biological mechanisms involved also remains incomplete. Nevertheless, the existing body of evidence is adequately consistent, coherent, and plausible enough to draw several conclusions.[193] At the very least, short-term exposure to elevated PM significantly contributes to increased acute cardiovascular mortality, particularly in certain at-risk subsets of the population. Hospital admissions for several cardiovascular and pulmonary diseases acutely increase in response to higher ambient PM concentrations. The evidence further implicates prolonged exposure to elevated levels of PM in reducing overall life expectancy on the order of a few years.

On the basis of these conclusions and the potential to improve the public health, the AHA writing group supports the promulgation and implementation of regulations to expedite the attainment of the existing National Ambient Air Quality Standards. Moreover, because a number of studies have demonstrated associations between particulate air pollution and adverse cardiovascular effects even when levels of ambient $PM_{2.5}$ were within current standards,[5,11] even more stringent standards for $PM_{2.5}$ should be strongly considered by the EPA. Additional approaches to reduce the burden of disease related to air pollution should be highlighted. The levels of O_3 and PM in many US cities are published daily by the EPA, along with a health alert system that reflects recommended changes in activity. This information is also available and updated daily on the EPA AIRNow web site (http://www.epa.gov/airnow). The AHA supports these recommendations as guidelines for activity restriction for per-

sons with known heart disease (or with an "at-risk" profile by Framingham or another scoring system), and pulmonary disease, the elderly, and those with diabetes mellitus. A concerted effort should be made to educate healthcare providers and at-risk patients alike about this source of information and about the potential health hazards of elevated air pollution levels. The AHA should also actively work to educate the public and public policy makers about the effects of air pollution on cardiovascular disease by featured presentations at the annual Scientific Sessions, AHA-sponsored public education activities, and advocacy.

In October 2003, the EPA expanded its Air Quality Index program to include information on particle pollution, or fine particles. Next-day forecasts and real-time air quality information about particle pollution are available on the AIRNow Web site for more than 150 cities across the country. Air quality forecasts and reports for particle pollution are available in the local media (newspapers, television, and radio) in these cities and in the national media. The EPA is working to increase the number of state and local air quality agencies that forecast and report real-time particle pollution levels. It is expected that within a few years, this program will mirror the O_3 program in terms of geographic coverage and availability to the public. The AIRNow Web site also contains information about the health effects of particle pollution, and the EPA is developing a section with information and tools for healthcare professionals.

Although there is a strong case that air pollution increases the risk of cardiovascular disease, we recognize the need to address a number of remaining scientific questions. Both the US EPA and the National Institutes of Health have increased the priority of research funding in an effort to overcome these shortcomings, and a committee of the National Research Council set out a long-range research agenda in 1998.[194] A workshop sponsored by these and other agencies was convened in August 2002 to foster multidisciplinary research on the cardiovascular effects of PM. The AHA writing group supports these measures and recognizes several important areas for future research[80,192]:

1. Improve our understanding of the underlying biological mechanisms.
   - Better describe the basic mechanisms (mediators, cell signaling, pathways) involved in altering HRV (autonomic tone), vascular function, and atherogenesis.
   - Increased use of relevant animal models of exposure when investigating cardiovascular outcomes (eg, inhalation chambers at meaningful CAP concentrations). Experiments using intrapulmonary installation provide insight into basic mechanisms; however, the ability to extrapolate findings to humans is limited owing to the route of administration of extraordinarily high quantities of PM.
   - Determine the pathophysiological relevance of the many pathways that may contribute to the development of both acute and chronic disease.
   - Demonstrate reproducibility of the relevant potential mechanisms under a variety of pollutant regimens and subject risk profiles.
   - Demonstrate the occurrence of such cardiovascular end points at environmentally relevant concentrations of ambient pollutants.
   - Determine causal pathways, which may become targets for future means of preventive strategies
   - Determine whether long-term exposure to PM at environmentally relevant concentrations promotes the genesis/progression of atherosclerosis in humans.
2. Identification of the differential toxicity of various constituents and sources of air pollution, including:
   - Specific chemical and biological constituents of PM (eg, metals, carbon, polycyclic aromatic hydrocarbons, endotoxin).
   - The role of different PM size fractions, including UFPs (<0.1 μm) and the coarse fraction ($PM_{10\ to\ 2.5}$).
   - The effects of gaseous copollutants alone or in combination with PM.
3. Epidemiological investigations designed to address some of the limitations of prior reports, including studies that involve the following:
   - Better characterization of the populations of individuals at high risk related to short-term elevations in PM (eg, comorbidities).
   - Improvement of exposure estimates and metrics (eg, use of personal monitoring systems).
   - Examination of the relationships between traffic emissions and adverse cardiac effects.
   - Investigation of the roles of copollutants and confounders.
   - Assessment of the effect of medications on the acute cardiovascular effect of air pollution (eg, HMG-CoA reductase inhibitors).
   - Evaluation of the shape of the dose-response curve (identification of any threshold concentrations of various pollutants).
   - Improved estimations of the population-wide health benefits of reducing PM and other pollutants.
   - More thorough examination of the relationships between ambient air pollution concentrations and adverse reproductive outcomes, including those involving congenital cardiac anomalies

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