

# Environmental Influences on Cardiovascular Health

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A growing body of evidence indicates that the respiratory system is not the only target organ that may be injured by the inhalation of airborne particulate matter. Increased attention is now focused on research showing a link between particulate matter air pollution and cardiovascular morbidity and mortality, raising complex questions about the mechanism by which dirty air affects the heart. At the same time, the population at risk of cardiovascular continues to grow, including the obese, overweight, hypertensive and senior citizens. This pervasive and growing public health and medical care issue elevates into sharp relief the need for physicians and other healthcare practitioners to understand the clinical consequences exposure to particulate air pollution. This review is designed to further that understanding.

**Key words:** pollution ■ cardiovascular

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In this review, we discuss advances in our understanding of the influence of the ambient environment, specifically particulate air pollution, on cardiovascular health. Although ambient concentrations of most particulate matter (PM) have decreased, widespread concerns about its acute and chronic health effects are intensifying. This concern is fueled by research finding on the array of adverse health impacts caused by PM.

In approaching this topic, we first provide a panoramic view of selected dimensions of today's cardiovascular challenge. Background on ambient PM is then provided followed by a description of the current evidence demonstrating PM as a risk factor for cardiovascular disease (CVD). We conclude with a discussion of some unresolved issues.

## RELEVANCE TO HEALTH SERVICES

The advances described here are increasingly relevant to contemporary health services and medical care for  $\geq 3$  reasons. First, it is now clearly evident that the respiratory tract is not the only target organ for injury by inhaled solid particles. Recent evidence shows that extrapulmonary organs may also be affected such as the cardiovascular system and the central nervous system. Second, the community health and medical care burden attributable to PM is pervasive and growing. While the relative risks associated with exposure to PM may be small compared to other cardiovascular risk factors, the attributable health effects are enormous because of the ubiquitous nature of exposure. As many as 60,000 deaths annually are related to particulate air pollution.<sup>1</sup> Moreover, the population at risk of CVD continues to grow, including the obese, overweight, hypertensive and senior citizens, which comprise approximately 40% of the U.S. population and is projected to increase in the years ahead. Equally important is the likelihood that in susceptible subpopulations there may be a range of vulnerability reflecting the severity of the underlying disease. Third, although control of air pollution is a societal challenge requiring governmental policies and an array of regulatory and voluntary interventions, evidence abounds that physicians and other health service professionals need to understand the clinical consequences of exposure to ambient air pollution. This understanding could well be critical to the care of individual patients and to broader community concerns, including the disproportionate pollutant burden on poor and underserved groups, physical and mental health disparities, and global warming, with its rise in ambient temperature that has the potential to “stress” the cardiovascular system.

## CARDIOVASCULAR DISEASE CHALLENGES

Any objective review of recent morbidity and mortality data leads to the conclusion that despite progress in both the prevention and treatment, and the advance in practically all areas of cardiovascular research, CVD

remains a significant medical practice and public health challenge. For instance, the decline in CVD risk has been uneven across both socioeconomic positions, racial and ethnic groups, resulting in increasing health disparities. For instance, minority and low-income populations have a disproportionate burden of death and disability from CVD. This disparity spurred the development of the U.S. 2010 national health objective<sup>2</sup> to “reduce death from heart disease among African Americans by 30%.” Equally important is the economic burden of the disease. CVD costs an estimate of \$300 billion annually as measured in healthcare expenditures, cost of medications and lost of productivity due to disability and death.<sup>3</sup>

Further evidence of the CVD challenge is seen in the World Health Organization’s expectation that CVD will be the major killer globally within 15 years, owing to its rapidly increasing prevalence in developing countries and eastern Europe, and an accumulation of metabolic risk factors, including obesity and diabetes in the western world.<sup>4</sup> In developing countries, CVD is now striking a younger age group, leading to suggestions that the economic and social impact of CVD in the next generation may dwarf infectious diseases as the leading health problem. CVD is on the rise in the developing nations of the global community for the same reason that made it a killer in the developed nations: a rise in cigarette smoking, higher-fat diet and lack of physical exercise. These risk factors are components of the “personal” environment over which people have control, unlike the ambient or outdoor environment over which they may have essentially no control. While the “personal” environment continues to be a significant concern in prevention and intervention services, the contribution of these risk factors does not explain a significant fraction of coronary artery disease. Indeed, public health officials and medical care practitioners have been unable to explain the etiology of a significant number of CVD deaths.<sup>5</sup> These unexplained factors, along with related social and economic factors, have prompted more attention to ambient environmental risk factors in both the occupational and nonoccupational settings. In fact, laboratory and epidemiologic research has established that air pollution, a number of chemical exposures (e.g., arsenic, lead, carbon disulfide) and thermal stress contribute to or cause CVD. While important, a detailed treatment of chemical and thermal stress is beyond the boundary of this paper. These topics are covered in a voluminous literature published in a broad array of journals, environmental and occupational medicine textbooks and technical reports.

## ENVIRONMENTAL AND CARDIOVASCULAR DISEASE

Although concentrations of ambient PM have been decreasing over the past several decades, evidence has been building to indicate that exposure to particulate air pollutants can have a significant influence on heart health.

As one writer observed; “A decade ago, most cardiologists never suspected that breathing tiny particles of soot and dust could damage their patients’ heart, let alone trigger a heart attack.”<sup>6</sup> Concerned about the gathering body of evidence that linked of PM to CVD, the American Heart Association, an 80-year-old organization that has traditionally focused on the “personal” environment (e.g., substandard diet, lack of exercise), has published a scientific statement that concluded that air pollution poses a serious public health problem for CVD.<sup>7</sup> In addition, governmental agencies and private-sector groups have increased investments in environmental cardiology research with primary focus on environmental determinants of cardiovascular abnormalities.

## PARTICULATE MATTER

Before reviewing evidence of a link between PM and CVD, it is useful to describe key background information on PM. PM is a generic term applied to a broad class of chemically and physically diverse substances that exist as discrete particles in the atmosphere. It consists of mixtures of byproducts of combustion, car brake debris (e.g., metals) and resuspended crustal material. PM also includes biological materials, such as pollens, endotoxins, bacteria, beta-glucans and fungal spores. Mineral particles may dominate in areas where sand is used to increase friction on icy roads. Polycyclic aromatic hydrocarbons (PAHs) and similar compounds are emitted from vehicular traffic but are also abundant in PM from biomass combustion. Airborne particulates are generally classified by aerodynamic diameter, which is the diameter of a sphere of uniform density that has the same settling velocity as the particle of interest, regardless of actual size density or shape of the particle. The classification includes coarse particles or PM 10 (PM <10  $\mu\text{m}$ ), fine particles or PM 2.5 (<2.5  $\mu\text{m}$ ), ultrafine particles or PM 0.1 (<0.1  $\mu\text{m}$ ). Ultrafine particles come directly out of smokestacks and tailpipes and grow rapidly into fine-size range. Endotoxins seem to occur predominantly in the coarse fraction of PM and, to a lesser extent, in fine particles. The contribution to PM from different sources varies with time, season, location, climate, resulting in spatial and season-dependent variations in concentrations and properties. For instance, there can be marked concentration differences between urban (e.g., inner city) and nonurban locations. Of particular relevance to clinicians advising at-risk patients on precautions to be taken during global travel is that PM concentrations—both developed and combustion—in other countries can be dramatically higher than those in the United States. The concentration of fine particles in Mexico City are among the highest in North America. New Delhi experiences among the highest PM concentrations in the entire global community. Moreover, the complexity of PM may account for the diversity of effects induced by this airborne pollutant.<sup>8</sup>

There is now a significant literature on PM and morbidity. Epidemiological and laboratory studies have demonstrated that exposure to elevated concentrations of particulate air pollution contribute to cardiovascular morbidity, hospitalization and mortality. In fact, since the early 1990s, there has been a cascade of research on the cardiovascular consequences of exposure to PM, pointing to short-term and long-term effects of PM on cardiovascular health. The first large study to address this relationship was the Harvard Six Cities Study.<sup>9</sup> This study showed that chronic exposure to air pollutants is independently related to cardiovascular mortality. The study adjusted for a range of individual-level risk factors, including tobacco smoking, gender, educational attainment, occupational exposures, hypertension and diabetes, which did not significantly alter the relationship. The largest single category of increased mortality reported was cardiovascular deaths. Subsequent studies have confirmed that particulate air pollution is linked to increased rates of CVD.

Samet and colleagues<sup>10</sup> strengthened our understanding of the epidemiological evidence and addressed the criticism of earlier investigations. In this direction, they found consistent evidence that the levels of PM in air are associated with risk of death from all causes and from cardiovascular illness. This investigation assessed daily mortality in 20 of the largest cities in metropolitan areas of the United States. The combined analysis for all 20 cities confirmed the association between PM levels and rate of cardiovascular deaths. Moreover, the design of this study was such that it minimized the limitations identified in previous investigations, making the results more applicable to the United States in general. Another significant consideration of this study was socioeconomic factors, which often permeate health disparities discussions. Surprisingly, no evidence was found that key socioeconomic factors such as low socioeconomic status affected the association between PM levels and the risk of cardiovascular deaths. However, data on selected demographic characteristics of the study population were obtained from U.S. Census. Such data may not adequately reflect medical conditions and poor health status that increase the risk of death. Thus, more specific information on health status, rather than on social factors, should be explored, particularly in relation to susceptibility of particular populations to particulate air pollution such as the poor and underserved.

Other studies have added to the weight of evidence. The Women's Health Initiative (WHI) study found that nonfatal cardiovascular events are associated with fine-particulate concentration in the community. An interesting aspect of the WHI study was that it considered all community air pollutants, sulfur oxide, nitrogen oxide, carbon monoxide and ozone. However, cardiovascular risk was associated with PM concentrations. This study has a number of methodological strengths. For instance,

the study did not rely solely on death certificates, which vary greatly in quality of data. The researchers used an objective review of medical records to define the occurrence of CVD death. Unlike earlier studies that compared CVD death rates between various cities, the WHI study was able to compare death rates in areas within individual cities. In this approach, they demonstrated a relationship between increased levels of fine-particulate pollution and a higher death rate and complication from CVD. This relationship was dependent on where in the city the individuals lived. These results are consistent with those of other studies that have focused on residential variations in assessing the influence of PM on CVD mortality. An analysis of 107,925 deaths recorded by the Massachusetts Department of Public Health showed that both traffic and power plant particles were associated with increased deaths in Boston, with larger effects for traffic particles. The finding of an association with traffic particles and cardiovascular deaths is consistent with exposure studies indicating that traffic particles may be associated with myocardial infarction, alteration in heart rate variability and impaired endothelial function.<sup>11-13</sup> It has also been observed that an increased risk of cardiovascular hospitalization in 14 cities was associated with a fixed increment in exposure to airborne particles. The risk varied with the particle composition in the city, increasing with the percent of particles from traffic sources and decreasing with percent of particles from wind blown dust. Taken together, these observations further underscore the CVD risk associated with living near major roadways and the resulting risk of exposure to vehicular traffic particles, which are considered the most toxic component of PM.<sup>14</sup>

Another significant dimension of the WHI study was its focus on postmenopausal women (65,893) with no history of cardiovascular health problems. Previous investigation included persons from the entire community. In postmenopausal women, clusters of conditions that increase risk of vascular disease (e.g., diabetes, obesity) have been observed more frequently than in men. In this regard, it has been posited that gender may not define susceptibility to particulate air pollution, but may well be an indicator of an underlying cardiac substrate that put women at increased risk. It is worth emphasizing here that 34% of U.S. women are living with CVD and many more are at risk. Moreover, many women remain unaware of CVD risk factors. A recent survey of 1,008 women found that only 55% knew that CVD was the leading cause of death in women.<sup>15</sup>

The susceptibility factors for men have also been identified. Men with higher Framingham cardiovascular risk score, exposed to fine-particulate air pollution, experienced variability in heart rate. In addition, fine PM was strongly associated with impaired autonomic cardiovascular function in men with genotypic and phenotypic indicators of increased systemic inflammation

and oxidative stress. This association was not demonstrated in men without such markers.

Still, other studies strengthen the case for the PM-CVD relationship. These studies include consistent evidence of an association between PM and cardiac hospital admissions in the general population, the elderly and subgroups with comorbidities. Out-of-hospital deaths associated with particulate air pollution have also been recorded. The deaths were mostly sudden deaths, many of which were due to arrhythmia and myocardial infarctions.

## BIOLOGICAL UNDERPINNINGS

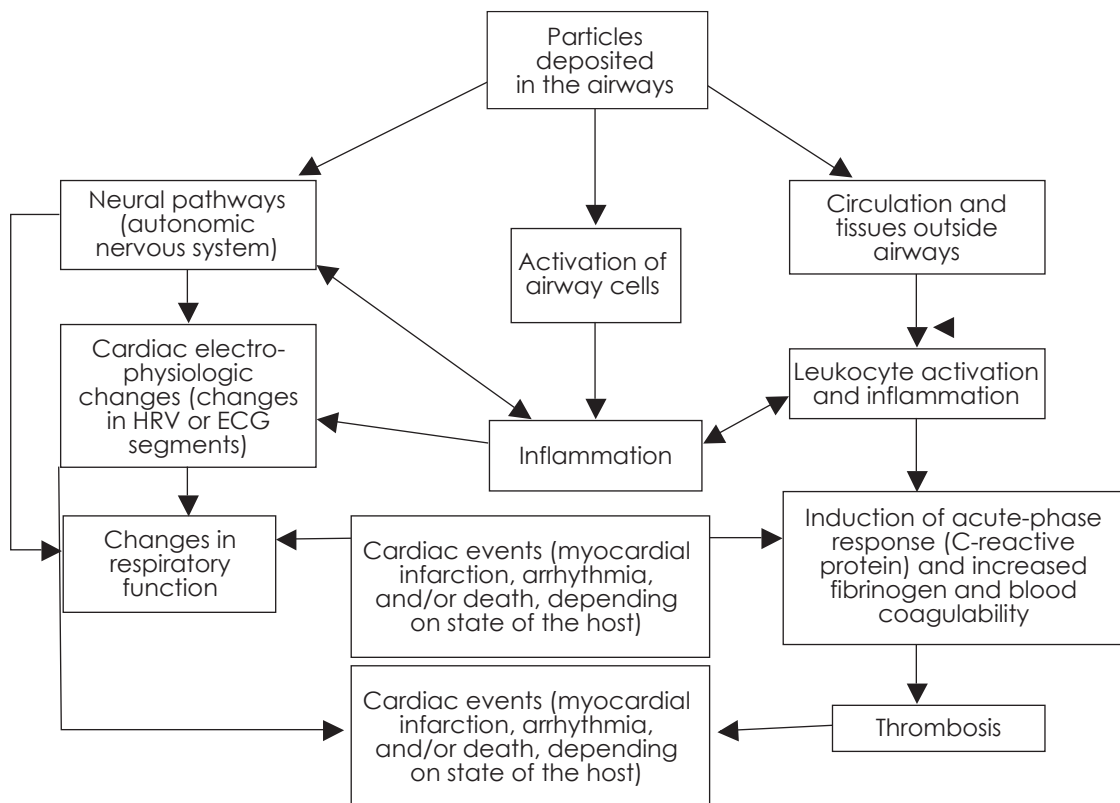
An area of uncertainty—and yet pivotal to CVD prevention, diagnosis and treatment—is the mechanism, or complex biological process, by which PM elicits adverse cardiovascular response. Encouragingly, an aggressive research program is underway to identify the harmful components of fine PM because, as indicated earlier, PM itself is a heterogeneous mixture of particles that vary in chemical composition. Already it is evident that identifying the key components responsible for adverse effects is a substantial challenge. For instance, several studies have shown that PM may be cytotoxic and induce both apoptotic and necrotic cell death, although the importance of cell death in PM-induced disease is less

clear. In addition, it has also been revealed that inhaled ultrafine particles pass rapidly into systemic circulation, and this process could account for the well-established extrapulmonary effects of air pollution.<sup>16-18</sup> However, the exact mechanism for this translocation has not been fully established. Other prominent hypotheses advanced to explain how PM pulmonary exposure can affect the cardiovascular system point to mechanisms that likely include systemic inflammation, accelerated atherosclerosis and altered cardiac autonomic function (Figure 1).

Several studies have shown an association between increased levels of inflammatory markers such as interleukin (IL) 6; C-reactive proteins (CRP); and coagulation factors, such as fibrinogen, with coronary heart disease and mortality. Equally relevant for the development of CVD is the probability that PM may induce a hypertrophic response in the myocardium. Cardiac hypertrophy is known to be a major risk factor for the heart failure. Inflammation may also be involved in the hypertrophic response of the heart, in addition to the atherosclerotic response of the endothelium.<sup>20</sup> Other studies have focused on understanding the contribution of airborne particulate population on subclinical anatomical changes that play a role in cardiovascular morbidity and mortality.

These and other hypotheses raise numerous questions regarding the biological underpinnings of PM

**Figure 1. How particulate matter can affect the airway and the cardiovascular system<sup>19</sup>**



HRV: heart rate variability ECG: electrocardiogram

influence on cardiovascular health. Answers to these questions will require more research which will further strengthen the bridge among fundamental biology (e.g., disease mechanism and pathways at a molecular level), clinical medicine and community health services. Such research should apply the new tools afforded researchers by discoveries in molecular biology.

## INFORMATION RESOURCES

The venues for professionals interested in learning more about the links between environmental pollutants and CVD are expanding. The issue is increasingly on the agenda of conferences and continuing education programs sponsored by health and medical organizations such as the American Heart Association and the American Thoracic Society. Discussions of the latest developments routinely appear on the NIH e-mail group EnviroHeart (<http://list.nih.gov/archives/environment.html>). A tool to help patients avoid air pollution exposure is the Environmental Protection Agency's AIRNow website. Daily reports on local particulate and ozone levels can help people decide whether to limit activities and thus exposure ([www.epa.gov/airnow/](http://www.epa.gov/airnow/)).

## CONCLUDING COMMENT

This review gives but a sampling of the evidence that exposure to levels of PM is associated with the rate of cardiovascular morbidity and mortality. It is recognized that there are limitations in studies cited here and elsewhere, including exposure measurements, statistical power and other methodological issues. Despite these limitations, the body of evidence is consistent and plausible enough to conclude that exposure to elevated PM contributes to increased cardiovascular morbidity and mortality. In summary, the general internal consistency of the epidemiologic database enhances the confidence accorded the reported research results and has contributed to increasing public health and medical care concerns about the adverse effects of exposure to PM.

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