AHA Scientific Statement

Particulate Matter Air Pollution and Cardiovascular Disease

An Update to the Scientific Statement From the American Heart Association

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Abstract—In 2004, the first American Heart Association scientific statement on "Air Pollution and Cardiovascular Disease" concluded that exposure to particulate matter (PM) air pollution contributes to cardiovascular morbidity and mortality. In the interim, numerous studies have expanded our understanding of this association and further elucidated the physiological and molecular mechanisms involved. The main objective of this updated American Heart Association scientific statement is to provide a comprehensive review of the new evidence linking PM exposure with cardiovascular disease, with a specific focus on highlighting the clinical implications for researchers and healthcare providers. The writing group also sought to provide expert consensus opinions on many aspects of the current state of science and updated suggestions for areas of future research. On the basis of the findings of this review, several new conclusions were reached, including the following: Exposure to PM <2.5 μm in diameter ($PM_{2.5}$) over a few hours to weeks can trigger cardiovascular disease–related mortality and nonfatal events; longer-term exposure (eg, a few years) increases the risk for cardiovascular mortality to an even greater extent than exposures over a few days and reduces life expectancy within more highly exposed segments of the population by several months to a few years; reductions in PM levels are associated with decreases in cardiovascular mortality within a time frame as short as a few years; and many credible pathological mechanisms have been elucidated that lend biological plausibility to these findings. It is the opinion of the writing group that the overall evidence is consistent with a causal relationship between $PM_{2.5}$ exposure and cardiovascular morbidity and mortality. This body of evidence has grown and been strengthened substantially since the first American Heart Association scientific statement was published. Finally, $PM_{2.5}$ exposure is deemed a modifiable factor that contributes to cardiovascular morbidity and mortality. **(*Circulation*. 2010;121:2331-2378.)**

Key Words: AHA Scientific Statements ■ atherosclerosis ■ epidemiology ■ prevention ■ air pollution ■ public policy

In 2004, the American Heart Association (AHA) published its first scientific statement regarding air pollution and cardiovascular disease (CVD).[1] The rationale was to provide researchers, healthcare providers, and regulatory agencies with a comprehensive review of the evidence linking air pollution exposure with cardiovascular morbidity and mor-

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This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on February 22, 2010. A copy of the statement is available at http://www.americanheart.org/presenter.jhtml?identifier=3003999 by selecting either the "topic list" link or the "chronological list" link (No. KB-0038). To purchase additional reprints, call 843-216-2533 or e-mail kelle.ramsay@wolterskluwer.com.

The American Heart Association requests that this document be cited as follows: Brook RD, Rajagopalan S, Pope CA 3rd, Brook JR, Bhatnagar A, Diez-Roux AV, Holguin F, Hong Y, Luepker RV, Mittleman MA, Peters A, Siscovick D, Smith SC Jr, Whitsel L, Kaufman JD; on behalf of the American Heart Association Council on Epidemiology and Prevention, Council on the Kidney in Cardiovascular Disease, and Council on Nutrition, Physical Activity and Metabolism. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. *Circulation*. 2010;121:2331–2378.

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Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIR.0b013e3181dbece1**

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tality. There was also an explicit aim to educate clinicians about the importance of this issue, because the cardiovascular health consequences of air pollution generally equal or exceed those due to pulmonary diseases.[1–4] Finally, a list of key remaining scientific questions and strategic avenues for investigation were provided to help foster and guide future research.

The first AHA writing group concluded that short-term exposure to particulate matter (PM) air pollution contributes to acute cardiovascular morbidity and mortality[1] and that exposure to elevated PM levels over the long term can reduce life expectancy by a few years. Although some mechanistic details remained incompletely described, the existing science was deemed adequate to substantiate several plausible biological pathways whereby PM could instigate acute cardiovascular events and promote chronic disease.

There is mounting evidence from a rapid growth of published data since the previous statement related to the harmful cardiovascular effects of air pollution.[3,4] Most, but not all, epidemiological studies corroborate the elevated risk for cardiovascular events associated with exposure to fine PM <2.5 μm in aerodynamic diameter ($PM_{2.5}$). $PM_{2.5}$ generally has been associated with increased risks of myocardial infarction (MI), stroke, arrhythmia, and heart failure exacerbation within hours to days of exposure in susceptible individuals. Several new studies have also demonstrated that residing in locations with higher long-term average PM levels elevates the risk for cardiovascular morbidity and mortality. Some recent evidence also implicates other size fractions, such as ultrafine particles (UFPs) <0.1 μm, gaseous copollutants (eg, ozone and nitrogen oxides [NO_x]), and specific sources of pollution (eg, traffic). In addition, there have been many insights into the mechanisms whereby PM could prove capable of promoting CVDs.[2–4] Air pollutants have been linked with endothelial dysfunction and vasoconstriction, increased blood pressure (BP), prothrombotic and coagulant changes, systemic inflammatory and oxidative stress responses, autonomic imbalance and arrhythmias, and the progression of atherosclerosis. In the interim, the US Environmental Protection Agency (EPA) completed its updated "Air Quality Criteria for Particulate Matter"[5] and afterward strengthened the National Ambient Air Quality Standards (NAAQS) for daily $PM_{2.5}$ levels starting in 2006 (down from 65 to 35 $\mu g/m^3$).[6] The most recent scientific review coordinated by the EPA, the final report of the Integrated Science Assessment for Particulate Matter (http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=216546), has also been made available publicly. These numerous changes and advances provide the rationale for the present updated AHA scientific statement on PM air pollution and CVD. This updated statement is similar in scope, content, and overall structure to the first document; however, it provides many additional conclusions and recommendations that can now be made because of the expanded number and quality of studies.

Objectives and Methods

The primary objective of this scientific statement is to provide a comprehensive updated evaluation of the evidence linking PM exposure with CVDs. The focus of this review is explicitly on PM because the majority of air pollution studies have centered on its cardiovascular effects, and the strength of the evidence makes it possible to provide consensus opinions and recommendations. Except for in a few circumstances, such as when copollutants have been shown to (or not to) modify the responses to PM exposure or to have independent cardiovascular effects in epidemiological studies of major importance, a detailed discussion of other air pollutants (eg, ozone and NO_2) is beyond the scope of this document. Additional objectives are to provide expert consensus opinions on aspects related to the current state of science, to specifically highlight the health and clinical implications of the reviewed findings, and to provide prudent and practical recommendations for measures to reduce PM exposure that might thereby lower the associated cardiovascular risk. This updated scientific statement is structured to first provide a clinical perspective on the cardiovascular risks posed by PM exposure and then briefly review the components of air pollution. The following sections highlight the major findings from epidemiological studies, including mortality, morbidity, and surrogate outcome results. Next, the animal and human mechanistic studies are reviewed, and an overall framework whereby PM exposure could cause CVDs is outlined. Finally, updated consensus opinions and conclusions are provided, followed by suggestions for areas of future research and policy considerations.

Members of the current writing group were selected from across a broad range of disciplines, including cardiovascular and environmental epidemiology and statistics, atmospheric sciences, cardiovascular and pulmonary medicine, basic science research, and public policy. The writing group identified studies published in the English language between January 1, 2004, and March 31, 2009, by a World Wide Web–based literature search using Medline, PubMed, and Google search engines. Key terms included *air pollution* or *particulate matter* plus any of the following: *cardiovascular, myocardial, heart, cardiac, stroke, heart failure, arrhythmia, heart rate variability, autonomic, sympathetic, atherosclerosis, vascular, blood pressure, hypertension, diabetes, metabolic, thrombosis,* and *coagulation*. Additional studies were identified within the references of these publications and by the personal knowledge of the writing group members. A few studies published after March 31, 2009, were added during the review process. All of the identified epidemiological studies that provided mortality data or hard cardiovascular outcomes (eg, MIs) and controlled human exposure protocols were included. In a few circumstances, studies before 2004 were included briefly in the discussion or tables when it was believed that they provided contextual background and/or relevant findings from earlier analyses of ongoing studies (eg, Harvard Six Cities and American Cancer Society [ACS] cohorts) from which new results after 2004 have been published. It is a limitation of the present review that it was not possible to cite all surrogate outcome human studies because of the enormous number of publications. Some were not included, without intentional bias with regard to results, when multiple referenced studies demonstrated similar findings. In such a situation (eg, heart rate variability [HRV]), this

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limitation was noted within the specific section. A main theme of the present statement is to provide clinical context and recommendations for healthcare providers, and thus, it was beyond the scope and not the intent of this document to include all animal, ex vivo, or toxicological studies. A number of these publications were also not included, without intentional bias with regard to results. The writing group included publications that were believed to have relevant implications for human cardiovascular health, those that formed the foundation of the mechanistic hypotheses, and studies that were deemed of major importance. Finally, the "evidence summary" statements and all points in the conclusions and recommendations represent consensus expert opinions agreed on by all members of the writing group during formal discussions. It is explicitly stated when no such agreement was reached. These statements and the points within Tables 6 and 7 do not represent the result of applying the standard AHA criteria (ie, level and class) to the sum findings of the present review, because those do not apply, but rather the qualitative consensus opinions agreed on by the writing group. The purpose is to provide expert opinions on the comparative relative ranking and the strength of the overall evidence regarding different areas within this field of science.

Perspective on the Air Pollution–Cardiovascular Risk Association

Traditional cardiovascular risk factors account for the major portion of the risk for ischemic cardiac events within a population.[7] Individuals with optimal levels of all risk factors have been shown to have a low lifetime cardiovascular event rate.[8] Thus, control of the traditional risk factors is recognized to be of paramount importance to prevent CVDs. In this context, there has been some debate about the overall clinical relevance and utility of adding novel risk factors to risk-prediction models to incrementally improve their overall predictive value, even when assessed by multiple methodologies.[9] On the other hand, the ability to predict future events by existing models remains imperfect. In addition to several mathematical and statistical explanations for this shortcoming,[10,11] it is important to recognize that the development of vascular or atherosclerotic disease (the factor predicted by most statistical models) is usually a necessary but insufficient cause of future ischemic events in and of itself. Cardiovascular events must also be triggered by an additional factor at some unknowable future time, and therefore, they transpire as a stochastic process within a population.[12] This is one of several reasons why PM air pollution is a uniquely important public health issue among the list of novel risk factors; PM inhalation is an established trigger of cardiovascular events that occur within hours to days after exposure.[12] Because of the ubiquitous and involuntary nature of PM exposure, it may continuously enhance acute cardiovascular risk among millions of susceptible people worldwide in an often inconspicuous manner. Moreover, beyond serving as a simple trigger, PM elicits numerous adverse biological responses (eg, systemic inflammation) that, in premise, may further augment future cardiovascular risk over the long term after months to years of exposure.

Effects of Short-Term Exposure

Time-series studies estimate that a 10-μg/m^3 increase in mean 24-hour $PM_{2.5}$ concentration increases the relative risk (RR) for daily cardiovascular mortality by approximately 0.4% to 1.0%.[3] Despite theoretical statistical risks ascribed to all individuals, this elevated risk from exposure is not equally distributed within a population. At present-day levels, $PM_{2.5}$ likely poses an acute threat principally to susceptible people, even if seemingly healthy, such as the elderly and those with (unrecognized) existing coronary artery or structural heart disease.[13] Therefore, the absolute risk rather than the RR of exposure may more effectively convey the tangible health burden within a population. A 10-μg/m^3 increase during the preceding day contributes on average to the premature death of approximately 1 susceptible person per day in a region of 5 million people (based on annual US death rates in 2005).[3,14] Although the dangers to 1 individual at any single time point may be small, the public health burden derived from this ubiquitous risk is enormous. Short-term increases in $PM_{2.5}$ levels lead to the early mortality of tens of thousands of individuals per year in the United States alone.[1,3,5]

Effects of Long-Term Exposure

Cohort studies estimate that the RR associated with living in areas with higher PM levels over the long term is of greater magnitude than that observed from short-term exposure increases (RR between 1.06 and 1.76 per 10 μg/m^3 $PM_{2.5}$).[3] In this context, the World Health Organization estimated that $PM_{2.5}$ contributes to approximately 800 000 premature deaths per year, ranking it as the 13th leading cause of worldwide mortality.[15] Hence, PM air pollution appears to be an important modifiable factor that affects the public health on a global scale.

Air Pollution

The first AHA statement on air pollution reviewed the size fractions, sources, and chemical constituents of PM and the main gaseous air pollutants: Nitrogen oxides (NO_x; ie, $NO+NO_2$), carbon monoxide (CO), sulfur dioxide (SO_2), and ozone (O_3).[1] Therefore, this section within the updated statement focuses on several other contemporary aspects of air pollution characterization and exposure assessment, particularly in relation to their potential influences on cardiovascular health. In brief, PM is broadly categorized by aerodynamic diameter: All particles <10 μm (thoracic particles [PM_{10}]), all particles <2.5 μm (fine particles [$PM_{2.5}$]), all particles <0.1 μm (UFP), and particles between 2.5 and 10 μm (coarse particles [$PM_{10-2.5}$]). Hence, PM_{10} contains within it the coarse and $PM_{2.5}$ fractions, and $PM_{2.5}$ includes UFP particles. The concentrations of PM_{10} and $PM_{2.5}$ are typically measured in their mass per volume of air (μg/m^3), whereas UFPs are often measured by their number per cubic centimeter (Table 1). The major source of $PM_{2.5}$ throughout

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Table 1. Ambient Air Pollutants

Pollutant	US Average Range	US Typical Peak*	Most Recent NAAQS for Criteria Pollutants (Averaging Time)
O_3†	0–125 ppb	200 ppb	75 ppb (8 h)‡
NO_2†	0.5–50 ppb	200 ppb	100 ppb (1 h)§ 53 ppb (Annual mean)
NO†	0–100 ppb	200 ppb	
SO_2†	0.1–50 ppb	150 ppb	140 ppb (24 h)‖ 30 ppb (Annual mean)
CO†	0.1–5 ppm	20 ppm	35 ppm (1 h)‖ 9 ppm (8 h)‖
PM_{10}¶	10–100 $\mu g/m^3$	300 $\mu g/m^3$	150 $\mu g/m^3$ (24 h)#
$PM_{2.5}$¶	5–50 $\mu g/m^3$ (Mean=13.4±5.6)	100 $\mu g/m^3$	15 $\mu g/m^3$ (Annual mean) 35 $\mu g/m^3$ (24 h)**
$PM_{2.5}$ lead¶	0.5–5 ng/m^3	150 ng/m^3	0.15 $\mu g/m^3$ (Rolling 3-month average)††
NH_3†	0.1–20 ppb	100 ppb	
HNO_3†	0–5 ppb	10 ppb	
Methane†	1–2 ppm	5 ppm	
Formaldehyde†	0.1–10 ppb	40 ppb	
Acetaldehyde†	0.1–5 ppb	20 ppb	
NMHC (VOC)¶	20–100 $\mu g/m^3$	250 $\mu g/m^3$	
Propane¶	2–20 $\mu g/m^3$	500 $\mu g/m^3$	
Benzene¶	0.5–10 $\mu g/m^3$	100 $\mu g/m^3$	
1,3-Butadiene¶	0.1–2 $\mu g/m^3$	10 $\mu g/m^3$	
Total suspended particles¶	20–300 $\mu g/m^3$	1000 $\mu g/m^3$	
$PM_{10-2.5}$¶	5–50 $\mu g/m^3$	200 $\mu g/m^3$	
Sulfate¶	0.5–10 $\mu g/m^3$	30 $\mu g/m^3$	
Nitrate¶	0.1–5 $\mu g/m^3$	20 $\mu g/m^3$	
Organic carbon¶	1–20 $\mu g/m^3$	30 $\mu g/m^3$	
Elemental carbon¶	0.1–3 $\mu g/m^3$	10 $\mu g/m^3$	
PAH¶	2–50 ng/m^3	200 ng/m^3	
UFP†	1000–20 000/cm^3	100 000/cm^3	

ppb Indicates parts per billion; ppm, parts per million; and PAH, polycyclic aromatic hydrocarbon.

*Generally not in concentrated plumes or locations of direct source emission impact.

†Typical hourly average concentrations reached in US cities.

‡The 8-hour standard is met when the 3-year average of the 4th highest daily maximum 8-hour average is less than or equal to the indicated number. In January 2010, the EPA proposed a more stringent 8-hour standard within the range of 60 to 70 ppb (http://www.epa.gov/air/ozonepollution/actions.html).

§To attain this standard, the 3-year average of the 98th percentile of the daily maximum 1-hour average at each monitor within an area must not exceed this value.

‖The level is not to be exceeded more than once per year.

¶Typical 24-hour average concentrations.

#The level is not to be exceeded more than once per year on average over 3 years.

**The daily standard is met when the 3-year average of the 98th percentile of 24-hour PM level is less than or equal to the indicated number.

††Although the typical concentrations shown in the table are for $PM_{2.5}$, the lead standard continues to be based on measurements in total suspended particulate.

the world today is the human combustion of fossil fuels from a variety of activities (eg, industry, traffic, and power generation). Biomass burning, heating, cooking, indoor activities, and nonhuman sources (eg, fires) may also be relevant sources, particularly in certain regions.

Common air pollutants and those designated as EPA criteria pollutants (ie, specifically targeted in regulations through limits on emissions or government standards such as the NAAQS) are listed in Table 1. The World Health Organization also provides ambient guidelines (http://www.euro.who.int/Document/E90038.pdf). As a result, many pollutant concentrations are tracked in the United States by nationwide monitoring networks, with up to approximately 1200 sites for O_3 and $PM_{2.5}$. Data are archived by the EPA and are available to the public (http://www.epa.gov/ttn/airs/airsaqs/). O_3 levels exceed the national standard in many areas, and thus, daily information is provided to assist the public in reducing their exposure. A lower standard for ozone concentrations was proposed recently, which will lead to more frequent occurrences of outdoor exposures deemed to be excessive (Table 1). The reporting of $PM_{2.5}$ is also becoming common because of its impact on public health and frequent violations of standards. Current and forecast air quality indices and information on both $PM_{2.5}$ and ozone are available (http://airnow.gov/). At the end of 2008, 211 US counties (or portions of counties) were in nonattainment of the 2006 daily $PM_{2.5}$ NAAQS (http://www.epa.gov/pmdesignations/2006standards/state.htm). On a positive note, the various regulations that have been established have led to substantial reductions in PM and other pollutant levels over the past 40 years in the United States and contributed toward similar improvements in other countries. However, reducing the levels of some pollutants, such as O_3, remains a challenge because of the complex chemical processes that lead to their formation in the atmosphere.[16] The population of many developing nations (China, India, Middle Eastern countries) continues to be exposed to high levels, particularly of PM, which can routinely exceed 100 $\mu g/m^3$ for prolonged periods (http://siteresources.worldbank.org/DATASTATISTICS/Resources/table 3_13.pdf).

Air Pollution Mixtures, Chemistry, and Sources

Detailed information regarding PM sizes, composition, chemistry, sources, and atmospheric interactions is beyond the scope of this document but can be found in the 2004 US EPA Air Quality Criteria for Particulate Matter final report (http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=87903). The source for much of the information provided in this brief summary is this document, unless otherwise specifically referenced. The typical range of ambient concentrations for several air pollutants in the United States, including the latest US NAAQS for the criteria pollutants, is given in Table 1. Classification of air quality according to 1 single pollutant and by size or mass provides an incomplete picture, because ambient air pollution is a complex mixture of gases, particles, and liquids that are continually changing and interacting with each other and natural atmospheric gases. Although $PM_{2.5}$ mass has rightfully attracted considerable attention as a target for regulation and epidemiological study, more than 98% of

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the air pollutant mass in the mixture we breathe in urban settings is from gases or vapor-phase compounds such as CO, nonmethane hydrocarbons or volatile organic carbons (VOCs), NO_2, NO, O_3, and SO_2. Each of these can have independent and potentially synergistic or antagonistic effects with each other and with PM; however, at present, the cardiovascular health impact of exposure to combinations of air pollutants is not well understood.

Most of the studies linking CVDs with PM exposures have focused on particle mass; thus, this association is evaluated and reported in the majority of epidemiological and toxicological studies reviewed. Although PM is regulated by mass concentration, the aspect of PM most harmful to cardiovascular health may not be best quantified by mass measurement alone. The sum effect of many features related to chemical composition and size/morphology (eg, oxidative stress potential, solubility, charge, surface area, particle count, lung deposition, and stability within the atmosphere and biological tissues) is important to consider. With regard to specific "toxic" compounds within PM, several lines of existing evidence support the idea that transition metals, organic compounds, semiquinones, and endotoxin are likely relevant in relation to promoting CVDs. In addition, certain characteristics of UFPs (eg, high surface area, particle number, metal and organic carbon content) suggest that they may pose a particularly high cardiovascular risk after short-term exposure.[17] Both the additional characterization of "criteria" pollutants and the measurement of several other pollutants (discussed below) are important to inform air quality management practices that involve air quality modeling, as well as epidemiological studies and risk assessment, which ultimately aim to improve risk-reduction strategies.

In addition to their mass concentration, pollutants can be characterized on the basis of their origin or chemical and physical properties. In terms of origin, nitrogen oxides ($NO+NO_2$), CO, SO_2, and $PM_{2.5,}$ as well as carbon dioxide (CO_2), are mainly associated with combustion of fuel or other high-temperature industrial processes. Combustion PM is composed of many chemical compounds, including organic carbon species, elemental or black carbon, and trace metals (eg, lead and arsenic). They range in size from molecular clusters a few nanometers in diameter to light-scattering particles that peak on a mass contribution basis in the diameter range of 200 to 1000 nm (0.2 to 1 μm). UFP numbers are also strongly linked to fresh combustion and traffic-related pollution. Ammonia, methane, pesticides (persistent organic pollutants), reduced sulfur compounds, resuspended dust, and natural coarse particles ($PM_{10-2.5}$) are associated with noncombustion surface or fugitive releases that arise from a variety of human (eg, agriculture) and natural (eg, erosion) activities. Agricultural emissions and releases from a range of industrial processes and waste management are also important sources. Road and wind-blown dust from agricultural practices and from certain industrial facilities (eg, mineral industry) also contribute to these particles, which are typically in the coarse ($PM_{10-2.5}$) or even larger ($>PM_{10}$) range.

In addition to pollutants formed directly by combustion, many others are produced primarily through chemical reactions in the atmosphere among directly emitted pollutants. These are known as secondary pollutants. Sunlight, water vapor, and clouds are often involved in this atmospheric chemistry, which leads to greater oxidation of the pollutants. Examples include PM-associated sulfate, nitrate, and ammonium and many of the organic compounds within $PM_{2.5}$. Besides O_3, which is the most prevalent secondary gaseous oxidant, a number of inorganic and organic acids and VOCs form in the atmosphere. Examples are the hydroxyl radical, peroxyacetyl nitrate, nitric acid, formic and acetic acid, formaldehyde, and acrolein.

VOCs and semivolatile organic compounds (SVOCs), the latter of which are found in both the gas and particle phase, are an additional large class of pollutants. They are associated with both combustion and fugitive emissions, as well as with secondary formation. Key examples are benzene, toluene, xylene, 1,3-butadiene, and polycyclic aromatic hydrocarbons. VOCs are among the 188 hazardous air pollutants listed by the EPA, and their main emission sources have been identified and are regulated (http://www.epa.gov/ttn/atw/mactfnlalph.html). VOCs can undergo reactions that convert toxic substances to less toxic products or vice versa. Many VOCs contribute to the formation of O_3 and are oxidized in the atmosphere, becoming SVOCs, and subsequently partition within particles and contribute to the composition of $PM_{2.5}$, as well as to its mass. A great deal of research has focused on $PM_{2.5}$ in the past decade, which has led to advances in measurement technologies[18] and greater understanding of its chemistry and atmospheric behavior.[19] Nonetheless, understanding is incomplete, particularly with regard to formation of the secondary organic fraction, the relative role of anthropogenic and biogenic emissions to organics, surface chemistry, oxidative potential,[20] and gas-to-particle partitioning.

An alternative to attempting to identify one by one which pollutant(s) or chemical compounds are most harmful is to focus on identifying the sources, which typically emit mixtures of pollutants, of greatest concern. It may be the mixture of pollutants (along with the source from which it is derived, which determines its characteristics) that is most pertinent to human health outcomes. Such information may actually be more relevant for aiding the development of effective air quality policies. One important example reviewed in the epidemiology section is that the evidence continues to grow regarding the harmful cardiovascular effects of traffic-related pollution. Traffic is ubiquitous in modern society, with a sizeable proportion of the population, particularly persons disadvantaged by low socioeconomic status, living close enough (within 500 m) to a major road or a freeway to be chronically exposed to elevated concentrations. Additionally, daily behavior brings most people close to this source, with the average US citizen over 15 years of age spending 55 minutes each day traveling in motor vehicles.[21] However, despite the consistent epidemiological findings, these studies have yet to elucidate which of the many pollutants or other associated risks (ie, noise) produced by traffic are responsible for the increase in risk for CVD. Until the most harmful agents are identified, the only practical manner to potentially reduce health consequences would be to reduce overall traffic and related emissions and to configure cities and lifestyles

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such that there is greater separation between the people and the source, so that we could spend less time in traffic (a major source of personal exposures in our society). There are also a myriad of other important pollutant sources of known toxic pollutants that have been implicated in health-effect studies (eg, power generation, industrial sources, steel mills, and wood smoke). A better understanding of the factors that influence population exposure to these sources, of how their emissions and mixtures of different sources affect health, and about the factors that make individuals more susceptible will aid in the development of more effective environmental health policies.

Determinants of Air Pollution Exposure

Many aspects of air pollution play a role in the characteristics of population- and individual-level exposures. Pollutants vary on multiple time scales, with emission rates, weather patterns, and diurnal/seasonal cycles in solar radiation and temperature having the greatest impact on concentrations. The temporal behavior of a pollutant is also governed by its formation rate and the length of time it remains in the atmosphere. As such, the concentrations of many air pollutants tend to co-vary. For example, NO_x and CO are emitted during combustion, as are some particle constituents (eg, elemental carbon) and VOCs, and thus, their concentrations peak during rush hour. On the other hand, O_3 and other photochemical oxidants, including secondary $PM_{2.5}$ and secondary VOCs, peak in the afternoon, particularly given certain meteorologic conditions (eg, more sunshine). Among the common air pollutants, O_3 and $PM_{2.5}$ have the longest atmospheric lifetime and thus can build up over multiple days and spread, by the prevailing winds, over large geographic regions. This can lead to similarities in their temporal and spatial patterns over broad regions and to greater numbers of people being exposed to similar levels, thus lessening interindividual variability in exposure.

Periods of suppressed horizontal and vertical mixing in the lower atmosphere lead to the buildup of multiple pollutants. These situations are most common under slow-moving or stationary high-pressure systems, which bring light winds, a stable atmosphere, and more sunshine. The frequency and seasonality of these meteorologic conditions and how they affect concentrations vary geographically, which leads to differences in the characteristics of pollution episodes from the western to the eastern United States, as well as within these regions.

The commonality of meteorology and emission sources leads to covariation in pollutant concentrations on multiple temporal and spatial scales, which makes it more challenging for epidemiological studies to identify the health effects of individual pollutants and the effects of copollutants or mixtures. Studies that depend on daily counts of mortality or morbidity events have difficulties separating the effects of the different pollutants in the urban mix. Even prospective panel studies measuring specific end points on a subdaily time scale are hindered by pollutant covariation. Some of these challenges could potentially be addressed by undertaking studies covering multiple geographic locations with differences in the structure of pollutant covariation due to different meteorology and source mixes. Indeed, this has been done, at least in part, by several existing multicity studies. Consistency in the findings in individual studies conducted in different cities also helps isolate the pollutants that may be more responsible for the health effects. The consistent positive findings with certain pollutants (eg, PM mass concentration) have helped strengthen the evidence regarding PM_{10} and $PM_{2.5}$ effects, but regardless of location, there remains the strong underlying commonality of fossil fuel combustion for many pollutants.

A final issue to consider is the cardiovascular health effects of exposures that occur at the personal level because of the different microenvironments or activities an individual experiences (eg, time in traffic, indoor sources, secondhand tobacco smoke, occupational exposure, and degree of indoor penetration of ambient PM into homes) versus the effects of exposures from less variable urban- to regional-scale ambient concentrations (ie, background pollution that most individuals encounter more uniformly). Personal monitoring demonstrates substantial variations among individual pollution exposures or characteristics among those living within the same metropolitan area and even the same neighborhood.[22,23] However, the differing additive, synergistic, and/or confounding effects on cardiovascular health of these 2 contrasting components of a person's overall exposure have not been well described. For the most part, the magnitude of the findings reported by the major epidemiological studies (see next section) are indicative of the effects of the urban- to regional-scale ambient concentrations. Actual exposures to all pollutants also vary at the personal level. The cardiovascular health importance of these individual-level variations (above and beyond the effect of urban/regional levels) remains largely unknown, in part because it has been difficult to quantify. The degree to which measurement of personal exposures or more precise exposure assessment (eg, use of geographic information systems, land-use regression models, spatial-temporal models, and adjustments for indoor penetration) can reduce the effects of exposure misclassification in epidemiological studies also remains to be fully elucidated.[24–26]

Epidemiological Studies of Air Pollution

Epidemiological studies of air pollution have examined the health effects of exposures observed in real-world settings at ambient levels. Associations between relevant health end points and measures of air pollution are evaluated while attempting to control for effects of other pertinent factors (eg, patient and environmental characteristics). Despite substantial study and statistical improvements and the relative consistency of results, some potential for residual confounding of variables and publication bias[27] of positive studies are limitations to acknowledge. Probably the most relevant, well-defined, and extensively studied health end points include mortality (all-cause and cause-specific), hospitalizations, and clinical cardiovascular events. This section reviews the results of the epidemiological research with a focus on new studies since the first AHA statement was published,[1] as well as on the cardiovascular health implications. In sum, numerous studies of varied design have been published in the interim that significantly add to the overall weight of evi-

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Table 2. Comparison of Pooled Estimated of Percent Increase (and 95% CI or Posterior Interval or *t* Value) in RR of Mortality Estimated Across Meta-Analyses and Multicity Studies of Daily Changes in Exposure

			Percent Increases in Mortality (95% CI)		
	Primary Source	Exposure Increment	All-Cause	Cardiovascular	Respiratory
Meta-estimate with and without adjustment for publication bias	Anderson et al[27] 2005	20 $\mu g/m^3$ PM_{10}	1.0 (0.8–1.2) 1.2 (1.0–1.4)	…	…
Meta-estimates from COMEAP report to the UK Department of Health on CVD and air pollution	COMEAP[31] 2006	20 $\mu g/m^3$ PM_{10} 10 $\mu g/m^3$ $PM_{2.5}$	… …	1.8 (1.4–2.4) 1.4 (0.7–2.2)	… …
NMMAPS, 20 to 100 US cities	Dominici et al[34] 2003	20 $\mu g/m^3$ PM_{10}	0.4 (0.2–0.8)	0.6 (0.3–1.0)*	…
APHEA-2, 15 to 29 European cities	Katsouyanni et al[35] 2003 Analitis et al[36] 2006	20 $\mu g/m^3$ PM_{10}	1.2 (0.8–1.4)	1.5 (0.9–2.1)	1.2 (0.4–1.9)
US, 6 cities	Klemm and Mason[37] 2003	10 $\mu g/m^3$ $PM_{2.5}$	1.2 (0.8–1.6)	1.3 (0.3–2.4)†	0.6 (−2.9, 4.2)‡
US, 27 cities, case-crossover	Franklin et al[38] 2007	10 $\mu g/m^3$ $PM_{2.5}$	1.2 (0.3–2.1)	0.9 (−.1, 2.0)	1.8 (0.2, 3.4)
California, 9 cities	Ostro et al[39] 2006	10 $\mu g/m^3$ $PM_{2.5}$	0.6 (0.2–1.0)	0.6 (0.0, 1.1)	2.2 (0.6, 3.9)
France, 9 cities	Le Tertre et al[40] 2002	20 $\mu g/m^3$ BS	1.2 (0.5–1.8)§	1.2 (0.2–2.2)§	1.1 (−1.4, 3.2)§
Japan, 13 cities, age >65 y	Omori et al[41] 2003	20 $\mu g/m^3$ SPM	1.0 (0.8–1.3)	1.1 (0.7–1.5)	1.4 (0.9–2.1)
Asia, 4 cities	Wong et al[42] 2008	10 $\mu g/m^3$ PM_{10}	0.55 (0.26–0.85)	0.59 (0.22–0.93)	0.62 (0.16–1.04)
US, 112 cities	Zanobetti et al[43] 2009	10 $\mu g/m^3$ $PM_{2.5}$	0.98 (0.75–1.22)	0.85 (0.46–1.24)	1.68 (1.04–2.33)
		10 $\mu g/m^3$ $PM_{10-2.5}$‖	0.46 (0.21–0.71)	0.32 (0.00–0.64)	1.16 (0.43–1.89)
		10 $\mu g/m^3$ $PM_{2.5}$¶	0.77 (0.43–1.12)	0.61 (0.05–1.17)	1.63 (0.69–2.59)
		10 $\mu g/m^3$ $PM_{10-2.5}$¶	0.47 (0.21–0.73)	0.29 (−0.04, 0.61)	1.14 (0.043–1.85)

CI indicates confidence interval or posterior interval.
*Cardiovascular and respiratory deaths combined.
†Ischemic heart disease deaths.
‡Chronic obstructive pulmonary disease deaths.
§Includes general additive model–based analyses with potentially inadequate convergence.
‖Results for $PM_{10-2.5}$ are from 47 cities.
¶Results of 2 pollutant models controlling for alternate PM size in 47 cities.

dence that exposure to air pollutants at present-day levels contributes to cardiovascular morbidity and mortality.

Mortality and Air Pollution

Time-Series and Related Studies

Time-series and case-crossover studies explore associations between short-term changes in air pollution and daily changes in death counts. The sum of current evidence supports the findings of an earlier review[28] that demonstrated that short-term elevations in daily PM levels lead to a greater absolute risk for CVD-related mortality than for all other causes. Even if similar acute RR elevations (≈1.01) are estimated between cardiovascular and pulmonary mortality, CVDs account for 69% of the increase in absolute mortality rates compared with 28% for pulmonary diseases attributable to short-term PM exposure. Recently, more rigorous modeling techniques have been used in attempts to better estimate pollution-mortality associations while controlling for other time-dependent confounding covariables.[29,30] There have been well over 100 published daily time-series studies reporting small but statistically significant PM-mortality associations that have been the subject of quantitative reviews or meta-analyses.[3,27,31–33] Table 2 summarizes recent multicity analyses and studies published since 2004.

To address concerns about city selection bias, publication bias, and influences of copollutants, several large, multicity, daily time-series studies have been conducted worldwide. One of the largest was the National Morbidity, Mortality, and Air Pollution Study (NMMAPS). Published reports from this study included as few as 20 US cities,[44,45] as many as 100 cities,[46,47] and more recently, data for hundreds of counties (Table 2).[48] The observed relationship between PM exposure and excess mortality remained independent of several gaseous copollutants (NO_2, CO, or SO_2). Recent analyses suggest that O_3 may also independently contribute to cardiopulmonary mortality risk[49,50]; however, coexposures to secondary particle pollutants may be responsible in part for this latter association.[51]

Several studies have also been conducted outside the United States, including the Air Pollution and Health: A European Approach (APHEA and APHEA-2) projects, which examined daily PM-related mortality effects in multiple cities.[36,52] PM air pollution was significantly associated with daily mortality counts for all-cause, cardiovascular, and respiratory mortality (Table 2). Further analyses of the European data suggest that CVD deaths are also associated with exposure to NO_2[53] and CO.[54] A few new time-series studies have also confirmed similar increases in cardiovascular mortality related to short-term PM exposure in China[55–57] and Bangkok, Thailand.[42] Additional multicity studies have been conducted worldwide with analyses of CVD deaths (Table 2).[38–42,58–60] Finally, in a recent analysis that included several Asian

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cities, SO_2, NO_2, O_3, and PM_{10} were all associated with excess cardiovascular mortality.[42]

In an attempt to evaluate the coherence of multicity studies across continents, the Air Pollution and Health: A Combined European and North American Approach (APHENA) study analyzed data from the APHEA, NMMAPS, and Canadian studies.[61] The combined effect on all-cause mortality ranged from 0.2% to 0.6% for a 10-μg/m^3 elevation in daily ambient PM_{10}, with the largest effects observed in Canada. Among individuals older than 75 years, the effects were greater for cardiovascular mortality than for overall and pulmonary mortality (0.47% to 1.30%). Older age (>75 years) and higher rates of unemployment were related to greater PM mortality risks in both continents. Higher NO_2 levels were associated with larger PM_{10} effects on mortality, particularly in Europe. Finally, there appeared to be no lower-limit threshold below which PM_{10} was not associated with excess mortality across all regions.

Evidence Summary

The overall evidence from time-series analyses conducted worldwide since publication of the first AHA statement[1] confirms the existence of a small, yet consistent association between increased mortality and short-term elevations in PM_{10} and $PM_{2.5}$ approximately equal to a 0.4% to 1.0% increase in daily mortality (and cardiovascular death specifically) due to a 10-μg/m^3 elevation in $PM_{2.5}$ during the preceding 1 to 5 days (Table 2).

Cohort and Related Studies

Although short-term changes in PM concentrations have deleterious health effects, longer-term exposures may have a more pertinent clinical health effect on cardiovascular morbidity and mortality given that individuals are typically exposed to higher air pollution levels over extended periods of time. An additional source of exposure variability that has been exploited in epidemiological studies is spatial variability, which includes differences in average ambient concentrations over extended periods of time across metropolitan areas or across smaller communities within local areas. Recent emphasis has been on prospective cohort studies that control for individual differences in multiple confounding variables and cardiovascular risk factors. A summary of these studies is presented in Table 3 and Figure 1. These cohort studies generally demonstrate larger overall mortality effects than the results of time-series analyses.

Harvard Six Cities and ACS Studies

Two landmark cohort-based mortality studies, the Harvard Six Cities[62] and the ACS studies,[66] were reported in the mid 1990s and were discussed previously.[1] In both, $PM_{2.5}$ and sulfate particulate pollution were associated with increases in all-cause and cardiopulmonary disease (Table 3). In addition, intensive independent reanalyses[63] corroborated the original findings of both studies and resulted in innovative methodological contributions that demonstrated the robustness of the results to alternative modeling approaches. In both the Harvard Six Cities[62,64] and the ACS[67] studies, PM air pollution–related mortality was substantially higher for cardiovascular- than for pulmonary-related causes.

Since 2004, there have been further analyses of both studies. Laden et al[64] extended the mortality follow-up of the Harvard Six Cities cohort for an additional 8 years. $PM_{2.5}$ associations, similar to those found in the original analysis, were observed for all-cause and CVD mortality (Table 3). Furthermore, reductions in $PM_{2.5}$ concentrations for the extended follow-up period were associated with reduced mortality risk. Further analysis suggested that the health effects of changes in exposure were seen primarily within 2 years.[84] In addition to confirming the earlier mortality relationship, the recent observations suggest that the adverse health effects mediated by longer-term PM air pollution exposure can be estimated reasonably accurately by the previous few years of particle levels.

Extended analyses of the ACS cohort that emphasize efforts to control for the effects of other covariates and risk factors have corroborated the previously reported mortality associations with particulate and sulfur oxide pollution.[68] Elevated mortality risks were most strongly associated with $PM_{2.5}$. Coarse particles ($PM_{10-2.5}$) and gaseous pollutants, except for SO_2, were generally not significantly related to mortality. In another extended analysis,[67] the death certificate classifications of underlying causes of death due to $PM_{2.5}$ exposures were observed to be principally ischemic heart disease, arrhythmias, heart failure, and cardiac arrest. Finally, recent additional analyses attempted to control for the fact that variations in exposure to air pollution across cities or within cities may correlate with socioeconomic or demographic gradients that influence health and susceptibility to environmental exposures.[85,86] When controlled for individual risk factor data, the mortality associations for intrametropolitan $PM_{2.5}$ concentration differences within the Los Angeles, Calif, area were generally larger than those observed in the full cohort across metropolitan areas.[69] However, the results were somewhat sensitive to the inclusion of zip code–level ecological variables, which suggests potential contextual neighborhood confounding. Krewski et al[70] subsequently observed that full adjustments for multiple ecological covariates did not reduce the estimated $PM_{2.5}$-related mortality effect. The association for ischemic heart disease mortality in particular was highly robust across various study areas and modeling strategies and after controlling for both individual and ecological covariates.

An additional recent analysis of the ACS cohort evaluated the health effects of ozone compared with $PM_{2.5}$.[87] The findings reconfirmed the independent cardiovascular mortality increase related to fine-particle exposure. However, after adjustment for $PM_{2.5}$, ozone was associated solely with an elevated risk of death due to respiratory causes; there was no independent risk of ozone exposure on CVD-related mortality. This suggests that the positive findings reported in NMMAPS[50] regarding cardiopulmonary mortality and short-term ozone exposure could be explained at least in part by the enhanced risk of mortality due to lung disease categories.

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Table 3. Summary of Cohort Study Results

Study	Size of Cohort (000s)	Follow-Up Period	Covariates Controlled for	Percent Increases in Mortality (95% CI) Associated With 10 $\mu g/m^3$ $PM_{2.5}$ (or Other When Indicated)			
				All-Cause	Cardiopulmonary	Cardiovascular	Ischemic Heart Disease
Harvard Six Cities, original (Dockery et al[62] 1993)	≈8	1974–1991	Individual (smoking+others)	13 (4.2–23)	18 (6.0–32)	…	…
Harvard Six-Cities, HEI reanalysis, Krewski et al[63] 2004	≈8	1974–1991	Individual (smoking+others)	14 (5.4–23)	19 (6.5–33)	…	…
Harvard Six-Cities, extended, Laden et al[64] 2006	≈8	1974–1998	Individual (smoking+others)	16 (7–26)	…	28 (13–44)	…
Six-Cities Medicare cohort, Eftim et al[65] 2008	≈340	2000–2002	Individual (age, sex)	21 (15–27)	…	…	…
ACS, Original, Pope et al[66] 1995	≈500	1982–1989	Individual (smoking+others)	6.6 (3.5–9.8)	12 (6.7–17)	…	…
ACS, HEI reanalysis, Krewski et al[63] 2004	≈500	1982–1989	Individual (smoking+others) +ecological	7.0 (3.9 10)	12 (7.4–17)	13 (8.1–18)	…
ACS, extended I, Pope et al[67,68] 2002, 2004	≈500	1982–1998	Individual (smoking+others)	6.2 (1.6–11)	9.3 (3.3–16)	12 (8–15)	18 (14–23)
ACS, intrametro Los Angeles, Jerrett et al[69] 2005	≈23	1982–2000	Individual (smoking+others) +ecological	17 (5–30)	12 (−3–30)	…	39 (12–73)
ACS, extended II, Krewski et al[70] 2009	≈500	1982–2000	Individual (smoking+others) +ecological	5.6 (3.5–7.8)	13 (9.5–16)	…	24 (20–29)
ACS, Medicare cohort, Eftim et al[65] 2008	7333	2000–2002	Individual (age, sex)+ecological +COPD	11 (9–13)	…	…	…
US Medicare cohort, east/central/west, Zeger et al[71] 2008	13 200	2000–2005	Individual (age, sex)+ecological +COPD	6.8 (4.9–8.7),* 13 (9.5–17) −1.1 (−3 to 0.8)	…	…	…
Women's Health Initiative, Miller et al[72] 2007	≈66	1994–2002	Individual (smoking+others)	…	…	76 (25–147), 24 (9–41)†	…
Nurses' Health Study, Puett et al[73] 2008	≈66	1992–2002	Individual (smoking+others) ecological	7.0 (−3.0 to 18)‡	…	30 (0–71)‡	…
AHSMOG, males only, McDonnell et al[74] 2000	≈4	1977–1992	Individual (smoking+others)	8.5 (−2.3 to 21)	23 (−3 to 55)	…	…
AHSMOG, females only, Chen et al[75] 2005	≈4	1977–2000	Individual (smoking+others)	…	…	42 (6–90)	…
VA hypertensive male I study, Lipfert et al[76] 2006	≈42	1989–1996	Individual (smoking+others) +ecological	15 (5–26)§	…	…	…
VA hypertensive male II study, Lipfert et al[77] 2006	≈30	1997–2001	Individual (smoking+others) +ecological	6 (−6 to 22)	…	…	…
11 CA county, elderly, Enstrom[78] 2005	≈36	1973–2002	Individual (smoking+others) +ecological	4 (1–7)‖, 1 (−0.6 to 2.6)	…	…	…
French PAARC, Filleul et al[79] 2005	≈14	1974–2000	Individual (smoking+others)	7 (3–10)‡	5 (−2 to 12)‡	…	…
German women, Gehring et al[80] 2006	≈5	1980s, 1990s–2003	Individual smoking and socioeconomic status	12 (−8 to 38)	52 (9–115)	…	…

(*Continued*)

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Table 3. Continued

Study	Size of Cohort (000s)	Follow-Up Period	Covariates Controlled for	Percent Increases in Mortality (95% CI) Associated With 10 $\mu g/m^3$ $PM_{2.5}$ (or Other When Indicated)			
				All-Cause	Cardiopulmonary	Cardiovascular	Ischemic Heart Disease
Oslo, Norway, intrametro, Naess et al[81] 2007	≈144	1992–1998	Individual age, occupational class, education	…	…	10 (5–16),¶ 14 (6–21), 5 (1–8), 3 (0–5)	…
Dutch cohort, Beelen et al[82] 2008	≈121	1987–1996	Individual (smoking+others) +ecological	6 (−3 to 16)	…	4 (−10 to 21)	…
Great Britain, Elliott et al[83] 2007	≈660	1966–1998	Socioeconomic status	1.3 (1.0–1.6)‡#	1.7 (1.3–2.2)‡#	1.2 (0.7–1.7)‡#	

HEI indicates Health Effects Institute; VA, Veterans Affairs; COPD, chronic obstructive pulmonary disease; and CA, California.

*Three estimates are for the East, Central, and West regions of the United States, respectively.

†Any cardiovascular event.

‡Associated with 10 $\mu g/m^3$ British Smoke (BS) or PM_{10}.

§Estimates from the single-pollutant model. Effect estimates were smaller and statistically insignificant in analyses restricted to counties with nitrogen dioxide data. County-level traffic density was a strong predictor of survival, and stronger than $PM_{2.5}$ when included with $PM_{2.5}$ in joint regressions.

||Two estimates are for the follow-up period 1973–1982 and the follow-up period 1983–2002, respectively.

¶Four estimates are for men 51–70 y old, women 51–70 y old, men 71–90 y old, and women 71–90 y old, respectively.

#Using last 0- to 4-year exposure window.

Additional Cohort Studies

Several additional cohort studies have been published in the past few years (Table 3). Eftim and colleagues[65] studied 2 very large "cohorts" of US Medicare participants who lived in locations included in the Harvard Six Cities and ACS studies. Effects of $PM_{2.5}$ exposure on mortality for the period 2000 to 2002 were estimated after controlling for multiple factors, although not at the individual patient level. For all-cause mortality, the $PM_{2.5}$-mortality associations were larger than those observed in the Harvard Six Cities or ACS cohorts. In an additional analysis of 13.2 million US Medicare participants for the time period 2000 to 2005,[71] $PM_{2.5}$-mortality associations were shown to be similar to those observed in the Harvard Six Cities and ACS studies in the East and Central regions of the United States (and when the data were pooled for the entire United States). However, $PM_{2.5}$ was not associated with mortality in the Western United States or for the oldest age group (>85 years old). These findings generally corroborate the earlier cohort studies and add evidence that aspects of exposure (PM sources or composition) and patient susceptibility might play important roles in determining the health risks.

In a cohort of postmenopausal women without prior CVD from the Women's Health Initiative Observational Study,[72] an association between longer-term $PM_{2.5}$ exposure (median follow-up of 6 years) and cardiovascular events (primary end point) was observed. After adjustment for age and other risk factors, an incremental difference of 10 $\mu g/m^3$ $PM_{2.5}$ was associated with a 24% (95% confidence interval [CI]9% to 41%) increase in all first cardiovascular events (fatal and nonfatal, with a total of 1816 cases). Notably, an incremental difference of 10 $\mu g/m^3$ $PM_{2.5}$ was also associated with a large 76% (95% CI 25% to 147%) increase in fatal cardiovascular events, based on 261 deaths. The risks for both coronary heart disease and strokes were found to be similarly elevated. Interestingly, within-city $PM_{2.5}$ gradients appeared to have larger cardiovascular effects than those between cities, although this difference was not statistically significant. Finally, overweight women (body mass index >24.8 kg/m^2) were at relatively greater cardiovascular risk due to particulate air pollution than leaner women. Noteworthy aspects of this study were improved assessment of the end points by medical record review (rather than by death certificate) and long-term particle exposure estimation. The control for individual-level confounding variables was also superior to that of previous cohort studies.

In another cohort of women, a subset of the Nurses' Health Study from the northeastern United States,[73] an increase of 10 $\mu g/m^3$ modeled estimates of PM_{10} exposures was associated with an approximately 7% to 16% increased risk of all-cause mortality and a 30% to 40% increase in fatal coronary heart disease, depending on the level of adjustment for covariates. This study found that the strongest health risks for all-cause and cardiovascular mortality were seen in association with the average PM_{10} exposure during the previous 24 months before death. Similar to the findings of the Women's Health Initiative, the cardiovascular mortality risk estimates were larger than those of previous cohort studies. In addition, obese women (body mass index >30 kg/m^2) were at greater relative risk, and the increases in mortality (all-cause and cardiovascular) were larger than the effects on nonfatal events. The results were also in accordance with the latest Harvard Six Cities analyses[64] that show that exposure over the most recent preceding 1 to 2 years can accurately estimate the majority of the health risks due to longer-term PM air pollution exposures.

The pollution-mortality association has also been assessed in several other cohort studies in the United States and Europe (Table 3).[76–83] In a recent analysis of the Adventist Health Study of Smog (AHSMOG) cohort with a much

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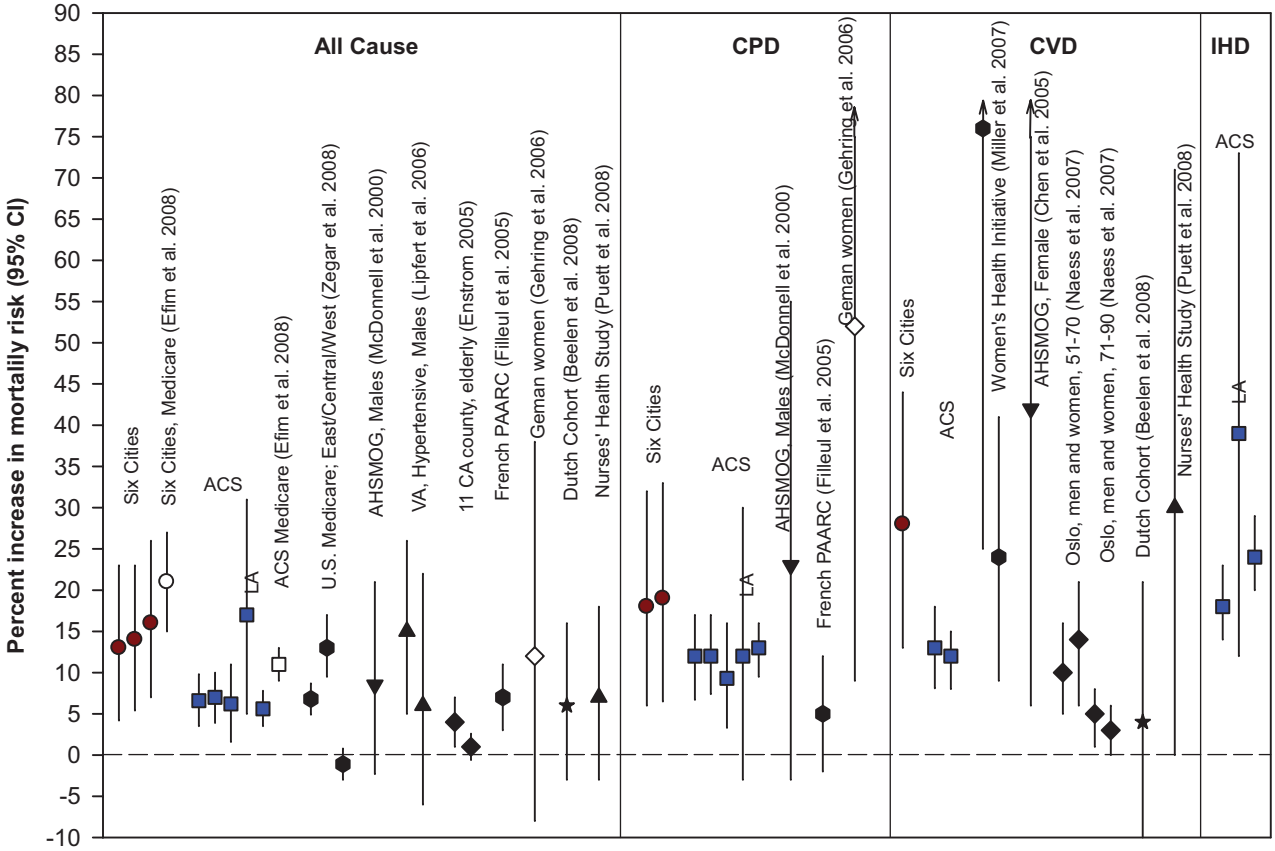

Figure 1. Risk estimates provided by several cohort studies per increment of 10 $\mu g/m^3$ in $PM_{2.5}$ or PM_{10}. CPD indicates cardiopulmonary disease; IHD, ischemic heart disease.

longer follow-up than the original studies,[74,88] fatal coronary heart disease was significantly associated with $PM_{2.5}$ among females but not males.[75] These observations along with the remarkably robust health effects in the Women's Health Initiative Observational Study and Nurses' Health Study suggest that women may be at special risk from PM exposure. The overall cohort study evidence demonstrates that a 10-$\mu g/m^3$ increase in $PM_{2.5}$ exposure is in general positively associated with excess mortality, largely driven by increases in cardiopulmonary or cardiovascular deaths (Figure 1). Independent results from the Women's Health Initiative Study,[72] the US Medicare cohorts,[71] the German women cohort,[80] and the intracity Oslo (Norway) study[81] contribute substantially to this evidence. Although the Dutch cohort,[82] AHSMOG,[74,75] French PAARC (Pollution Atmosphérique et Affections Respiratoires Chroniques [air pollution and chronic respiratory diseases]),[79] Veterans Affairs hypertensive male study,[77] and 11 CA county[78] studies observed increased mortality risks associated with higher $PM_{2.5}$ exposure that were statistically significant in some analyses, the observed health risks were less robust. A finding that is somewhat consistent across the Veterans Affairs hypertensive male study,[77] 11 CA county,[78] Oslo,[81] and US Medicare cohorts[71] is that the $PM_{2.5}$-mortality effect estimates tend to decline with longer periods of follow up or in a substantially older cohort. These studies also often observed elevated mortality risks according to alternative indicators of air pollution exposure, especially metrics of traffic-related exposure.

Evidence Summary

The overall evidence from the cohort studies demonstrates on average an approximate 10% increase in all-cause mortality per 10-$\mu g/m^3$ elevation in long-term average $PM_{2.5}$ exposure. The mortality risk specifically related to CVD appears to be elevated to a similar (or perhaps even greater) extent, ranging from 3% to 76% (Table 3). This broader estimated range in risk compared with the short-term effects observed in time series is due to several recent cohort studies[72,73] that demonstrated larger cardiovascular mortality risks (eg, >30%) than in earlier cohort observations. This may reflect superior aspects of these studies that allowed for a better characterization of the cardiovascular risk of long-term exposure, the fact that these cohorts consisted of only women, or other unclear reasons. Compared with cardiovascular mortality, there is less existing evidence to support an increase in the risk for nonfatal cardiovascular events related to $PM_{2.5}$ exposure among the existing cohort studies, because many of them did not specifically investigate nonfatal outcomes, and several of the more recent studies reported nonsignificant relationships.[72,73]

Natural Experiment and Intervention Studies

Several studies have shown improvements in health outcomes in association with exposures using well-defined natural experiments or interventions, such as abrupt reductions in air pollution[89–91] or changes over a longer period of time.[64,92]

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Table 4. Comparison of Pooled Estimated of Percent Increase in Risk of Hospital Admission for CVD Estimated Across Meta-Analyses and Multicity Studies of Daily Changes in Exposure

	Primary Source	Exposure Increment	% Increase (95% CI)
Cardiac admissions, meta-analysis of 51 estimates	COMEAP[31] 2006	20 $\mu g/m^3$ PM_{10}	1.8 (1.4–1.2)
Cardiac admissions, 8 US cities	Schwartz[96] 1999	20 $\mu g/m^3$ PM_{10}	2.0 (1.5–2.5)
Cardiac admissions, 10 US cities	Zanobetti et al[97] 2000	20 $\mu g/m^3$ PM_{10}	2.6 (2.0–3.0)
Cardiac admissions, 14 US cities	Samet et al[98] 2000	20 $\mu g/m^3$ PM_{10}	2.0 (1.5–2.5)
	Schwartz et al[99] 2003		
Cardiac admissions, 8 European cities	Le Tertre et al[40] 2002	20 $\mu g/m^3$ PM_{10}	1.4 (0.8–2.0)
Cardiovascular admissions, 14 Spanish cities	Ballester et al[100] 2006	20 $\mu g/m^3$ PM_{10}	1.8 (7–3.0)
Cardiovascular admission, 8 French cities	Larrieu et al[101] 2007	20 $\mu g/m^3$ PM_{10}	1.6 (0.4–3.0)
Cardiovascular admissions, 202 US counties	Bell et al[102] 2008	20 $\mu g/m^3$ PM_{10}	0.8 (0.6–1.0)
Medicare national claims history files	Dominici et al[103] 2006	10 $\mu g/m^3$ $PM_{2.5}$	
Ischemic heart disease,			0.44 (0.02–0.86)
Cerebrovascular disease			0.81 (0.30–1.32)
Heart failure			1.28 (0.78–1.78)
Heart rhythm			0.57 (−0.01 to 1.15)

Small but statistically significant drops in mortality were associated with an 8½-month copper smelter strike that resulted in sharp reductions in sulfate PM and related air pollutants across 4 Southwest states, even after controlling for other factors.[93] Data from US Medicare enrollment files were used to estimate the association between changes in monthly mortality rates for US counties and average $PM_{2.5}$ concentrations for the previous 12 months.[94] $PM_{2.5}$-mortality associations were observed at the national scale but not the local scale, which raises concerns about possible statistical confounding due to unmeasured individual and ecological variables as a cause for any positive findings in this study. However, a recent large study found that reductions in PM air pollution exposure on a local scale (across US counties) over a 2-decade period (1980s and 1990s) were associated with increased life expectancy even after controlling for changes in socioeconomic, demographic, and proxy smoking variables.[95] Indeed, a decrease of 10 $\mu g/m^3$ in the long-term $PM_{2.5}$ concentration was related to an increase in mean life expectancy of 0.61 ± 0.20 years.

Hospitalization Rates

There are many daily time-series or case-crossover studies that have evaluated associations between cardiovascular hospitalizations and short-term changes in air pollution. Because of the great number of publications, all studies (particularly those focusing on nonparticulate air pollutants) cannot be discussed individually. Nevertheless, Table 4 presents a comparison of pooled estimates of percent increase in RR of hospital admission for general cardiac conditions across a previous meta-analysis of 51 published estimates (COMEAP [Committee on the Medical Effects of Air Pollutants]) and results from many selected multicity studies published after 2004. Several studies before 2004 are included in Table 4 only to demonstrate the consistency of effect.

Because of its comparatively large size and importance, the results of a recent analysis of Medicare files in 204 US urban counties with 11.5 million individuals older than 65 years merit discussion. Daily changes in $PM_{2.5}$ levels were associated with a variety of cardiovascular hospital admission subtypes.[103] A 10-$\mu g/m^3$ increase in $PM_{2.5}$ exposure was related to increases in hospitalizations for cerebrovascular disease by 0.81% (95% CI 0.3% to 1.32%), peripheral vascular disease by 0.86% (95% CI −0.06% to 1.79%), ischemic heart disease by 0.44% (95% CI 0.02% to 0.86%), arrhythmias by 0.57% (95% CI −0.01% to 1.15%), and heart failure by 1.28 (95% CI 0.78% to 1.78%). The most rapid effects, which occurred largely on the same day of $PM_{2.5}$ elevation, were seen for cerebrovascular, arrhythmia, and heart failure admissions. Ischemic heart disease events tended to increase to a greater extent 2 days after exposures. A consistent finding was that the cardiovascular effects of pollution were much stronger in the Northeast than in other regions. In fact, there were few significant associations in Western US regions. It was speculated that these differences reflected variations in particle composition (eg, greater sulfate in the East and nitrate components in the West) and pollution sources (eg, power generation in the East and transportation sources in the West). In a follow-up analysis by Peng et al,[104] $PM_{10-2.5}$ levels were not statistically associated with cardiovascular hospitalizations after adjustment for $PM_{2.5}$. This suggests that the smaller particles (ie, $PM_{2.5}$) are principally responsible for the cardiovascular hospitalizations attributed in prior studies to the combination of both fine and coarse particles (ie, PM_{10}). Given the differences between the size fractions, the results imply that particles and their components derived from combustion sources (ie, $PM_{2.5}$) are more harmful to the cardiovascular system than larger coarse particles. Finally, there is some evidence that gaseous pollutants may also instigate hospitalizations. Hospital admissions for cardiovascular causes, particularly ischemic heart disease, were found to rise in relation to the previous-day and same-day level of SO_2, even after adjustment for PM_{10} levels.[105]

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Table 5. Comparisons of Estimated Percent Increase in Risk of Ischemic Heart Disease Events due to Concurrent or Recent Daily PM Exposure

Event/Study Area	Primary Source	Exposure Increment	% Increase (95% CI)
MI events–Boston, Mass	Peters et al[110] 2001	10 μg/m^3 $PM_{2.5}$	20 (5.4–37)
MI, 1st hospitalization–Rome, Italy	D'Ippoliti et al[112] 2003	30 μg/m^3 TSP	7.1 (1.2–13.1)
MI, emergency hospitalizations–21 US cities	Zanobetti and Schwartz[113] 2005	20 μg/m^3 PM_{10}	1.3 (0.2–2.4)
Hospital readmissions for MI, angina, dysrhythmia, or heart failure of MI survivors–5 European cities	Von Klot et al[114] 2005	20 μg/m^3 PM_{10}	4.2 (0.8–8.0)
MI events–Seattle, Wash	Sullivan et al[115] 2005	10 μg/m^3 $PM_{2.5}$	4.0 (−4.0–14.5)
MI and unstable angina events–Wasatch Front, Utah	Pope et al[13] 2006	10 μg/m^3 $PM_{2.5}$	4.8 (1.0–6.6)
Tokyo metropolitan area	Murakami et al[109] 2006	TSP >300 μg/m^3 for 1 h vs reference periods <99 μg/m^3	40 (0–97)*
Nonfatal MI, Augsburg, Germany	Peters et al[111] 2004	Exposure to traffic 1 h before MI (note: not PM but self-reported traffic exposure)	292 (222–383)
Nonfatal MI, Augsburg, Germany	Peters et al[116] 2005	Ambient UFP, $PM_{2.5}$, and PM_{10} levels	No association with UFP or $PM_{2.5}$ on same day. Positive associations with $PM_{2.5}$ levels on 2 days prior

TSP indicates total suspended particulate matter.
*Adjusted rate ratio for MI deaths.

Evidence Summary

Excess cardiovascular mortality and increased rates of hospitalizations are similarly associated with day-to-day changes in PM air pollution (Tables 2 and 4). However, significant differences between geographic regions in the risk relationships have been observed, and more investigation is required to explain this heterogeneity.

Specific Cardiovascular Events/Conditions

Ischemic Heart Disease

Among the cohort studies that provided relevant results, the ACS study found a relationship between increased risk for ischemic heart disease death and long-term exposure to elevated $PM_{2.5}$ levels (Table 3).[67,69,106] Indeed, ischemic cardiac events accounted for the largest relative (RR 1.18, 95% CI 1.14 to 1.23) and absolute risk for mortality per 10-μg/m^3 elevation in $PM_{2.5}$.[67] A survival analysis of US Medicare data for 196 000 survivors of acute MI in 21 cities showed the risk of an adverse post-MI outcome (death, subsequent MI, or first admission for congestive heart failure) was increased with higher exposure to PM_{10}.[107] Data from the Worcester Heart Attack study also found that long-term exposure to traffic-related air pollution was associated with significantly increased risk of acute MI.[108] However, in the Women's Health Initiative[72] and the Nurses' Health Study,[73] only disease categories that included fatal coronary events, but not nonfatal MI alone, were statistically elevated in relation to $PM_{2.5}$. The effect size for cardiovascular mortality was much larger and much more statistically robust than for nonfatal events such as MI in both studies.

Various time-series and case-crossover studies have also reported increased ischemic heart disease hospital admissions associated with short-term elevated concentrations of inhalable and/or fine PM air pollution.[31,40,103] In the US Medicare study, a reduction of $PM_{2.5}$ by 10 μg/m^3 was estimated to reduce ischemic heart disease admissions in 204 counties by 1523 (95% posterior interval 69 to 2976) cases per year.[103] Several studies have also found positive associations between elevated PM or traffic exposures over a period as brief as a few hours[109–111] or a few days and an elevated risk for MI (Table 5).[13,110,112–115] In general, acute increases in risk for ischemic heart disease events have been observed consistently, even as rapidly as 1 to 2 hours after exposure to elevated PM, in case-crossover analyses.[109–111] Other studies have reported an increased risk for MI shortly after exposure to traffic. Peters et al[111] reported in 691 subjects in Augsburg, Germany, a strong association (odds ratio 2.92, 95% CI 2.22 to 3.83) between onset of MI and traffic exposure within the past hour, although whether this was a result of the air pollution or a combination of other factors (eg, noise and stress) is not certain. Additional analyses did not report an association between recent UFP exposures and MI onset; however, the levels of $PM_{2.5}$ and several gaseous pollutants 2 days earlier were related to MI risk.[116] The lack of relationship between MI and UFPs may be due to the fact that the levels were measured regionally and remote from the localized source and may therefore reflect exposure misclassification. Finally, in the only study in which participating subjects had coronary angiograms performed previously, ischemic cardiac events were found to occur in relation to PM air pollution exposure solely among individuals with obstructive coronary atherosclerosis in at least 1 vessel.[13] This finding suggests the importance of patient susceptibility (eg, the presence of preexisting coronary artery disease) for PM to trigger an acute ischemic event within hours to days after exposure.

Heart Failure

In the ACS cohort study, it appeared that deaths due to arrhythmias, heart failure, and cardiac arrest (RR 1.13, 95% CI 1.05 to 1.21 per 10 μg/m^3) were also associated with

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prolonged exposure to $PM_{2.5}$, although not as strongly as ischemic heart disease mortality,[67] although potential mortality misclassification on death certificates makes the actual cause of death not entirely certain in all circumstances. Heart failure rates or mortality associations were not reported in the other cohort studies.

Daily hospitalizations for heart failure have also been associated with short-term changes in PM exposure.[31] Heart failure associations with PM were observed in a large daily time-series analysis of $PM_{2.5}$ and cardiovascular and respiratory hospitalizations by use of a national database constructed from US Medicare files.[103] A 10-$\mu g/m^3$ increase in concurrent-day $PM_{2.5}$ was associated with a 1.28% (95% CI 0.78% to 1.78%) increase in heart failure admissions, the single largest cause for hospitalization in this cohort. A reduction of $PM_{2.5}$ by 10 $\mu g/m^3$ was estimated to reduce heart failure admissions in 204 counties by 3156 (95% posterior interval 1923 to 4389) cases per year.[103] Another analysis in Medicare recipients in 7 US cities found a 10-$\mu g/m^3$ increase in concurrent-day PM_{10} was associated with a 0.72% (95% CI 0.35% to 1.10%) increase in heart failure admissions.[117] Traffic-related air pollution has also been shown to be significantly associated with increased mortality risk after acute heart failure.[118] Finally, a study from Utah's Wasatch Front area explored longer lagged-exposure periods and found that a 14-day lagged cumulative moving average of 10 $\mu g/m^3$ $PM_{2.5}$ was associated with a 13.1% (95% CI 1.3% to 26.2%) increase in heart failure admissions.[119]

Cerebrovascular Disease

Among the cohort studies that provided pertinent results, the Women's Health Initiative reported significant increases in both nonfatal stroke (hazard ratio 1.28, 95% CI 1.02 to 1.61) and fatal cerebrovascular disease (hazard ratio 1.83, 95% CI 1.11 to 3.00) per 10-$\mu g/m^3$ elevation in prolonged exposure to $PM_{2.5}$.[72] However, no significant association between stroke mortality and PM air pollution was found in the ACS study.[67]

Several studies have also reported small but statistically significant associations between short-term PM exposure and cerebrovascular disease. Daily time-series studies of stroke mortality in Seoul, Korea,[120,121] observed that elevated air pollution (including measures of PM, NO_2, CO, and O_3) was associated with increases in stroke mortality. When analyzed separately by stroke type,[121] the pollution association was associated with ischemic but not hemorrhagic stroke. Risk of stroke mortality was also associated with daily increases in PM_{10} and NO_2 in Shanghai, China.[56] A daily time-series study in Helsinki, Finland,[122] found that $PM_{2.5}$ and CO were associated with stroke mortality in the warm but not the cold seasons. Several studies have also observed increased stroke or cerebrovascular hospital admissions associated with increased exposure to PM or related pollutants.[31,38,40,46,123–125] For example, a study of hospital admissions for Medicare recipients in 9 US cities[125] found that several measures of air pollution (PM_{10}, CO, NO_2, and SO_2) 0 to 2 days before admission were associated with ischemic but not hemorrhagic stroke. Studies of ischemic stroke and transient ischemic attacks based on population-based surveillance have also been conducted in Dijon, France,[126] where O_3 exposure (but not PM_{10}) was associated with ischemic stroke, and in Corpus Christi, Tex,[127] where both $PM_{2.5}$ and O_3 were associated with ischemic strokes and transient ischemic attacks.

Peripheral Arterial and Venous Diseases

There have been only a few studies that have explored a relationship between air pollution and peripheral vascular diseases. Studies using Medicare data for 204 US counties observed nearly statistically significant positive associations between daily changes in measures of PM pollution and hospitalizations for peripheral vascular diseases.[103,104] The ACS cohort found no association between other atherosclerotic and aortic aneurysm deaths and long-term $PM_{2.5}$ exposure.[67]

Recently, a case-control study from the Lombardy region of Italy found a 70% increase in risk of deep vein thrombosis per 10-$\mu g/m^3$ elevation in long-term PM_{10} level.[128] This is the first observation that particulate air pollution can enhance coagulation and thrombosis risk in a manner that adversely affects the venous circulation in addition to the arterial cardiovascular system.

Cardiac Arrhythmias and Arrest

Several studies have observed associations between fine PM and related pollutants and cardiac arrhythmias, often based on data from implanted cardioverter-defibrillators.[129–136] However, no clear pollution-related associations were observed in studies from a relatively clean metropolitan area, Vancouver, British Columbia, Canada,[137,138] or from a relatively large study in Atlanta, Ga.[139] Similarly, pollution-related associations have been observed with cardiac arrest in Rome, Italy,[140] and Indianapolis, Ind,[141] but not in Seattle, Wash.[142,143] The mixed results may reflect different PM compositions due to different sources or variations among the methods used.

Evidence Summary

On the basis of the available epidemiological studies that have reported the associations between PM exposures with specific subsets of cardiovascular outcomes (morbidity, mortality, or hospitalizations), the existing level of overall evidence is strong for an effect of PM on ischemic heart disease, moderate (yet growing) for heart failure and ischemic stroke, and modest or mixed for peripheral vascular and cardiac arrhythmia/arrest (Table 6).

Ambient Air Pollution and Subclinical Pathophysiological Responses in Human Populations

It is likely that many subclinical physiological changes occur in individuals in response to $PM_{2.5}$ exposures that do not become overtly manifest as a cardiovascular event (eg, death or MI). The illustration of these more subtle responses bolsters the plausibility of the observable outcome associations and provides insight into the pathways whereby air

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Table 6. Overall Summary of Epidemiological Evidence of the Cardiovascular Effects of $PM_{2.5}$, Traffic-Related, or Combustion-Related Air Pollution Exposure at Ambient Levels

Health Outcomes	Short-Term Exposure (Days)	Longer-Term Exposure (Months to Years)
Clinical cardiovascular end points from epidemiological studies at ambient pollution concentrations		
Cardiovascular mortality	↑ ↑ ↑	↑ ↑ ↑
Cardiovascular hospitalizations	↑ ↑ ↑	↑
Ischemic heart disease*	↑ ↑ ↑	↑ ↑ ↑
Heart failure*	↑ ↑	↑
Ischemic stroke*	↑ ↑	↑
Vascular diseases	↑	↑†
Cardiac arrhythmia/cardiac arrest	↑	↑
Subclinical cardiovascular end points and/or surrogate measures in human studies		
Surrogate markers of atherosclerosis	N/A	↑
Systemic inflammation	↑ ↑	↑
Systemic oxidative stress	↑	
Endothelial cell activation/ blood coagulation	↑ ↑	↑
Vascular/endothelial dysfunction	↑ ↑	
BP	↑ ↑	
Altered HRV	↑ ↑ ↑	↑
Cardiac ischemia	↑	
Arrhythmias	↑	

The arrows are not indicators of the relative size of the association but represent a qualitative assessment based on the consensus of the writing group of the strength of the epidemiological evidence based on the number and/or quality, as well as the consistency, of the relevant epidemiological studies.

↑ ↑ ↑ Indicates strong overall epidemiological evidence.
↑ ↑ Indicates moderate overall epidemiological evidence.
↑ Indicates some but limited or weak available epidemiological evidence.
Blank indicates lack of evidence.
N/A indicates not applicable.
*Categories include fatal and nonfatal events.
†Deep venous thrombosis only.

pollutants mediate CVDs. The "Biological Mechanisms" section discusses the hypothesized global pathways and reviews the studies related to the fundamental cellular/molecular mechanisms elucidated by controlled human and animal exposures and toxicological/basic science experiments. The following section reviews the recent evidence that ambient exposure to air pollution can mediate potentially harmful subclinical cardiovascular effects. In general, many positive associations are found (Table 6). Numerous complex interactions between variations in the characteristics, sources, and chemistry of the particles, coupled with diversity in time frames, mixtures of exposures, and degrees of individual susceptibility, likely explain some of the disparity among findings.

Systemic Inflammation

There is evidence that under some circumstances, exposure to ambient PM can be associated with elevated circulating proinflammatory biomarkers that are indicative of a systemic response after PM air pollution inhalation that is not limited to the confines of the lung. Early reports found associations with day-to-day variation in acute-phase proteins, such as C-reactive protein (CRP), fibrinogen, or white blood cell counts,[144–147] as reviewed previously.[1] Limited evidence on the association between cumulative PM exposures and fibrinogen levels and counts of platelets and white blood cells was also available.[148]

A number of more recent studies have reported positive associations with short-term ambient PM exposure and day-to-day elevations in inflammatory markers. These include increases in CRP in an elderly population[149] and individuals with coronary atherosclerosis[150]; CRP and fibrinogen in young adults[151] and elderly overweight individuals[152]; and CRP, tumor necrosis factor-α (TNF-α), and interleukin (IL)-1β in children.[153] Recent evidence has also been found for an upregulation of circulating soluble adhesion molecules (eg, intercellular adhesion molecule-1) in 92 Boston, Mass–area individuals with diabetes[154] and 57 male subjects with coronary artery disease in Germany.[150] In a larger analysis of 1003 MI survivors, also in Germany, CRP was not related to PM exposure; however, ambient particle number concentration and PM_{10} were associated with increased IL-6 and fibrinogen, respectively.[155] Short-term levels of in-vehicle $PM_{2.5}$ have also been linked to increases in CRP among healthy highway patrol troopers.[156] In a follow-up analysis, elevations in certain particulate components of traffic pollution (eg, chromium) were associated with increased white blood cell counts and increased IL-6 levels.[157] Short-term changes in ambient PM levels have also been linked to acute (1 to 3 days later) alterations in biomarkers of inflammation, oxidative stress, and platelet activation among elderly adults with coronary artery disease living in retirement communities in Los Angeles, Calif.[158,159] Pollutants associated with primary combustion (eg, elemental and black carbon, primary organic carbon) and UFPs rather than $PM_{2.5}$ appeared to be strongly associated with adverse responses in this population.

Regarding more long-term exposures,[160] a positive association between white blood cell count and estimated long-term 1-year exposure to PM_{10} was reported in the Third National Health and Nutrition Examination Survey. Among 4814 adults in Germany, small increases in annual mean $PM_{2.5}$ (3.9 $\mu g/m^3$) were associated with increases in high-sensitivity CRP by 23.9% and in fibrinogen by 3.9% among men only. Estimated long-term traffic exposure was not related to inflammatory changes in either sex.[161]

Several studies, including some with improved exposure assessment,[162] some that included analyses of large population cohorts,[163,164] and a recent evaluation of long-term annual PM_{10} levels in England,[165] have not found a relationship between particulate exposure and inflammation. It is

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conceivable that differences in the magnitude or character of the inflammatory response will occur because of variations in the particulate chemistry and duration/intensity of exposures. Certain individuals may also be more susceptible. The evidence suggests that subjects with underlying cardiovascular risk factors and the metabolic syndrome may exhibit stronger associations.[152,160,166] Conversely, antiinflammatory medications such as statins may mitigate the actions of ambient particles.[152,155] All together, there is some evidence for a positive association between recent and long-term PM exposure and a systemic proinflammatory response; nevertheless, there is variation in the strength and consistency of changes among the variety of biomarkers and patient populations evaluated (Table 6).

Systemic Oxidative Stress

A state of oxidative stress refers to a condition in which levels of free radicals or reactive oxygen/nitrogen species (eg, O_2^-, H_2O_2, $ONOO^-$) are higher than normal (eg, healthy individuals in whom they are countered by homeostatic processes such as antioxidants) and thus are capable of exerting many adverse biological effects (eg, lipid/protein/deoxyribonucleic acid [DNA] oxidation, initiation of proinflammatory cascades). Although many biomarkers of differing systemic responses are available (eg, lipid or protein oxidation products), oxidative stress may occur at the local cellular/tissue level and not be directly observable by circulating markers. In addition, oxidative stress is often induced by and elicits inflammatory processes. The 2 processes are biologically linked. Therefore, human studies investigating the effect of PM on oxidative stress per se are difficult to perform. Only a few studies have directly investigated the occurrence of systemic oxidative stress in humans in relation to ambient PM exposure. Three studies of young adults conducted in Denmark demonstrated elevations in biomarkers of protein, lipid, or DNA oxidation in relation to PM exposure from traffic sources.[167–169] In a study of 76 young adults from Taipei, Taiwan,[151] the investigators found evidence of increased levels of 8-hydroxy-2′-deoxyguanosine adducts in DNA in relation to short-term elevations in ambient PM. Two studies have also demonstrated increases in plasma homocysteine, evidence that exposure to ambient PM can elevate this circulating mediator of oxidative stress.[170,171] Finally, Romieu et al[172] found that dietary supplementation with omega-3 polyunsaturated fatty acids might be capable of altering the systemic oxidative stress response (reduction in copper/zinc superoxide dismutase and glutathione) induced by air pollutants among residents living in a nursing home in Mexico City, Mexico. Because of the relatively small number of studies, more investigation is required to make firm conclusions and to understand the nature of the systemic oxidative stress response potentially induced by ambient PM (Table 6).

Thrombosis and Coagulation

Early reports indicated that increased plasma viscosity[144] and elevated concentrations of fibrinogen[146] are associated with short-term changes in ambient PM concentrations. More recent evidence was found for an upregulation of circulating von Willebrand factor in 57 male subjects with coronary artery disease in Germany[150] and 92 Boston-area individuals with diabetes.[154] Riediker[157] found that components of in-vehicle $PM_{2.5}$ were also related to increased von Willebrand factor and decreased protein C among highway patrol troopers. In the Atherosclerosis Risk in Communities study, a 12.8-$\mu g/m^3$ elevation in ambient PM_{10} was associated with a 3.9% higher von Willebrand factor level,[173] but only among those with diabetes. There was no linkage between PM_{10} exposure and fibrinogen or white blood cell levels.

Alterations in other markers that indicate changes in thrombosis, fibrinolysis, and global coagulation have also been reported. An immediate elevation in soluble CD40-ligand concentration, possibly reflecting platelet activation, recently was found to be related to ambient UFP and accumulation-mode particle ($PM_{0.1–1.0}$) levels in patients with coronary artery disease.[155] Ambient PM_{10} levels have also been associated with augmented platelet aggregation 24 to 96 hours after exposure among healthy adults.[174] In this study, there were no concomitant observable changes in thrombin generation, CRP, or fibrinogen induced by PM_{10}. Increases in plasminogen activator inhibitor-1 and fibrinogen levels have been noted in healthy subjects,[151] as well as elevated plasminogen activator inhibitor-1 in patients with coronary artery disease only,[175] in association with ambient PM levels in Taipei. Chronic indoor pollution exposure to biomass cooking in rural India has also been associated with elevated circulating markers of platelet activation.[176] Recently, Baccarelli et al[128,177] demonstrated in healthy subjects and among individuals with deep venous thrombosis living in the Lombardy region of Italy that prothrombin time was shortened in relation to recent and long-term ambient PM_{10} concentrations. Nevertheless, some studies found no effects of ambient pollution,[178] nor have significant changes been reported among all the biomarkers or subgroups of individuals investigated.[150,154,170,173] Similar to the study on systemic inflammation, the results related to thrombosis/coagulation are quite variable given the differences in study designs, patients, biomarkers evaluated, and pollutants; however, these adverse effects appear somewhat more consistent among higher-risk individuals (Table 6).

Systemic and Pulmonary Arterial BP

Several studies have reported that higher daily PM levels are related to acute increases in systemic arterial BP (approximately a 1- to 4-mm Hg increase per 10-$\mu g/m^3$ elevation in PM).[179–184] In a small study of patients with severe heart failure,[185] pulmonary artery and right ventricular diastolic BP were found to increase slightly in relation to same-day levels of PM. Chronic exposure to elevated $PM_{2.5}$ was associated with increased levels of circulating endothelin (ET)-1 and elevated mean pulmonary arterial pressure in children living in Mexico City.[186] These results may explain in part the risk for heart failure exacerbations due to PM

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exposure; however, not all studies of systemic arterial BP have been positive.[187–189]

Recently, Dvonch et al[190] demonstrated significant associations between increases in systolic BP and daily elevations in $PM_{2.5}$ across 347 adults living in 3 distinct communities within metropolitan Detroit, Mich. Much larger effects were observed 2 to 5 days after higher $PM_{2.5}$ levels within a specific urban location of southwest Detroit (8.6 mm Hg systolic BP increase per 10-$\mu g/m^3$ $PM_{2.5}$) than throughout the entire region or cohort (3.2 mm Hg). This suggests that specific air pollution sources and components contribute significantly to the potential for PM exposure to raise BP. Interestingly, it was recently reported in a crossover study of 15 healthy individuals that systolic BP was significantly lower (114 versus 121 mm Hg) during a 2-hour walk in Beijing, China, while the subjects were wearing a high-efficiency particulate-filter facemask than when they were not protected.[191] Wearing the facemask was also associated with increased HRV, which suggests that the rapid BP-raising effects of particle inhalation may be mediated through the autonomic nervous system (ANS). In a similar fashion,[192] reducing exposure to particulate pollution from cooking stoves was shown to be associated with lower systolic (3.7 mm Hg, 95% CI −8.1 to 0.6 mm Hg) and diastolic (3.0 mm Hg, 95% CI −5.7 to −0.4 mm Hg) BP among Guatemalan women than among control subjects after an average of 293 days. These findings demonstrate that indoor sources of PM (eg, cooking, biomass) may have important cardiovascular health consequences and that reductions in particulate exposure are capable of lowering BP, and they suggest that chronic exposure to PM air pollution may alter long-term basal BP levels. Even given the rapid variability of BP on a short-term basis and the numerous factors involved in determining individual responses (eg, patient susceptibility, PM composition, and time frames of exposure), overall, it appears that ambient PM can adversely affect systemic hemodynamics, at least under certain circumstances (Table 6).

Vascular Function

In the first ambient PM study related to changes in vascular function, O'Neill et al[193] reported that both endothelium-dependent and -independent vasodilation were blunted in relation to air pollution levels in Boston. The largest changes occurred in association with sulfate and black carbon, suggestive of coal-burning and traffic sources, respectively. Significant adverse responses were observed within 1 day yet were still present and slightly more robust up to 6 days after exposure. Moreover, the adverse responses occurred solely among diabetic individuals and not in patients at risk for diabetes mellitus. Two other studies[184,194] also demonstrated impaired vascular function due to short-term changes in ambient PM among diabetic patients. In the study by Schneider et al,[194] endothelium-dependent vasodilation was blunted during the first day, whereas small-artery compliance was impaired 1 to 3 days after elevated ambient PM levels. Interestingly, higher concentrations of blood myeloperoxidase were related to a greater degree of endothelial dysfunction, which suggests that white blood cell sources of reactive oxygen species (ROS) may be involved.

In healthy adults, very short-term exposure to elevated levels of ambient PM from traffic sources while exercising for 30 minutes near roadways[195] and when resting by bus stops for 2 hours[196] has been related to impaired endothelium-dependent vasodilation. Daily changes in ambient gaseous pollutants (SO_2 and NO_x) in Paris, France, have also been associated with impaired endothelium-dependent vasodilation among nonsmoking men.[197] Finally, indoor particulate air pollution may also be harmful to vascular function. Bräuner and colleagues[198] recently reported that reductions in 48-hour $PM_{2.5}$ levels due to filtering of air in subjects' homes resulted in improved microvascular vascular function among elderly subjects. Nevertheless, changes in short-term ambient PM levels have not been linked with impaired conduit[197] or microvascular[178] endothelial function in all studies. Even when the few negative studies are considered, the overall evidence supports the concept that ambient PM is capable of impairing vascular function, particularly among higher-risk individuals (eg, those with diabetes) and after traffic-related exposure (Table 6).

Atherosclerosis

A few cross-sectional studies have reported an association between measures of atherosclerosis in humans and long-term exposures to ambient air pollution levels. The first study to demonstrate this relationship was an analysis of data from 798 participants in 2 clinical trials conducted in the Los Angeles area. A cross-sectional contrast in exposure of 10 $\mu g/m^3$ $PM_{2.5}$ was associated with an adjusted nonsignificant 4.2% (95% CI −0.2% to 8.9%) increase in common carotid intima-media thickness[199]; however, in certain subgroups of patients, such as women, the effect was much larger (13.8%, 95% CI 4.0% to 24.5%). In a population-based sample of 4494 subjects from Germany,[200] it was found that residential proximity to major roadways was associated with increased coronary artery calcification. A reduction in distance from a major road by half was associated with a 7% (95% CI 0.1% to 14.4%) higher coronary artery calcium score. Proximity to traffic was also related to an increased risk for peripheral artery disease in women but not men.[201] In an analysis of 3 measures of subclinical disease (carotid intima-media thickness, coronary calcium, and ankle-brachial index) among 5172 adults from the Multi-Ethnic Study of Atherosclerosis, only common carotid intima-media thickness was modestly (yet significantly) associated with 20-year exposure to $PM_{2.5}$.[202] In a related study from the same cohort, abdominal aortic calcium was associated with long-term $PM_{2.5}$ exposure, especially for residentially stable participants who resided near a $PM_{2.5}$ monitor.[203] Although it appears that long-term exposure to higher levels of ambient PM might accelerate the progression of atherosclerosis, more investigations are needed (Table 6).

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Heart Rate Variability

Numerous studies have continued to explore associations between daily changes in PM air pollution exposure and alterations (typically reductions) in HRV metrics, putative markers of cardiac autonomic balance.[129,149,156,204–242] Recent observations in the Normative Aging Study cohort have shown strong effect modification of the PM-HRV relationship by obesity and genes that modulate endogenous oxidative stress or xenobiotic metabolism, such as glutathione S-transferase M1, methylenetetrahydrofolate reductase, and the hemochromatosis gene.[207,243,244] Additional findings suggest protective effects of statins, dietary antioxidants, and B vitamins, as well as omega-3 polyunsaturated fatty acids.[205,207,215,243,244] These results suggest that pathways that reduce endogenous oxidative stress have a protective effect that mitigates reductions in HRV due to ambient PM exposure.

However, the overall results are not entirely consistent. Some studies have reported increases in HRV mediated by PM, specifically among younger healthy people and patients with chronic obstructive lung disease.[156,208,216] Nevertheless, the general pattern suggests that PM exposure is associated with increased heart rate and reductions in most indices of HRV among older or susceptible individuals, such as those with obesity and the metabolic syndrome. Typically, time-domain measures (eg, standard deviation of normal RR intervals) and total power are reduced within hours after exposure. Most, but not all, pertinent studies have also found that the largest reduction in power is within the high-frequency domain. In sum, these observations provide some evidence that ambient PM air pollution exposure rapidly reduces HRV, a surrogate marker for a worse cardiovascular prognosis (Table 6). Although studies corroborating changes in autonomic activity by other methods (eg, microneurography or norepinephrine kinetics) have not been performed, the HRV findings are perhaps reflective of the instigation of a generalized cardiovascular autonomic imbalance due to relatively greater parasympathetic than sympathetic nervous system withdrawal.

Cardiac Ischemia and Repolarization Abnormalities

There has been limited direct evidence for the actual induction of cardiac ischemia or repolarization abnormalities in the electrocardiogram (ECG) by exposure to ambient levels of PM.[223,245] Recent follow-up analyses from the initial ULTRA study (Exposure and Risk Assessment for Fine and Ultrafine Particles in Ambient Air)[245] suggested that traffic-related combustion pollutants were most strongly related to the promotion of ST-segment depression among elderly nonsmokers during exercise stress testing.[246] Moreover, even very acute $PM_{2.5}$ exposure within the past 1 or 4 hours has been associated with cardiac ischemia during exercise.[247] New findings support these associations in elderly subjects[248] and in patients with coronary artery disease in Boston.[249] In the latter study, traffic-related PM was most strongly related to the incidence of ST-segment depression during 24-hour Holter monitoring, and the risk for ischemia was greatest within the first month after a cardiac event among patients with diabetes. Overall, there is a modest level of evidence that PM exposure can promote cardiac ischemia in susceptible individuals (Table 6).

Epigenetic Changes

There have been relatively few studies examining gene–air pollution exposure interactions, and most have done so while investigating a small number of loci for genetic polymorphisms. Although some studies have suggested greater air pollution susceptibility with one or another genomic polymorphism,[207,243,244] few have evaluated the potential for epigenetic changes after exposures. Reduced levels of DNA methylation have been linked to aging, oxidative stress, and CVD. Recently, Baccarelli et al[250] have shown among 718 elderly participants in the Normative Aging Study that short-term exposures (over 1 to 7 days) to $PM_{2.5}$ and black carbon are associated with decreased "global" DNA methylation in long interspersed nucleotide elements. It was posited that oxidative stress from air pollution exposure could have interfered with the capacity for methyltransferases to interact with DNA or altered the expression of genes involved in the methylation process. This observed effect of pollution exposure was analogous to changes seen with 3.4 years of aging in the cohort. Additional findings among workers in a furnace steel plant support these observations.[251] Nevertheless, the mechanisms involved and the cardiovascular implications of these preliminary, although provocative, epigenetic changes require more investigation.

Traditional Cardiovascular Risk Factors

In addition to the fact that individuals with traditional risk factors are likely to be at higher risk for cardiovascular events due to PM exposure, air pollutants may also promote the development of these risk factors over a prolonged period of time. Few published studies have investigated this possibility. A report from the Multi-Ethnic Study of Atherosclerosis has demonstrated that residential proximity to major roadways was associated with a higher left ventricular mass index as measured by cardiac magnetic resonance imaging.[252] The degree of increase was analogous to a 5.6-mm Hg increase in systolic BP among the study participants. This suggests that traffic-related exposures may have increased left ventricular mass by chronically elevating systemic arterial BP, a common cause of left ventricular hypertrophy. However, other mechanisms cannot be excluded, such as systemic inflammation and oxidative stress, which could potentially activate neurohormonal pathways (eg, ANS imbalance, renin-angiotensin system) that could directly mediate such a finding. In addition, a recent study of adults older than 30 years of age (n=132 224) participating in the National Health Interview Survey reported a significant association between self-reported hypertension and estimated annual $PM_{2.5}$ exposure using US EPA monitoring data.[253] A 10-$\mu g/m^3$ elevation in $PM_{2.5}$ was associated with an

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adjusted odds ratio of 1.05 (CI 1.00 to 1.10) for the presence of hypertension. The increase in risk was found only among non-Hispanic whites. These studies provide some initial evidence that longer-term PM exposures may augment the risk for developing chronically elevated BP levels or even overt hypertension.

Brook et al[254] have also demonstrated a novel relationship between a metric of long-term traffic exposure (NO_2 level by residence) and the odds of having the diagnosis of diabetes mellitus among patients in 2 respiratory clinics in Ontario, Canada. In women only, the odds ratio of diabetes was 1.04 (95% CI 1.00 to 1.08) for each increase of 1 parts per billion (ppb) of NO_2. Across the interquartile range (4 ppb NO_2), exposures were associated with nearly a 17% increase in odds for diabetes mellitus. The first biological support for this finding comes from a study in Iran that demonstrated that the previous 7-day-long exposure to PM_{10} was independently associated with worse metabolic insulin sensitivity among 374 children 10 to 18 years of age.[255] These findings suggest that the systemic proinflammatory and oxidative responses due to long-term PM air pollution exposure could potentially increase the risk for developing clinically important aspects of the metabolic syndrome, such as hypertension and diabetes mellitus. Further studies in this regard are warranted.

Evidence Summary

Table 6 provides a consensus qualitative synopsis based on the expert opinions of the writing group members of the overall level of existing support, linking each surrogate or intermediate cardiovascular outcome with exposures to PM at ambient concentrations, based solely on the database of observational studies.

Additional Epidemiological Findings and Areas of Continued Research

Responsible Sources and Pollution Constituents

Although PM concentration (mass per cubic meter) has been associated with cardiovascular events in numerous studies, the specific particulate constituents and the sources responsible remain less clear. Despite the fact that it is a difficult undertaking, several epidemiological studies have attempted to identify the culprit components within the PM mixtures. With regard to PM-associated inorganic ions (nitrate and sulfate), it has been suggested that the overall toxicological data do not clearly implicate these compounds as responsible for mediating the cardiovascular health effects of $PM_{2.5}$.[256] Nevertheless, sulfate particles have been associated with cardiopulmonary mortality in the ACS and Harvard Six Cities studies.[62,68] A recent time-series analysis among 25 US cities found that cardiovascular risk was increased when PM mass contained a higher proportion of sulfate, as well as some metals (aluminum, arsenic, silicon, and nickel).[257] It is possible that these positive findings represent sulfate serving as a marker for an effect mediated by a toxic PM mixture derived from commonly associated sources (eg, coal combustion). Nevertheless, a direct role for particle sulfate in causing cardiovascular events cannot be excluded entirely.[256]

In California, short-term exposures to several different PM constituents that likely reflect combustion-derived particulates, including organic and elemental carbon and nitrates, were most strongly associated with higher cardiovascular mortality.[258] Certain metals (zinc, titanium, potassium, and iron) and sulfate levels in the winter months were also positively related. Similarly, ambient levels of organic and elemental carbon have been most strongly linked among PM constituents with hospitalizations for CVDs in multipollutant models in a study among 119 US cities.[259] Finally, $PM_{2.5}$ composed of higher levels of elemental carbon, along with the metals nickel and vanadium,[48] has also been linked with greater risks for cardiovascular hospitalizations.[260] These results support that the chemistry or composition of the $PM_{2.5}$ (eg, organic/elemental carbon and certain metals) along with the responsible source from which these mixtures are derived (eg, fresh combustion, traffic) may play important roles in determining the risk for cardiovascular events. However, the extent to which these constituents mediate specific responses, alone or together, and their importance beyond the concentration of $PM_{2.5}$ mass alone represent an area of active research that requires more investigation to reach firm conclusions.

Many experiments have demonstrated the especially toxic properties and strong oxidizing potential of the smallest particle sizes (eg, UFP) and of the specific chemical species typically rich within this size fraction (eg, transition metals, organic compounds, and semiquinones).[261] Although some epidemiological evidence suggests that exposure to ultrafine compounds[17] may be associated with higher cardiovascular risk (eg, an elevation of UFP count by 9748/cm^3 has been associated with an increase in cardiovascular mortality of approximately 3% within 4 days in Erfurt, Germany[262]) and adverse responses,[158,159] there have been few such studies because they are challenging to conduct, for numerous reasons. Moreover, there are few UFP monitors, and the levels measured at regional sites may not accurately reflect an individual person's exposure because of marked spatial heterogeneity, because the concentrations are dominated by local point sources of fresh combustion (eg, roadways). This could help explain some of the previously negative study findings.[116]

Similarly, coarse particulates between 0.25 and 1.0 μm in diameter may affect the cardiovascular system,[221,264,265] and although the available data related to hard events and cardiovascular mortality have suggested a relationship,[265,266] recent findings have been less consistent.[104] In the most recent time-series analysis of 112 US cities, coarse PM was independently associated with elevated all-cause, stroke, and pulmonary, but not cardiovascular, mortality after controlling for $PM_{2.5}$.[43] Coarse PM was also not associated with either fatal or nonfatal cardiovascular events after controlling for $PM_{2.5}$ levels in the Nurses' Health Study[267] or the Women's Health Initiative cohort analyses.[72] Additional research is required to establish whether there are independent health effects of the other

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particulate size fractions beyond those posed by fine particles. On the other hand, $PM_{2.5}$ mass concentration is the metric most consistently associated with cardiovascular morbidity and mortality. It remains to be determined whether this reflects limitations of available data, the long-lived and regionally homogenous atmospheric nature of $PM_{2.5}$, that few studies have investigated the independent effects of the other sizes, difficulties in performing epidemiology studies with adequate UFP exposure estimates, or that specific constituents within the fine PM fraction (or another unidentified agent correlated with that fraction) are actually responsible for causing cardiovascular events. Although particles <0.1 μm (ie, UFPs) do make up a small fraction of $PM_{2.5}$ mass, the correlation between UFP particle number and total $PM_{2.5}$ mass concentration is often weak. Because of their minute size, UFPs make up only a small portion of the total $PM_{2.5}$ mass, even though they represent the largest actual number of particles within fine PM. They also have the highest surface area and a differing surface chemistry. Therefore, changes in the underlying UFP concentration do not likely account for or explain the linkages between $PM_{2.5}$ mass concentration and cardiovascular events observed in large multicity studies. The overall epidemiological evidence thus indicates that fine PM poses an independent cardiovascular risk and that any putative effects of these other size fractions cannot fully explain the observed $PM_{2.5}$–cardiovascular morbidity/mortality relationship.

On the other hand, there is mounting evidence for a distinctive role played by motor vehicle traffic–related exposures in elevating cardiovascular risk.[108,111,268,269] Lipfert et al[76,77] interpreted the results of their analysis of the Veterans Affairs hypertensive male cohort as suggesting that traffic density was a more "significant and robust predictor of survival in this cohort" than $PM_{2.5}$. Analyses of the Oslo,[81] Dutch,[82] AHSMOG,[74,75,88] French PAARC,[79] and German women cohorts[80] and related studies from areas in the United Kingdom,[270] Canada,[271] Norway,[272] and Rome[273] found that measures that often indicate traffic-related exposure (NO_2, NO_x, traffic density, and living near major roads) were also associated with increased mortality. Long-term 5-year average traffic-generated air pollution exposure has been associated with an increased risk of fatal MI (odds ratio 1.23, 95% CI 1.15 to 1.32 per 31-μg/m^3 increase in NO_2) but not nonfatal MI in Stockholm County, Sweden.[274] The results mirror the results of several cohort studies[72,73] that found that air pollution exposures appeared to be more strongly linked with cardiovascular mortality than nonfatal events. Recently, an analysis from a cohort in the Netherlands demonstrated that several metrics of traffic-related air pollution exposure remained significantly associated with increased risk for cardiovascular events even after adjustment for higher levels of traffic noise.[275]

The effect of long-term traffic-related exposure on incidence of fatal and nonfatal coronary heart disease was recently assessed after adjustment for background air pollutants and cardiovascular risk factors in 13 309 adults in the Atherosclerosis Risk in Communities study.[276] Interestingly, background chronic ambient $PM_{2.5}$ concentrations were not related to the interpolated traffic exposure levels or to heart disease outcomes, which supports the highly localized nature of traffic sources of exposure. After 13 years of follow-up in 4 US communities, individuals residing within the highest quartile of traffic density had a relative risk of 1.32 (95% CI 1.06 to 1.65) for fatal and nonfatal heart disease events. Despite multiple statistical adjustments, the investigators also acknowledged the possibility for residual confounding as a potential source of bias. The specific traffic-related pollution components, such as UFP or gaseous-phase chemicals (eg, SVOCs), that are responsible for the positive findings among these studies remain unknown. The close proximity to roadways within these epidemiological studies (eg, 400 m) required to observe an association with elevated cardiovascular risk, however, matches the atmospheric fate of these shorter-lived pollutants. The findings may thus suggest the existence of cardiovascular health effects mediated by specific air pollutants rather than $PM_{2.5}$ per se. There is room for improvement in assessment of traffic exposures in epidemiological research, and better approaches are now being incorporated into research projects, such as accounting for associated factors (eg, noise or spatial autocorrelation with socioeconomic status).[275,277]

Geographic differences in cardiovascular risk due to PM have also been observed across US regions, with more consistent or stronger effects observed in Eastern versus Western states.[71,103,257] Differences between North American and European cities have also been reported.[61] PM exposures are typically, but not always,[258] associated with larger effects during warmer months (spring through fall) than in the winter.[45,103,257] Variations in pollution characteristics (eg, sulfate), time spent outdoors, air conditioning usage and particle penetration indoors, ambient temperature and meteorology, and mobile (eg, diesel) or stationary (eg, coal combustion) sources of exposure may help explain these differences. Finally, variations in the cardiovascular risk posed by PM may also occur because of heterogeneity in the metric of exposure, such as personal versus background regional,[25] indoor versus outdoor sources, and differences in intracity versus intercity gradients.[69] A better understanding of the responsible constituents and sources is important and could potentially lead to more targeted and effective regulations. On the other hand, finding continued evidence that the adverse cardiovascular health effects cannot be linked conclusively to a particular or specific chemical species or source of pollution but rather that they occur in response to a variety of exposure types or mixtures would support the present-day policy of reducing exposure to overall fine particulate mass to achieve public health benefits.

Time Course and Concentration-Response Relationships

Many studies have demonstrated that PM air pollution exposure does not simply advance the mortality by a few days of critically ill individuals who would have otherwise died (eg, mortality displacement or "harvesting").[278,279] There also appears to be a monotonic (eg, linear or log-linear) concentration-response relationship between $PM_{2.5}$ and mor-

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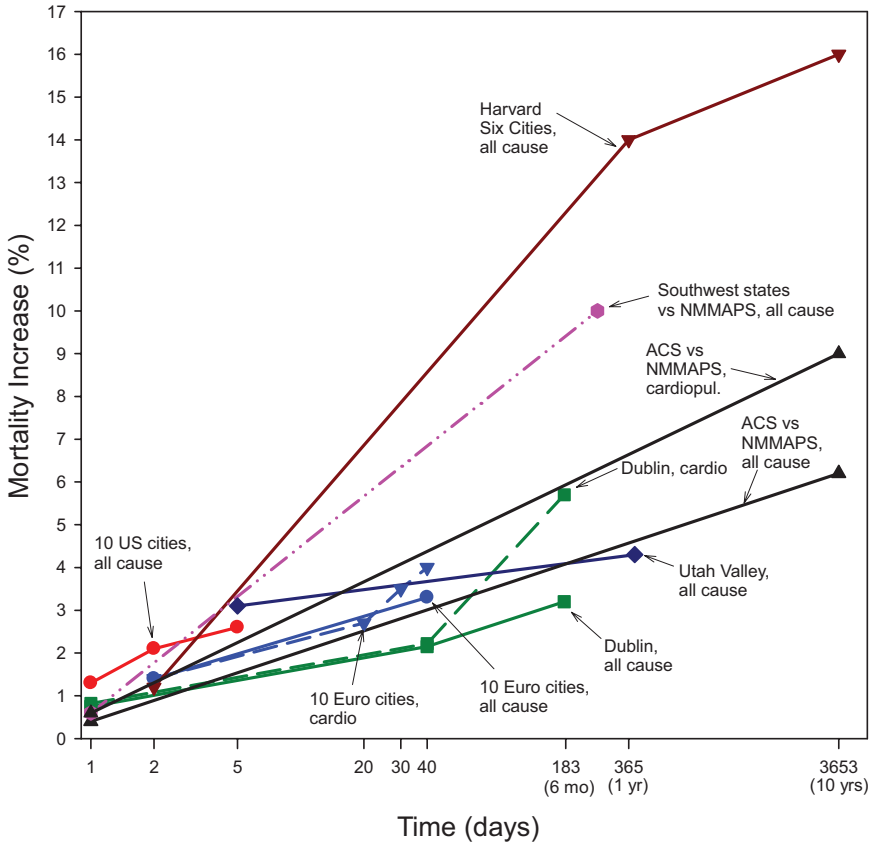

Figure 2. Comparison of estimates of percent change in mortality risk associated with an increment of 10 $\mu g/m^3$ in $PM_{2.5}$ or 20 $\mu g/m^3$ of PM_{10} or British Smoke (BS) for different time scales of exposure (log scale of approximate number of days, updated and adapted from Pope[281a]). Euro indicates European; cardio, cardiovascular disease; and cardiopul, cardiopulmonary.

tality risk observed in cohort studies that extends below present-day regulations of 15 $\mu g/m^3$ for mean annual levels, without a discernable "safe" threshold.[67,70,84] Cardiovascular risk due to particle exposure was also shown to extend below 15 $\mu g/m^3$ in the recent analysis of the Women's Health Initiative Observational Study.[72] This monotonic association supports the idea that any reduction in particulate pollution will translate into health benefits within a population of people, each with their own individual level of susceptibility. It also suggests that a larger decrease in $PM_{2.5}$ exposures will produce a greater reduction in mortality. Finally, a recent analysis of the literature provided important new insights into the nature of the PM exposure-response relationship.[280] The risk for cardiovascular mortality was shown to increase in a linear fashion across a logarithmically increasing dosage of inhaled fine-particle levels that ranged from ambient PM air pollution (≈0.2 mg/d), through secondhand smoke (≈1 mg/d), to active smoking (200 mg/d). This means that the exposure response is extremely steep at very low PM levels (ie, ambient air pollution) and flattens out at higher concentrations (ie, active smoking). This may help explain the seemingly incongruent and comparatively very high degree of cardiovascular risk posed by the much lower levels of PM exposure from ambient pollution and secondhand smoke versus the much higher doses due to active smoking. Thus, the cardiovascular system may be extremely sensitive to very low levels of PM inhalation as encountered with ambient pollution.

At present, the underlying nature and full scope of the temporal-risk relationship posed by longer-term PM exposures remain uncertain.[2,281] The writing group members did concur that the available epidemiological studies demonstrate larger cardiovascular risks posed by more prolonged exposures to higher PM levels than observed over only a few days (Figure 2). Cohort studies using Cox regression survival analyses (over months to years) are capable of evaluating a more complete portion of the temporal-risk relationship than time-series analyses over only a few days that use Poisson regression. However, given the lack of complete information, no conclusions could be drawn on the full magnitude of the augmented risk posed by chronic exposures, the time window (a few months versus decades) required to exhibit this enhanced risk, the underlying biological causes, the extent to which statistical differences between study types explain the variations in risk, and whether clinically relevant chronic CVDs are precipitated by chronic exposures. Some writing group members believe it is important to differentiate as 2 distinct issues the potentially greater effect of long-term exposures on increasing the risk for acute events (eg, cardiovascular mortality) compared with the putative effect on initiating or accelerating the development of chronic CVD processes per se (eg, coronary atherosclerosis). As such, it is possible that the greater risks observed in cohort studies could be capturing the fact that repetitive exposures over months or years augment the risk for sudden cardiovascular events in susceptible people, without actually worsening an underlying "chronic" disease process.

On the one hand, the available studies demonstrate that the majority of the larger risk-effect sizes posed by longer-term versus short-term exposures appear to be manifested within

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only 1 to 2 years of follow-up. Extending the duration of follow-up increases cardiovascular risk, but to a progressively smaller degree over time (Figure 2). The discrepancy in the effect sizes among study types (eg, cohort versus time-series studies) could also reflect differences in statistical methodologies or population susceptibilities.[282–284] Recent attempts to investigate this matter[64,84] suggest that the risk for acute events associated with chronic exposures may be reasonably well estimated by only the most proximal 1 to 2 years of PM levels. The most recent time frames of exposure also explain a substantial portion of the excess cardiovascular risk observed in several cohort studies.[70,72,73,83] These findings bolster the argument that relatively rapid and pliable (and potentially reversible) biological responses, such as the instigation of plaque instability or the enhanced thrombotic potential caused by PM-mediated inflammation or endothelial dysfunction (which can occur and abate over only a few weeks to months), could explain the biology responsible for this greater relative risk.

On the other hand, cogent alternative arguments can be made to explain the differences in relative risk between the cohort and time-series studies. The likely high correlation of a recent year's exposure levels with exposures over many years, as well as the uniform rank ordering of exposure severity over time among cities, can explain why only a short period of PM exposure assessment is required to understand the risk of longer-term exposures. In addition, no studies have evaluated the potential risks of exposure over decades or a lifetime. PM augments the ability of traditional risk factors to accelerate the development of atherosclerosis in experimental settings. As such, it is also plausible that long-term exposures may enhance cardiovascular risk to an even greater extent by increasing an individual's susceptibility for future cardiovascular events or acute exposures. In addition, the full extent of this possibility may not be illustrated by the limited follow-up period (4 to 5 years) of the majority of cohort studies. The writing group thus agreed that this important issue requires more investigation.

It is also possible that these 2 explanations are not mutually exclusive. Furthermore, it cannot be concluded from available information that a long period of time is required for reductions in PM levels to translate into a decrease in cardiovascular risk. On the contrary, reductions in secondhand smoke[285] and PM air pollution levels[64,84,90,95] appear to produce fairly rapid decreases in cardiovascular event rates, within a few months to years.[284] At present, the available data do not allow for firm conclusions regarding the underlying biology and the full extent of the potentially nonuniform PM exposure–to–cardiovascular risk temporal relationship.

Susceptibility to Air Pollution Exposure

Susceptibility refers to a heightened risk for a particular cardiovascular end point or event to occur compared with the general population at the same concentration of PM exposure. Typically, this is indicative of an underlying medical condition (eg, diabetes) or personal characteristic (eg, old age) that causes this enhanced risk. This is in contrast to the term "vulnerability," which refers to a population of individuals at greater risk for more frequent or high levels of exposures.

Earlier studies reviewed in the first AHA scientific statement[1] suggested that susceptible populations include the elderly; individuals with diabetes; patients with preexisting coronary heart disease, chronic lung disease, or heart failure; and individuals with low education or socioeconomic status. In the ACS study, current and previous smokers appeared to be at the same or greater degree of risk.[67] Among more recent studies, the Women's Health Initiative also reported positive findings among active smokers and an elevated risk for cardiovascular mortality induced by $PM_{2.5}$.[72] Conversely, current smokers were found to be at no increased risk for cardiovascular mortality in response to $PM_{2.5}$ exposure in the Nurses' Health Study.[73] Thus, the effect modification of smoking status requires more investigation. The APHENA study of European and North American cities recently confirmed that elderly and unemployed individuals are at higher risk of short-term PM exposure.[61] In a multicity time-series study in Asia, women, the elderly, and individuals with lower education and socioeconomic status were also shown to be at elevated risk.[286] A few additional studies have reported some evidence of susceptibility to short-term PM exposures among older individuals, people with diabetes, and those with a lower level of education.[287–289] Finally, a recent study illustrated that present-day levels of $PM_{2.5}$ likely increase the risk for a cardiac event within a few days of exposure principally (or even solely) among individuals with preexisting significant coronary artery disease, even if they are seemingly healthy (eg, without anginal symptoms). Patients without obstructive lesions on heart catheterization were not at any risk for $PM_{2.5}$-induced myocardial events over the short term.[13] This is not surprising, because most acute cardiovascular events occur among individuals with underlying vulnerable substrate (eg, unstable plaques) and not in individuals with normal coronary arteries.

Obesity has been newly recognized as a possible susceptibility factor. Two cohort studies have shown that a greater body mass index enhances the susceptibility for PM-induced cardiovascular mortality, at least among women.[72,73] Although individuals with diabetes showed a trend toward greater risk in the Women's Health Initiative,[72] hypertension, high cholesterol, smoking, elderly age, education, and income did not alter the risk association. Overall, there appears to be little effect modification by race, hypercholesterolemia, or BP among the studies. Finally, sex may also be a risk-effect modifier. The particularly robust risk estimates of the 2 cohort studies that included only women,[72,73] the fact that PM increased cardiovascular risk in female but not male participants of the AHSMOG study,[75] and the multicity time-series findings in Asia[286] suggest that women may be at greater risk for cardiovascular mortality related to PM. Further studies are needed to clarify whether obese individuals and women are indeed susceptible populations.

Biological Mechanisms

There has been substantial improvement in our understanding of the biological mechanisms involved in PM-mediated

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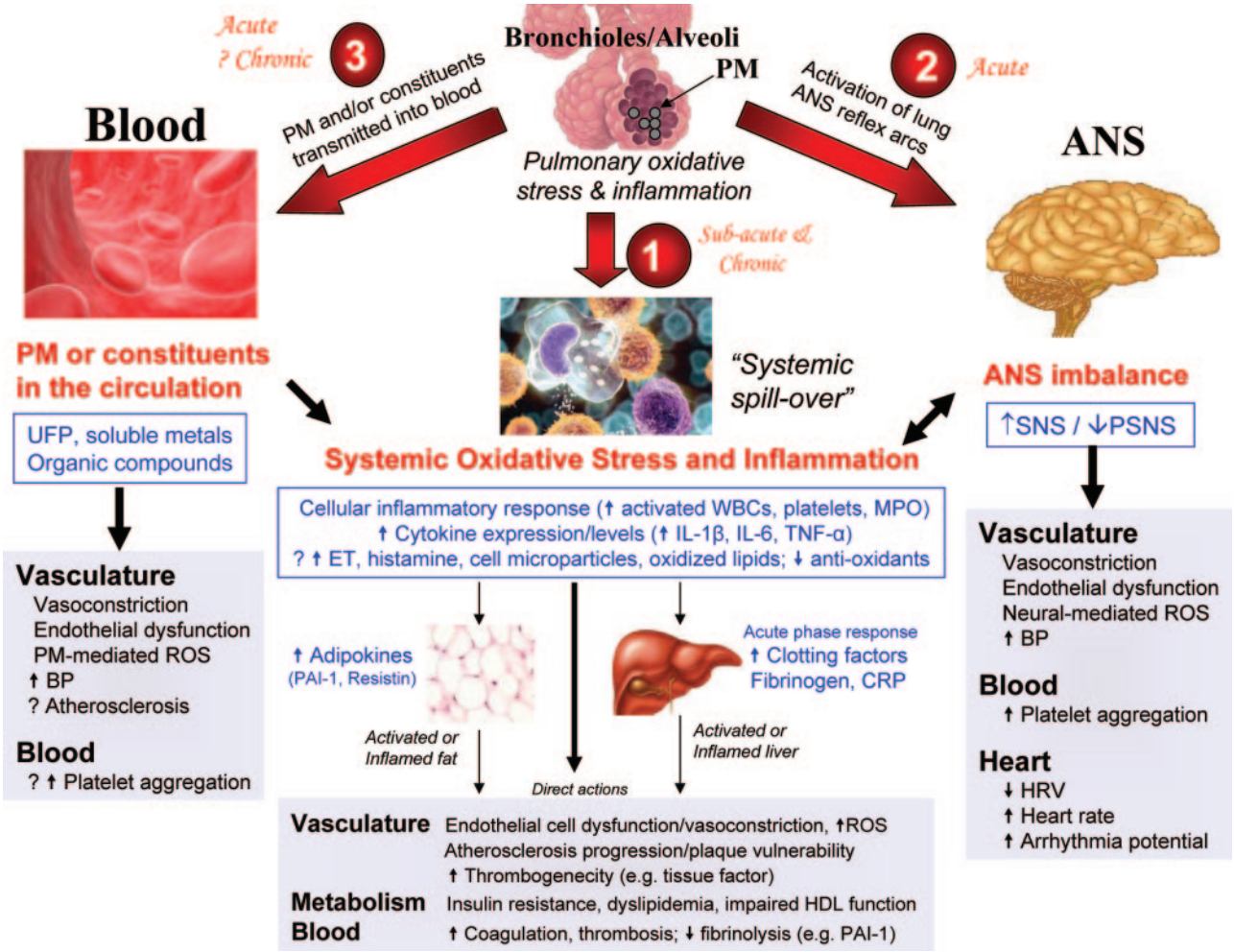

Figure 3. Biological pathways linking PM exposure with CVDs. The 3 generalized intermediary pathways and the subsequent specific biological responses that could be capable of instigating cardiovascular events are shown. MPO indicates myeloperoxidase; PAI, plasminogen activator inhibitor; PSNS, parasympathetic nervous system; SNS, sympathetic nervous system; and WBCs, white blood cells. A question mark (?) indicates a pathway/mechanism with weak or mixed evidence or a mechanism of likely yet primarily theoretical existence based on the literature.

cardiovascular effects. Studies before 2004 were reviewed previously,[1] and only some are again discussed here for contextual background. A number of new experiments have demonstrated very rapid effects of air pollution, such as vascular dysfunction, which argues for the existence of pathways that convey signals systemically within hours of PM inhalation. On the other hand, there is also support for chronic biological effects, such as the promotion of atherosclerosis. At the molecular level, persuasive evidence supports an integral role for ROS-dependent pathways at multiple stages, such as in the instigation of pulmonary oxidative stress, systemic proinflammatory responses, vascular dysfunction, and atherosclerosis. In sum, new studies continue to support the idea that inhalation of PM can instigate extrapulmonary effects on the cardiovascular system by 3 general "intermediary" pathways. These include pathway 1, the release of proinflammatory mediators (eg, cytokines, activated immune cells, or platelets) or vasculoactive molecules (eg, ET, possibly histamine, or microparticles) from lung-based cells; pathway 2, perturbation of systemic ANS balance or heart rhythm by particle interactions with lung receptors or nerves; and pathway 3, potentially the translocation of PM (ie, UFPs) or particle constituents (organic compounds, metals) into the systemic circulation (Figure 3).

Exposure Considerations

Animal and human exposure studies are discussed separately and apart from the effect of ambient PM because their methodologies and clinical relevancies vary widely. Controlled exposure studies involve exposing a subject to various size fractions of PM within a chamber connected to ambient air (concentrated or nonconcentrated) or a source of aerosolized particles. Virtual impactor systems that deliver concentrated ambient particles (CAPs) from "real-world" ambient air are a commonly used approach for mimicking exposures to higher levels of ambient particles without requiring invasive methods or the generation of artificial particles.[3] Both a strength and limitation, however, is that CAPs can vary considerably from day to day in composition. Additionally, only certain particle size ranges are typically concentrated (eg, PM from 0.1 to 2.5 μm in the fine-CAP system), whereas

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ambient air contains a mixture of particle sizes, volatile organics, and gases that are not concentrated (and can be lowered). Potential interactions between PM and gaseous copollutants on health end points are therefore excluded, unless the latter are reintroduced in an artificial fashion. Other methods of controlled-inhalation exposures include diesel engine exhaust (diluted and aged mixtures of high numbers of fresh combustion UFPs with vapor-phase components), roadside aerosols, and wood-burning sources. Regarding animal exposures, intratracheal instillation methods may sometimes be required because of the limited availability of inhalation exposure systems. Unfortunately, particle size and surface characteristics—mostly retained in inhalation systems with fresh sources of pollution and which may be important in influencing biological effects—are likely significantly altered in instillation systems or by methods that use previously collected particulate. However, the use of carefully modeled exposures (eg, deposition calculation) and the recognition that areas of "hot spots" containing markedly higher PM levels within the lung may occur even during normal inhalation make the results of these experiments potentially relevant.[2] Further detailed discussions of exposure considerations are reviewed elsewhere.[290]

The protocol details vary considerably among the studies. Many aspects of exposure, including the duration, concentration, PM size ranges and composition, and gaseous copollutants, are important to consider. A wide variety of outcomes may be anticipated depending on the biological pathways evoked by differing exposures. Moreover, there are multiple determinants of the subsequent physiological responses, including the time frames of investigation, preexisting susceptibility, animal models, and the details of the outcomes investigated. All of these factors may explain some of the heterogeneity in the reported study results and must be taken into consideration when interpreting the findings.

Animal Exposure and Toxicological Studies

Studies that investigate the effects of exposure on susceptible animals (eg, those with preexisting cardiovascular or metabolic abnormalities) may be preferable in many circumstances because of the increasing recognition that the pathways underlying the biological effects of PM overlap (ie, modify and/or enhance) those of conventional cardiovascular risk factors. Such factors (eg, hypertension or atherosclerosis) may also be necessary or at least responsible for the evocation of a more readily observable or robust response. For example, in the context of systemic oxidative stress or inflammation, the cellular machinery for the generation of excess ROS and proinflammatory responses (eg, adhesion molecule and cytokine expression) is already primed or operational in susceptible animals.

Pulmonary Oxidative Stress and Inflammation

The molecular events responsible for triggering pulmonary oxidative stress and inflammation, along with the interactions between lung and immune cells, the inhaled PM, and the protective secretions (eg, surfactant, proteins, and antioxidants), are highly complex,[4–6] as reviewed in detail elsewhere.[290a,290b,414] In brief, size, charge, solubility, aggregation, ROS-producing potential, and chemistry play roles in determining the responses. These include the particle fate (eg, lung clearance versus retention rates), the nature of the PM-cell interactions (eg, immune versus lung cell uptake, host cell responses, and intracellular sequestration/location), and the dose (likely typically a small percentage of inhaled PM) and pathways of potential systemic transmission of PM or its constituents, such as in the circulation [free, intracellular within circulating cells, (lipo)protein-bound] or via lymphatic spread.[4,5,290a,290b] Because of their nano-scale size, UFPs may directly enter multiple lung cell types via nonphagocytic pathways and adversely affect organelles, such as mitochondria.[6,290a,290b] Larger unopsonized fine particles are more typically taken up by phagocytes through interactions with innate immunity receptors such as MARCO (macrophage receptor with collagenous structure) or other scavenger receptors.[5,290a,290b] This may in fact be a protective mechanism that sometimes prevents harmful lung inflammation. Certain particle compounds may directly generate ROS in vivo because of their surface chemistry (eg, metals, organic compounds, and semiquinones) or after bioactivation by cytochrome P450 systems (eg, polycyclic aromatic hydrocarbon conversion to quinones).[6,290a,290b] A particle surface or anions present on otherwise more inert particles may disrupt iron homeostasis in the lung and thereby also generate ROS via Fenton reactions.[291] Other PM constituents may do so indirectly by the upregulation of endogenous cellular sources (eg, nicotinamide adenine dinucleotide phosphate [NADPH]) oxidase)[292,293] or by perturbing organelle function (eg, mitochondria) by taken-up PM components.[261] Particle stimulation of irritant and afferent ANS fibers may also play a role in local and systemic oxidative stress formation.[294] Given the rich antioxidant defenses in the lung fluid, secondarily generated oxidization products of endogenous molecules (eg, oxidized phospholipids, proteins) or a reduction in endogenous antioxidants per se may be responsible at least in part for the state of oxidative stress in the lungs (along with instigating the subsequent cellular responses) rather than ROS derived directly from PM and its constituents.

Subsequent to oxidative stress, antioxidant and phase II defenses may be activated (eg, inducible nitric oxide synthase, glutathione) via transcription factor Nrf2-dependent pathways.[261] When inadequate, pathological oxidative stress can initiate a variety of pulmonary inflammatory responses. For example, ROS in the lungs has been shown to augment the signal transduction of membrane ligand (eg, epidermal growth factor by disrupting phosphatases) or pattern-recognition receptors (eg, toll-like receptors [TLR])[295–299] and/or stimulate intracellular pathways (eg, mitogen-activated protein kinases) that lead to the activation of proinflammatory transcription factors (eg, nuclear factor-$\kappa\beta$) that upregulate expression of a variety of cytokines and chemokines.[261] Alteration in lung cell redox status may itself stimulate nuclear factor-$\kappa\beta$. Biological components within coarse PM could also directly trigger inflammation (eg, nuclear factor-$\kappa\beta$ pathways) by binding to TLR2 or TLR4 receptors or other innate immune pattern-recognition receptors.[297] It is also possible that other components of metal-rich

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PM could instigate inflammatory pathways via TLR activation directly or via the oxidation of endogenous biological compounds that then serve as TLR ligands.[300] Finally, there is some evidence that PM can activate inflammatory mitogen-activated protein kinase signaling by angiotensin II receptor–dependent pathways.[295] These inflammatory responses can also exacerbate the initial oxidative stress [eg, via upregulation of cellular NAD(P)H oxidase] and thus initiate a positive-feedback cycle.

Available studies support important contributions to pulmonary inflammation from innate immune cells such as neutrophils and macrophages (TNF-α, IL-6), as well as from the adaptive immune system, such as T cells (IL-1, IL-4, IL-6, and IL-10). Although the dominant source of cytokines likely represents the alveolar macrophages and lung epithelial cells, the role of other innate and adaptive immune cells cannot be ruled out.[299,301,302] Recently, myeloperoxidase activity was shown to increase after PM exposure in the same time course of appearance of cellular inflammation (primarily neutrophils) in the lung.[303] Gaseous components such as ozone may also amplify the toxicity of PM.[304]

Systemic Inflammation

In the context of examining the cardiovascular effects of air pollution, it is important to consider the inflammatory mediators that are released from lung cells after contact with PM, because some could conceivably spill over to the general circulation or increase liver production of acute-phase proteins (eg, CRP, fibrinogen). An increase in circulating proinflammatory mediators (eg, activated immune cells, cytokines) could thus serve as a pathway to instigate adverse effects on the heart and vasculature. Numerous experiments have demonstrated increased cellular and inflammatory cytokine content, such as IL-6, IL-1β, TNF-α, interferon-γ, and IL-8, of bronchial fluid and sometimes in circulating blood after acute exposure to a variety of pollutants.[292,305–311]

Critical roles for the elevations in systemic and pulmonary levels of IL-6 and TNF-α have been observed after PM exposure, typically coincident with pulmonary inflammation.[292,302,306,309,311–314] There is at least some evidence that the degree of pulmonary inflammation and systemic inflammation (IL-6) correlates with the elevation of systemic cytokines and systemic vascular dysfunction.[314] In a 4-week inhalation exposure to freshly generated diesel exhaust, IL-6 knockout mice did not demonstrate increased cellular inflammation or TNF-α in bronchial fluid, which implies a role for IL-6.[315] Consistent with these findings, acute intratracheal exposure to PM_{10} resulted in an increase in IL-6, TNF-α, and interferon-γ in the bronchial fluid.[316] However, in this study, IL-6$^{-/-}$ mice showed roughly the same levels of TNF-α in bronchial fluid as wild-type mice, although interferon-γ was decreased to control values.[316] The results also suggested that lung macrophages play an important role, because depletion of these cells abolished the increases in some of the cytokines and systemic cardiovascular responses. Although our understanding of the source of IL-6 and TNF-α and their involvement in the systemic inflammatory response after PM exposure remains incomplete, these and other experiments appear to suggest that at least with PM_{10} particles, alveolar macrophages play a dominant role.[309,314,316]

Among remaining uncertainties, the upstream signaling pathway responsible for the recognition of PM components that in turn produce the systemic inflammation has not been fully elucidated[317]; however, there is some evidence with other particulates and experimental models of lung injury that ROS generated by NADPH oxidase or pattern-recognition receptors may modulate some of these responses.[292,299,318] NADPH-oxidase knockout mice demonstrated significantly lower IL-6 and macrophage inflammatory protein-2 responses to collected PM than wild-type mice.[292] Extrapulmonary sources may also be involved in promulgating the systemic inflammation. $PM_{2.5}$ exposure in a model of diet-induced obesity in C57Bl/6 mice for a duration of 24 weeks resulted in elevations in TNF-α and IL-6. In addition, there were increases in circulating adipokines, such as resistin and plasminogen activator inhibitor-1.[319] The elevation in cytokines, thought to be derived from adipose sources, in addition to findings of adipose inflammation in that study, raises the possibility of additional systemic nonpulmonary sources of such cytokines.

Systemic Oxidative Stress

Numerous in vitro studies have demonstrated activation of ROS-generating pathways by PM incubation, such as NADPH oxidases, mitochondrial sources, cytochrome P450 enzymes, and endothelial nitric oxide synthase in cultured cells or in pulmonary and vascular tissue.[293,311,320–329] Similar to inflammation, the oxidative stress after PM inhalation may not always stay confined within the lungs.[330] The sources of excess ROS within cardiovascular tissue may include circulating immune cells or cytokines, depletion of defense mechanisms (eg, impaired high-density lipoprotein function), oxidation of lipoproteins or other plasma constituents,[331] activation of ANS pathways,[294] or circulating PM constituents (eg, soluble metals, organic compounds) reaching the vasculature.[261] Activation of ROS-dependent pathways modulates diverse responses with far-reaching consequences, including vascular inflammation/activation, atherosclerosis, impaired basal vasomotor balance, enhanced coagulation/thrombosis, and platelet activation.[290b]

Recent experiments have indeed confirmed the existence of footprints or markers of oxidative stress within the cardiovascular system in the in vivo context. Acute-exposure studies[332] have shown a relationship between the vascular dysfunction in spinotrapezius microvessels and the release of myeloperoxidase from leukocytes into the vasculature within only hours after the pulmonary instillation of PM.[332] Interestingly, an insoluble particle (TiO_2) induced very similar effects. More long-term studies[333] have demonstrated that 10 weeks of exposure to $PM_{2.5}$ increased superoxide production in response to angiotensin II and resulted in upregulation of NAD(P)H oxidase subunits and depletion of tetrahydrobiopterin in the vasculature. These effects had functional consequences in terms of increases in systemic vascular resistance and BP. In another investigation that involved apolipoprotein E–deficient (ApoE$^{-/-}$) fed a high-fat diet, chronic exposure

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to $PM_{2.5}$ exacerbated vascular oxidant stress and promoted atherosclerosis progression.[334] The proatherogenic effects of ambient UFPs[331] versus $PM_{2.5}$ in genetically susceptible $ApoE^{-/-}$ mice in a mobile facility close to a Los Angeles freeway have also been compared. Exposure to UFPs resulted in an inhibition of the antiinflammatory capacity of plasma high-density lipoprotein and greater systemic oxidative stress, as evidenced by increased hepatic malondialdehyde and upregulation of Nrf2-regulated antioxidant genes.[331]

Other experiments[294] have suggested that ANS imbalance may play an important role in PM-induced cardiac oxidative stress. Pharmacological inhibition of the ANS could significantly reduce chemiluminescence in the heart after exposure.[303] More recently, an upstream modulator, the transient receptor potential vanilloid receptor-1, within the lung was identified as central to the inhaled CAP-mediated induction of cardiac chemiluminescence.[335] In these studies, capsazepine was able to abrogate ECG alterations in rats during the 5-hour exposure, which suggests that neural ANS pathways are crucial.

Thrombosis and Coagulation

Earlier studies using intratracheal instillation of high concentrations of diesel exhaust particles demonstrated the induction of lung inflammation, platelet activation, and increased peripheral vascular thrombosis in both arteries and veins after photochemical injury.[336,337] Thrombosis susceptibility was ascribed to direct passage of the instilled UFPs in the blood, because large polystyrene particles unlikely to cross the lung-blood barrier did not increase peripheral thrombosis. In a subsequent study, a persistent increase in thrombosis susceptibility to diesel exhaust particles was shown after 24 hours, an effect that was mitigated by pretreatment with sodium cromoglycate, which indicates that this response was secondary to histamine release from basophil degranulation.[338] These same effects, however, were mimicked by 400-nm polystyrene particles with a low likelihood of transgressing the pulmonary barrier, which implicates pulmonary release of histamine as a mediator of thrombosis at the later time point. Because histamine was increased in the plasma at 6 and 24 hours after exposure, and diphenhydramine mitigated diesel PM–induced thrombosis at later time points but not at 1 hour, it was hypothesized that additional direct effects of PM constituents reaching the circulation may be responsible for the earliest prothrombotic effects.[339] No increase in circulating von Willebrand factor was observed after instillation of both particles. Finally, pulmonary instillation of carbon nanotubes produced neutrophil lung influx 24 hours later. Circulating platelet-leukocyte conjugates were elevated 6 hours after exposure, whereas procoagulant microvesicular tissue factor activity and peripheral thrombotic potential were increased 24 hours later. Inhibition of P-selectin abrogated these responses, which demonstrates that rapid activation of circulating platelets by the pulmonary deposition of PM plays a vital role.[340] This series of studies suggests that release of lung cell–derived mediators (eg, histamine) after several hours along with the more rapid activation of circulating platelets by lung inflammation via P-selectin–dependent processes may mediate distant system prothrombotic effects without necessarily inducing systemic endothelial damage.

In a study using C57BL/6J mice, intratracheal PM_{10} particles rich in transition metals decreased bleeding, prothrombin, and activated partial thromboplastin times and enhanced the levels of several coagulation factors as well as thrombosis times in response to experimental $FeCl_3$ injury.[316] This prothrombotic effect was mitigated in $IL\text{-}6^{-/-}$ and macrophage-depleted mice, which suggests that IL-6, lung macrophages, and pulmonary inflammation are necessary initial steps. It is possible, however, that coarse-particle components (eg, endotoxin) could have been important mechanistically via TLR activation. The effect of fine PM or UFPs per se requires more investigation. Chronic ambient exposure to $PM_{2.5}$ has also been shown to increase tissue factor expression in macrophages and smooth muscle cells in atherosclerotic lesions. Complementary in vitro studies with cultured human smooth muscle cells and monocytes demonstrate dose-dependent increases in tissue factor in response to collected ambient particles.[341] Other findings also support potential procoagulant and thrombotic effects of PM.[342,343] These collective studies suggest that both short- and long-term PM inhalation can enhance thrombotic and coagulation tendencies, potentially via increases in circulating histamine and inflammatory cytokines and/or activated white cells and platelets. The plausibility of these pathways is supported by the well-recognized cross talk between inflammation and thrombosis.[344] Potential additional roles for UFPs or soluble constituents that reach the circulation and directly enhance platelet aggregation or systemic oxidative stress (thus activating the endothelium and blunting platelet-derived nitric oxide) require more investigation.

Systemic and Pulmonary Hypertension

Early animal studies suggested small or inconsistent effects of PM on BP,[345–347] sometimes dependent on the season[348] of exposures. A potential explanation may be variations in experimental protocols, including differences in the delivery, duration, and composition of exposure and the methods used to measure BP. Moreover, PM by itself may represent a relatively weak stimulus but may act more robustly in concert with other predisposing factors to affect BP. Sun et al[333] recently demonstrated a significant interactive effect of fine-CAP exposure with the vasoconstrictor angiotensin II in rats. Preexposure to $PM_{2.5}$ for a 10-week period resulted in enhancement of its prohypertensive response measured continuously by intra-arterial radiotelemetry. The exaggerated BP elevation was accompanied by endothelial dysfunction, including blunted endothelium-dependent vasodilation and enhanced vasoconstrictor reactivity, along with upregulation of NAPDH oxidase and Rho-kinase–signaling pathways. In vitro exposure to UFPs and $PM_{2.5}$ was also associated with an increase in Rho-kinase activity, phosphorylation of myosin light chain, and myosin phosphatase target subunit. Pretreatment with the nonspecific antioxidant *N*-acetylcysteine and Rho-kinase inhibitors prevented these responses, which suggests an ROS-mediated mechanism for particle-mediated effects on vascular smooth muscle constriction. Further

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studies corroborated the role of exaggerated Rho-kinase pathway activity in potentiating the hypertensive response to angiotensin II in mice exposed to $PM_{2.5}$.[349] Moreover, particle exposure augmented angiotensin-mediated cardiac hypertrophy and collagen deposition. Blockade of Rho-kinase abolished these effects. These responses suggest that chronic $PM_{2.5}$ exposure disrupts normal vascular homeostasis and vasoactive mediator balance through ROS-dependent mechanisms in a manner that sensitizes the vessel toward vasoconstrictors. Activation of RhoA/Rho-kinase signaling pathways appears to play an important mechanistic role.

In conscious canines with implanted BP catheters, systemic arterial BP increased and baroreceptor sensitivity was rapidly altered over a few hours during CAP exposure.[350] Interestingly, α-adrenergic antagonism abrogated the responses. The findings support a mechanistic role for acute activation of the sympathetic nervous system by inhaled particles. In a study with Wistar-Kyoto male rats, CAP exposure for 4 days upregulated ET-A receptor expression in the heart. This alteration was also weakly correlated with an increase in BP, which suggests a role for enhance ET activity.[351] PM has also been demonstrated to alter the release of ET-1 and ET-3 from the lungs.[352] Elevation in pulmonary vascular resistance and pulmonary arterial pressure, which suggests constriction of the pulmonary vessels, has also been demonstrated in response to respirable carbon black particles.[353] Recently, ultrafine carbon particles were shown to increase BP in spontaneously hypertensive rats 1 to 3 days after a 24-hour exposure.[354] This response occurred concomitant with increased ET-1 messenger ribonucleic acid levels in lung tissue and small elevations in plasma renin concentration and angiotensin I and II in the systemic circulation. These findings further support the idea that ET may play a role in cardiovascular responses to PM exposure and suggest that activation of the renin-angiotensin system may also be involved. It is not clear whether the elevated circulating ET levels reflect increased release from the lungs and whether this mediates a systemic vasoconstrictor response. Alternatively, the increase may be more indicative of enhanced vascular tissue activity of these systems. Longer-term exposures of carbon black for 4 weeks in Sprague-Dawley rats has also been shown to significantly increase systolic BP concomitant with increases in serum levels of IL-6 and CRP.[355]

Finally, in vitro exposure to soluble and insoluble components of UFPs induces constriction in isolated pulmonary arterial rings and activates intracellular signaling pathways such as phosphorylation of extracellular signal–regulated kinase-1/2 and p38 mitogen-activated protein kinase in pulmonary endothelial cells. These effects were antagonized by losartan, and several metal components (copper and zinc) could replicate the responses.[295] This suggests a possible role for activation of angiotensin II receptor pathways relevant for the maintenance of vasomotor tone and smooth muscle constriction after inhalation of metal constituents within PM.

In sum, the studies demonstrate that long-term PM exposures over a period of weeks are capable of enhancing vasoconstrictive responsiveness of the vasculature (eg, increased Rho-kinase activity and reduced nitric oxide bioavailability) by inflammatory and ROS-dependent cell-signaling pathways. Shorter-term exposures over several hours to days may lead to vasoconstriction and increased pulmonary and systemic BP by pathways dependent on enhanced ET or angiotensin II signaling. Lung cells may release ET into the systemic circulation and thus increase its systemic activity, or the vascular ET system may be relatively upregulated because of increased ROS or reduced nitric oxide. Activation of the renin-angiotensin system may also occur because of systemic oxidative stress or inflammation or as a consequence of ANS imbalance. The very acute increase in BP that occurs concomitant with the inhalation of particles or within only minutes to hours after exposure appears to be mediated by autonomic imbalance that favors a relative activation of the sympathetic nervous system. No study has evaluated the effect of air pollution on renal sodium handling or long-term pressure natriuresis mechanisms, which are fundamental to the generation of chronic hypertension.

Vascular Dysfunction and Atherosclerosis

Many early experiments demonstrated the capacity of PM constituents to blunt nitric oxide–dependent dilation and enhance vasoconstrictor tone in ex vivo vascular studies because of excess ROS formation.[1] The first in vivo experiment demonstrated the proatherosclerotic actions of intratracheal PM_{10} instillation.[356] More recently, the pulmonary instillation of several different PM types was shown to rapidly impair microvascular endothelium-dependent vasodilation within days, likely by proinflammatory or ROS-dependent mechanisms (eg, myeloperoxidase).[332] Several animal studies have now demonstrated that long-term exposure to ambient $PM_{2.5}$, by use of ambient-exposure facilities without direct pulmonary instillation, not only causes endothelial dysfunction but also accelerates the progression of atherosclerosis. Sun et al[334] demonstrated that exposure of atherosclerosis-prone $ApoE^{-/-}$ mice to environmentally relevant levels of CAP, derived from regional northeastern $PM_{2.5}$, for 6 months in conjunction with a high-fat chow diet potentiated plaque development and heightened vascular inflammation (CD68+ macrophage infiltration and inducible nitric oxide synthase expression) and oxidant stress. The atherosclerotic plaque progression was also accompanied by alterations in vasomotor tone, including decreased endothelium-dependent vasodilation and heightened vasoconstriction to adrenergic stimuli. Importantly, the normalized average $PM_{2.5}$ concentration over the entire period was 15.2 $\mu g/m^3$, which approximates the annual NAAQS. Similar findings were reported in other chronic CAP exposures that involved an $ApoE^{-/-}$ model.[357] However, exposures to a double-knockout model of ApoE-deficient and low-density lipoprotein receptor–deficient mice increased plaque cellularity, reflective of inflammation, but did not enhance plaque burden. It is possible that the atherosclerotic severity of this phenotype precluded the observation of more subtle effects of CAP exposures.

Intratracheal instillation of UFP can acutely impair aortic endothelium-dependent vasodilation.[358] Moreover, repeated 10-week-long endotracheal dispersion of UFP carbon black increased atherosclerosis in low-density lipoprotein receptor–

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knockout mice.[359] This occurred without evidence of systemic translocation of particles into the cardiovascular tissues. UFP inhalation by use of exposure facilities has also recently been shown to augment atherosclerosis, perhaps to a greater degree than $PM_{2.5}$. When investigating the effects of different PM size fractions, Araujo et al[331] compared the proatherogenic potential of exposure over 40 days to ambient particles <0.18 μm versus $PM_{2.5}$ in $ApoE^{-/-}$ mice. UFPs caused more adverse cardiovascular responses (eg, systemic oxidative stress, impaired high-density lipoprotein function) and greater potency in accelerating atherosclerotic lesion formation, although $PM_{2.5}$ did demonstrate qualitatively similar effects. Recent studies have also demonstrated that PM exposure likely promulgates systemic atherosclerosis by mechanisms that overlap those of other conventional cardiovascular risk factors.[360] Intratracheal instillation of PM_{10} particles caused a rapid impairment in endothelium-dependent vasodilation, stimulation of bone marrow–derived cells, and increased migration of monocytes into atherosclerotic plaques.[361,362] Systemic inflammation (IL-6) was also related to the degree of endothelial dysfunction.[314] Finally, the most compelling evidence for rapid impairment in nitric oxide bioavailability being directly involved in the origin of PM-induced endothelial dysfunction was demonstrated recently. Both fine-PM and UFM inhalation for only a few hours in normal rats blunted agonist-stimulated nitric oxide production within the microvasculature, measured by direct electrochemical sensors, concomitant with an observed impairment in vasomotor relaxation. Inhibition of myeloperoxidase or NADP(H) oxidase partially restored normal nitric oxide bioavailability and endothelial function, which suggests a role of activation of these endogenous radical-generating enzymes in this biological response.[363]

Potentially relevant adverse vascular effects of nonparticulate PM components should not be discounted. There may also exist some synergy between vapor phase, gas, and particle constituents in relation to instigation of cardiovascular responses. Recently,[364] it was demonstrated in $apoE^{-/-}$ mice that whole gasoline engine exhaust over 1 or 7 days increased vascular messenger ribonucleic acid expression of matrix metalloproteinase (MMP)-2 and MMP-9. Levels of ET-1 and ROS were similarly increased. The vascular ROS and MMP-2 elevations were attenuated by tempol. Endothelial receptor antagonism ameliorated the vascular expression of MMP-2, MMP-9, and ROS. In separate experiments, diesel exhaust exposure to rats for 5 hours augmented ET-induced vasoconstriction, potentially via a blunting of ET-B–induced nitric oxide release.[365] The findings suggest that exposure to a fresh mixture of PM, gases, and vapors may play a role in rapidly triggering atherosclerotic plaque vulnerability via ROS and ET-dependent upregulation of MMP levels.

Some studies suggest that predisposed animals may be more susceptible to air pollution–mediated vascular dysfunction. Diesel exhaust particles delivered by intraperitoneal injection impaired nitric oxide–dependent vasodilation only in $apoE^{-/-}$ mice with atherosclerosis and not in healthy control animals.[366] Aortas from prediabetic rats were found to be more susceptible to repeated exposures to oil combustion particles in causing noradrenergic-mediated constriction and impaired endothelium-dependent vasodilation.[367]

Taken together, the available studies suggest that short- and long-term particle exposures (including PM_{10}, $PM_{2.5}$, and UFP) can impair conduit and resistance arterial endothelium-dependent vasodilation. Chronic exposures have been shown to be capable of promoting atherosclerosis progression and enhancing plaque vulnerability. The underlying mechanisms likely involve vascular sequelae of systemic inflammation (due to interactions with innate immune cells and cytokines) or exaggerated oxidative stress pathways. Excess vascular ROS and inflammation will impair endogenous vasodilator bioavailability (eg, nitric oxide), enhance vasoconstrictor tone (eg, ET), and chronically activate multiple intracellular pathways that promote atherosclerosis.[368–370]

Heart Rate Variability

Some of the earliest indications of systemic effects of PM came from ECG studies in rats.[371] In general, reductions in several measures of HRV have been shown.[372–376] Most of the recent research has focused on exploring the roles of susceptibility and exposure characteristics. Decreases in heart rate and HRV indices have been reported to be pronounced in senescent mice, which indicates that aging may be a susceptibility factor.[353] Using an anesthetized model of postinfarction myocardium sensitivity, Wellenius and colleagues[377] did not demonstrate an effect of 1 hour of CAP exposure on heart rate or spontaneous ventricular arrhythmias. In contrast, in a post-MI heart failure model in Sprague-Dawley rats, diesel exhaust emissions reduced HRV in both healthy and heart failure groups and increased the incidence of premature ventricular contractions. Studies in mice have also indicated a potential role for transition metals and nickel in HRV alterations[376] and provide initial clues on the PM components that could influence autonomic tone.[48]

Some beginning insight into the neural pathways involved has been reported recently. PM-induced ECG changes in rats were shown to be prevented by inhibiting the transient receptor potential vanilloid receptor in the lungs. This suggests that the relevant neural mechanism that leads to alterations in HRV or heart rhythm may be induced by activation of receptor-mediated autonomic reflexes in the lung.[335] Circulating particle constituents or inflammatory mediators interacting with myocardial ion channels or electrophysiology did not appear to be a pertinent mechanism, at least in these studies.[335] However, it is unknown whether similar mechanisms can account for the HRV changes observed in humans, and a more detailed understanding of the anatomic pathways involved is required. Finally, it remains unclear whether the changes in cardiac HRV are actually caused by or merely illustrate an underlying alteration in ANS balance. Experiments that clearly define the direct contribution of sympathetic and parasympathetic nervous system activities (eg, microneurography, norepinephrine spillover rates, or autonomic receptor or ganglionic blockade) are needed.

MI and Arrhythmia

PM exposure can increase experimental infarct size and potentiate myocardial ischemia and arrhythmias in experi-

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mental MI models. Relatively high concentrations of intratracheal UFP instillation induced pulmonary inflammation and doubled MI size in mice.[358] Conscious dogs exposed to fine CAP for several days experienced greater ST-segment changes during transient coronary artery occlusion.[378] These studies suggested that particulate-related changes in myocardial blood flow may be responsible, a hypothesis recently supported by experiments in chronically instrumented dogs exposed to fine CAP before transient occlusion of the left anterior descending artery. PM exposure was associated with a small but significant decrease in total myocardial flow, especially in the ischemic zone, and increases in coronary vascular resistance without an alteration in rate-pressure product.[379] The abnormalities were inversely related to PM mass, particle number, and black carbon concentration.

Exposure to residual oil fly ash increases arrhythmia frequency in rats with preexisting premature ventricular complexes, which suggests that PM sensitizes ischemic myocardium to abnormal automaticity[372]; however, CAP had no effect in rats.[380] Nevertheless, the data suggest that PM exposure may potentially be capable increasing the sensitivity of the myocardium to ischemia, likely by impairing myocardial blood flow and perfusion. In theory, this could play a role in enhancing the propensity for ventricular arrhythmias.

Insulin Resistance

Recently, Sun et al[319] exposed C57BL/6 mice fed high-fat chow to fine CAP or filtered air for 24 weeks. Mice exposed to $PM_{2.5}$ exhibited marked worsening of whole-body insulin resistance, systemic inflammation (increased IL-6 and TNF-α), and higher levels of adipokines, such as resistin and plasminogen activator inhibitor-1. $PM_{2.5}$ increased visceral adiposity and inflammation (F4/80$^+$ cells), with stromal vascular cells expressing higher TNF-α and IL-6 and lower IL-10 levels. Exposure also induced insulin-signaling abnormalities and reduced phosphorylation of Akt and endothelial nitric oxide synthase in aortic tissue, accompanied by abnormalities in vascular relaxation to insulin. Additionally, there was evidence that $PM_{2.5}$ exaggerated adhesion of monocytes in mesenteric microvessels, culminating in accumulation in visceral adipose. These intriguing findings suggest that longer-term exposure to PM air pollution may promote the chronic development of insulin resistance, obesity, and the metabolic syndrome.

Controlled-Exposure Studies in Humans

Several new human exposure studies have been published, a few of which have even included patients with CVD or risk factors. Similar to the animal studies, large variations among the exposure protocols, measured outcomes, and subject susceptibilities likely explain much of the differences among findings and must be considered when interpreting the results.

Systemic Inflammation

Controlled human exposure studies have measured the effects on circulating inflammatory markers such as CRP, IL-6, and TNF-α. In many of these single-episode short-term exposures, no overt changes in plasma cytokine levels were observed after CAP[381–383] or diesel exhaust.[345,384–386] Similarly, CRP levels have not consistently been found to increase in the time frame and context of most of these studies.[313,384–386]

However, there have also been some positive findings. Increases in IL-6[313] and TNF-α 24 hours after exposure to diesel exhaust in healthy adults have been reported. High levels of ambient particles can stimulate the bone marrow to enhance the release of neutrophils, band cells, and monocytes into the circulation, which causes a cellular inflammatory response.[387,388] Some controlled-exposure studies corroborate the existence of a cellular proinflammatory response that manifests as increases in circulating white blood cell or immune cell counts. In 1 study, increased peripheral basophils in healthy older adults were noted 4 hours after a 2-hour exposure to fine CAP.[389] In a similar study, increased white blood cell counts were observed in healthy young adults 12 hours after exposure.[381] Recently, investigators observed an increased in total white blood cell and neutrophil levels immediately after a 2-hour exposure to CAP in downtown Toronto, Ontario, Canada.[390] Conversely, decreases in blood monocytes, basophils, eosinophils, and CD54 and CD18 adhesion molecule expression on monocytes after exposure to ultrafine carbon (10 to 50 $\mu g/m^3$) among exercising asthmatic individuals and healthy adults have also been reported.[391] The authors suggested in the latter study that these results may represent the sequestration of these cells in tissue compartments such as the lung or vasculature, where there may be selective expression of the corresponding receptors for these ligands.[362] However, other recent human clinical studies have found no association between peripheral blood cell counts and exposure to fine PM or UFPs such as zinc oxide,[392] ultrafine carbon,[393] or diesel exhaust.[313,384,385]

More subtle, yet physiologically relevant or functional proinflammatory changes may be overlooked by the measurement of circulating cytokines or cell counts alone in human studies. Peretz et al[394] recently evaluated gene expression using an expression array in monocytes after 2 hours of exposure to diesel exhaust. Although initially a small study, 10 genes involved in the inflammatory response were modulated in response to exposure (8 upregulated, 2 downregulated). These findings will need to be reproduced in larger studies and raise the possibility that functional changes in inflammatory cells may occur without discernible changes in their levels in the peripheral circulation.[394]

In sum, the findings from controlled human exposures do not demonstrate a robust inflammatory response; however, they have been limited by the fact that they are, by necessity, of short duration and relatively low concentration. Additionally, the results do not preclude an effect of higher exposures, the presence of more subtle responses, or alterations in other cellular inflammatory pathways not measurable by circulating markers.

Systemic Oxidative Stress

The demonstration of systemic oxidative stress is difficult in human studies. Nonetheless, a few studies have reported positive findings. These include an increase in urinary excre-

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tion of free 8-iso-prostaglandin-2α among healthy adults after a 4-hour exposure to concentrated wood smoke[395] and an increase in plasma antioxidant capacity 24 hours after a 1-hour exposure to diesel exhaust in a group of healthy volunteers.[313] The investigators speculated that systemic oxidative stress after exposure may have been responsible for this upregulation in antioxidant defense.[313] Other investigators[394] have observed significant differences in expression of genes involved in oxidative stress pathways due to diesel exhaust exposure. Bräuner et al[167] recently investigated the effect of ultrafine traffic particles on oxidative stress–induced damage to DNA in healthy young adults exposed to low concentrations of ambient urban particles ($PM_{2.5}$ and $PM_{10-2.5}$ mass of 9.7 and 12.6 $\mu g/m^3$, respectively) in an exposure chamber above a busy road with high traffic density. The authors observed increased levels of DNA strand breaks and formamidopyrimidine-DNA glycosylase sites in monocytes after exposure to PM but no changes in the DNA repair enzyme 7,8-dihydro-8-oxoguanine-DNA glycosylase. Similar to their previous findings with ambient levels,[168] the results suggest that short-term exposure to UFPs may result in damage to DNA. This may occur through oxidative stress pathways, although there was no increase in messenger ribonucleic acid levels in heme oxygenase-1, a gene known to be regulated by Nrf2, a transcription factor regulated by oxidative stress.[396] Moreover, more recent observations by the same investigators failed to demonstrate significant biomarker signals for lipid or protein oxidative damage after similar near-roadway exposures.[178] Although not entirely consistent, the available studies demonstrate that acute exposure to PM, perhaps even at ambient levels, may be capable of inducing acute systemic oxidative stress in human subjects under certain circumstances. The assays used to assess the footprint of systemic "oxidative stress" or damage may also play a significant role in the results.

Thrombosis and Coagulation

Several new studies of controlled human exposure have evaluated the effects of PM on hemostatic markers (eg, factor VII, fibrinogen, platelet count, D-dimer, and von Willebrand factor). Although some of these studies have not observed changes after acute exposures,[392] others have reported increases in fibrinogen levels at 8 to 24 hours after exposure to CAP.[381,397] Mills and colleagues[384,385] recently demonstrated a significant effect of diesel exhaust on fibrinolytic function in response to intermittent exercise both in healthy men and in men with coronary heart disease. In both groups of volunteers, bradykinin-induced release of tissue plasminogen activator was observed to decrease compared with filtered air at 6 hours after exposure to diesel exhaust. These perturbations in tissue plasminogen activator release did not persist 24 hours after exposure.[313] In a randomized, controlled crossover study involving "at-risk" metabolic syndrome patients, no changes in plasminogen activator inhibitor-1 were noted over a 24-hour duration; paradoxically, a decrease in von Willebrand factor was noted in this study.[398] In a similar experiment conducted in healthy adults, diesel exhaust had no effect on D-dimer, von Willebrand factor, CRP, or platelet counts compared with filtered air up to 22 hours after exposure.[386] Other investigators[395] recently evaluated the effect of wood smoke on markers of coagulation, inflammation, and lipid peroxidation in young healthy subjects. Serum amyloid A and the ratio of factor VIII to von Willebrand factor, an indicator of an increased risk of venous thromboembolism, were increased at 4 hours after exposure.[395] Samet et al[383] reported an association between various coagulation markers and exposure to ultrafine, fine, and thoracic coarse CAP among healthy young adults. Although exposure to coarse CAP did not result in significant changes in hemostatic variables, the overall trend suggested a prothrombotic effect. Exposure to UFPs increased D-dimer levels, whereas fine-CAP effects tended to increase fibrinogen, similar to previously reported findings.[381]

The measurement of blood levels of coagulation factors or biomarkers of thrombosis could potentially miss a relevant biological effect at the vascular wall. Recently, ex vivo thrombus formation was assessed by use of the Badimon chamber after controlled exposures to dilute diesel exhaust in healthy volunteers.[399] This protocol measures thrombus formation in native (nonanticoagulated) whole blood triggered by exposure to a physiologically relevant substrate, under flow conditions that mimic those found in diseased coronary arteries. It may therefore provide a superior estimate of actual in vivo conditions related to thrombosis potential. Interestingly, dilute diesel exhaust exposure increased thrombus formation within 2 hours, in association with increased platelet activation (ie, increased circulating platelet-monocyte aggregates and soluble CD40 ligand). Taken together, these new studies have provided additional evidence that short-term exposure to PM at near-ambient levels may have small yet potentially significant effects on hemostasis in humans. Whether direct interactions of circulating PM constituents with platelets, activation of platelets due to lung inflammation or secondary to elevated systemic cytokine levels, or an increase in procoagulant factors (eg, fibrinogen) as an acute-phase response to inflammation (or a combination of these pathways) is responsible warrants attention in future studies.

Arterial BP

Although several studies have evaluated the BP response to acute exposures, many inconsistencies in results have been reported.[400] This must be considered in the context that BP was not the primary outcome of interest in most studies, nor was it typically assessed with adequate sophistication. In one of the earliest studies, $PM_{2.5}$ increased systolic BP in healthy subjects but decreased it in asthmatic individuals.[401] Three other controlled studies did not report changes among healthy adults.[345,402,403] However, in a more detailed reanalysis of the changes in BP during the actual period of exposure to CAP plus ozone, Urch et al[404] found a significant increase in diastolic BP of 6 mm Hg. The magnitude of response was associated with the concentration of organic carbon within $PM_{2.5}$.[405] Recent follow-up studies redemonstrated an acute prohypertensive response during the inhalation of CAP in 2 separate cities.[390] The $PM_{2.5}$ mass during exposure and decreases in several HRV metrics were associated with the

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magnitude of the short-lived diastolic BP elevation. This suggested that the most plausible mechanism for this acute response was CAP-induced ANS imbalance that favored sympathetic over parasympathetic cardiovascular tone. Whether this reaction occurred because of a generalized stress response, as a consequence of specific soluble PM constituents directly altering central nervous system activity, or via altered ANS reflex arcs due to the interaction of inhaled particles with lung receptors/nerve endings remains to be elucidated.

The effect of inhaled particulates on BP has also been investigated in several other recent controlled human exposure studies. Two new studies assessed BP changes after a 1-hour exposure to diesel exhaust. Mills et al[384] found a 6-mm Hg increase in diastolic BP 2 hours after exposure, which was of marginal statistical significance ($P=0.08$); however, this trend did not persist for 24 hours,[384] nor was it found among patients with coronary artery disease.[385] The available data to date suggest that short-term exposure to $PM_{2.5}$ or diesel exhaust is capable in certain circumstances of rapidly raising BP. The most consistent and largest effects were seen concomitant with the inhalation of particles. Thus far, the most likely mechanism for such rapid hemodynamic responses appears to be ANS imbalance. However, it is possible that reductions in nitric oxide bioavailability that modulate basal arterial tone toward vasoconstriction or increases in ET among other hemodynamically active molecules (eg, angiotensin II) also play a role in some circumstances.

Vascular Dysfunction

The first controlled human exposure study related to vascular function reported that CAP plus ozone exposure caused acute conduit arterial vasoconstriction in healthy adults.[1] Endothelium-dependent and -independent vasodilation remained intact. Recent follow-up experiments determined that $PM_{2.5}$, not ozone, was responsible for the adverse vascular effects. However, in these subsequent and larger experiments, fine-CAP exposure did prove capable of diminishing conduit artery endothelium-dependent vasodilation 24 hours (but not immediately) after exposure.[390] Postexposure $PM_{2.5}$ mass and TNF-α level were both associated with the degree of endothelial dysfunction, which suggests that systemic inflammation induced by higher levels of particles was likely responsible. Finally, the CAP-induced endothelial dysfunction occurred during exposures in Toronto, Canada, but not Ann Arbor, Mich, which suggests that the composition of the particles is probably an important determinant of the vascular responses.

An acute alteration in vascular function/tone after short-term controlled PM air pollution exposure was corroborated recently.[406] In 27 adults (10 healthy adults and 17 with the metabolic syndrome), a 2-hour exposure to dilute diesel exhaust caused a dose-dependent constriction of the brachial artery and elevation in plasma ET level without impairing endothelium-dependent vasodilation. Contrary to the hypothesis that metabolic syndrome patients would show greater effects, vasoconstriction was greater in magnitude among the healthy participants. In an additional study, 2-hour exposure to UFPs composed of elemental carbon impaired peak forearm blood flow response to ischemia 3.5 hours later. There were no other vascular changes or alterations at other time points. BP was also not affected.[407]

Several recent studies have also shown that dilute diesel exhaust can impair peripheral resistance vessel responses to acetylcholine, bradykinin, and nitroprusside 6 hours after exposure.[384] The blunted responses to acetylcholine persisted for 24 hours in healthy adults.[313] In contrast, bradykinin and sodium nitroprusside–mediated vasodilation and bradykinin-induced acute plasma tissue plasminogen activator release were not altered 24 hours later. In subsequent studies, patients with stable coronary artery disease exposed to dilute diesel exhaust for 1 hour during intermittent exercise demonstrated reduced bradykinin-mediated tissue plasminogen activator release; however, microvascular endothelial function was not impaired.[385] This may be related to some degree of preexisting endothelial dysfunction in these patients. However, exercise-induced ST-segment depression and ischemic burden were significantly greater during diesel compared with filtered air exposure. These important findings experimentally highlight that PM air pollution exposure can trigger, or augment existing, myocardial ischemia extremely rapidly (in fact, concomitant with exposure). Reduced coronary flow reserve (that was not observed or resolved at the time of the postexposure brachial artery studies) due to rapid alterations in coronary microvascular function may have contributed to the acute myocardial ischemia. Alternatively, acute ANS imbalance induced by diesel exhaust inhalation may have acutely altered coronary tone and impaired myocardial perfusion.

In a study that exposed healthy young adults to 100 $\mu g/m^3$ of diesel exhaust for 2 hours,[364] it was recently demonstrated that this air pollution mixture acutely raised plasma ET-1 and MMP-9 expression and activity within 30 minutes. These results corroborate the animal data that even short-term exposures can rapidly alter factors, such as MMP activity, that are mechanistically linked with causing atherosclerotic plaque disruption (and thus acute MI). The increase in ET levels also corroborates previous studies[406] that showed that diesel exhaust can acutely affect important endogenous regulators of vasomotor tone.

Controlled air pollution exposures have not always been shown to impair endothelial function or vasomotor tone. Despite an increase in exhaled 8-isoprostane concentrations that suggested pulmonary oxidative stress, fine CAP did not affect brachial flow–mediated dilation or basal diameter in northern Scotland exposures.[382] However, the $PM_{2.5}$ consisted of relatively inert ambient sea-salt particles and was extremely low in combustion-derived sources. This is in contrast to the particle chemistry in the investigators' previous diesel exposure studies that showed positive findings.[408,409] Moreover, 24-hour exposure to ambient pollution shunted into a chamber next to a busy street did not impair microvascular endothelial function in 29 healthy subjects, as assessed by digital tonometry.[178] This exposure to near-roadway ambient air, which consisted of ambient UFP and $PM_{2.5}$, did not alter biomarkers of inflammation, hemostasis,

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or protein and lipid oxidation. The authors speculated that the relatively low concentrations of UFP numbers and PM mass or the young, healthy status of the subjects could explain the null findings. Taken together, these studies suggest that brief PM exposure can trigger conduit arterial vasoconstriction, possibly in relation to increased ET activity or augmented sympathetic ANS tone. Under certain circumstances, conduit and resistance arteriole endothelium-dependent vasodilation can also be impaired within a few hours. This abnormality is more likely due to reduced nitric oxide bioavailability as a consequence of systemic proinflammatory and oxidative responses; however, alternative mechanisms and endogenous vasoactive pathways have not been fully explored. It is also apparent that the composition, source, and concentration of pollution, along with the susceptibility of the human subjects, play important roles in determining the vascular effects of acute air pollution exposure.

Heart Rate Variability

The results of several new controlled human exposure studies provide limited evidence to suggest that acute exposure to near-ambient levels of PM may be associated with small changes in HRV. There are at least 4 studies to support this. In the first study, healthy elderly individuals experienced significant decreases in HRV immediately after exposure.[233] Some of these changes persisted for at least 24 hours. Gong et al[410] studied healthy and asthmatic adults exposed to coarse CAPs with intermittent exercise. HRV was not affected immediately after the exposure but decreased in both groups at 4 and 22 hours after the end of the exposure; greater responses were observed in nonasthmatic individuals.[410] In another study, healthy elderly subjects and patients with chronic obstructive pulmonary disease were exposed to approximately 200 $\mu g/m^3$ CAP and filtered air for 2 hours with intermittent mild exercise. HRV over multihour intervals was lower after CAP than after filtered air in healthy elderly subjects but not in subjects with lung disease. A significant negative effect of CAP on ectopic heartbeats during or after CAP exposure relative to filtered air was noted in the healthy subjects, whereas the group with pulmonary disease experienced an improvement during or after CAP relative to filtered air.[389] Other investigators recently compared the effects of 2-hour exposures with intermittent exercise to ultrafine (average concentration 47 $\mu g/m^3$), fine (average concentration 120 $\mu g/m^3$), and coarse (average concentration 89 $\mu g/m^3$) CAP among healthy subjects.[383] In both the ultrafine and coarse studies, a crossover design was used in which each subject was exposed to both PM and filtered air. In the case of the fine-PM study, subjects did not serve as their own control but were exposed to either PM or filtered air. Thoracic coarse fraction CAP produced a statistically significant decrease in the standard deviation of normal-to-normal heart rate 20 hours after exposure compared with filtered air. No statistically significant effects on HRV were observed after exposure to UFPs as measured during controlled 5-minute intervals. However, the authors did observe a significant decrease in the standard deviation of normal-to-normal heart rate after exposure to UFPs based on an analysis of the 24-hour measurements. No differences were reported in HRV with fine-PM exposures. Although some controlled-exposure studies have reported either no acute changes[390] or, on occasion, increases in HRV metrics in subsets of individuals,[208,393,401] these studies generally demonstrate that acute PM exposure is capable of reducing HRV. More consistent reductions have been found among older adults (compared with younger subjects or those with lung diseases, who show mixed responses) and perhaps with exposures to larger particles.[233,389] Whether pulmonary ANS reflex arcs are activated by the deposition of PM within the lung or whether other pathways are responsible for these physiological changes in human exposure studies requires more investigation.

Table 7. Summary of Level of Evidence Supporting Global Biological Pathways and Specific Mechanisms Whereby $PM_{2.5}$, Traffic-Related, or Combustion-Related Air Pollution Exposure Can Affect the Cardiovascular System

	Animal Studies	Human Studies
General "intermediary" pathways whereby PM inhalation can instigate extrapulmonary effects on the cardiovascular system		
Pathway 1: Instigation of systemic proinflammatory responses	↑ ↑ ↑	↑ ↑ ↑
Pathway 2: Alterations in systemic ANS balance/activity	↑	↑ ↑
Pathway 3: PM and/or associated constituents directly reaching the systemic circulation	↑	↑
Specific biological mechanisms directly responsible for triggering cardiovascular events		
Vascular dysfunction or vasoconstriction	↑ ↑ ↑	↑ ↑
Enhanced thrombosis or coagulation potential	↑ ↑	↑ ↑
Elevated arterial BP	↑ ↑	↑ ↑
Enhanced atherosclerosis or plaque vulnerability	↑ ↑	↑
Arrhythmias	↑	↑

The arrows are not indicators of the relative size of the association but represent a qualitative assessment based on the consensus of the writing group of the strength of the mechanistic evidence based on the number and/or quality, as well as the consistency, of the relevant studies.

↑ ↑ ↑ Indicates strong overall mechanistic evidence.

↑ ↑ Indicates moderate overall mechanistic evidence.

↑ Indicates some but limited or weak available mechanistic evidence.

Blank indicates lack of evidence.

Evidence Summary and Contextual Framework for Biological Mechanisms

Table 7 provides an outline of the level of evidence supporting the generalized intermediary pathways and specific mechanisms whereby PM exposures can be capable of eliciting

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cardiovascular events. At the molecular level, oxidative stress as a critically important cause and consequence of PM-mediated cardiovascular effects has a sound experimental basis.[261,290b,294,319,333,334,345–349,351,361–364,411] At the integrated physiological level, the collective body of evidence continues to support the existence of 3 general pathways (Figure 3). Some of these responses, such as systemic inflammation (via pathway 1), likely require antecedent pulmonary oxidative stress or inflammation in order to be initiated. Others, including ANS imbalance (via pathway 2) and PM or its constituents reaching the systemic circulation (via pathway 3), may not. Although PM-associated metals[412] and certain UFPs[261,413–415] might be capable of translocating into the blood stream, some studies have been negative in this regard.[355,416] Many issues related to this pathway are controversial and require resolution.[416] These include the relevance of the dosages delivered to cardiovascular organs, the consequences of particle constituent modifications after interactions with lung tissue/fluids and plasma components, the means of transport within the circulation (eg, protein bound or within cells),[417] and the time course and ultimate sites of PM sequestration. It is also possible that increases in some vasoactive mediators or molecules with adverse effects on cardiovascular tissue, such as ET-1,[351–354] may occur in the lung and systemic circulation without the need for antecedent lung inflammation. Moreover, the 3 general pathways represent a simplification of complicated biological processes. They may not be mutually exclusive, may overlap temporally, and likely exhibit synergies in causing manifest cardiovascular disease events. Many of the biological pathways are also known to exhibit mutual interactions (eg, inflammation with thrombosis/coagulation and with autonomic function). The pathways are also likely to be principally active at differing time points (eg, more rapid cardiovascular effects of autonomic imbalance than systemic inflammation) and likely vary in importance in relation to different durations of exposure and in causing different cardiovascular sequelae. The chemical characteristics and sizes of inhaled PM may also determine the pathways activated. As opposed to UFPs or some particulate components or chemicals, larger fine and coarse PM are not likely transported into the circulation to any large degree and therefore are more apt to require intermediary pathways to cause extrapulmonary effects. It may also be that surface-bound components may be delivered into the circulation, whereas larger particles themselves serve as a means to deliver the responsible constituent into the pulmonary tree.

The hyperacute physiological responses that occur minutes to hours after PM inhalation are likely mediated principally via pathways 2 and 3. These include ANS-mediated changes (eg, elevated BP, arrhythmias, and vasoconstriction), along with direct effects of circulating PM constituents on platelets (eg, procoagulant and thrombotic changes) and the endothelium (eg, oxidative stress and vasoconstriction). These responses are liable to be the dominant mechanisms responsible for the actual triggering of acute cardiovascular events. Clinically meaningful effects undoubtedly become manifest only in the context of a susceptible patient, typified by the individual with "vulnerable plaque" in the case of acute coronary syndromes or strokes, "vulnerable myocardium" in the context of arrhythmias, or the "vulnerable circulation" in the context of a heart failure patient at risk for circulatory overload. On the other hand, the biological consequences of systemic inflammation, such as activated white cells and elevated cytokines (via pathway 1), typically require longer periods. Their penultimate effect is the induction of a chronic underlying vulnerable milieu that leads to atherosclerotic plaque vulnerability, enhanced coagulation/thrombotic and arrhythmia potential, and impaired basal vasomotor balance. These actions thereby predispose individuals for future cardiovascular events, particularly when they occur in conjunction with traditional risk factors or prompt susceptibility to the acute biological actions (via pathways 2 and 3) of later air pollution exposures.

This hypothetical segregation of the biological effects of PM exposure as acute or chronic and into the broad pathways is artificial. It is useful in the broad context of understanding potential pathways; however, there is no doubt a large degree of overlap among the mechanisms and the timing of physiological responses. This is most aptly conveyed as the influence of "acute on chronic" actions of exposure. For example, the activation of circulating platelets by the pulmonary deposition of particles or lung inflammation (eg, by P-selectin–dependent pathways, histamine, or IL-6) could occur within hours and more rapidly than typical of the other consequences of inflammation (eg, progression of atherosclerosis). In the presence of a vulnerable or eroded coronary plaque due to long-term air pollution exposure, this sudden prothrombotic tendency could instigate an acute ischemic event (alone or in conjunction with other effects of short-term PM exposure via pathways 2 and 3). Furthermore, the epidemiological cohort studies demonstrate a larger relative risk for increased cardiovascular-related mortality than for morbidity.[72,73,227,274] If this is a true biological response and not simply a statistical phenomenon or a shortcoming of the available data, it not only suggests that exposures are capable of triggering acute cardiovascular events but that PM air pollution may also exaggerate their severity even if they would have otherwise occurred for reasons unrelated to air pollution. Therefore, exposure to PM could also be responsible for promoting fatal over nonfatal events.

Conclusions and Recommendations

A wide array of new studies that range from epidemiology to molecular and toxicological experiments have provided additional persuasive evidence that present-day levels of air pollutants contribute to cardiovascular morbidity and mortality. Although not unexpected given the numerous and heterogeneous nature of the published studies, all findings related to every single cardiovascular end point have not been consistent. However, the overall weight of scientific evidence now supports several new conclusions since the 2004 statement. These consensus points are given below by the AHA writing group after considering the strength, consistency, and coherence of the epidemiological findings, as well as in the context of evaluating the extent of the studies that provided related mechanistic support.

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- The preponderance of findings indicate that short-term exposure to $PM_{2.5}$ over a period of a few hours to weeks can trigger CVD-related mortality and nonfatal events, including myocardial ischemia and MIs, heart failure, arrhythmias, and strokes.
- The increase in risk for acute $PM_{2.5}$-associated cardiovascular morbidity and mortality is principally among susceptible, but not necessarily critically ill, individuals. Several studies suggest that susceptible individuals at greater risk may include the elderly, patients with preexisting coronary artery disease, and perhaps those with diabetes. Recent data suggest that women and obese individuals might also be at higher risk.
- Most studies support the idea that longer-term $PM_{2.5}$ exposures increase the risk for cardiovascular mortality to an even greater extent than short-term exposures. Because most studies have focused on mortality data, the effect of long-term exposures on nonfatal cardiovascular events is less consistent and requires more investigation.
- The $PM_{2.5}$ concentration–cardiovascular risk relationships for both short- and long-term exposures appear to be monotonic, extending below 15 $\mu g/m^3$ (the 2006 annual NAAQS level) without a discernable "safe" threshold.
- Long-term exposure to elevated concentrations of ambient $PM_{2.5}$ at levels encountered in the present-day environment (ie, any increase by 10 $\mu g/m^3$) reduces life expectancy within a population probably by several months to a few years. Given that $PM_{2.5}$ is most strongly associated with cardiovascular deaths in the cohort studies, the reduced life expectancy is most likely predominantly due to excess cardiovascular mortality.
- The available studies are suggestive that reductions in PM levels decrease cardiovascular mortality within a time frame as short as a few years.
- Many potential biological mechanisms exist whereby PM exposure could exacerbate existing CVDs and trigger acute cardiovascular events (over the short term) and instigate or accelerate chronic CVDs (over the long run). Experimental support is increasingly strong for several mechanisms, which lends biological plausibility for the epidemiological findings.
- The existing evidence suggests that PM air pollution is capable of augmenting the development and progression of atherosclerosis. There is some support for a potential effect on several other chronic CVDs, including hypertension, heart failure, and diabetes.
- Most recent studies support the conclusion that the overall absolute risk for mortality due to PM exposure is greater for cardiovascular than pulmonary diseases after both short- and long-term exposures.

There are several additional areas worthy of highlighting in which the study results are reasonably consistent but in which the writing group believed further research was required to formulate firm conclusions.

- Although there is only limited epidemiological evidence directly linking UFPs with cardiovascular health problems,[262] the toxicological and experimental exposure evidence is suggestive that this size fraction may pose a particularly high risk to the cardiovascular system. The likelihood of health effects and the causal pathways mediated specifically by UFP exposure have been debated among experts recently.[418] Future research may help to more fully elucidate whether particles within the ultrafine size range (0.001 to 0.1 μm) and/or their constituents are more harmful to the cardiovascular system or pose a relatively greater cardiovascular risk than particles between 0.1 and 2.5 μm in diameter.
- Similarly, many studies have found a strong association between metrics of traffic-related air pollution exposure and elevated cardiovascular risk. Whether this represents the harmful effects of UFPs or diesel exhaust particulates, major components of the traffic mixture, or other pollution components is unclear. Diesel and UFPs possess toxic properties that instigate harmful biological responses in experimental models. However, the particle size fraction(s) and roles played by other copollutants (gases, VOCs, SVOCs) within the traffic-related mixture have not been fully elucidated. Nevertheless, traffic-related pollution as a whole appears to be a specific source associated with cardiovascular risk. It likely poses a major public health burden, regardless of a putative higher toxicity, because of the commonness of exposure in modern society (eg, accounting for ≈60% of daily UFP exposure; http://www.catf.us/projects/diesel/).
- The importance of other specific sources, regional differences in pollution composition, and other specific constituents remains less clear. However, toxicological studies have identified several transition metals (eg, iron, vanadium, nickel, copper, and zinc), organic carbon species, semiquinones, and endotoxin as specific PM-related components capable of prompting oxidative stress and inflammation and thus likely imparting biological harm. Some source-apportionment studies also demonstrate that attention should be given to these compounds as being among the most likely mediators of clinical CVD. More studies are required in this regard to clarify this issue and to better define these and other potentially responsible constituents and sources.
- Although the focus of the present statement is on PM, we recognize that other air pollutants may also pose cardiovascular risk alone or in conjunction with fine-particle exposure. In this context, we believe additional research is necessary to make firm conclusions regarding the independent cardiovascular risks posed by several gaseous pollutants (eg, ozone and NO_2). Although ozone has been linked to increased cardiopulmonary mortality,[50] strokes,[126] and MIs[419] in some short-term studies, long-term exposure was not associated with cardiovascular mortality after accounting for PM in a recent analysis.[87] The recent finding that small changes in low levels of ambient carbon monoxide concentrations are related to cardiovascular hospitalizations also merits further exploration.[420]
- Several secondary aerosols (eg, nitrate and sulfate) are often associated with cardiovascular mortality; however, whether these compounds are directly harmful or are surrogate markers of toxic sources of exposure requires

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more investigation. Similarly, the current literature regarding the independent cardiovascular risks posed by coarse particles is mixed, with most recent findings not supporting an association after accounting for the effects of $PM_{2.5}$.[43,72,104]

- Several recent cohort studies and intermediate end-point experiments suggest that obese individuals (and/or those with the metabolic syndrome) may be a susceptible population at greater risk for cardiovascular events due to $PM_{2.5}$ exposure. This is a tremendously important public health issue to corroborate because of the enormous and growing prevalence of obesity worldwide.

This updated review by the AHA writing group corroborates and strengthens the conclusions of the initial scientific statement. In this context, we agree with the concept and continue to support measures based on scientific evidence, such as the US EPA NAAQS, that seek to control PM levels to protect the public health. Because the evidence reviewed supports that there is no safe threshold, it appears that public health benefits would accrue from lowering $PM_{2.5}$ concentrations even below present-day annual (15 $\mu g/m^3$) and 24-hour (35 $\mu g/m^3$) NAAQS, if feasible, to optimally protect the most susceptible populations. Evaluations of the effectiveness of such efforts would be warranted as well. Within the framework of attempting to establish causality between associated variables in epidemiological studies, there are several generally accepted "aspects" that have been evaluated (the following phrases in italics per the Bradford Hill criteria)[421]: With regard to cardiovascular mortality and $PM_{2.5}$ exposure, there is a *consistent association* that satisfies both a *temporal and exposure-response relationship*. There is *coherence of findings* among several fields of science, including toxicology, human and animal exposures, and different types of epidemiological studies and time frames of exposure. Rigorous experiments demonstrate multiple *plausible biological mechanisms*. Finally, natural experiments have confirmed that a change (ie, reduction) in exposure produces a change (ie, decrease) in cardiovascular mortality. In this case, *specificity of outcomes* and *strength of the observation* are less pertinent, because PM exposure could be capable of causing multiple different types of events (eg, MIs, arrhythmias, and heart failure exacerbations), and the overall cardiovascular mortality relative risk posed for any single individual is expected to be small. Nevertheless, given the ubiquity of exposure, the overall public health consequences can be substantial and observable in population- or large cohort–based studies.

It is the opinion of the writing group that the overall evidence is consistent with a causal relationship between $PM_{2.5}$ exposure and cardiovascular morbidity and mortality. This body of evidence has grown and has been strengthened substantially since publication of the first AHA scientific statement.[1] At present, no credible alternative explanation exists. These conclusions of our independent review are broadly similar to those found in the EPA's Integrated Science Assessment for Particulate Matter final report (http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=216546). In summary, the AHA writing group deems that $PM_{2.5}$ exposure is a "modifiable factor contributing to cardiovascular morbidity and mortality."

Clinical Recommendations

Several precautionary recommendations can be made for healthcare providers who interact with individuals who are at risk for CVDs. Although they have not been clinically tested or proven to reduce mortality, they are practical and feasible measures that may help to reduce exposures to air pollution and therefore potentially lower the associated cardiovascular risk. Moreover, a recent observational study found that patient awareness of air quality indices and media alerts along with health professional advice can significantly affect reported changes in outdoor activity to avoid exposure to air pollution.[422]

- Evidence-based appropriate treatment of the traditional cardiovascular risk factors should be emphasized. This may also lessen the susceptibility of patients to air pollution exposures.
- All patients with CVD should be educated about the cardiovascular risks posed by air pollution.
- Consideration should also be given to educating patients without CVD but who are at high risk (eg, the elderly, individuals with the metabolic syndrome or multiple risk factors, and those with diabetes).
- Part of patient education should include the provision of information regarding the available sources (local and national newspapers [*USA Today*], EPA World Wide Web site [http://airnow.gov/], and The Weather Channel and its World Wide Web site [http://www.weather.com/]) that provide a daily EPA Air Quality Index.
- On the basis of the forecast Air Quality Index, prudent recommendations for reducing exposure and limiting activity should be provided based on the patient's level of risk. A list of such recommendations is provided on the EPA World Wide Web site (http://airnow.gov/). For example, when the Air Quality Index for PM is "unhealthy" (151 to 200), then the recommendations are as follows: "People with heart or lung disease, older adults, and children should avoid prolonged or heavy exertion. Everyone else should reduce prolonged or heavy exertion." The action recommendations are as follows: "You can reduce your exposure to particles by 1) planning strenuous activity when particle levels are forecast to be lower, 2) reducing the amount of time spent at vigorous activity, or 3) choosing a less strenuous activity (eg, going for a walk instead of a jog). When particle levels are high outdoors, they also can be high indoors. Certain filters and room air cleaners are available that can help reduce particles indoors."
- Practical recommendations to reduce air pollution exposure should be given to at-risk patients. Although unproven to reduce cardiovascular events, there are a number of prudent and feasible measures, including reducing optional or unnecessary exposures. Additional measures could include eliminating or reducing nonmandatory travel to highly polluted regions and avoiding exposures or outdoor activities (eg, exercising, commut-

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ing) during highly polluted times (eg, rush hours) or in proximity to major sources of pollution (eg, roadways, industrial sources). Choosing to exercise indoors with windows closed and using efficient air conditioning and filtering systems may be prudent for certain high-risk patients, particularly during peak pollution periods. Indeed, not only can central air conditioners reduce the indoor exposure level to PM from outdoor sources, there is some evidence that they might reduce the risk for cardiovascular hospitalizations associated with higher ambient pollution levels.[423] If travel/commutes cannot be avoided, maintaining optimal car filter systems, driving with windows closed, and recycling inside vehicle air may help reduce PM exposures (http://www.catf.us/projects/diesel/).[424,425]

However, at present, no specific recommendations regarding the appropriateness of undertaking more aggressive measures, even those shown to provide some benefits in a few studies (eg, wearing facemasks, installing PM filters in households), can be made based on the limited evidence. Similarly, although measures that decrease long-term PM exposures may produce even greater cardiovascular health benefits than the provided recommendations that focus on reducing short-term exposures, no specific recommendations (eg, moving to less polluted regions) can be prudently made at this time given the limited evidence. We acknowledge that occupational and indoor sources along with secondhand tobacco smoke are additional significant sources of personal PM exposures that should be avoided or reduced as much as possible. Finally, in developing nations, reducing exposure to indoor cooking sources of PM and air pollution from biomass combustion is a major issue of concern.[426] Additional suggestions are available on the EPA World Wide Web site.

Finally, although the existing evidence supports a causal relationship between $PM_{2.5}$ and cardiovascular mortality, we acknowledge the importance of continued research in areas of controversy and uncertainty to further understand the full nature of this issue. Although numerous insights have greatly enhanced our understanding of the PM-cardiovascular relationship since the first AHA statement was published,[1] the following list represents broad strategic avenues for future investigation:

Mechanistic Studies

- Better describe the physiological relevance in humans and the fundamental details of the mechanisms underlying the intermediate general mediating pathways (ie, PM or constituent transport into the circulation versus effects of inflammatory cytokines or activated immune cells versus ANS imbalance or other pathways) through which PM inhalation might mediate cardiovascular effects remote from the site of pulmonary deposition.
- Understand the clinical significance and relative importance of the observed biological responses (eg, vascular dysfunction, thrombosis, arrhythmia, ANS imbalance) in relation to the various causes of PM-mediated cardiovascular morbidity and mortality.
- Examine the efficacy of preventive measures (eg, patient education) and treatment modalities (eg, statins, antioxidants, fish oil, treatment of traditional risk factors, and reducing exposures by engineering controls, including filtration, personal protection via facemasks, or behavior modification) on cardiovascular health outcomes.
- Investigate the interaction between preexisting traditional cardiovascular risk factors (eg, diabetes, hypertension) and PM exposure, as well as the potential of air pollutants to exacerbate or worsen these risk factors. Determine the extent to which treatment of such factors (eg, with statins, aspirin, or angiotensin-converting enzyme inhibitors), especially among patients with known CVD, may modify the risk associated with PM exposure.
- Describe the biological effects of acute on top of chronic exposures (eg, synergistic effects versus reduced susceptibility to acute exposures due to augmented protective mechanisms).
- Determine the ability of long-term exposure to precipitate the development of chronic diseases, including clinically relevant atherosclerosis, hypertension, diabetes, and other vascular, metabolic, renal, or neurological diseases.

Epidemiological and Exposure Studies

- Expand our knowledge related to the "responsible" PM pollution constituents (eg, metals, organic compounds, semiquinones, endotoxin, and VOC and SVOC compounds), size fractions (eg, UFPs), sources (eg, traffic, power generation, and biomass combustion), and mixtures of pollutants.
- Investigate the cardiovascular health implications and importance of regional and intracity differences in composition and combinations of pollutants.
- Better understand the effects of mixtures of ambient pollutants (ie, potential synergism between PM and gaseous or vapor-phase pollutants such as ozone).
- Investigate the feasibility and utility of quantifying risk coefficients (concentration-response functions) according to PM source or relevant indices of pollutant mixtures, as a function of susceptibility (eg, age, preexisting disease), for reliable application in integrated, multipollutant risk assessments.
- Investigate the relative importance of various time frames of exposure in relation to PM causing cardiovascular events, including the relevance of epochs not well described, such as ultra-acute peak PM excursions (eg, 1 to 2 hours) and exposures of intermediate duration (eg, 1 to 12 months).
- Better document the time course and specific cardiovascular health benefits induced by reductions in PM.
- Better define susceptible individuals or vulnerable populations.
- Determine whether any "safe" PM threshold concentration exists that eliminates both acute and chronic cardiovascular effects in healthy and susceptible individuals and at a population level.

Acknowledgments

We would like to thank Robert Bard Consulting for reviewing and editing the manuscript and Tom Dann from Environment Canada and Joseph Pinto from the US EPA for assistance in the preparation of Table 1.

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Disclosures

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Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/ Honoraria	Expert Witness	Ownership Interest	Consultant/ Advisory Board	Other
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Jeffrey R. Brook	University of Toronto, Environment Canada	None	None	None	None	None	None	None
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Sanjay Rajagopalan	Ohio State University	None	None	Takeda*	None	None	None	None
David Siscovick	University of Washington	MESA AIR (ancillary study to MESA) funded by EPA†; NIEHS Discovery Center Study focused on air pollution and CVD†; NIH†	None	None	None	None	None	None
Sidney C. Smith, Jr	University of North Carolina	None	None	None	None	None	None	None
Laurie Whitsel	American Heart Association	None	None	None	None	None	None	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (1) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (2) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

‡Dr Hong is currently with the Centers for Disease Control and Prevention, Atlanta, Ga.

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Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
Michael Brauer	University of British Columbia	Health Canada†; British Columbia Lung Association†	None	None	None	None	MESA-Air Study (US EPA, University of Washington) External Scientific Advisory Committee*; British Columbia Lung Association, Air Quality and Health Steering Committee*	None
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This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (1) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (2) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

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Particulate Matter Air Pollution and Cardiovascular Disease: An Update to the Scientific Statement From the American Heart Association

Robert D. Brook, Sanjay Rajagopalan, C. Arden Pope III, Jeffrey R. Brook, Aruni Bhatnagar, Ana V. Diez-Roux, Fernando Holguin, Yuling Hong, Russell V. Luepker, Murray A. Mittleman, Annette Peters, David Siscovick, Sidney C. Smith, Jr, Laurie Whitsel and Joel D. Kaufman on behalf of the American Heart Association Council on Epidemiology and Prevention, Council on the Kidney in Cardiovascular Disease, and Council on Nutrition, Physical Activity and Metabolism

Circulation. 2010;121:2331-2378; originally published online May 10, 2010;
doi: 10.1161/CIR.0b013e3181dbece1
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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