THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Air Pollution and Cardiovascular Disease

JACC State-of-the-Art Review

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ABSTRACT

Fine particulate matter <2.5 μm ($PM_{2.5}$) air pollution is the most important environmental risk factor contributing to global cardiovascular (CV) mortality and disability. Short-term elevations in $PM_{2.5}$ increase the relative risk of acute CV events by 1% to 3% within a few days. Longer-term exposures over several years increase this risk by a larger magnitude (~10%), which is partially attributable to the development of cardiometabolic conditions (e.g., hypertension and diabetes mellitus). As such, ambient $PM_{2.5}$ poses a major threat to global public health. In this review, the authors provide an overview of air pollution and health, including assessment of exposure, impact on CV outcomes, mechanistic underpinnings, and impact of air pollution reduction strategies to mitigate CV risk. The review concludes with future challenges, including the inextricable link between air pollution and climate change, and calls for large-scale trials to allow the promulgation of formal evidence-based recommendations to lower air pollution–induced health risks. (J Am Coll Cardiol 2018;72:2054–70) © 2018 by the American College of Cardiology Foundation.

Environmental pollution is the largest cause of premature reversible death and disability in the world today (1). Scientific understanding of the scale and scope of pollution and its association with a wide range of diseases, particularly noncommunicable diseases, has provided a better framework for understanding pollution's true global impact and helping focus attention on the environment as a poorly understood, yet major determinant of health outcomes (2). The Lancet Commission developed the framework of the "pollutome," a subset of the "exposome," defined as the totality of all influences of pollution on human health, including exposures across the lifespan (1). When considered within this broader context, health effects of air pollution had the largest footprint, likely attributable to the pernicious, pervasive, persistent, and protracted nature of air pollution exposure. The widely cited Global Burden of Disease (GBD) study estimates that around 9.0 million total deaths are directly attributable to environmental pollution (4.2 million to ambient air pollution and 2.9 million to household air pollution [HAP]) (**Figure 1**) (1,3). The health effects of pollution, and air pollution in particular, are likely the tip of the iceberg (**Figure 2**). Importantly, although chemicals in the air may potentiate risk factors for cardiometabolic disease, nonchemical environmental factors, such as temperature, noise exposure, mental/psychosocial stress, socioeconomic factors, electromagnetic fields, occupational risks, built environments, agricultural methods, and man-made climate and ecosystem changes, may cosegregate with air pollution and potentially amplify its association with cardiovascular (CV) events (1).

In the present review, we review the impact of air pollution on global CV morbidity and mortality. We address the evidence supporting a link between the effects of particulate matter and gaseous components

on cardiometabolic disease; discuss our current understanding of the molecular mechanisms; and evaluate strategies to mitigate CV effects of air pollution. Finally, we attempt to address the gap in guidance, where possible, on how to combat adverse health effects of air pollution.

AIR POLLUTION COMPOSITION, CHEMISTRY, AND SOURCES

Air pollution is a complex mixture of gaseous phase and particulate constituents that vary in time and location (4-7). The effects of air pollution are a function of chemistry, and simple schemes based on single pollutants, size, or mass provide an incomplete picture. For simplicity, the particulate matter (PM) fraction of air pollution is broadly categorized by aerodynamic diameter: <10 μm (thoracic particles [PM_{10}]), <2.5 μm (fine particles [$PM_{2.5}$]), <0.1 μm (ultrafine particles), and between 2.5 and 10 μm (coarse [$PM_{2.5-10}$]) (**Figure 3A**). PM is quantified by the particles (mass) contained per cubic meter ($\mu g/m^3$). Over 90% of the pollutant mass in the mixture we breathe in urban settings is, however, from gases or vapor-phase compounds, including volatile organic carbons (4). Ozone is the most prevalent secondary pollutant, in addition to a number of inorganic and organic acids, and volatile and semivolatile organic compounds found in both the gas and particle phases. Although a growing body of studies supports the toxicity of ultrafine particles as well as possibly coarse PM (8-10), the overwhelming burden of evidence impugns $PM_{2.5}$ as the principal air pollutant posing the greatest threat to global public health.

HOUSEHOLD AIR POLLUTION. HAP levels typically encountered in low-middle income countries can be an order of magnitude higher than ambient outdoor levels in the same geographic location, contributing to steep indoor-outdoor gradients (11). For instance, mean indoor 24-h PM_{10} levels between 200 and 2,000 $\mu g/m^3$ are quite common. Peak exposures of >30,000 $\mu g/m^3$ during periods of cooking with exposure to low-efficiency combustion of biomass fuels have been reported (11,12). Compared with a decade ago, the decrease in contribution of HAP to global morbidity/mortality is encouraging.
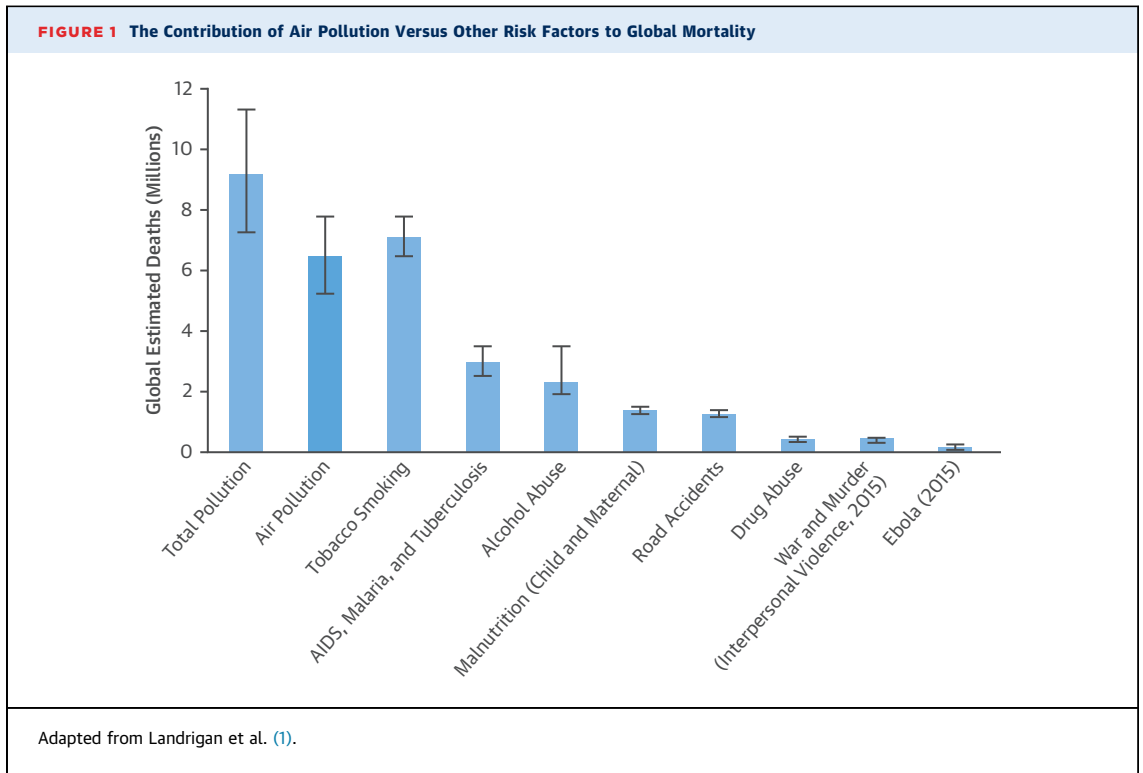
CONTRIBUTION OF DUST FROM NATURAL SOURCES. Recently, attention has been drawn to the health effects of particles from natural events, such as desert dust, wildfires, and volcanic eruptions. It is estimated that natural dust contributes to 18% of total premature mortality attributable to air pollution (13).

AIR POLLUTION THRESHOLDS, EXPOSURE ASSESSMENT, AND EXPOSURE-RESPONSE FUNCTION

More than 90% of the global population is exposed to levels exceeding World Health Organization air quality guidelines (AQG) of <10 $\mu g/m^3$ for annual levels and <20 $\mu g/m^3$ for daily levels (14). Air pollution over many parts of Asia (70% of the population) routinely exceeds 35 $\mu g/m^3$, where over 99% of people are exposed to levels above annual AQG. During extreme ambient air pollution episodes, $PM_{2.5}$ can even reach extraordinary concentrations above 500 to 1,000 $\mu g/m^3$, levels that are on par with high levels of HAP or active smoking (11,15). By contrast, in the United States and Canada, values routinely average <12 $\mu g/m^3$ (**Figure 3B**). The current improvement in knowledge of global exposure to air pollution is in no small measure on account of the dramatic improvement in ground-level air-monitoring data, with hourly air quality index data from regulatory monitoring data networks from over 9,000 stations in 800 major cities from 70 countries. Nontraditional measurement sources, such as independent stations, social media (through personal level monitoring), and air monitors, have also contributed to increased awareness and, in some cases, policy changes. The breadth and scope of personalized monitoring devices have also expanded dramatically, with many of these devices now available to provide unprecedented personal exposure information (16). Satellite-based techniques use the optical properties of aerosol columns (aerosol optical depth) in satellite images to produce indirect estimates of ground-level pollutant concentrations and were the basis of GBD study estimates for air pollution. The need to have credible risk estimates for countries with concentrations of air pollution above those of the range of study populations was addressed by the development of the integrated exposure response curve, which integrated relative risks of $PM_{2.5}$ pollution from diverse sources (HAP, ambient air pollution, secondhand smoke, and tobacco smoking) into a single curve from which risk estimates for air pollution were obtained (**Figure 3C**) (17,18). Notably, the totality of evidence demonstrates that there is no lower concentration threshold below which exposures can be considered safe at the population level. Even low $PM_{2.5}$ levels within annual AQG targets (<10 $\mu g/m^3$), faced by hundreds of millions of people pose significant

FIGURE 1 The Contribution of Air Pollution Versus Other Risk Factors to Global Mortality

Adapted from Landrigan et al. (1).

threats to public health and, in particular, CV events (10,19-23). Moreover, other air pollutants (e.g., ozone) can present their own independent risks (22,24). In contrast to $PM_{2.5}$, ozone, in the most recent estimates, does show a threshold effect with short-term exposure (**Figure 4**) (23).

BURDEN OF AIR POLLUTION–MEDIATED MORBIDITY AND MORTALITY

Though $PM_{2.5}$ affects nearly everyone worldwide, the ecological-economic shifts during the past century have resulted in $PM_{2.5}$ disproportionately affecting

FIGURE 2 The Zones of Evidence Linking Air Pollution and CV Disease

Zone 1
Well-characterized adverse cardiovascular effects
- All-Cause Mortality
- Cardiovascular Mortality

Zone 2
Emerging evidence remains unquantified
- Hypertension
- Diabetes
- Non-fatal MI
- Non-fatal Stroke
- Heart Failure

Zone 3
Inadequate evidence of association
Need further research
- Thromboembolic Disease
- Atrial and Ventricular Arrhythmias

Adapted from Landrigan et al. (1). CV = cardiovascular; MI = myocardial infarction.
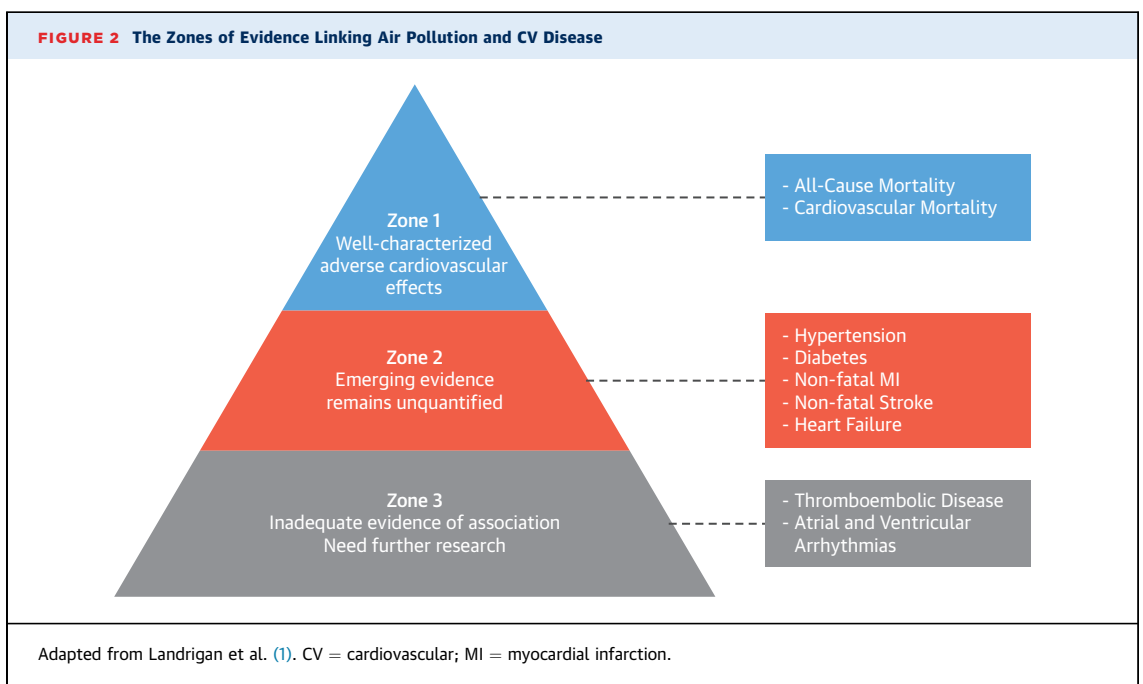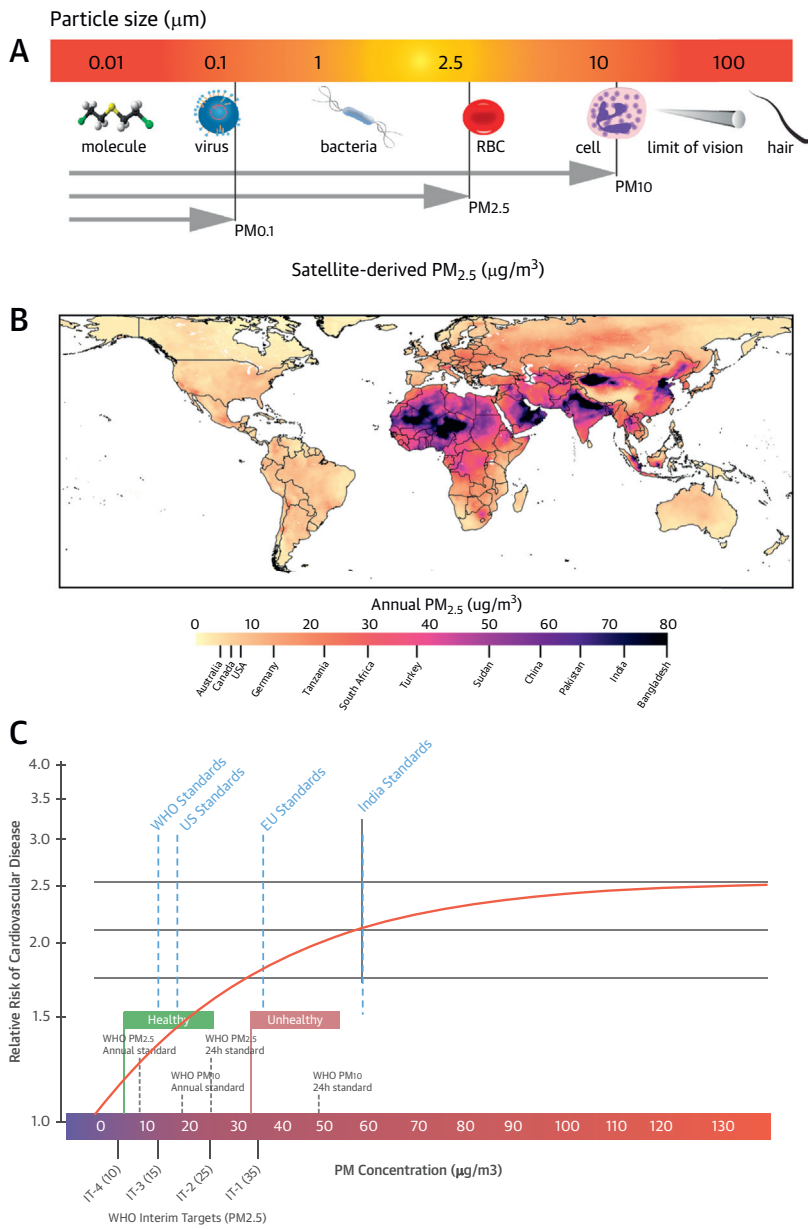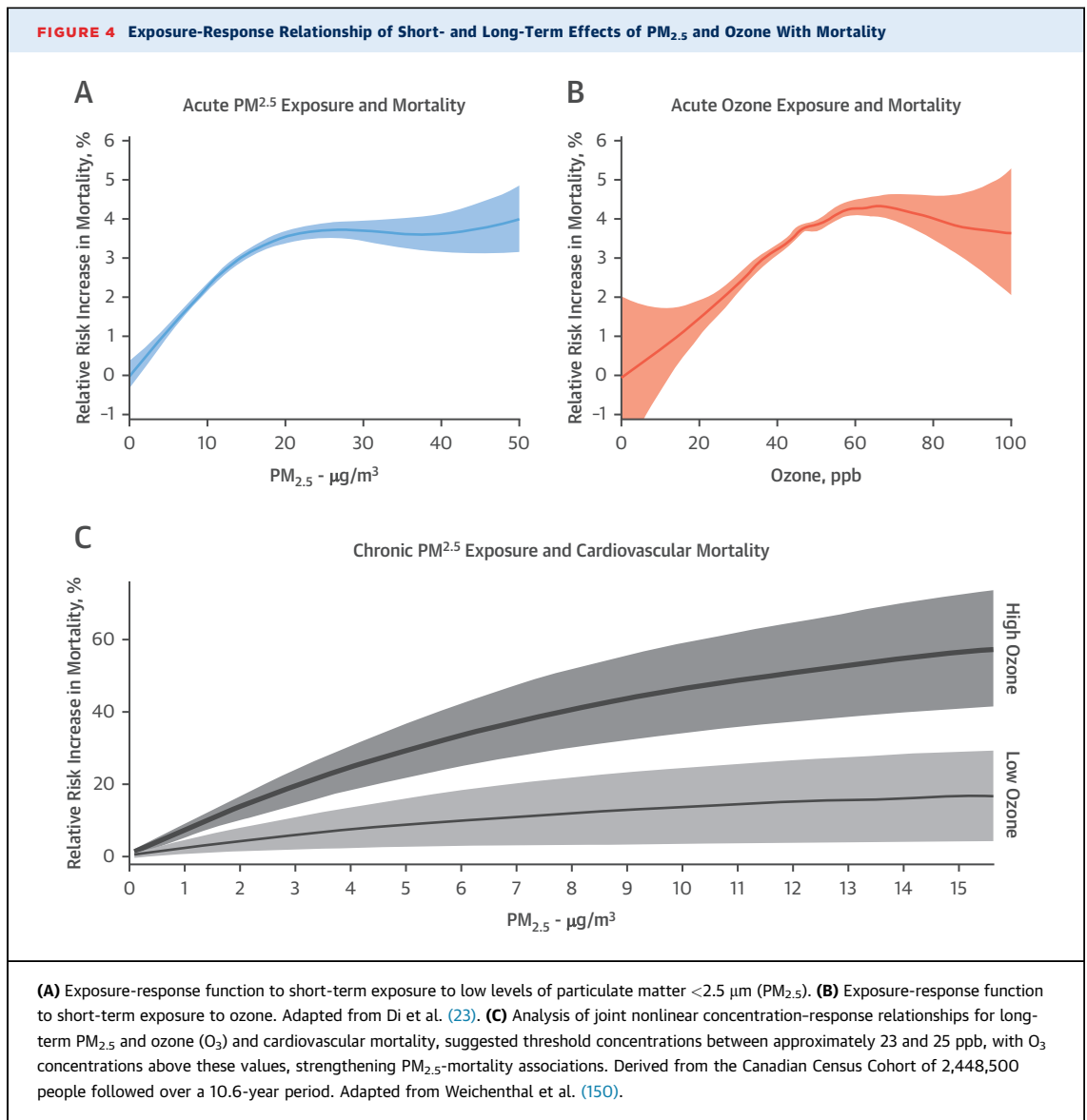
FIGURE 3   PM Concentration and Mortality

(A) Size and various types of air pollutants. Ultrafine particles (UFP) smaller than 100 nm are generally short-lived species (airborne for hours) directly derived from fresh combustion sources (traffic, diesel exhaust particles, among others). Fine particles <2.5 μm in diameter ($PM_{2.5}$) are larger, yet still many times smaller than the diameter of a human hair. $PM_{2.5}$ is a heterogenous amalgam of numerous compounds formed from combustion (metals, carbon species) or secondarily involving reactions in the atmosphere (nitrates, sulfates). $PM_{2.5}$ may be longer-lived (airborne for days) and transported hundreds of miles. (B) Global $PM_{2.5}$ levels depicted as a heat map with individual annual population-weighted average for select countries on the color gradient bar. PM concentration is measured in μg/m³, with World Health Organization (WHO) air quality guidelines (AQG) set at <10 μg/m³ for an annual average concentration. These are the lowest levels at above which total, cardiopulmonary, and lung cancer mortality have been shown to increase with >95% confidence, in response to long-term exposure to $PM_{2.5}$. (C) Exposure-response curve for relative risk of cardiovascular disease associated with long-term exposure to $PM_{2.5}$. The WHO interim targets (ITs) are also highlighted. The ITs are successive targets of 35, 25, and 15 μg/m³, which were set up with the goal of reducing mortality. Exceeding IT-1 levels is associated with increasing mortality by 15%. IT-2 and IT-3 reduce mortality by 6% at or below each level. For typical days in U.S. cities, the levels range within 24-h standards (5 to 35 μg/m³). In India, peak daily levels exceeding 250 μg/m³ are common. The exposure response curve is adapted from Burnett et al. (17).

FIGURE 4   Exposure-Response Relationship of Short- and Long-Term Effects of PM$_{2.5}$ and Ozone With Mortality

(A) Exposure-response function to short-term exposure to low levels of particulate matter <2.5 μm (PM$_{2.5}$). **(B)** Exposure-response function to short-term exposure to ozone. Adapted from Di et al. (23). **(C)** Analysis of joint nonlinear concentration–response relationships for long-term PM$_{2.5}$ and ozone (O$_3$) and cardiovascular mortality, suggested threshold concentrations between approximately 23 and 25 ppb, with O$_3$ concentrations above these values, strengthening PM$_{2.5}$-mortality associations. Derived from the Canadian Census Cohort of 2,448,500 people followed over a 10.6-year period. Adapted from Weichenthal et al. (150).

countries such as China and India (1,6,7,15,25-27). The most recent GBD calculations estimate that exposure to ambient PM$_{2.5}$ caused 4.2 million (95% uncertainty interval [UI]: 3.7 million to 4.8 million) deaths and 103.1 million (95% UI: 90.8 million to 115.1 million) disability-adjusted life-years (DALYs) in 2015, representing 7.6% of total global deaths and 4.2% of global DALYs (1). HAP from solid fuel use was responsible for 2.8 million (95% UI: 2.2 million to 3.6 million) deaths and 85.6 million (95% UI: 66.7 million to 106.1 million) DALYs in 2015, with >50% of the health burden due to CV diseases (1,3). Exposure to ozone caused an additional 254,000 (95% UI: 97,000 to 422,000) deaths and a loss of 4.1 million (1.6 million

to 6.8 million) DALYs from chronic obstructive pulmonary disease in 2015 (1).

In a recent analysis, short-term increases in PM$_{2.5}$ and ozone in the Medicare population (61 million U.S. citizens) were associated with a relative risk of 1.0105 (95% confidence interval [CI]: 1.0095 to 1.0115) and 1.005 (95% CI: 1.0041 to 1.0061), respectively, in daily mortality rates (23). In the same population, longer-term increases in exposure by 10 μg/m^3 of PM$_{2.5}$ during the previous year (annual average PM$_{2.5}$ of 6 to 15.6 μg/m^3), and of 10 parts per billion (ppb) ozone were associated with a 7.3% (95% CI: 7.1% to 7.5%) and 1.1% (95% CI: 1.0% to 1.2%) relative increase in all-cause mortality, respectively. Although

cause-specific mortality data were not provided, a wealth of evidence supports that more than one-half of deaths attributable to air pollutants are due to CV causes. Importantly, although this analysis did not allow the interaction of factors such as income and smoking on the association to be tested, a separate analysis of the Medicare Current Beneficiary sample, did not find an interaction (22). When restricting the analysis to daily $PM_{2.5}$ levels below 25 μg/m³, the association between short-term $PM_{2.5}$ exposure and mortality remained significant and, in fact, was elevated. These results are consistent with studies from Europe and Canada that report an almost linear relationship between $PM_{2.5}$ and mortality to levels as low as 2 μg/m³ $PM_{2.5}$ (19,28,29).

## REVIEW OF THE CARDIOMETABOLIC EFFECTS OF AIR POLLUTION

CV MORTALITY. In 34 studies, short-term $PM_{2.5}$ exposure increased the relative risk for acute myocardial infarction (MI) by 2.5% per 10 μg/m³ (relative risk: 1.025; 95% CI: 1.015 to 1.036) (30). Although these relative risks are modest, short-term exposures to $PM_{2.5}$ account for up to 5% (population attributable fraction) of MI worldwide because hundreds of millions of people are continuously affected (31). Given the fact that air pollution exposure occurs over a lifetime, the repetitive, near-continuous exposure to air pollution has been hypothesized to promote atherosclerosis and recurrent events (32). Indeed, longer-term exposures over several years appear to pose amplified risks (6,7,32-34). In 2 Canadian national studies, ischemic heart disease deaths significantly increased, despite average $PM_{2.5}$ being <9 μg/m³ (19,21). Similar findings have been reported in the United States in the National Institutes of Health–AARP cohort (N = 517,043), in which long-term exposure increased CV mortality by a relative 10% (per 10 μg/m³), despite low $PM_{2.5}$ levels (10 to 13 μg/m³) (35). There are now many studies in China at high levels of $PM_{2.5}$ demonstrating an increase in acute CV mortality (36,37). In a meta-analysis of 59 studies, each 10 μg/m³ increment in $PM_{2.5}$ was associated with an absolute 0.63% increase in CV mortality, even though $PM_{2.5}$ ranged from 39 to 177 μg/m³ (36). There have been a few long-term cohort studies at high levels of $PM_{2.5}$, demonstrating a heightened impact of long-term exposure (38). However, an important recent study in China confirmed that the increased risk for morbidity and mortality persists, even at very high air pollution exposure (average $PM_{2.5}$ levels of 43.7 μg/m³) (39). The relative risk for CV mortality increased by

9%/10 μg/m³ elevation, which exceeds the integrated exposure-response curve function. This suggests that further cohort studies are required to better elucidate the shape of the full dose-response curve to fatal and nonfatal CV events at high levels of exposure, in light of the impact this may have on global public health burden.

MYOCARDIAL INFARCTION. Time-series and case-crossover studies across the globe have explored the association between short-term changes in air pollution and daily changes in MI. A systematic review and meta-analysis of studies of short-term air pollution exposures and MI showed that $PM_{2.5}$, along with nitrogen dioxide (NO_2), and sulfur dioxide and carbon monoxide were associated with increased risk of MI (30). The ESCAPE study (European Study of Cohorts for Air Pollution Effects) (N = 100,166 from multiple cohorts) showed a significant 13% relative increase in nonfatal acute coronary events, with a 5 μg/m³ elevation in long-term exposure to $PM_{2.5}$ (40). Patients with underlying coronary artery disease may be at particularly high risk. The best recent evidence for acute coronary syndrome (ACS) risk with $PM_{2.5}$ comes from Utah (Intermountain Health Care, N = 16,314), where concurrent-day $PM_{2.5}$ was associated with an increase in ACS (41). Excess risk was observed only among individuals with angiographic coronary artery disease, leading to an increase in ST-segment elevation MI. Long-term survival following ACS is also reduced by long-term $PM_{2.5}$ exposure (42,43). Online Table 1 summarizes large studies on the association between air pollution and nonfatal MI.

CEREBROVASCULAR DISEASE. In a systematic review and meta-analysis of 94 studies until 2014, involving 28 countries, a 10 μg/m³ increase in $PM_{2.5}$ and PM_{10} concentration was associated with a 1% increase in relative risk for admission to the hospital with stroke and stroke mortality (44). Living close to the roadway and poverty appear to be positively associated with ischemic stroke and stroke severity (45,46). In an analysis of the ESCAPE cohort, there was an association between $PM_{2.5}$ and stroke among subjects ≥60 years of age (hazard ratio [HR]: 1.40; 95% CI: 1.05 to 1.87 per 5 μg/m³ increase in $PM_{2.5}$), never-smokers (HR: 1.74; 95% CI: 1.06 to 2.88 per 5 μg/m3 increase in $PM_{2.5}$), and among participants with $PM_{2.5}$ exposure <25 μg/m³ (HR: 1.33; 95% CI: 1.01 to 1.77 per 5 μg/m³ increase in $PM_{2.5}$), although the association did not reach statistical significance in the main analysis (10). Higher risk was especially seen in subjects above 60 years of age and in non-smokers, and was consistently observed at $PM_{2.5}$ concentrations <25 μg/m³. In the United States,

CENTRAL ILLUSTRATION Biological Pathways Whereby PM$_{2.5}$ Promotes Cardiovascular Events

Rajagopalan, S. et al. J Am Coll Cardiol. 2018;72(17):2054–70.
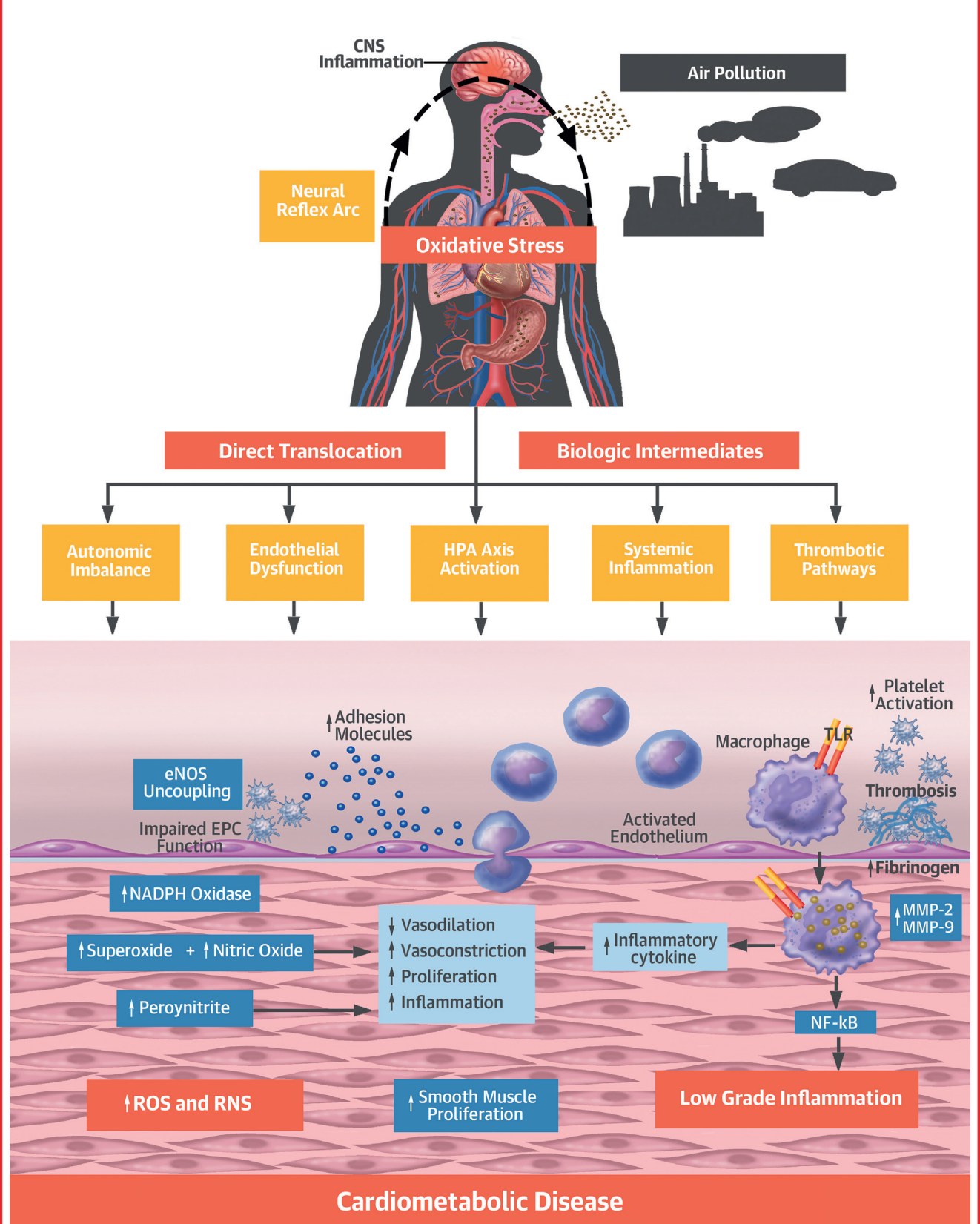
the Women's Health Initiative study reported some of the largest estimates of stroke and death from cerebrovascular disease due to $PM_{2.5}$, with relative increases in long-term $PM_{2.5}$ exposure of 35% and 83%/10 $\mu g/m^3$, respectively [33].

HEART FAILURE. In a systematic review and meta-analysis of 35 studies, a short-term increase in gaseous components and PM (both PM_{10} and $PM_{2.5}$) was associated with increased risk for heart failure hospitalization or death [47]. An increase of 10 $\mu g/m^3$ in $PM_{2.5}$ increased the relative risk of hospitalization or heart failure mortality by 2.1% (relative risk: 1.021; 95% CI: 1.014 to 1.028). In a recent study from China in 26 cities with high $PM_{2.5}$ concentrations, an interquartile increase in $PM_{2.5}$ was associated with a relative 1.3% increase in heart failure hospitalizations [48].

AIR POLLUTION–MEDIATED CARDIOMETABOLIC RISK. A large body of evidence now implicates air pollution in the development of cardiometabolic risk factors such as hypertension and insulin resistance.

Hypertension. The association between air pollution and hypertension has been previously reviewed extensively and has been the subject of at least 4 recent meta-analyses [49-52]. Increases in ambient $PM_{2.5}$ by 10 $\mu g/m^3$ are consistently associated with 1 to 3 mm Hg elevations in systolic and diastolic blood pressure over the ensuing few days. Longer-term exposures have been linked chronic elevations in blood pressure and with an increased prevalence or incidence of hypertension in many studies as well. In carefully performed, controlled studies in humans, where a variety of vascular alterations in response to air pollution have been evaluated, changes in blood pressure are routinely observed [6,7,53-61]. Online Table 2 compiles all randomized controlled studies that have demonstrated an elevation of blood pressures and/or alterations in vascular indexes in response to short-term exposure. Robust associations have been noted at extreme levels of the exposure response relationship in a Chinese megacity [62].

Importantly, personal strategies to lower air pollution demonstrate rapid effects in reducing blood pressure, further confirming the direct impact of inhalation of air particles on blood pressure (Online Table 2) [6,63]. This body of evidence strongly supports inclusion of higher blood pressure levels and hypertension-related morbidity in air pollution global burden estimates.

Insulin resistance/diabetes. The association between insulin resistance and type 2 diabetes has been reviewed in prior expert reviews [6,7,64,65]. In a meta-analysis of cohort studies involving a total of 2,371,907 participants and 21,095 incident cases of type 2 diabetes mellitus, the relative risk for diabetes increased by 39% per 10 $\mu g/m^3$ of $PM_{2.5}$ [66]. In a recent meta-analysis (13 studies), $PM_{2.5}$ and NO_2 increased the risk of diabetes (HR: 1.10; 95% CI: 1.02 to 1.18 and HR: 1.08; 95% CI: 1.00 to 1.17 per 10 $\mu g/m^3$ increase in $PM_{2.5}$ and NO_2, respectively) [67]. Online Table 3 summarizes studies on the association between air pollution and insulin resistance and diabetes.

Cardiac arrhythmias. Acute air pollution exposure has been shown to trigger atrial fibrillation. In a 2016 meta-analysis of 4 observational studies involving 461,441 participants, each 10-$\mu g/m^3$ of $PM_{2.5}$ was associated with a 0.89% (95% CI: 0.20% to 1.57%) increase in the population-attributable risk of atrial fibrillation [68]. The risk for ventricular arrhythmias with air pollution exposure also has been previously demonstrated, although the evidence is limited [5].

Venous thromboembolism. The relationship between exposure to ambient air pollution and venous thromboembolism is uncertain. Some studies have demonstrated an association, whereas others have not [69,70].

Other noncommunicable diseases. Other chronic illnesses related to the cardiometabolic syndrome, including chronic kidney disease [71], obesity [72], sleep-related breathing disorders [73], and neurological diseases (e.g., dementia, depression) [73], have been linked to air pollution but require more investigation.

CENTRAL ILLUSTRATION Continued

Inhaled $PM_{2.5}$ deposit deep within pulmonary tissues (i.e., alveoli), interact/activate local cells (e.g., resident macrophages, dendritic cells, alveolar/endothelial cells) and modify endogenous structures (e.g., cell membranes, surfactant lipids, antioxidants). Mediators of oxidative stress (e.g., free radicals) directly generated by particulate compounds (metals, organic species) or produced in response to biological intermediates (e.g., modified phospholipids) by activated cellular enzyme systems can instigate a local inflammatory response. The **orange rectangles** identify primary initiating pathways, whereas the **yellow rectangles** identify secondary effector pathways. The precise delineation between primary and secondary is somewhat artificial, because there may be considerable overlap. CNS = central nervous system; eNOS = endothelial nitric oxide synthase; EPC = endothelial progenitor cells; HPA = hypothalamic-pituitary axis; MMP = matrix metalloproteinase; NADPH = nicotinamide adenine dinucleotide phosphate; NF-kB = nuclear factor kappa; RNS = reactive nitrogen species; ROS = reactive oxygen species; TLR = Toll-like receptor.

CLINICAL INTERPRETATION OF EPIDEMIOLOGICAL FINDINGS OF HEIGHTENED CV RISK AND RELATIONSHIP TO INTERMEDIATE CV ENDPOINTS

A number of observations over the years support the concept of the "vulnerable plaque" and the "vulnerable patient," where stochastic (and often partially defined) variables of risk collude in determining the susceptibility to CV. $PM_{2.5}$ operates in the context of underlying susceptibility, and vulnerability is essential to the mediation of adverse CV endpoints. Indeed, it is often argued that the "harvesting" phenomenon is the likely major mechanism of PM-associated mortality, where the fatalities are observed only in frail individuals for whom life expectancy is short, even in the absence of pollution. Although this may certainly be true for some patients, it may not be true for all (74). The largest proportion of the CV risk attributable to $PM_{2.5}$ observed in the cohort studies occurs with exposures of short- and intermediate-term durations (hours to several months), with progressively smaller relative increases in CV effects (i.e., in a less than additive fashion) seen when one prolongs the follow-up period beyond 1 to 2 years. This temporal gradient would imply that the transduction of $PM_{2.5}$ into events occurs principally in the short or intermediate term, arguing for a harvesting phenomenon. The data from epidemiological studies also suggest that longer-term exposures are associated with larger CV health risks than short-term studies (4,32). Cumulative exposure over long periods ("exposure over time") may promote the development of a chronic underlying "vulnerable" state, which may exponentially augment future CV risk in the short term, consistent with any risk factor, such as low-density lipoprotein cholesterol or glycemic burden. Given the fact that short-term exposure occurs almost exclusively in the milieu of long-term persistent exposure over decades, this argument likely is the context in which air pollution studies have to be considered. From a statistical standpoint, exposure concentrations in the 1 to 2 years before an event are highly correlated with exposures over many years, and their uniform rank ordering of exposure severity over time is enough to help explain why only a short period of PM exposure assessment is required to understand the risk of longer-term exposures (32).

Air pollution has been linked to biomarkers of atherosclerosis, including carotid intima-media thickness, carotid plaques, and coronary artery calcium. The MESA (Multiethnic Study of Atherosclerosis)-Air cohort (N = 6,795 across 6 U.S. regions) showed that a 5 μg/m³ increase in long-term $PM_{2.5}$ was associated with progression of coronary artery calcium (4.1 Agatston units/year). A recent meta-analysis of 8 cross-sectional (N = 18,349) and 3 prospective (N = 7,268) studies showed significant associations with greater intima-media thickness (75). Air pollution has also been shown to be associated with increased arterial stiffness, impaired conduit artery flow-mediated dilation, resistance arteriolar dysfunction, and retinal artery changes (5-7). Online Table 4 details the controlled trials that have demonstrated changes in vascular surrogates.

MECHANISMS OF AIR POLLUTION–MEDIATED CARDIOMETABOLIC DISEASE

The knowledge of mechanisms underlying air pollution-mediated systemic CV risk is still evolving but can be encapsulated into 6 broad secondary "effector" pathways: 1) endothelial barrier dysfunction/disruption; 2) inflammation, involving both innate and adaptive immune components; 3) prothrombotic pathways; 4) autonomic imbalance favoring sympathetic tone via afferent pathways the upper airways and/or lung; 5) central nervous system effects on metabolism and hypothalamic-pituitary-adrenal axis activation; and 6) epigenomic changes. Many of these pathways are interdependent, can cross-react (e.g., "feed-forward" and amplify each other) with considerable overlap, and underlying susceptibility and other baseline risk factors may be required to unmask disease. It is also important to (somewhat artificially) separate the mechanisms based upon time courses of exposure and the resultant temporal importance of biological responses. Some pathways have more relevance to short-term exposures (e.g., autonomic imbalance, heightened thrombosis potential) and likely factor mostly in a triggering role. Others likely play a more long-term role. A fundamental question is what are the primary initiating pathways of secondary effects? Among the 3 primary initiating pathways are oxidative stress, direct translocation, or effects of particles and secondary mediators formed in response to air pollution effects that may then mediate systemic effects. Of note, neural reflexes triggered by the sensing of inhaled particles in the lungs by various receptors (perhaps without a prerequisite for the generation of oxidative stress) may also be considered a primary effector pathway but, for purposes of clarity, will be considered separately.

PRIMARY INITIATING PATHWAYS. Role of oxidative stress in PM-mediated effects. Oxidative stress, which could occur in the lung and/or systemically across various vascular beds, including the blood-brain

barrier, may initiate many of the secondary processes (76-79). The traditional graded response paradigm (80) has now been replaced by a more nuanced model, where reactive oxygen species (ROS) and reactive nitrogen species act in a complex manner as both site-specific mediators of cell signaling and as central regulators of inflammation (81-83). Oxidative stress to air pollution is the first hierarchical response in humans, followed by a more delayed response in other CV variables when specifically examined, suggesting that oxidative stress may be an early step (84). Membrane-associated receptors have been noted to be involved in sensing particles, and particle components and transducing effects, including activation of inflammatory cascades (85,86). Multiple families, including Toll-like receptors (TLR2/TLR4) and the nucleotide-binding domain leucine-rich repeats of Nod-like receptors, may be involved and may be activated directly or indirectly through secondary mediators including ROS themselves (87-89). Transient receptor potential (TRP) channels have also been implicated and may be activated by oxidative stress related to combustion particles or soluble organics (TRPA1 and TRPV1). Depletion of low molecular weight antioxidants may result in potentiation of oxidative stress, as may genetic predisposition exemplified by polymorphisms in antioxidant genes (78). An increase of ozone from typical background concentration levels ($\sim$30 ppb) to summer smog conditions ($\approx$100 ppb) may reduce the chemical half-life from days to hours for antioxidants and from hours to minutes for surfactants (90). Thus, ozone plus high $PM_{2.5}$ and high ozone concentrations are expected to amplify the effects of $PM_{2.5}$. With long-term exposure, progressive accumulation of particles in macrophages via phagocytosis may eventually lead to activation of proinflammatory pathways, so-called frustrated phagocytosis (91). Recently, 2 studies provided evidence that up-regulation of the pulmonary antioxidant barrier using overexpression of extracellular superoxide dismutase may diminish adverse systemic vascular effects of air pollution, suggesting that pulmonary oxidative stress may be critical in modulation of systemic responses (92,93).

Direct translocation. In some instances, leachable components or other small ultrafine particles may directly penetrate into the systemic circulation, resulting in direct effects in remote deposition sites (78,94). In a landmark study in mice and humans with inert gold particles, facile translocation into the systemic circulation was demonstrated (94). In mice, ultrafine particles have been shown in prior studies

to directly penetrate the blood-brain barrier and may also be transported through axonal transport or through generation of secondary mediators and regulate efferent pathways controlling inflammation, metabolism, and blood pressure (**Central Illustration**) (95).

Biological intermediates as transducers of systemic effects. Formation of biological intermediates in response to exposure also deserves special attention (78,86,96-101). Long-term ongoing exposure to air pollution may attenuate surfactant defenses (102) and increase oxidatively modified derivatives of phospholipids in surfactant fluid, such as 1-palmitoyl-2-arachidonyl-sn-glycero-3-phosphorylcholine (PAPC) and other oxidized by products that may participate in endothelial barrier dysfunction and inflammatory cell recruitment (**Central Illustration**), allowing facile translocation of these and other signals to the systemic circulation (86). These mediators may enhance oxidative stress in the vasculature via activation of TLR4 pathways (86). Deficiency of TLR4, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 2 (NOX2), and neutrophil cytosolic factor 1 (p47^{phox}) have all been shown to attenuate ROS generation, reduce inflammatory monocyte infiltration into the vasculature, and improve vascular function in response to inhalational exposure to concentrated $PM_{2.5}$ (86,103). The formation of oxidized derivatives such as 7-ketocholesterol in response to long-term $PM_{2.5}$ exposure, its translocation within low-density lipoproteins, and subsequent uptake by CD36, may represent another unique pathway for air pollution-mediated endothelial dysfunction and potentiation of atherosclerosis (98,104). Exposure to ultrafine particles, such as from diesel, may result in 5-lipoxygenase-mediated formation of 12-hydroxyeicosatetraenoic acid (12-HETE) and 13-hydroxyoctadecadienoic acid (13-HODE), peroxidation products in the plasma, liver, and small intestine, potentiating oxidative stress and inflammation in these locations (105,106).

SECONDARY EFFECTOR PATHWAYS. Systemic vascular dysfunction and CV remodeling with air pollution. The preponderance of evidence supports rapid and persistent effects of particulate air pollutants on vascular function in both animals and humans (4,6,7). In animal studies, short-term, medium-term, and long-term exposure to air pollution alone and/or in conjunction with agents such as angiotensin II results in increased superoxide (O_2^-) and potentiation of vasoconstrictor responses, whereas reduction of ROS sources ameliorates endothelial function, nitric acid availability, endothelial cell activation (adhesion

molecule expression), and inflammation. Superoxide production due to NADPH oxidases and uncoupled nitric oxide synthase may be an important mechanism inducing adverse vascular effects (107,108). Increased microvascular adhesion of inflammatory monocytes has been noted with concentrated PM$_{2.5}$ exposure, together with perivascular deposition of mononuclear cells, with deficiency of Nox2 and Tlr4 improving vascular responsiveness and inflammation (86,109). Although there are limited comparative studies of ultrafine particles relative to PM$_{2.5}$, these generally show equal or, in some cases, larger effects, with at least 1 study showing that exposure of apolipoprotein E knockout (*ApoE*$^{-/-}$) mice to ultrafine particles resulted in greater atherosclerosis (110). The mechanism may relate to enhanced systemic penetration, greater ROS, and inflammation, with additional pathways that include greater inhibition of the anti-inflammatory capacity of high-density lipoproteins and greater systemic oxidative stress, as evidenced by increased hepatic malondialdehyde and lipid peroxidation products in the plasma and liver.

Several controlled exposure studies in humans demonstrate that short-term exposure to PM$_{2.5}$ and dilute diesel exhaust results in conduit or microvascular dysfunction to agonists, inferred by reduced endothelium-dependent or smooth muscle dilation or transient constriction of a peripheral conduit vessel that is reversible (Online Table 2). Studies of ultrafine particles, including inhalation of elemental carbon as well as diluted diesel exhaust, have shown that they induce rapid endothelial dysfunction in the microcirculation (111,112). Exercise-induced ST-segment depression and ischemic burden were also noted to be significantly greater during diesel exhaust exposure compared with filtered air exposure (113). Although ozone exposures have been shown to impair endothelial function in animal studies, the data in humans are limited and may relate to the high concentrations used in animal studies (0.5 to 1 ppm against the current U.S. National Ambient Air Quality Standard of 0.075 ppm). Depletion of endothelial progenitor cells or circulating angiogenic cells may also represent an important mechanism of sustained endothelial dysfunction and has been demonstrated in human panel studies, as well as in the response to exposure with concentrated PM$_{2.5}$, although the results are not always consistent (93,114-116). Prevention of lung oxidative stress, through overexpression of extracellular superoxide dismutase in the lung, appears to improve endothelial progenitor function. Endothelial dysfunction and up-regulation of vasoconstrictor pathways may result in sustained hypertension, increased cardiac afterload, diastolic dysfunction, alteration in coronary flow reserve, and eventually, left ventricular hypertrophy and myocardial fibrosis (117). At a molecular level, increased beta-myosin heavy chain and downregulation of the sarco/endoplasmic reticulum calcium-ATPase SERCA2a, indicative of abnormal calcium cycling, have been demonstrated (117).

AUTONOMIC DYSFUNCTION AND ACTIVATION OF CENTRAL NERVOUS SYSTEM PATHWAYS. Autonomic nervous system changes have been observed in humans, manifesting as rapid alterations in sympathovagal balance, typically evidenced by changes in blood pressure and heart rate variability in response to both coarse and fine particle exposures (Online Table 2). It is now clear that nasal, bronchial, and pulmonary C-nerve fiber subtypes play a role in the response to air pollution components through the activation of a number of receptors such as transient receptor potential ankyrin 1 (TRPA1), transient receptor potential vanilloid 1 (TRPV1), and purinergic P2X channels (118-122). These receptors may act like innate environmental sensors and initiate sensory nerve excitation as part of an afferent loop (123). Indeed, in controlled exposure studies in humans, changes in blood pressure occur in conjunction with alterations in heart rate variability, suggesting a sympathetic predominance at both ends of the air pollution spectrum (Online Table 2). Short-term experiments in canine models and studies in mice cannulated long term that are exposed to concentrated air particles have confirmed development of hypertension, with evidence of central sympathetic nervous system activation in response to PM$_{2.5}$ exposure, likely mediated by neuroinflammation (124,125). Ultrafine particulates, nanomaterials, and ozone may either directly disrupt the blood-brain barrier or result in circulating factors that may influence neuronal function in humans and mice (95,101,126,127).

Systemic inflammatory response. Multiple early studies in animals and humans have demonstrated a short-term bone marrow response to air pollution exposure (4). Recent experimental studies have clarified the nature of this response by demonstrating that long-term exposure to concentrated ambient PM$_{2.5}$ promotes an efflux of Ly6^{hi+} monocytes (CD11b$^+$Gr-1^{low}7/4^{hi} cells) from the bone marrow and promotes their eventual migration to adipose tissue, vasculature, and other inflamed tissue (6). TLR4 and NADPH oxidase appear to mediate the effect of PM$_{2.5}$, because deficiency of TLR4 diminished the effect of PM$_{2.5}$ in increasing peripheral Ly6C^{high} cells (F4/80$^+$, CD11b$^+$, CD115$^+$) cells and abolished tissue infiltration

and ROS generation in systemic tissues, suggesting involvement of these pathways in mediating exposure effects (86). C-C chemokine receptor type 2 (CCR2) is critically involved in the mobilization of these cells and may play a role in adipose inflammation in insulin resistance/type 2 diabetes. $CCR2^{-/-}$ mice demonstrated reduction in whole-body insulin resistance and improvements in hepatic lipid accumulation in the liver via sterol regulatory element-binding protein-1c (SREBP1c)-mediated transcriptional reprogramming (128). Chemokine (C-X-C motif) receptor 3 knockout (CXCR3) may also be involved in transduction of $PM_{2.5}$ effects and play a role in migration of activated T-cell populations $(CD44^{+}CD62L^{-}\ CD4^{+})$ (86). Unequivocal links between exposure and inflammation have been less consistently observed in controlled short-term human exposure studies, possibly due to differences in study protocols, individual vulnerability, or unmeasured prior exposures (4).

Prothrombotic pathways. Studies in a hamster model of arterial thrombosis have demonstrated rapid activation of platelets with intratracheal exposure (129). In human studies, inhalation of diluted diesel exhaust particulate matter increased thrombotic response, as assessed by ex vivo flow chamber perfusion studies, and increased platelet-leukocyte aggregates with exposure (130). Rapid platelet sensitization could occur due to direct contact in the lung or translocation of ultrafine PM. Activation of platelets as well as alteration of the plasminogen activator inhibitor/tissue plasminogen activator balance in patients with other risk factors may heighten their susceptibility to CV events (113,131).

Hypothalamic and pituitary-adrenal axis activation. Recent data appear to suggest metabolic reprogramming through hypothalamic pathways that involve brown adipose dysfunction, white adipose inflammation, and insulin resistance (6,64,65). Studies in humans appear to suggest short-term metabolic effects consistent with insulin resistance (6,59,64,65,132,133). Intracerebroventricular delivery of an inhibitor of nuclear factor kappa-B kinase subunit beta (IKKβ) prevented adverse effects of air pollution on peripheral inflammation, insulin resistance, and whole-body metabolism (125,134). $PM_{2.5}$ exposure increased the level of oxidatively modified lipids (PAPC) that may activate TLR/nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) pathways in the brain (134). Adrenal axis activation, manifested as elevation in glucocorticoids, may also represent an important pathway by which air pollution may modulate CV risk (135).

Epigenomic changes. Extensive human and animal model data indicate that environmental influences during critical periods of prenatal and postnatal development influence developmental trajectories and chronic disease susceptibility. A common finding in environmental epigenetic studies is the small magnitude of epigenetic changes that are associated with exposure (136). However, even small changes in methylation can have a strong effect on transcriptional activity. Although limited panel studies have noted global methylation status, other epigenetic marks, including chromatin modifications, microRNAs, and noncoding RNAs warrant further consideration as the technological and economic hurdles of assessing these marks in large numbers decrease (137).

SUBSETS VULNERABLE TO AIR POLLUTION EFFECTS

The Clean Air Act requires the Environmental Protection Agency to identify "sensitive" populations that are overtly vulnerable to air pollution effects and estimate effect sizes to inform regulatory policy. Deaths due to all forms of pollution, particularly HAP, show a peak among children younger than 5 years of age, but most pollution-related deaths in high-income countries occur among adults older than 60 years of age (3,138). By contrast, DALYs resulting from pollution-related disease are highly concentrated among infants and young children, reflecting the many years of life lost with each death and case of disabling disease in a child (1). In countries at every level of income, the health effects of pollution were most frequent and severe among the poor and the marginalized (3,138). Blacks and other socioeconomically disadvantaged groups may experience a higher risk (22,139). Elderly individuals are consistently at greater risk, with some studies suggesting the same for coronary disease patients, women, those at lower socioeconomic status, and patients with hypertension or diabetes (5,140–142).

STRATEGIES TO MITIGATE CV EFFECTS OF AIR POLLUTION

A recent viewpoint paper outlined several approaches for mitigation of the CV effects of air pollution, with a focus on how health care providers can help play a vital role in long-term solutions (143). These investigators provide a rational clinical approach on how to help tackle the problem of air pollution at the level of the individual patient. The Lancet Commission report stresses leadership, resources, and a clear roadmap as key components of successful

FIGURE 5 Personal- and Local-Level Interventions to Reduce Exposures or Susceptibility to Air Pollution

SOCIETAL AND GOVERNMENTAL INTERVENTIONS		
Shifting to Clean Fuels	• Switch coal-fired power plants to low-polluting renewable energy sources such as wind, tidal, geothermal, and solar.
Transportation Reform	• Promote use of low-emission and zero-emission vehicles, Reduce sulfur content of motor fuels, Restrict trucks from city centers, encourage active transport (walking and cycling)
Reduce Traffic Emission(s)	• Diesel particle traps, catalytic converters, alternative fuels (natural gas, electric cars)
Urban landscape reform	• Land use assessment, minimum distances between sources and people, relocation of traffic sources (including major trafficked roads), avoidance of mixed-use areas (industrial-residential)
Emission Trading Programs	• Revenues raised through taxes can be directed to pollution control. Emissions trading programs compensate companies who adhere to controls through credits that can be traded akin to carbon credits
Redirection of science and funding	• Modifying priorities of climate change mitigation investments to a focus on near-term health co-benefits. Focus on the imminent near term danger of health effects of air pollution.
Empowering civil society	• Publicity and awareness campaigns through local data on air pollution within cities, counties
Governmental and NGO-led publicity	• Hard-hitting media campaigns akin to smoking on media to mitigate lobbying by industries involved in power and automobiles

PERSONAL INTERVENTIONS		
Face masks and Air purifiers	• Wearing face masks and installing air purifiers in homes
Reduce in-traffic exposures	• Avoid commutes during rush hour
Reduce in-home penetration of outdoor air pollution	• Indoor air purifiers and closing windows; Air conditioners
Lifestyle changes and Preventive Medicine	• Exercise and healthy diet • Preventive medications and screening programs

programs (1). Furthermore, legal enforcement, backed by technology, targets, and timetables, is important and, paradoxically, may be most wanting in countries where air pollution control is most needed (**Figure 5**). As we have previously reviewed, several interventions have been shown to be at least partially effective in reducing $PM_{2.5}$ exposures and in improving some biomarkers of cardiometabolic health (Online Table 5) (6,7,144). One promising and relatively inexpensive method is the use of portable indoor air purifiers. Portable air filters can lower indoor $PM_{2.5}$ levels by >50% and are proven to improve a growing list of surrogate endpoints, including blood pressure, insulin sensitivity, inflammatory markers, stress hormones, and metabolomic profiles (Online Table 5).

At present, all personal protection strategies have the limitation that no trial has yet demonstrated that they reduce clinical CV events. We have made several calls to the global health care and scientific community to suggest that the time has come to formally test the benefits of these approaches in large-scale outcome trials (15,144). There is some evidence that therapeutic interventions such as statins and dietary components may reduce the impact of air pollution on surrogate measures (145). Exercise may attenuate the adverse impact of air pollution. However, there may be a limit where excessive inhalation of pollutants during exercise may overshadow any protective benefit (Online Figure 1) (146). In a recent randomized crossover study, responses in patients with chronic obstructive pulmonary disease or ischemic heart disease who walked in a crowded street in London were compared with those who took a similar walk in Hyde Park. Walking in Hyde Park led to an increase in lung function and decreases in pulse wave velocity

and augmentation index, whereas the converse was observed while walking in a crowded street (147).

CHALLENGES AND OUTLOOK FOR THE FUTURE

GLOBAL WARMING AND POLLUTION. Aggressive policies directed toward carbon dioxide reduction, although necessary for the long term, are by themselves insufficient to reduce the rate of warming in the next few decades because of the long atmospheric lifetime of this gas. The choice of policies with positive health and ecosystem effects may provide the greatest opportunity for substantial and immediate cobenefits, rather than a policy focused on carbon dioxide (1,148). The increasing risk from natural events worsened by global warming, such as forest fires, volcanic eruptions, and dust storms, has also created an urgent need to understand the health impact and importantly the exposure-response relationship of particle constituents originating from natural events, with the intent of preventing natural-event related diseases (27).

AIR POLLUTION EXPOSURE, RISK ASSESSMENT, AND PERSONALIZED MEDICINE. The convergence of epidemiology and personal medicine/health is

occurring rapidly (53), but how air pollution exposure assessment (and environmental exposures more generally) will fit into this equation has not been adequately explored. Most precision medicine/health initiatives do not include environmental components beyond common biomarkers (e.g., lead), but inclusion of low-cost air pollution sensors may help facilitate sophisticated integrated assessments. The personalization of pollution risk and assessment of susceptibility are in their infancy but have great potential to identify patients at risk and characteristics that define resistance to air pollution exposure.

Recent challenges to regulation of air pollution through promotion of fossil fuels and abandonment of measures to curb greenhouse gas emissions and move away from science-based decision making is not only alarming, but regressive (149). Air pollution and CV health deserves renewed attention and focus to eliminate this archaic risk factor.

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APPENDIX For supplemental tables and a figure, please see the online version of this paper.