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Cardiovascular Effects of Particulate Air Pollution

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Abstract

Inhalation of fine particulate matter ($PM_{2.5}$), produced by the combustion of fossil fuels, is an important risk factor for cardiovascular disease. Exposure to $PM_{2.5}$ has been linked to increases in blood pressure, thrombosis, and insulin resistance. It also induces vascular injury and accelerates atherogenesis. Results from animal models corroborate epidemiological evidence and suggest that the cardiovascular effects of $PM_{2.5}$ may be attributable, in part, to oxidative stress, inflammation, and the activation of the autonomic nervous system. Although the underlying mechanisms remain unclear, there is robust evidence that long-term exposure to $PM_{2.5}$ is associated with premature mortality due to heart failure, stoke, and ischemic heart disease.

INTRODUCTION

Most eukaryotic organisms on Earth are obligate aerobes. They breathe air from which they extract oxygen for generating energy. This strict dependence on breathing makes air an essential requirement for most forms of life. Although the composition of Earth's atmosphere has changed over many millennia, its relative stability over the last 600 million years has enabled tellurian life to evolve and flourish, both in sea and over land. At present, Earth's atmosphere contains 78% nitrogen, 21% oxygen, and traces of argon and carbon dioxide. In addition, the ambient air contains aerosolized particles of different sizes, including PM_{10}, particulate matter (PM) with aerodynamic diameter <10 μm; $PM_{2.5}$, particles <2.5 μm in diameter; $PM_{0.1}$, ultrafine particles; and volatile gases. High levels of such particles and gases are generated naturally by forest fires and volcanic eruptions, although they can also be produced by non-combustion processes such as desert storms. While natural events have occasionally led to a sharp rise in PM levels, the most pervasive and persistent increase in the Anthropocene has been due to burning of fossil fuels by humans.

Historical records show that, since its beginning, human civilization has been associated with an increase in the production of air particulates (1). The lung tissues of mummies from places as far flung as Peru, Egypt, and Britain show signs of anthracosis and gradual blackening due to pneumoconiosis acquired by spending long hours over the acrid smoke of domestic fires. As early as 200 CE, the Hebrew Mishnah sought to control sources of air pollution in Jerusalem, and in 10 CE, Seneca wrote of the poisonous fumes of Rome. In Europe, air quality continued to deteriorate during the Middle Ages and the Industrial Revolution. A turning point, however, came in 1948, when 20 people died and 400 required hospitalization in Donora, Pennsylvania, a town of 14,000 residents, due to a sudden increase in air pollution (2), and in 1952, when the Great Smog of London killed 12,000 people (3). These events triggered widespread concern over the health impacts of air pollution, and over the last several decades researchers have acquired a formidable body of knowledge providing comprehensive and incontrovertible evidence that breathing polluted air adversely affects human health (4–6).

Evidence accumulated in the last 25 years shows that inhaling high levels of $PM_{2.5}$ can induce oxidative stress, trigger inflammation, and stimulate the autonomic nervous system. This insidious damage accumulates over decades, increasing the risk of cardiovascular disease (CVD) and leading to premature mortality (7–9). Although $PM_{2.5}$ exposure has been linked to a wide range of health conditions, most deaths (70–90%) associated with $PM_{2.5}$ (8), as with smoking (10), are due to CVD. Reasons for the high sensitivity of cardiovascular tissue to inhaled pollutants remain unclear, but may relate to the fact that in aerobes blood is in direct contact with pulmonary air, or that, in comparison with liver or lung, cardiovascular tissue has a lower detoxification capacity and is therefore more vulnerable to oxidative stress and inflammation (11). Importantly, it remains unclear how particles deposited in the lung can induce profound and often fatal dysfunction in distal tissues such as blood vessels and heart.

Some investigators have suggested that inhaled $PM_{2.5}$ traverses the lung, appears in circulation, and is deposited in peripheral tissues. In support of this view is the finding that inhaled gold nanoparticles can translocate from the lung to systemic circulation. However, significant translocation is observed only at primary particle sizes below 30 nm (12), which is much lower than the diameter of most particles in $PM_{2.5}$ (1 μm). In contrast, more than 99% of inhaled 100 nm ^{99m}Tc-carbon particles are retained in the lung for 24–70 h in humans (13), and in rats 90–94% of instilled 100 nm polystyrene particles remain in the lung (14). Although nanoparticles have been detected in the human brain, these are small (mean diameter 18 nm) and are believed to enter the brain directly via the olfactory bulb (15). The origin or the toxicological significance of these

nanoparticles is unclear. Therefore, it seems likely that most particles of ≥100 nm diameter are retained in the lung, where they exert local toxicity.

Once deposited in the lung, fine particles, which contain organic chemicals and metals, generate reactive oxygen species (ROS) by undergoing redox cycling, depleting cellular thiols, or activating lymphocytes. The key role of pulmonary toxicity in initiating systemic oxidative stress is supported by the observations that lung-specific overexpression of the antioxidant enzyme extracellular superoxide dismutase (ecSOD) prevents some of the systemic effects of inhaled $PM_{2.5}$ (16, 17) and that club cell–specific disruption of an autophagic mediator (Atg5) in the bronchial epithelium reduces PM-induced airway inflammation (18). Additional evidence that $PM_{2.5}$-induced injury originates in the lung is provided by a temporal hierarchical pathway analysis of $PM_{2.5}$-induced injury in humans, which showed that pulmonary inflammation and the oxidative stress pathway are the first to respond to ambient air (within 24 h), and then the systemic, hemostasis pathway responds gradually over a 2–3 day period (19).

PM-induced inflammation can be triggered either by the particles themselves or by damage-associated molecular patterns (DAMPs) (20), generated from tissue damage induced by particle-generated ROS. Recruitment of neutrophils by DAMPs can then activate other immune cells. Mild inflammation and an increase in neutrophils in the lung have been reported in both mice (21) and humans (22) inhaling $PM_{2.5}$. That this inflammatory response is secondary to oxidative stress is supported by studies showing that treatment with antioxidants such as *N*-acetylcysteine (21), TEMPOL, and ecSOD (16) inhibits pulmonary (21) as well as systemic (16) inflammation. Several studies have reported large changes in other inflammatory mediators, but their significance is unclear because many of these studies used intratracheal instillation, which delivers a high bolus of particles rapidly. A large load of particles delivered instantly to the lung may trigger inflammation, which may not be observed in animals inhaling low doses of aerosolized particles over time. Moreover, intratracheal instillation leads to patchy or inhomogeneous lung distribution of particles and often induces cough, which can clear part of the dose into the stomach and mouth. Nevertheless, the results of such studies consistently show an increase in pulmonary oxidative stress and inflammation after PM exposure.

Once initiated in the lung, oxidative stress and inflammation could then spread to distal tissues. In women (23) and the elderly (24), $PM_{2.5}$ exposure is associated with a slight increase in urinary or blood levels of malondialdehyde, a product of lipid peroxidation. $PM_{2.5}$ exposures are also positively associated with in urinary levels of the lipid peroxidation products F_2-isoprostane metabolite (25) and 8-iso-prostaglandin F2α (26). A similar positive association between $PM_{2.5}$ and 8-epi-prostaglandin 2α was reported for the 2,035 participants of the Framingham Offspring cohort (27). Moreover, increased levels of biomarkers of ROS-induced DNA damage such as 8-oxo-deoxyguanosine have been detected in the urine of children (28) and in the DNA of lymphocytes in adults (29). Collectively, these data support the notion that $PM_{2.5}$ exposures are associated with systemic oxidative stress, although the sources and targets of this stress have not been identified.

Potential effects of systemic oxidative stress and inflammation include vascular injury and dysfunction. It has been reported that exposure to PM is associated with deficits in vascular compliance and flow-mediated dilation (30) and an increase in arterial stiffness (31). Such deficits in function seem to be accompanied by deficiencies in endothelial growth and repair. In healthy, young adults, exposure to $PM_{2.5}$ is associated with an increase in the levels of microparticles generated from the apoptosis of endothelial cells (32), indicating significant endothelial damage. This vascular injury was associated with a suppression of the circulating levels of proangiogenic cells (33) and the plasma levels of angiogenic mediators (32), suggesting that exposure to $PM_{2.5}$ not only inflicts vascular injury but also prevents vascular repair—changes that, in conjunction with

Table 1 Risk of cardiovascular outcomes associated with a 10 μg/m^3 increase in ambient levels of fine particulate matter

Cardiovascular disease	Risk estimate[a]		Reference
Cardiovascular mortality	RR	1.14 (1.08–1.21)	71
Ischemic heart disease mortality	RR	1.23 (1.15–1.31)	71
Incident acute myocardial infarction	RR	1.08 (0.99–1.18)	71
Atrial fibrillation	OR	1.11 (1.03–1.19)	79
Heart failure hospitalization or death	RR	2.12 (1.42–2.82)	75
Mortality in heart transplant recipients	HR	1.25 (1.1–1.43)	76
Incident stoke	RR	1.13 (1.11–1.15)	71
Incident ischemic stoke	RR	1.18 (1.14–1.22)	71
Incident hemorrhagic stoke	RR	1.10 (1.05–1.16)	71
Hypertension	RR	1.05 (1.01–1.09)	36
Systolic blood pressure (adult)	mm Hg	1.39 (0.87–1.91)	34
Diastolic blood pressure (adult)	mm Hg	0.89 (0.49–1.30)	34
Systolic blood pressure (children)	mm Hg	1.09 (0.96–2.65)	37
Diastolic blood pressure (children)	mm Hg	0.93 (0.16–1.70)	37
Dyslipidemia	OR	1.14 (1.10–1.18)	40
Type 2 diabetes (incidence)	HR	1.10 (1.04–1.17)	50
Type 2 diabetes (prevalence)	HR	1.08 (1.04–1.12)	51

[a]Values in parentheses are 95% confidence intervals.
Abbreviations: HR, hazard ratio; OR, odds ratio; RR, relative risk.

diminished vascular function, could significantly elevate CVD risk CVD and accelerate the progression of atherosclerosis.

FINE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR DISEASE RISK FACTORS

In addition to causing changes in vascular function, exposure to $PM_{2.5}$ affects several other risk factors that contribute to CVD and mortality.

Blood Pressure and Hypertension

Many studies have shown that PM exposure affects both systolic and diastolic blood pressure (34). The effects vary with age, sex, and geographic location and are generally higher in countries with higher levels of air pollution (35). A meta-analysis of 20 studies found that long-term exposure to $PM_{2.5}$ is associated with hypertension (36) (**Table 1**). The effects of $PM_{2.5}$ on blood pressure have also been reported in children (37) (**Table 1**). Exposure to $PM_{2.5}$, even in children as young as 5 years, is associated with reduced carotid artery distensibility (38). Because children's lungs may be exposed to higher concentrations of ambient air particles than adults' lungs, they might be particularly susceptible to the adverse effects of $PM_{2.5}$. The plausibility of the relationship between PM exposure and blood pressure is further supported by data from animal models showing that exposure to PM increases blood pressure, which is prevented by treatment with a centrally acting α_{2a}-agonist (39). These findings suggest that, at least in mice, $PM_{2.5}$-induced increases in blood pressure may be secondary to sympathetic nervous system activation, although it remains unclear whether a similar mechanism underlies the effects of $PM_{2.5}$ on blood pressure and hypertension in humans.

Dyslipidemia

Increased levels of $PM_{2.5}$ have been associated with an increase in the risk of dyslipidemia (40), increases in total cholesterol and low-density lipoprotein, and decreases in high-density lipoprotein (HDL), especially in elderly and overweight/obese adults. Some studies have reported increases in triglycerides as well (41), while others have found no significant association (42). Data from a panel study of young, healthy adults show that brief exposure to $PM_{2.5}$ alters the anti-inflammatory functionality of HDL (43). However, the significance of this finding remains to be assessed.

Diabetes and Insulin Resistance

Early studies in mice showed that chronic exposure to $PM_{2.5}$ exaggerates diet-induced insulin resistance and visceral inflammation (44). Even when placed on a normal chow diet, mice exposed to $PM_{2.5}$ develop vascular (16) and whole-body insulin resistance (45). These changes are accompanied by systemic glucose intolerance (46), visceral adiposity (44), vascular dysfunction (44), hepatic steatosis (47), and hypothalamic inflammation (48). Because $PM_{2.5}$-induced vascular insulin resistance can be prevented by the overexpression of ecSOD in the lung (16), it seems that pulmonary oxidative stress causes tissue-specific changes in insulin sensitivity. That such insulin resistance, in turn, activates tissue inflammation is supported by the observation that treatment of $PM_{2.5}$-exposed mice with an insulin sensitizer prevented not only $PM_{2.5}$-induced vascular insulin resistance but also the activation of nuclear factor κB and the inflammasome (49). Taken together, these findings suggest that, at least in animal models, multiorgan insulin resistance may be a key step linking pulmonary injury to systemic inflammation.

Data gathered from animal studies provide strong plausibility and mechanistic support to epidemiologic studies showing that long-term exposure to $PM_{2.5}$ increases the risk of both incident and prevalent type 2 diabetes (T2D) (50, 51). Short-term exposure has been linked to risk of hospitalization for diabetes (52) and long-term exposure to diabetes mortality (53). $PM_{2.5}$ exposure increases not only the risk of diabetes but also the risk of CVD in diabetics. In a study of 114,537 women in the Nurses' Health Study, PM-associated CVD risk was significantly higher among women with T2D (54), suggesting that diabetic patients have a greater risk of CVD mortality than the nondiabetic population. However, a modification of the CVD–$PM_{2.5}$ relationship by cardiometabolic disorders was not observed in an analysis of data from 669,046 participants from the American Cancer Society Cancer Prevention Study II cohort (55).

That PM exposure worsens diabetes is supported by studies showing that the inflammatory effect of $PM_{2.5}$ (increased antigen-presenting cell phenotype on circulating cells) was exacerbated in individuals with T2D (56) and that decreasing the ambient levels of $PM_{2.5}$ was associated with a decrease in fasting plasma glucose levels and T2D incidence in 151,398 individuals from Taiwan (57). Even in nondiabetics, PM exposure has been linked with a small (1.02 mg/dL) increase in fasting blood glucose levels (58) and HbA1c (59). Such effects have also been reported in children, in whom exposure to a 10 $\mu g/m^3$ increase in $PM_{2.5}$ is associated with (2.3%) higher fasting blood glucose levels (60, 61). It has been estimated that a reduction in PM levels could protect 1,298,920 children in China from impaired fasting plasma glucose and diabetes (61). Collectively, this body of evidence strongly supports the view that exposure to $PM_{2.5}$ can induce T2D in susceptible individuals and that, when exposed to $PM_{2.5}$, individuals with T2D may be at a greater risk of CVD morbidity and mortality.

Thrombosis

Significant epidemiological research suggests that both short- and long-term exposures to $PM_{2.5}$ are associated with changes in hemostasis, such as an increase in fibrinogen levels, increased

platelet aggregation, and thrombin generation (62). In contrast, short-term reductions in $PM_{2.5}$ have been associated with decreases in the biomarkers of hemostasis, namely soluble P-selectin and von Willebrand factor. Panel studies have shown that direct exposure to diesel exhaust impairs fibrinolysis in both healthy volunteers and patients with coronary artery disease. Upon exposure to PM, young, healthy volunteers also showed an increase in the circulating levels of platelet–leukocyte aggregates (33, 62), indicating as in vivo increase in platelet activation. Data from animal models corroborate and substantiate the link between $PM_{2.5}$ and thrombosis (62). Platelets from mice exposed to concentrated air particles show an increase in fibrinogen binding in response to ADP, and those instilled with PM particles show platelet aggregation, thrombin generation, and reduced clotting time. Because many of the prothrombotic effects of PM could be prevented by inhibiting interleukin-6 or tumor necrosis factor α, it appears that the prothrombotic response to $PM_{2.5}$ may be due in part to inflammation instigated by alveolar macrophages (62).

Atherogenesis

Several studies in atherosclerosis-prone mice have shown that exposure to $PM_{2.5}$ can increase atherogenesis (63). Studies on rabbits instilled with PM_{10} and apoE-null mice exposed to concentrated $PM_{2.5}$ show increased vascular inflammation, macrophage inflammation, and potentiated plaque development (63). In addition, exposed mice show increased levels of tissue factor and smooth muscle cells in atherosclerotic lesions, as well as alterations in the vasomotor tone—phenotypic characteristics that are consistent with greater plaque vulnerability (63). Although the mechanisms by which $PM_{2.5}$ exposure affects atherosclerotic plaques remain obscure, it seems likely that the increase in atherosclerotic burden in $PM_{2.5}$-exposed animals may be secondary to systemic inflammation, which increases the recruitment of inflammatory cells (63) while suppressing the recruitment of angiogenic cells (64) from the bone marrow. Studies in humans corroborate the evidence obtained from animal models. In participants from the MESA cohort, exposure to $PM_{2.5}$ was associated with the progression of coronary calcification (65), providing key evidence that $PM_{2.5}$ exposure accelerates the progression of subclinical atherosclerotic disease.

FINE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR MORTALITY

Extensive evidence gathered in recent decades indicates that exposure to $PM_{2.5}$ increases the risk of CVD mortality. Both episodic and chronic exposures seem significant. Brief exposures trigger acute clinical events such as myocardial infarction and stroke, and chronic exposures accelerate the progression of subclinical disease, leading to premature cardiovascular mortality (7–9). In a meta-analysis of 110 peer-reviewed time-series studies on the association between $PM_{2.5}$ and daily mortality, a 10 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with a 1.04% (95% CI, 0.52–1.56%) increase in the risk of death and a 0.84% (95% CI, 0.41–1.28%) increase in death from cardiovascular causes (66).

Like acute exposures, chronic exposures are associated with an increase in the risk of CVD mortality (**Table 1**), and the global impact of $PM_{2.5}$ on cardiovascular mortality has been estimated. These estimates initially relied on the integrated exposure–response model (IER), which, in the absence of data from high-pollution countries, combined information from secondhand smoke, household air pollution, and active smoking (67). However, with the recent availability of data acquired at higher levels of exposure from China, the shape of the IER has been reevaluated to construct the global exposure mortality model (GEMM), which uses data only from cohort studies of outdoor air pollution (68). This model estimates that, globally, exposure to ambient fine

particulate air pollution is associated with 8.9 million deaths due to noncommunicable diseases and lower respiratory infections (which represent almost all nonaccidental deaths). This estimate is 120% higher than that from the IER, and suggests that the health burden of air pollution may be comparable to that of smoking (6.3 million) and diet (10.3 million) (68), making air pollution a leading cause of preventable deaths worldwide.

Nonetheless, uncertainties remain. The GEMM does not account for causes of death not estimated in the 2019 Global Burden of Disease (67). Moreover, even though both the IER and the GEMM assume that toxicity of polluted air is a function of mass concentration alone and that the effects of $PM_{2.5}$ do not vary with chemical composition of the particles, the veracity of these assumptions remains uncertain. The health effects of pollution vary by source and location, and fixed site monitoring or the use of satellite data with limited resolution, employed in most studies, obscures such spatial variability. Therefore, additional local and high-resolution exposure assessments, which take into consideration the full range of air pollutants (particles and gases), are required to obtain more accurate estimates of air pollution–associated mortality.

The accuracy and the specificity of existing models could be further increased by identifying the shape of the dose–response curve. In IER, the relationship between $PM_{2.5}$ and mortality due to ischemic heart disease (IHD) was relatively steep at low levels of exposure but flattened out at higher exposure levels (69). In contrast, GEMM shows supralinear association over lower levels of exposures, and then a near-linear association at higher concentrations (68). In contrast, recent data from China over a wider range of exposures suggest a concentration response function that is steeper at high $PM_{2.5}$ levels, indicating that, instead of saturation, the effect increases at higher levels of $PM_{2.5}$ (70). Clearly, additional research is required to reconcile these differences, which may arise from several factors, such as variations in $PM_{2.5}$ composition and in individual exposures and susceptibilities. Dose response and $PM_{2.5}$ sensitivity may also vary with CVD outcomes, as discussed in the following subsections.

Ischemic Heart Disease

A meta-analysis of 42 studies clearly indicates that long-term $PM_{2.5}$ exposure is associated with an increase in mortality due to IHD (71). While a nearly twofold increase in risk has been reported for recurrent acute myocardial infarction (AMI), the effects of $PM_{2.5}$ on incident AMI are somewhat smaller (8%) (72). Patients with a previous history of myocardial infarction are likely to be more susceptible to PM because they have preexisting CVD, but it is unclear why the effects on incident AMI are much lower than on IHD. It is likely that because most IHD deaths occur in younger individuals, before they can seek medical attention, the effects of PM are more significant in this population than in those with AMI, who tend to be older and who, because of hospitalization, are more likely to survive. Whether age or some other demographic or mechanistic difference underlies the differential sensitivity of IHD and AMI mortality remains to be established.

Stroke

Exposure to $PM_{2.5}$ is associated with an increase in the risk of both ischemic and hemorrhagic stroke (71). Why the risk of ischemic stroke is slightly higher than that of hemorrhagic stroke is not known, but the relative insensitivity of hemorrhagic stroke to $PM_{2.5}$ is similar to that observed with tobacco smoke exposure, which has a much greater effect on coronary heart disease and ischemic stroke than on hemorrhagic stroke (73). The higher sensitivity of ischemic stroke may be because hypertension is more prevalent among patients with ischemic stroke, who also tend to be older and to have more severe atherosclerotic disease than those with hemorrhagic stroke (74).

Heart Failure

Increases in ambient $PM_{2.5}$ levels have been linked to upticks in heart failure hospital admissions and death (75). The strongest associations between $PM_{2.5}$ levels and heart failure have been seen on the day of exposure, indicating acute exacerbation of heart failure. The risk seems to be even greater in heart transplant recipients (76) (**Table 1**). Lung and kidney transplant patients show a similarly high sensitivity to environmental pollutants, suggesting that their unique immunological status may render transplant patients particularly vulnerable to adverse environmental exposures (77). In addition to affecting heart failure, $PM_{2.5}$ exposure seems to directly affect cardiac function. Even in a randomly recruited middle-aged population, left ventricular function was cross-sectionally correlated with long-term residential exposure to $PM_{2.5}$ (78), suggesting significant remodeling, which may be related to either the autonomic effects of $PM_{2.5}$ or to vascular and electrophysiological consequences of PM exposure.

Atrial Fibrillation

Autonomic and electrophysiological disturbances caused by $PM_{2.5}$ exposure may affect the risk of atrial fibrillation (AF) (79). The effects seem to be rather prompt. In a study of patients with an implantable cardioverter defibrillator, the odds of AF were increased by elevated $PM_{2.5}$ levels within 2 h (80). In older adults with hypertension, hourly changes in PM were associated with a greater risk of acute episodes of both asymptomatic and symptomatic AF (81). $PM_{2.5}$ exposure has also been associated with an increase in the incidence of new-onset AF in susceptible patients (82). In such patients, PM may trigger AF because of changes in atrial ischemia, atrial pressure, or autonomic tone. How these changes occur—and how they are related to pulmonary oxidative stress and inflammation—remains unclear.

PREVENTION AND MITIGATION

Because the generation of PM seems to be an inevitable consequence of using current technologies for urbanization, transportation, and agriculture, it is difficult to remove all sources of PM from contemporaneous environments. Nevertheless, even with current technologies the health burden of PM could be attenuated by either decreasing emissions or preventing exposures. Additionally, key environmental and individual factors that magnify the adverse health effects of $PM_{2.5}$ could be modified. The selection and success of specific strategies will depend on the location and the source of PM within the natural, social, and personal domains of individual enviromes (83). Emission from natural sources such as forest fires and desert dust could be reduced by implementing validated mitigation strategies (**Figure 1**). Knowing more about the role of meteorological conditions, altitude, forest cover, climate, and temperature will help researchers develop more effective mitigation approaches.

For PM generated in social environments (by industry, traffic, and agriculture), changes in regulatory policies and manufacturing/production practices are likely to yield the most durable gains. Some such strategies are employing stricter automobile emission and air quality standards, decreasing the use of fossil fuels, and changing agricultural and animal husbandry practices (9). Also, the health effects of $PM_{2.5}$ could be decreased by mitigating the effects of co-exposures that magnify the effects of $PM_{2.5}$, such as volatile organic gases, noise, and temperature. In addition, characteristics of the built environment that increase exposure could be modified to decrease exposure, for instance, by developing person-centric built environments (9), increasing urban green spaces and parks, and building vegetative buffers along highways (84). Because of historic legacies of social and economic discrimination in the United States, Black and Hispanic/Latino

	Sources	Effect modifiers	Mitigation strategies
NATURAL	Volcanos		Depressurization, increased vent aperture, cooling
	Forest fires		Dissemination of wildfire prevention tips, prescribed burning, improvements in forest health
	Desert dust		Surface stabilization, decreases in intensive tillage, soil conservation
		Altitude	
		Seasons	
		Temperature	Decreases in greenhouse gas emissions
		Green spaces	Increases in forest cover
SOCIAL	Traffic		Use of emission reduction-particle traps, alternative fuels, converters
	Industry		Increased use of green energy, clean energy sources (solar, wind, geothermal)
	Agriculture		Controlled prescribed burning, reductions in ammonia emissions
		Built environment	Land use reassessment, traffic relocation, decreased mix use
		Urban green spaces	Increases in green parks, street trees, roadside vegetative buffers
		Noise	Installation of sound walls, land use change, traffic relocation
		Socioeconomic factors	Increases in public awareness, media campaigns
PERSONAL	Cooking		Use of low-emission stoves and renewable sources, ventilation
	Heating		Use of low-emission fuels
	Indoor activities		Increased awareness and avoidance
		Race	
		Sex	
		Age	
		Nutrition	Good nutrition, omega-3, vitamin B12
		Smoking	Smoking cessation, prevention of second hand exposure
		Physical activity	Increased physical activity in areas of low pollution
		Sleep	Improvements in circadian alignment and sleep quality
		Medication use	
		Income	
		Individual behavior	Use of face masks, traffic avoidance
		Home	Use of indoor air filtration

Figure 1

Potential mitigation strategies and effect modifiers of fine particulate matter generated from different sources in the natural, social, and personal domains of the environment.

communities and individuals with low socioeconomic status are exposed to higher concentrations of ambient air pollution due to their closer residential proximity to traffic and higher exposure while walking and using public transportation (9). This is particularly concerning because Black and Hispanic communities bear a disproportionately high CVD burden (9). Therefore, addressing such disparities and inequities should be a cornerstone of any mitigation strategy, and additional studies are needed not only to assess the burden of air pollution on marginalized and vulnerable communities but also to identify their unique sensitivities to air pollution.

The success of social interventions could be bolstered through the modification of personal environments. Individual activities such as cooking, heating, smoking indoors, or lighting candles and incense are important sources of PM exposure. Modifying such activities or adopting

personalized approaches (e.g., the use of low-emission stoves, appropriate ventilation, indoor air filtration) could also be effective in significantly decreasing PM exposure. Because the effects of PM (as for those of other respiratory insults, such as SARS-CoV-2) differ by health status and are exaggerated by individual choices such as smoking (85), adopting a healthier lifestyle is likely to enhance resilience against the more severe consequences of PM exposure. Therapeutic interventions such as vitamin B_{12} (86) or omega-3 (87) supplements or wearing face masks (**Figure 1**) could provide additional individual-level protection against PM (4).

PERSPECTIVE

The adverse health effects of air pollution have been demonstrated repeatedly, and as discussed above, there is comprehensive, rigorous, and persuasive evidence to support the notion that populations living in areas of high pollution have higher rates of mortality and a greater risk of chronic disease. This high, extraneous, and preventable disease burden constitutes a paradigmatic case in environmental cardiology (5), as it reinforces the view that much of CVD arises not from biological malfunction intrinsic to an individual but rather from adverse environmental exposures or a mismatch between individual biology or behavior and the prevailing environmental conditions (88). PM exposure is a modifiable risk factor, attributable to the environment and not the individual. Accordingly, to understand the impact of PM, we must look beyond biologic explanations, toward distal environmental "causes of causes," because solutions may be found outside the current domain of medical science. Such an extended search for feasible solutions may require a range of experts—engineers, sociologists, economics, atmospheric scientists, policy makers—to work in partnership with affected communities. Only by such widespread collaboration, informed by an understanding of the distal environmental causes of CVD, will we be able to devise enduring, feasible, and sustainable ways to manage cardiovascular risk and prevent CVD. The task is becoming increasingly urgent. CVD has become the leading cause of death worldwide, and even in high-income countries such as the United States, declines in CVD prevalence have stalled (88). This increase in CVD and other noncommunicable diseases is particularly ominous in the context of climate change. After its relative stability over several thousand years, Earth's atmosphere is rapidly changing, which could not only increase the levels of air pollution but also create new vulnerabilities. Managing this double threat will be challenging, but how we respond to the challenge will determine the health of the planet and its people.

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