3 Impact of the Environment on Cardiovascular Health

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The Lancet Commission on pollution and health defines pollution as unwanted, often dangerous, chemical material introduced into the environment as the result of human activity, that threatens health and harms ecosystems.[1] Given the diversity of environmental exposures that an individual may encounter, the term "pollutome" is a useful encompassing term that refers to the aggregate of all exposures in the air, soil, and water (or indoor physical environment) that one is exposed to. The pollutome in turn is a subset of the exposome (i.e., the sum totality of all exposures). A framework for understanding the pollutome where zone 1 contains pollutants with well-characterized health effects; zone 2 with pollutants with emerging, but not yet definite, health effects (known and some unknowns), zone 3 including pollutants with inadequately characterized health effects (known unknowns), and finally zone 4, which may include unknown chemical exposures that are not yet recognized. The phrase "gene-environment interaction" infers that the direction and magnitude of the clinical effect that a genetic variant has on the disease phenotype can vary as the environment changes and importantly acknowledges the importance of genetic predisposition in determining the magnitude of effects. The cardiovascular system is especially vulnerable to a variety of environmental insults, including smoke, solvents, pesticides, and other inhaled or ingested pollutants, as well as extremes in noise and temperature. Our understanding of environmental factors continues to evolve with an increasing footprint attributable to pollutants than previously suspected. Thus, it is vitally important that cardiologists understand the impact of the environment on cardiovascular disease.

GLOBAL FOOTPRINT AND IMPACT OF POLLUTANTS ON HUMAN HEALTH

The global footprint of environmental pollution is very large, ranging from about 9 million deaths based on the most recent global burden of disease (GBD) estimate in 2019, to 12.6 million deaths based on a World Health Organization (WHO) estimate in 2012. These differences arise from variable definitions of the environment in the estimates. The GBD estimates are based on a more limited inventory of risk factors including air pollution: household, ambient (fine particulate matter [$PM_{2.5}$], and tropospheric ozone pollution); (2) water pollution: unsafe sanitation and unsafe water sources; (3) soil, chemical, and heavy metal pollution: lead (including contaminated sites polluted by lead from battery recycling operations), and mercury from gold mining; and (4) occupational pollution: occupational carcinogens, and occupational particulates, gases, and fumes. The WHO definition also includes noise, electromagnetic fields, occupational psychosocial risks, built environment, agricultural methods, and human-made climate and ecosystem change. It is important to emphasize that these estimates are likely a vast underestimate because all of these analyses are based on known risk factors (zone 1) for which there is convincing evidence of causal association (Fig. 3.1). Total pollution is estimated to contribute to approximately 20% of all cardiovascular disease and 25% of ischemic heart diseases (IHDs) of which air pollution is the largest contributor, responsible for over 6 million deaths annually worldwide. As such, the global impact of environmental pollution is high and is expected to worsen as population-weighted exposures increase with urbanization and increased population density.[2]

AIR POLLUTION

The GBD 2019 lists air pollution as the fourth leading risk factor for global mortality, responsible for 6.67 million deaths globally.[3] The disease burden attributable to ambient $PM_{2.5}$ estimated in disability-adjusted life-years (DALYs), increased from 70.5 (95% uncertainty interval [UI] 47.3 to 98.9) million DALYs in 1990, to 118.2 (95.9 to 138.4) million DALYs in 2019. Air pollution together with high body mass index and glucose are the only three risk factors among 87 others that account for greater than 1% of DALYs and continue in prevalence by greater than 1% per year.[3] The increase globally is almost entirely attributable to urbanization and increasing exposures in Asia, parts of the Middle East, and Africa. Although many gaseous pollutants have been linked with health effects (e.g., ozone, nitrogen oxides, sulfur oxides), fine PM (particles ≤2.5 μm, $PM_{2.5}$), principally derived from fossil fuel combustion (for the purposes of power, residential energy use, and industry) is the most extensively implicated component, and has a disproportionate impact on adverse health effects.[4–6] Over 50% of deaths attributable to air pollution is from cardiovascular causes (Fig. 3.2).[7–9]

Composition and Sources of Air Pollution

Air pollution is a complex mixture of gaseous phase and particulate constituents that varies spatially and temporally.[4] From a regulation perspective, the Environmental Protection Agency (EPA) has set National Ambient Air Quality Standards (NAAQS) for six principal pollutants, which are called "criteria" air pollutants (carbon monoxide, lead, nitrogen dioxide, ozone, particulate matter, and sulfur dioxide, Table 3.1).[10] Primary air pollutants are those that are released directly into the atmosphere, including both gaseous and particulates, whereas secondary pollutants are formed through chemical transformation

through interaction with other constituents and/or in response to prevalent atmospheric conditions (sunlight, water, vapor, etc.). Many primary air pollutants such as nitrogen oxides (NO + NO_2), carbon monoxide, sulfur dioxide (SO_2), $PM_{2.5}$, as well as carbon dioxide (CO_2), originate from combustion of fuel or other anthropogenic processes. Combustion $PM_{2.5}$ is composed of many organic compounds, including organic carbon species (OC), elemental or black carbon, and trace metals (Table 3.1 and eTable 3.3).[4] In addition to O_3, which is the most prevalent secondary oxidant, a number of inorganic and organic acids and volatile organic carbons (VOCs) and semivolatile organic compounds (SVOCs) formed secondarily and are found in both the gas and particle phase, are an additional large class of pollutants. Key examples are benzene, toluene, xylene, 1,3- butadiene, and polycyclic aromatic hydrocarbons (PAHs). Many VOCs contribute to the formation of O_3 and are oxidized in the atmosphere, becoming SVOCs and subsequently contribute to $PM_{2.5}$ mass. Examples of secondary pollutants include sulphates, nitrate, and ammonium which also contribute to the PM fraction of air pollution. The particulate fraction of air pollution may be broadly categorized by aerodynamic diameter: less than 10 μm (thoracic particles [PM_{10}]), less than 2.5 μm (fine particles [$PM_{2.5}$]), less than 0.1 μm (ultrafine particles [UFPs]), and between 2.5 to 10 μm (coarse [$PM_{2.5–10}$]). Although most studies have focused on one or two pollutants at a time, the reality is that pollutants coexist and vary spatially and temporally. Even though some epidemiologic studies adjust for copollutants, the significant collinearity makes it complex to separate these effects.

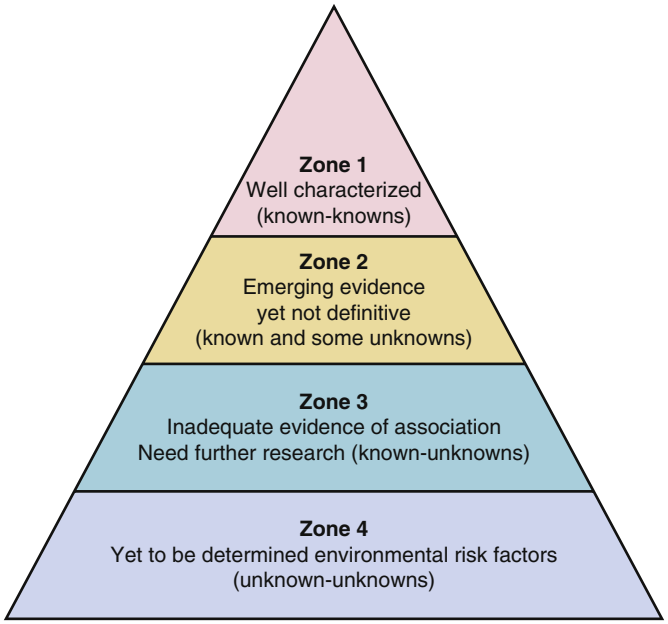


FIGURE 3.1 Zones of evidence linking environmental pollution with health effects. (Adapted from Landrigan P, Fuller R, Acosta NJ, et al. The Lancet Commission on pollution and health. *Lancet*. 2018;391:462–512.)

Particulate Air Pollutants

PM air pollution is by far the most studied and with the most evidence for health effects. The categorization of PM based on size thresholds reflects the ease of quantification and is a rough barometer of chemical composition, geographic distribution, and sources. Although regulatory thresholds exist for PM_{10} and $PM_{2.5}$ (see Table 3.1), no standards exist for UFP. PM_{10} and $PM_{2.5}$ often derive from different emissions sources and also have different chemical compositions. Emissions from combustion of gasoline, oil, diesel fuel, or wood produce much of the $PM_{2.5}$ pollution found in ambient air, as well as a significant proportion of PM_{10}. Dust from crustal material and agricultural and industrial practices contribute to the course ($PM_{10–2.5}$) or even larger particle (>PM_{10}) size ranges and may dominate composition in certain environments. PM_{10} may also include dust from road dust, tire and road wear particles, dust from construction, agricultural emissions, wildfires and brush/waste burning, industrial sources, wind-blown dust from open lands, pollen, and fragments of bacteria and lipopolysaccharide (LPS). $PM_{0.1}$ or UFPs are generated through primary combustion of fossil fuels from automobile sources, are characterized by large surface area to size ratio, and can serve as a nidus for gaseous copollutants. UFPs are short lived and are highly influenced by proximity to the sources (typically <1 km from source). The spatial and temporal colocalization of gaseous copollutants with UFPs makes it difficult to separate the health effects in epidemiologic and mechanistic research. In addition, UFP monitoring is not widely available and requires

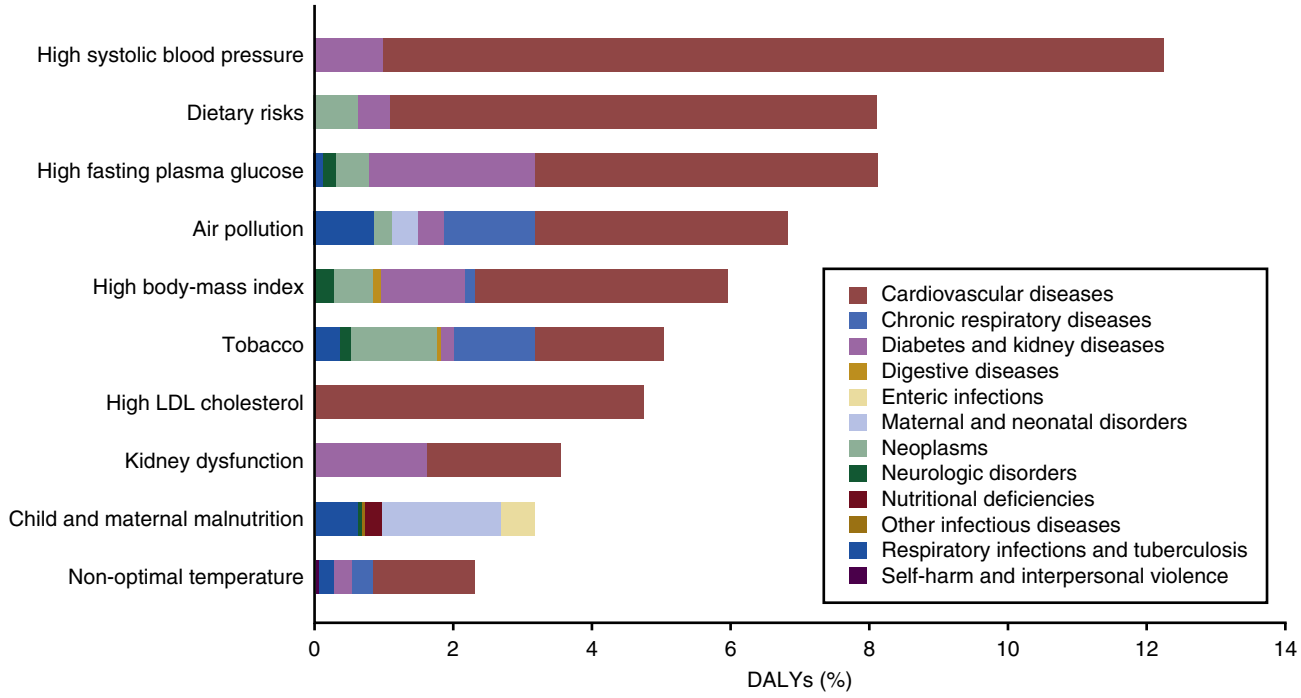
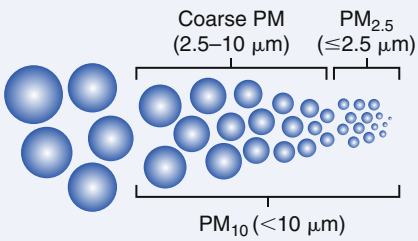
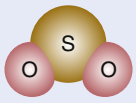
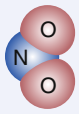
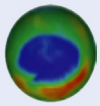
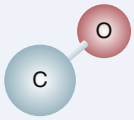
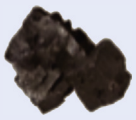


FIGURE 3.2 Estimates of global attributable deaths from various risk factors. DALYs, disability-adjusted life-years. (Adapted from GBD 2019 Risk Factors Collaborators. *Lancet*. 2020; 396:1223–1249.)

TABLE 3.1 U.S. and European Standards for Air Pollutants

Air pollution component	Size or structure	U.S. standards	European standards
PM		$PM_{2.5}$: 12 μg/m³ (1 year); 35 μg/m³ (24h)	$PM_{2.5}$: 25 μg/m³ (1 year)
		PM_{10}: 150 μg/m³ (24h)	PM_{10}: 40 μg/m³ (1 year); 50 μg/m³ (24 h)
Sulfur dioxide		75 ppb (1h)	350 μg/m³ (1 h); 125 μg/m³ (24h)
Nitrogen dioxide		100 ppb (1h)	40 μg/m³ (1 year); 200ppb (1h)
Ozone gas		0.070 ppm (8h)	120 μg/m³ (8 h)
Carbon monoxide		10 μg/m³ (8 h)	35 ppm (1h); 9ppm (8h)
Lead		0.15 μg/m³ (3 months)	0.5 μg/m³ (1 year)

PM, particulate matter; $PM_{2.5}$, fine particulate matter; PM_{10}, coarse and fine particulate matter.

Adapted from Al-Kindi SG, Brook RD, Biswal S, et al. Environmental determinants of cardiovascular disease: lessons learned from air pollution. *Nat Rev Cardiol*. 2020;17:656–672.

specialized equipment. Recent studies have suggested heightened cardiovascular risk of UFP.[11]

Gaseous Pollutants

Ground level ozone (O_3) is the most studied gaseous pollutant with respect to health effects.[12–15] It is a secondary pollutant which is created through reaction between nitrogen oxide and volatile organic compounds, facilitated by sunlight. Although high levels of ozone clearly confer adverse health effects including increased risk of mortality and asthma, recent evidence suggests a continued relationship between ozone and health effects at levels lower than the U.S. NAAQS of 70 ppb over 8 hours.[14] The association between long-term ozone exposures and CV mortality is lower than other causes of mortality.[16] The mechanisms of ozone-related cardiovascular and mortality effects appear to be related to oxidant stress and a prothrombotic response.[5] There is paucity of data for other gaseous copollutants present in fossil fuel emissions such as VOCs and atherosclerotic cardiovascular disease (ASCVD) events, although mechanistically it is highly likely that these compounds may have important health effects. Copollutants such as NO_2 and SO_2 may not be directly toxic but function as surrogates for other copollutants and have been linked to cardiovascular events, including myocardial infarction (MI), stroke, and heart failure (HF).[17,18]

Particulate Matter Sources, Composition, and Cardiovascular Risk

Air pollution chemistry and hence health effects vary substantially by source. There is a substantial spatial and temporal variation of air pollution levels that may be important in health effects. Large urban-rural differences are found for primary combustion pollutants that originate from traffic such as nitrogen oxides (NO and NO_2), and particulate black carbon, that may drive risk. Meteorologic conditions such as atmospheric stability can significantly alter the horizontal propagation of particles and thus the size of the population exposed. Given the fact that the dynamics of air pollution chemistry and concentration may vary substantially, the detailed chemical characterization of pollution is a static time frame that in addition to being expensive may not accurately portray the chemical composition particularly for components such as ultrafine. However, speciation of common pollutants such as sulfates and nitrates or the corresponding gaseous pollutants such as NO_2 and SO_2 have been shown to be predictive of health effects.[19] A 2014 systematic review that quantified the associations between chemical components, such as sulfate, nitrate, and elemental and organic carbons, demonstrated that they were all linked to all-cause, cardiovascular, and respiratory mortality.[17] In an analysis of the American Cancer Society Cancer Prevention Study II, mortality from ischemic heart disease (IHD) associated with $PM_{2.5}$ derived from coal combustion was fivefold higher than the risk with overall $PM_{2.5}$ mass, suggesting that the source of $PM_{2.5}$ may be important in determining cardiovascular risk.[18] Examination of sources may sometimes represent a more efficient way of thinking about health effects, including regulation. For instance, traffic air pollution is perhaps the largest health threat from a source perspective in the West, with a sizeable proportion of the population living within 150 meters of a major highway and thus likely to be exposed to traffic-related ultrafine air pollution. The average Western

adult spends 55 minutes a day exposed to vehicular emissions.[20] Traffic air pollution peaks during the late morning and evening rush hours, with $PM_{0.1}$ and gaseous components demonstrating substantial variation within a span of 400 m. The substantial spatial variation and reactivity of $PM_{0.1}$ fraction pose challenges for accurate quantification, and thus a simple metric such as distance from a highway has been an effective surrogate for traffic-related exposures. Fossil fuel–burning coal power plants, shipping and airplane, and agricultural emissions (e.g., crop burning) may dominate emissions in certain environments. Most individuals across the globe spend preponderant majority of time indoors and are also exposed to indoor sources. Household air pollution (HAP) encompass a range of particles from diverse sources that vary dramatically depending on geography and socioeconomic and cultural factors. For instance, with exposure to high concentrations of emissions from wood/coal-burning stoves for cooking and heat, kerosene stoves may dominate the indoor environment in developing countries reliant on solid fuels for heat and cooking. In countries with high levels of ambient air pollution, it is estimated that up to 65% of inhalation of outdoor air particles occurs when people are indoors.[21] In the West, cooking on gas stoves, burning incense and candles, use of aerosol sprays, and cleaning activities may contribute to indoor particle levels. Wood-burning communities in North America may experience high levels of UFPs during winter. The expansion of the human habitats and climate change have expanded the likelihood of exposure to air pollution from natural events such as wildfires and volcanic eruptions. Both PM and gaseous pollutants from these events can affect large populations and produce health effects in millions of people across the world.[22] For instance, crustal material from dust storms can cause dramatic increases in outdoor and indoor PM counts.[23] Mortality and respiratory morbidity have been the most frequently studied and most consistently reported outcomes of smoke exposure. Recent evidence suggests that smoke exposure from natural sources such as wildfires may be associated with cardiovascular effects with effect estimates comparable with ambient $PM_{2.5}$ from anthropogenic sources.[24]

Household Versus Ambient Air Pollution

Although the vast majority of studies on air pollution have focused on ambient air pollution owing to exposure data availability, HAP is a major contributor to global mortality, particularly in developing countries.[25,26] The burden of disease attributable to HAP has been steadily decreasing, with the most recent GBD 2019 indicating that the percentage of DALYs attributable to HAP decreasing 56%, demoting HAP as the 4th leading risk factor in 1990 to the 10th leading risk factor in 2019.[3] Although HAP is a significant cause of childhood morbidity including predisposition to respiratory tract infections and COPD, links between CVD have been recently elucidated, including association with hypertension and coronary artery disease.[27] An issue with HAP has been the estimation of reliable exposure estimates and ascertainment of mortality causes, because the predominant majority of events occur in communities with limited access to health care and standardized reporting procedures. HAP encompasses gaseous and particulate pollution generated from solid fuel use for cooking and indoor heat in developing countries.[27] In Western countries, wood-burning furnaces, indoor candle lighting, and aerosol spray use may all contribute to HAP. It is important to note that HAP and ambient air pollution also coexist, such as in developing countries and when outdoor ambient levels are very high.[25] In these environments, the indoor environment may be dominated by outdoor levels (and hence sources). The translocation of particles from ambient (outdoor) air to indoor air is determined by house insulation and the method of ventilation. Smaller particles (UFPs) have higher likelihood of translocating indoors, and this has been documented in residential areas with proximity to major highways as well as wood-burning communities in the United States.

Assessment of Exposure

Accurate assessment of exposure is of paramount importance to understand the health effects, regulate emissions, and mitigate adverse health effects. Given that studies associating exposure with health outcomes require a large number of participants who are geographically dispersed, exposure assessment needs to be pragmatic and widely available. There is a tradeoff between approaches in terms of spatial resolution (coverage), exposure assessment at the individual level, and finally temporal resolution. Satellite-based assessment approaches using aerosol optical depth of a vertical column from space, as an index of particulate air pollution, can provide ambient air annual and daily exposure assessments around the globe at spatial resolution down to 1 × 1 km.[28] These are frequently combined with chemical transport models, aided by statistical or machine learning–based adjustment based on ground monitors. Although these methods have been integral for GBD estimates, their accuracy for personal exposure is limited and furthermore their temporal resolution is limited.[15] Ground monitors in urban locations provide better spatial and temporal resolution, but their accuracy declines rapidly with distance, and thus some exposure models use data from multiple ground monitor sources to produce reliable estimates. It is important to emphasize that all exposure assessment approaches are only approximations of true exposure and thus can serve only as surrogates for "true personal" exposure. Personal exposure monitors (both indoor and portable) are increasingly available and promise to provide individual exposure information at a fine scale in a variety of environments, often at high temporal resolution. Such devices represent a practical way to expand the coverage of ground monitors and may facilitate real-time communication of air pollution levels and personalized assessment of environmental risk, that can be used to mitigate health risks.[15] A current challenge is their technical harmonization with current stationary approaches, especially with regards to standardization of measures and helping to resolve differential time scales.

Exposure-Response Function of Air Pollution, Mortality, and Cardiovascular Events

Understanding the relationship between continuous long-term and short-term exposure to air pollutants and health outcomes is critical for regulation, health policy, and intervention. The original integrated exposure response function (IER) used in the Global Burden of Disease 2013 study assigned estimated concentrations of $PM_{2.5}$ to inhalational exposure from a variety of sources, including secondhand smoking and active smoking, and assumed that risk is determined by the 24-hour $PM_{2.5}$ inhaled dose, regardless of the exposure source.[29] The nonlinear response curve, with steep increases at low exposure levels and flattening at higher doses, has been useful in providing a credible explanation for robust risk estimates from epidemiologic studies at low doses of air pollution, and yet reconciling studies with HAP and active smoking that are typically characterized by extremely high $PM_{2.5}$ levels. Importantly, the IER allowed derivation of credible estimates of disease events attributable to air pollution across the globe, including in areas with little to no ground level monitoring, using satellite-based assessment of $PM_{2.5}$. In GBD 2019, the inclusion of additional studies from China and India and studies of HAP allowed incorporation of a broad range of exposures and recalculation of estimates attributable to pollution from a variety of sources.[3] Importantly, the elimination of active smoking from the curves removed a significant degree of uncertainty in the estimates (Fig. 3.3). Although the epidemiology of air pollution and cardiovascular events is robust and controls for a number of factors, multiple limitations including the independent and potentially synergistic contribution by other environmental coexposures such as noise and other poorly understood socioeconomic determinants must be acknowledged.[30,31]

Cardiovascular and Metabolic Effects of Air Pollution

Both short-term and long-term exposure to $PM_{2.5}$ has been linked with the development of cardiovascular, renal, and metabolic disorders, including hypertension and type 2 diabetes. The epidemiology of the air pollution and cardiometabolic disorders involves both short-term variation typically examined in time series and case crossover analysis using referent time windows, as well as long-term exposure studies

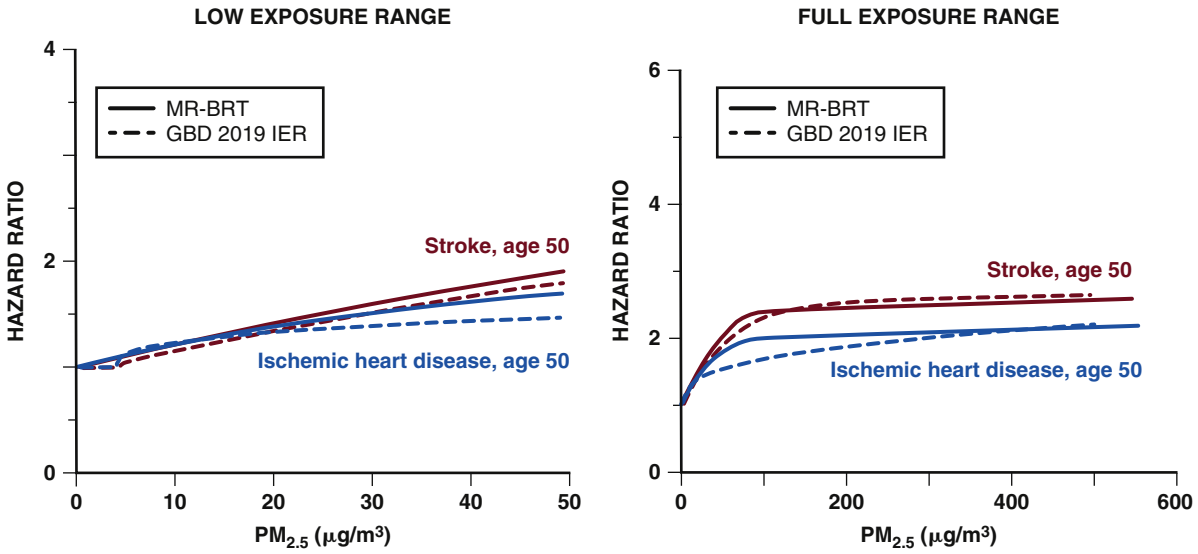


FIGURE 3.3 Ischemic heart disease (IHD) and stroke outcomes with $PM_{2.5}$. Meta-regression Bayesian, regularized, trimmed (MR-BRT). In global burden of disease (GBD) 2019, for a selected set of continuous risk factors, we modeled relative risks using MR-BRT, relaxing the log-linear assumption to allow for monotonically increasing or decreasing, but nonlinear functions using cubic splines. (Adapted from GBD 2019 Risk Factors Collaborators. *Lancet*. 2020;396 [appendix].)

involving large prospective cohorts. Together, these studies have provided a detailed portrait of the epidemiologic associations between components of air pollution and adverse cardiometabolic consequences and indeed support a strong associative link. Additional supportive mechanistic studies in animal models, short-term controlled exposure studies, interventional studies, and accountability studies have provided more or less definitive proof of air pollution as a causative environmental trigger in the genesis of cardiometabolic disease. Diabetes exposure response curves were included in GBD 2019 and suggest a steep dose response curve at lower doses with flattening at very high doses.

Ischemic Heart Disease and Cerebrovascular Events

The association between short-term $PM_{2.5}$ and cardiovascular mortality has been extensively described. Three early meta-analyses between 2012 and 2016 demonstrated that $PM_{2.5}$ was associated with cardiovascular mortality. Although some of these were at high-exposure environments, the preponderance was from low-exposure environments.[32–34] On the basis of these analyses, a short-term increase of 10 μg/m^3 in $PM_{2.5}$ was associated with a 0.1% to 1.0% excess in risk of cardiovascular death. In some of these analyses, an association was also seen with other gaseous copollutants such as NO_2 and SO_2.[32] Chronic exposure studies using annual $PM_{2.5}$ concentrations have shown much higher estimates ranging from an increase of 15% to 30% per 10 μg/m^3 $PM_{2.5}$ in relative risk for CV mortality at the lower range of exposures typically seen in North America.[35,36] Postinfarct mortality and quality of life are also influenced by prevailing concentrations of $PM_{2.5}$.[37] Figure 3.3 depicts the GBD 2019 IER and a meta-regression curve (meta-regression Bayesian, regularized, trimmed [MR-BRT]) that incorporates a range of cohort studies. The curves for the typical annual average exposures are depicted. In general, the incorporation of studies across the exposure range from ambient air pollution studies and some secondhand smoking studies have provided confidence across the exposure range. The GBD 2019 and meta-regression estimates are stronger than the 2017 estimates and importantly continue to demonstrate a flattening at extreme concentrations of $PM_{2.5}$ (>85 μg/m^3). Given the small number of studies at such high levels and because 97% of the global population lives in countries where population-weighted outdoor exposure was less than 84 μg/m^3, these results are largely relevant. An alternate Global Exposure Mortality Model (GEMM), using only ambient $PM_{2.5}$ data (excluding secondhand smoking) projected a much higher burden of disease when compared with the GBD IER estimates.[38]

There is an association between nonfatal MI and $PM_{2.5}$ levels with the evidence for ST-elevation MI being stronger than NSTEMI and unstable angina.[39–41] Men, older patients,[40] and those with risk factors for or established coronary artery disease seem to be most susceptible. Cross-sectional and prospective longitudinal cohort studies have demonstrated a positive association between estimated long-term exposure to $PM_{2.5}$, as well as distance to roadway (as a proxy for exposure), to surrogates such as endothelial function and atherosclerosis burden, when assessed by carotid intimal media thickness and coronary and abdominal aortic calcium.[42] In at least one study, an increase of 1 μg/m^3 of $PM_{2.5}$ from use of CT was associated with a 62% increased incidence of "high-risk" plaque (plaque with low attenuation, spotty calcium, and positive remodeling) at follow-up.[43] The association between stroke and air pollution exposure is robust with a very consistent association between short-term exposure and stroke risk. A 2019 meta-analysis of 80 studies found a 1% increase in stroke per 10 μg/m^3 increment of short-term $PM_{2.5}$ exposure. Associations were strongest for ischemic and hemorrhagic stroke.[44] Figure 3.3 demonstrates the association between long-term exposure and stroke, using GBD 2019 estimates. In general, the association between stroke and annual $PM_{2.5}$ concentrations are higher compared with that for IHD. Mechanisms underlying the association between $PM_{2.5}$ and cerebrovascular disease are likely similar to those of coronary artery disease and MI.

Blood Pressure and Hypertension

Prior meta-analyses have shown a consistent association between short-term ambient $PM_{2.5}$ levels and blood pressure (BP) levels.[5,6] Short-term (in hours to days) variation in antecedent $PM_{2.5}$, as well as controlled exposure to both fine and coarse PM, is associated with increases in BP. In large prospective cohorts, annual average $PM_{2.5}$ was associated with not only correspondingly larger increases in BP (compared with short-term elevations) but was also associated with incident hypertension. The associations between $PM_{2.5}$ and hypertension have been observed at both low levels (United States and Canada) and at high levels of $PM_{2.5}$ (China and India), with no evidence of flattening of effect estimates.[5,6] Exposure to a range of particles, including UFPs (diesel exhaust) and $PM_{2.5}$ and PM_{10} particles, has been shown to increase BP within hours in carefully performed randomized studies.[5,6] Conversely, lowering $PM_{2.5}$ using air filtration devices in randomized trials has also shown a consistent decrease in BP, suggesting a cause-and-effect relationship.[28] The mechanisms underlying BP increases in the short term in humans might involve rapid alterations in autonomic tone, redox stress, and alteration in vascular stiffness and endothelial dysfunction.[31,45] Experimental models of hypertension involving both low and high renin forms of hypertension have suggested an exacerbation of BP with $PM_{2.5}$ exposure secondary to changes in vascular redox and inflammation. Central sympathetic activation related to

inflammation in the hypothalamus seems to be involved at least based on a few experimental studies.

Insulin Resistance and Diabetes

Studies in both low- and high-exposure environments have shown a clear association between $PM_{2.5}$ exposure incidence of diabetes and risk for diabetes-related mortality.[30,31,46] Based on exposure-response relationships derived from a cohort of veterans, ambient $PM_{2.5}$ has been suggested to contribute to approximately 3.2 million (95% UI 2.2 to 3.8) incident cases of diabetes, approximately 8.2 million (95% UI 5.8 to 11.0) DALYs and 206,105 (95% UI 153,408 to 259,119) diabetic deaths.[47] The mechanisms involve exaggeration of insulin resistance, inflammation in liver and white adipose tissue, reduced thermogenesis, and central nervous system inflammation resulting in alterations in metabolism.[46,48–50]

Heart Failure

The associations between $PM_{2.5}$ and HF are less consistent. A 2013 meta-analysis of 35 studies showed that 10 $\mu g/m^3$ increments in $PM_{2.5}$ were associated with 2.12% increase in HF hospitalizations or death, with strongest associations noted on the day of exposure.[51] Based on these relationships, it was estimated that reduction of 3.9 $\mu g/m^3$ of $PM_{2.5}$ in the United States would prevent approximately 8000 HF hospitalizations and save greater than 300 million U.S. dollars annually.[51] Acute increases in $PM_{2.5}$ are associated with increased right heart and filling pressures. Long-term exposure to $PM_{2.5}$ in mice leads to adverse ventricular remodeling as assessed by major histocompatibility complex isoform switch and fibrosis, alterations in flow reserve, reduced systolic function, contractile reserve, and worsening of diastolic function.[52] $PM_{2.5}$ inhalation may also lead to adverse remodeling of the right ventricle, partly due to lung inflammation and vascular remodelling.[53] The delineation of the types of HF that are most susceptible to $PM_{2.5}$ exposure need further work.

Arrhythmia

In a 2020 meta-analysis involving 572 patients with implantable cardioverter defibrillators and 1689 events, each 10 $\mu g/m^3$ increment in $PM_{2.5}$ was associated with 24% increase in odds for atrial fibrillation (AF).[54] $PM_{2.5}$ has also been associated with increased stroke risk in patients with AF. In healthy individuals and in those with prior cardiovascular disease, both acute and chronic exposure to $PM_{2.5}$ has been associated with increased burden of premature ventricular contractions. The mechanisms between arrhythmic risk and $PM_{2.5}$ are unclear, although changes in autonomic tone, loading conditions, and inflammation could play a role.

Venous Thromboembolism

Various studies have shown that acute and chronic exposure to $PM_{2.5}$ leads to increase in thrombosis markers (D-dimer, fibrinogen).[5,6] Several studies have examined the association between air pollution and venous thromboembolism (VTE) events. A 2016 systematic review of 11 studies and greater than 500,000 events suggested a link between multiple $PM_{2.5}$ with VTE risk (8/11 studies).[55]

Chronic Kidney Disease

Emerging evidence has linked air pollution to chronic kidney disease (CKD). Multiple studies have suggested links between long-term $PM_{2.5}$ exposure and decline in kidney function, incident or prevalent CKD, and kidney failure in general populations.[56–58] In a study in patients with CKD and with mean glomerular filtration rate of 35 mL/min/1.73 m^2, each 7.5 $\mu g/m^3$ (interquartile range) increase in $PM_{2.5}$ was associated with a 19% increase in risk for renal replacement therapy with evidence for a dose-response relationship. The mechanisms may involve both soluble nephrotoxic components and biologic mediators that may result in glomerular and podocyte injury.

Mechanistic Insights Into Air-Pollution and Cardiovascular Risk

Mechanistic studies have shown that a number of distinct, yet interrelated processes mediate the cardiovascular effects of $PM_{2.5}$.

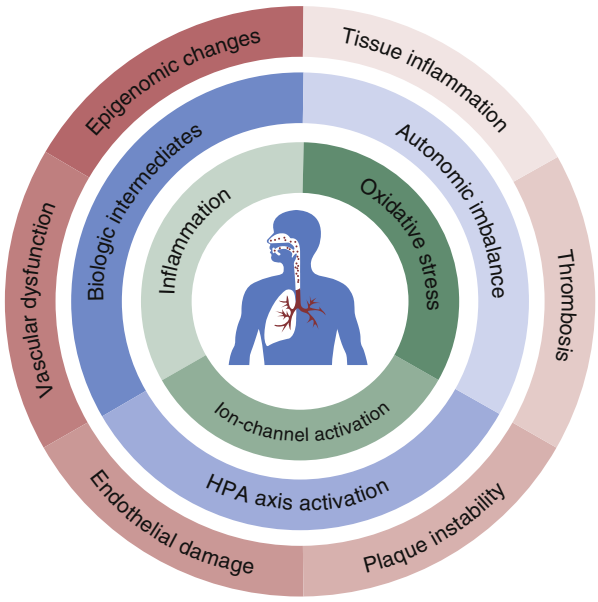


FIGURE 3.4 Mechanisms of air pollution–related cardiovascular disease. The *green circle* indicates recognition pathways. The *blue circles* indicate mechanisms of systemic transmission, and the *brown circles* indicate end-organ effector mechanisms. (Adapted from Al-Kindi S, Brook RD, Biswal S, et al. Environmental determinants of cardiovascular disease: lessons learned from air pollution. *Nat Rev Cardiol*. 2020;17:656–672.)

Importantly, these mechanisms largely overlap with conventional risk factors.[31] The mechanisms mediating cardiovascular disease in response to air pollution may be viewed as cascading responses beginning with pollutant inhalation in the lung that results in initiating responses; recognition and transmission of these responses; and finally end-organ effector mechanisms (Fig. 3.4). Initiating pathways include (a) exogenous/pollutant-mediated ion channel/receptor activation; (b) endogenous oxidative stress; and (c) pulmonary inflammation. Multiple receptors have been implicated in the initial recognition of pollutants, including families such as Toll-like receptors (TLRs) and nucleotide oligomerization domain (NOD)-like receptors (NLRs), which have been implicated in the initial sensing of particles and transduction of responses including generation of reactive oxygen species (ROS). The latter, although fundamentally important in physiology at low levels, may turn maladaptive, with generation of high levels of ROS with continued exposure over long durations and/or when antioxidant responses become inadequate.[59] Chronic oxidative stress with particulate pollution is likely facilitated through frustrated phagocytosis of particles in alveolar macrophages, depletion of antioxidant defense systems, and a failure of the inflammation to resolve not only in the lung but systemically.[60] Both innate and adaptive immune mechanisms in the lung, as well as systemically, in both human experimental animal models have been extensively implicated.[60] Transmission pathways include biologic intermediates (e.g., oxidized lipids, cytokines, microparticles, vasoconstrictors), activated immune cells, and autonomic imbalance/afferent neurologic circuits leading to sympathetic and/or hypothalamic pituitary adrenal axis activation and direct translocation of pollutants to the systemic circulation.[5,6,31,45] Nanoparticles in the ultrafine range have been shown to directly leach into the circulation and penetrate atherosclerotic plaque in humans and mice.[61] Finally, end-organ effector mechanisms responsible for cardiovascular and metabolic responses may vary in time scales from acute perturbations to chronically mediated consequences that occur with persistent exposure (see Fig. 3.4). These include: (1) endothelial barrier disruption and/or dysfunction, (2) tissue/organ inflammation, (3) heightened coagulation-thrombosis, (4) vasoconstriction/increased BP, and (5) secondary tissue damage/responses (plaque instability).[5]

Additional mechanisms can include direct disruption of the blood-brain barrier by ultrafine particulate and gaseous copollutants which may influence autonomic nervous system as well as resulting in CNS inflammation.[62–65] Acute vascular dysfunction, including arterial stiffness, conduit and microvascular alterations in flow, and alterations in thrombotic profile, that in predisposed individuals may potentiate ischemia, has been well described.[45] Chronic elevations in BP in response to exposure to $PM_{2.5}$ can result in left ventricular fibrosis and left ventricular diastolic dysfunction, progression of atherosclerosis, and multiple abnormalities associated with the insulin resistance phenotype.[66–72] Recent studies have implicated circadian rhythm alterations with $PM_{2.5}$ exposure.[73] These seem to affect both central and peripheral pathways in circadian rhythm and are similar to light at night exposure. Given the central role of circadian rhythm in organismal homeostasis including metabolic and cardiovascular responses, it is conceivable that such broad alterations may serve as common pathways that tilt the balance toward susceptibility to variety of disorders including cardiometabolic disorders and cancer. Epigenomic alterations occurring in response to pollutant exposure have been noted to occur with a number of pollutant exposures.[74] Although attractive as a facilitator of broad transcriptional reprogramming, the emerging view seems to suggest that alterations in chromatin dynamics may occur broadly, in response to any perturbation including air pollution, and may be reversible with air pollution exposure cessation at least in animal models.[73] In mice chronically exposed to $PM_{2.5}$, genome-wide reversible modifications in promoter and enhancer sequence were noted, many of which overlapped effects of high-fat diet.[73] A few studies have shown locus-specific methylation changes in CpG islands prenatally, in response to pollutants such as NO_2, that persist in the newborn, while limited human cohort studies have shown methylation changes in genes and/or within networks enriched for pathways related to inflammation, thrombosis, insulin resistance, and lipid metabolism.[75–78] These changes, although small, could be nevertheless important. The effect of air pollution exposure on genome-wide methylation status and chromatin structure in humans is not well understood.

Windows of Exposure, Susceptibility, and Vulnerability

Cohort studies involving assessment of long-term exposure consistently show higher estimates compared with short-term exposure suggestive of a cumulative effect (exposure over time).[79] Although exposure over years may promote anatomic progression of the burden of atherosclerotic plaque or other markers of cardiometabolic risk, this is ultimately not the process responsible for an acute event. However, chronic exposure may facilitate the development of "vulnerability" that may precipitate an acute coronary event including a milieu of predisposition to other triggers including acute changes in risk factors such as BP and air pollution.[43,80] The epidemiologic studies are indeed consistent with this notion, where attributable risk to $PM_{2.5}$ is related to exposures in the short and intermediate term (hours to 1 to 2 years). Larger but progressively smaller relative increases in health effects (i.e., in a less-than-additive fashion) are induced by prolonging the exposure window or follow-up period beyond 1 to 2 years.[80] Epidemiologic studies have shown that older individuals with multiple risk factors, and prior cardiovascular disease are more susceptible to $PM_{2.5}$ cardiovascular effects. Vulnerable populations include nonwhite populations in the United States living in densely populated urban environments. Nonwhites in the United States had 28% higher exposures (black individuals had 1.54 times the exposure compared with the overall population).[81] A review of 37 studies found that poorer communities often experience higher levels of air pollution in North America, Europe, Asia, Africa, and Oceania (with mixed results in Europe).[82] The interaction between susceptibility and vulnerability to $PM_{2.5}$ may identify extremely high-risk groups, for whom interventions may lead to significant improvement in health outcomes.

Air Pollution Alerts and Approaches to Communicate Risk

Currently, there is no accepted consensus on communication of air pollution levels and risk. The U.S. EPA's Air Quality Index (AQI) converts concentrations of the six regulated criteria air pollutants into levels of increasing health concern.[10] Although only a small proportion of the population follows the accompanying recommendations, those who do, can reduce exposure. Tools to communicate long-term exposure risk are needed to more accurately convey the major portion of the health risk due to air pollution. The increased access and availability of air pollution monitoring data from low-cost sensors may well have a transformative impact on understanding personal level exposures on cardiovascular health and, importantly, facilitating healthy behaviors. However, work in aligning current approaches of pollutant ascertainment with next-generation technologies is a barrier that will need to be addressed. A recent American Heart Association (AHA) statement provides a simple guide based on $PM_{2.5}$ levels and the underlying risk to help guide personal level interventions if necessary.[28]

Societal and Personal Strategies to Mitigate Cardiovascular Effects of Air Pollution

Urban strategies including land use, green belts, separation of pollution sources (industrial factories, roads), and planned residential communities that emphasize healthy living can avert not only air pollution but other concomitant exposures as well. The ultimate solution to avert air pollution exposure is its elimination. A shift to zero emissions by 2045 with near 90% elimination by 2035, a minimal requirement for averting catastrophic climate changes, should help improve air quality in the near term and produce large public health effects.[83] Two recent AHA statements reviewed policy interventions and personal-level protective measures against $PM_{2.5}$ exposure, many of which are low/no cost and logical.[28,84] Both societal (Fig. 3.5) and personal measures (eTable 3.4) are necessary to protect the public living in high air-pollution environments, susceptible patients, and individuals traveling to high exposure areas. Personal measures include avoiding commuting in traffic, use of car air conditioning, and closing windows while commuting in an automobile. Improvements in home and building designs that include home ventilation and air conditioning with appropriate induct air filters can help avert exposures while indoors. Face masks (cloth masks, surgical, N95, N99) are cheap, and widely available and have obtained widespread societal acceptance in the context of COVID-19 exposure. Cloth masks have the least filtration efficiency for $PM_{2.5}$, whereas N95 masks have the highest efficacy.[28] Multiple small randomized studies of N95 masks worn over periods of hours to days have demonstrated significant reduction in BP and improvement in markers of autonomic function (e.g., heart rate variability). Portable air cleaners (PACs) are practical and inexpensive in-home strategies suited for at-risk populations and can acutely reduce $PM_{2.5}$ exposures by as much as 30% to 60%.[85] Several small short-term human studies mostly in healthy populations but a few in susceptible patients have provided the proof of concept that reductions in $PM_{2.5}$ exposures with PACs can result in rapid, albeit small, reductions in BP and other markers of cardiometabolic risk. Ultimately, randomized controlled trials to test the efficacy of exposure mitigation on clinically relevant endpoints may be needed.

CLIMATE CHANGE

Climate change is by far the greatest existential threat confronting humanity and public health. In October 2018, the United Nations Intergovernmental Panel on Climate Change (IPCC) reported that global carbon emissions must be halved by 2030 to limit warming to 1.5°C. Greenhouse gas (GHG) emissions, primarily from fossil fuel emissions, lead to climate change but also contribute to adverse health effects, and conversely, climate change may lead to an increase in

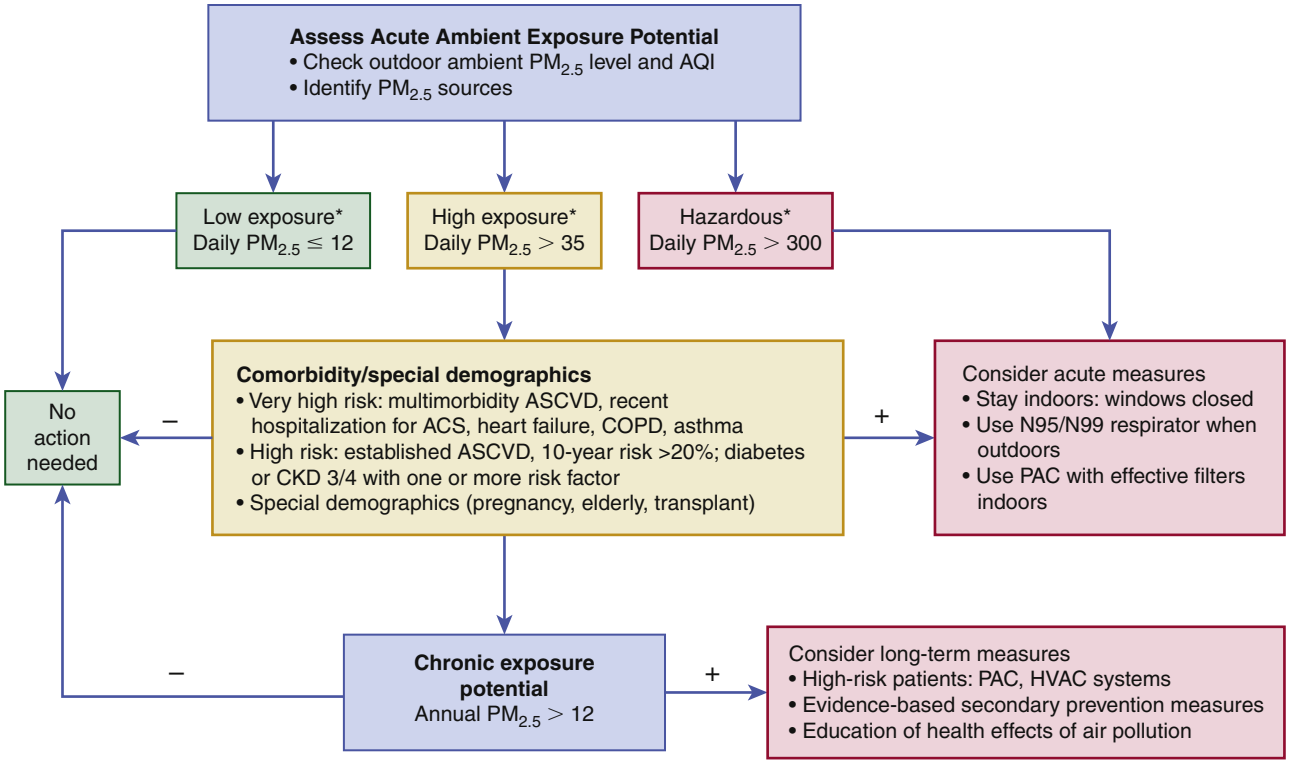


FIGURE 3.5 Public health approach based on $PM_{2.5}$ levels. (From Rajagopalan S, Brauer M, Bhatnagar A, et al. Personal-level protective actions against particulate matter air pollution exposure: a scientific statement from the American Heart Association. *Circulation*. 2010;121:2331–2378.)

PM and ground-level ozone.[19] GHGs and air pollutants are, to a large extent, emitted from the same sources. As part of climate change and global warming, extreme weather conditions, wildfires, and flooding can in turn increase both air pollution and water pollution. Rising temperature may also increase ground-level ozone that may be very difficult to eliminate. The solutions to mitigate climate change are fortunately the same that are needed to combat air pollution (see Fig. 3.5). These are structural in nature and importantly involve a total and complete shift to clean renewable energy sources. Recent data suggest that the technical and economic feasibility of achieving 90% clean (carbon-free) electricity in the United States by 2035 currently exists.[83] Not only is such a strategy imperative, but indeed strategy is critical in stimulating economic health while preserving human health.

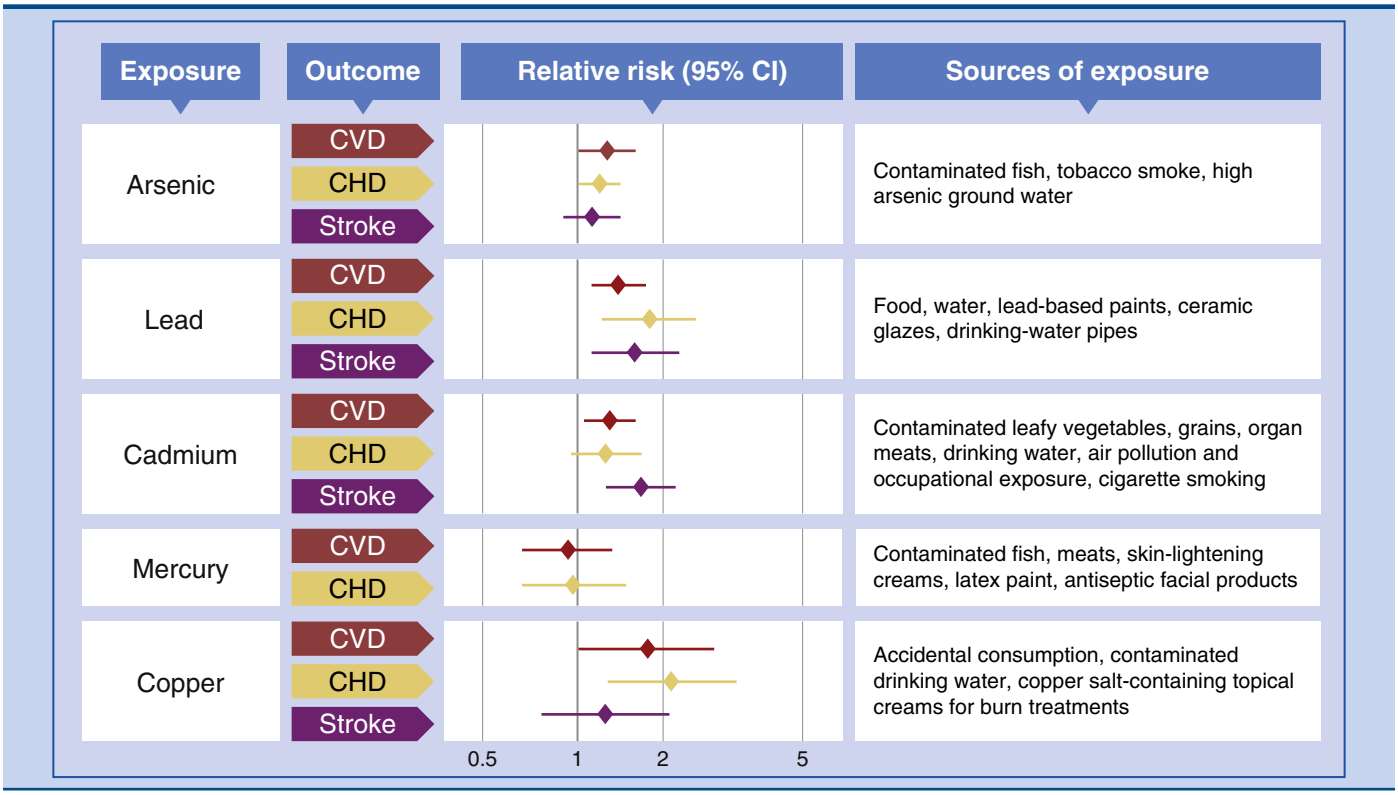
NOISE POLLUTION AND CARDIOVASCULAR DISEASE

Emerging epidemiologic and mechanistic evidence suggests a link between noise pollution and cardiovascular disease.[30,31] The major source of chronic noise exposure is transportation (cars, trains, and airplanes) and occupational settings. Noise may result in a stress response involving the hypothalamus, the limbic system, and the autonomic nervous system with activation of the hypothalamus-pituitary-adrenal (HPA) axis with an increase in heart rate and in levels of stress hormones (cortisol, adrenalin, and noradrenaline), enhanced platelet reactivity, vascular inflammation, and oxidative stress.[86] Subconscious biologic responses may continue during nighttime in sleeping subjects, at low noise levels, and may disrupt circadian rhythm and thereby induce chronic disease. Noise is measured by decibel scale (dbA, a-weighted decibel scale adapted to human hearing frequencies). In cities in Asia, the proportion of the population reaching L_{den} levels (day-evening-night level, i.e., the average sound pressure level measured over a 24-hour period) of 60 to 64 dBA is very high.[87] For reference, an aircraft taking off is approximately 120 dBA, and a car driving is approximately 70 dBA. Several meta-analyses (including by the WHO) have shown an association between noise and CAD, with a 6% to 8% increment in incidence of coronary artery disease for each 10 dBA above 50 dBA of traffic noise.[86] These findings were consistent and persisted after adjustment for air pollution and smoking. Noise has also been linked with hypertension in multiple studies. A meta-analysis of 24 cross-sectional studies have shown that road traffic noise was associated with 3.4% increased odds of elevated BP per 5 dBA above 45 dBA.[88] The data on occupational noise are conflicting, with results from a few studies providing conflicting evidence. Noise in animal models has been shown to lead to inflammation, oxidative stress, and neurohormonal activation and is accompanied by transcriptomic changes in genes regulating vascular function, remodeling, and cell death.[89] Likewise significant endothelial dysfunction, increase in stress hormone release and BP, and a decrease in sleep quality have been noted in response to nighttime aircraft noise.[90] Studies in humans have identified amygdalar activation (using ^{18}F-FDG PET/CT imaging) in response to transportation noise and its association with arterial inflammation and major adverse cardiovascular events.[91] It is important to note that noise pollution and air pollution may coexist, especially near roadways and airports. Thus, when estimating effects of noise pollution, it is important to account for air pollutants.

SYNTHETIC CHEMICALS AND CARDIOVASCULAR DISEASE

Exposure to synthetic chemicals is ubiquitous, and humans are often exposed to low levels. These are vastly heterogenous and include synthetic chemicals, industrial solvents, pharmaceuticals, pesticides/fungicides, phytochemicals, and plastics and are present in water, soil, food, and consumer products. Many are endocrine-disrupting compounds (EDCs). Two major chemical entities include persistent organic pollutants (POPs) and plastic-associated chemicals (PACs). POPs contain a backbone of halogens (Cl, Br, or F), demonstrate resistance to degradation, and may be lipophilic or

TABLE 3.2 Sources of Metallic Pollutants and Cardiovascular Risk



Adapted from Chowdhury R, Ramond A, O'Keeffe LM, et al. Environmental toxic metal contaminants and risk of cardiovascular disease: systematic review and meta-analysis. *BMJ*. 2018 Aug 29;362:k3310.

nonlipophilic. Lipophilic POPs include polychlorinated biphenyls (PCBs), dioxins, brominated flame retardants, and organochlorine (OC) pesticides. Nonlipophilic POPs include perfluoroalkyl substances (PFASs) encountered in water repellants and firefighting foam. Although almost all POPs and some PFASs have been banned, dietary intake from fat fish and meat from prior releases continue to be a problem. Although several cross-sectional studies link POPs with lipid abnormalities, carotid atherosclerosis, MI, and stroke, cohort studies with longitudinal data are limited. PACs are produced in high volumes for consumers and include bisphenol A (BPA), phthalates, and chemicals found in personal care products (e.g., parabens). The majority of chemicals in this group are measurable in blood routinely given their high rate of utilization in daily life. Although POPs have been associated with obesity and insulin resistance, the strongest evidence is for bisphenols and other nonpersistent chemicals.[92] A meta-analysis estimated the pooled relative risk for type 2 diabetes to be 1.45 (95% confidence interval [CI] 1.13 to 1.87) for BPA and 1.48 (95% CI 0.98 to 2.25) for phthalates.[93] Although biologic plausibility for cardiovascular disease with POPs and PACs exists, there is a need for high-quality studies to establish causation.[94]

METALLIC POLLUTANTS AND CARDIOVASCULAR DISEASE

Studies spanning greater than 50 years have linked heavy metal exposure with adverse cardiovascular health risks. The CDC's Agency for Toxic Substances and Disease Registry Priority List of Hazardous Substances provides a rank based on frequency, toxicity, and potential for human exposure. Arsenic, lead, and mercury are in the top 3 in this list, with cadmium coming in at 7. Table 3.2 provides the sources and relevant details for four major toxic metals, together with the relative risks for cardiovascular events based on a meta-analysis. Only arsenic, lead, and cadmium showed a dose-response relationship.[95] Regulations to limit lead exposure have resulted in a steep decline, and currently greater than 99% of the U.S. population have lead levels less than 10 μg/dL. However, living in older homes, occupational exposures, and atmospheric lead constitute sources of continued exposure.[96] Lead has been linked with hypertension, MI, and cardiovascular mortality.[97,98] The association between lead and BP and incident hypertension has been noted in multiple studies, with a variety of mechanisms being implicated, including kidney impairment, renin-angiotensin aldosterone system (RAAS) activation, oxidative stress, and nitric oxide dysregulation.[99–103] In the second National Health and Nutrition Examination Survey, individuals with blood lead levels of 20 to 29 μg/dL versus less than 10 μg/dL had a 46% relative increase in all-cause mortality (RR 1.46 [1.14 to 1.86]) and 39% in cardiovascular mortality (RR 1.39 [1.01 to 1.91]).[104] A meta-analysis showed that top versus bottom tertile of lead exposure was associated with an 85% risk of coronary artery disease (8 studies), 63% risk for stroke (6 studies), and 43% risk for cardiovascular disease (10 studies), with a linear dose-response relationship. Evaluation of lead exposure can be done using blood lead levels for recent exposures and x-ray fluorescence techniques for overall lead burden.

CHALLENGES AND OUTLOOK FOR THE FUTURE

Given the outsized effect of the environment on cardiovascular health, it is imperative that there be a new focus on preventable exposures.[105] The switch to green energy sources will help mitigate a number of copollutants related to air pollution but also help limit exposures to other toxic components that are released into the soil and water as well as noise. However, it is entirely conceivable that new exposures will emerge. With a high level of societal awareness facilitated through education and bold policy changes, it may be possible to eliminate almost all exposures at least to a point where their overall impact on human health is minimal.

ETABLE 3.3 Definitions and Description of Air Pollutants

COMPONENT	NOTES
Sulphate (SO_4^{2-})	Present mainly as a secondary ammonium sulphate component $(NH_4)2SO_4$ from oxidation of SO_2 followed by reaction with NH_3 mainly from agricultural sources.
Nitrate (NO_3^-)	A secondary component normally present as ammonium nitrate (NH_4NO_3), which results from the neutralization by NH_3 of HNO_3 vapor derived from oxidation of NOx emissions, or as sodium nitrate ($NaNO_3$) due to displacement of hydrogen chloride from NaCl by HNO_3 vapor.
Ammonium (NH_4^+)	Generally, in the form of $(NH_4)_2$ SO_4 or NH_4NO_3 from NH_3 emissions.
Sodium (Na^+) and chloride (Cl^-) ions	From primary emissions of sea-salt particles.
Elemental carbon	Black, graphitic carbon formed during the high-temperature combustion of fossil and contemporary biomass fuels.
Organic carbon	Carbon in the form of organics either primary from automotive/industry from oxidation of volatile organic compounds (VOCs).
Mineral material	Crustal materials are rich in Al, Si, Fe, and Ca. These are present in crustal PM_{10}. Nickel, cadmium, lead, and arsenic are present in combustion $PM_{2.5}$.
Water	Water-soluble components, especially $(NH_4)_2$ SO_4, NH_4NO_3, and NaCl, take up water from the atmosphere at high relative humidity, turning from crystalline solids into liquid droplets.

ETABLE 3.4 Personal Interventions to Mitigate Air Pollution Health Effects

INTERVENTION	PERSONAL PROTECTION TYPE	USE CONSIDERATIONS
Portable air cleaners (PACs)	Electronic air cleaners	• Electrostatic precipitators and electronic air filters that contain ionizers can produce ozone and should be avoided.
	Electrostatic precipitator	• Use of PACs with HEPA filters can reduce indoor $PM_{2.5}$ exposures and are preferred. A PAC with clean air delivery rate (CADR) to meet room size specifications should be used. • Consider use of indoor PACs with HEPA filters, especially in vulnerable and high-risk populations living in heavily polluted location or during heavy air pollution episode. If PACs cannot cover home, create clean sleeping room. • Replace HEPA filters periodically when their capacity is reached (saturated with particles). The California Air Resources Board has information on selecting portable and central air cleaners, including information on choosing the correct size for room(s). http://www.arb.ca.gov/research/indoor/acdsumm.pdf. EPA provides detailed technical information on air cleaners. http://www.epa.gov/indoor-air-quality-iaq/guide-air-cleaners-home.
Face masks* and respirators†	N95/N99 respirators	• Certified N95/N99 respirators with or without exhalation valves are validated as personal protection devices and can markedly reduce $PM_{2.5}$ when worn properly (e.g., tight facial seal). For information on how to use: http://oehha.ca.gov/air/risk_assess/wildfirev8.pdf Consider use of respirators outdoors when air pollution levels are high (heavily polluted city, air pollution event, wildfire) and in susceptible or high-risk individuals who visit/travel to locales with high levels of air pollution.
HVAC	Mechanical in-duct air filter	• Consider properly installed MERV 7–13 (or equivalent) filter and change filters frequently with high levels of indoor or ambient $PM_{2.5}$.
	Ventilation	• Consider closing windows to limit indoor penetration of outdoor $PM_{2.5}$ during heavy pollution.
	Air conditioning	• Use filters with a high MERV and run furnace/air conditioning fan continuously during high pollution.
Automobiles	Air conditioning and cabin air filters	• Consider closing windows and use air conditioning in polluted areas (such as freeways, rush-hour traffic, near diesel trucks). Recirculation mode can reduce exposures to ambient particles. • Consider using the highest efficiency air filter available for the cabin and frequent changes in areas with high levels of chronic $PM_{2.5}$ exposure.

*Cloth or procedural (e.g., surgical) masks are an inferior consideration, whose use may induce a false sense of health protection and do not reliably reduce $PM_{2.5}$ exposures. They are neither designed nor recommended for protection against air pollutants including $PM_{2.5}$. If personal respirators are not a viable option, surgical masks with attention to tight facial/oronasal seal may be considered. They need to be changed frequently in conditions of high ambient levels of $PM_{2.5}$.
†List of Certified Air Cleaning Devices: http://www.arb.ca.gov/research/indoor/aircleaners/certified.htm

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