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Environmental determinants of cardiovascular disease: lessons learned from air pollution

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Abstract

Air pollution is well recognized as a major risk factor for chronic non-communicable diseases and has been estimated to contribute more to global morbidity and mortality than all other known environmental risk factors combined. Although air pollution contains a heterogeneous mixture of gases, the most robust evidence for detrimental effects on health is for fine particulate matter (particles ≤2.5 μm in diameter ($PM_{2.5}$)) and ozone gas and, therefore, these species have been the main focus of environmental health research and regulatory standards. The evidence to date supports a strong Link between the risk of cardiovascular events and all-cause mortality with $PM_{2.5}$ across a range of exposure levels, including to levels below current regulatory standards, with no 'safe' lower exposure levels at the population level. In this comprehensive Review, the empirical evidence supporting the effects of air pollution on cardiovascular health are examined, potential mechanisms that Lead to increased cardiovascular risk are described, and measures to reduce this risk and identify key gaps in our knowledge that could help address the increasing cardiovascular morbidity and mortality associated with air pollution are discussed.

The *Lancet* Commission on pollution and health, formed on the basis of data from the Global Burden of Disease (GBD) study[1], has estimated that air pollution (both indoor and ambient) is the single most important environmental factor presenting a risk to health and represents a greater disease burden than polluted water, soil contamination and occupational exposures combined[2]. The populations that are most vulnerable to air pollution live in cities in low-income and middle-income countries, and make up 55% of the global population. Air pollution is a heterogeneous mixture of particulate matter (PM), gases (ranging in size from

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a few nanometres to several micrometres) and gaseous co-pollutants that can exist in a particulate phase. Although a variety of gases (such as ozone gas) have been shown to have adverse effects on health, the largest body of evidence supports fine PM (≤2.5 μm in diameter ($PM_{2.5}$)) as the most important environmental threat to global public health. Although $PM_{2.5}$ has been implicated as a cause in numerous non-communicable diseases, more than half of all the deaths associated with these diseases are from cardiovascular causes[1–6]. In this Review, we discuss the latest advances in our understanding of cardiovascular risk mediated by air pollution, including the relationship between air pollution, global warming and climate change, the mechanisms underlying the development of cardiovascular disease (CVD) caused by air pollution, and approaches to mitigate cardiovascular risk and improve health outcomes in individuals living in areas with high air pollution.

Nature of PM and gaseous co-pollutants

Guidance documents from Europe, the USA and the WHO have extensively reviewed the size fractions and chemical constituents of the main gaseous air pollutants and their effect on health[3–5]. Whereas previous regulatory standards have principally focused on PM mass in several different fractions, including $PM_{2.5}$ and coarse PM (2.5–10 μm), PM mass is well acknowledged to be an imperfect metric to understand effects on health. The reasons for assessing PM on the basis of size fractions are primarily related to the ease of quantitative estimation of the mass of each fraction and, conversely, the complexity of alternative measures to quantify pollutants in a mixture that varies by source as well as spatially and temporally. No standards exist for specific particulate constituents, such as organic or elemental carbon, metals or the ultrafine size fractions within the nanoparticulate range ($PM_{0.1}$). Similarly, although there is strong evidence that road traffic-related air pollution and coal combustion have adverse effects on health, specific sources of pollution are not treated differently in major air-quality standards[6,7].

$PM_{2.5}$ is derived primarily from fossil fuel combustion, industrial processes and power generation. $PM_{2.5}$ consists of a mixture of primary particulates, such as elemental carbon; secondary particulates, including organic aerosols derived from volatile compounds; and sulfate and nitrate particles generated by conversion from primary sulfur and nitrogen oxide emissions[8]. Ultrafine particles are mainly derived from primary combustion, are typically short-lived and are influenced by the proximity to the source of emission. Owing to the small diameter of ultrafine PM (<0.1 μm), these particles have a large surface area and wide-ranging reactive chemistry, and act as vectors for vapours and gases condensed on their surface. Some nanoparticulates might even be able to disseminate into the systemic circulation after inhalation[9]. Although ultrafine PM can be highly toxic, the epidemiological data to implicate this fraction as an independent predictor of cardiovascular events are only now starting to emerge. For example, in a prospective study involving 33,831 Dutch residents, exposure to ultrafine PM was associated with an increased risk of heart failure and myocardial infarction (MI)[10]. In the National Particle Component Toxicity Initiative research programme, pollutants from fossil fuel combustion were consistently associated with both short-term and long-term adverse effects of $PM_{2.5}$ exposure[11]. $PM_{2.5}$ that originated from residual oil combustion and road traffic sources was most closely associated

with short-term adverse effects, and PM from coal combustion was more closely associated with long-term effects.

Among the gaseous pollutants, tropospheric and ground-level ozone gas has been well established as a mediator of adverse effects on health[3,12–14]. Tropospheric ozone gas is a secondary pollutant created by chemical reactions between nitrogen oxide and volatile organic compounds in the presence of sunlight. The current standard for ozone gas, as defined by the US National Ambient Air Quality Standards, is 70 ppb averaged over 8 h (REF[6]) (TABLE 1). However, multiple epidemiological studies have shown an increased risk of severe asthma and cardiopulmonary mortality at levels of <70 ppb (REFS[15,16]). Of note, although 'criteria' pollutants (that is, those with air-quality standards) are regulated individually through limits on emissions or ambient air-quality standards set by governments, the effects of air pollution are driven by pollutant composition. Therefore, rather than these individual constituents being viewed as causal, they might actually serve as surrogate markers for other chemical species or the combinatorial chemistry of multiple components that might, in turn, interact with other aspects of the physical environment or combine with socioeconomic and biological factors to determine health effects (the so-called pollutome)[14,17–19].

PM sources and cardiovascular risk

The cardiovascular effects of $PM_{2.5}$ are known to vary according to source and pollutant composition (FIG. 1). From the perspective of exposure prevention, understanding the sources, composition and spatial and temporal characteristics of $PM_{2.5}$ is of critical importance. For example, road traffic-related air pollution peaks during the late morning and evening rush hours and varies in composition even within short distances[6,7]. Meteorological conditions, such as atmospheric stability, can substantially alter the horizontal propagation of particles and, therefore, the proportion of the population exposed[20]. Furthermore, marked differences in primary combustion pollutants that originate from road traffic, such as nitrogen oxides (NO and NO_2) and particulate black carbon, have been found between urban and rural areas[21]. Exposures from wildfires, dust storms and volcanic eruptions are becoming more prevalent with climate change, with close geographical proximity of large populations to these events precipitating high levels of exposure. Smoke from landscape fires can affect communities in both rural and urban areas, sometimes hundreds of kilometres from the source. Indeed, the pollutants released by wildfires, dust storms and volcanic eruptions seem to mediate similar cardiovascular effects as those mediated by fine PM ($PM_{2.5}$)[22–24].

From a compositional perspective, sulfates and organic carbon are most consistently associated with cardiovascular risk, given that they originate largely from fossil fuel combustion. The 2015 guidance statement from the UK Committee on the Medical Effects of Air Pollutants suggests that particulate sulfates are most consistently associated with adverse effects on health, with less evidence for nitrates and other components[25]. In the California Teachers Study[26], organic carbon and sulfates were more strongly associated with cardiopulmonary mortality than other $PM_{2.5}$ constituents, such as iron, potassium, silicon and zinc. A follow-up study revealed that among approximately 45,000 women enrolled,

sulfate from fuel combustion and nitrates was associated with mortality from CVD and ischaemic heart disease (IHD), with nitrates having the highest hazard ratio per interquartile range and best fit of the data[27]. In a 2014 systematic review that quantified the associations between particle components and mortality, sulfate, nitrate and elemental and organic carbons were all linked with all-cause, cardiovascular and respiratory mortality[28]. Finally, an analysis of 445,860 adults enrolled in the American Cancer Society Cancer Prevention Study II[29] showed that the risk of IHD mortality associated with $PM_{2.5}$ derived from coal combustion was five times higher than the risk associated with overall $PM_{2.5}$ mass, suggesting that strategies to limit IHD deaths associated with $PM_{2.5}$ might be achieved through reductions in exposure to fossil fuel combustion, particularly coal-burning sources.

Household air pollution and CVD

Household air pollution is one of the major contributors to global air pollution-related health effects. The GBD study[1] estimated that household air pollution was linked with 2.6 million premature deaths worldwide in 2016 alone. Household air pollution encompasses a range of particles from diverse sources. The composition of household air pollution can vary widely, depending on geographical, socioeconomic and cultural factors. Up to 65% of outdoor air particles that are inhaled are breathed in when people are indoors[30]. Household air pollution levels in low-income and middle-income countries might originate from cooking and heating with biomass fuels[31]. In developed countries, cooking on gas stoves, burning incense and candles, use of aerosol sprays and use of cleaning products all contribute to indoor particle release. Communities in the western part of the USA in which wood burning is common might be exposed to high levels of ultrafine particles during winter. Whereas the association between respiratory outcomes and lung cancer is well established, evidence on the relationship between indoor air pollution and cardiovascular outcomes continues to emerge. A prospective study involving 271,217 adults in China followed up for a mean of 7.2 years showed that, compared with clean energy, the use of solid fuel was significantly linked with increased cardiovascular mortality (HR 1.20 (95% CI 1.02–1.41) with solid fuel for cooking versus HR 1.29 (95% CI 1.06–1.55) with solid fuel for heating) and all-cause mortality (HR 1.11 (95% CI 1.03–1.20) versus HR 1.14 (95% CI 1.03–1.26), respectively)[32].

Assessment of air pollution exposure

At present, >10,000 ground-level monitors in >1,000 cities around the world monitor hourly and daily levels of air pollutants. These stations cover a small percentage of inhabited land and therefore offer very limited information on exposure to air pollution among people living at a distance from any of these monitors. Advances in satellite technology have facilitated the use of aerosol column data to estimate ground-level pollutant concentration. Estimates of aerosol optical depth from these aerosol columns can be combined using chemical transport models and integrated with available ground-level monitor data to generate fusion model estimates of air pollutants, mainly $PM_{2.5}$ concentrations with resolutions down to 1 × 1 km grids[33,34]. These integrated estimates were used in the 2016 GBD study[1]. Other models have also incorporated land use data, meteorological data, road traffic density and other data determinants to refine the estimates of $PM_{2.5}$ levels[35,36].

All large-scale exposure models and estimates have strengths and limitations (FIG. 1). One major shortcoming of these models is that they cannot estimate the effect of the microenvironment, such as road traffic pollutants, indoor pollutants and changes in the location of individuals, on $PM_{2.5}$ levels. The current approach of using satellite estimates or regional ground-level monitoring data as surrogates for personal exposure has the potential for exposure misclassification error, given that only a modest correlation exists between ambient air pollution measures and personal exposure[37,38]. This correlation also varies by type and level of pollutant, meteorological conditions, availability of indoor ventilation, location and other factors[38]. Hand-held and home air quality monitors can provide data on personal $PM_{2.5}$ exposure[39]. Although these monitors are not yet widely used, in an era of cloud-based internet technology, their capacity to provide continually updated, personalized air pollution data with ultra-high spatial resolution will greatly advance the assessment of personal pollutant exposure and its links with health outcomes. However, the use of personal monitors for estimating exposure is currently associated with challenges, including high temporal variability in individual exposures, a lack of standards for health risk and complexities linked with their integration into health messaging[39]. Furthermore, the accuracy of most available monitors can be heavily influenced by humidity levels. As the numbers and connectivity of stationary, non-regulatory air quality monitors increase, location-specific, real-time estimates of air pollutants might become widely available and, importantly, integrated with navigation systems, facilitating real-time responses to avoid exposures in heavily polluted environments. However, their widespread use is currently hampered by the need for a better understanding of their use and integration into health messaging.

Global $PM_{2.5}$ levels and disease burden

Over 90% of the global population live in areas with $PM_{2.5}$ exposure exceeding WHO-recommended thresholds (<10 $\mu g/m^3$ annually and <25 $\mu g/m^3$ daily)[40]. This statistic is mostly driven by high $PM_{2.5}$ exposure in densely populated regions in Asia and Africa. The global average $PM_{2.5}$ exposure (weighted by population) increased from 39.6 $\mu g/m^3$ in 1990 to 49.6 $\mu g/m^3$ in 2016, with the majority of the increase occurring between 2010 and 2016 (REF[41]), mainly attributable to increasing global urbanization and industrialization. Pollution-attributed health effects disproportionately affect heavily populated countries, especially China and India[41]. In India, 77% of the population are exposed to an annual average $PM_{2.5}$ level of >40 $\mu g/m^3$.

Both short-term and long-term exposures to $PM_{2.5}$ concentrations above levels recommended by the WHO and the US Environmental Protection Agency (annual and daily levels of <12 $\mu g/m^3$ and <35 $\mu g/m^3$, respectively) are known to be associated with increases in morbidity and mortality[7–12]. The 2016 GBD study, using the Integrated Exposure-Response (IER) model, estimated that ambient $PM_{2.5}$ exposure resulted in 4.2 (95% CI 3.7–4.8) million deaths and 103.1 (95% CI 90.8–115.1) million disability-adjusted life years (DALYs) in 2015, which accounted for 7.6% of global mortality and 4.2% of global DALYs[41]. Moreover, household air pollution contributed an additional 2.8 million deaths and 85.6 million DALYs, whereas ozone gas added another 0.3 million deaths and 4.1 DALYs. A modelling study analysing a hypothetical scenario in which fossil fuels and all

anthropogenic emissions were completely eliminated showed that 3.61 (95% CI 2.96–4.21) million deaths per year could be avoided by removing fossil fuel-related emissions, with an additional 1.94 million lives saved per year if all anthropogenic sources of emission were also eliminated[42]. The rate of death associated with all anthropogenic emissions was threefold higher than the rate of death from other avoidable environmental risks, such as unsafe water and poor sanitation and hygiene, emphasizing the relative importance of air pollution for health on a global scale.

$PM_{2.5}$ and all-cause and IHD mortality

Understanding the dose-response relationship between $PM_{2.5}$ and cardiovascular events and mortality is critical in deriving credible estimates of the burden of disease. The development of such an IER is limited by the use of data from cohort studies of outdoor $PM_{2.5}$ levels and mortality conducted in areas with relatively low annual concentrations (<35 μg/m^3) of $PM_{2.5}$ compared with the global average (49.6 μg/m^3 in 2016)[43]. This lack of direct data from areas with higher concentrations of $PM_{2.5}$ has led to the integration of information from multiple sources of pollutants (including second-hand smoke, household air pollution and active smoking) by estimating the total mass of inhaled particles from each source, combining it with the equivalent concentration in the ambient atmosphere and deriving a single dose-response curve across a range of concentrations. The IER approach necessitates the assumption that PM composition from diverse sources is mostly the same, with uniform effects on health (an obvious oversimplification)[43,44]. The shape of an IER (a nonlinear response curve, with steep increases in a supralinear fashion at low levels of exposure and flattening at higher levels) has, however, been useful in providing a credible explanation for robust estimates of the risk from low doses of second-hand smoke or air pollution. Meanwhile, higher levels, although associated with higher absolute risk, are also linked with attenuation in the degree of increase in relative risk (FIG. 2). A meta-analysis of estimates from studies of long-term exposure to air pollution seems to confirm this relationship, especially at lower levels of exposure[45]. Despite the limitations of this IER (such as the assumption of equivalent toxicity from various sources, assumptions on uniform dose estimates and assumptions related to scaling exposures to $PM_{2.5}$ from various sources), it has been critical for estimating disease burden and continues to be refined with new empirical evidence. In a separate analysis that used an alternative Global Exposure Mortality Model (GEMM) that incorporates risk estimates derived from outdoor air pollution studies (41 cohorts from 16 countries, including China), an estimated 8.9 million avoidable deaths in 2015 were attributable to ambient air pollution alone, 120% larger than the risk function used in the GBD study[46]. Furthermore, the number of deaths attributed to ambient air pollution alone was much higher than the sum of the deaths attributed to IHD, stroke, chronic obstructive pulmonary disease (COPD), lung cancer and lower respiratory tract infections. The shape of the response curve of the GEMM is nearly linear at higher doses, with no evidence of flattening as the relative risk increases (FIG. 2). Regardless of whether the IER or the GEMM is used, on the basis of the dose-response relationship between $PM_{2.5}$ and mortality, no lower concentration threshold exists at which exposures can be considered safe at the population level[14].

Time frames of exposure

An important question in air pollution research is the time frames of exposure that are required to mediate acute cardiovascular events, such as MI. The concept of 'vulnerability' mandates that a series of events spatially clustered around an acute time frame combine to precipitate a seemingly stochastic event. A vulnerable individual who is at risk of an acute MI might experience high levels of road traffic air pollution and other factors, such as noise and external stressors, that combine to trigger an acute event. In this setting, acute variations in risk factors seem to be directly causative of the event. However, the occurrence of the acute event requires the concatenation of both a trigger and an underlying vulnerability. Time windows of chronic exposure, although relevant in the pathogenesis of atherosclerosis, or indeed in the vulnerable plaque that leads to an acute event, are not directly responsible for, but are permissive of, the acute event. Indeed, air pollution has been shown to contribute to the progression of atherosclerosis in animals and humans[19,47]. In atherosclerosis-prone mice, long-term exposure to low concentrations of $PM_{2.5}$ altered vasomotor tone, induced vascular inflammation, increased the accumulation of oxidized lipids and potentiated atherosclerosis[48,49]. Cohort and cross-sectional studies have also shown changes in plaque burden with prolonged exposure windows, which suggests that air pollution might affect the progression of lesion formation[14]. At the same time, chronic exposure to $PM_{2.5}$ might also facilitate the transition to a more vulnerable lesion[50].

In air pollution studies, the concept of the harvesting effect, or mortality displacement, is often used to illustrate the idea that air pollution-related deaths might occur in individuals whose health is already compromised, resulting in a reduction in the expected number of deaths after an initial increase[51]. Studies have used various statistical approaches to provide support for the idea that the phenomenon of harvesting not only affect these individuals, but also might affect individuals who were not previously thought to be 'at risk'[14]. Placing this phenomenon in the context of the modern concept of 'vulnerability· air pollution might be reinterpreted as indeed contributing to harvesting, in the sense that seemingly healthy at-risk individuals might succumb acutely to an episode of air pollution. This at-risk group includes a large population of individuals with asymptomatic (non-obstructive) coronary or peripheral vascular disease who are otherwise seemingly healthy, and is not limited to severely ill or extremely old individuals, as was the case in previous concepts of harvesting. The corollary of this concept is that only susceptible individuals can have a cardiovascular event or die in response to exposure to pollution. Those without any underlying atherosclerosis (or predisposing conditions) are extraordinarily unlikely to suffer a fatal or non-fatal event owing to short-term exposure to $PM_{2.5}$ at any global concentration. Given the large population of asymptomatic but at-risk individuals globally, even a small elevation in air pollution levels translates into hundreds of thousands of deaths.

Pathophysiology of $PM_{2.5}$-induced CVD

Our understanding of the pathophysiological mechanisms underlying $PM_{2.5}$-related effects on cardiovascular health has undergone considerable reassessment in the past decade. Mechanistic studies in animal models and humans have shown that multiple processes are involved in mediating the cardiovascular effects of $PM_{2.5}$ inhalation (FIG. 3). These

mechanisms, although distinct, are closely linked and can be broadly divided into primary initiating responses to pollutant inhalation, transmission pathways and end-organ effector mechanisms. The three major primary initiating pathways originate in the lungs, given the inhalational nature of air pollution, and include pollution-mediated oxidative stress, local inflammation and ion channel or receptor activation[52–55]. The transmission-mediating pathways include: signal transduction via the systemic release of numerous biological intermediates (such as oxidized lipids, cytokines, activated immune cells, microparticles and endothelins); autonomic imbalance and activation of the hypothalamic-pituitary-adrenal (HPA) axis; and nanoparticles or pollutant constituents reaching the circulation or transmitted via neurological pathways. In turn, these three pathways lead to end-organ effector mechanisms most proximally responsible for eliciting cardiovascular events, including endothelial barrier disruption or dysfunction, tissue (vascular or adipocyte) inflammation, heightened coagulation and thrombosis, increased potential for cardiac arrhythmia and responses owing to autonomic imbalance or HPA activation (such as vasoconstriction and increased blood pressure (BP)), secondary tissue damage (leading to plaque instability) and epigenomic changes. Finally, this paradigm of responsivity includes a fourth layer of response: chronic end-organ changes owing to long-term exposures that promote future susceptibility. These changes include the potentiation of cardiometabolic disorders, such as hypertension, diabetes mellitus, left ventricular hypertrophy or remodelling, vascular hypertrophy, proteinuria or renal disease, and the progression of atherosclerosis.

The timing and scale of these effects vary and might depend on numerous pollutant characteristics, the duration of exposure and the degree of susceptibility, which is influenced by genetic predisposition and homeostatic pathways. All these effects occur at different time points, and the convergence of some (or all) of these pathways leads to the development of cardiovascular risk factors (such as high glucose levels and BP) and diseases (such as coronary artery disease, heart failure, arrhythmia and stroke).

Primary initiating mechanisms

Oxidative stress.—Oxidative stress is the first hierarchical response that occurs after exposure to air pollution[56]. Oxidative stress responses occur initially in the respiratory tract in a variety of cell types, but can propagate systemically and contribute to the initiation of many of the effector pathways, including inflammation[52–55]. In the lungs, chronic accumulation of particles in alveolar macrophages via phagocytosis can eventually lead to frustrated phagocytosis, depletion of antioxidant defence systems and a failure of the inflammation to resolve[57]. Chronic, protracted inflammation in the lung and other organ systems (including the heart, liver, brain and adipose tissue) might eventually affect organ function. Many families of pattern recognition receptors, including Toll-like receptors (TLRs) and the nucleotide-binding domain leucine-rich repeats of NOD-like receptors, are involved in the initial sensing of particles and transduction of inflammatory processes, either directly or indirectly through secondary mediators, including reactive oxygen species (ROS) generated through a variety of different pathways[58–60]. Deficiency of TLR4, NADPH oxidase 2 (NOX2) or neutrophil cytosolic factor 1 (NCF1; also known as $p47^{phox}$) have all been shown to attenuate ROS generation, reduce inflammatory monocyte infiltration into the

vasculature and improve vascular function in response to inhalational exposure to concentrated $PM_{2.5}$ levels[61,62]. The transient receptor potential ankyrin 1 (TRPA1) and transient receptor potential vanilloid 1 (TRPV1) channels have also been implicated in this process and might be activated by oxidative stress related to combustion particles or soluble organics[63]. Some data indicate that gaseous co-pollutants might amplify the effects of $PM_{2.5}$. An increase in ozone gas from typical background concentration levels (~30 ppb) to summer smog conditions (≥100 ppb) might reduce the chemical half-life of antioxidants from days to hours and the half-life of surfactants from hours to minutes[64].

Systemic inflammation.—Heightened inflammation in response to $PM_{2.5}$ exposure has been proposed as a hall-mark of air pollution exposure. However, no explicit links have been observed between $PM_{2.5}$ exposure and inflammation in controlled acute exposure studies in humans, possibly owing to differences in study protocols, individual vulnerability or unmeasured previous exposures[3]. Several human cohort studies have shown an association between $PM_{2.5}$ exposure and plasma inflammatory markers, such as C-reactive protein, IL-6 and tissue necrosis factor, but the relationship between pollutant exposure and these markers has not always been consistent[65–68]. Experimental studies have demonstrated an efflux of monocytes from the bone marrow with chronic exposure to concentrated ambient $PM_{2.5}$, which resulted in $LY6C^{high}$ ($CD11B^{+}GR1^{low}7/4^{high}$) monocytes migrating systemically to organ depots[19,62]. TLR4 seems to be critical in mediating the effects of $PM_{2.5}$ on health, given that a deficiency in TLR4 diminished the effect of $PM_{2.5}$ in increasing peripheral $LY6C^{high}$ ($ADGRE1^{+}CD11B^{+}CD115^{+}$) cells and abolished tissue infiltration[62]. CC-chemokine receptor 2 (CCR2) and CXC-chemokine receptor 3 (CXCR3) seem to be involved in the inflammatory response to $PM_{2.5}$ through distinct monocyte-mediated and T cell mediated pathways. $Ccr2^{-/-}$ mice had less adipose inflammation, better whole-body insulin resistance and less hepatic lipid accumulation in the liver than wild-type mice[69]. Conversely, CXCR3 has a role in the migration of activated T cell populations[70].

Pollutant translocation.—Whether pollutants translocate across the lung barrier was unclear and much debated for many years. Furthermore, even if the particles did translocate, the temporal and spatial scales of this translocation were unknown. In 2016, an autopsy study demonstrated the presence of combustion-derived magnetite particles in both the brain and the heart[71]. In particular, soluble components of $PM_{2.5}$, including trace metals and gaseous co-pollutants, undergo systemic translocation when inhaled. Identifying the precise contribution of pollutant translocation might be difficult, but crude instillation studies in a mouse model seem to suggest that intra-arterial infusion of carbon nanoparticles induce only mild effects in secondary (non-pulmonary) target organs, whereas inhalation of carbon nanoparticles results in both pulmonary and extra-pulmonary responses[72]. Importantly, these extra-pulmonary responses seem to occur through indirect methods such as particle-cell interactions in the lung, rather than direct methods such as translocation of the carbon nanoparticles. Translocation of particles through more traditional routes, such as the gastrointestinal tract and the central nervous system, has also been observed[73,74]. In a study involving healthy individuals, patients with atherosclerotic CVD and mouse models of atherosclerosis, inert gold particles that were inhaled were found to be deposited in carotid tissues in humans and aortic tissue in mice[9]. Furthermore, gold was detected in the blood

and urine of healthy volunteers within 15 min to 24 h after acute inhalational exposure and remained detectable 3 months after the initial exposure. The levels of systemic accumulation were inversely correlated with particle size, with greater levels detected after inhalation of 5-nm particles compared with 30-nm particles. Similarly, particles can cross the blood-brain barrier, given the close proximity of the nasal tract to the central nervous system[71].

Secondary effector pathways

Signal transduction via biological intermediates.—Systemic effects of exposure to air pollution can be mediated by the formation of reactive biological intermediates, which can exert effects on other remote tissues directly or through secondary effector pathways. A growing body of evidence supports this mechanism for many inhaled pollutants. Several oxidatively modified phospholipid and cholesterol products have been implicated in the systemic response to $PM_{2.5}$ inhalation. Oxidized phospholipids (such as 1-palmitoyl-2-arachidonoyl-*sn*-glycero-3-phosphorylcholine) can readily participate as secondary mediators to facilitate the recruitment of inflammatory cells, the synthesis of cytokines and the increase in oxidative stress levels in the vasculature via TLR4, NOX2 and the NCF1 pathways[62]. Interruption of these pathways has been shown to reduce inflammation in the vasculature mediated by inhalation of concentrated $PM_{2.5}$. Other oxidative derivatives that might form in response to $PM_{2.5}$ exposure, such as 7-ketocholesterol, can contribute to air pollution-mediated endothelial dysfunction, thrombosis and atherosclerosis via CD36-dependent pathways[49]. Peroxidation product formation in the gastrointestinal tract in response to ultrafine particles might also induce inflammation and potentiate other pro-inflammatory pathways[75]. The contribution of biological intermediates and inflammation resolution to mitigating the effects of pollutant exposure remains poorly understood.

Autonomic dysregulation.—Dysregulation of the autonomic nervous system in response to $PM_{2.5}$ exposure has been described in animal models and humans, occurring rapidly within a few hours and manifesting as acute elevations in BP and reductions in heart rate variability. Animal studies seem to suggest the involvement of C-fibre nerves in airways (nasal, bronchial and lung) that might participate as the afferent loop through activation of TRPA1, TRPV1 and purinergic P2X channels[63,76,77]. Autonomic dysregulation might indeed underlie the acute changes in BP in response to $PM_{2.5}$, given that the BP changes occur concurrently with alterations in heart rate variability in controlled-exposure studies in humans[78,79]. Studies in dog models and in chronically cannulated mice exposed to concentrated air particles have confirmed the development of hypertension in response to $PM_{2.5}$ exposure, with evidence of central sympathetic nervous system activation[80,81]. Ultrafine particulate constituents and ozone gas can either directly disrupt the blood-brain barrier or result in circulating factors that might influence neuronal function in mice and humans[82–85]. Data from a large cohort study seem to implicate urinary catecholamines as a marker of sympathetic activation related to long-term exposure to air pollution[86].

End-organ effector mechanisms

Vascular dysfunction.—Air pollution has also been shown to be associated with increased arterial stiffness, impaired conduit artery flow-mediated dilatation, arteriolar dysfunction and retinal artery changes[5,18,19,87]. In human controlled-exposure studies, short-

term inhalational exposure to concentrated $PM_{2.5}$ or diesel exhaust resulted in reversible endothelial dysfunction for up to 4 h, indicated by a reduction in flow-mediated or agonist-mediated vasodilatation[88,89]. Although abnormalities in flow-mediated vasodilatation were not observed immediately (that is, within hours) after exposure to $PM_{2.5}$, these adverse effects were detected at the end of 24 h of exposure[90]. In patients with coronary artery disease, exercise-induced ST segment depression and ischaemic burden were shown to be significantly greater during exposure to diesel exhaust than during exposure to filtered air[91]. In humans, exposure to diesel exhaust increases nitric oxide generation that might serve to maintain steady-state vascular tone. However, in the presence of a dysfunctional nitric oxide synthase (NOS) system, blockade of endogenous NOS using the exogenous inhibitor l-NMMA (via a NO clamp) resulted in an exacerbated increase in BP levels and central arterial stiffness in response to diesel exhaust inhalation[92]. These data suggest that individuals who have underlying endothelial dysfunction might experience exaggerated haemodynamic responses to inhalational exposure to air pollution, an observation that is supported by human studies of inhalational exposure[91].

In animal studies, acute, subacute or chronic exposure to $PM_{2.5}$ alone or in conjunction with agents such as angiotensin II results in increased superoxide release from a variety of sources and potentiated vasoconstrictor responses[93,94]. Conversely, a reduction in ROS sources ameliorated endothelial dysfunction, endothelial cell activation (adhesion molecule expression) and inflammation[93,94]. Increased ROS production might also result from perivascular deposition of mononuclear cells in response to protracted inhalational exposure to concentrated $PM_{2.5}$. Indeed, deficiency of TLR4 and the NOX2 subunit of NADPH oxidase might limit vascular redox stress-induced inflammation through a reduction in vascular infiltration[62,95]. Another potential mechanism of pollution-induced vascular dysfunction is the depletion of endothelial progenitor cells, which could explain the vascular remodelling effects of long-term exposure to PM described in both animal and human studies[96,97]. Alterations in endothelial function translate into changes in vascular tone and stiffness and, in this regard, the effects of fine, coarse and diesel exhaust particles seem to be quite similar as they all mediate acute increases in BP levels[14,87,98,99]. Chronic endothelial dysfunction and a persistent increase in systemic vascular resistance might lead to increased cardiac afterload, diastolic dysfunction, alterations in coronary flow reserve and, eventually, left ventricular hypertrophy and fibrosis[100]. At the molecular level, increased expression of a fetal gene programme, including upregulation of β-myosin heavy chain and downregulation of the sarcoplasmic/endoplasmic reticulum calcium ATPase (SERCA2a), indicative of abnormal calcium cycling, has been demonstrated, and is linked with a phenotype of incipient heart failure[100]. However, the data on the effects of gaseous co-pollutants on human vascular function are limited and derived mainly from panel studies[101]. Findings from animal studies suggest that these effects are related to the rapid depletion of NO and a decrease in aortic endothelial NOS levels[19]. A small number of studies have examined the differential effects of gases on vascular function using limited end points[102–104]. For example, Lund and colleagues[102] showed that acute exposure to vehicular sources of air pollutants increase circulating factors linked with progression of atherosclerosis, such as matrix metalloproteinases.

Thrombosis.—Intratracheal instillation of particles has been shown to heighten systemic thrombosis[105,106] through pulmonary inflammation involving activation of macrophages and release of IL-6 (REF[107]). Macrophage catecholamines might have a role in the prothrombotic response, given that genetic loss or pharmacological inhibition of the β_2-adrenergic receptor on murine alveolar macrophages attenuated PM-induced IL-6 release and the prothrombotic state[108]. Acute inhalation of $PM_{2.5}$ has also been shown to affect plasma levels of tissue plasminogen activator[109]. Although several panel studies have suggested an association between markers of thrombosis and $PM_{2.5}$ levels and gaseous pollutants, insufficient evidence exists to suggest that heightened levels of circulating markers are a uniform biomarker of exposure[110–112]. This inconsistency might be related to differences in study design and end points and also the varying nature of pollution-induced prothrombotic effects, which are dependent on the chemical composition of the pollutants. In a double-blind, controlled-exposure study in healthy human volunteers, exposure to diesel exhaust increased platelet-leukocyte aggregates and thrombotic area, as assessed by ex-vivo flow chamber perfusion[113]. By contrast, exposure to wood smoke in healthy firefighters did not alter many of the same parameters[104]. In a double-blind, controlled study in patients with coronary artery disease, exposure to diesel exhaust led to reduced release of tissue plasminogen activator in response to bradykinin, suggesting a prothrombotic milieu[91].

Central nervous system activation.—Disruption of blood-brain barrier integrity and consequent neuroinflammation has been documented in a number of disease states and implicated as a causal pathway in obesity and Alzheimer disease[19,114]. Blood-brain barrier disruption has been associated with exposure to $PM_{2.5}$ and might be central to peripheral effects, including brown adipose dysfunction, white adipose inflammation and insulin resistance. Findings from human studies suggest that hypothalamic inflammation might be important in mediating short-term effects of $PM_{2.5}$ inhalation, such as peripheral inflammation and insulin resistance[19,114,115]. Indeed, intracerebroventricular delivery of an inhibitor of nuclear factor-κB (NF-κB) kinase subunit-β (IKKβ) prevented the adverse effects of air pollution on peripheral inflammation, insulin resistance and whole-body metabolism[81,116]. Additionally, exposure to $PM_{2.5}$ seemed to increase levels of oxidized phospholipids in the brain, which might activate TLR and NF-κB pathways[116]. Furthermore, components of air pollution (for example, ozone gas) might activate the adrenal axis, which manifests as an elevation in glucocorticoid levels, and could further potentiate cardiovascular effects, such as increased BP and insulin resistance[117].

Epigenomic changes.—Animal and human studies have shown that environmental exposure and the epigenome interact during critical periods of development[118,119]. Although the effect of environmental exposure on the epigenome might be small[119], even minor epigenomic changes can translate to large downstream effects. Targeted methylation studies have suggested an effect of $PM_{2.5}$ exposure on DNA methylation, which could mediate a thrombo-inflammatory response[120,121]. However, the effect of exposure to air pollution on genome-wide methylation status and chromatin structure are not well understood. Small cohort studies have shown various epigenomic changes within networks enriched for pathways related to inflammation, thrombosis, insulin resistance and lipid metabolism, all of which can increase the risk of CVD[122,123].

Epidemiology of pollution-induced CVD

Cardiovascular mortality

The link between $PM_{2.5}$ and cardiovascular mortality has been noted at both low and high levels of exposure. The association between $PM_{2.5}$ and cardiovascular mortality has been described in a time series analysis that assessed the hourly, daily and monthly variations in $PM_{2.5}$ levels as contributors to cardiovascular death[3,124]. For example, in total, short-term elevations in regions with low daily levels of exposure to $PM_{2.5}$ (<35 μg/m^3) translates to a 0.3–1.0% increase in the relative risk of cardiovascular mortality per 10 μg/m^3 increase in $PM_{2.5}$. At higher levels of daily exposure (such as in China, where daily $PM_{2.5}$ levels are 39–177 μg/m^3), on the basis of data from a meta-analysis of seven studies (mostly time series and case-crossover studies), each 10 μg/m^3 increase in $PM_{2.5}$ was associated with a 0.35% (95% CI 0.06–0.65%) excess risk of cardiovascular death[125].

Chronic exposure studies follow a cohort design, generally use annual $PM_{2.5}$ concentrations as the exposure and follow up individuals to track their long-term risk of cardiovascular mortality. For example, the American Cancer Society Study (involving 1.2 million people from 172 metropolitan areas), one of the largest cohort studies on chronic pollution to date in the USA, showed that after adjustment for 44 variables, each 10 μg/m^3 increment in $PM_{2.5}$ was associated with a 15% relative increase in IHD deaths (HR 1.15, 95% CI 1.11–1.20)[126]. In a study involving 2.1 million people in Canada (mean daily $PM_{2.5}$ of 8.7 μg/m^3) followed up from 1991 to 2001, each 10 μg/m^3 increment in $PM_{2.5}$ was associated with a 31% relative increase in deaths from IHD (HR 1.31, 95% CI 1.27–1.35)[127], representing an almost linear relationship. A study in regions of China with long-term very high levels of $PM_{2.5}$ has shown similar results[46]. Continued exposure even at low levels seems to result in an increase in risk of cardiovascular death after an acute MI. In a study in patients after an MI event, long-term exposure to $PM_{2.5}$ was associated with poorer quality of life and increased 5-year mortality[128]. In contrast to $PM_{2.5}$, the association between long-term exposure to ozone gas and cardiovascular mortality is modest and weaker than for other causes of death, including COPD[129].

Atherosclerosis

Several cross-sectional and longitudinal epidemiological studies have demonstrated a positive association between estimated long-term exposure to $PM_{2.5}$ and the burden of atherosclerosis in humans, measured in terms of carotid intima-media thickness and coronary and abdominal aortic calcium levels[14]. The Multi-Ethnic Study of Atherosclerosis and Air Pollution (n = 6,795, across six regions in the USA) showed that a 5 μg/m^3 increase in long-term exposure to $PM_{2.5}$ was associated with progression of coronary artery calcification (4.1 Agatston units per year)[130]. A meta-analysis of eight cross-sectional (n = 18,349) and three prospective (n = 7,268) studies showed a significant association between $PM_{2.5}$ and increased carotid intima-media thickness[131].

Hypertension

Controlled-exposure studies have convincingly shown that short-term increases in systolic BP (SBP; 1–5 mmHg) and diastolic BP (DBP; 1–3 mmHg) occur in response to PM

exposure (fine, coarse and diesel exhaust)[18,19,87]. At least four meta-analyses have shown a consistent association between ambient $PM_{2.5}$ levels and BP levels[132–135]. Acute exposure to $PM_{2.5}$ of 10 μg/m^3 correlated with an increase in SBP of 1–3 mmHg. The association between $PM_{2.5}$ and BP seemed to be stronger among men, Asian individuals and individuals living in areas with levels of high air pollution[135]. Chronic exposure to $PM_{2.5}$ is associated with correspondingly larger increases in BP and has also been associated with incident hypertension[134,136]. Importantly, associations between $PM_{2.5}$ and hypertension have been observed in studies from countries with low levels of pollution (Canada and the USA) and from those with extremely high levels of exposure to $PM_{2.5}$ (China), with no evidence of flattening of the response at higher doses[137].

Small randomized, controlled trials of air filtration have shown a consistent decrease in BP with a reduction in exposure to air pollution[138–140], confirming the causality of exposure in mediating the increase in BP. In a trial involving low-income senior citizens (mean age 67 years) in the USA, air filtration systems reduced $PM_{2.5}$ from 15 μg/m^3 to 7.4–10.9 μg/m^3, which was also associated with a reduction in SBP of 3.2 mmHg (95% CI −6.1 to −0.2 mmHg)[140]. The mechanisms underlying BP increases in the short term might involve rapid alterations in autonomic tone that are exacerbated in the presence of endothelial dysfunction[92]. In at least one study in humans, exposure to concentrated $PM_{2.5}$, but not ozone gas, led to a linear increase in DBP levels, which correlated with changes in measures of autonomic function, such as heart rate variability[90]. In the same study, no correlation was observed between levels of inflammatory markers and BP changes, and inhibition of oxidative stress (using vitamin C) and endothelin activity (using the endothelin receptor antagonist bosentan) did not abrogate the BP response to exposure to concentrated $PM_{2.5}$. Whether the cardiovascular effects of air pollution can be modulated by intensive control of BP remains to be elucidated.

Acute coronary syndrome and non-fatal MI

A large body of evidence (time series and case-cross-over studies) has shown an association between $PM_{2.5}$ exposure and the risk of non-fatal MI[14]. The evidence is stronger for ST segment elevation MI (STEMI) than for non-STEMI, showing a higher risk in patients with angiographic evidence of coronary artery disease[141]. In a meta-analysis of 34 studies, each 10 μg/m^3 increase in $PM_{2.5}$ (same day levels or lag of 0 days) was associated with a 2.5% relative increase in the risk of MI (relative risk 1.025, 95% CI 1.015–1.036), with risk associations also noted for other gaseous co-pollutants[142]. Given the near-continuous exposure to $PM_{2.5}$, this relative risk translates into a large population attributable fraction (2.5% with 100% exposure). These associations occur irrespective of sociodemographic characteristics[143], and the relationship between long-term exposure and incident IHD events seem to be linear (FIG. 2), without an apparent threshold effect.

Arrhythmias

Several studies have shown an association between air pollutants and ventricular arrhythmias in patients with an automated implantable cardioverter-defibrillator (ICD)[144–146]. In a 2017 study involving patients with left ventricular dysfunction (mean left ventricular ejection fraction of 35%) and an automated ICD or ICD plus cardiac resynchronization therapy

device, exposure to $PM_{2.5}$ was associated with an increased risk of ventricular tachycardia or ventricular fibrillation, and patients with a previous MI seemed to be most at risk[145]. Furthermore, in a meta-analysis of four studies involving >450,000 individuals, each 10 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with a 0.89% (95% CI 0.2–1.6%) increase in the relative risk of atrial fibrillation[146].

Heart failure

A meta-analysis of 35 studies showed that each 10 $\mu g/m^3$ increment in short-term exposure to $PM_{2.5}$ was associated with a 2.1% relative increase in heart failure hospitalization or death (HR 2.1, 95% CI 1.4–2.8), with the strongest associations observed on the day of exposure[147]. On the basis of these results, the researchers estimated that a reduction by 3.9 $\mu g/m^3$ in $PM_{2.5}$ would prevent 7,978 heart failure hospitalizations per year in the USA, which translates to an annual saving of approximately US$300 million. Furthermore, in a study involving 136,094 residents of Seoul, South Korea, without CVD who were followed up for a median of 7 years (with mean personal exposure $PM_{2.5}$ levels of 25.6 $\mu g/m^3$), each 1 $\mu g/m^3$ increment in $PM_{2.5}$ was associated with a 1.44% (95% CI 1.29–1.61%) increase in the risk of incident heart failure[148]. Currently, no studies have investigated whether patients with ischaemic or non-ischaemic heart failure are more sensitive to air pollution levels.

Peripheral arterial disease

Numerous studies have shown that acute exposure to $PM_{2.5}$ impairs endothelial function. Many human studies used brachial artery flow-mediated dilatation as a surrogate of endothelial dysfunction[87]. Population-based studies investigating the association between long-term exposure to $PM_{2.5}$ and incidence of peripheral arterial disease are scarce. One study showed that admissions to hospital for peripheral arterial disease increased by 0.26% (95% CI 0.08–0.45%) and 4.40% (95% CI 3.50–5.35%) for every 10 $\mu g/m^3$ increase in acute and chronic exposure to $PM_{2.5}$, respectively[149]. In a population-based study from Germany involving 4,544 participants, a 5th to 95th percentile incremental increase in exposure to $PM_{2.5}$ was associated with a higher prevalence of both low and high ankle-brachial index[150].

Venous thromboembolism

Studies describing the relationship between exposure to $PM_{2.5}$ and venous thromboembolism are scarce and have generated mixed results. In a study involving 453,413 hospital admissions for deep-vein thrombosis (DVT) and 151,829 hospital admissions for pulmonary embolism, $PM_{2.5}$ levels (per 10 ug/m^3) were associated with increased risk of both DVT (0.63% for short-term exposure and 6.98% for long-term exposure) and pulmonary embolism (0.38% for short-term exposure and 2.67% for long-term exposure)[151]. Further investigation is needed to confirm this relationship.

Insulin resistance and diabetes

A large body of evidence, including both animal and clinical studies, suggests that $PM_{2.5}$ inhalation is associated with induction of insulin resistance and diabetes[18,19,114,152]. In a meta-analysis of 13 published studies, each 10 $\mu g/m^3$ increment in $PM_{2.5}$ was associated with a 10% relative increase in incident diabetes (HR 1.10, 95% CI 1.02–1.18), with some

data suggesting a stronger association in women[67]. Another meta-analysis of ten studies showed that each 10 μg/m^3 increase in long-term exposure to $PM_{2.5}$ was associated with a 39% increased risk of developing diabetes, an association that persisted even at very low levels of exposure[153]. Furthermore, each 10 μg/m^3 increment in $PM_{2.5}$ exposure was also associated with a 49% increase in the risk of diabetes-related mortality (HR 1.49, 95% CI 1.37–1.62)[154]. Globally, ambient $PM_{2.5}$ has been suggested to contribute to approximately 3.2 million (95% uncertainty interval (UI) 2.2–3.8 million) incident cases of diabetes, approximately 8.2 million (95% UI 5.8–11.0 million) DALYs caused by diabetes and 206,105 (95% UI 153,408–259,119) deaths from diabetes[155]. The mechanisms underlying the susceptibility to insulin resistance and diabetes seem to mirror those of other chronic risk factors, including diet, and might involve inflammation in brown and white adipose tissue, insulin resistance in skeletal muscle, inflammation in hepatic tissue and central nervous system inflammation in the hypothalamus[114,152]. A role for pulmonary oxidative stress in mediating pollution-induced insulin resistance has been suggested, given that treatment with the antioxidant Tempol or lung-specific overexpression of the endogenous antioxidant extracellular superoxide dismutase prevented vascular insulin resistance and inflammation induced by exposure to concentrated $PM_{2.5}$ (REF[156]).

Cerebrovascular disease

In a 2019 meta-analysis of 80 studies in 26 countries, exposure to $PM_{2.5}$ (per 10 μg/m^3 increments) was associated with both short-term and long-term risks of stroke (short-term OR 1.01, 95% CI 0.01–1.02; long-term OR 1.14, 95% CI 1.08–1.21) and risks of death from stroke (short-term OR 1.02, 95% CI 1.01–1.04; long-term OR 1.15, 95% CI 1.07–1.24)[157]. The associations were strongest for ischaemic and haemorrhagic stroke. Long-term exposure to $PM_{2.5}$ was also associated with increased risks of dementia (OR 1.16, 95% CI 1.07–1.26), Alzheimer disease (OR 3.26, 95% CI 0.84–12.74) and Parkinson disease (OR 1.34, 95% CI 1.04–1.73)[157]. These reported risks were similar to those from a previous meta-analysis of 103 studies that found a relative increase in the risk of stroke or death from stroke of 1.1% per 10 μg/m^3 increase in $PM_{2.5}$ that was strongest on the day of exposure[158]. In the USA, the Women's Health Initiative study found some of the largest estimated risk of stroke and death from cerebrovascular disease owing to $PM_{2.5}$, with relative increases of 35% and 83%, respectively, per 10 μg/m^3 increase in long-term exposure to $PM_{2.5}$ (REF[159]). Importantly, the stroke-$PM_{2.5}$ dose-response relationship seems to be linear (FIG. 2), without a clear threshold of 'safe' $PM_{2.5}$ levels. Mechanisms underlying the association between $PM_{2.5}$ and cerebrovascular disease are likely to be similar to those between coronary artery disease and MI. Further investigation of the association between $PM_{2.5}$ and other neurological diseases, such as Parkinson disease and Alzheimer disease, is warranted.

Control of exposure to air pollution

Role of societal and governmental reform

There is a substantial body of evidence confirming that legislative mandates to reduce $PM_{2.5}$ levels result in demonstrable benefits to public health[2] (FIG. 4). The improvement in air quality across the USA over the past two decades has been independently associated with increased life expectancy[160]. Accountability and quasi-experimental studies have shown that

local community actions to reduce air pollutants also yield public health benefits within months of implementation[161]. The *Lancet* Commission report stresses leadership, resources and a clear roadmap as key components of successful programmes[2]. Societal and governmental measures, such as a mandatory or voluntary reduction in greenhouse gas emissions, transition to lower-carbon fuels, legislating the use of motorized vehicles or kilometres driven, adoption of electric mass transit vehicles and increases in congestion pricing plus vehicle and fuel taxes, might help alleviate both air and noise pollution and help to achieve climate action goals.

Improvements in transportation technologies (such as increased adoption of electric, hybrid, plug-in hybrid and fuel-cell cars) are likely to continue to reduce air pollution. However, even with decreasing per-vehicle emissions, it is widely anticipated that the heavy reliance of the global economy on anthropogenic fuels, population growth and economic development imperatives will offset any short-term gains. Urban planning that takes into account land-use assessment, green belt (naturally green regions surrounding cities), distances between sources of pollutants and individuals, relocation of pollutant sources (including major roadways and airports), avoidance of mixed-use areas (such as industrial-residential areas) and improved roads is important in reducing exposure to air pollution. Modification of the infiltration of outdoor pollutants and noise into indoor environments, which is mostly a function of air exchange and building design, might offer further opportunities for exposure reduction.

Emerging evidence suggests the existence of a negative association between residential greenness and air pollution exposure[162,163]. Trees have been hypothesized to trap PM on leaf surfaces and absorb gaseous pollutants. Epidemiological studies have also shown that residential greenness can mitigate the cardiovascular risk of $PM_{2.5}$ exposure[164]. Trees and forests in the USA were estimated to be responsible for the removal of 17.5 tonnes of air pollution (<1%) in 2010, saving approximately US$6.8 billion through benefits to health[165]. Most of this reduction in pollution occurred in rural areas, whereas the majority of health effects occurred in urban areas. The $PM_{2.5}$ levels near trees have also been estimated to be reduced by 7–24%[166]. Given these benefits, reforestation could be a cost-effective approach to reducing air pollution[167]. A 2018 paper outlined several approaches for the mitigation of the cardiovascular effects of air pollution, with a focus on how health-care providers have a critical role in implementing long-term solutions[168].

Personalized mitigation measures

Although national policy changes to reduce emissions and control air pollution are the only assured mechanisms for addressing air pollution-mediated cardiovascular risk, the challenges associated with a rapid transition from a fossil fuel-based economy to one that is clean power-based are numerous, particularly in many fragile geopolitical regions where decision-making generates only short-term solutions. Therefore, personal measures for mitigating cardiovascular risk have become all the more important, given that dramatic changes in air pollution are not likely to be achievable in many parts of the world. As we have previously reviewed, several personalized mitigation measures are at least partially

effective in reducing exposure to $PM_{2.5}$ and in improving some biomarkers of cardiometabolic health[18,19,169].

Personal masks.—In regions of high exposure to pollution, such as China and India, face masks are commonly used to avoid the harmful effects of air pollution. Inexpensive face masks made from cloth, cotton or gauze are widely available and can reduce the inhalation of PM. However, they are not uniformly effective or reliable in filtering $PM_{2.5}$ and should not be recommended routinely to protect against the risks of air pollution. Disposable surgical masks have been found to be more effective than cloth masks in preventing the inhalation of particles, but N95 respirators are the most effective[170]. The performance of cloth masks was unpredictable (15–57% effectiveness), given that the masks could not form a tight seal around the face. Unfortunately, the least effective cloth masks are also inexpensive and reusable and therefore are widely used in developing countries. The ideal personal masks for protection from $PM_{2.5}$ exposure are N95 respirators, which are designed to seal tightly around the mouth and nose and can block 95% of particles >0.3 μm. Small studies on the use of N95 face masks over a few hours have demonstrated that they can consistently reduce SBP and increase heart rate variability[139,171,172]. In a randomized, controlled trial with a crossover design involving 15 healthy volunteers in Beijing who walked for 2 h wearing a highly efficient face mask filter, face mask use reduced SBP by 7 mmHg and increased heart rate variability over 24 h (REF[172]). In a larger, randomized, case-crossover trial involving 98 patients with coronary artery disease walking along a predefined route in Beijing, the use of a face mask reduced maximal ST segment depression, increased heart rate variability and decreased mean BP by 3 mmHg[138]. In another trial involving 24 healthy young adults in Shanghai, the use of a high-efficiency particle-absorbing respirator for 48 h was associated with a 2.7 mmHg decrease in SBP and an increase in heart rate variability, without significant changes in the expression of thrombotic biomarkers (endothelin 1, fibrinogen, P-selectin, vascular cell adhesion molecule 1 or von Willebrand factor)[139]. In New Jersey, USA, where $PM_{2.5}$ levels are much lower than in Beijing or Shanghai, China, mask use among 21 young adults led to non-significant decreases in levels of nitrites in exhaled breath[173]. An important limitation in the use of personal face masks is lack of compliance. Moreover, the benefits of the extended use of masks over protracted periods (weeks) have not been tested.

High-efficiency home air filtration.—Indoor pollution poses another major environmental exposure, given that the majority of the population spends more time indoors than outdoors, and the sources of indoor pollutants might differ from those of outdoor pollutants. Exposure to high levels of indoor air pollution can result from outdoor pollutants and indoor burning of fossil fuels (such as cooking oil). Portable or central home air-filtration systems have been shown to reduce indoor $PM_{2.5}$ levels by 50–60% and are more convenient than the use of face masks, allowing use for longer durations. Central home filters have a high-efficiency membrane that traps fine particles and can be added to pre-existing heating, ventilation and air-conditioning systems. These filter systems provide more uniform reductions in air pollution, but can be expensive. Portable air cleaners are small units that can circulate air in a confined space to trap $PM_{2.5}$ particles. In a trial involving 45 adults living in a wood smoke-affected community in British Columbia, Canada, the use of

portable home air filters for 7 days reduced PM concentration by 60% and improved endothelial function as measured by tonometry[174]. In another study involving 37 residents in Manitoba, Canada, the use of portable home air filters for 7 days reduced $PM_{2.5}$ levels by 37 $\mu g/m^3$, SBP by 7.9 mmHg and DBP by 4.5 mmHg (REF[175]). In addition, home air filtration systems seemed to reduce air pollution-induced inflammation. In a study of 35 healthy adults in Shanghai, China, 48 h of portable home air filtration reduced SBP and DBP levels, as well as the levels of several circulating inflammatory and thrombogenic biomarkers, including IL-1β, monocyte chemoattractant protein 1, myeloperoxidase and soluble CD40 ligand[176].

Avoiding exposure to sources of pollution.—Given the importance of road traffic sources in pollutant exposure, simple avoidance through the use of alternative routes without heavy traffic has potential health benefits. A measure to reduce the number of vehicles passing in one street by 50% in an area of low overall exposure in the Netherlands has been predicted to be equivalent to the benefit of avoiding 4.3 passively smoked cigarettes at home per day[177]. Use of car air conditioning, car air purifiers and closing windows could also reduce cabin air pollution concentrations and has been associated with improved heart rate variability[14]. Landscape reform through the placement of highways away from residential areas, use of green belt barriers and diversion of traffic to alternative routes or restricted hours of use have a large effect on reducing population exposures. Similarly, reducing exposure to sources such as power plants and ports is also important. Finally, exposure to indoor sources of pollutants should also be mitigated.

Exercise.—The health benefits of exercise are well established. Exercise can attenuate the adverse effects of air pollution, a finding that has been corroborated by experimental animal studies[178,179]. However, the degree, duration and location of exercise (such as a high-pollution versus a low-pollution environment) are variables that might have opposing outcomes, given the potential effects of these factors on either decreasing or increasing exposure with the magnitude of exercise. Therefore, a threshold might exist whereby excessive inhalation of pollutants during exercise outweighs any protective health benefits of exercise[180]. In a randomized, crossover study, responses in patients with COPD or IHD who walked in a crowded street in London, UK, were compared with those in disease-matched patients who took a walk in Hyde Park[181]. Compared with walking in a crowded street, walking in Hyde Park led to an increase in lung function and decreases in pulse wave velocity and augmentation index. In a systematic review, many studies involving exercise in the presence of high pollutant co-exposure were associated with detrimental effects on airway inflammation, pulmonary function, vascular function and BP[182]. In the absence of definitive data, high-intensity exercise in heavily polluted environments should be avoided.

Dietary supplements.—The benefits of several dietary supplements in reducing the effects of air pollution on the respiratory and cardiovascular systems have been described[183]. Given that oxidative stress is a major initiating pathway for pollution-mediated cardiovascular effects, the use of antioxidant supplementation has been explored[184]. Vitamin C supplementation has been shown to prevent acute lung effects induced by NO_2 and ozone gas exposure and can reduce COPD or asthma hospitalizations associated with exposure to

PM_{10}[185–187]. In a study involving workers at a coal power plant in Brazil, 6 months of supplementation with vitamins C and E normalized markers of oxidative stress, such as superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase and glutathione *S*-transferase[188]. However, in a randomized trial conducted in Detroit, USA, one-time supplementation with vitamin C did not attenuate acute BP effects induced by exposure to concentrated PM[90], but vitamin C and the antioxidant *N*-acetyl-cysteine increased vasoconstriction in response to inhalation of diesel exhaust[189]. At the population level, a study that included more than half a million individuals in the USA who were followed up for 17 years showed that a Mediterranean diet could attenuate the association between exposure to $PM_{2.5}$ and adverse cardiovascular events[190]. Furthermore, in a double-blinded, placebo-controlled trial in 65 healthy young adults in China, fish-oil supplementation (2.5 g per day) prevented the $PM_{2.5}$-mediated increase in blood markers of inflammation, coagulation, endothelial function, oxidative stress and neuroendocrine stress response[191]. Together, these findings show that, although vitamins and nutrient supplementation might be protective against air pollution-mediated damage, the studies were designed to assess only the effects of short-term administration on surrogate end points. Further research is needed to identify whether additional dietary supplements or specific diets can attenuate or prevent the direct cardiovascular effects of air pollution.

Staying indoors during peak pollution days.—Given the daily variations in air pollution levels in heavily polluted areas, avoiding peak exposure times, especially among susceptible populations, could be a simple strategy to improve public health. Therefore, avoidance of outdoor activities during times of poor air quality could be a good strategy to minimize the harmful health effects of air pollution. Local daily air-quality data provide a valuable resource enabling individuals to avoid going outdoors on days of high levels of air pollution. Large air-quality monitors often report air pollution levels below those that are detectable by individuals. In developed countries, a network of air monitors provides accurate data on levels of several pollutants, which can be used to forecast pollution levels over 24–48 h. Simplified aggregate indices that combine multiple aspects of air quality (for example, the air quality index used by the Environmental Protection Authority and the Common Air Quality Index used in Europe) might prove to be useful in driving behavioural changes to reduce personal exposure.

Studies have also focused on identifying public awareness of air quality alerts. In one study involving 12,599 adults living in the USA surveyed between 2014 and 2016, 49% of respondents were aware of air quality alerts and 27% always or usually avoided busy roads to reduce exposure[192]. Interestingly, existing respiratory disease, but not heart disease, was associated with increased air quality awareness. Approaches to raising awareness of the harmful effects of air pollution on health would be of benefit to the general population and especially for susceptible patients with heart and/or lung disease.

Air pollution and climate change

Climate change is by far the greatest existential threat confronting humanity and public health. The 2018 Climate and Health Assessment Report of the US Global Change Research Program summarizes the available evidence on the health effects of climate change[193]. Air

pollution and climate change not only share common precipitants (such as fossil fuel use) but also have a complex, bi-directional relationship. Greenhouse gas emissions, primarily from the burning of fossil fuels, both contribute to climate change and have adverse effects on health, and, conversely, climate change might lead to an increase in levels of PM and ground-level ozone gas. Greenhouse gases and air pollutants are, to a large extent, emitted from the same sources. As part of climate change and global warming, extreme weather conditions will contribute to more substantial acute increases in air pollution. Global warming is also expected to increase wildfires, which in turn lead to increased carbon monoxide and PM levels. Rising temperatures will result in increases in ground-level ozone gas that will be very difficult to eliminate, given the precise relationship between ambient temperature and ozone gas levels[194,195]. The choice of climate change policies with simultaneous, discernible positive health and ecosystem effects might provide the greatest opportunity for reductions in greenhouse gas emissions and global warming, rather than a policy focused solely on reducing carbon dioxide levels[2,12]. Indeed a study has demonstrated that greenhouse gas mitigation strategies in domains such as energy generation, transport, food and agriculture industries can bring substantial and rapid public health benefit, in an economically feasible manner[196].

Conclusions

The strength of the data on the association between air pollution and CVD offers the greatest opportunity for improving population health. Although the American Heart Association and the European Society of Cardiology formally recognize $PM_{2.5}$ as an independent risk factor for CVDs, air pollution as a modifiable risk factor is yet to be included in prevention guidelines. The lack of randomized, controlled clinical trials for personalized protection devices is a current limitation, and addressing this deficit could help to provide recommendations for individuals. We have previously reviewed the importance of clinical trials in demonstrating the efficacy of personalized devices in reducing exposure[169]. Intervention trials would be of the greatest relevance and would be most effective in heavily polluted countries, where a reduction in inhaled $PM_{2.5}$ levels would be likely to translate into substantial decreases in disease events. A better understanding of vulnerable populations is needed to design effective trials aimed at high-risk populations and to promulgate WHO air-quality guidelines that optimally protect public health. The integration of real-time, high-quality air pollution information in navigation systems and media could have an important role in limiting exposures and protecting public health, and the current convergence of technologies in social media, 5G and the Internet of Things may help facilitate the achievement of this goal. Air pollutants seldom occur in isolation and often coexist with other environmental pollutants (pollutome) and exposures (exposome) as part of a complex network of factors. The independent and potentially additive (or synergistic) cardiovascular risks posed by these multiple exposures are yet to be fully understood. Ultimately, the integration of environmental exposures as part of personal medicine and health (with air pollution providing a prototypical environmental exposure) could provide the most important opportunity to link the external environment with internal health, the ultimate aim of personalized medicine. Finally, the impending climate catastrophe might provide the greatest and most serious mandate to bring about both the immediate health

benefits of reducing exposure to pollution and the harder-to-discern long-term benefits of reducing greenhouse gas emissions in achieving climate change goals.

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Key points

- Air pollution is the most important environmental cardiovascular risk factor, with fine particulate matter ($PM_{2.5}$) and ozone gas being the most-studied air pollutants.
- The health effects of air pollution might depend on chronic exposure, pre-existing medical conditions and sources or composition of the pollutants.
- Multiple primary initiating and secondary effector mechanisms are responsible for the cardiovascular effects of air pollution.
- Numerous animal and human studies have shown that inhalation of $PM_{2.5}$ pollution can contribute to cardiovascular disease and mortality.
- The most widely studied personalized approaches to reducing the cardiovascular risk of air pollution include the use of face masks and in-home air purifiers.

Ozone gas

An inorganic molecule composed of three atoms of oxygen, which mainly exists in the Earth's stratosphere (ozone layer) and troposphere (low-level ozone).

Primary particulates

Particulates that are directly released into the atmosphere by the source (such as combustion).

Secondary particulates

Particulates that form in the atmosphere from primary gases (such as oxidation of nitrogen into nitric acid).

Primary combustion

The release of unburned combustible gases from wood burning with heat, as opposed to secondary combustion, which involves gases that react secondarily (oxidize) to form other pollutants.

Atmospheric stability

The measure of atmospheric resistance to vertical motion, which determines the movement of air and storm formation.

Integrated Exposure-Response

(IER). A meta-analytical approach integrating data from studies of ambient air pollution, second-hand smoking, household pollution and active smoking to estimate the shape of the association between air pollution and mortality.

Disability-adjusted life years

(DALYs). Number of years alive, adjusted for disability, which estimates the burden of life years lost to the disease.

Anthropogenic emissions

Emissions originating from human activity, such as burning of fossil fuels for cooking, mining and manufacturing.

Global Exposure Mortality Model

(GEMM). An integrated approach including only ambient air pollution studies to define the shape of the association between air pollution and mortality.

Harvesting effect

(Also known as mortality displacement). The hypothesis that excess deaths that occur after an environmental trigger (such as air pollution) would have occurred in the short term, regardless of the presence of the trigger.

Frustrated phagocytosis

Occurs when phagocytic cells do not internalize the target, resulting in its release into the environment.

Intratracheal instillation

Direct inoculation of a substance into the trachea.

Ankle-brachial index

A non-invasive marker of the presence of peripheral arterial disease, estimated using the ratio of lower-extremity to upper-extremity blood pressure.

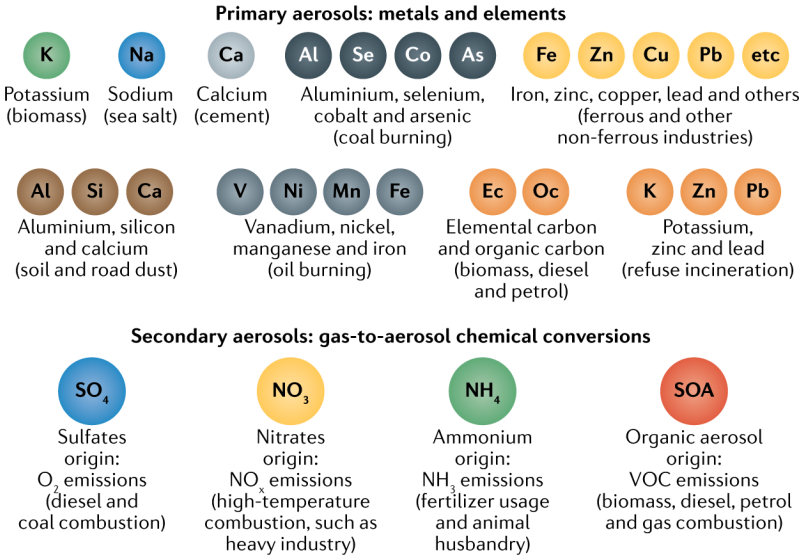


Fig. 1 |. Composition of particulate matter.

Primary aerosols include metals and other elements, whereas secondary aerosols result from the chemical conversion of gases to aerosols. Emerging evidence suggests that these components of particulate matter might have varying health effects. VOC, volatile organic compound. Reprinted with permission from REF[197], Urban Emissions.

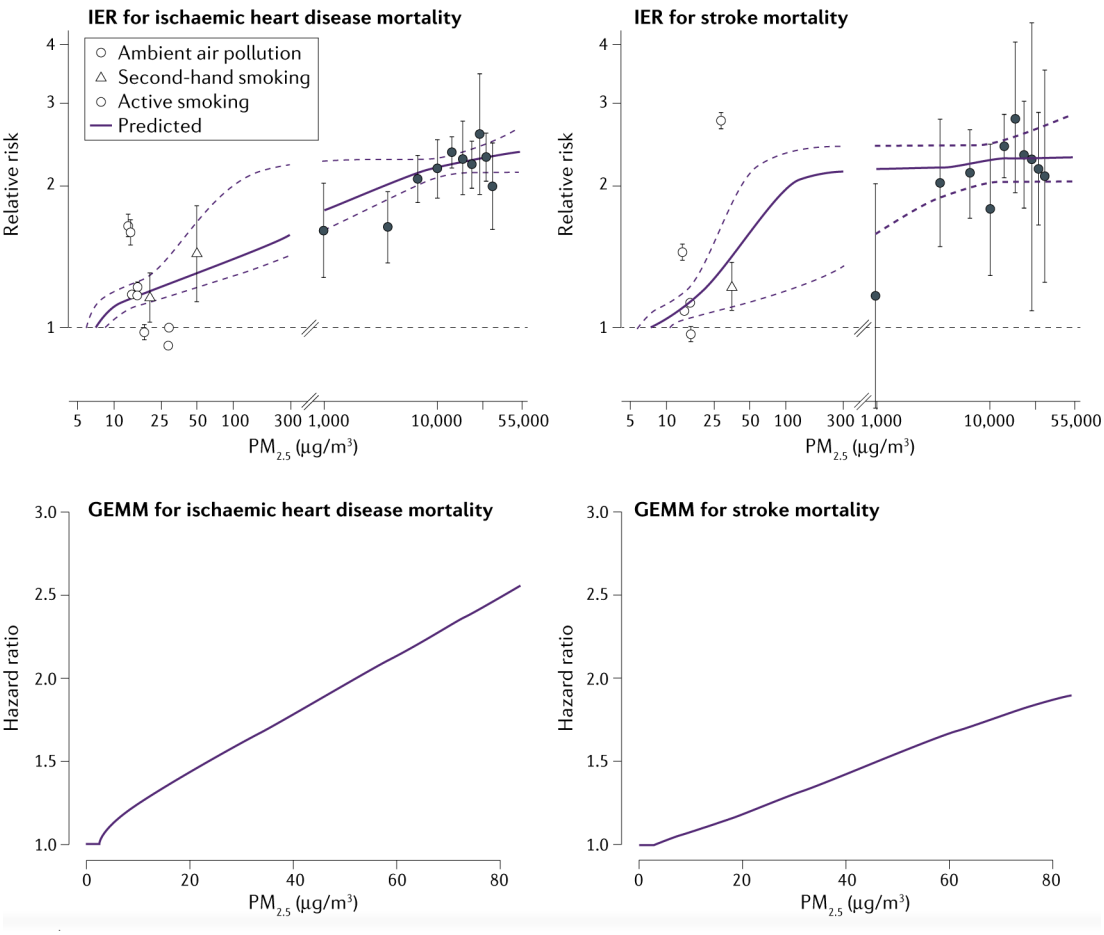


Fig. 2 |. Association between $PM_{2.5}$ levels and ischaemic heart disease and stroke mortality.
The relationships between fine particulate matter ($PM_{2.5}$) and death from ischaemic heart disease or stroke were determined using the Integrated Exposure-Response (IER) and the Global Exposure Mortality Model (GEMM) methods. Adapted with permission from authors REF[43], EHP, and REF[46], PNAS.

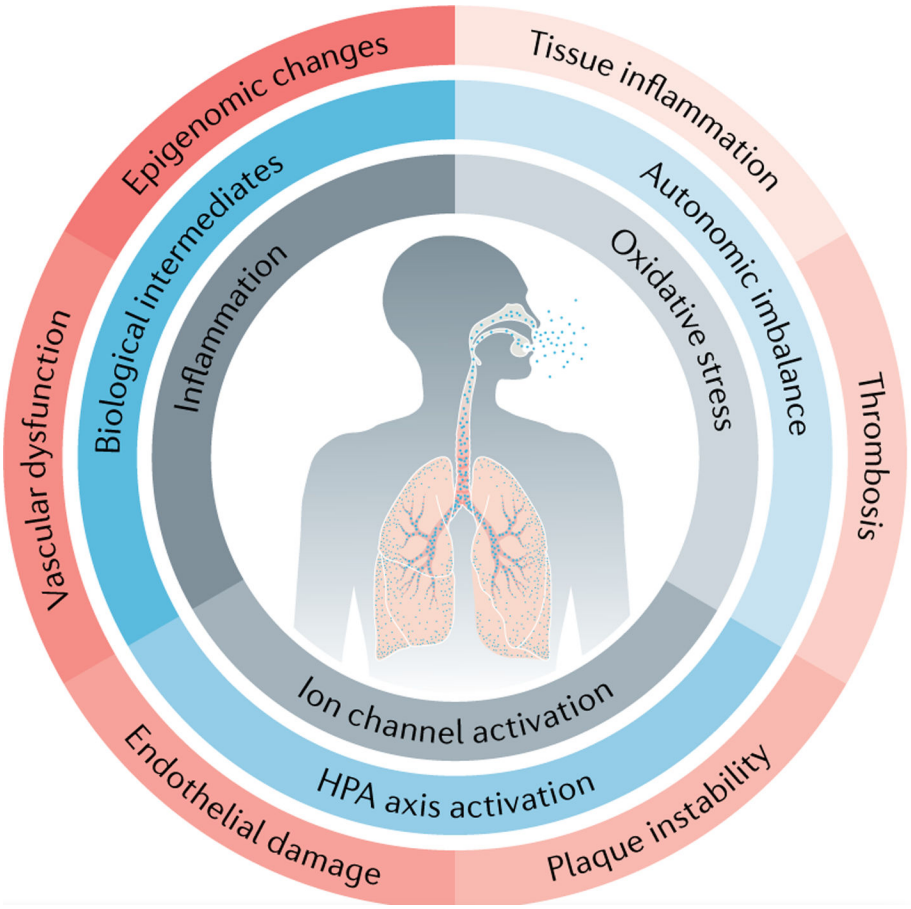


Fig. 3 |. Mechanisms of air pollution-related cardiovascular disease.

Numerous molecular and physiological mechanisms mediate the effects of air pollution on the cardiovascular system. These mechanisms result in various interlinked cardiovascular manifestations, including atherosclerosis, vascular dysfunction and endothelial damage. HPA, hypothalamic-pituitary-adrenal.

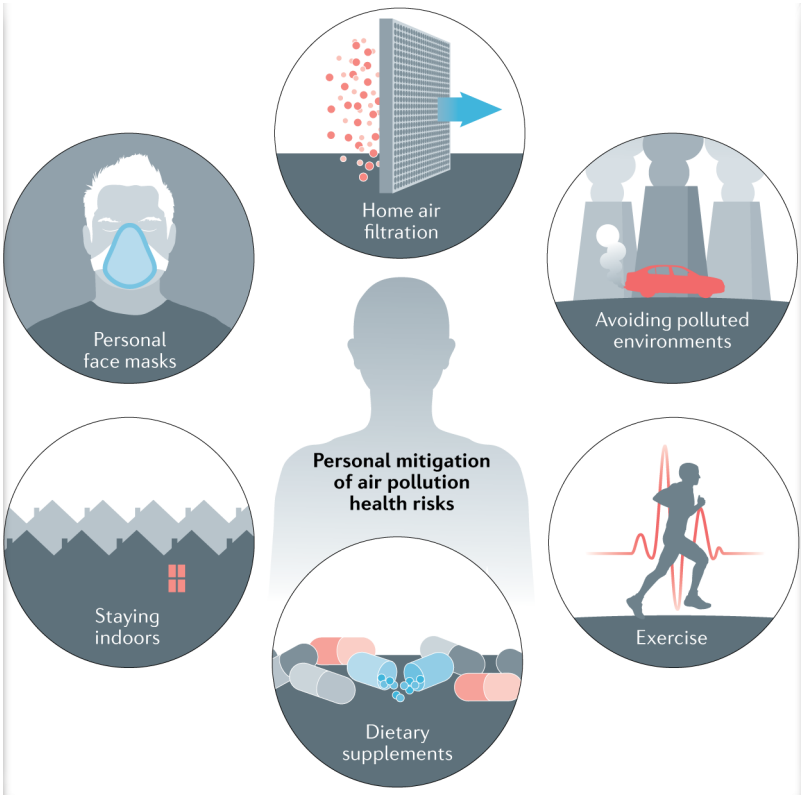
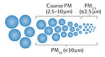
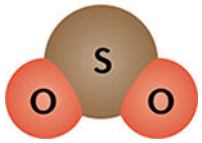
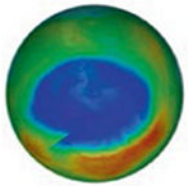
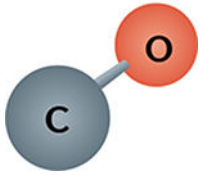


Fig. 4 |. Personalized measures to reduce exposure to air pollution.

Personal face masks and home air-filtration systems are effective in decreasing exposure to air pollution. Behavioural changes (such as avoidance of polluted environments and staying indoors) can be adopted particularly during times of acutely worsened air quality. Exercise and certain dietary supplements (such as fish oil) might counteract the effects of air pollution on the cardiovascular system.

Table 1 |

Criteria for air pollutants standards

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

Air pollution component	Size or structure	US standards	European standards
Lead		0.15 μg/m^3 (3 months)	0.5 μg/m^3 (1 year)

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