Air Pollution and Cardiometabolic Disease: An Update and Call for Clinical Trials

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Fine particulate matter <2.5 μm ($PM_{2.5}$) air pollution is a leading cause of global morbidity and mortality. The largest portion of deaths is now known to be due to cardiovascular disorders. Several air pollutants can trigger acute events (e.g., myocardial infarctions, strokes, heart failure). However, mounting evidence additionally supports that longer-term exposures pose a greater magnified risk to cardiovascular health. One explanation may be that $PM_{2.5}$ has proven capable of promoting the development of chronic cardiometabolic conditions including atherosclerosis, hypertension, and diabetes mellitus. Here, we provide an updated overview of recent major studies regarding the impact of $PM_{2.5}$ on cardiometabolic health and outline key remaining scientific questions. We discuss the relevance of emerging trials evaluating personal-level strategies (e.g., facemasks) to prevent the harmful effects of $PM_{2.5}$, and close with a call for large-scale outcome trials to allow for the promulgation of formal evidence-base recommendations regarding their appropriate usage in the global battle against air pollution.

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Humanity faces many harmful environmental factors endemic to modern civilization including polluted drinking water, excessive noise (e.g., traffic, airports), persistent organic pollutants (e.g., pesticides), household chemicals (e.g., phthalates, bisphenol A), as well as the mounting risks posed by climate change (e.g., extreme temperatures).[1] However, the largest threat to public health comes from air pollution which ranks among the leading risk factors for global morbidity and mortality.[2–4] Over 90% of the global population is exposed to levels exceeding World Health Organization (WHO) Air Quality Guidelines (AQG).[3] This pervasive, persistent, and involuntary nature of exposure explains why air pollution ranks among the leading risk factors for morbidity and mortality worldwide.[2–4]

AIR POLLUTION

While several anthropogenic (e.g., cooking) and natural (forest fires) sources have been present for millennia, the most concerning air pollutants impacting contemporary society are derived from fossil fuel combustion (e.g., coal, diesel). This pollution is a complex mixture of gases (e.g., ozone, oxides of nitrogen and sulfur), volatile organic compounds, and particulate matter (PM) (Figure 1). This latter component represents a variety of solid particles ranging in size from 10–100 nanometers (ultrafine particles) to large coarse PM between 2.5–10 μm in diameter with concentrations measured in mass (μg) per volume of air (m^3). A growing body of studies supports the toxicity of ultrafine particles[5] as well as possibly coarse PM. However, the overwhelming burden of evidence impugns fine PM <2.5 μm in diameter ($PM_{2.5}$) as the principal air pollutant posing the greatest threat to global public health and as such it has remained the focus of most scientific and regulatory attention.[2–11] $PM_{2.5}$ itself is a complex amalgam of compounds (elements, carbon species) derived from numerous sources that are small enough to deposit deep within airways and thereby elicit a host of adverse biological responses.[11]

Global public health effects

The most recent calculations estimate that 3.15 million deaths per year are attributable to $PM_{2.5}$, which places it among the leading 10 risk factors for global mortality.[2–4] This represents 3.1% of all disability-adjusted life years lost, an alarming figure projected to double by 2050. While promoting lung diseases and cancers, more than half of the health burden is in fact due to cardiovascular diseases. Though $PM_{2.5}$ impacts nearly everyone worldwide, the ecological-economic shifts during the past century have changed who is most vulnerable. $PM_{2.5}$ now disproportionately concentrates among developing nations, particularly China (1.35 million deaths/year) and India. In addition to the enormous population, 99%

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of individuals across East Asia face average annual $PM_{2.5}$ levels (~45.2 μg/m^3) exceeding WHO AQG (<10 μg/m^3). This is compared to <20% of people in the United States who reside in locations exceeding current AQG. In fact, average levels are now much lower across the United States (9.6 μg/m^3) than past decades due in large part from National Ambient Air Quality Standards (NAAQS) beginning in the 1970s.[2,12] In addition to widespread and chronic poor air quality, daily peaks of $PM_{2.5}$ commonly exceed 100 μg/m^3 in megacities such as Beijing and Delhi.[12–14] During extreme air pollution episodes, $PM_{2.5}$ can even reach extraordinary concentrations above 500–1000 μg/m^3. To place this in perspective, these levels are on par with or exceed indoor secondhand smoke.[15] Fortunately, such disastrous episodes have not typically threatened North America and Western Europe since the mid-20th century (e.g., 1952 London "killer smog").[6,7]

While high levels of $PM_{2.5}$ are well-established to prompt cardiovascular events, it is critical to note that the totality of evidence demonstrates that there is no lower concentration threshold below which exposures can be considered safe at the population-level.[7,15] Even low $PM_{2.5}$ levels within annual AQG targets (<10 μg/m^3) faced by hundreds of millions of people living in nations with improved air quality pose significant threats to public health.[2,11,15] Moreover, other air pollutants (e.g., ozone) can present their own independent risks.[2,4] Many comprehensive reviews regarding the health effects of air pollution have been published.[7–11] As such, our goals are to provide an updated overview of the most impactful recent studies with an emphasis on the cardiometabolic effects of $PM_{2.5}$ in humans and to outline key issues we believe important to address during the next decade.

REVIEW OF THE CARDIOMETABOLIC EFFECTS OF AIR POLLUTION

Hard cardiovascular events

A wealth of evidence links air pollution to heightened cardiovascular morbidity and mortality.[6–11] Several recent meta-analyses assessing the impact of short-term exposures to $PM_{2.5}$ (per 10 μg/m^3 increase during the prior few hours-to-days) have been published. In 34 studies, $PM_{2.5}$ exposure significantly increased the risk for acute myocardial infarction by 2.5%.[16] Hospitalization or death from heart failure (2.1%; 35 studies),[17] stroke (1.1%; 94 studies),[18] and arrhythmia (1.5%; 23 studies)[19] have also been shown to be

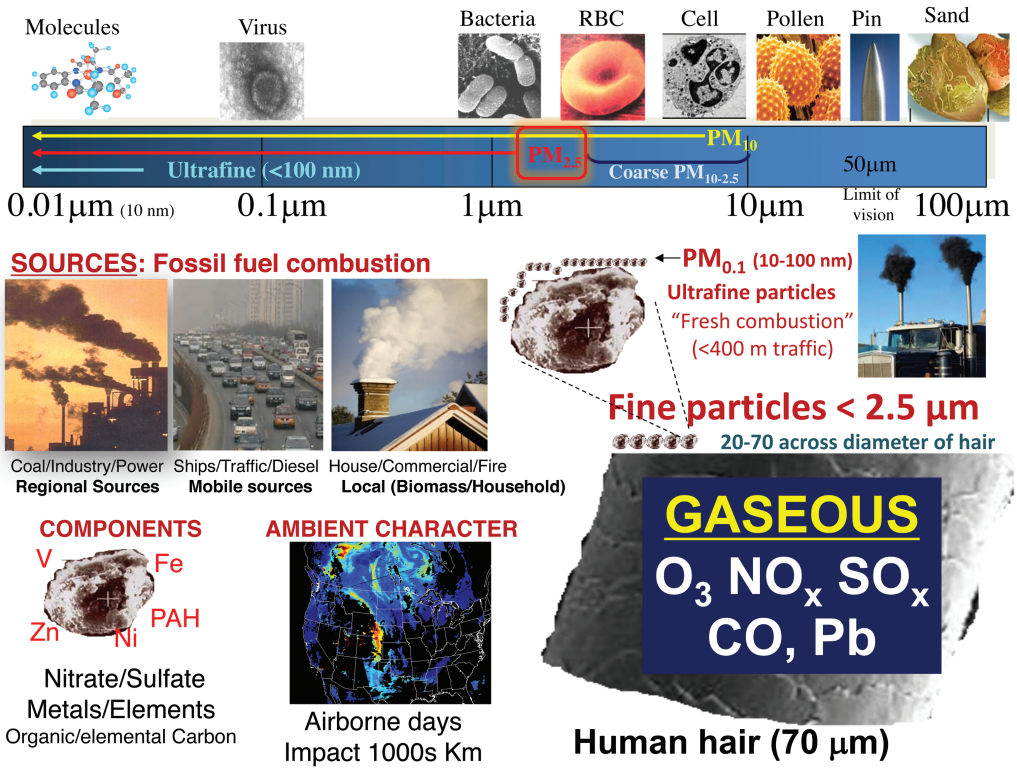

Figure 1. The complex mixture of air pollution. The combustion of from fossil fuels (coal, oil, gas, diesel) from a variety of sources (industry, traffic, power-generation, shipping) produces gaseous and particulate pollutants. Ultrafine particles (UFP) smaller than 100 nm are generally short-lived species (airborne hours) directly derived from and at highest concentrations nearby (<100–400 m) fresh combustion sources (traffic, diesel). Fine particles <2.5 μm in diameter ($PM_{2.5}$) are larger yet still many times smaller than the diameter of a human hair. They are a heterogenous amalgam of numerous compounds formed from combustion (metals, carbon species) or secondarily involving reactions in the atmosphere (nitrates, sulfates). $PM_{2.5}$ may be longer-lived (airborne days) and transported hundreds of miles impacting entire regions, all of which is influenced by geography and meteorological conditions. PM concentration is measured in μg/m^3, with WHO AQG set at <10 μg/m^3 for an annual average. For typical days in US cities, the levels range within 24-hour standards (5–35 μg/m^3). In China, peak levels exceed 250–500 μg/m^3 which is on par with that of secondhand smoke in indoor venues. However, the exposure dose from the active smoking of a pack of cigarettes is at least 100 times greater. Abbreviations: CO, carbon monoxide; NOx, nitrogen oxides; O_3, ozone; PAH, polycyclic aromatic hydrocarbon; SOx, oxides of sulfur.

increased. Similar risks were also reported for short-term exposures to several gaseous pollutants (NO_2, CO, CO_2) with less consistent evidence for ozone.[16–19] While these relative risks are modest, short-term exposures to $PM_{2.5}$ account for up to 5% (population-attributable fraction) of myocardial infarctions worldwide because hundreds of millions of people are continuously impacted.[20]

Longer-term exposures over several years appear to pose amplified risks over and above the acute risks.[6] A recent meta-analysis demonstrated that living within an area facing a chronic elevation in $PM_{2.5}$ leads to a 10.6% increase (per 10 μg/m^3) in cardiovascular mortality—roughly 5- to 10-fold the risks following acute exposures.[21] This has led to the hypothesis that repetitive exposures may promote chronic disease states (e.g., hypertension, diabetes) and/or enhance the progression or vulnerability of atherosclerotic lesions.[7,8,22–24] These responses could magnify health risks by heightening the underlying susceptibility for future events.

Recent epidemiological studies. Some of the most impactful recently published data derive from the ESCAPE project—a pooling of multiple cohorts across Europe. These results largely confirm the harmful impacts of living in more polluted regions. In 11 studies (n = 100,166), a 5 μg/m^3 elevation in long-term exposure to $PM_{2.5}$ was associated with a 13% increase in nonfatal acute coronary events.[25] However, cardiovascular mortality (hazard ratio = 1.21, 95% confidence interval = 0.87–1.69; n = 367,383; 22 cohorts),[26] and strokes (hazard ratio = 1.19 95% confidence interval = 0.88–1.62; n = 99,446; 11 cohorts) showed nonsignificant upward trends.[27]

There has been a growth of important evidence that individuals with underlying coronary heart disease may be at particularly high risk. In the CATHGEN cohort of 5,679 patients who had a coronary angiogram for clinical reasons at Duke University, a 1 μg/m^3 increase in annual average $PM_{2.5}$ was associated with an 11.1% increased risk of having coronary atherosclerosis and a 14.2% increased risk of having a myocardial infarction during the prior year.[28] In the Intermountain Healthcare hospital system in Utah (n = 16,314 patients), concurrent-day $PM_{2.5}$ was associated with a significant increase for acute coronary syndromes.[29] However, the excess risk was observed only among individuals with angiographic coronary artery disease and ST-segment elevation myocardial infarctions were preferentially triggered. This suggests that preexisting vulnerable atherosclerotic plaques are required in order to be susceptible to the acute effects of $PM_{2.5}$ exposure. Accruing evidence also supports that long-term survival following an acute coronary syndrome is also reduced by chronic $PM_{2.5}$ exposure.[30,31] Among 8,873 patients with a myocardial infarction living in a region with good air quality (Ontario), a 10 μg/m^3 increase in $PM_{2.5}$ exposures over the ensuing few months-to-years increased cardiovascular mortality (hazard ratio = 1.35, 95% confidence interval = 1.09–1.67) and death from recurrent myocardial infarction (hazard ratio = 1.64, 95% confidence interval = 1.13–2.40).[31]

There has been a notable increase in studies evaluating the health effects of extreme high as well as low $PM_{2.5}$ concentrations. Two Canadian studies have demonstrated that long-term exposures remain capable of promoting cardiovascular events even at very low exposure levels (within annual WHO AQG < 10 μg/m^3).[32,33] In 2.1 million Canadians,[33] ischemic heart disease deaths significantly increased by 30% (per 10 μg/m^3) despite average $PM_{2.5}$ being 8.7 μg/m^3. Increased risks were also shown in a study with even lower mean levels (6.3 μg/m^3). No lower population threshold of risk was observed.[32] Similar findings have been reported in the United States including in rural Iowa and North Carolina,[34] as well as in the NIH-AARP[35] cohort (n = 517,043) in which long-term exposure increased cardiovascular mortality by 10% (per 10 μg/m^3) despite $PM_{2.5}$ levels averaging 10–13 μg/m^3. At the other end of the spectrum, the adverse health effects due to short-term $PM_{2.5}$ exposures have recently been shown to persist even at very high concentrations.[36,37] In a meta-analysis of 59 Chinese studies,[36] cardiovascular mortality significantly increased by 0.36% (per 10 μg/m^3) even though $PM_{2.5}$ ranged from 39 to 177 μg/m^3. In a time-series study in Beijing ($PM_{2.5}$ ranged from 3.9 to 494 μg/m^3), ischemic heart disease mortality increased by 0.25% (per 10 μg/m^3).[37] The shape of the dose–response was shown to be supra-linear, which accords with prior analyses.[15,38] There was a steeper increase in risk at lower concentrations up to 75–100 μg/m^3, with a shallower slope of the dose–response for higher exposures.[37] Finally, there have been far fewer cohort studies regarding the long-term health impacts of air pollution at very high levels.[39,40] In a recent analysis of 66,820 elderly residents of Hong Kong (annual $PM_{2.5}$ ~35 μg/m^3), mortality due to cardiovascular causes and ischemic heart disease significantly increased by 22 and 42%, respectively (per 10 μg/m^3).[39] These findings suggest that the adverse health effects due to chronic exposures persist at extreme $PM_{2.5}$ concentrations. Further cohort studies in this regard are warranted.

Remaining challenges. Despite substantial increases in knowledge gained during the past few years, several important questions remain. More studies are required to better elucidate the shape of the full dose–response curve because of the tremendous impact it has on the estimated global public health burden. The evidence thus far supports a supra-linear association with no (or a very low) lower threshold and an attenuation of the magnitude of increase in risk at higher levels of exposure.[38] Elderly individuals are consistently at greater risk, whereas some studies suggest the same for coronary disease patients, women, those at lower socioeconomic status, and diabetics.[7–11,29,41] A better understanding of both susceptible and vulnerable populations is needed, particularly in order to promulgate AQG that optimally protect the public health.[41]

Numerous short-[42,43] and long-term[44,45] studies have also attempted to identify the most toxic components (e.g., elements, carbon species) and sources (e.g., coal, traffic) of pollution responsible for eliciting adverse health effects. This is enormously difficult for methodological (e.g., variable measurement availabilities and accuracies), statistical (e.g., high intercorrelations and clustering), and study design reasons (e.g., variations in risks in regards to different health outcomes evaluated). The European ESCAPE project recently provided evidence that particle sulfur (principally derived from coal) may be of particular concern in relation to long-term exposures.[44] Results from the US American Cancer Society study (n = 445,860) also support coal as being a

harmful source for ischemic heart disease, but they also implicate diesel traffic.[45] A growing body of evidence has implicated traffic-related air pollution as one of the most commonly encountered as well as harmful exposures.[9,46] However, it remains uncertain if any specific component or source can be consistently incriminated with a high degree of confidence. Given that many pollutants likely pose differing health risks, it remains to be established if a targeted approach to regulatory policies translates into superior outcomes compared to using particle mass alone. In the meantime, the latter continues to serve as a widely available global metric of harmful exposure.

Air pollutants rarely occur in isolation to each other or other environmental exposures (e.g., noise, temperature).[1,9] The totality of the ill effects elicited by mixtures of pollutants including particles of various sizes combined with gases (ozone, NO_2) has only recently begun to be evaluated.[9] As a prominent example, near-roadway environments lead to exposures to noise, particulate, and gaseous traffic-related air pollution, as well as psychological stressors.[9,46] The independent and potentially additive (or synergistic) cardiovascular risks posed by these multiple exposures impacting most of the world's population on a daily basis (e.g., commutes) has yet to be fully understood. Regardless, it is well-known that recent traffic exposure ranks as the single largest triggering event for myocardial infarctions worldwide.[20] Many epidemiological studies have shown that residence proximity to major roadways is strongly linked to adverse cardiometabolic health effects.[8–11] More work on identifying the most harmful aspects of traffic are warranted.

Chronic cardiometabolic conditions

A growing body of evidence has linked several air pollutants with the chronic development of cardiometabolic disorders.[22,23,47–63] $PM_{2.5}$ inhalation can trigger acute elevations in BP over hours-to-days. However, longer-term exposures can promote the development of hypertension per se.[48–53] Living in a region (Ontario) with even low levels of $PM_{2.5}$ (mean 10.7 μg/m^3) led to a 13% increased risk for new onset hypertension (per 10 μg/m^3).[48] At the other end of the spectrum, extreme exposures near 100 μg/m^3 in China can also trigger acute and chronic BP elevations.[51,54] Several studies suggest that traffic-related air pollution may pose a particularly high risk.[55,56] Not all published observations have been significant; nonetheless, overall positive associations are supported by at least 2 recent meta-analyses and comprehensive reviews of the literature.[22,52,53]

$PM_{2.5}$ and other air pollutants can worsen insulin resistance and promote the development of DM.[54,57–61] This adverse metabolic effect has been observed in regions with extremely poor as well as overall good air quality.[57,58] Not all studies have reported positive findings. However, in-depth reviews[62] and recent meta-analyses[61] support an increase in risk (by approximately 8–13% per 10 μg/m^3). The manifold mechanisms whereby $PM_{2.5}$ can promote high BP and DM have been reviewed elsewhere. These include a constellation of responses such as activation of the sympathetic nervous system, endothelial dysfunction, systemic and tissue (e.g., adipocyte) inflammation and oxidative stress, altered adipocytokine expression, hypothalamic activation, impaired renal function, obesity and weight gain, and perhaps by direct actions of inhaled nanoparticulates.[22,23,62–64]

Remaining challenges. It has been speculated that acute air pollution-mediated increase in BP may play a mechanistic role in the triggering of cardiovascular events (e.g., strokes, heart failure).[22] Indeed, excess hypertension and DM-related mortality have been shown to occur among individuals living in more polluted locations.[65,66] However, the extent to which the development of chronic cardiometabolic conditions explain the magnified risks for cardiovascular events posed by long-term exposure remains to be fully elucidated. The degree to which air pollution and environmental exposures (e.g. traffic) are contributing to the global epidemic of the cardiometabolic syndrome also awaits further clarification. Finally, other chronic illnesses related to the cardiometabolic syndrome including chronic kidney disease,[63] obesity,[64] sleep-related breathing disorders,[67] pregnancy-related hypertension[68] and diabetes,[69] and neurological diseases (e.g., dementia, depression)[70,71] may also be linked to air pollution and require more investigation.

Intermediate endpoints

The demonstration that air pollutants can adversely impact surrogate markers of cardiovascular risk informs on putative mechanistic pathways and provides corroboratory evidence supporting the plausibility of the epidemiological observations.[7] $PM_{2.5}$ has been linked to biomarkers of atherosclerosis including carotid intima-media thickness, carotid plaques, coronary artery calcium, and aortic calcification.[7–11,24] Other studies show adverse vascular changes including increased arterial stiffness, impaired conduit artery flow-mediated dilatation, resistance arteriolar dysfunction, and retinal artery changes.[7–11] Metabolic derangements including impaired insulin sensitivity have also been demonstrated.[54,59,62]

Recent studies. There have been several publications within the past few years linking long-term air pollution and traffic exposure with an increase in biomarkers of atherosclerosis.[72–75] Perhaps the largest study (n = 6,795 across 6 US regions) with the longest follow-up (mean 10 years) comes from the MESA-Air cohort.[72] Each 5 μg/m^3 increase in long-term $PM_{2.5}$ exposure was associated with a greater progression of coronary artery calcium (4.1 Agatston units/year). $PM_{2.5}$ was not associated with intima-media thickness progression in this study.[72] However, a recent meta-analysis of 8 cross-sectional (n = 18,349) and 3 prospective (n = 7,268) studies showed significant associations with greater intima-media thickness.[75] The overall evidence, therefore, supports that $PM_{2.5}$ likely promotes an increase in intima-media thickness and coronary artery calcium, validated markers of atherosclerosis and heightened cardiovascular risk.

Earlier studies linked short-term air pollution exposures with acute endothelial dysfunction.[7–11] More recently, both MESA-Air and the Framingham cohort have further demonstrated that long-term exposures to ambient levels of $PM_{2.5}$

are linked to chronic reductions in brachial flow-mediated dilatation. This supports that air pollution causes vascular endothelial dysfunction, the hallmark physiological change underlying the initiation and progression of atherosclerosis and an established surrogate marker of cardiovascular risk.[76,77] Traffic-related air pollution and $PM_{2.5}$ have both also been linked to left and right ventricular structural changes in MESA-Air and the Jackson Heart Study.[78–81] Finally, a few studies have begun to show associations between adverse cerebral changes linked to dementia (e.g., white matter disease, reduced volume, covert infarcts).[82–85]

Remaining challenges. While several air pollutants have been associated with adverse changes in intermediate markers of cardiovascular damage/risk, the extent to which these alterations explain the "hard" epidemiological findings remains unknown. It is not clear to what extent these endpoints represent true "mediating" pathways of disease versus simple markers of heightened risk. It is also critical to identify the optimal endpoints to investigate that represent valid "surrogate outcomes" in interventional trials of personal-level exposure reduction.

Mechanistic evidence

$PM_{2.5}$ inhalation can trigger acute events and promote chronic cardiometabolic conditions by 3 broad mediating pathways (Figure 2). Depending upon the dose and time course of exposure, as well as the individual level of susceptibility, each pathway alone or altogether can elicit a host of adverse responses. These include vascular dysfunction (e.g., vasoconstriction, impaired vasodilatation); altered hemodynamics (e.g., increased BP and arterial stiffness); augmented thrombosis (e.g., activated platelets, adhesion molecule, and coagulation factor expression); heightened arrhythmia potential (e.g., autonomic imbalance, cardiac repolarization abnormalities); as well as numerous proatherosclerotic changes (e.g., oxidized lipids, plaque progression, and inflammation/instability). A full update on the wealth of recent basic science, toxicological, and animal experiments is beyond the scope of this review. Details in this regard can be found elsewhere.[10,22–24,62,86–88] However, noteworthy human studies providing important novel mechanistic insights include the demonstration that $PM_{2.5}$ can induce high-density lipoprotein dysfunction,[89] trigger several epigenetic changes,[90] and adversely alter circulating endothelial-platelet microparticles, growth factors (e.g., VEGF), and endothelial progenitor cell levels.[91,92] Finally, a recent experiment using gold nanoparticles has provided some of the most compelling evidence supporting the potential biological relevance of mediating pathway 3 (Figure 2). The investigators demonstrated that a fraction of particles <30 nm in size were capable of reaching the systemic circulation and vascular issues following inhalation.[93] Further studies in this regard are warranted.

PERSONAL-LEVEL PREVENTIVE STRATEGIES

Overall air quality has dramatically improved across the United States during the past few decades due in large part from clean air regulations. Most counties are now in compliance with the latest NAAQS. The reduction in long-term levels of $PM_{2.5}$ has translated into clear benefits to public health and significantly contributed to the increase in overall life expectancy since the 1980s.[13] Unfortunately, air quality has dramatically worsened throughout much of the developing world during this same period.[2,12,14] Hundreds of millions of individuals living across East and South Asia (e.g., China, India) face extraordinarily high air pollution levels far exceeding WHO AQG on a daily basis.[2] It appears likely that substantial improvements in air quality remain decades off in the future in these regions due to population growth, increasing energy and transportation demands, and numerous geopolitical-economic factors.[14] In the meantime, unless some actions are taken to protect the health of millions of at-risk individuals, the burden of air pollution-related cardiometabolic diseases (already a leading risk factor for morbidity and mortality across Asia)[2] will only further increase.

Several "personal-level" strategies to reduce exposures and prevent the harmful effects of air pollution have been proposed (Table 1). We recently reviewed the effectiveness of these approaches from the growing number of small trials.[13] A few important studies in the most germane location, heavily polluted China, have thereafter been published. The use of air purifiers with HEPA filters reduced indoor $PM_{2.5}$ by 57% (96 to 41 $\mu g/m^3$) among 35 college students in Shanghai. This led to significant improvements in several biomarkers of cardiometabolic health (MCP-1, IL-1, MPO, CD40L) and BP within 48 hours.[94] Wearing N95 respirators facemasks in the same cohort was also protective, as BP and heart rate variability were improved within 48 hours.[95] We and others are undertaking similar trials in lower polluted cities in the United States. Preliminary results from our recently completed RAPIDS trial in Detroit Michigan (ambient $PM_{2.5}$ levels ranging from 10–20 $\mu g/m^3$) showed that air purifiers with HEPA filters can reduce time-averaged personal-level exposures by 30–50%. Decreases in BP were observed within 1–3 days among elderly residents living in a senior residence facility (unpublished data).

A call for clinical outcome trials

Both the American Heart Association and the European Society of Cardiology formally recognized $PM_{2.5}$ as an independent risk factor for cardiovascular diseases.[7,8] While prudent precautionary recommendations were provided on how to reduce exposures, it was explicitly acknowledged that no "evidence-based" guidance could be officially promulgated. $PM_{2.5}$ poses an equal or greater risk to global cardiometabolic public health than most traditional risk factors (high cholesterol or blood sugar).[4] Nevertheless, there has not been a single randomized outcome trial that has tested the efficacy of any preventive strategy to reduce air pollution-induced cardiovascular events. We recently reviewed the importance as well as the putative design and plausibility of clinical trials in this regard.[96] Given the evidence supporting improvements in biomarkers of cardiovascular health in studies of facemasks and air purifiers,[13] and the high risk for recurrent cardiovascular events among individuals with

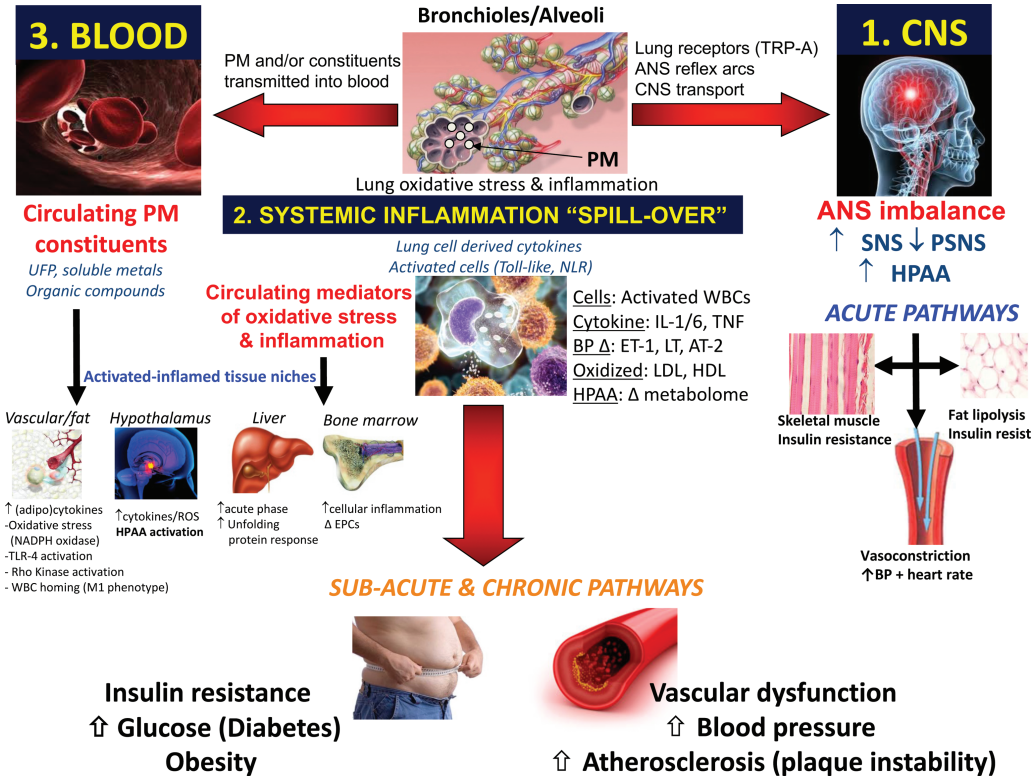

Figure 2. Biological pathways whereby $PM_{2.5}$ promotes cardiovascular events. Inhaled $PM_{2.5}$ deposit deep within pulmonary tissues (i.e., alveoli) and interact/activate local cells (e.g., resident macrophages, dendritic cells, alveolar/endothelial cells) and modify endogenous structures (e.g., cell membranes, surfactant lipids, antioxidants). Mediators of oxidative stress (e.g., free radicals) directly generated by particulate compounds (metals, organic species) or secondarily produced (e.g., modified phospholipids) by activated cellular enzyme systems (e.g., NADPH oxidase) can instigate a local inflammatory response. Several innate immune pathways may be important in coordinating this response such as *via* activated toll-like receptors (TLR). In pathway 1, the inhaled particles and/or oxidative stress impact a variety of afferent nerves (e.g., transient receptor potential receptors [TRP]) and rapidly alter central nervous system (CNS) autonomic nervous system (ANS) balance typically favoring sympathetic (SNS) activity over parasympathetic (PSNS) nervous system activity. In pathway 2, numerous mediators of inflammation and oxidative stress generated in the lungs (e.g., cytokines, activated immune cells, oxidized lipids) "spill-over" into the systemic circulation and thereafter carry this danger signal to remote cardiovascular tissues. In hypothetical pathway 3, nanoparticles (10–30 nm) or particulate components penetrate lung barriers and are carried within immune cells or lipoproteins or directly reach the systemic circulation. Harmful chemicals (organic carbon species, metals) deposit into cardiovascular tissues and elicit inflammatory-oxidative stress responses without the need for the signal to be indirectly transmitted *via* pathway 2. Abbreviations: BP, blood pressure; HPAA, hypothalamic pituitary adrenal axis; PM, particulate matter; UFP, ultrafine particles.

Table 1. Personal and local-level interventions to reduce exposures or susceptibility to air pollution

Intervention type	Examples
Air purifiers	Portable indoor HEPA filter systems in living spaces and bedrooms HEPA designated filters remove PM at 0.3 microns in diameter by 99.97%
Facemasks	N95 respirators, surgical facemasks worn in heavily polluted regions N95 designated respirators remove at least 95% of PM at 0.3 microns
Reduce in-traffic exposures	In cabin HEPA filters, closing car windows, recirculating in-cabin air
Reduce traffic emissions	Diesel particle traps, catalytic converters, alternative fuels (natural gas, electric cars)
Reduce in-home penetrance	Closing windows, central air conditioning filtration, improved home efficiency
Cleaner cook-stoves	Cleaner-burning liquid fuel stoves, improved stove emission ventilation
Lifestyle changes	Avoiding point sources (roadways), exercising indoors during peak exposure times (rush hour). Awareness of health risks of travel to heavily polluted regions
Medications and diet	Fish oil, antioxidants, maintaining healthy diet (vegetables), evidence-based medications (statins)
Municipality and city changes	Green-spaces, natural (trees) barriers from roadways, improved urban design (bike paths >400 m from roadways)

established heart disease due to long-term $PM_{2.5}$ exposures, we proposed that clinical outcome trials in this population of patients are both important and feasible.[96] Intervention trials would be of greatest relevance and effectiveness in heavily polluted countries where a 50% reduction in inhaled $PM_{2.5}$ afforded by N95 respirators and indoor air purifiers would likely translate in substantial decreases in time-averaged exposures over months-to-years (e.g., 30–50 $\mu g/m^3$). Despite the complete lack of evidence supporting or refuting their benefits on hard outcomes, many low-efficiency facemasks are already widely used across China. Here, we make another emphatic call to the scientific-medical community to design and launch large-scale randomized clinical outcome trials to test the health benefits of validated (e.g., N95 respirators, air purifiers with HEPA filters) personal-level preventive strategies among high-risk patients (e.g., acute coronary syndrome survivors). We can think of no other research effort to be undertaken during the next decade that could provide more important data. Positive results would provide a critical piece of much-needed scientific evidence that further supports a "causal role" for $PM_{2.5}$ in the etiology of cardiovascular disease. Finally, the findings would be of immediate real-world relevance. They could be rapidly translated into action by widespread dissemination and evidence-based usage of simple inexpensive approaches to reduce $PM_{2.5}$ exposures and thereby positively impact the health and welfare of millions of individuals worldwide.[96]

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DISCLOSURE

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