HHS Public Access

Author manuscript

Pharmacol Ther. Author manuscript; available in PMC 2022 July 01.

Published in final edited form as:

Pharmacol Ther. 2021 July ; 223: 107890. doi:10.1016/j.pharmthera.2021.107890.

Particulate matter air pollutants and cardiovascular disease: Strategies for intervention

Ankit Aryal, **Ashlyn C. Harmon**, **Tammy R. Dugas***

Louisiana State University School of Veterinary Medicine, Department of Comparative Biomedical Sciences, Skip Bertman Drive, Baton Rouge, Louisiana 70803

Abstract

Air pollution is consistently linked with elevations in cardiovascular disease (CVD) and CVD-related mortality. Particulate matter (PM) is a critical factor in air pollution-associated CVD. PM forms in the air during the combustion of fuels as solid particles and liquid droplets and the sources of airborne PM range from dust and dirt to soot and smoke. The health impacts of PM inhalation are well documented. In the US, where CVD is already the leading cause of death, it is estimated that $PM_{2.5}$ (PM < 2.5 μm in size) is responsible for nearly 200,000 premature deaths annually. Despite the public health data, definitive mechanisms underlying PM-associated CVD are elusive. However, evidence to-date implicates mechanisms involving oxidative stress, inflammation, metabolic dysfunction and dyslipidemia, contributing to vascular dysfunction and atherosclerosis, along with autonomic dysfunction and hypertension. For the benefit of susceptible individuals and individuals who live in areas where PM levels exceed the National Ambient Air Quality Standard, interventional strategies for mitigating PM-associated CVD are necessary. This review will highlight current state of knowledge with respect to mechanisms for PM-dependent CVD. Based upon these mechanisms, strategies for intervention will be outlined. Citing data from animal models and human subjects, these highlighted strategies include: 1) antioxidants, such as vitamins E and C, carnosine, sulforaphane and resveratrol, to reduce oxidative stress and systemic inflammation; 2) omega-3 fatty acids, to inhibit inflammation and autonomic dysfunction; 3) statins, to decrease cholesterol accumulation and inflammation; 4) melatonin, to regulate the immune-pineal axis and 5) metformin, to address PM-associated metabolic dysfunction. Each of these will be discussed with respect to its potential role in limiting PM-associated CVD.

Keywords

cardiovascular disease; particulate matter; statins; melatonin; metformin; omega-3 fatty acids

*Address all correspondence to this author at: LSU School of Veterinary Medicine, Department of Comparative Biomedical Sciences, Skip Bertman Drive, Baton Rouge, LA 70803. tammydugas@lsu.edu.

Declarations of competing interests

T.R.D has two approved US patents peripherally related to this work. T.R.D. is a cofounder of ReQuisite Biomedical, a medical device company. A.A. and A.C.H have no conflicts or competing interests.

1. Introduction

Cardiovascular disease (CVD) and its associated events like myocardial infarction and stroke remain the number one cause of death in the US and in many developed countries (Lozano et al., 2012). Lifestyle choices, including high-fat diets and sedentary behaviors, contribute to the prevalence and progression of CVD, but the environment is also an important contributor (Cosselman et al., 2015).

The etiology of CVD is complex in nature, involving a series of cellular events occuring within the vascular wall. In normal vascular homeostasis, a single layer of endothelial cells in intimate contact with the blood maintains the vessel in a dilated state through its production of vasodilating factors such as nitric oxide and prostacyclin (van Hinsbergh, 2001). These agents act in a paracrine manner to impact signaling pathways within vascular smooth muscle cells, relaxing the layers of smooth muscle that form the majority of the vascular wall (Radonnski et al., 1993; Vane et al., 2003). A functional endothelium also provides a barrier against the entry of blood components such as lipids and lipoproteins, as well as inflammatory cells, thus protecting the vasculature from pathological insult (Michiels, 2003). However, when endothelial cells become injured or inflamed, this homeostasis is disrupted, culminating in lesion formation within the wall that can eventually occlude the vessel and impede blood flow to tissues (Molitoris et al., 2004). There are several theories for how these lesions develop. Chief among these is the "response to injury" hypothesis (Ross et al., 1977), positing that atherosclerosis begins with injury to the endothelial layer. This endothelial injury disrupts the vessel's barrier function, allowing for increased permeability to lipoproteins and their lipid cargo. These dysfunctional and injured endothelial cells begin to increase their expression of chemokines that promote the recruitment of monocytes and other inflammatory cells from the blood to the endothelium. Their increased expression of adhesion molecules promotes the adherence of these monocytes to the cell layer and their subsequent migration into the sub-endothelial space (Walpola et al., 1995). There, the monocytes differentiate into macrophages and begin to accumulate lipoprotein, eventually forming foam cells (Moore et al., 2013). The accumulation of foam cells and their eventual apoptosis culminates in the apoptosis and necrosis of neighboring smooth muscle cells (Hegyi et al., 1996). This cascade of cell death leads to the formation of a lipid-rich milieu often referred to as the "necrotic core.” Finally, the injured endothelial cells and resident inflammatory cells produce growth factors and cytokines that stimulate smooth muscle cell migration from the media to the intima, where they proliferate. The resulting expansion of the intimal layer, a process known as neointimal hyperplasia, culminates in a narrowing of the diseased artery to restrict blood flow (Hui, 2008). Blockages due to atherosclerosis, if left unchecked, can result in catastrophic clinical events such as stroke or myocardial infarction (Hollander et al., 2003). Given the complexity of atherogensis and the involvement of numerous cell types, toxicants have to potential to intervene at a number of cellular events to exacerbate the progression of atherosclerosis.

Air pollution promotes CVD initiation and progression and likely contributes to the pervasiveness of CVD (Seaton, et al., 1995). Although air pollution is a complex mixture of gases, liquids and particulate matter (PM), a wealth of scientific literature to date has focused on the role of PM as a contributor to CVD initiation and progression. PM is defined

as a mixture of solid particles and liquid droplets that form in air when organic matter, fuels or wastes are burned. Sources of PM include automobile exhaust, industry, power plants, waste incinerators, wildfires and fireplaces, to name a few (Harrison, 2020). In 2004, the American Heart Association (AHA) released a consensus statement and exhaustive review documenting epidemiologic evidence supporting the contribution of PM to cardiovascular morbidity and mortality in the US and elsewhere (Brook et al., 2004). Their statement was intended to guide clinicians in identifying environmental causes underlying clinical cases of CVD and to suggest practical approaches for reducing risk to patients. After a wealth of new literature, in 2010, the AHA exanded their analysis, particularly highlighting roles for fine (<2.5 μm in size) and ultrafine (PM < 0.1 μm) PM, the role of co-pollutant gases such as ozone, nitrous oxides (NOx), as well as sources of PM, e.g., traffic compared to industrial sources (Brook et al., 2010). In this review, we will highlight a sampling of the epidemiology documenting PM-associated CVD, discuss putative mechanisms by which PM may induce CVD and then suggest potential dietary interventions and pharmacologic approaches for reducing CVD in populations at most risk for exposure.

2. Endothelial dysfunction and its assessment

As will become evident in this review, endothelial dysfunction is a common physiologic mechanism by which toxicants such as PM promote CVD. A critical initiating event and important biomarker for atherogenesis (Vanhoutte, 1997), endothelial dysfunction in humans and animal models can be assessed through a number of well-defined endpoints. For the purposes of orienting the reader, we will briefly highlight the more common endpoints. First, a key feature of endothelial dysfunction is an inability of arteries to fully dilate in response to physiologic stimuli (Endemann et al., 2004). In this regard, endothelial dysfunction can be assessed in human subjects as a decrease in flow-mediated dilation (Korkmaz et al., 2008), which is typically determined by cuffing the brachial artery and measuring changes in artery diameter. For experiments in rodent models, endothelial dysfunction is measured as a decreased dilation of arteries in response to endothelium-dependent vasodilators (Schuler et al., 2014). In many cases, the arteries are excised and exposed to these stimuli within a temperature-controlled bath. Endothelial dysfunction can also be defined as an imbalance between vasodilating factors, such as nitric oxide and prostacyclin, and vasoconstricting factors, like endothelin-1 or thomboxane A2 (Schiffrin, 2001), all of which can be measured in the plasma of both humans and animals. Furthermore, while endothelial nitric oxide is produced by the membrane-bound endothelial nitric oxide synthase (eNOS), its function is regulated by many factors, including its phosphorylation and levels of its critical substrates and co-factors like L-arginine and tetrahydrobiopterin (Alp et al., 2004; Zembowicz et al., 1991). Thus, decreases in NO, typically measured as its stable metabolite nitrite, coupled to increases in levels of vasoconstricting factors would suggest a potential decrease in a vessel's dilative capacity. Alterations in levels of eNOS expression and/or phosphorylation, as well as levels of its co-factors can used to elucidate mechanisms by which toxicants promote endothelial dysfunction (Vanhoutte et al., 2009). Another important mechanism that impacts NO bioavailability is its destruction when high levels of reactive oxygen, i.e., superoxide, are formed during oxidative stress conditions (Förstermann, 2010). Thus, decreases in NO levels and eNOS function are also commonly associated with biomarkers

for oxidative stress (Pierini et al., 2015). Finally, in response to inflammatory stimuli, endothelia respond by adopting an “activated” phenotype, where a number of antigens and adhesion molecules become highly expressed on the cell surface to promote inflammatory cell adhesion. Endothelial activation is typically characterized by a loss of vascular integrity, an increased expression of adhesion molecules, adoption of a prothrombotic phenotype, and an increased cytokine production (Liao, 2013). Systemic inflammation, including elevations in circulating cytokines like IL-6 and TNF-α, is often associated with endothelial activation, and biomarkers for endothelial activation typically include either vascular expression of adhesion molecules or increased circulating levels of soluble adhesion molecules, like soluble intracellular adhesion molecule-1 (sICAM-1), soluble vascular cell adhesion molecule (sVCAM-1), or soluble E-selectin, along with biomarkers associated with coagulation, e.g., von Willebrand Factor (vWF) and thrombomodulin (Hasper et al., 1998; Martin et al., 2013; Blann & McCollum, 1994; Vischer, 2006). It was also shown that upon activation, endothelial microparticles are shed and released into the circulation, where they have roles in modulating inflammation, coagulation, and angiogenesis (Markiewicz, et al., 2013). Thus, elevations in their levels in the circulation may be indicative of a local inflammation.

3. Epidemiological evidence for PM-associated CVD

Episodes of marked increases in airborne PM in cities around the world are correlated with an elevated incidence of myocardial infarction, stroke and other cardiovascular events (Pope III et al., 2006). Using data obtained in 6 US cities, the National Center for Health Statistics demonstrated that for every 10 $\mu g/m^3$ increase in coal- and automobile-derived $PM_{2.5}$ (particles < 2.5 μm), mortality increases by 3.4% (Laden, et al., 2000). In another epidemiological study using data collected by the American Cancer Society, long-term PM exposures in US metropolitan areas were correlated with increased heart disease-related events, including cardiac arrest. In this study, for every 10 $\mu g/m^3$ increase in PM, mortality increased 8-18% (Pope III et al., 2002). Interestingly, deaths attributed to respiratory disease were only weakly associated with increases in PM. However, patients with pre-existing cardiopulmonary diseases exhibit a greater risk of mortality from CVD when the environment where they reside is polluted (Godleski et al., 2000; Pope III, 2021). Moreover, chronic childhood exposure to air pollution predisposes subjects to a greater risk for CVD, atherosclerosis, stroke and other systemic effects later in life (Calderon-Garciduenas et al., 2008). Patients with metabolic syndrome are at even greater risk for developing CVD when exposed to air pollution (Park et al., 2010).

Studies emerging over the last several years from the Multi-Ethnic Study of Atherosclerosis (MESA), involving 6000 men and women from six communities in the US, have further solidified the epidemiologic association between PM exposure and CVD progression. In one such study, higher ambient PM levels were associated with higher systolic blood and pulse pressures (Auchincloss et al., 2008). Children exposed to high PM levels exhibited elevations in pulmonary arterial pressures, suggesting that the lung vasculature may be a particular target and that the impacts of PM exposure span adults and children alike (Calderón-Garcidueñas et al., 2007). In support of findings of increased pulmonary arterial pressures, long-term exposure to black carbon from diesel exhaust particles (DEP) was

associated with increased pulmonary vascular remodeling (Aaron et al., 2019). Long-term PM exposure was also shown to promote vascular effects outside of the lung. For example, higher PM exposures were linked with endothelial dysfunction, assessed as a decreased flow-mediated dilation in the brachial artery (Krishnan et al., 2012), suggesting that the endothelium may be an early target of injury. Interestingly, even small increases in short-term or long-term PM exposure levels reduced microvascular diameter in older subjects (Adar et al., 2010). There is also epidemiologic evidence that PM exacerbates atherosclerotic lesion progression, evidenced by indices reflective of later stages of atherogenesis. For example, long-term exposure to PM increased intima-medial thickness in the carotid artery (Adar et al., 2013). In a 10-year cohort, progression of coronary calcification and atherosclerosis were associated with increased exposure to PM and traffic-related air pollution (Kaufman et al., 2016). Thus, a wealth of evidence supports the role of PM in promoting the progression of CVD.

4. Mechanisms for PM-induced CVD

To identify mechanisms for how air pollution promotes cardiovascular disease, researchers have utilized well-controlled animal experiments, as well as *in vitro* approaches. However, the inherent complexity in the components of air pollution and its many combustion sources presents considerable challenges in the systematic study of PM-induced cardiovascular injury. PM consists of a mixture of gases, combustion by-products, resuspended crystalline matter, as well as biologics like bacteria, viruses and pollen (Menetrez et al., 2000). The chemical composition of PM likely plays an important role in the etiology of air pollution-associated CVD (S. Wu et al., 2012), with individual components acting in concert to influence cellular and tissue-specific responses. PM has been shown to impact almost every cellular and physiological aspect of atherogenesis, including oxidative stress, inflammation, metabolic dysfunction, lipid metabolism, and autonomic dysfunction. Thus, in the next section, we will provide an overview of the mechanisms contributing to PM-associated atherosclerosis.

4.1. Mechanism 1. Oxidative stress.

Numerous studies have provided evidence for the role of oxidative stress in PM-dependent CVD. For example, PM inhalation in mice reportedly induces an increase in monocyte and vascular NADPH oxidase-derived superoxide formation through a mechanism involving toll-like receptor-4 (TLR-4) signaling (Kampfrath et al., 2011). These and other oxidative stress-related phenomena promote vascular dysfunction, which is characterized by an increase in blood pressure, impairment of normal endothelial homeostasis, and increased vascular permeability (Rao et al., 2018). In rats, 12 weeks exposure to $PM_{2.5}$ culminated in atherosclerosis in the middle cerebral artery, marked by inflammation and oxidative stress, including elevations in NADPH oxidase activity, increases in reactive oxygen species (ROS) and lipid oxidation products, as well as reductions in levels of the antioxidant superoxide dismutase (SOD; Guan et al., 2019). In a malnourished mouse model of growth retardation - a rodent model for disease-susceptible individuals - PM exposure increased the level of ROS but did not alter SOD and catalase activities, leading to lipid membrane damage evident by increased lipid peroxidation (Kurtz et al., 2018). One potential mechanism for PM-induced

oxidative stress may be through activation of the aryl hydrocarbon receptor (AhR). Polycyclic hydrocarbons (PAH) arising from pyrolytic processes such as combustion often adsorb to PM in the air (Schuetzle et al., 1984). These PAH, in turn, can activate the AhR, and depending upon the ligand, can impart either immune stimulatory or suppressive actions (Suzuki et al., 2020). In general, the pathophysiology of PM is known associated with AhR activation and inflammation-related pathways such as nuclear factor-kappa (NF_kB) signaling, as well as nuclear factor erythroid 2-related factor (Nrf2) signaling, an important regulator of a cell's resistance to oxidants (Lawal 2017; Vogel et al., 2014; Wardyn et al., 2015). Nrf2 is a transcription factor that under normal physiologic conditions is bound to KEAP1, a repressor protein (R. Li et al., 2019). However, when a critical thiol residue in KEAP1 becomes modified by electrophiles and other oxidants such as those formed during oxidative stress, Nrf2 is released and available for binding to antioxidant response elements (ARE) within genes that regulate the expression of antioxidant enzymes (Nguyen et al., 2009). Thus, PM exposure often results in the upregulation of inflammatory cytokines and ROS, and as a protective mechanism, increased expression of antioxidant enzymes (Lawal 2017; Vogel et al., 2014). Another interesting pathway proposed as an oxidative stress-dependent mechanism for PM-associated CVD involves microRNA (miRNA) signaling. Environmental stressors such as PM play an important role in the epigenetic regulation of miRNA signaling, where miRNA expression contributes to oxidative stress (Münzel et al., 2018). Moreover, miRNA contributes to cardiovascular development and blood vessel formation, and their expression is aberrant in heart and vascular disease (C. Zhang, 2008). Elevations in circulating levels of miRNA associated with elevated PM exposures has now been demonstrated in a number of population studies (Mancini et al., 2020; Rodosthenous et al., 2018; Ruiz-Vera et al., 2019). Thus, aberrant miRNA signaling could be a factor in PM-mediated oxidative stress and CVD. In summary, through multiple overlapping mechanisms, PM exposure can promote oxidative stress, a well-known contributor to the pathophysiology of CVD (Kelly et al., 2017).

It is noteworthy that oxidant gases such as O_3 and NO_2 are also associated with an increased risk for $PM_{2.5}$-associated mortality (Weichenthal et al., 2017). Oxidant gases including ozone (O_3) and nitrogen dioxide (NO_2) are free radical species that, when inhaled, are highly reactive in lung tissues (Freeman et al., 1982; Mudway et al., 2000). Ozone is a powerful oxidant in the lung, reacting so rapidly that circulation to distal tissues is considered unlikely (Menzel, 1984). NO_2 readily dimerizes to form dinitrogen tetroxide, and these species induce the nitrosation of amines, amides and thiols (Wainright, 1986). Furthermore, in a cohort of >2 million Canadians followed over 10 years, exposure to oxidant gases such as ozone and NO_2 strengthened the association between $PM_{2.5}$ and both cardiovascular and respiratory mortality, with increases in $PM_{2.5}$ of 3.86 $\mu g/m^3$ most strongly correlated with mortality in the highest tertile of oxidant gas levels (Weichenthal et al., 2017). Oxidant gases may thus synergize with $PM_{2.5}$ to accelerate oxidative stress. Although inflammatory and oxidative stress responses in lungs may contribute to downstream systemic effects in other tissues including the cardiovascular system, specific mechanisms linking ozone air pollution and exacerbation of CVD are lacking. However, it is posited that these oxidant gases may serve to accelerate a deterioration of the lung's barrier function, providing a greater opportunity for transit of $PM_{2.5}$ beyond the lung (Sokolowska

et al., 2019). Thus, maintenance of antioxidant levels within the lung and by extension, its barrier function, would reasonably be important for the prevention of $PM_{2.5}$-associated CVD.

4.2. Mechanism 2. Pulmonary and systemic inflammation.

It is generally appreciated that PM induces systemic effects *via* oxidative stress pathways (Rao et al., 2018). However, its overall pathophysiological effect on the cardiovascular system is linked with both the formation of ROS, either by the particle itself or *via* endogenous ROS producing systems, and the activation of immune cells (Kampfrath et al., 2011; Miyata et al., 2011). Inflammation and oxidative stress are integrally linked, with oxidative stress typically culminating in tissue injury and an induction in inflammation (Kim et al., 2013). In brief, oxidized lipids and proteins formed during oxidative stress serve as damage-associated molecular patterns, or DAMPs, that bind to pattern recognition receptors to activate Toll-like receptor (TLR) signaling and inflammation (Imai et al., 2000; Choi et al, 2009; Lahoute et al., 2011). Inflammation then results in the formation of ROS, and chronic bouts of inflammation culminate in oxidative stress. Cycles of inflammation and oxidative stress contribute to the etiology of a number of pathophysiologic conditions, including CVD (Steven et al., 2019).

These integrally related mechanisms have also been demonstrated in models of PM exposure. For example, PM can cross the air-blood interface within the alveolar-capillary membrane and achieve direct access to the vascular endothelium and blood cells, resulting in tissue damage and local and systemic inflammation (Nemmar et al., 2001; Farini et al., 2013). Danger signals resulting from PM exposures act *via* receptors such as TLR4, triggering classical kinase signaling, activation of NF_kB, and synthesis of cytokines (Kampfrath et al., 2011). Such activation is accompanied by inflammation and the formation of reactive oxygen and nitrogen species, potentially resulting in tissue oxidant injury and CVD pathogenesis (Lucas et al., 2013).

As explained in the introductory section, vascular inflammation is an important contributor to atherogenesis (Moore et al., 2013). The recruitment of monocytes from the blood to a dysfunctional endothelium and an elevated adhesion molecule expression by the endothelial cells promotes the adhesion of these monocytes and their migration into the vascular wall. The monocytes then differentiate into macrophages and accumulate low-density lipoprotein to form foam cells. Vascular biomarkers like the cell adhesion molecules ICAM-1 and VCAM-1 play important roles in the adhesion of monocytes and their trans-endothelial migration, and increased blood levels of adhesion molecules are associated with CVD and cardiovascular death (Cook-Mills et al., 2011; Pradhan et al., 2002; Blankenberg et al., 2001). Among $PM_{2.5}$ species, vanadium is associated with an increase in both ICAM-1 and VCAM-1 levels (Dai et al., 2016). Other evidence that PM promotes vascular and systemic inflammation are that long-term exposure to $PM_{2.5}$ results in an increase in the inflammatory biomarker C-reactive protein and is associated with an increased risk for CVD (Q. Liu et al., 2019). Moreover, the use of statins and moderate alcohol consumption aimed at reducing inflammation showed protective effects, reducing PM-induced cardiovascular injury (Ostro et al., 2014).

Another interesting mechanism for PM-mediated inflammation include its regulation of telomere length in inflammatory cells. A telomere is a repetitive nucleotide sequence located at the end of linear chromosomes and typically associated with specialized proteins. These structures protect these terminal regions from degradation during cell division (Vaiserman et al., 2020). However, after repetitive cell divisions, i.e., as the cell ages, these telomeres are shortened and at a critical point of shortening, the cell undergoes either cell cycle arrest, leading to cellular senescence or apoptosis (Vaiserman et al., 2020). The role of the telomere in inflammation is only just becoming clear; however, it seems that chronic inflammation can result in telomere shortening and immunosenescence, a process commonly referred to as "inflammaging" (Jose et al., 2017). When inflammatory cells such as macrophages or T-cells senesce, they release higher levels of cytokines such as TNF-α and IL-6 (Jose et al., 2017), and higher circulating levels of these cytokines are associated with atherogenesis (Branen et al., 2004; Huber et al., 1999; Ohta et al., 2005). Thus, immunosenescence can potentially increase the rate of atherogenesis, and the evidence to date suggests that PM may promote immunosenescence *via* telomere shortening. Short-term exposure to $PM_{2.5}$ increases telomere length, likely due to an increase in immature leukocytes (Dioni et al., 2011). However, long-term exposure to $PM_{2.5}$ in the elderly shortens telomere length in peripheral leukocytes, culminating in oxidative stress and an elevated pro-inflammatory phenotype (Pieters et al., 2016). To support these mechanistic findings, in a longitudinal study of boilermakers continuously exposed to $PM_{2.5}$, PM exposure decreased telomere length in leukocytes (Wong et al., 2014).

4.3. Mechanism 3. Autonomic dysfunction and other neurohumoral mechanisms.

The sympathetic branch of the autonomic nervous system produces catecholamines that act as both hormones and neurotransmitters to regulate blood pressure and heart rate (HR). Increased levels of catecholamines are also associated with blood coagulation, myocardial infarction, and arterial infarction (Mustonen et al., 1996). Relevant to this review, at least one epidemiological study has documented correlations between long-term air pollution exposure and urinary catecholamines, including epinephrine, norepinephrine and dopamine (Hajat et al., 2019). In heart failure-prone rats, DEP inhalation causes modulation in cardiac electrophysiology and mechanical function induced through autonomic imbalance (Carll et al., 2013). Mechanisms proposed for PM-mediated activation of a neurohumoral mechanism include the activation of the autonomic nervous system and of the hypothalamus-pituitary axis (HPA; Bartoli et al., 2009), though as yet, both pathways are poorly delineated. Nevertheless, current evidence documenting the role of each in PM-associated CVD will be described in this section.

Both *in vivo* and *in vitro* studies demonstrate that upon inhalation, the cationic component of PM activates sensory receptors in the lungs (Deering-Rice et al., 2011). Activation of receptors like the transient receptor potential (TRP) channels at sensory nerve endings sends a neural stimulus *via* ganglia to the CNS and a feedback response *via* autonomic outflow to the heart (Deering-Rice et al., 2011; Hazari et al., 2011). Selective blockade of TRPV1 in rats demonstrated that TRPV1 is integral to DEP-mediated elevations in blood pressure and cardiac dysfunction (Robertson et al., 2014).

Heart rate variability (HRV) represents a prototypical biomarker for autonomic dysfunction in the cardiovascular system and is considered a prognostic marker for lethal arrhythmias (Camm et al., 1996). Numerous studies demonstrate that PM exposure induces acute changes in HR and HRV by stimulation of the autonomic nervous system (Pieters et al., 2012; Tankersley et al., 2004). For example, in atherogenic mice exposed to CAP for 4 months, CAP exposure enhanced HRV for the first 12 weeks of exposure but decreased HRV over the following 2 months (L.C. Chen et al., 2005). PM exposure also exhibits a diurnal variation in cardiac autonomics, inducing sympathetic hyper-stimulation during daytime hours (Tsai et al., 2019). Moreover, PM induces alterations in HRV that oscillate between sympathetic and parasympathetic control, although cardiac dysfunction *per se* was shown dependent upon sympathetic tone (Carll et al., 2013). Interestingly, exposure of PM in mice exhibiting terminal senescence (i.e., in the senescent mouse model) produces alterations in HR and HRV that are mediated predominantly by parasympathetic tone, while in healthy mice, modulations in HRV are dependent upon sympathetic tone (Tankersley et al., 2004). In rats exposed to PM, autonomic signaling in the heart promoted cardiac oxidative stress and functional alterations that were reversed by sympathetic and parasympathetic antagonists (Rhoden et al., 2005). These results thus suggest a role for both branches of the autonomic nervous system in regulating HR and HRV after PM exposure.

With respect to the sympathetic nervous system, research has suggested that both β1 and α2-adrenergic receptors are involved in PM-associated cardiovascular dysfunction. β-adrenergic receptors include three distinct subtypes- β1, β2, and β3. β1-adrenergic receptors are activated in an earlier stage of cardiac failure, initiating myocardial hypertrophy and remodeling, apoptosis, and necrosis, while β2 receptors expressed in cardiac progenitor cells counteract the pro-apoptotic action of β1, protecting the myocardium against apoptosis (Khan et al., 2013). The combined use of β1 blockade and a β2 agonist demonstrated protection against PM exposure by attenuating myocardial inflammation and inhibiting apoptosis, thus improving cardiac function (Y. Gao, et al., 2014). In contrast, activation of the α2B adrenergic receptor (Adra2b) stimulates sympathetic nerve tone and thus, increases blood pressure (Kanagy, 2005). PM exposure promotes the overexpression of Adra2b in the brain, producing anxiety and behavioral changes as well as an elevated blood pressure in response to high salt intake (Rao et al., 2019). It has also been shown that PM exposure activates β2-adrenergic receptor signaling in macrophages, resulting in pulmonary and systemic inflammation and even thrombosis (Chiarella et al., 2014).

Finally, there are several reports that PM exposure may activate the HPA axis to indirectly promote cardiovascular dysfunction. For example, 4 repeat exposures of healthy adults to fine PM resulted in elevations of corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH) and cortisol in serum (Niu et al., 2018). Elevations in cortisol typically suggest HPA activation. HPA activation induces the hypothalamus to release CRH, which in turn stimulates the anterior pituitary to release ACTH. ACTH release into the circulation then stimulates the adrenal glands to release cortisol (Herman et al., 2011). In support of this mechanism, numerous human and rodent studies have demonstrated increased cortisol levels in the blood after PM exposure (Toledo-Corral et al., 2021; L. Liu et al., 2018; Y. Xu et al., 2019). Increased systemic glucocorticoids induce increases in cardiac pressure *via* increased retention of sodium and water (McKay et al., 2003). Thus, PM-

associated cardiac dysfunction may be indirectly linked to HPA activation. However, HPA activation can also support sympathetic stimulation by inducing catecholamine release (Al-Damluji et al., 1987). In brief, glucocorticoids released by an activated HPA stimulates the sympathetic-adrenal-medullary axis to release catecholamines through an induction of phenylethanolamine-*N*-methyltransferase (Wurtman, 2002). In a double-blind crossover study, PM exposure resulted in elevations in cortisol and cortisone as well as in epinephrine and norepinephrine (H. Li et al., 2017), suggesting that this mechanism may be a factor in PM-associated cardiovascular dysfunction. Thus, numerous lines of evidence link elevated airborne PM with stimulation of both the HPA axis and the autonomic nervous system, resulting in increased blood pressure, modulations in HRV, and reduced cardiac function.

4.4. Mechanism 4. Cholesterol transport and accumulation.

Numerous, emerging epidemiologic studies now also implicate PM in elevating blood lipid levels, a well-known risk factor for CVD. For example, $PM_{2.5}$ levels are generally associated with elevations in total cholesterol and LDL and reductions in HDL. Specifically, for every 1 $\mu g/m^3$ increment in $PM_{2.5}$ exposure, total serum lipid levels were increased by 2% (McGuinn et al., 2019). A longitudinal study in U.S. demonstrated that people living in polluted areas or areas with higher temperatures exhibited an increased risk for developing hypertriglyceridemia (Wallwork et al., 2017). In a longitudinal study in China, exposures to $PM_{2.5}$ and PM_{10} were associated with elevations in triglycerides, along with total and LDL cholesterol, but reduced levels of HDL cholesterol (K. Zhang et al., 2020). In another study in China, elevations in PM_1 (diameter $\leq$ 1.0 μm) were associated with dyslidemias reflected as elevations in total and LDL cholesterol, with lower levels of triglycerides and HDL cholesterol (Mao et al., 2020). Of note, in China, PM_1 accounts for >80% of total $PM_{2.5}$ by mass (G. Chen et al., 2018; Y. Li et al., 2015). Finally, in Mexico City, maternal $PM_{2.5}$ exposure in the third trimester was associated with increases in total and LDL cholesterol, but decreases in triglycerides and HDL levels during childhood (McGuinn et al., 2020).

Studies carried out in small animals suggest mechanisms for these PM-related dyslipidemias. In rodent studies, PM inhalation induced inflammation and oxidative stress in the liver, contributing to dyslipidemia and fatty liver (M. Xu et al., 2019). Inhalation of PM affects various metabolic pathways in the liver including fatty acid metabolism (Y. Zhang et al., 2019). Increased fatty acid levels and a dysregulation between lipogenesis and lipolysis in the liver can result in elevations in triglyceride levels via an increased esterification of fatty acids (J. Liu et al., 2016). A metabolic shift such as this was recently described for PM exposures of mice (Yang et al., 2021). PM-associated polychlorinated biphenyls (PCBs) may also contribute to PM-induced dyslipidemias. PCBs are adsorbed on PM in some environments (Hinwood et al., 2014), and exposure to PCBs in the Native American community has been shown correlated with elevated blood levels of cholesterol and triglycerides (Goncharov et al., 2008). In LDL receptor null (LDLr (−/−)) mice, PCBs also promoted systemic inflammation and atherosclerotic lesion development. In studies from the same laboratory, dietary fat was shown to interact with PCBs to modulate hepatic genes associated with fatty acid metabolism, triacylglycerol synthesis and cholesterol catabolism (Arzuaga et al., 2009), many of which are regulated *via* peroxisome proliferator activated receptor-alpha. Still other studies have implicated alterations in lipid metabolism in the gut

(Chi et al., 2019). For example, in LDLr $^{(-/-)}$ mice, ultrafine PM exposure increased lipid metabolism and macrophage infiltration within the small intestine (R. Li et al., 2015). Thus, given the well-appeciated role for elevated lipid levels in risk for developing CVD, and the now numerous reports of dyslipidemias associated with PM exposures, it is reasonable to propose that PM-mediated dyslipidemia is a contributing factor in PM-associated CVD.

4.5. Mechanism 5. Metabolic dysfunction.

A wealth of epidemiological evidence has demonstrated an association between airborne PM exposures and the incidence and mortality from Type 2 Diabetes Mellitus (T2DM). For example, in a cross-sectional survey of nearly 1800 elderly, non-diabetic women in Germany, the incidence of T2DM was significantly correlated with levels of airborne PM_{10} and NO_x (Krämer et al., 2010). In 25 healthy adults living in rural areas who were purposefully exposed to urban air for 5 consecutive days, elevations of $PM_{2.5}$ as small as 10 $\mu g/m^3$ increased insulin resistance (Brook et al., 2013). Also, people living in polluted areas in the US and/or areas with higher temperatures showed an increased risk for developing metabolic disorders (Wallwork et al., 2017), including abdominal obesity, high fasting blood glucose, low HDL, hypertension, and/or hypertriglyceridemia. Moreover, elevations of $PM_{2.5}$ as little as a 1 $\mu g/m^3$ increased these risks and the statistical associations were further enhanced by a 1 °C increase in temperature (Wallwork et al., 2017). Interestingly, for all subjects followed in this study, $PM_{2.5}$ exposures ranged from 4.2 to 13.6 $\mu g/m^3$, which falls below the National Ambient Air Quality Standard (Environmental Protection Agency, 2013). Similarly, a meta-analysis of published cohort studies showed an association between long-term particulate matter exposure and T2DM, where risk for developing diabetes increased by 25% for every 10 $\mu g/m^3$ increase in levels of $PM_{2.5}$ (He et al., 2017). Another systematic review of studies conducted in Europe and North America likewise revealed that the risk for T2DM increased by 8-10% for every 10 $\mu g/m^3$ increase in levels of $PM_{2.5}$ (Eze et al., 2015). Of note, the authors stress that while most of these studies were conducted in high-income countries, studies in low-income or developing countries, where PM levels tend to be much higher, are still needed. Though there are discrepancies in the composition and source of particulate matter in high-income compared to low-and middle-income countries (LMICs), a systematic review of epidemiologic studies focused on LMICs suggested that increments of 10 $\mu g/m^3$ airborne PM levels increased the risk of T2DM by 10-27% (Jaganathan et al., 2019). Thus, the evidence to date strongly links PM exposures with risk of T2DM. While T2DM is causally associated with the development of CVD such as atherosclerosis (Christine et al., 2015), these PM-mediated increases in T2DM risk presumably contribute to PM-associated CVD.

Potential mechanisms for the development of T2DM in PM-rich environments include: PM-mediated endothelial dysfunction, leading to decreased glucose uptake (Tabit et al., 2010); systemic inflammation and tissue oxidative stress (Shi et al., 2019; Walters, et al., 2002); dysregulated phosphorylation of insulin receptors (J. Xu et al., 2017); visceral adipose dysfunction mediated by inflammation (Sun et al., 2009); and altered lipid metabolism (Parhofer et al., 2015).

Since the level of estrogen regulates numerous functions across many organs, a decreased level of estrogen can potentially exacerbate PM-mediated cardiovascular injury. In fact, PM exposure after menopause may increase the vulnerability of females to metabolic diseases (Costa-Beber et al., 2021). In support of these findings, in rodents, ovariectomy increased PM-mediated susceptibility to oxidative stress, heat shock protein levels, and pro-inflammatory profiles in the liver, as well as glucose intolerance (Goettems-Fiorin et al., 2019).

Finally, air pollution exposure during pregnancy has the potential to compromise several developmental stages that can impact metabolic function in the offspring. Studies have shown that maternal exposure to PM increases the risk of premature births, shortens the gestational period, promotes low birthweight and stillbirths, and induces adverse pulmonary and systemic health conditions during postnatal development (Klepac et al., 2018; Tan et al., 2017). Maternal PM exposure reduces placental growth and alters placental structure, likely due to placental dysfunction and thus, diminished nutrient supply from the mother to the fetus (Valentino et al., 2015). Prenatal exposure to PM also selectively impairs organogenesis and promotes metabolic dysfunction exhibited by decreased body and organ weights (G. Wu et al., 2019).

5. Potential therapeutic agents and their molecular targets of therapy

5.1. Combating oxidative stress and inflammation through antioxidant supplementation.

Given the demonstrated correlation between oxidative stress biomarkers and both PM exposures and PM-associated CVD, it is logical to predict that antioxidant supplementation would alleviate PM-associated CVD. However, though substantial epidemiologic evidence implicates a role for oxidative stress and ROS in CVD progression (Cervantes Gracia, et al., 2017), intervention studies have failed to demonstrate decreased oxidative stress biomarkers and a decreased risk for CVD with CVD-related events in patients supplemented with antioxidants (Albert, et al., 2008; Cook, et al., 2007; Hercberg, et al., 2004; Hercberg, et al., 2010; Kelemen, et al., 2005; Waters, et al., 2002; Zureik, et al., 2004). The Women's Health Study is an example of the mixed findings reported for one prototypical antioxidant supplementation – vitamin E. In this large cohort, healthy women were administered 600 IU vitamin E every other day and were assessed over a period of years for their risk of aging-related diseases, including CVD. Results showed that vitamin E supplementation had no impact on overall mortality or cancer risk but did reduce CVD-related mortality (I.-M. Lee, et al., 2005). In addition, vitamin E did not impact risk for developing T2DM (S. Liu, et al., 2006) or rheumatoid arthritis (Karlson, et al., 2008), but did reduce chronic lung diseases (Agler, et al., 2011) and venous thromboembolism (Glynn, et al., 2007). The latter finding may suggest a role for vitamin E as an anti-thrombotic agent, perhaps contributing to the reduction in CVD-related mortality observed in the earlier study (I.-M. Lee, et al., 2005). Given the lack of definitive findings for antioxidant supplementation in general, experts have posited that 1) the lack of an "antioxidant-free control group" in these and other reported population studies minimizes an ability to detect measurable differences between groups, and 2) the subjects used for these trials are not representative of a general population (Angelo, et al., 2015). Others have argued that oxidative stress biomarkers do not predict

risk stratification (Pastori, et al., 2014). As suggested by Ho, et al (2013), the functional role of protein oxidation within signaling domains in vascular cells may not be adequately quantified by assessing urinary or plasma biomarkers. Furthermore, many of these trials used supplementation with fat-soluble antioxidants such as vitamin E that are already at appreciable levels in plasma/plasma lipoproteins (Guirguis-Blake, 2004; Hodis, et al., 2002; Yusuf, et al., 2000). Thus, it is possible that supplementation with other dietary antioxidants such as polyphenols may have the potential to impact cellular ROS signaling so as to reduce CVD or even PM-mediated CVD progression. Finally, as explained in a previous section, inflammation and oxidative stress are integrally linked and form a vicious cycle that contributes to atherogenesis and other CVD pathways. Antioxidant supplementation may thus also inhibit inflammatory pathways activated by PM exposure. To date, however, the vast majority of studies aimed at modeling the impact of micronutrient supplementation to combat CVD (Houston, 2010) or PM-mediated CVD progression (Takyi, et al., 2020) have been conducted mainly in small animal studies or small human cohorts. Nevertheless, we will highlight the current state of published findings, beginning with vitamin E and will expand our review to polyphenols and other micronutrients.

In one pilot study involving a small cohort of subjects in South Brazil, daily supplementation with vitamins E and C for 6 months attenuated blood biomarkers of oxidative stress and normalized antioxidant defense systems in workers from a coal-burning electric power plant exposed to high levels of PM (Possamai, et al., 2010). Selenium is a micronutrient essential to the function of the antioxidant enzyme glutathione peroxidase (GPx), and selenium supplements such as selenium yeast are available commercially. In rats administered selenium yeast orally for 28 days and then challenged every other day with $PM_{2.5}$ for 6 days, $PM_{2.5}$ decreased myocardial GPx and blood SOD activities, but increased lipid oxidation products and inflammatory cytokines such as TNF-α and IL-1β and soluble ICAM-1 (Zeng, et al., 2018). Selenium supplementation restored antioxidant enzyme activities, while also decreasing levels of inflammatory markers. Several studies have now demonstrated a role for sulforaphane-mediated stimulation of the Nrf-2 antioxidant response system in protecting against PM-induced toxicities. Noteworthy are three studies utilizing standardized broccoli sprout homogenates (BSH) containing high levels of the sulforaphane precursor glucoraphanin. In one pilot study, subjects were administered oral BSH for 3 days, after which nasal lavages were collected and assessed for mRNA levels of phase II enzymes associated with the Nrf-2-dependent antioxidant response system. Significant increases in expression of all antioxidant biomarkers were observed, verifying the bioavailability of the product and its ability to alter redox status in the lung (Riedl, et al., 2009). In a similar pilot study, a BSH suspended in mango juice was administered for four days, after which, subjects were challenged with DEP intranasally. Nasal lavages collected from these subjects demonstrated that BSH dramatically attenuated DEP-induced elevations in white blood cells (Heber, et al., 2014). While Nrf-2 dependent phase II enzymes such as glutathione-S-transferase are known to conjugate electrophilic aldehydes often associated with PM, such as benzene, acrolein and crotonaldehyde (Berhane, et al., 1994), a study conducted in subjects living in an industrialized city in China demonstrated that oral BSH for 12 weeks elevated urinary excretion of glutathione-conjugated benzene and acrolein (Egner, et al., 2014). Thus, standardized products containing sulforaphane/sulforaphane precursors appear

to be promising interventions for preventing PM-related cardiopulmonary diseases. Finally, in mice exposed to concentrated ambient particles (CAPs), $PM_{2.5}$ reduced circulating levels of hematopoietic stem cells important in vascular repair, but oral administration of carnosine, a nucleophilic di-peptide with antioxidant properties and also shown to bind reactive electrophiles such as acrolein, provided protection (Abplanalp, et al., 2019). Thus, antioxidant intervention can not only serve to reduce oxidative stress *via* reductions in ROS levels but can also provide protection against the oxidizing action of electrophilic intermediates.

Other studies of assorted antioxidant supplements show promise for future interventional strategies. For example, in mice exposed for 16 months to air from two polluted areas of Mexico City, myocardial mRNA levels for inflammatory cytokines were upregulated, but mice co-administered dark chocolate every other day were protected (Villarreal-Calderon, et al., 2012). The mice receiving dark chocolate also exhibited elevations in myocardial genes encoding antioxidant enzymes and downregulation of genes associated with TLR signaling (Villarreal-Calderon, et al., 2012). While moderate- and long-term consumption of red wine is well-known to prevent CVD (Saleem, et al., 2010), it is reasonable to predict that resveratrol administration or moderate red wine consumption may prevent PM-associated CVD, and a handful of reports generally support this assertion. In pigs exposed to second-hand smoke particulate matter for 28 days, fragmentation of myocardial proteins including myosin light chain-1, myosin-7, β-myosin heavy chain and both lactate and pyruvate dehydrogenases were observed, coupled to dramatic elevations in matrix metalloproteinase-2 (Arcand, et al., 2013). However, myocardial protein fragmentation was attenuated in mice co-administered resveratrol (Arcand, et al., 2013). Similarly, in zebrafish embryos $PM_{2.5}$ extracts induced cardiac malformations associated with DNA damage, oxidative stress and apoptosis (Ren, et al., 2020). Resveratrol co-administration provided protection against PM-induced malformations and oxidative stress, but not AhR signaling (Ren, et al., 2020), suggesting that resveratrol protection was mediated by its properties as an antioxidant and not as an AhR antagonist. Finally, vitamin B supplementation in human subjects prevented the methylation of the genes associated with mitochondrial oxidative energy metabolism after a controlled challenge with $PM_{2.5}$, suggesting that in individuals experiencing frequent peaks in $PM_{2.5}$ exposure, B vitamins may potentially protect against mitochondrial oxidative stress (Zhong, et al., 2017). Thus, numerous small animal experiments and pilot studies in human subjects support a potential benefit of antioxidant and phytonutrient supplementation in preventing PM-induced CVD; however, large, well-controlled human studies may be warranted.

5.2. Targeting oxidative stress, inflammation and autonomic dysfunction using omega-3 fatty acids. Lessons learned from the Mediterranean diet.

A vast number of studies now document that adherence to a Mediterranean diet consisting of fish, olive oil, fruits, vegetables, whole grains, legumes/nuts, and moderate alcohol consumption reduces the risk of aging-related diseases such as CVD (Widmer, et al., 2015). Polyunsaturated fatty acids, i.e., omega-3 fatty acids, have been implicated as a key component of the diet contributing to reduced CVD risk factors such as lipid levels and systemic inflammation. In a large cohort followed for 17 years (the NIH-AARP Health

Study), the Mediterranean diet also decreased PM-associated CVD mortality (Lim, et al., 2019). In a smaller study, short-term PM exposure reduced endothelial function, assessed as reductions in vasodilation in the brachial artery and also increased markers for vasoconstriction and fibrinolysis. Four-week supplementation with olive oil, however, protected subjects from PM-induced vascular dysfunction (Tong, et al., 2015). In a similar study, subjects exposed to short-term $PM_{2.5}$ exhibited an elevation in HRV that was attenuated in subjects receiving fish oil for 4 weeks prior to exposure (Tong, et al., 2012). Additionally, nursing home residents exposed to high levels of indoor $PM_{2.5}$ in Mexico City exhibited marked elevations in HRV, increased blood levels of lipid oxidation products, and decreased levels of antioxidants/antioxidant enzymes, while fish oil supplementation seemed to reverse these findings (Romieu, et al., 2005; Romieu, et al., 2008).

Small animal studies generally support these findings in human subjects. Supplementation with a combination of vitamin E and omega-3 fatty acid in rats protected animals against PM-induced cardiac injury, systemic inflammation and oxidative stress (Du, et al., 2017). Studies using a rat intracranial atherosclerosis model demonstrated the benefits of omega-3 fatty acids in protecting against $PM_{2.5}$-induced systemic inflammation, vascular oxidative injury, and atherosclerosis (Guan, et al., 2019). Interestingly, although the bulk of these studies examined a role for omega-3 fatty acids in cardiovascular protection, the Mediterranean diet likely also contains antioxidants that are effective in promoting cardiovascular protection. For example, virgin olive oil is rich in an antioxidant known as hydroxytyrosol (Xynos, et al., 2015). Mice exposed to $PM_{2.5}$ for 4 weeks exhibited increased visceral fat mass, glucose intolerance, insulin insensitivity, reduced hepatic glycogenesis, and elevations in hepatic inflammation and oxidative stress (Wang, et al., 2019). However, oral administration of hydroxytyrosol protected animals against adipogenesis, oxidative stress and hepatic inflammation (Wang, et al., 2019). Thus, the Mediterranean diet is enriched in antioxidant and anti-inflammatory compounds that can potentially intervene in the toxicologic mechanisms associated with PM-related health effects, including those related to endothelial dysfunction, oxidative stress, metabolic dysregulation and/or autonomic dysfunction. These studies furthermore imply that supplementation with omega-3 fatty acids may have the potential to protect against PM-associated CVD.

5.3. Targeting cholesterol accumulation and inflammation using statin therapy.

Given the documented impact of PM on cholesterol metabolism and the fact that elevated blood cholesterol is a risk factor for developing CVD (Shanley, et al., 2016), it is likewise reasonable to predict that statin administration may prove beneficial in reducing the risk of PM-associated CVD. Statins are a class of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors that reduce serum cholesterol by inhibiting a key step in cholesterol biosynthesis (Sirtori, 2014). In fact, studies in humans and animals generally support its use for this purpose and even suggest that statins may promote health benefits through non-lipid dependent pathways. For example, in rabbits with heritable hyperlipidemia, progression of PM-mediated atherosclerosis was positively correlated with alveolar macrophage recruitment and increased lipid accumulation within fatty streaks (Suwa, et al., 2002). Thus, the etiology of PM-associated atherosclerosis likely also involves lipid accumulation at some

level. Interestingly, in rabbits subjected to PM_{10} exposures, lovastatin inhibited inflammation and the recruitment of lung macrophages (Miyata, et al., 2013a) and furthermore promoted PM removal from the lungs. In other studies, rabbits subjected to cholesterol and vascular injury exhibited an exacerbated vascular inflammation, endothelial dysfunction and vasoconstriction following PM_{10} exposures, and although lovastatin attenuated all of these pathologies, lovastatin did not reduce blood lipid levels (Miyata, et al., 2013b). In still other studies from the same group, lovastatin dampened the PM-induced inflammatory response by decreasing circulating levels of IL-6, thereby decreasing bone marrow differentiation, release of polymorphonuclear leukocytes (PMNs), and retention of newly released PMNs in the lungs (Miyata, et al., 2012). In support of these studies in animals, in a cohort of patients with chronic obstructive pulmonary disease, statin administration promoted the clearance of PM deposits in lung tissues and reduced inflammation (Hiraiwa, et al., 2017). Additional findings suggest that statins reduce the retention of PM in alveolar macrophages, but increase PM load in regional lymph nodes, suggesting the transfer of PM from alveolar macrophages to lymph nodes (Hiraiwa, et al., 2017). Thus, with respect to PM exposures, many of the cardiovascular benefits of statin exposure are likely due to their pleiotropic effects in reducing inflammation and promoting vascular function.

5.4. Targeting neurohumoral regulation with melatonin.

Melatonin is a hormone that regulates sleep-wake cycles and is produced predominately by the pineal gland in circadian cycles (Pevet, et al., 2011). However, new evidence suggests that melatonin is also produced by a number of other tissues and cells, including inflammatory cells (Markus, et al., 2018), and a growing body of evidence suggests that both pineal-derived and extra-pineal melatonin regulate immune responses elicited by cytokines, DAMPs and PAMPs (pathogen-associated molecular patterns; Markus, et al., 2018). For example, after DEP exposure in rats, PM activated NF_kB and TLR4 signaling in alveolar macrophages, resulting in an increased synthesis of melatonin locally, an increased rate of macrophage engulfment of PM and a decreased oxidative stress (Carvalho-Sousa, et al., 2020). In guinea pigs exposed intranasally to $PM_{2.5}$, melatonin treatment prevented PM-induced inflammation and oxidative stress in the lung and brain by decreasing the expression of TRP channel subfamily M member 2 (TRPM2; Ji, et al., 2018). Short-term exposure to PM in animals with acute ischemia-reperfusion lung injury worsened lung function, lowered arterial oxygen saturation, promoted inflammatory cell infiltration, induced tracheal thickening and increased lung fibrosis. Many of these pathologic features were alleviated in animals co-administered melatonin (F.-Y. Lee, et al., 2019). Thus, exogenous melatonin may potentially be exploited as an intervention to reduce inflammation and oxidative stress and promote PM clearance from the lung, so as to reduce the risk of PM-associated CVD.

5.5. Targeting metabolic effects using metformin.

Given the multitude of studies linking PM exposures with metabolic disturbances, and the fact that insulin resistance is a significant risk factor for developing CVD (Ginsberg, 2000), interventions aimed at improving insulin sensitivity seem a viable option for PM-associated CVD. Metformin is a hypoglycemic drug commonly used in the treatment of T2DM. By some mechanism, metformin acts to stimulate AMP-dependent protein kinase (AMPK),

which in turn accelerates metabolic pathways such as glucose uptake and fatty acid oxidation, while inhibiting gluconeogenesis and lipogenesis (Zhou, et al., 2001). Studies conducted in animal models suggest that metformin administration may be a promising strategy for intervention. For example, Haberzettl et al., showed that in mice, $PM_{2.5}$ exposure reduced vascular insulin sensitivity, activated inflammasome pathways and decreased levels of circulating endothelial progenitor cells (EPCs), while increasing stores of EPCs within the bone marrow (Haberzettl, et al., 2016). These findings suggest that PM decreases vascular repair capacity by reducing the ability of EPCs to mobilize from the bone marrow to the circulation (Haberzettl, et al., 2016). However, treatment with metformin restored vascular repair capacity and alleviated insulin insensitivity. In other studies using $PM_{2.5}$-exposed mice, metformin treatment reduced systemic and pulmonary inflammation, oxidative stress and fibrosis, reversed deficits in left ventricular function and preserved mitochondrial antioxidant enzyme expression (J. Gao, et al., 2020). Interestingly, these findings were maintained in AMPK-α2-deficient mice, suggesting that metformin acts *via* both AMPK-dependent and -independent pathways (J. Gao, et al., 2020). Moreover, metformin administration decreased mitochondrial ROS and IL-6 activation in alveolar macrophages derived from PM-exposed mice and reduced PM-mediated thrombogenesis (Soberanes, et al., 2019). In summary, animal studies suggest a benefit of metformin intervention, but studies in human cohorts are needed to confirm these findings.

6. Conclusions and Future Directions

There is a clear link between PM exposures in industrialized areas and CVD progression. Mechanisms to explain these findings include PM-mediated oxidative stress in the lungs and cardiovascular system, pulmonary and systemic inflammation, metabolic dysfunction, elevations in circulating cholesterol and triglycerides and autonomic dysfunction. With these molecular targets in mind, herein we outlined potential dietary and pharmacologic strategies for combatting these toxicologic mechanisms and provided supporting evidence from small animal and human studies. Large-scale intervention studies in populations at risk for PM-associated CVD are the logical and necessary next step. However, given the lack of definitive results obtained for studies examining the efficacy of vitamin E in combatting CVD mortality in largely healthy cohorts (Ye, et al., 2013), caution must be exercised in population selection. While PM exposures are often more prevalent in marginalized communities where pre-existing CVD, metabolic disorders and other comorbidities are likely (Nawrot, et al., 2011), it stands to reason that population selection should include subjects of mixed-socioeconomic status. Thus, future studies will require collaborations across scientific disciplines to successfully delineate the efficacy of proposed interventions.

Acknowledgements

This work was supported by the National Institutes of Environmental Health Sciences (ES013648). TRD is funded by NIH ES030062, GM13055, and HL142403.

Abbreviations:

ACTH	adrenocorticotropic hormone

AhR	aryl hydrocarbon receptor
AMPK	AMP-dependent protein kinase
BSH	broccoli sprout homogenate
CAP	concentrated ambient $PM_{2.5}$
CRH	corticotropin-releasing hormone
CVD	cardiovascular disease
DEP	diesel exhaust particles
eNOS	endothelial nitric oxide synthase
EPC	endothelial progenitor cells
HRV	heart rate variability
ICAM-1	intracellular adhesion molecule-1
IL-1β	interleukin-1β
LDL	low-density lipoprotein
miRNA	micro-RNA
NFkB	nuclear factor kappa beta
Nrf-2	nuclear factor erythroid 2–related factor 2
PCB	polychlorinated biphenyl
PM	particulate matter
$PM_{2.5}$	particulate matter < 2.5 μm
PM_{10}	particulate matter < 10 μm
PAH	polycyclic aromatic hydrocarbon
ROS	reactive oxygen species
SOD	superoxide dismutase
T2DM	type 2 diabetics mellitus
TF	tissue factor
TNF-α	tumor necrosis factor-α
TLR-4	toll-like receptor 4
TRPV1	transient receptor potential cation channel subfamily V member 1
VCAM-1	vascular cell adhesion molecule-1

vWF von Willebrand Factor.

References cited

Aaron CP, Hoffman EA, Kawut SM, Austin JH, Budoff M, Michos ED, et al. (2019). Ambient air pollution and pulmonary vascular volume on computed tomography: the MESA Air Pollution and Lung cohort studies. European Respiratory Journal, 53, 1802116..

Abplanalp W, Haberzettl P, Bhatnagar A, Conklin DJ, & O'Toole TE (2019). Carnosine supplementation mitigates the deleterious effects of particulate matter exposure in mice. Journal of the American Heart Association, 8, e013041. [PubMed: 31234700]

Adar SD, Klein R, Klein BE, Szpiro AA, Cotch MF, Wong TY, et al. (2010). Air pollution and the microvasculature: a cross-sectional assessment of in vivo retinal images in the population-based Multi-Ethnic Study of Atherosclerosis (MESA). PLoS Medicine, 7, e1000372. [PubMed: 21152417]

Adar SD, Sheppard L, Vedal S, Polak JF, Sampson PD, Roux AVD, et al. (2013). Fine particulate air pollution and the progression of carotid intima-medial thickness: a prospective cohort study from the multi-ethnic study of atherosclerosis and air pollution. PLoS Medicine, 10, e1001430. [PubMed: 23637576]

Agler AH, Kurth T, Gaziano JM, Buring JE, & Cassano PA (2011). Randomised vitamin E supplementation and risk of chronic lung disease in the Women's Health Study. Thorax, 66, 320–325. [PubMed: 21257986]

Al-Damluji S, & Rees L (1987). Effects of catecholamines on secretion of adrenocorticotrophic hormone (ACTH) in man. Journal of Clinical Pathology, 40, 1098–1107. [PubMed: 2822768]

Albert CM, Cook NR, Gaziano JM, Zaharris E, MacFadyen J, Danielson E, et al. (2008). Effect of folic acid and B vitamins on risk of cardiovascular events and total mortality among women at high risk for cardiovascular disease: a randomized trial. Journal of the American Medical Association, 299, 2027–2036. [PubMed: 18460663]

Alp NJ, & Channon KM (2004). Regulation of endothelial nitric oxide synthase by tetrahydrobiopterin in vascular disease. Arteriosclerosis, Thrombosis, and Vascular Biology, 24, 413–420.

Angelo G, Drake VJ, & Frei B (2015). Efficacy of multivitamin/mineral supplementation to reduce chronic disease risk: a critical review of the evidence from observational studies and randomized controlled trials. Critical Reviews in Food Science and Nutrition, 55, 1968–1991. [PubMed: 24941429]

Arangino S, Cagnacci A, Angiolucci M, Vacca AM, Longu G, Volpe A, et al. (1999). Effects of melatonin on vascular reactivity, catecholamine levels, and blood pressure in healthy men. American Journal of Cardiology, 83, 1417–1419.

Arcand S, Sharma K, Al-Dissi AN, Cadete VJ, Sawicki G, & Weber LP (2013). Resveratrol protects against functional impairment and cardiac structural protein degradation induced by secondhand smoke exposure. Canadian Journal of Cardiology, 29, 1320–1328.

Arzuaga X, Ren N, Stromberg A, Black EP, Arsenescu V, Cassis LA, et al. (2009). Induction of gene pattern changes associated with dysfunctional lipid metabolism induced by dietary fat and exposure to a persistent organic pollutant. Toxicology Letters, 189, 96–101. [PubMed: 19467301]

Auchincloss AH, Diez Roux AV, Dvonch JT, Brown PL, Barr RG, Daviglus ML, et al. (2008). Associations between recent exposure to ambient fine particulate matter and blood pressure in the Multi-Ethnic Study of Atherosclerosis (MESA). Environmental Health Perspectives, 116, 486–491. [PubMed: 18414631]

Bartoli CR, Wellenius GA, Diaz EA, Lawrence J, Coull BA, Akiyama I, et al. (2009). Mechanisms of inhaled fine particulate air pollution-induced arterial blood pressure changes. Environmental Health Perspectives, 117, 361–366. [PubMed: 19337509]

Berhane K, Widersten M, Engström Å, Kozarich JW, & Mannervik B (1994). Detoxication of base propenals and other alpha, beta-unsaturated aldehyde products of radical reactions and lipid peroxidation by human glutathione transferases. Proceedings of the National Academy of Sciences, 91, 1480–1484.

Bhetraratana M, Orozco LD, Hong J, Diamante G, Majid S, Bennett BJ, et al. (2019). Diesel exhaust particles dysregulate multiple immunological pathways in murine macrophages: Lessons from microarray and scRNA-seq technologies. Archives of Biochemistry and Biophysics, 678, 108116. [PubMed: 31568751]

Blankenberg S, Rupprecht HJ, Bickel C, Peetz D, Hafner G, Tiret L, et al. (2001). Circulating cell adhesion molecules and death in patients with coronary artery disease. Circulation, 104, 1336–1342. [PubMed: 11560847]

Blann AD, & McCollum CN (1994). Circulating endothelial cell/leukocyte adhesion molecules in atherosclerosis. Thrombosis and Haemostasis. 72, 151–154. [PubMed: 7526483]

Branen L, Hovgaard L, Nitulescu M, Bengtsson E, Nilsson J, & Jovinge S (2004). Inhibition of tumor necrosis factor-α reduces atherosclerosis in apolipoprotein E knockout mice. Arteriosclerosis, Thrombosis, and Vascular Biology, 24, 2137–2142.

Brook RD, Franklin B, Cascio W, Hong Y, Howard G, Lipsett M, et al. (2004). Air pollution and cardiovascular disease: a statement for healthcare professionals from the Expert Panel on Population and Prevention Science of the American Heart Association. Circulation, 109, 2655–2671. [PubMed: 15173049]

Brook RD, Rajagopalan S, Pope CA III, Brook JR, Bhatnagar A, Diez-Roux AV, et al. (2010). Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. Circulation, 121, 2331–2378. [PubMed: 20458016]

Brook RD, Xu X, Bard RL, Dvonch JT, Morishita M, Kaciroti N, et al. (2013). Reduced metabolic insulin sensitivity following sub-acute exposures to low levels of ambient fine particulate matter air pollution. Science of the Total Environment, 448, 66–71.

Calderón-Garcidueñas L, Vincent R, Mora-Tiscareño A, Franco-Lira M, Henríquez-Roldán C, Barragán-Mejía G, et al. (2007). Elevated plasma endothelin-1 and pulmonary arterial pressure in children exposed to air pollution. Environmental Health Perspectives, 115, 1248–1253. [PubMed: 17687455]

Calderon-Garciduenas L, Villarreal-Calderon R, Valencia-Salazar G, Henriquez-Roldan C, Gutiérrez-Castrellón P, Torres-Jardon R, et al. (2008). Systemic inflammation, endothelial dysfunction, and activation in clinically healthy children exposed to air pollutants. Inhalation toxicology, 20, 499–506. [PubMed: 18368620]

Camm AJ, Malik M, Bigger JT, Breithardt G, Cerutti S, Cohen RJ, et al. (1996). Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Circulation, 93, 1043–1065. [PubMed: 8598068]

Carll AP, Hazari MS, Perez CM, Krantz QT, King CJ, Haykal-Coates N, et al. (2013). An Autonomic Link Between Inhaled Diesel Exhaust and Impaired Cardiac Performance: Insight From Treadmill and Dobutamine Challenges in Heart Failure-Prone Rats. Toxicological Sciences, 135, 425–436. [PubMed: 23872579]

Carvalho-Sousa CE, Pereira EP, Kinker GS, Veras M, Ferreira ZS, Barbosa-Nunes FP, et al. (2020). Immune-pineal axis protects rat lungs exposed to polluted air. Journal of Pineal Research, 68, e12636. [PubMed: 32043640]

Cervantes Gracia K, Llanas-Cornejo D, & Husi H (2017). CVD and oxidative stress. Journal of Clinical Medicine, 6, 22.

Chen G, Knibbs LD, Zhang W, Li S, Cao W, Guo J, et al. (2018). Estimating spatiotemporal distribution of PM1 concentrations in China with satellite remote sensing, meteorology, and land use information. Environmental Pollution, 233, 1086–1094. [PubMed: 29033176]

Chen LC, & Hwang J-S (2005). Effects of subchronic exposures to concentrated ambient particles (CAPs) in mice: IV. Characterization of acute and chronic effects of ambient air fine particulate matter exposures on heart-rate variability. Inhalation Toxicology, 17, 209–216. [PubMed: 15804938]

Chi Y, Wang H, Lin Y, Lu Y, Huang Q, Ye G, et al. (2019). Gut microbiota characterization and lipid metabolism disorder found in PCB77-treated female mice. Toxicology, 420, 11–20. [PubMed: 30935970]

Chiarella SE, Soberanes S, Urich D, Morales-Nebreda L, Nigdelioglu R, Green D, et al. (2014). β 2-Adrenergic agonists augment air pollution–induced IL-6 release and thrombosis. The Journal of Clinical Investigation, 124, 2935–2946. [PubMed: 24865431]

Choi SH, Harkewicz R, Lee JH, Boullier A, Almazan F, Li AC, Witztum JL, Bae YS, and Miller YI (2009). Lipoprotein accumulation in macrophages via toll-like receptor-4-dependent fluid phase uptake. Circulation Research, 104, 1355–1363. [PubMed: 19461045]

Choi YJ, Arzuaga X, Kluemper CT, Caraballo A, Toborek M, & Hennig B (2010). Quercetin blocks caveolae-dependent pro-inflammatory responses induced by co-planar PCBs. Environment International, 36, 931–934. [PubMed: 19608276]

Christine PJ, Auchincloss AH, Bertoni AG, Carnethon MR, Sánchez BN, Moore K, et al. (2015). Longitudinal associations between neighborhood physical and social environments and incident type 2 diabetes mellitus: the Multi-Ethnic Study of Atherosclerosis (MESA). JAMA Internal Medicine, 175, 1311–1320. [PubMed: 26121402]

Clark ML, Butler LM, Koh W-P, Wang R, & Yuan J-M (2013). Dietary fiber intake modifies the association between secondhand smoke exposure and coronary heart disease mortality among Chinese non-smokers in Singapore. Nutrition, 29, 1304–1309. [PubMed: 23911218]

Connor AJ, Laskin JD, & Laskin DL (2012). Ozone-induced lung injury and sterile inflammation. Role of toll-like receptor 4. Experimental and Molecular Pathology, 92, 229–235. [PubMed: 22300504]

Cook-Mills JM, Marchese ME, & Abdala-Valencia H (2011). Vascular cell adhesion molecule-1 expression and signaling during disease: regulation by reactive oxygen species and antioxidants. Antioxidants & Redox Signaling, 15, 1607–1638. [PubMed: 21050132]

Cook NR, Albert CM, Gaziano JM, Zaharris E, MacFadyen J, Danielson E, et al. (2007). A randomized factorial trial of vitamins C and E and beta carotene in the secondary prevention of cardiovascular events in women: results from the Women's Antioxidant Cardiovascular Study. Archives of Internal Medicine, 167, 1610–1618. [PubMed: 17698683]

Cosselman KE, Navas-Acien A, & Kaufman JD (2015). Environmental factors in cardiovascular disease. Nature Reviews Cardiology, 12, 627. [PubMed: 26461967]

Costa-Beber LC, Goettems-Fiorin PB, Dos Santos JB, Friske PT, Frizzo MN, Heck TG, et al. (2021). Ovariectomy enhances female rats' susceptibility to metabolic, oxidative, and heat shock response effects induced by a high-fat diet and fine particulate matter. Experimental Gerontology, 145, 111215. [PubMed: 33340683]

Dai L, Bind M-A, Koutrakis P, Coull BA, Sparrow D, Vokonas PS, et al. (2016). Fine particles, genetic pathways, and markers of inflammation and endothelial dysfunction: analysis on particulate species and sources. Journal of Exposure Science & Environmental Epidemiology, 26, 415–421. [PubMed: 26732377]

Deering-Rice CE, Romero EG, Shapiro D, Hughen RW, Light AR, Yost GS, et al. (2011). Electrophilic components of diesel exhaust particles (DEP) activate transient receptor potential ankyrin-1 (TRPA1): a probable mechanism of acute pulmonary toxicity for DEP. Chemical Research in Toxicology, 24, 950–959. [PubMed: 21591660]

Dioni L, Hoxha M, Nordio F, Bonzini M, Tarantini L, Albetti B, et al. (2011). Effects of short-term exposure to inhalable particulate matter on telomere length, telomerase expression, and telomerase methylation in steel workers. Environmental Health Perspectives, 119, 622–627. [PubMed: 21169126]

Du X, Jiang S, Bo L, Liu J, Zeng X, Xie Y, et al. (2017). Combined effects of vitamin E and omega-3 fatty acids on protecting ambient PM2. 5-induced cardiovascular injury in rats. Chemosphere, 173, 14–21. [PubMed: 28104476]

Egner PA, Chen J-G, Zarth AT, Ng DK, Wang J-B, Kensler KH, et al. (2014). Rapid and sustainable detoxication of airborne pollutants by broccoli sprout beverage: results of a randomized clinical trial in China. Cancer Prevention Research, 7, 813–823. [PubMed: 24913818]

Endemann DH, & Schiffrin EL (2004). Endothelial dysfunction. Journal of the American Society of Nephrology, 15, 1983–1992. [PubMed: 15284284]

Environmental Protection Agency (2013). U. CFR Parts 50, 51, 52, 53, and 58-National Ambient Air Quality Standards for Particulate Matter: Final Rule. Federal Register, 78, 3086–3286.

Eze IC, Hemkens LG, Bucher HC, Hoffmann B, Schindler C, Künzli N, et al. (2015). Association between ambient air pollution and diabetes mellitus in Europe and North America: systematic review and meta-analysis. Environmental Health Perspectives, 123, 381–389. [PubMed: 25625876]

Farina F, Sancini G, Longhin E, Mantecca P, Camatini M, & Palestini P (2013). Milan PM1 induces adverse effects on mice lungs and cardiovascular system. Biomedical Research International, 2013, 583513.

Ferraro SA, Astort F, Yakisich JS, & Tasat DR (2016). Particulate matter cytotoxicity in cultured SH-SY5Y cells is modulated by simvastatin: Toxicological assessment for oxidative damage. Neurotoxicology, 53, 108–114. [PubMed: 26773838]

Förstermann U (2010). Nitric oxide and oxidative stress in vascular disease. Pflügers Archive-European Journal of Physiology, 459, 923–939. [PubMed: 20306272]

Freeman BA, & Crapo JD (1982). Biology of disease: free radicals and tissue injury. Laboratory Investigation, 47, 412–426. [PubMed: 6290784]

Gao J, Yuan J, Lei T, Shen X, Cui B, Zhang F, et al. (2020). Metformin protects against PM2. 5-induced lung injury and cardiac dysfunction independent of AMP-activated protein kinase α2. Redox Biology, 28, 101345. [PubMed: 31669973]

Gao Y, Lv J, Lin Y, Li X, Wang L, Yin Y, et al. (2014). Effects of β-adrenoceptor subtypes on cardiac function in myocardial infarction rats exposed to fine particulate matter (PM2. 5). BioMed research international, 2014.

Ginsberg HN (2000). Insulin resistance and cardiovascular disease. The Journal of Clinical Investigation, 106, 453–458. [PubMed: 10953019]

Glynn RJ, Ridker PM, Goldhaber SZ, Zee RY, & Buring JE (2007). Effects of random allocation to vitamin E supplementation on the occurrence of venous thromboembolism: report from the Women's Health Study. Circulation, 116, 1497–1503. [PubMed: 17846285]

Godleski J, Verrier R, Koutrakis P, Catalano P, Coull B, Reinisch U, et al. (2000). Mechanisms of morbidity and mortality from exposure to ambient air particles. Research Report (Health Effects Institute), 5.

Goettems-Fiorin PB, Costa-Beber LC, Dos Santos JB, Friske PT, Sulzbacher LM, Frizzo MN, et al. (2019). Ovariectomy predisposes female rats to fine particulate matter exposure's effects by altering metabolic, oxidative, pro-inflammatory, and heat-shock protein levels. Environmental Science and Pollution Research, 26, 20581–20594. [PubMed: 31104233]

Goncharov A, Haase RF, Santiago-Rivera A, Morse G, McCaffrey RJ, Rej R, et al. (2008). High serum PCBs are associated with elevation of serum lipids and cardiovascular disease in a Native American population. Environmental Research, 106, 226–239. [PubMed: 18054906]

Guan L, Geng X, Stone C, Cosky EE, Ji Y, Du H, et al. (2019). PM2. 5 exposure induces systemic inflammation and oxidative stress in an intracranial atherosclerosis rat model. Environmental Toxicology, 34, 530–538. [PubMed: 30672636]

Guirguis-Blake J (2004). Routine vitamin supplementation to prevent cancer and cardiovascular disease. American Family Physician, 70, 559. [PubMed: 15317443]

Haberzettl P, McCracken JP, Bhatnagar A, & Conklin DJ (2016). Insulin sensitizers prevent fine particulate matter-induced vascular insulin resistance and changes in endothelial progenitor cell homeostasis. American Journal of Physiology-Heart and Circulatory Physiology, 310, H1423–H1438. [PubMed: 27016579]

Hajat A, Diez Roux AV, Castro-Diehl C, Cosselman K, Golden SH, Hazlehurst MF, et al. (2019). The association between Long-term air pollution and urinary Catecholamines: evidence from the multi-ethnic study of atherosclerosis. Environmental Health Perspectives, 127, 057007.

Harrison RM (2020). Airborne particulate matter. Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences. 378, 20190319.

Hasper D, Hummel M, Kleber F, Reindl I, & Volk H-D (1998). Systemic inflammation in patients with heart failure. European Heart Journal, 19, 761–765. [PubMed: 9717010]

Hazari MS, Haykal-Coates N, Winsett DW, Krantz QT, King C, Costa DL, et al. (2011). TRPA1 and sympathetic activation contribute to increased risk of triggered cardiac arrhythmias in hypertensive

rats exposed to diesel exhaust. Environmental Health Perspectives, 119, 951–957. [PubMed: 21377951]

He D, Wu S, Zhao H, Qiu H, Fu Y, Li X, et al. (2017). Association between particulate matter 2.5 and diabetes mellitus: A meta-analysis of cohort studies. Journal of Diabetes Investigation, 8, 687–696. [PubMed: 28122165]

Heber D, Li Z, Garcia-Lloret M, Wong AM, Lee TYA, Thames G, et al. (2014). Sulforaphane-rich broccoli sprout extract attenuates nasal allergic response to diesel exhaust particles. Food & Function, 5, 35–41. [PubMed: 24287881]

Hegyi L, Skepper J, Cary N, & Mitchinson M (1996). Foam cell apoptosis and the development of the lipid core of human atherosclerosis. The Journal of Pathology, 180, 423–429. [PubMed: 9014864]

Hercberg S, Galan P, Preziosi P, Bertrais S, Mennen L, Malvy D, et al. (2004). The SU. VI. MAX Study: a randomized, placebo-controlled trial of the health effects of antioxidant vitamins and minerals. Archives of Internal Medicine, 164, 2335–2342. [PubMed: 15557412]

Hercberg S, Kesse-Guyot E, Druesne-Pecollo N, Touvier M, Favier A, Latino-Martel P, et al. (2010). Incidence of cancers, ischemic cardiovascular diseases and mortality during 5-year follow-up after stopping antioxidant vitamins and minerals supplements: A postintervention follow-up in the SU. VI. MAX Study. International Journal of Cancer, 127, 1875–1881. [PubMed: 20104528]

Herman JP, McKlveen JM, Ghosal S, Kopp B, Wulsin A, Makinson R, et al. (2011). Regulation of the hypothalamic-pituitary-adrenocortical stress response. Comprehensive Physiology, 6, 603–621.

Hinwood AL, Callan A, Heyworth J, Rogic D, De Araujo J, Crough R, et al. (2014). Polychlorinated biphenyl (PCB) and dioxin concentrations in residential dust of pregnant women. Environmental Science: Processes & Impacts, 16, 2758–2763. [PubMed: 25343442]

Hiraiwa K, Miller S, Ngan DA, Vasilescu DM, Hackett T-L, Kinose D, et al. (2017). Statins reduce the burden of ambient particulate matter and inflammatory cells within the lung tissues of smokers with and without COPD. European Respiratory Journal, 49, 1601689.

Ho E, Galougahi KK, Liu C-C, Bhindi R, & Figtree GA (2013). Biological markers of oxidative stress: applications to cardiovascular research and practice. Redox Biology, 1, 483–491. [PubMed: 24251116]

Hodis HN, Mack WJ, LaBree L, Mahrer PR, Sevanian A, Liu C.-r., et al. (2002). Alpha-tocopherol supplementation in healthy individuals reduces low-density lipoprotein oxidation but not atherosclerosis: the Vitamin E Atherosclerosis Prevention Study (VEAPS). Circulation, 106, 1453–1459. [PubMed: 12234947]

Hollander M, Hak A, Koudstaal P, Bots M, Grobbee D, Hofman A, et al. (2003). Comparison between measures of atherosclerosis and risk of stroke: the Rotterdam Study. Stroke, 34, 2367–2372. [PubMed: 12958327]

Houston MC (2010). The role of cellular micronutrient analysis, nutraceuticals, vitamins, antioxidants and minerals in the prevention and treatment of hypertension and cardiovascular disease. Therapeutic Advances in Cardiovascular Disease, 4, 165–183. [PubMed: 20400494]

Huber S, Sakkinen P, Conze D, Hardin N, & Tracy R (1999). Interleukin-6 exacerbates early atherosclerosis in mice. Arteriosclerosis, Thrombosis, and Vascular Biology, 19, 2364–2367.

Hui DY (2008). Intimal hyperplasia in murine models. Current Drug Targets, 9, 251–260. [PubMed: 18336244]

Jaganathan S, Jaacks LM, Magsumbol M, Walia GK, Sieber NL, Shivasankar R, et al. (2019). Association of long-term exposure to fine particulate matter and cardio-metabolic diseases in low- and middle-income countries: a systematic review. International Journal of Environmental Research and Public Health, 16, 2541.

Imai Y, Kuba K, Neely GG, Yaghubian-Malhami R, Perkmann T, van Loo G, et al. (2008). Identification of oxidative stress and Toll-like receptor 4 signaling as a key pathway of acute lung injury. Cell 133, 235–249. [PubMed: 18423196]

Ji Z, Wang Z, Chen Z, Jin H, Chen C, Chai S, et al. (2018). Melatonin attenuates chronic cough mediated by oxidative stress via transient receptor potential melastatin-2 in guinea pigs exposed to particulate matter 2.5. Physiological Research, 67, 293–305. [PubMed: 29303602]

Jones MR, Magid HS, Al-Rifai M, McEvoy JW, Kaufman JD, Hinckley Stukovsky KD, et al. (2016). Secondhand smoke exposure and subclinical cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis. Journal of the American Heart Association, 5, e002965. [PubMed: 27993830]

Jose SS, Bendickova K, Kepak T, Krenova Z, & Fric J (2017). Chronic inflammation in immune aging: role of pattern recognition receptor crosstalk with the telomere complex? Frontiers in Immunology, 8, 1078. [PubMed: 28928745]

Kampfrath T, Maiseyeu A, Ying Z, Shah Z, Deiuliis JA, Xu X, et al. (2011). Chronic fine particulate matter exposure induces systemic vascular dysfunction via NADPH oxidase and TLR4 pathways. Circulation Research, 108, 716–726. [PubMed: 21273555]

Kanagy NL (2005). α2-adrenergic receptor signalling in hypertension. Clinical science, 109, 431–437. [PubMed: 16232127]

Karlson EW, Shadick NA, Cook NR, Buring JE, & Lee I. m. (2008). Vitamin E in the primary prevention of rheumatoid arthritis: the Women's Health Study. Arthritis Care & Research, 59, 1589–1595. [PubMed: 18975365]

Kaufman JD, Adar SD, Barr RG, Budoff M, Burke GL, Curl CL, et al. (2016). Association between air pollution and coronary artery calcification within six metropolitan areas in the USA (the Multi-Ethnic Study of Atherosclerosis and Air Pollution): a longitudinal cohort study. The Lancet, 388, 696–704.

Kelemen M, Vaidya D, Waters DD, Howard BV, Cobb F, Younes N, et al. (2005). Hormone therapy and antioxidant vitamins do not improve endothelial vasodilator function in postmenopausal women with established coronary artery disease: a substudy of the Women's Angiographic Vitamin and Estrogen (WAVE) trial. Atherosclerosis, 179, 193–200. [PubMed: 15721027]

Kelly FJ, & Fussell JC (2017). Role of oxidative stress in cardiovascular disease outcomes following exposure to ambient air pollution. Free Radical Biology and Medicine, 110, 345–367. [PubMed: 28669628]

Khan M, Mohsin S, Avitabile D, Siddiqi S, Nguyen J, Wallach K, et al. (2013). β-Adrenergic regulation of cardiac progenitor cell death versus survival and proliferation. Circulation Research, 112, 476–486. [PubMed: 23243208]

Kim Y-W, West XZ, & Byzova TV (2013). Inflammation and oxidative stress in angiogenesis and vascular disease. Journal of Molecular Medicine, 91, 323–328. [PubMed: 23430240]

Klepac P, Locatelli I, Korošec S, Künzli N, & Kukec A (2018). Ambient air pollution and pregnancy outcomes: A comprehensive review and identification of environmental public health challenges. Environmental Research, 167, 144–159. [PubMed: 30014896]

Knuckles TL, Stapleton PA, Minarchick VC, Esch L, McCawley M, Hendryx M, et al. (2013). Air pollution particulate matter collected from an Appalachian mountaintop mining site induces microvascular dysfunction. Microcirculation, 20, 158–169. [PubMed: 22963349]

Koike E, Hirano S, Shimojo N, & Kobayashi T (2002). cDNA microarray analysis of gene expression in rat alveolar macrophages in response to organic extract of diesel exhaust particles. Toxicological Sciences, 67, 241–246. [PubMed: 12011483]

Kook D, Wolf AH, Alice LY, Neubauer AS, Priglinger SG, Kampik A, et al. (2008). The protective effect of quercetin against oxidative stress in the human RPE in vitro. Investigative Ophthalmology & Visual Science, 49, 1712–1720. [PubMed: 18385095]

Korkmaz H, & Onalan O (2008). Evaluation of endothelial dysfunction: flow-mediated dilation. Endothelium, 15, 157–163. [PubMed: 18663619]

Krämer U, Herder C, Sugiri D, Strassburger K, Schikowski T, Ranft U, et al. (2010). Traffic-related air pollution and incident type 2 diabetes: results from the SALIA cohort study. Environmental Health Perspectives, 118, 1273–1279. [PubMed: 20504758]

Krishnan RM, Adar SD, Szpiro AA, Jorgensen NW, Van Hee VC, Barr RG, et al. (2012). Vascular responses to long-and short-term exposure to fine particulate matter: MESA Air (Multi-Ethnic Study of Atherosclerosis and Air Pollution). Journal of the American College of Cardiology, 60, 2158–2166. [PubMed: 23103035]

Kurtz ML, Astort F, Lezon C, Ferraro SA, Maglione GA, Orona NS, et al. (2018). Oxidative stress response to air particle pollution in a rat nutritional growth retardation model. Journal of Toxicology and Environmental Health, Part A, 81, 1028–1040. [PubMed: 30239279]

Laden F, Neas LM, Dockery DW, & Schwartz J (2000). Association of fine particulate matter from different sources with daily mortality in six US cities. Environmental Health Perspectives, 108, 941–947. [PubMed: 11049813]

Lahoute C, Herbin O, Mallat Z, & Tedgui A (2011). Adaptive immunity in atherosclerosis: mechanisms and future therapeutic targets. Nature Reviews Cardiology, 8, 348–358. [PubMed: 21502963]

Lawal AO (2017). Air particulate matter induced oxidative stress and inflammation in cardiovascular disease and atherosclerosis: The role of Nrf2 and AhR-mediated pathways. Toxicology Letters, 270, 88–95. [PubMed: 28189649]

Lee F-Y, Lee MS, Wallace CG, Huang C-R, Chu C-H, Wen Z-H, et al. (2019). Short-interval exposure to ambient fine particulate matter (PM2. 5) exacerbates the susceptibility of pulmonary damage in setting of lung ischemia-reperfusion injury in rodent: Pharmacomodulation of melatonin. Biomedicine & Pharmacotherapy, 113, 108737. [PubMed: 30852418]

Lee I-M, Cook NR, Gaziano JM, Gordon D, Ridker PM, Manson JE, et al. (2005). Vitamin E in the primary prevention of cardiovascular disease and cancer: the Women's Health Study: a randomized controlled trial. Journal of the American Medical Association, 294, 56–65. [PubMed: 15998891]

Li H, Cai J, Chen R, Zhao Z, Ying Z, Wang L, et al. (2017). Particulate matter exposure and stress hormone levels: a randomized, double-blind, crossover trial of air purification. Circulation, 136, 618–627. [PubMed: 28808144]

Li R, Jia Z, & Zhu H (2019). Regulation of Nrf2 signaling. Reactive oxygen species (Apex, NC), 8, 312.

Li R, Navab K, Hough G, Daher N, Zhang M, Mittelstein D, et al. (2015). Effect of exposure to atmospheric ultrafine particles on production of free fatty acids and lipid metabolites in the mouse small intestine. Environmental Health Perspectives, 123, 34–41. [PubMed: 25170928]

Li Y, Chen Q, Zhao H, Wang L, & Tao R (2015). Variations in PM10, PM2. 5 and PM1. 0 in an urban area of the Sichuan Basin and their relation to meteorological factors. Atmosphere, 6, 150–163.

Liao JK (2013). Linking endothelial dysfunction with endothelial cell activation. The Journal of Clinical Investigation, 123, 540–541. [PubMed: 23485580]

Lim CC, Hayes RB, Ahn J, Shao Y, Silverman DT, Jones RR, et al. (2019). Mediterranean diet and the association between air pollution and cardiovascular disease mortality risk. Circulation, 139, 1766–1775. [PubMed: 30700142]

Liu D, Perkins JT, & Hennig B (2016). EGCG prevents PCB-126-induced endothelial cell inflammation via epigenetic modifications of NF-κB target genes in human endothelial cells. The Journal of Nutritional Biochemistry, 28, 164–170. [PubMed: 26878794]

Liu J, Han L, Zhu L, & Yu Y (2016). Free fatty acids, not triglycerides, are associated with non-alcoholic liver injury progression in high fat diet induced obese rats. Lipids in Health & Disease, 15, 27. [PubMed: 26868515]

Liu L, Urch B, Szyszkowicz M, Evans G, Speck M, Van Huang A, et al. (2018). Metals and oxidative potential in urban particulate matter influence systemic inflammatory and neural biomarkers: A controlled exposure study. Environment International, 121, 1331–1340. [PubMed: 30420132]

Liu Q, Gu X, Deng F, Mu L, Baccarelli AA, Guo X, et al. (2019). Ambient particulate air pollution and circulating C-reactive protein level: a systematic review and meta-analysis. International Journal of Hygiene and Environmental Health, 222, 756–764. [PubMed: 31103472]

Liu S, Lee I-M, Song Y, Van Denburgh M, Cook NR, Manson JE, et al. (2006). Vitamin E and risk of type 2 diabetes in the women's health study randomized controlled trial. Diabetes, 55, 2856–2862. [PubMed: 17003353]

Liu Y.-y., Zhang W.-y., Wang C.-g., Huang J.-a., Jiang J.-h., & Zeng D.-x. (2020). Resveratrol prevented experimental pulmonary vascular remodeling via miR-638 regulating NR4A3/cyclin D1 pathway. Microvascular Research, 130, 103988. [PubMed: 32057731]

López-Sepúlveda R. o., Jiménez R, Romero M, Zarzuelo MJ, Sánchez M, Gómez-Guzmán M, et al. (2008). Wine polyphenols improve endothelial function in large vessels of female spontaneously hypertensive rats. Hypertension, 51, 1088–1095. [PubMed: 18259008]

Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. (2012). Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet, 380, 2095–2128.

Lucas K, & Maes M (2013). Role of the Toll Like receptor (TLR) radical cycle in chronic inflammation: possible treatments targeting the TLR4 pathway. Molecular Neurobiology, 48, 190–204. [PubMed: 23436141]

Mancini FR, Laine JE, Tarallo S, Vlaanderen J, Vermeulen R, van Nunen E, et al. (2020). microRNA expression profiles and personal monitoring of exposure to particulate matter. Environmental Pollution, 263(Pt B), 114392. [PubMed: 32276129]

Mao S, Li S, Wang C, Liu Y, Li N, Liu F, et al. (2020). Is long-term PM1 exposure associated with blood lipids and dyslipidemias in a Chinese rural population? Environment International, 138, 105637. [PubMed: 32155508]

Markiewicz M, Richard E, Marks N, & Ludwicka-Bradley A (2013). Impact of endothelial microparticles on coagulation, inflammation, and angiogenesis in age-related vascular diseases. Journal of Aging Research, 2013.

Markus RP, Fernandes PA, Kinker GS, da Silveira Cruz-Machado S, & Marçola M (2018). Immune-pineal axis–acute inflammatory responses coordinate melatonin synthesis by pinealocytes and phagocytes. British Journal of Pharmacology, 175, 3239–3250. [PubMed: 29105727]

Martin FA, Murphy RP, & Cummins PM (2013). Thrombomodulin and the vascular endothelium: insights into functional, regulatory, and therapeutic aspects. American Journal of Physiology-Heart and Circulatory Physiology, 304, H1585–H1597. [PubMed: 23604713]

Matsumura N, Takahara S, Maayah ZH, Parajuli N, Byrne NJ, Shoieb SM, et al. (2018). Resveratrol improves cardiac function and exercise performance in MI-induced heart failure through the inhibition of cardiotoxic HETE metabolites. Journal of Molecular and Cellular Cardiology, 125, 162–173. [PubMed: 30381233]

McGuinn LA, Coull BA, Kloog I, Just AC, Tamayo-Ortiz M, Osorio-Yáñez C, et al. (2020). Fine particulate matter exposure and lipid levels among children in Mexico city. Environmental Epidemiology (Philadelphia, Pa.), 4, e088.

McGuinn LA, Schneider A, McGarrah RW, Ward-Caviness C, Neas LM, Di Q, et al. (2019). Association of long-term PM2. 5 exposure with traditional and novel lipid measures related to cardiovascular disease risk. Environment International, 122, 193–200. [PubMed: 30446244]

McKay L, & Cidlowski J (2003). Physiologic and pharmacologic effects of corticosteroids. In Kufe DW, Pollock RE, Weichselbaum RR et al., (Eds.), Holland-Frei Cancer Medicine, 6th edition, BC Decker, Inc.

Menetrez MY, Foarde KK, & Ensor DS (2000). Fine Biological PM: Understanding Size Fraction Transport and Exposure Potential (Extended Abstract). The Air and Waste Management Association Specialty Conference, PM2000: Particulate Matter and Health—The Scientific Basis for Regulatory Decision-making. January 24–28.

Menzel DB (1984). Ozone: an overview of its toxicity in man and animals. Journal of Toxicology and Environmental Health, 13, 183–204. [PubMed: 6376815]

Michiels C (2003). Endothelial cell functions. Journal of Cellular Physiology, 196, 430–443. [PubMed: 12891700]

Miyata R, & van Eeden SF (2011). The innate and adaptive immune response induced by alveolar macrophages exposed to ambient particulate matter. Toxicology and Applied Pharmacology, 257, 209–226. [PubMed: 21951342]

Miyata R, Bai N, Vincent R, Sin DD, & Van Eeden SF (2012). Novel properties of statins: suppression of the systemic and bone marrow responses induced by exposure to ambient particulate matter (PM10) air pollution. American Journal of Physiology-Lung Cellular and Molecular Physiology, 303, L492–L499. [PubMed: 22797249]

Miyata R, Bai N, Vincent R, & Sin DD, Van Eeden SF. (2013a). Statins reduce ambient particulate matter-induced lung inflammation by promoting the clearance of particulate matter, < 10 μm from lung tissues. Chest, 143, 452–460. [PubMed: 22910717]

Miyata R, Hiraiwa K, Cheng JC, Bai N, Vincent R, Francis GA, et al. (2013b). Statins attenuate the development of atherosclerosis and endothelial dysfunction induced by exposure to urban

particulate matter (PM10). Toxicology and Applied Pharmacology, 272, 1–11. [PubMed: 23756175]

Molitoris BA, & Sutton TA (2004). Endothelial injury and dysfunction: role in the extension phase of acute renal failure. Kidney International, 66, 496–499. [PubMed: 15253696]

Moore KJ, Sheedy FJ, & Fisher EA (2013). Macrophages in atherosclerosis: a dynamic balance. Nature reviews immunology, 13, 709–721.

Mudway I, & Kelly F (2000). Ozone and the lung: a sensitive issue. Molecular Aspects of Medicine, 21, 1–48. [PubMed: 10804262]

MOnzel T, & Daiber A (2018). Environmental stressors and their impact on health and disease with focus on oxidative stress. Antioxidants & Redox Signaling, 28, 735–740. [PubMed: 29278923]

Mustonen P, & Lassila R (1996). Epinephrine augments platelet recruitment to immobilized collagen in flowing blood-evidence for a von Willebrand factor-mediated mechanism. Thrombosis and Haemostasis, 75, 175–181. [PubMed: 8713798]

Nawrot TS, Perez L, Künzli N, Munters E, & Nemery B (2011). Public health importance of triggers of myocardial infarction: a comparative risk assessment. The Lancet, 377, 732–740.

Nemmar A, Vanbilloen H, Hoylaerts M, Hoet P, Verbruggen A, & Nemery B (2001). Passage of intratracheally instilled ultrafine particles from the lung into the systemic circulation in hamster. American Journal of Respiratory and Critical Care Medicine, 164, 1665–1668. [PubMed: 11719307]

Ng TP, Niti M, Yap KB, & Tan WC (2014). Dietary and supplemental antioxidant and anti-inflammatory nutrient intakes and pulmonary function. Public Health Nutrition, 17, 2081–2086. [PubMed: 24074036]

Nguyen T, Nioi P, & Pickett CB (2009). The Nrf2-antioxidant response element signaling pathway and its activation by oxidative stress. Journal of Biological Chemistry, 284, 13291–13295.

Niu Y, Chen R, Xia Y, Cai J, Ying Z, Lin Z, et al. (2018). Fine particulate matter constituents and stress hormones in the hypothalamus-pituitary-adrenal axis. Environment International, 119, 186–192. [PubMed: 29960262]

Oakes JL, O'Connor BP, Warg LA, Burton R, Hock A, Loader J, et al. (2013). Ozone Enhances Pulmonary Innate Immune Response to a Toll-Like Receptor–2 Agonist. American Journal of Respiratory Cell and Molecular Biology, 48, 27–34. [PubMed: 23002100]

Ohta H, Wada H, Niwa T, Kirii H, Iwamoto N, Fujii H, et al. (2005). Disruption of tumor necrosis factor-α gene diminishes the development of atherosclerosis in ApoE-deficient mice. Atherosclerosis, 180, 11–17. [PubMed: 15823270]

Ostro B, Malig B, Broadwin R, Basu R, Gold EB, Bromberger JT, et al. (2014). Chronic PM2. 5 exposure and inflammation: determining sensitive subgroups in mid-life women. Environmental Research, 132, 168–175. [PubMed: 24792413]

Parhofer KG (2015). Interaction between Glucose and Lipid Metabolism: More than diabetic dyslipidemia. Diabetes & Metabolism Journal, 39, 353–62. [PubMed: 26566492]

Park SK, Auchincloss AH, O'Neill MS, Prineas R, Correa JC, Keeler J, et al. (2010). Particulate air pollution, metabolic syndrome, and heart rate variability: the multi-ethnic study of atherosclerosis (MESA). Environmental Health Perspectives, 118, 1406–1411. [PubMed: 20529761]

Pastori D, Carnevale R, & Pignatelli P (2014). Is there a clinical role for oxidative stress biomarkers in atherosclerotic diseases? Internal and Emergency Medicine, 9, 123–131. [PubMed: 24057419]

Pechanova O, Paulis L, & Simko F (2014). Peripheral and central effects of melatonin on blood pressure regulation. International Journal of Molecular Sciences, 15, 17920–17937. [PubMed: 25299692]

Pevet P, & Challet E (2011). Melatonin: both master clock output and internal time-giver in the circadian clocks network. Journal of Physiology-Paris, 105, 170–182.

Pierini D, & Bryan NS (2015). Nitric oxide availability as a marker of oxidative stress. In Advanced Protocols in Oxidative Stress III (pp. 63–71): Springer.

Pieters N, Plusquin M, Cox B, Kicinski M, Vangronsveld J, & Nawrot TS (2012). An epidemiological appraisal of the association between heart rate variability and particulate air pollution: a meta-analysis. Heart, 98, 1127–1135. [PubMed: 22628541]

Pieters N, Janssen BG, Dewitte H, Cox B, Cuypers A, Lefebvre W, et al. (2016). Biomolecular markers within the core axis of aging and particulate air pollution exposure in the elderly: a cross-sectional study. Environmental Health Perspectives, 124, 943–950. [PubMed: 26672058]

Pope CA III, Burnett RT, Thun MJ, Calle EE, Krewski D, Ito K, et al. (2002). Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. Journal of the American Medical Association, 287, 1132–1141. [PubMed: 11879110]

Pope CA III, & Dockery DW (2006). Health effects of fine particulate air pollution: lines that connect. Journal of the Air & Waste Management Association, 56, 709–742. [PubMed: 16805397]

Pope CA III (2021) Are adults with COPD vulnerable to air pollution and cardiovascular risk? American Journal of Respiratory Critical Care Medicine. 2021 4 9. doi: 10.1164/rccm.202103-0647ED. Online ahead of print.

Possamai FP, Júnior SÁ, Parisotto EB, Moratelli AM, Inácio DB, Garlet TR, et al. (2010). Antioxidant intervention compensates oxidative stress in blood of subjects exposed to emissions from a coal electric-power plant in South Brazil. Environmental Toxicology and Pharmacology, 30, 175–180. [PubMed: 21787649]

Pradhan AD, Rifai N, & Ridker PM (2002). Soluble intercellular adhesion molecule-1, soluble vascular adhesion molecule-1, and the development of symptomatic peripheral arterial disease in men. Circulation, 106, 820–825. [PubMed: 12176954]

Prasad S, Sajja RK, Kaisar MA, Park JH, Villalba H, Liles T, et al. (2017). Role of Nrf2 and protective effects of Metformin against tobacco smoke-induced cerebrovascular toxicity. Redox Biology, 12, 58–69. [PubMed: 28212524]

Radonnski MV, & Moncada S (1993). Regulation of vascular homeostasis by nitric oxide. Thrombosis and Haemostasis, 70, 36–41 [PubMed: 7694388]

Rao X, Asico LD, Zanos P, Mahabeleshwar GH, Singh Gangwar R, Xia C, et al. (2019). Alpha2B-Adrenergic receptor overexpression in the brain potentiate air pollution-induced behavior and blood pressure changes. Toxicological Sciences, 169, 95–107. [PubMed: 30812033]

Rao X, Zhong J, Brook RD, & Rajagopalan S (2018). Effect of particulate matter air pollution on cardiovascular oxidative stress pathways. Antioxidants & Redox Signaling, 28, 797–818. [PubMed: 29084451]

Ren F, Huang Y, Tao Y, Ji C, Aniagu S, Jiang Y, et al. (2020). Resveratrol protects against PM2. 5-induced heart defects in zebrafish embryos as an antioxidant rather than as an AHR antagonist. Toxicology and Applied Pharmacology, 398, 115029. [PubMed: 32376357]

Rhoden CR, Wellenius GA, Ghelfi E, Lawrence J, & González-Flecha B (2005). PM-induced cardiac oxidative stress and dysfunction are mediated by autonomic stimulation. Biochimica et Biophysica Acta (BBA)-General Subjects, 1725, 305–313. [PubMed: 16005153]

Riedl MA, Saxon A, & Diaz-Sanchez D (2009). Oral sulforaphane increases Phase II antioxidant enzymes in the human upper airway. Clinical Immunology, 130, 244–251. [PubMed: 19028145]

Robertson S, Thomson AL, Carter R, Stott HR, Shaw CA, Hadoke PW, et al. (2014). Pulmonary diesel particulate increases susceptibility to myocardial ischemia/reperfusion injury via activation of sensory TRPV1 and β1 adrenoreceptors. Particle and Fibre Toxicology, 11, 1–10. [PubMed: 24382024]

Rodosthenous RS, Kloog I, Colicino E, Zhong J, Herrera LA, Vokonas P, et al. (2018). Extracellular vesicle-enriched microRNAs interact in the association between long-term particulate matter and blood pressure in elderly men. Environmental Research, 167, 640–649. [PubMed: 30216846]

Romieu I, Garcia-Esteban R, Sunyer J, Rios C, Alcaraz-Zubeldia M, Velasco SR, et al. (2008). The effect of supplementation with omega-3 polyunsaturated fatty acids on markers of oxidative stress in elderly exposed to PM2. 5. Environmental Health Perspectives, 116, 1237–1242. [PubMed: 18795169]

Romieu I, Téllez-Rojo MM, Lazo M, Manzano-Patiño A, Cortez-Lugo M, Julien P, et al. (2005). Omega-3 fatty acid prevents heart rate variability reductions associated with particulate matter. American Journal of Respiratory and Critical Care Medicine, 172, 1534–1540. [PubMed: 16210665]

Ross R, Glomset J, & Harker L (1977). Response to injury and atherogenesis. The American Journal of Pathology, 86, 675–684. [PubMed: 842616]

Ruiz-Vera T, Ochoa-Martínez ÁC, Pruneda-Álvarez LG, Zarazúa S, Pérez-Maldonado IN (2019). Exposure to biomass smoke is associated with an increased expression of circulating miRNA-126 and miRNA-155 in Mexican women: a pilot study. Drug and Chemical Toxicology. 42, 335–342. [PubMed: 30486697]

Saleem TM, & Basha SD (2010). Red wine: A drink to your heart. Journal of Cardiovascular Disease Research, 1, 171–176. [PubMed: 21264180]

Schiffrin EL (2001). A critical review of the role of endothelial factors in the pathogenesis of hypertension. Journal of Cardiovascular Pharmacology, 38, S3–S6.

Schuetzle D, Lee FS & Prater TJ (1981). The identification of polynuclear aromatic hydrocarbon (PAH) derivatives in mutagenic fractions of diesel particulate extracts. International Journal of Environmental Analalytical Chemistry, 9, 93–144.

Schuler D, Sansone R, Freudenberger T, Rodriguez-Mateos A, Weber G, Momma TY, et al. (2014). Measurement of endothelium-dependent vasodilation in mice—brief report. Arteriosclerosis, thrombosis, and vascular biology, 34, 2651–2657.

Seaton A, Godden D, MacNee W, & Donaldson K (1995). Particulate air pollution and acute health effects. The Lancet, 345, 176–178.

Shanley RP, Hayes RB, Cromar KR, Ito K, Gordon T, & Ahn J (2016). Particulate air pollution and clinical cardiovascular disease risk factors. Epidemiology (Cambridge, Mass.), 27, 291–298.

Shi C, Han X, Mao X, Fan C, & Jin M (2019). Metabolic profiling of liver tissues in mice after instillation of fine particulate matter. Science of The Total Environment, 696, 133974.

Sirtori CR (2014). The pharmacology of statins. Pharmacological Research, 88, 3–11. [PubMed: 24657242]

Sivandzade F, & Cucullo L (2019). Assessing the protective effect of rosiglitazone against electronic cigarette/tobacco smoke-induced blood–brain barrier impairment. BMC Neuroscience, 20, 15. [PubMed: 30947684]

Soberanes S, Misharin AV, Jairaman A, Morales-Nebreda L, McQuattie-Pimentel AC, Cho T, et al. (2019). Metformin targets mitochondrial electron transport to reduce air-pollution-induced thrombosis. Cell Metabolism, 29, 335–347. e335. [PubMed: 30318339]

Sokolowska M, Quesniaux VF, Akdis CA, Chung KF, Ryffel B, & Togbe D (2019). Acute respiratory barrier disruption by ozone exposure in mice. Frontiers in Immunology, 10, 2169. [PubMed: 31608051]

Springer TA (1994). Traffic signals for lymphocyte recirculation and leukocyte emigration: the multistep paradigm. Cell, 76, 301–314. [PubMed: 7507411]

Stassen FR, van Eijck PH, Savelkoul PH, Wouters EF, Rohde GG, Briedé JJ, et al. (2019). Cell type- and exposure-specific modulation of CD63/CD81-positive and tissue factor-positive extracellular vesicle release in response to respiratory toxicants. Oxidative Medicine and Cellular Longevity, 2019, 5204218. [PubMed: 31485294]

Steven S, Frenis K, Oelze M, Kalinovic S, Kuntic M, Bayo Jimenez MT, et al. (2019). Vascular inflammation and oxidative stress: major triggers for cardiovascular disease. Oxidative Medicine and Cellular Longevity, 2019, 7092151. [PubMed: 31341533]

Sun Q, Yue P, Deiuliis JA, Lumeng CN, Kampfrath T, Mikolaj MB, et al. (2009). Ambient air pollution exaggerates adipose inflammation and insulin resistance in a mouse model of diet-induced obesity. Circulation, 119, 538–546. [PubMed: 19153269]

Suwa T, Hogg JC, Quinlan KB, Ohgami A, Vincent R, & van Eeden SF (2002). Particulate air pollution induces progression of atherosclerosis. Journal of the American College of Cardiology, 39, 935–942. [PubMed: 11897432]

Suzuki T, Hidaka T, Kumagai Y, & Yamamoto M (2020). Environmental pollutants and the immune response. Nature Immunology, 21, 1486–1495. [PubMed: 33046888]

Tabit CE, Chung WB, Hamburg NM, & Vita JA (2010). Endothelial dysfunction in diabetes mellitus: Molecular mechanisms and clinical implications. Reviews in Endocrine and Metabolic Disorders, 11, 61–74. [PubMed: 20186491]

Takyi SA, Basu N, Arko-Mensah J, Botwe P, Nti AAA, Kwarteng L, et al. (2020). Micronutrient-rich dietary intake is associated with a reduction in the effects of particulate matter on blood pressure

among electronic waste recyclers at Agbogbloshie, Ghana. BMC Public Health, 20, 1–14. [PubMed: 31898494]

Tan Y, Yang R, Zhao J, Cao Z, Chen Y, & Zhang B (2017). The associations between air pollution and adverse pregnancy outcomes in China. In Ambient Air Pollution and Health Impact in China (pp. 181–214): Springer.

Tankersley CG, Campen M, Bierman A, Flanders SE, Broman KW, & Rabold R (2004). Particle effects on heart-rate regulation in senescent mice. Inhalation Toxicology, 16, 381–390. [PubMed: 15204754]

Tobaldini E, Bollati V, Prado M, Fiorelli EM, Pecis M, Bissolotti G, et al. (2018). Acute particulate matter affects cardiovascular autonomic modulation and IFN-γ methylation in healthy volunteers. Environmental Research, 161, 97–103. [PubMed: 29102669]

Toledo-Corral CM, Alderete TL, Herting MM, Habre R, Peterson AK, Lurmann F, et al. (2021). Ambient air pollutants are associated with morning serum cortisol in overweight and obese Latino youth in Los Angeles. Environmental Health, 20, 39. [PubMed: 33832509]

Tong H, Rappold AG, Caughey M, Hinderliter AL, Bassett M, Montilla T, et al. (2015). Dietary supplementation with olive oil or fish oil and vascular effects of concentrated ambient particulate matter exposure in human volunteers. Environmental Health Perspectives, 123, 1173–1179. [PubMed: 25933197]

Tong H, Rappold AG, Diaz-Sanchez D, Steck SE, Berntsen J, Cascio WE, et al. (2012). Omega-3 fatty acid supplementation appears to attenuate particulate air pollution–induced cardiac effects and lipid changes in healthy middle-aged adults. Environmental Health Perspectives, 120, 952–957. [PubMed: 22514211]

Totlandsdal AI, Herseth JI, Bølling AK, Kubátová A, Braun A, Cochran RE, et al. (2012). Differential effects of the particle core and organic extract of diesel exhaust particles. Toxicology Letters, 208, 262–268. [PubMed: 22100492]

Tsai T-Y, Lo L-W, Liu S-H, Cheng W-H, Chou Y-H, Lin W-L, et al. (2019). Diurnal cardiac sympathetic hyperactivity after exposure to acute particulate matter 2.5 air pollution. Journal of Electrocardiology, 52, 112–116. [PubMed: 30553983]

Valentino SA, Tarrade A, Aioun J, Mourier E, Richard C, Dahirel M, et al. (2015). Maternal exposure to diluted diesel engine exhaust alters placental function and induces intergenerational effects in rabbits. Particle and Fibre Toxicology, 13, 1–14.

van Es N, Bleker S, Sturk A, & Nieuwland R (2015). Clinical significance of tissue factor–exposing microparticles in arterial and venous thrombosis. In Seminars in Thrombosis and Hemostasis (Vol. 41, pp. 718–727): Thieme Medical Publishers. [PubMed: 26408926]

van Hinsbergh VW (2001). The endothelium: vascular control of haemostasis. European Journal of Obstetrics & Gynecology and Reproductive Biology, 95, 198–201. [PubMed: 11301171]

Vane J, & Corin R (2003). Prostacyclin: a vascular mediator. European Journal of Vascular and Endovascular Surgery, 26, 571–578. [PubMed: 14603414]

Vanhoutte PM (1997). Endothelial dysfunction and atherosclerosis. European Heart Journal, 18, 19–29.

Vanhoutte PM, Shimokawa H, Tang EH, & Feletou M (2009). Endothelial dysfunction and vascular disease. Acta Physiologica, 196, 193–222. [PubMed: 19220204]

Vaiserman A, & Krasnienkov D (2020). Telomere length as a marker of biological age: State-of-the-art, open issues, and future perspectives. Frontiers in Genetics, 11.

Villarreal-Calderon R, Reed W, Palacios-Moreno J, Keefe S, Herritt L, Brooks D, et al. (2012). Urban air pollution produces up-regulation of myocardial inflammatory genes and dark chocolate provides cardioprotection. Experimental and Toxicologic Pathology, 64, 297–306. [PubMed: 20932730]

Vischer U (2006). von Willebrand factor, endothelial dysfunction, and cardiovascular disease. Journal of Thrombosis and Haemostasis, 4, 1186–1193. [PubMed: 16706957]

Vogel CF, Khan EM, Leung PS, Gershwin ME, Chang WW, Wu D, et al. (2014). Cross-talk between Aryl hydrocarbon receptor and the inflammatory response a role for nuclear factor-κB. Journal of Biological Chemistry, 289, 1866–1875.

Wainright T (1986). The chemistry of nitrosamine formation: relevance to malting and brewing. Journal of the Institute of Brewing, 92, 49–64.

Wallwork RS, Colicino E, Zhong J, Kloog I, Coull BA, Vokonas P, et al. (2017). Ambient fine particulate matter, outdoor temperature, and risk of metabolic syndrome. American Journal of Epidemiology, 185, 30–39. [PubMed: 27927620]

Walpola PL, Gotlieb AI, Cybulsky MI, & Langille BL (1995). Expression of ICAM-1 and VCAM-1 and monocyte adherence in arteries exposed to altered shear stress. Arteriosclerosis, Thrombosis, and Vascular Biology, 15, 2–10.

Walters DM, Breysse PN, Schofield B, & Wills-Karp M (2002). Complement factor 3 mediates particulate matter–induced airway hyperresponsiveness. American Journal of Respiratory Cell and Molecular Biology, 27, 413–418. [PubMed: 12356574]

Wang N, Ma Y, Liu Z, Liu L, Yang K, Wei Y, et al. (2019). Hydroxytyrosol prevents PM2. 5-induced adiposity and insulin resistance by restraining oxidative stress related NF-κB pathway and modulation of gut microbiota in a murine model. Free Radical Biology and Medicine, 141, 393–407. [PubMed: 31279968]

Wardyn JD, Ponsford AH, & Sanderson CM (2015). Dissecting molecular cross-talk between Nrf2 and NF-κB response pathways. Biochemical Society Transactions, 43, 621–626. [PubMed: 26551702]

Waters DD, Alderman EL, Hsia J, Howard BV, Cobb FR, Rogers WJ, et al. (2002). Effects of hormone replacement therapy and antioxidant vitamin supplements on coronary atherosclerosis in postmenopausal women: a randomized controlled trial. Journal of the American Medical Association, 288, 2432–2440. [PubMed: 12435256]

Wei Y, Zhang J, Li Z, Gow A, Chung KF, Hu M, et al. (2016). Chronic exposure to air pollution particles increases the risk of obesity and metabolic syndrome: findings from a natural experiment in Beijing. The FASEB Journal, 30, 2115–2122. [PubMed: 26891735]

Weichenthal S, Pinault LL, & Burnett RT (2017). Impact of oxidant gases on the relationship between outdoor fine particulate air pollution and nonaccidental, cardiovascular, and respiratory mortality. Scientific Reports, 7, 1–10. [PubMed: 28127051]

Widmer RJ, Flammer AJ, Lerman LO, & Lerman A (2015). The Mediterranean diet, its components, and cardiovascular disease. The American Journal of Medicine, 128, 229–238. [PubMed: 25447615]

Wiest EF, Walsh-Wilcox MT, & Walker MK (2017). Omega-3 polyunsaturated fatty acids protect against cigarette smoke-induced oxidative stress and vascular dysfunction. Toxicological Sciences, 156, 300–310. [PubMed: 28115642]

Wong JY, De Vivo I, Lin X, & Christiani DC (2014). Cumulative PM2. 5 exposure and telomere length in workers exposed to welding fumes. Journal of Toxicology and Environmental Health, Part A, 77, 441–455. [PubMed: 24627998]

Wood AD, Strachan AA, Thies F, Aucott LS, Reid DM, Hardcastle AC, et al. (2014). Patterns of dietary intake and serum carotenoid and tocopherol status are associated with biomarkers of chronic low-grade systemic inflammation and cardiovascular risk. British Journal of Nutrition, 112, 1341–1352.

Wu G, Brown J, Zamora ML, Miller A, Satterfield MC, Meininger CJ, et al. (2019). Adverse organogenesis and predisposed long-term metabolic syndrome from prenatal exposure to fine particulate matter. Proceedings of the National Academy of Sciences, 116, 11590–11595.

Wu S, Deng F, Wei H, Huang J, Wang H, Shima M, et al. (2012). Chemical constituents of ambient particulate air pollution and biomarkers of inflammation, coagulation and homocysteine in healthy adults: a prospective panel study. Particle and Fibre Toxicology, 9, 49. [PubMed: 23231781]

Wurtman RJ (2002). Stress and the adrenocortical control of epinephrine synthesis. Metabolism-Clinical and Experimental, 51, 11–14. [PubMed: 12040535]

Xu J, Zhang W, Lu Z, Zhang F, & Ding W (2017). Airborne PM2.5-induced hepatic insulin resistance by Nrf2/JNK-mediated signaling pathway. International Journal of Environmental Research and Public Health, 14, 787.

Xu MX, Ge CX, Qin YT, Gu TT, Lou DS, Li Q, et al. (2019). Prolonged PM2.5 exposure elevates risk of oxidative stress-driven nonalcoholic fatty liver disease by triggering increase of dyslipidemia. Free Radical Biology & Medicine, 130, 542–556. [PubMed: 30465824]

Xu Y, Wang W, Zhou J, Chen M, Huang X, Zhu Y, et al. (2019). Metabolomics analysis of a mouse model for chronic exposure to ambient PM2.5. Environmental Pollution, 247, 953–963. [PubMed: 30823350]

Xynos N, Abatis D, Argyropoulou A, Polychronopoulos P, Aligiannis N, & Skaltsounis A-L (2015). Development of a sustainable procedure for the recovery of Hydroxytyrosol from table olive processing wastewater using adsorption resin technology and centrifugal partition chromatography. Planta Medica, 81, 1621–1627. [PubMed: 26460673]

Yang GH, Li YC, Wang ZQ, Liu B, Ye W, Ni L, et al. (2014). Protective effect of melatonin on cigarette smoke-induced restenosis in rat carotid arteries after balloon injury. Journal of Pineal Research, 57, 451–458. [PubMed: 25251422]

Yang S, Chen R, Zhang L, Sun Q, Li R, Gu W, et al. (2021).Lipid metabolic adaption to long-term ambient PM(2.5) exposure in mice. Environmental Pollution, 269, 116193. [PubMed: 33302088]

Ye Y, Li J, & Yuan Z (2013). Effect of antioxidant vitamin supplementation on cardiovascular outcomes: a meta-analysis of randomized controlled trials. PloS One, 8, e56803. [PubMed: 23437244]

Yusuf S, Dagenais G, Pogue J, Bosch J, & Sleight P (2000). Vitamin E supplementation and cardiovascular events in high-risk patients. The New England Journal of Medicine, 342, 154–160. [PubMed: 10639540]

Zembowicz A, Hecker M, Macarthur H, Sessa WC, & Vane JR (1991). Nitric oxide and another potent vasodilator are formed from NG-hydroxy-L-arginine by cultured endothelial cells. Proceedings of the National Academy of Sciences, 88, 11172–11176.

Zeng X, Liu J, Du X, Zhang J, Pan K, Shan W, et al. (2018). The protective effects of selenium supplementation on ambient PM 2.5-induced cardiovascular injury in rats. Environmental Science and pollution Research, 25, 22153–22162. [PubMed: 29804245]

Zhang C (2008). MicroRNAs: role in cardiovascular biology and disease. Clinical science, 114, 699–706. [PubMed: 18474027]

Zhang K, Wang H, He W, Chen G, Lu P, Xu R, et al. (2020). The association between ambient air pollution and blood lipids: A longitudinal study in Shijiazhuang, China. Science of The Total Environment, 752, 141648.

Zhang Y, Ji X, Ku T, Li B, Li G, & Sang N (2019). Ambient fine particulate matter exposure induces cardiac functional injury and metabolite alterations in middle-aged female mice. Environmental Pollution, 248, 121–132. [PubMed: 30784831]

Zhong J, Karlsson O, Wang G, Li J, Guo Y, Lin X, et al. (2017). B vitamins attenuate the epigenetic effects of ambient fine particles in a pilot human intervention trial. Proceedings of the National Academy of Sciences, 114, 3503–3508.

Zhou G, Myers R, Li Y, Chen Y, Shen X, Fenyk-Melody J, et al. (2001). Role of AMP-activated protein kinase in mechanism of metformin action. The Journal of Clinical Investigation, 108, 1167–1174. [PubMed: 11602624]

Zureik M, Galan P, Bertrais S, Mennen L, Czernichow S, Blacher J, et al. (2004). Effects of long-term daily low-dose supplementation with antioxidant vitamins and minerals on structure and function of large arteries. Arteriosclerosis, Thrombosis, and Vascular Biology, 24, 1485–1491.

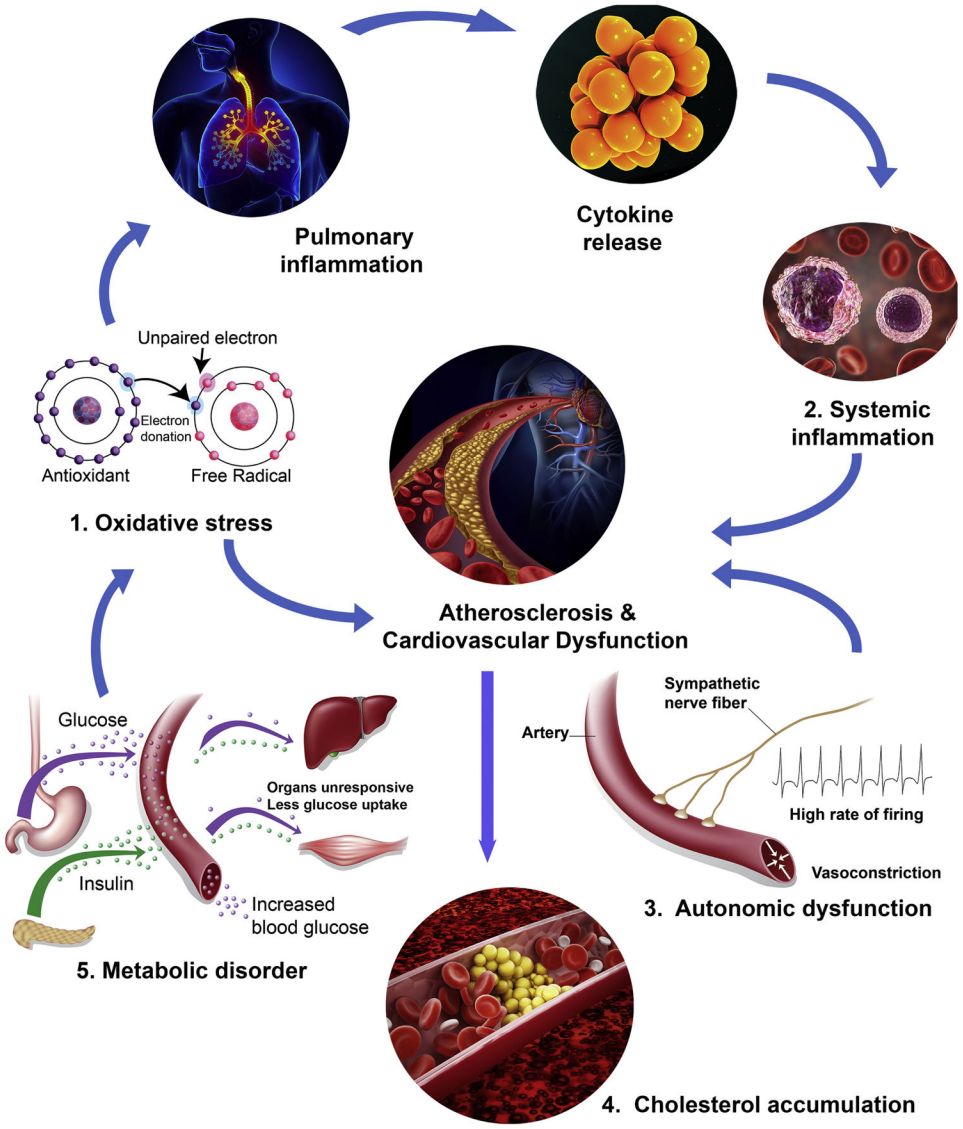

Figure 1.

Schematic representation of the mechanisms contributing to particulate matter (PM)-associated cardiovascular diseases, including 1) oxidative stress and decreased pulmonary barrier function, 2) pulmonary and systemic oxidative stress, 3) autonomic dysfunction, 4) cholesterol accumulation, and 5) metabolic disorder.

Table 1.

Molecular targets of therapy for preventing air contaminant-associated cardiovascular disease, as evidenced by animal and population data.

Molecular Target	Pollutant	Experimental Model	Experimental Findings	Reference
Oxidative stress and pulmonary barrier function	$PM_{2.5}$	$Nox2^{-/-}$ mice, TLR4(−/−) mice	↓Inflammatory monocytes and generation of ROS via NADPH oxidase and TLR4 activation	(Kampfrath, et al., 2011)
	Residual oil fly ash	Male rats with nutritional growth retardation	↓Alveolar space and recruitment of lung PMN, ↑ hepatic lymphocytes and binucleated hepatocytes, cardiac oxidative metabolism and ↑ oxidative stress.	(Kurtz, et al., 2018)
	$PM_{2.5}$	Male Sprague Dawley rats	↑Cerebrovascular ROS, oxidized lipids, ↓SOD, ↑Nrf2 response system.	(Guan, et al., 2019)
	$PM_{2.5}$	Male Sprague Dawley rats	↓Oxygen saturation, ↑ MMP-3, TNF-α, NF-kB, NADPH oxidase and apoptotic markers in lungs	(Ji, et al., 2018)
	Diesel exhaust particles (DEP), DEP extracts	BEAS-2B cells	↑Cytotoxicity and expression of COX-2, IL-6 and IL-8	(Totlandsdal, et al., 2012)
	$PM_{2.5}$ and O_x	2001 Canadian Census Health and Environment Cohort (CanCHEC)	CVD and respiratory mortality associated with ↑ oxidizing gases and PM	(Weichenthal, et al., 2017)
Pulmonary and systemic inflammation	DEP	Peritoneal macrophages of C57BL/6J mice	Differential expression of the gene enrichment pathways associated with antioxidant defense and immune response	(Bhetraratana, et al., 2019)
	$PM_{2.5}$	Children in Mexico City and Polotitlan	↑Inflammatory mediators and vasoconstrictors (TNF-α, PG-E2, CRP, IL-1β, ET-1) ↓ iCAM-1, VCAM-1, sE and sL- selectins.	(Calderon-Garciduenas, et al., 2008)
	$PM_{2.5}$	Study of Women's Health Across the Nation (SWAN) cohort	Strong association between $PM_{2.5}$ and CRP	(Ostro, et al., 2014)
	$PM_{2.5}$	Normative Aging Study (NAS) cohort	Association between $PM_{2.5}$ Vanadium mass and ICAM-1/VCAM-1	(Dai, et al., 2016)
		Male Sprague Dawley rats	↑Serum TNF-α, IL-6, IL-1β and IFN-γ	(Guan, et al., 2019)
	$PM_{2.5}$ and PM_{10}	Data from 40 observational studies	Strong association between CRP and PM with increasing duration of exposure	(Q. Liu, et al., 2019)
	$PM_{2.5}$	Cross-Sectional Study	↓SIRT1, mtDNA content and telomerase length	(Pieters, et al., 2016)
	$PM_{2.5}$	Male Wistar rats (2-3 months old)	↑ Immune-pineal axis, ↓ pineal synthesis, ↑ melatonin in lungs.	(Carvalho-Sousa, et al., 2020)
Autonomic dysfunction	$PM_{2.5}$	α2b-adrenergic receptor (Adra2b) transgenic mice	↑ Adra2b, inflammatory genes (TLR2, TLR4, and IL-6), activated effector T-cells, and oxidative stress	(Rao, et al., 2019)
	$PM_{2.5}$ from mountaintop mining site	Male Sprague Dawley rats	Microvascular dysfunction *via* endothelial dysfunction and sympathetic stimulation	(Knuckles, et al., 2013)
	PM_{10}, $PM_{2.5}$, $PM_{1.0}$, $PM_{0.5}$	Cross-sectional study of healthy males	↑ Parasympathetic modulation and ↑ interferon γ methylation.	(Tobaldini, et al., 2018)
	DEP	Heart failure prone rats	↑HR, BP, cardiac contractility in a manner reversed by atenolol	(Carll, et al., 2013)

Molecular Target	Pollutant	Experimental Model	Experimental Findings	Reference
	Carbon black	Senescent mice	↓HR without change in LF/HF ratio, changes in HRV parameters.	(Tankersley, et al., 2004)
	DEP	Male Wistar rats	↑ BP, duration of ventricular arrhythmia, edema, and reperfusion injury. Normalization of BP and arrhythmias with antagonist for TRPV1.	(Robertson, et al., 2014)
	$PM_{2.5}$	Randomized, double-blind crossover trail in healthy college students	↑BP, ↑insulin resistance, ↑oxidative and inflammation markers, and ↑ cortisol, cortisone, epinephrine, and norepinephrine.	(H. Li, et al., 2017)
	$PM_{2.5}$	Male Sprague Dawley rats	Combined effects of β1 and β2 adrenergic receptor agonists alleviate cardiac dysfunction.	(Y. Gao, et al., 2014)
	Concentration ambient $PM_{2.5}$ (CAP)	Apolipoprotein E (−/−) mice	Perturbed autonomic function in heart	(L. C. Chen, et al., 2005)
	CAP	Adrb2 and Adrb2 deficient mice	↑ Release of catecholamines via β2 receptor activation and increased IL-6 level	(Chiarella, et al., 2014)
Cholesterol accumulation	$PM_{2.5}$	6587 CVD patients in North Carolina	↑ LDL, apoB, total cholesterol, and triglycerides for every 1-μg/m3 increment in $PM_{2.5}$	McGuinn et al., 2019
	Prenatal $PM_{2.5}$	465 mother–child pairs	↑ Total cholesterol, LDL, ↓ HDL and triglycerides during childhood	McGuinn et al., 2020
	$PM_{2.5}$	7063 participants in Shijiazhuang, China	↑ Total cholesterol, LDL, triglycerides ↓ HDL	K. Zhang et al., 2020
	$PM_{2.5}$	C57BL/6 mice	↑ liver free fatty acids and triglycerides	Yang et al., 2021
	PM-associated PCBs	335 Native American adults	PCBs associated with ↑ cholesterol and triglycerides	Goncharov et al., 2008
	Ultrafine PM collected in urban Los Angeles	LDLr (−/−) mice	↑ lipid levels and macrophages in small intestine	R. Li et al., 2015
Metabolic dysfunction	Clean ambient air plus ammonium sulfate particles	Male and female Sprague Dawley rats	↑ Stillbirths, ↓ birth weight and gestation period, ↑plasma glucose and fatty acids, lipid in liver and ↓endothelial function.	(G. Wu, et al., 2019)
	Traffic-related PM	Cohort study in industrialized Ruhr district in West Germany	Serum C3c is associated with PM at baseline; Women with high C3c serum level more susceptible to PM-related Type 2 diabetes (T2DM).	(Krämer, et al., 2010)
	Residual oil fly ash	Female Wister rats	↑Neutrophils, neutrophil/lymphocyte ratios and liver iHSP70 levels, ↓ SOD activity in ovariectomized rats	(Goettems-Fiorin, et al., 2019)
	$PM_{2.5}$	SPE Kunming mice	Altered TCA and urea cycle, amino acids, and purine metabolism.	(Shi, et al., 2019)
	$PM_{2.5}$	Middle-aged female C57BL/6 mice	↓Cardiac growth and ↑dysfunction. Altered mitochondrial structure and function and carbohydrate, fatty acid, amino acid, nucleotide, nicotinate, and nicotinamide metabolism	(Y. Zhang, et al., 2019)
	Ambient $PM_{2.5}$	Human Adults	↑Insulin resistance, ↓HRV	(Brook, et al., 2013)
	$PM_{2.5}$	Systematic review	Association between hypertension, insulin resistance, Type 2 diabetes mellitus and cardio-metabolic diseases	(Jaganathan, et al., 2019)
	$PM_{2.5}$	587 men participants in Normative Aging Study (NAS)	Increasing $PM_{2.5}$ concentration is associated with increasing risk of metabolic syndrome, fasting glucose level and hypertriglyceridemia	(Wallwork, et al., 2017)

Molecular Target	Pollutant	Experimental Model	Experimental Findings	Reference
	$PM_{2.5}$	10 Article database analysis	Association of PM and incidence of T2DM	(He, et al., 2017)
	$PM_{2.5}$	Six-week-old male C57BL/6 mice	↑Protein kinase C, ↓ Akt phosphorylation and endothelial nitric oxide synthase (eNOS)	(Sun, et al., 2009)
	$PM_{2.5}$	Sprague Dawley rats	↑ Inflammation *via* TLR2/4, ↑ weight gain and metabolic dysfunction	(Wei, et al., 2016)

Table 2.

Therapeutic strategies for preventing air-contaminant-associated cardiovascular disease.

Molecular Target	Therapeutic	Experimental Model	Experimental Findings	Reference(s)
Oxidative stress	Dietary antioxidants	Randomized trial in 5442 women	↓Relative risk of myocardial infarction, stroke, CVD mortality and plasma level of homocysteine	(Albert, et al., 2008)
	Carnosine (1 mg/mL in drinking water for 16 d)	C57BL/6 mice	↓ Endothelial progenitor cells after CAP exposure	(Abplanalp, et al., 2019)
	Selenium (70 μg/kg for 28 d)	Male Sprague Dawley rats	↑ Antioxidant biomarkers, ↓oxidative and inflammatory markers such as oxidized lipids, sICAM-1, TNF-α and IL-1β.	(Zeng, et al., 2018)
	Mediterranean diet	Prospective cohort: NIH-American Association for Retired Persons Diet and Health Study	↓ Incidence of CVD, ischemic heart disease mortality for higher Mediterranean Diet Index score	(Lim, et al., 2019)
	Flavonoids (50 μM)	Human RPE cells	↑ Mitochondrial function, cell viability, ↓ Caspase 3 and caveolin-1	(Kook, et al., 2008)
	(10 μM)	Primary endothelial cells	↓ CYP1A1, VCAM-1, E-selectin, P-selectin, and caveolin-1.	(Choi, et al., 2010)
	(15 μM)	Human endothelial cells (EA. hy926)	Hypoacetylation of H3, ↓ nuclear import of p65, IL-6, CRP, ICAM-1, VCAM-1 IL-1α/β	(D. Liu, et al., 2016)
	Red wine (40 mg/kg/d for 33 d)	Spontaneously hypertensive rats	↓ Caveolin-1, ↓NADPH oxidase $p22^{phox}$ and $p47^{phox}$. ↑relaxation of vessels and ↓ BP	(López-Sepúlveda, et al., 2008)
Pulmonary and systemic inflammation	Dietary carotenoids and vitamin E	Longitudinal Study of Scottish postmenopausal women	↓ Inflammatory biomarkers such as hs-CRP, IL-6 associated with serum carotenoid and vitamin E.	(Wood, et al., 2014)
	Omega-3 fatty acids (3 mg/kg for 14 d)	Sprague Dawley rats	↓ TNF-α, IL-1β, IL-6 and ↑ antioxidant activity.	(Du, et al., 2017)
	Dietary antioxidants, including omega-3 fatty acids	Cross-sectional study	↑ Lung function correlated with ↑omega-3 fatty acids and antioxidants	(Ng, et al., 2014)
	Moderate alcohol consumption	SWAN cohort of women	↓ CRP level in blood	(Ostro, et al., 2014)
Other inflammatory or miRNA targeting CVD	Polyphenols (25 mg/kg/d for 28 d)	Pulmonary arterial smooth muscle cells of adult male Wister rats	Promotes vascular remodeling regulating *via* miR-638 through NR4A3/cyclin D1 pathway	(Y.-y. Liu, et al., 2020)
	Resveratrol (0.2 g/kg for 2 wk)	Male Sprague Dawley rats	↓ CYP1BI and cardiotoxic HETE levels, ↑ cardiac function.	(Matsumura, et al., 2018)
	Extra virgin olive oil (3 g/d for 28 d)	42 Human volunteers exposed to CAP	↑ endothelial function, ↓vasoconstriction ↓inflammation and fibrinolysis	(Tong, et al., 2015)
Metabolic dysfunction	Metformin (200 mg/kg/d for 4 wk)	Male C57BL/6 mice	↓ CS-neurotoxicity by ↓inflammation and oxidative stress at the BBB and restoring tight junction protein expression	(Prasad, et al., 2017)
	Metformin (150 mg/kg/d for 4 d)	C57BL/6J mice and human alveolar macrophages	↓ PM-mediated mitochondrial ROS and release of IL-6, ↓ PM-induced arterial thrombosis.	(Soberanes, et al., 2019)
	Metformin (300 mg/kg/d for 4 wk)	C57BL/6J and $AMPK\alpha2^{-/-}$ mice	Independent to AMPKα2, ↓ PM-induced cell death and oxidative stress, ↓ pulmonary and systemic inflammation, ↑cardiac function & mitochondrial antioxidants, ↓ fibrosis.	(J. Gao, et al., 2020)

Molecular Target	Therapeutic	Experimental Model	Experimental Findings	Reference(s)
	Metformin (300 mg/kg/d for 11 d)	Male C57/BL6 mice	↓ CAP-induced vascular insulin resistance and vascular inflammation	(Haberzettl, et al., 2016)
	Statins (1 μM)	SH-SY5Y human neuroblastoma cells	↓ PM-induced neurotoxicity by ↑Nrf2 antioxidant defense system.	(Ferraro, et al., 2016)
	(5 mg/kg/d for 4 wk)	Male New Zealand White rabbits	↓ Intimal macrophages and lipids, ↑ recruitment of smooth muscle cells within plaques, ↓ atherosclerosis and ↑ endothelial function.	(Miyata, et al., 2013)
	(5 mg/kg/d for 4 wk)	Female New Zealand White rabbits	↓ Inflammatory cytokines and recruitment of PMN in lungs	(Miyata, et al., 2012)
Autonomic dysfunction	Melatonin (5 mg/kg/d for 7 d)	Sprague Dawley rats	↓ Inflammatory markers and ↑ eNOS expression.	(Yang, et al., 2014)
	Melatonin (10 mg/kg/d for 28 d)	Male Hartley guinea pigs	↓ activation of TRPM2 and oxidative stress	(Ji, et al 2018)