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Effects of Ambient Particulate Matter on Vascular Tissue: a Review

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Abstract

Fine and ultra-fine particulate matter (PM) are major constituents of urban air pollution and recognized risk factors for cardiovascular diseases. This review examined the effects of PM exposure on vascular tissue. Specific mechanisms by which PM affects the vasculature include inflammation, oxidative stress, actions on vascular tone and vasomotor responses, as well as atherosclerotic plaque formation. Further, there appears to be a greater PM exposure effect on susceptible individuals with pre-existing cardiovascular conditions.

Keywords

particulate matter; air pollution; lungs; vascular tissue; endothelial cells; inflammation; vascular tone; oxidative stress; atherosclerotic plaque

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Authors' contributions

KS performed literature search and contributed to writing and revision of the manuscript. KLF, MC, AP performed section specific literature searches and contributed to writing parts and revising the manuscript. GB, HB, QL performed literature searches and helped with tables and figures preparations. TEM and CS contributed to manuscript revisions and critical comments and edits. WJM contributed to manuscript writing, revision, editing and critical assessment. All authors read and approved the final manuscript.

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Introduction

The 2004 American Heart Association statement and subsequent 2010 update on “Air Pollution and Cardiovascular Disease” concluded that air pollution exposure contributes to cardiovascular morbidity and mortality (Brook et al. 2004; 2010; Cohen et al. 2017). Short-term exposure to particulate matter (PM) immediately impacts cardiovascular health and long-term exposure reduces life expectancy by months to years (Brook et al. 2010; Chen et al. 2019). PM smaller than 10 μm in diameter (PM_{10}) and fine PM ($PM_{2.5}$ or smaller than 2.5 μm) are major constituents of urban air pollution and recognized as risk factors for mortality (Tsai et al. 2014; Pinichka et al. 2017; Burnett et al. 2018; Landrigan et al. 2018; Initiative 2019). Studies over a broad range of geographical regions indicate that each 10μg/m^3 rise in ambient fine particulate matter ($PM_{2.5}$) concentrations increases daily mortality rates by approximately 1–5% (Pope et al. 2002, Vodonos et al. 2018; Burnett et al. 2018; Initiative 2019; Lelieveld et al. 2019). The size and composition of PM, including water soluble inorganic ions such as sulfate, nitrate, ammonium, sodium, water insoluble particles such as black carbon, redox active trace elements and metals including copper, vanadium, chromium, manganese, iron and nickel, as well as organic compounds such as polycyclic aromatic hydrocarbons (PAHs), were shown to influence its potential toxicity (Schroeder et al. 1987, See et al. 2007, Zou et al. 2016, Forman and Finch 2018).

Although debate exists as to whether PM produces vascular dysfunction via direct particulate entry into the systemic circulation, or through release of mediators into the bloodstream via affected lung tissue (Donaldson et al. 2001, Utell et al. 2006; Robertson et al. 2012), defining potential modes and routes of PM entry is beyond the scope of this review. This article examines the current experimental and clinical literature to provide a comprehensive review focused on the effects of air pollution, specifically PM, on vascular inflammation, vessel tone, reactive oxygen species (ROS) generation, and atherosclerotic plaque formation (Figure 1 for visual depiction). A clear understanding of these relationships may help identify at-risk populations and determine targets for future interventions and/ or treatments.

Methods

A keyword search of recent PubMed articles published between 2000 and 2020 was performed. The literature search rationale included published review articles that focused on: 1)global overviews of epidemiological and population studies relating PM effect to cardiovascular morbidity and mortality; 2) effects of air pollution constituents on cardiovascular health; 3) review studies that examine the negative effects of PM exposure on cardiac tissue, brain, and other organs; 4) reviews that provide an overview of the inflammatory, oxidative, vasoconstrictive, and atherosclerotic mechanisms of PM effects in the setting of cardiovascular disease. In addition, the literature search included original research articles that examined the relationship between air pollution and the following vascular processes: inflammation, vascular tone, oxidative stress, and atherosclerotic plaque formation (Table 1 for literature search terms used). Titles, abstracts, and full-text articles of potentially relevant studies were screened at different stages of the literature search (flow chart of literature search presented in Figure 2).

Study selection criteria

This review includes investigations that used *in-vitro* cell cultures of animal and human origins, animal subjects, healthy participants, and patients with relevant medical conditions. Study selection was not limited by age or gender. Studies with experimental exposures derived from ambient, vehicular, or combustion-related sources were included. Investigations that used cigarette smoke as exposure were excluded. Studies examining the effects of air pollution on carotid arteries, aorta, coronary arteries, arteries of the lung, cerebral arteries, and umbilical cord veins were considered for this review. The literature regarding systemic inflammation and circulating factors was included only when vascular effects were incorporated as outcomes. Selection of outcome variables was not limited. Eligible study designs included experimental research, clinical trials, epidemiology/ population studies, and crossover investigations. The literature search was not limited by study sample size or the impact factor of the study journal. Only articles written in English were included. The following data was extracted from each investigation: first author and publication year, study design, exposure type, sample size, sample characteristics, outcome measures, and study findings.

Survey of current vascular/cardiovascular published reviews: existing data and knowledge gaps (Table 2)

Over 50 published literature reviews describe the effects of air pollution on cardiovascular health and disease which are referenced in Table 2. The papers in Table 2 Section A provide global overviews of the epidemiological and population studies relating PM effect to cardiovascular morbidity and mortality. Reviews in Table 2 Section B examine the effects of air pollution constituents on cardiovascular health. Table 2 sections C-E reviews provide an overview of the distinct mechanisms of PM effects in the setting of cardiovascular disease. These mechanisms include inflammation (See Table 2 Section C), oxidative stress and vasoconstriction (See Table 2 Section D), and atherosclerosis (See Table 2 Section E). Table 2 Section F includes a large number of review studies that examine the adverse effects of PM exposure on cardiac tissue, brain, and other organs.

Although prior review articles described the effects of PM with respect to cardiovascular diseases, this review is unique in its reporting and analysis of recent evidence supporting a link between PM exposure and cardiovascular diseases attributed to actions specifically on vascular tissue. Several other reviews described inflammatory, oxidative, and atherosclerotic processes in vascular tissue associated with PM exposure, however the evidence is not from recent studies (Table 2 Section G). A more current single review by Rajagopala et al (2018) provides an overview of these processes in the context of cardioembolic and autonomic nervous system pathogenesis; however, an in-depth focus on vascular mechanisms was not the purpose of this paper. No apparent prior reviews focused exclusively on vascular tissue. The current review provides a detailed report and analysis of endothelium-specific inflammatory, vasomotor, oxidative, and atherosclerotic effects of air pollution, specifically fine and ultrafine PM. In addition, this review addresses the susceptibility of individuals with underlying cardiovascular conditions to adverse effects of PM from a vascular perspective.

Effect of particular matter on vascular inflammation (Table 3, Figure 1)

Experimental models

Vascular endothelium, which mediates vasodilation, inflammation, and platelet aggregation, is susceptible to the effects of PM (Saura et al. 2006, Knuckles et al. 2008, Cherng et al. 2011) It has long been recognized that systemic inflammation results in vascular endothelial dysfunction and triggers cardiovascular events (Scapellato and Lotti 2007). In rats, administration of intratracheal $PM_{2.5}$ (3.2 mg/rat dose) twice a week for three weeks resulted in a 50% increase in plasma C-reactive protein (CRP) levels and a 20% elevation in plasma endothelin-1 levels (Wang et al. 2013). Following murine diesel exhaust particle (DEP) inhalation, pro-inflammatory cytokines were upregulated in the lungs (66% increase in tumor necrosis factor-alpha (TNF-α), 127% rise in interleukin-6 (IL-6), and 87% elevation in IL-13 over controls). In addition to observed inflammation in the lungs, apoptosis of endothelial cells on the pulmonary artery was observed by a 450% increase in α -smooth muscle actin (α -SMA - marker of apoptosis) in TUNEL assays (estimated from graph data) (Liu et al. 2018). Although experimental evidence supports PM exposure-induced endothelial inflammation, significant variability exists between studies. Rats exposed to 2-weeks of $PM_{2.5}$ via inhalation exhibited decreased endothelial nitric oxide synthase (eNOS) expression with elevated TNF-α protein expression in pulmonary arteries. However, no marked changes were detected in systemic inflammatory markers, including plasma blood cell count, cytokine levels, and coagulation factors (Davel et al. 2012). These inconsistencies may relate to variation in animal age, exposure duration and/ or unique assay kits produced by different manufacturers (Wang et al. 2013). Further, variations in data exist based upon mouse strain and underlying genetic differences.

In-vitro cell culture studies also demonstrate the effects of particulate exposure on vascular inflammation. Primary human coronary artery endothelial cells (hCAECs) treated with blood plasma obtained from humans before and after exposure to 100 $\mu g/m^3$ DEP or filtered air for 2 hr displayed 20% elevations in levels of vascular cellular adhesion molecule 1 (VCAM-1), and 10% rise in IL-8 following DEP exposure (Channell et al. 2012). In the same model, genomic analysis of hCAEC culture exposed to the plasma of subjects after DEP inhalation confirmed upregulation of inflammatory pathways related to ligand-receptor interactions directly on endothelial cells (Schisler et al., 2015). Two additional studies (Kristovich et al., 2004; Lee et al. 2012) demonstrated that *in-vitro* endothelial cell activation increased ICAM-1 (300% in both studies) and VCAM-1 (1000% and 230%, respectively) expression following administration of peripheral blood monocytes exposed to DEP through NFk-b activation. hCAEC methodologies allow for identification of receptors, ligands and mechanistic pathways that mitigate endothelial cell responses. However, *in-vitro* approaches often do not use inhalation/aerosol exposure for PM delivery, which may affect mechanisms of PM translocation into the system.

The relationship between systemic inflammation and cytokine expression is complicated not only by experimental design but also by heterogeneity in the inflammatory time course and PM dose effects. A single intratracheal dose of $PM_{2.5}$ administration in rats resulted in a marked 1000% increase in BALF protein levels of IL-6 expression in pulmonary arteries

despite no observed changes in BALF protein levels of CRP and TNF-α 6 hr after treatment. However, roughly 400% rise in plasma TNF-α and 200% rise in plasma IL-6 blood concentrations were noted at 24 hr after exposure when compared to 6 hr (estimated from graph data) (Robertson, Gray et al. 2012). Guo et al (2012) exposed Wistar rats to aerosolized PM_{10} at different concentrations (0.3,1, 3 or 10 mg/kg) for 15 days. Plasma endothelin-1 was elevated at all concentrations of PM_{10} (1.55, 1.62, 1.67, and 1.7 over controls for each concentration, respectively), and mRNA levels of IL-1 and ICAM-1 were increased at the 3mg/kg exposure dose (127 and 245% respectively compared to controls). Data suggest that PM exposure produced delayed systemic inflammation following the pulmonary response and overall inflammatory profile is dose dependent.

The precise inflammatory mechanisms resulting from PM exposure remain unclear. Experimental evidence suggests parallel endothelial dysfunction from inflammatory substrates and blood brain barrier (BBB) disruption. In particular, activation of the nitric oxide pathways through uncoupling of the endothelial nitric oxide enzyme and subsequent reduction in local expression of nitrogen oxide in the vascular endothelium is associated with reduction in tight junction protein expression (Saura et al., 2006). Mice exposed to mixed vehicle (gasoline and diesel engine) exhaust for 30 days were injected with the molecular tracer, sodium fluorescein, on the final day of exposure. Elevated levels of inflammatory biomarkers (iNOS by 300% and IL-1b by 200%) in cerebral tissue and arteries correlated with decreased levels of tight junction proteins, including a 200% fall in occludin and claudin-5. Elevated endothelial monolayer tracer transfer suggestive of a leaky BBB was observed in mice exposed to vehicle exhaust (Oppenheim et al. 2013). These findings indicated that vehicular pollutants might increase inflammation and endothelial monolayer permeability of peripheral vessels through modification of intracellular gaps and alterations in protein structure of endothelial tight junctions. Evidence suggests that PM-induced endothelial cell and vascular flow changes are multifactorial, which contribute to systemic inflammatory responses through circulating plasma proteins, decreased vascular tone, changes in endothelial cell dynamics, and BBB alterations.

Clinical Studies

Studies of healthy human subjects demonstrated changes in inflammatory biomarkers following air pollution exposure. Blood CRP levels are used clinically as an indicator of the presence and intensity of inflammation and were directly linked to cardiovascular health. In a longitudinal women's health study, CRP was a reliable predictor of future cardiovascular events. This association was present in subgroups of women with no history of hyperlipidemia, hypertension, smoking, diabetes, or family history of coronary artery disease (CAD) (Mehta et al 2015). Blood CRP levels exhibit strong associations with PM exposure. Analysis of a German population-based cohort study of 4814 participants demonstrated that a 2.4μg/m^3 increase in daily surface concentration of PM_{10} and $PM_{2.5}$ was associated with a 5.4% elevation in plasma CRP (Viehmann et al. 2015). Similarly, in the Longitudinal Study of Women's Health Across the Nation (2086 women), plasma CRP rose 21% per 10μg/m^3 increase in $PM_{2.5}$ (Green et al. 2016). Further, prolonged exposure to PM when residing in close proximity to a busy road (> 10,000 vehicles per day) was associated with a 10% elevation in blood CRP levels compared to living on a quiet, residential road

(<1000 vehicles per day), as illustrated in a cross-sectional cohort study of 22,561 adults from Central and Northern Europe (Lanki et al. 2015). However, other investigators noted that the correlations between CRP and PM exposure are not straightforward. Hoffmann et al (2009) reported association between CRP levels and annual PM exposure lost significance after adjusting for daily PM exposure levels. This suggests that short-term variations in daily PM levels may impact long term PM-mediated effects.

To evaluate temporal effects of air pollution on inflammatory cytokines, a study of 2360 participants from a diverse Japanese population (participants aged 20 and above from 300 randomly selected districts from all 47 prefectures in Japan) examined short- and long-term effects of background concentration of suspended PM on serum CRP and WBC count (Michikawa et al. 2016). On the day of blood draw, high background concentrations of suspended particulate matter (sPM) and gaseous co-pollutant concentrations were associated with elevated serum WBC counts (113%), while 1-month average sPM concentrations were correlated with increased serum CRP levels (142%). Rich et al (2012) studied 125 healthy adults over the period of the Beijing Olympic Games and concluded that CRP blood levels diminished from 55% during the pre-Olympic period (high pollutant levels) to 46% during the Olympic games, when pollutant levels were strictly controlled. Similarly, Chuang et al. (2007) examined 76 healthy young non-smokers in China and found that variations in 1 and 3 day PM_{10} exposure levels associated with changes in CRP blood concentrations. However, in 40 healthy volunteers recruited in the Netherlands, 13 consecutive CPR blood measurements throughout 1 year were not correlated with 1 to 4-day changes in PM exposure levels (Rudez et al. 2009). Differences in exposure location, levels, and assessment accuracy need to be taken into account when interpreting clinical studies on PM exposure. It is clear that CRP is a key factor in PM-induced inflammatory responses. Blood CRP levels display more robust elevation trends in longer term studies, while short duration exposures with variable PM levels may not be sufficient to stimulate discernable CRP responses (Johannesson et al. 2014).

Blood samples from healthy human subjects exposed to 50 $\mu g/m^3$ of $PM_{2.5}$ over a 3-day period revealed elevations in circulating endothelial apoptosis microparticles (CD14, CD16, CD8, CD4) and T lymphocytes (Pope et al. 2016). With a 10 $\mu g/m^3$ incremental rise in $PM_{2.5}$ concentration there was an associated elevation in plasma endothelial adhesion molecules sICAM-1 and sVCAM-1. Further, a 5 $\mu g/m^3$ increase in long-term ambient $PM_{2.5}$ was associated with 6% higher IL-6 levels (Pope et al. 2016). In an analysis of participants in the population based CoLaus Swiss cohort study, short-term PM_{10} exposure (day of visit) induced significant effects on circulating inflammatory markers (van Eeden et al. 2001, Tsai et al. 2012). For every 10 $\mu g/m^3$ elevation in PM_{10}, IL-1β levels increased by 0.034 pg/mL, IL-6 by 0.036 pg/mL, and TNF-α by 0.024 pg/mL in the blood. In contrast, a study of healthy subjects exposed to particle-rich ($PM_{10–2.5}$ and $PM_{2.5}$) air while biking (cross-over study) demonstrated no significant differences in blood inflammatory biomarkers (CRP, fibrinogen, IL-6, TNF-α, lag time to copper-induced oxidation of plasma lipids and protein oxidation measured as 2-aminoadipic semialdehyde in plasma) compared to trials in which subjects were exposed to particle filtered air (Brauner et al. 2008).

Specific elemental PM components may directly influence levels of inflammatory mediators. Niu et al (2013) examined $PM_{2.5}$ levels in Jinchang and Zhangye, China and noted personal and daily exposure levels along with concentrations of inflammatory biomarkers in female residents of each city. Data demonstrated $PM_{2.5}$ levels to be comparable between the cities (47.4 and 54.5μg/m^3, respectively), but nickel (8200%), copper (2600%), arsenic (1200%) and selenium (600%) levels to be higher in Jinchang. Plasma concentrations of CRP (3.44±3.46 vs. 1.55±1.13), IL-6 (1.65±1.17 vs. 1.09±0.60), and vascular endothelial growth factor (117.6±217.0 vs. 22.7±21.3) were significantly elevated in the Jinchang population, suggesting a relationship between elemental PM components and inflammation (Niu et al. 2013). Long-term exposure to transitional metals within ambient PM was associated with elevated inflammatory blood markers [5 ng/m^3 increases in $PM_{2.5}$ copper and 500 ng/m^3 rise in PM_{10} iron associated with 6.3% and 3.6% elevation in hs-CRP, respectively]. Ten ng/m^3 increases in $PM_{2.5}$ zinc was associated with a 1.2% rise in hs-CRP (Hampel, Peters et al. 2015) (Table 2a).

There appears to be a more robust PM exposure effect in susceptible individuals or those with pre-existing cardiovascular conditions. Lee et al (2014) demonstrated that $PM_{2.5}$ exposure is associated with increased heart rate and reduced heart rate variability in adults living in urban settings with preexisting systemic inflammation. An interquartile range rise in $PM_{2.5}$ (13.6 μg/m^3) was correlated with a reduction in standard deviation of night-time normal to normal heart rate intervals (8.4%, marker of autonomic function). Significantly greater decrease was noted in individuals with elevated blood WBC, platelet counts, serum CRP, plasma fibrinogen, and urinary 8-hydroxy-2-deoxyguanosine (8-OHdG) (Lee et al. 2014). In a nationally representative sample of 16,160 individuals in the United States with air pollution data modeled according to zip code, there were no significant relationships between higher $PM_{2.5}$ concentration (mean 11.88 SD±0.37) and inflammatory biomarkers (blood CRP and WBC) in healthy subjects. However, in subgroups of individuals with CAD or diabetes there were positive correlations between $PM_{2.5}$ levels and blood CRP and WBC values (Dabass et al. 2016). Similarly, in a study of 56 non-smoking subjects with CAD residing in an urban area in Germany, increased traffic-related and combustion generated PM_{10} and $PM_{2.5}$ were associated with elevated plasma CRP levels (Yue et al. 2007). In a study of 52 patients with ischemic heart disease in Finland, $PM_{2.5}$ exposure from traffic and biomass combustion sources was correlated with elevated blood CRP levels (Siponen et al. 2015). In the same cohort, personal photometer measures of PM exposure correlated with plasma CRP and IL-12 levels (Huttunen et al. 2012).

Patients with glucose intolerance and diabetes mellitus (DM) are also vulnerable to the adverse effects of air pollution (Li et al 2018). A study of 2944 patients with DM demonstrated an association between traffic-related air pollution (PM_{10}, $PM_{2.5}$, and NO_2) and increased insulin (14.5%) (Wolf et al. 2016). In a cohort of 92 diabetic patients, changes in daily ambient levels of $PM_{2.5}$ correlated with changes in plasma concentrations of ICAM-1 and VCAM-1. (O'Neill et al. 2007) Traffic-related air pollution exposure based upon geocoded address location in 642 elderly non-smoking individuals demonstrated that for averages of 4-, 8-, and 12-week exposures, black carbon levels (estimated by land use regression) were associated with elevated soluble plasma ICAM-1 concentrations. An interquartile range rise in 8-week black carbon exposure was associated with a 1.58%

elevation in plasma ICAM-1. Subgroup analysis indicated that $PM_{2.5}$ exposure exerted greater effects (interaction) on plasma ICAM-1 concentrations in diabetic individuals (Alexeeff et al. 2011). Krishnan et al (2013) conducted a cross-over study of 17 metabolic syndrome patients and 15 controls, in which subjects inhaled DEP or filtered air for two hr and then crossed over to the other exposure following a 2-week washout period. There was an increase in matrix metalloproteinase (MMP)-9, IL-10, and IL-1b in patients with metabolic syndrome 7 and 22 hr post-inhalation of DEP. Data suggest that while DM and glucose intolerance are independently associated with vascular inflammation (Wang et al. 2018); PM susceptibility may contribute to further vascular risk (Rask-Madsen and King 2013). Overall, epidemiological studies support an association between vascular diseases and both short-term spikes in PM levels as well as prolonged exposure to PM in urban settings. (See Table 2b). Although there is a large body of literature available on PM and vascular health, it is difficult to determine a precise mechanism of action due to the large number of associated inflammatory mediators and their complex interactions. Moreover, variability in individual exposure levels and PM compositions makes it particularly challenging to draw overarching conclusions from diverse PM exposure studies.

Effect of Particulate Matter on Vascular Tone (Table 4, Figure 1)

Experiential Models

Vascular tone is regulated by both endothelial derived factors and smooth muscle. The vasodilatory effects attributed to PM exposure may be mediated by widespread endothelial dysfunction (Mirowsky et al. 2017). Sprague-Dawley rats exposed to TiO2 nano-particulates showed impairment of endothelium-dependent vasodilation in subepicardial coronary arterioles as evidenced by increases in spontaneous tone and blunted responses to flow-, acetyl choline (AcH) -, and Ca+-ionophore- induced vasodilation (LeBlanc et al. 2009). In another study Tamagawa et al. (2008) exposed male Wistar rats to 16 weeks of DE and reported increased levels of mRNA biomarker of endothelin-1, endothelin receptors A and B, and endothelial NO synthase in the aorta. Although no changes were observed in the heart ventricles following the same exposure, PM exposure through DE resulted in impairments of vascular tone. In addition, carotid arteries from white rabbits exposed to acute (5 days) or chronic (4 week) intratracheal PM_{10} demonstrated decreased endothelial-dependent AcH-mediated relaxation of the carotid artery by 34%, with no marked effect on endothelial-independent sodium nitroprusside(SNP)-mediated vasoconstriction (Tamagawa et al. 2008). In rats exposed to intratracheal administration of TiO2 or residual oil fly ash (average diameter 2.2um), Nurkiewicz et al (2004) demonstrated impairment in Ca^{2+} ionophore-induced endothelial-dependent arteriolar dilation in the spinotrapezius muscle, indicative of systemic microvascular dysfunction. Evidence indicates that the robust inflammatory response and endothelial activation following PM exposure may play a critical role in arterial stiffening (Zanoli et al. 2017).

Clinical Studies

Clinical studies in healthy adults suggest exposure to air pollution derived PM and subsequent arterial inflammation initiate dysregulated vasoconstriction (Louwies et al. 2013). Louwies et al (2013) demonstrated that each $10\mu g/m^3$ increase in PM_{10} exposure

(averaged over the 24 hr prior to examination) was associated with a 0.93μm decrease in central retinal artery diameter. Inhalation of concentrated ambient fine particles (CAP; 150 μg /m^3) plus ozone (120 ppb) produced significant brachial artery vasoconstriction (1100%, measured by diameter) compared to inhalation of filtered air (Brook et al. 2002). In a controlled exposure study, Wauters et al. (2015) found that healthy adults exposed to DE concentration of 300 μg/m^3 for 2 hr exhibited a 40% elevation (as estimated from the raw data presented in study tables) in pulmonary vasomotor tone when undergoing stress tests An investigation that measured arterial stiffness in 12 healthy volunteers exposed to 350 μg /m^3 DE or filtered air for one hr during moderate exercise found that acute exposure resulted in an immediate and transient rise in arterial stiffness (2.5 mmHg increase in arterial augmentation pressure and 7.8% elevation in augmentation index) (Lundback et al. 2009). Further, increased ambient NO2 and SO2 levels were associated with accelerated arterial-wall stiffening in young adults, as indicated by a 4.1% rise in pulse wave velocity and a 37.6% elevation in vascular augmentation index (Lenters et al. 2010). Short-term exposure studies indicate that alterations in vascular diameter as well as secondary markers of vascular tone closely follow PM concentration changes, which may play an important role in cardiovascular diseases such as hypertension. PM might interrupt vascular homeostasis through pro-inflammatory changes in the vascular wall, reducing endothelial dilatory capacity.

Vascular reactivity and arterial stiffness may occur in a time and dose dependent manner following PM exposure. Peretz et al (2008) demonstrated that healthy adults exposed to 200 μg/m^3 DE for 2 hr exhibited decreased brachial artery diameters and increased plasma levels of endothelin-1 compared to adults exposed to only 100 μg /m^3 DE or filtered air. Exposure to elevated levels of ambient $PM_{2.5}$ was associated with a lower reactive hyperemia-peripheral arterial tonometry ratio in healthy young adults. However, no marked change was seen after acute 3 hr experimental exposure to combustion generated $PM_{2.5}$. Findings suggest that prolonged exposure times are necessary to produce clinically significant results in healthy populations (Pope et al. 2011). Rundell et al (2007) exposed 16 healthy athletes to low number (inner campus location, 5309±1,942 particles cm^{-3}) or high number (near major highway, 143,501±58,565 particles cm^{-3}) PM_1 concentrations during exercise. Flow-mediated brachial artery dilation (FMD) and forearm oxygen kinetics were measured before and after exercise. Significant vasoconstriction of brachial artery diameter (4% change) was found after exercise in high PM_1, but not low PM_1 concentrations (Rundell et al. 2007).

The decreased vascular compliance seen in conditions of PM exposure may be the consequence of a muted response to vasodilators. Brook et al (2002) noted in short-term exposure to CAP and ozone a resultant arterial vasoconstriction occurred without effects on endothelial-dependent flow-mediated vasodilation or endothelial-independent nitroglycerin-mediated vasodilation in healthy adults. However, Briet et al (2007) implicated PM in endothelial dysfunction where exposure to ambient nitrogen, sulfur, and carbon oxides, as well as $PM_{2.5}$ and PM_{10} produced impairment of both large and small artery vasodilation, as evidenced by brachial artery endothelium-dependent flow-mediated dilatation and reactive hyperemia, respectively. There was no correlation with endothelium-independent glyceryl trinitrate dilatation of the brachial artery (Briet et al. 2007). One-hr exposure to dilute DE (300 μg /m^3) in healthy individuals initiated reduction in vascular tone and endogenous

fibrinolysis, with diminished responses to vasodilators and decreased release of tissue plasminogen activator (Mills et al. 2005). Inhalation of DE by healthy volunteers during exercise impairs the vasodilatory response to bradykinin, AcH, and SNP in forearm vessels. This impaired response to AcH-induced endothelial-dependent vasodilation in forearm vessels appears to persist for at least 24 hr after exposure (Tornqvist et al. 2007). In addition, healthy males exposed to 1 hr 250 μg /m^3 DEP exhibited attenuated calcium channel-dependent vasodilation within 6 hr treatment (Barath et al. 2010). The previously described microvascular changes may be vessel specific or markers of more widespread cardiovascular disease, such as hypertension, in which vascular tone plays in important role. Taken together, researchers examining the effects of PM induced vasoconstriction suggest primary involvement of endothelial-dependent mechanisms with select investigations demonstrating the presence of endothelial-independent activation. The dose and time dependent manner by which PM activates the smooth muscle response and triggers endothelial dysfunction may play a role in the observed variation.

Those with underlying cardiovascular disease or risk factors may be vulnerable to the adverse effects of PM exposure on vascular tone, even at low levels. O'Neill et al (2005) suggested that ambient levels of $PM_{2.5}$, black carbon, sulfates, and particle number were associated with decreased flow-mediated vascular wall reactivity (measured by percent brachial artery diameter change) in diabetic patients, but not individuals at risk. $PM_{2.5}$ was correlated with nitroglycerin-mediated reactivity (−7.6%). Type I diabetes conferred greater vulnerability than type II diabetes (O'Neill et al. 2005). Similarly, Frampton (2006) attributed changes in heart rate variability in cardiovascular patients to endothelial activation and/ or vasoconstriction in the systemic circulation. Investigations on vascular tone suggest that PM promotes vasoconstriction in both healthy and diseased individuals by endothelial inflammation which, in turn, affects smooth muscle cell interactions and promotes dysregulation of vascular tone.

Effects of Particulate Matter on Oxidative Stress (Table 5, Figure 1)

Experimental Studies

Reactive oxygen species produce endothelial cell apoptosis and promote monocyte adhesion through expression of VCAM-1 and ICAM-1 (Cook-Mills et al. 2011). Further, ROS impair endothelium-dependent vasorelaxation by inactivating nitric oxide (NO) (Meza et al. 2019). Miller et al (2009) demonstrated that aortic rings from rats exposed to DE exhibited an impaired response to AcH-induced endothelial-dependent vasorelaxation. Diesel exhaust particle exposure resulted in an oxidative stress response characterized by a 900% increase in oxygen free radicals (at 10 μg/ml DE) and a 36% decrease in NO (at 100 μg/ml DE).High DE exposure concentrations were used in this model, which may exaggerate the effects of DE on vascular tissue. ROS are known to induce both vascular smooth muscle cell (VSMC) apoptosis and proliferation and play an important role in VSMC migration (Taniyama and Griendling 2003). Gurgueira et al. (2002) exposed Sprague-Dawley rats to CAPs and reported significant oxidative stress levels in lung and heart tissues, determined as *in situ* chemiluminescence accompanied by 200% increases in lactate dehydrogenase (LDH). CAP exposure was also found to produce a tissue-specific activation of superoxide dismutase

(SOD) and catalase (CAT). PM leads to generation of ROS but also activates mechanisms that mitigate their detrimental effects (Gurgueira et al. 2002).

Isolated rat brain capillaries exposed to DEP displayed a concentration-dependent increase in P-glycoprotein, an efflux transporter and key BBB mediator. Pretreatment of the capillaries with radical scavengers counters P-glycoprotein upregulation (Hartz et al. 2008). Hartz et al. (2008) suggested that PM may gain access to other organ systems in a similar manner: a marked elevation in vascular permeability was noted in human lung endothelium following traffic-generated PM (aerodynamic diameter 0.1–0.3 μm) exposure. The change in vascular integrity was attributed to ROS. Generation of ROS following PM exposure not only induces tight junction protein relocation from the cell periphery, but also leads to activation of the calcium-dependent caplain protease, which results in tight junction degradation and endothelial cell barrier disruption (Wang et al. 2012).

Sun et al (2008b) performed experiments in which Sprague-Dawley rats were exposed to $PM_{2.5}$ or filtered air for 10 weeks and angiotensin-II was introduced during the final week of treatment in order to induce hypertension. The aortas of $PM_{2.5}$ exposed animals showed 220% increased superoxide production accompanied by elevated NADPH oxidase expression in the smooth muscle cells. While $PM_{2.5}$ itself did not markedly affect mean arterial pressure (MAP), these particles potentiated the effect of angiotensin-II by sensitizing the vasculature (Sun et al. 2008). In the same experiment model, data demonstrated that $PM_{2.5}$-induced ROS production activated the Rho/ROCK pathway which increases vascular tone through Ca++ sensitization (Sun et al. 2008).

Human pulmonary artery endothelial cells are damaged by DE particle extracts through generation of oxygen-derived free radicals and NO (Bai et al. 2001). A similar effect was noted at the level of the microvasculature, Sprague-Dawley rats exposed to intratracheal instillation of residual oil fly ash with an average diameter of 2.2μm exhibited a rise in markers of leukocyte rolling and adhesion in the microvascular wall, accompanied by reduction in endothelium-dependent arteriolar dilation in the spinotrapezius muscle microvessels (Nurkiewicz et al. 2006). Wauters et al (2013) incubated human umbilical vein endothelial cells with the serum of healthy volunteers exposed to $PM_{2.5}$ DE and found that enhanced ROS production correlated with total inhaled $PM_{2.5}$ exposure. Acute experimental exposure to DE $PM_{2.5}$ impaired AcH-induced vasodilation in skin microvasculature of healthy adults (Wauters et al. 2013). This investigation used a male-only cohort with a small sample size (n=12), limiting the generalizability of its results.

Clinical Studies

In elderly Los Angeles residents, elevated markers of airway inflammation (FeNO) and oxidative stress (malondialdehyde (MDA)) were associated with $PM_{0.18}$, transition metals, and traffic-derived air pollutants, including black carbon (BC), carbon monoxide (CO), and nitrogen oxides (NOx) (Zhang et al 2016a). Reactive hyperemia index was inversely correlated with ambient $PM_{2.5}$, BC, NOx, and CO. Zhang et al (2016b), in a similar cohort, detected altered microvascular endothelial function, characterized by the reactive hyperemia index of the brachial artery inversely associated with traffic related pollutant exposure ($PM_{2.5}$, BC, NOx, CO) and other mobile-source components and tracers with high oxidative

potential. Combined house dust ($PM_{2.5}$ concentration of 275 μg/m^3) and ozone (100 ppb) exposure enhanced ROS production capacity in granulocytes and monocytes (Jantzen et al. 2018). Following exposure, CD34+KDR+ late endothelial progenitor cell number decreased by 48% in the blood of elderly individuals … Exposure data was collected from central monitoring stations, which may introduce measurement error. Individual diets were not recorded, a potential confounding factor influencing vascular function. A controlled human exposure study demonstrated increased levels of urinary 8-OHdG in healthy nonsmoking adults exposed to coarse (2.5–10 μm) or ultrafine concentrated ambient particles (CAPs) (< 0.3 μm). Urinary MDA levels were elevated in those exposed to fine CAPs (0.15–2.5 μm) (Liu et al. 2015).

Li et al (2017) conducted a randomized, crossover trial in 60 college students and noted that systolic blood pressure (SBP) was 2.61% higher (95% Cl 0.39–4.79) when exposed to $PM_{2.5}$ versus filtered air. For every 10 μg/m^3 rise in $PM_{2.5}$ exposure, SBP increased by 0.85% (95% Cl 0.10–1.62). Exposure to $PM_{2.5}$ elevated markers of oxidative stress, including serum MDA, iso-prostaglandin F2α, SOD, and 8-OHdG compared to filtered air exposure. Compared to Sun et al (2008a), Li et al (2017) used a shorter exposure period (9 days versus 10 weeks). The exposure concentration of $PM_{2.5}$ was greater in Li et al (2017) (46.8 μg/m^3 daily average) than in Sun et al (2008a) (14.1 μg/m^3 over the ten-week period).

Oxidative stress biomarkers were examined in 125 Beijing participants during-Olympic Games period, which coincided with strict air pollution reduction, and in pre-Olympic Games period, during which pollutant levels were high. There was a significant decrease ranging from −72.5 to −4.5% in levels of airway inflammation, measured by fractional exhaled NO testing and urinary 8-OHdG levels, respectively, between pre-Olympic games period and during-Olympic Games period (Huang et al. 2012)

Particulate matter exposure may enhance oxidative stress and result in endothelial dysfunction. Studies showed conflicting results on the effect of PM on blood pressure (Sun et al. 2008, Li et al. 2017). The blood group RH 1 is often used as a marker of vascular function (Zhang et al. 2016). However, increased sympathetic activity may significantly affect RH1 and this cannot be directly compared to other markers of vascular function, such as flow-mediated vasodilation. Exposure concentrations varied between the aforementioned studies, with some experimental models using elevated exposure concentrations (Miller et al. 2009, Wang et al. 2012). These results may overestimate the effect of PM on oxidative stress.

Effect of Particulate Matter on Atherosclerotic Plaque Formation (Table 6, Figure 1)

Experimental Models

Air pollution derived PM exposure contributes to atherosclerotic plaque formation and progression in experimental models. The potential for deposition of nanoparticles (NP) in atherosclerotic plaques was suggested by Miller et al (2017) in ApoE knockout mice using intratracheal administration of engineered gold nanomaterial to simulate environmental NP.

Similar findings were demonstrated in human studies. Patients undergoing carotid endarterectomy who inhaled AuNP prior to surgery subsequently possessed gold present in their carotid artery plaques. Further, $PM_{2.5}$ exposure-induced oxidative stress was found to enhance atherosclerosis in mice (Ying et al. 2009). ApoE knockout mice exhibited elevated ROS levels (300% increases in inducible NOS), and greater atherosclerotic plaque areas following $PM_{2.5}$ exposure.

Plaque formation starts in the presence of endothelial dysfunction when low density lipoprotein (LDL) particles enter the arterial wall and accumulate in the vascular intima. Accumulation eventually leads to the pathologic oxidation of LDL (ox-LDL). Multiple studies reported that PM exposure was correlated with increased levels of ox-LDL (Lund, Lucero et al. 2011, Li, Navab et al. 2013). ApoE knockout mice fed normal chow and exposed to a mixture of inhaled $PM_{2.5}$ and PM_{10} exhibited a 43% rise in LDL. LDL and cholesterol values were further elevated in mice fed a high-fat diet. The exposed mice demonstrated lower serum antioxidant capacities and greater degrees of atherosclerosis, as evidenced by increased plaque area in cross-sectional slices of the ascending aorta (Chen et al. 2013, Du et al. 2018). Mice exposed to $PM_{2.5}$ exhibit greater lipid content and 700% rise in plasma 7-ketocholesterol, a form of oxidative cholesterol, which correlates with increased plaque formation in both ApoE and LDL receptor (LDLR) knockout mice (Rao et al. 2014, Cao et al. 2016). Yatera et al (2008) found that PM_{10} exposure in heritable hyperlipidemic rabbits treated with BrdU-labeled monocytes showed monocyte adhesion to endothelium over plaques and increased deposition of monocytes in the plaques and below the plaques in smooth muscle. In addition, a 160% elevation in ICAM-1 and a 60% rise in VCAM-1 expression was observed in the plaque tissue of PM_{10} exposed rabbits (Yatera et al. 2008). Similar findings were demonstrated in mice (Sun et al. 2005; 2008b, Cao et al. 2016). Inhalational $PM_{2.5}$ exposure was associated with increased lipid content, plaque area, and macrophage infiltration in plaques of ApoE−/− mice fed a high-fat diet. ApoE−/− mice exposed to concentrated ambient ultrafine particles ($PM_{0.20}$) exhibited a 200% elevation in plaque area in the brachiocephalic artery compared to filtered air controls (Keebaugh et al. 2015). Molecular analysis of aortic plaques in ApoE−/− mice exposed to concentrated ambient air particles revealed a 325% upregulation of CD68 (a marker of macrophage infiltration) (Floyd et al. 2009), suggesting that PM alters gene expression in a manner that may promote atherosclerosis.

DEP exposure induced lipid droplet accumulation in macrophage cell lines in a concentration-dependent manner compared to controls 24 hr after exposure (Cao et al. 2015). Miyata et al (2013) noted that PM_{10} exposure in white rabbits was correlated with a 200% rise in macrophage accumulation in plaque area, increased foam cell generation, and accelerated plaque progression (300% elevation in intima/media ratio).

In airway epithelial cell cultures, PM_{10} from an urban commercial zone increased matrix metalloprotease-9 (MMP-9; by 23.2%) and matrix metalloprotease-2 (MMP-2; by 23.7%) activity 48 hr after incubation. There was no change in MMP-9 and MMP-2 mRNA at 48 hr, suggesting that mRNA decayed at an earlier time-point (Morales-Barcenas et al. 2015). Similarly, mixed whole engine exhaust exposure in ApoE−/− mice was related to upregulation of factors implicated in vascular remodeling and atherogenesis, including

MMP-9, MMP-3, MMP-7, endothelin-1, and heme oxygenase-1 (Lund et al. 2007, Campen et al. 2010). Diesel exhaust exposure increased endothelin-1 mRNA by 100%, MMP-9 mRNA by 60%, and lipid peroxides by 300% in the aortas of ApoE−/− mice (Campen et al. 2005).

High density lipoprotein (HDL) is an antioxidant that reduces ox-LDL levels, counters atherogenesis, and removes cholesterol from macrophage foam cells present in plaque (Toth et al. 2013). The protective, anti-inflammatory effect of HDL was reduced in ApoE knockout mice exposed to $PM_{2.5}$ (Araujo et al. 2008). Particulate size impacted both HDL function and atherosclerotic plaque volume. Exposure to ultra fine particles (particles < 0.18 μm) was associated with a 25% greater plaque volume and reduction in HDL-mediated protective capacity (measured by comparing the anti-inflammatory capacity of HDL against LDL-induced chemotaxis) when compared to fine particulate (<2.5 μm) exposure (Araujo et al. 2008). These findings corroborate a study in LDLR−/− mice, in which ultrafine PM exposure engendered atherogenic lipid metabolism and reduced antioxidant capacity (HDL) in fat-fed LDLR−/− mice (Li et al 2013). These mice also exhibited increased atherosclerotic lesion ratios and aortic cross sectional lesion areas (62% elevation in atherosclerotic lesion thickness and 220% rise in cross-sectional lesion area) following ultrafine PM treatment (Li et al. 2013). Air pollution derived PM also affects plaque stability. Aortic plaques from ApoE−/− mice exposed to PM demonstrated decreased alpha-actin expression by 360%, suggesting plaque instability (Floyd et al 2009). However, MMP-8, which is typically increased in rupture-prone plaques, was diminished in ApoE−/− mice exposed to concentrated ambient air particles. These plaques may not have progressed to the point of rupture. ApoE−/− mice tend to exhibit plaque rupture in the brachiocephalic artery, while Floyd et al (2009) analyzed the larger aortic plaques. Analysis of the brachiocephalic artery in ApoE−/− mice may further characterize the effects of particles on plaque stability. After PM_{10} exposure, Watanabe heritable hyperlipidemic rabbits exhibited a 250% increase in number of foam cells in atherosclerotic plaques and ultrastructural plaque alterations (Tranfield et al 2010). Changes included reduction and fragmentation of the subendothelial extracellular membrane, which contributes to plaque instability. Oropharyngeal aspirate instillation of DEP increased the size of plaques by 200% and number of plaques by 133% in the brachiocephalic arteries of ApoE−/− mice fed western diets to induce complex atherosclerotic plaques (Miller et al 2013). Exposure generated increased fibrous caps and plaque complexity with more buried fibrous layers. Bai et al (2011) examined aortic plaque composition in ApoE−/− mice following inhalational DEP exposure and noted 150 to 300% elevation in plaque lipid content, cellularity, foam cell formation, and smooth muscle cell content. Further, inducible NOS, CD36, and nitrotyrosine expression were increased by 1.5 to 200% in arterial wall plaques of DEP exposed animals. All these data are suggestive of plaque instability (Bai et al. 2011).

These studies suggest that air pollution contributes to atherosclerosis by increasing LDL levels, promoting macrophage infiltration into plaques, altering plaque stability, and decreasing antioxidant capacity of HDL. Particulate matter is suggested to alter gene expression in a way that promotes vessel remodeling, which may diminish plaque stability. Most experimental models investigated the effects of PM on atherogenesis in animals susceptible to atherosclerosis. These observations may be representative of air pollution-

mediated effects on vulnerable populations. Those less susceptible to atherogenesis may exhibit less or none of the reported effects. Exposure concentrations and time-periods varied among the studies reviewed. Some exposures were at pollution levels similar to ambient air concentrations (Chen et al. 2013), while others were at higher levels (Sun et al. 2005). Increased exposure concentrations may lead to exaggerated effects on the vasculature that would not be observed clinically. The chemical composition of the exposures differed among studies, which may influence results.

Clinical studies

While the specific effects of PM exposure on different stages of atherosclerosis have been examined in animal models, clinical studies focused largely on associations between air pollution exposure and plaque formation/ progression. Carotid intimal-media thickness (CIMT) is a common marker for subclinical atherosclerosis. A population-based study of 3,380 subjects demonstrated that those in the 90th percentile of residential PM exposure had 0.028mm greater CIMT measurements than those in the 10th percentile (Bauer et al. 2010). Su et al (2015) demonstrated that long-term exposure to traffic-related $PM_{2.5}$, PM_{10}, as well as gaseous pollutants originating from traffic emissions (NO_2 and NOx) was associated with increased CIMT (4.23% per 1.0×10^{-5}/m rise in $PM_{2.5}$ and 3.72% per 10 μg/m^3 elevation in PM_{10}) in 35–65 year old individuals. One-interquartile increase in 1-year average BC concentration was correlated with a 1.1% rise in CIMT (Wilker et al 2013). Analysis of African American and pediatric cohorts reported similar results, with increased CIMT measurements in those living in close proximity to a major roadway compared to individuals in more rural areas (Armijos et al. 2015; Wang et al. 2016). Estimating air pollution exposure by calculating the residential distance from a heavily trafficked road may lead to exposure misclassification. Residential traffic noise is a potential confounder and was not controlled for in these studies (Armijos et al 2015; Wang et al. 2016). Other studies failed to demonstrate significant relationships between PM exposure and increased CIMT, although positive trends were noted (Kunzli et al. 2011, Gan et al. 2014, Akintoye et al. 2016). A meta-analysis found no significant association between PM and elevated CIMT, although there was heterogeneity among the CIMT estimates (Akintoye et al. 2016) which may limit the study generalizability. To investigate the relationship between air pollution and cardiovascular health, the Multi-Ethnic Study of Atherosclerosis and Air Pollution estimated each individual's air pollution exposure and measured CT evidence of coronary artery calcium in 6,795 participants aged 45–84 years over a 10-year period (Kaufman et al. 2016). For an increase of 5 μg/m^3 of $PM_{2.5}$ exposure, coronary artery calcium (CAC) progressed by 4.1 units per year (95% CI 1.4–6.8). An elevation of 40 parts per billion (ppb) of NOx exposure increased CAC by 4.8 units per year (95% CI 0.9–8.7). However, PM and NOx exposure were not correlated with intima-media thickness change (Kaufman et al. 2016). During the study period, levels of ambient $PM_{2.5}$ were relatively low, at an annual average of 14.2 μg/m^3, compared to air quality standards in the United States and the European Union (which allow for 12 μg/m^3 and 25 μg/m^3 $PM_{2.5}$ per year, respectively). Data suggest that ambient $PM_{2.5}$ exposure, at concentrations encountered worldwide, might be associated with atherosclerosis progression (Kaufman et al. 2016). A further analysis of the Multi-Ethnic Study of Atherosclerosis found that a rise of 5 μg/m^3 $PM_{2.5}$ over a 3-month period decreased HDL particle levels, but not HDL cholesterol, in the blood (Bell et al. 2017). Small HDL

particles may be important in cholesterol efflux and a reduction may decrease the ability of HDL to remove cholesterol (Du et al. 2015). Short-term exposure to $PM_{2.5}$ significantly lowered antioxidant capacity of HDL in participants with a higher pre-exposure antioxidant capacity (Ramanathan et al 2016).

Clinical studies investigating the relationship between air pollution and atherosclerosis yielded mixed results. There are several limitations in these investigations. Models used to estimate air pollution levels are susceptible to measurement error. Many are cross-sectional studies and are unable to describe a temporal relationship between PM exposure and atherogenesis. Further studies are needed to both clearly define the association and understand the mechanisms underlying PM-initiated atherosclerosis.

Summary and Conclusions

Experimental and clinical studies discussed in this review strongly implicate systemic and local endothelial cell inflammation and oxidative stress in the pathogenesis of vascular disease in conditions of PM exposure. Air pollution also affects atherosclerotic plaque formation, vascular tone, fibrinolysis, and platelet activity. Individuals with underlying cardiovascular diseases or diabetes may exhibit increased susceptibility.

Questions remain regarding the route and mechanisms by which PM exerts biologic effects discussed in this review on vascular tissue. Experimental and clinical particle model systems are limited by challenges in recapitulating and representing the high chemical and physical diversity of ambient PM. Relevant particle diameter sizes range from coarse (PM 2.5–10 μm) to fine (PM smaller than 2.5 μm), and ultrafine (PM smaller than approximately 200nm). Further, particles originate from a wide variety of sources including vehicular, biomass, meat cooking, sea salt, dust, and secondary photochemical formation (Forman and Finch 2018). These particulate substrates further undergo chemical transformations and conversions. Metal contents differentially affect free radical propagation and toxicity (Forman and Finch, 2018). For example, the hydroxyl radical ($HO^{\bullet}$) is highly reactive, with a half-life of approximately one nanosecond. Because of rapid reactions with molecules immediately around its production, the reactions are only to that local cell membrane domain. If $HO^{\bullet}$ is produced in extracellular fluids, none of it reaches the cell surface. The production of $HO^{\bullet}$ at the surface requires the presence of iron or another transition metal. Cell surface production of $HO^{\bullet}$ produces a small amount of lipid peroxidation, which results in lipid raft disruption and calcium release. Subsequent cell signaling might increase production of pro-inflammatory cytokines (Premasekharan et al. 2011).

Experimental PM collection methods account for particulate composition, temporal/ seasonal variance, and modifications during storage and delivery. Synthetic experimental particulate models designed to recapitulate complex exposure-host interactions need to consider mechanisms of entry into the body, diffusion capabilities, movement of particles through membranes and barriers, interaction with immune mediators/ host defenses, and deposition within diverse tissues and target organ systems. The broad physical and chemical diversity of PM renders these challenges significant.

Clearly, PM impacts the cardiovascular system through multiple, diverse physiologic pathways. Further animal and human studies are needed to determine the specific air pollution constituents and PM sizes that impact the vasculature through each of these mechanisms. As exposure duration and onset age affect vascular responses to PM, toxicology studies may help establish differential vascular effects according to PM level, age, and temporal exposure patterns. Future investigations are needed to understand why specific populations remain more susceptible to the vascular effects of PM. These questions may be addressed by experiments that expand on the foundational information presented in this review. Improving air quality standards, reducing personal exposures, and redesigning engine and fuel technologies could all impact air quality and potentially mitigate the effects of air pollution on the cardiovascular system and human health.

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Highlights

1. We review the current literature and outline the effects of particulate matter (PM) on vascular tissue.
2. PM exposure induces inflammation, vasoconstriction, oxidative stress, and atherosclerotic plaque formation.
3. PM exposure is particularly detrimental to individuals with underlying cardiovascular conditions.
4. Further studies examining the vascular effects of specific PM compositions, concentrations, and particle sizes are warranted.

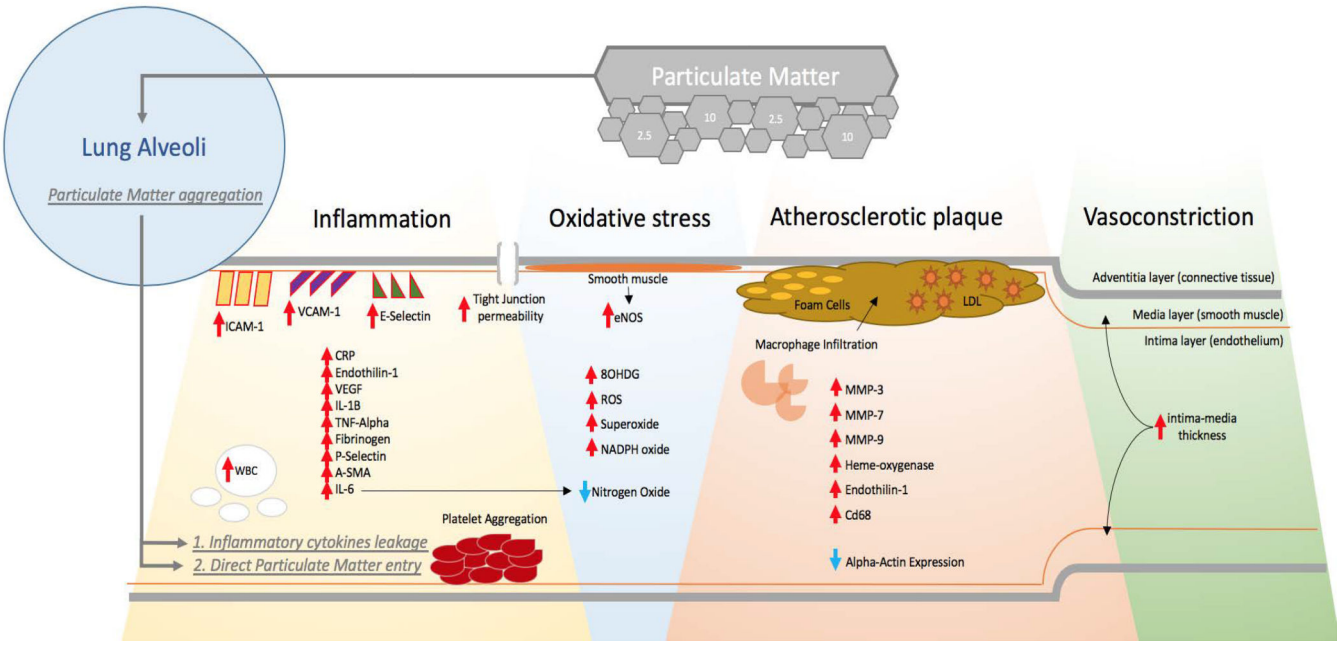

Figure 1.

Schematic of the Particulate Matter effects on Vasculature

Particulate matter (PM) effects the vasculature either via direct entry into the bloodstream or by inciting an inflammatory response in the lung alveoli that results in secondary cytokine leakage into the systemic circulation. PM exposure is associated with increased platelet aggregation, and elevated levels of WBCs, CRP, Endothilin-1, VEGF, IL-1B, TNF-alpha, Fibrinogen, P-Selectin, A-SMA, and IL-6 in the peripheral blood. PM activates endothelial adhesion molecules including ICAM-1, VCAM-1, and E-Selectin. Exposure decreases eNOS production in smooth muscles and generates oxidative stress through 8OHDG, ROS, superoxide, and NADPH Oxide production. At the endothelial cell level, PM alters tight junction permeability and causes BBB leakage. PM exposure promotes macrophage infiltration, foam cell formation, and elevations in LDL, MMP-3, MMP-7, MMP-9, Heme-oxygenase, Endothelin-1, and CD68. Changes in endothelial function secondary to PM exposure cause vasoconstriction, increases in intima-media thickness and impaired vascular tone.

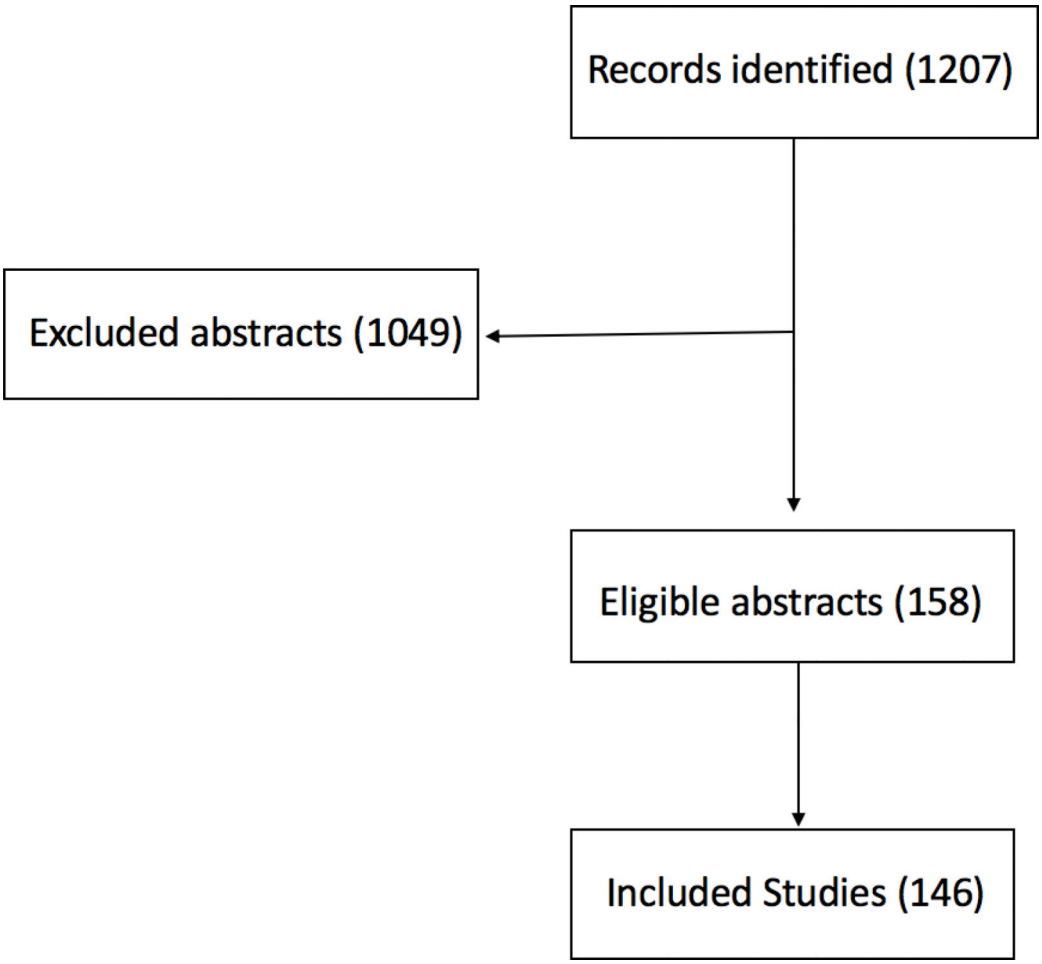

Figure 2:
Flow Chart of Literature Search

Table 1.

Search Criteria

Section	Search terms
Particulate Matter and Vascular Inflammation	Air pollution arteries inflammation
	Particulate matter arteries inflammation
	Air pollution inflammation cardiovascular endothelial cells
	Particulate matter inflammation cardiovascular endothelial cells
Effect of Particulate Matter on Vascular Tone	Air pollution vascular tone
	Particulate matter vascular tone
	Air pollution arterial tone
	Particulate matter arterial tone
Effects of Particulate Matter on Oxidative Stress	Air pollution vasculature oxidative stress
	Particulate matter vasculature oxidative stress
	Air pollution arteries oxidative stress
	Particulate matter arteries oxidative stress
Effect of Particulate Matter on Atherosclerotic Plaque Formation	Air pollution atherosclerosis
	Particulate matter atherosclerosis
	Air pollution and plaque formation
	Air pollution plaque remodeling

Table 2.

Current vascular/cardiovascular published reviews

Author, Year	Title	Review Summery
Section A		
(Alfaro-Moreno et al. 2007)	Particulate matter in the environment: pulmonary and cardiovascular effects	Respiratory effect of particulate matter, pre and postnatal effects of air pollution, lung function, allergic reactions in air pollution exposure and extrapulmonary transition of air pollution and the effect of Pm on cardiovascular morbidity and mortality
(Simkhovich, et al. 2008)	Air pollution and cardiovascular injury epidemiology, toxicology, and mechanisms	Size and composition of ambient particles, morbidity and mortality of PM in CVD in clinical studies. Pulmonary toxicity, ROS mechanisms in heart and lung tissue
(Franchini and Mannucci 2009)	Particulate air pollution and cardiovascular risk: short-term and long-term effects	Mechanisms of air pollution entry, clinical and epidemiological studies of short-term and long-term effect of PM on cardiovascular system morbidity and mortality
(Hassing et al. 2009)	Air pollution as noxious environmental factor in the development of cardiovascular disease	Short and long-term air pollution exposure general effects on CVD in the Netherlands
(Fang, et al. 2010)	A Systematic Review of Occupational Exposure to Particulate Matter and Cardiovascular Disease	Epidemiological data on Ischemic heart disease, cerebrovascular disease morbidity and mortality risks in occupational exposure to PM
(Sun, et al. 2010)	Cardiovascular effects of ambient particulate air pollution exposure	Cardiac events and rates of hospital admission and exposure to PM, cardiac function, effect of PM on heart rate variability, and hypertension
(Franchini and Mannucci 2011)	Thrombogenicity and cardiovascular effects of ambient air pollution	Pulmonary inflammation and direct entry of PM into the systemic circulation and population studies of short-term and long-term effect of PM on cardiovascular system morbidity and mortality
(Lippmann 2014)	Toxicological and epidemiological studies of cardiovascular effects of ambient air fine particulate matter (PM2.5) and its chemical components: coherence and public health implications	PM toxicity and Air pollution related morbidity and mortality in cerebrovascular and cardiovascular diseases
(Cosselman, et al. 2015)	Environmental factors in cardiovascular disease	Epidemiological data on air pollution exposure and cardiovascular risks (Stroke, cardiac dysfunctions), effect of CVD of arsenic, cadmium, lead. Public health implications of PM exposure
(Nasser, et al. 2015)	Outdoor particulate matter (PM) and associated cardiovascular diseases in the Middle East	Regional characteristics of association of PM levels and incidence on CVD in the middle east
(Du et al. 2016)	Air particulate matter and cardiovascular disease: the epidemiological, biomedical and clinical evidence	Direct and indirect actions of PM on cardiovascular system, epidemiological data on cardiovascular mortality, ischemic heart disease, cardiac arrest, blood pressure and thrombosis in PM exposure
(Bourdrel, et al. 2017)	Cardiovascular effects of air pollution	Outdoor air pollution sources, epidemiological evidence for air pollution exposure and cardiovascular morbidity and mortality, coronary artery disease, other cardiac outcomes and air pollution exposure, effects of air pollution policies, review cites only clinical studies
(An, et al. 2018)	Impact of Particulate Air Pollution on Cardiovascular Health	Long-term and short-term cardiovascular effect of PM exposure (hospital admissions rate and hypertension), clinical studies describing PM modes of entry, dietary and pharmacological intervention
Section B		
(Watkinson, et al. 2001)	Cardiovascular and systemic responses to inhaled pollutants in rodents: effects of ozone and particulate matter	Ozone metals and PM in cardiovascular models of rodents

Author, Year	Title	Review Summery
(Gray, et al. 2015)	Respiratory and cardiovascular effects of metals in ambient particulate matter: a critical review	The effect of metal components of air pollution on the respiratory and CVD
(Luben, et al. 2017)	A systematic review of cardiovascular emergency department visits, hospital admissions and mortality associated with ambient black carbon	Exposure to PM and CVD risks with particular emphasis on the effects of black carbon. CVD related emergency department visits, hospital admissions and mortality are reviewed.
(Boovarahan and Kurian 2018)	Mitochondrial dysfunction: a key player in the pathogenesis of cardiovascular diseases linked to air pollution	Air pollution and non-communicable diseases, mitochondrial dysfunction in air pollution, relationship between carbon monoxide, nitric oxide, sulfur dioxide, hydrogen sulfide, heavy metals and cardiovascular disease.
(Kirrane, et al. 2019)	A systematic review of cardiovascular responses associated with ambient black carbon and fine particulate matter	Comparison of Black Carbon and PM effects on CVD, including autonomic nervous system tone, heart rate, ischemia and repolarization abnormalities
Section C		
(Sandhu, et al. 2005)	Ambient particulate matter, C-reactive protein, and coronary artery disease	Association of CRP and inflammatory markers with morbidity and mortality in cardiac and CVD outcomes in patients exposed to PM
(Frampton 2006)	Inflammation and airborne particles	Lung vascular inflammation and PM effect on cardiovascular system via lung inflammation
(Frampton 2007)	Does inhalation of ultrafine particles cause pulmonary vascular effects in humans?	Clinical studies of pulmonary inflammation and systemic effects and mode of PM entries
(Polichetti, et al. 2009)	Effects of particulate matter (PM(10), PM(2.5) and PM(1)) on the cardiovascular system	Association between PM and smoking with CVD morbidity and mortality and mechanisms of tissue inflammation and oxidative stress are discussed
(Nelin,et al. 2012)	Direct and indirect effects of particulate matter on the cardiovascular system	Direct and indirect effect of PM on hypertension, nervous system. Inflammatory responses and reactive oxygen species production in the lungs in PM exposure
(Grunig,et al. 2014)	Perspective: ambient air pollution: inflammatory response and effects on the lung's vasculature	Effect of urban air pollution and cigarette smoke on the airways and lung inflammation, pulmonary hypertension, arterial remodeling by inflammatory immune response.
Section D		
(Gonzalez-Flecha 2004)	Oxidant mechanisms in response to ambient air particles	Pro-oxidant properties of ambient particulate matter, mechanisms of CAPs induced oxidative stress and toxicity, cardiac effects of ambient air particles
(Huang and Ghio 2006)	Vascular effects of ambient pollutant particles and metals	Ambient pollutant particles and transition metal effects in vasoconstriction
(Nogueira 2009)	Air Pollution and Cardiovascular Disease	Oxidative stress literature in animals and humans discussed as a central pathway of endothelial dysfunction, heart rate variability, vasoconstriction, and hypertension in long term PM exposure. Short term PM exposure effect evaluated on myocardial and ischemic events and sudden death
(Miller, et al. 2012)	From particles to patients: oxidative stress and the cardiovascular effects of air pollution	Ultrafine particles and cardiovascular epidemiology, oxidative stress mechanisms in PM exposure and their effect on CVD development and progression
(Miller 2014)	The role of oxidative stress in the cardiovascular actions of particulate air pollution	Review of oxidative stress as a mediator of PM effect in CVD and potential interventions
(Kelly and Fussell 2015)	Linking ambient particulate matter pollution effects with oxidative biology and immune responses	Effects of PM on airways and pulmonary epithelium, cardiovascular system and oxidative potential of PM
(Lawal 2017)	Air particulate matter induced oxidative stress and inflammation in cardiovascular disease and atherosclerosis: The role of Nrf2 and AhR-mediated pathways	Oxidative stress and inflammation in PM induced cardiovascular disease and atherosclerosis with emphasis on Nrf2 and AhR dependent regulatory pathways

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Author, Year	Title	Review Summery
(Yan, et al. 2016)	Inflammatory cell signaling following exposures to particulate matter and ozone	ROS formation and oxidative stress induced by PM and O3 exposure, EGRF and TLR signaling pathways
(Zanoli, et al. 2017)	A systematic review of arterial stiffness, wave reflection and air pollution	PM effect on arterial stiffness
Section E		
(Gill, et al. 2011)	Air pollution and cardiovascular disease in the Multi-Ethnic Study of Atherosclerosis	Air pollution effect on CVD based on the findings Multi-Ethnic Study of Atherosclerosis
(Moller, et al. 2016)	Atherosclerosis and vasomotor dysfunction in arteries of animals after exposure to combustion-derived particulate matter or nanomaterials	Air pollution effect on vascular vasomotor function and atherosclerotic plaque formation, with emphasis on different chemical components of air pollution
(Moller, et al. 2011)	Hazard identification of particulate matter on vasomotor dysfunction and progression of atherosclerosis	Development of atherosclerosis, reduced vasoconstriction in animal and clinical models
(Prueitt, et al. 2015)	Evaluation of atherosclerosis as a potential mode of action for cardiovascular effects of particulate matter	PM effect on atherosclerosis and thrombosis in animal models
(Akintoye, et al. 2016)	Association between fine particulate matter exposure and subclinical atherosclerosis: A meta-analysis	Meta-analysis of carotid media intima thickness, arterial calcification, and ankle-brachial index as noninvasive measures of clinical and subclinical atherosclerosis
(Bai and Sun 2016)	Fine particulate matter air pollution and atherosclerosis: Mechanistic insights	Development of atherosclerotic plaque and mechanisms of PM mediated atherosclerosis
(Cao, et al. 2016)	Foam cell formation by particulate matter (PM) exposure: a review	Foam cell formation and development of atherosclerosis in PM exposure
Section F		
(Brook 2008)	Cardiovascular Effects of Air Pollution	Characteristics of PM air pollution, epidemiology of cerebrovascular disease and PM, geography and sources of pollution, arrhythmias, heart failure, thrombosis and atherosclerosis in PM exposure in clinical studies
(Donaldson, et al. 2001)	Ambient Particle Inhalation and the Cardiovascular System: Potential Mechanisms	Ultrafine particles in urban air, Pathogenesis of PM particles, oxidative stress and modulation of Calcium in tissues, PM effect on epithelial permeability and atherosclerosis in cardiovascular health, and epidemiological evidence of systemic oxidative stress in susceptible populations
(Fiordelisi, et al. 2017)	The mechanisms of air pollution and particulate matter in cardiovascular diseases	Cardiac morbidity and mortality in epidemiological studies of PM exposure, modes of translocation into the cardiovascular system and pulmonary oxidative stress and inflammation, disturbance of autonomic nervous system, discussion of potential therapeutic approaches
(Franchini, et al. 2012)	Air pollution, vascular disease and thrombosis: linking clinical data and pathogenic mechanisms	Epidemiological cardiovascular mortality and morbidity related to PM exposure, experimental studies and pathophysiological mechanisms of cardiac and vascular function, hemostatic unbalance, ROS and atherosclerosis
(Franklin, et al. 2015)	Air pollution and cardiovascular disease	Epidemiologic studies of air pollution and secondary smoke effect on short-term and long-term CVD and mortality risks. Air pollution and exercise. biological pathways in PM effect on hypertension, insulin resistance, diabetes, atherosclerosis, coagulation and thrombosis, autonomic imbalance, and global burden of disease.
(Grahame and Schlesinger 2010)	Cardiovascular health and particulate vehicular emissions: a critical evaluation of the evidence	Epidemiological evidence of association between CVD and PM, Mechanistic evidence of PM effect on heart rate variability, cardiac arrhythmia, tissue inflammation, atherosclerosis, and blood pressure

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Author, Year	Title	Review Summery
(Langrish, et al. 2012)	Cardiovascular effects of particulate air pollution exposure: time course and underlying mechanisms	Effect of PM on vasoconstriction, blood pressure, myocardial ischemia, heart rate variability, systemic inflammation, thrombosis, atherosclerosis in controlled human studies
(Martinelli et al. 2013)	Air particulate matter and cardiovascular disease: a narrative review	Measurements of PM, epidemiological studies linking PM to cardiovascular disease, autonomic and hemostatic system activation, pulmonary oxidative stress and inflammation. Effect of PM on susceptible populations.
(Newby et al. 2015)	Expert position paper on air pollution and cardiovascular disease	Air pollution related morbidity and mortality in cardiac diseases, venous thromboembolism, pulmonary inflammation and ROS, epigenetic changes, and air quality recommendations
(Shrey, et al. 2011)	Air pollutants: the key stages in the pathway towards the development of cardiovascular disorders	Review of mechanisms linking PM exposure to thrombosis, atherosclerosis, myocardial dysfunction, and cardiac autonomic control in CVD
(Wang, et al. 2017)	Toxicity of inhaled particulate matter on the central nervous system: neuroinflammation, neuropsychological effects and neurodegenerative disease	Routes of PM entry, neurotoxicity of PM and neurodegenerative disease, learning and memory impairment, neuroinflammation, behavioral changes, and oxidative stress
(Hamanaka and Mutlu 2018)	Particulate Matter Air Pollution: Effects on the Cardiovascular System	Air pollution composition and morbidity and mortality epidemiological data - clinical data only, effects of air pollution on inflammation in adipose tissues, oxidative stress and atherosclerosis, effect on blood pressure, metabolic syndrome and insulin resistance, epigenetic changes, and BMI role
(Vidale and Campana 2018)	Ambient air pollution and cardiovascular diseases: From bench to bedside	Air pollution composition and sources, pathways of air pollution entry into the system, atherosclerosis, thrombosis and coagulation pathways affected by air pollution, insulin resistance diabetes and metabolic syndrome, arterial hypertension, autoimmune imbalance
Section G		
(Brook, 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	Statement from Health Professionals from the Expert Panel on Population and Preventive Science of the American Heart Association: Ambient Air Pollution and Secondary smoke effect on and cardiovascular disease. Long- and short-term epidemiological health effect studies and at-risk populations, PM effect on congenital heart disease, biological mechanisms of pulmonary and systemic oxidative stress and inflammation
(Mills et al. 2007)	Air pollution and atherothrombosis	Pulmonary and systematic inflammation, effect PM on vascular inflammation atherosclerosis, vasomotor funcntion and plaque stability

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Table 3.

Particulate Matter and Vascular Inflammation: Literature Summary

Authors, Year	Methods	Main Findings
Liu et al. 2018	Mice exposed by inhalation to filtered or ambient air	Accumulation of CD45þ lymphocytes and CD68þ macrophages in pulmonary arterioles. TNF-a, IL-6 and IL-13 markedly elevated in lung tissues
Green et al. 2016	Women enrolled in the multi-ethnic, longitudinal Study of Women's Health Across the Nation (six sites)	Exposures to PM2.5 and ozone associated with adverse effects on inflammation and hemostatsis
Michikawa et al. 2016	2360 Japanese participants	Positive association of PM with hs-CRP and WBC count
Pope et al. 2016	24 healthy, non-smokers exposed to 3 periods of ambient PM	Elevated levels of circulating monocytes, T lymphocytes, iendothelial microparticles, sICAM-1, and sVCAM-1
Dabass et al. 2016	Adult NHANES trial participants from 2001 to 2008	No overall association between PM2.5 and biomarkers of cardiovascular risk
Wolf et al. 2016	2,944 participants of the KORA (Cooperative Health Research in the Region Augsburg)	Individuals with prediabetes have larger effects due to PM exposure
Shisler et al. 2015	Human coronary artery endothelial cells cultured with plasma from 6 healthy volunteers exposed to filtered air or diesel exhaust PM (100mg/m3) for 2 hours	Inflammatory pathways and cytokines upregulated both at 2 and 24 hours after DE exposure
Viehmann et al. 2015	Heinz Nixdorf Recall Study, a German population-based prospective cohort of 4814 participants	Long-term exposure to PM associated with increased hs-CRP and platelets
Lanki et al. 2015	Six adult cohorts from Central and Northern Europe	Living in close proximity to busy traffic associated with elevated CRP concentrations
Hampel et al. 2015	European ESCAPE and TRANSPHORM multi-center projects	Increase in PM2.5 copper and PM10 iron were associated with increase in hsCRP
Siponen et al. 2015	52 ischemic heart disease patients	C-reactive protein, interleukin-12 and myeloperoxidase elevation in air pollution
Johannesson et al. 2014	Panel study in healthy adults	CRP blood levels fluctuations in different dose PM exposures
Lee et al. 2014	Community adults in a densely populated inner city neighborhood in Boston, Massachusetts	At ambient levels oxidative stress and systemic inflammation exacerbate cardiac autonomic responses to PM2.5
Wang et al. 2013	Rats exposed to intrathecal PM2.5 alone, PM2.5 and ozone, ozone alone, or fresh air	Increased blood plasma concentrations of endothelin-1 and lower serum VEGF result in inflammation and endothelial damage
Oppenheim et al. 2013	Apolipoprotein (Apo) E−/− and C57Bl6 mice exposed to DE or filtered air (FA)	MVE-exposed Apo E−/− mice demonstrated BBB permeability, elevated ROS and MMP-2/ MMP-9 activity when compared to FA controls
Niu et al. 2013	Female residents of Jinchang and Zhangye, China	The levels of CRP, IL-6, and VEGF were significantly higher in more polluted areas
Krishnan et al. 2013	17 individuals with metabolic syndrome (MetS) and 15 healthy subjects inhaled filtered air or diesel exhaust in two-hour different day sessions with a minimum 2-week washout period	short-term DE exposure resulted in cardiovascular events (hemoconcentration and thrombocytosis)
Rask-Madsen at al. 2013	DM and glucose	DM and glucose intolerance are independently associated with vascular inflammation
Davel et al. 2012	Wistar rats exposed to urban PM2.5 for two weeks	Decreased endothelial-dependent relaxation and eNOS expression with high local TNF-a levels
Channell et al. 2012	hCAES obtained from healthy individuals exposed to filtered air, diesel exhaust PM (100mg/m3), or NO2 (500ppb) for 2 hours	Exposure to both diesel PM and NO2 leads to a proinflammatory response marked by increases ICAM-1, VCAM-1, and IL-8

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Authors, Year	Methods	Main Findings
Lee et al. 2012	Cells of the human monocytic leukemia cell line and human umbilical vein endothelial cells	mRNA and protein expression of vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion mole- cule-1 (ICAM-1) were upregulated in HUVECs after incubation with exhaust particles
Robertson et al. 2012	Wistar rats exposed to DEP or saline vehicle by intratracheal instillation and hind-limb blood flow	DEP instillation increased cell counts, total protein and IL-6 in BALF 6 h after exposure. Levels of IL-6 and TNFa were only raised in blood 24 h after DEP exposure
Guo et al. 2012	Wistar rats with intratracheal PM10 exposure	Upregulation of endothelial mediators (ET-1 and eNOS) and inflammatory markers (IL-1, TNF-, COX-2, iNOS and ICAM-1)
Rich et al. 2012	125 healthy adults	CRP blood levels went down from 55% during the pre-Olympic period (high pollutant levels) to 46% during the Olympic games
Tsai et al. 2012	Individuals exposed to short-term PM	Increased circulating levels of IL-1b, IL-6, and TNF-a
Huttunen et al. 2012	52 elderly individuals with history of ischemic heart disease	Upregulation of IL-12 and CRP within days of exposure
Cherng et al. 2011	Coronary artery of rats exposed to diesel PM or filtered air	NOS uncoupling and generation of reactive oxygen species results in endothelial dysfunction and impaired vasodilation
Alexeeff et al. 2011	642 elderly men from the Veterans Administration (VA) Normative Aging Study	positive associations between air pollution and sICAM-1 for aver- ages of 4, 8, and 12 weeks
Hoffmann et al. 2009	Population based prospective cohort study of 4,814 subjects	Elevated circulating hs-CRP and fibrinogen
Rudez et al. 2009	40 healthy volunteers	13 consecutive CPR blood measurements over the throughout 1 year were not associated with 1 to 4-day changes in PM exposure levels
Knuckles et al. 2008	Isolated arteries and veins of animals immersed in diesel PM	DE induced uncoupling of eNOS in-vivo and ex-vivo
Bräuner et al. 2008	29 subjects participated in a randomized, two-factor crossover study with or without biking exercise	Exposure to outdoor air pollution particles was not associated with systemic inflammation
Scapellato et al. 2007	Systematic review of evidence	Activated leukocytes and endothelial PDGF and IL-8 regulate inflammation
Chuang et al. 2007	76 healthy young non-smokers in China	Variations in 1 and 3 day PM10 exposure levels were associated with changes in CRP blood concentrations
Yue et al. 2007	Male coronary artery disease patients	Increases in CRP correlation with traffic-related particles and combustion-generated aerosols
O'Neill et al. 2007	92 Boston area residents with type 2 diabetes	Consistently positive association between air pollution and inflammatory markers
Saura et al. 2006	Culture of human aortic endothelial cells	IL-6 inhibits eNOS via a Stat3 dependent mechanism, reducing NOS levels and leading to endothelial dysfunction
Kristovich et al. 2004.	Human endothelial cells treated with human monocyte derived macrophages exposed to sublethal particulate matter for 24 hrs	Upregulation of ICAM-1, VCAM-1, E-selectin on endothelial cells
Van Eeden et al. 2001	30 healthy males exposed to PM10 for 2 months	Increased levels of circulating of IL-1b, IL-6, GM-CSF, and TNF-a
Ridker et al. 2000	Longitudinal women's health study	CRP - a strong predictor of future cardiovascular events

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Table 4.

Effect of Particulate Matter on Vascular Tone: Literature Summary

Authors, Year	Methods	Main Findings
Zanoli et al. 2017	Review	Arterial stiffening
Mirowsky et al. 2017	Monitored ozone and ambient $PM_{2.5}$ in 13 patients with CAD.	Increase in LAEI, tPA, PAI-1, neutrophils, monocytes, IL-6, and TNF-alpha
Wauters et al. 2015	18 healthy male subjects exposed to DE or filtered air for 2 hours at rest, during dobutamine stress ECG, or exercise stress ECG w/ hypoxia (12% O_2)	DE had no effect at rest or in hypoxic conditions. Serum ET-1, exhaled NO not increased after DE
Louwies et al. 2013	Ambient PM_{10} exposure monitored in 84 healthy adults	Every 10μg/m^3 increase in PM_{10} decreased (0.86μm decrease) central retinal artery and (0.93 μm) vein diameter
Pope et al. 2011	26 healthy young adults exposed to Filtered Air or PM	Decline in MVRI after increased ambient $PM_{2.5}$
Barath et al. 2010	18 healthy male volunteers exposed to DE or Filtered Air for 1 hour during intermittent exercise	Decreased vasodilatation to Ach, bradykinin, sodium nitroprusside, and verapamil
Lenters et al. 2010	Monitored NO_2, SO_2, $PM_{2.5}$ in young adults	Increase in pulse wave index, AIx with increased NO_2, SO_2
LeBlanc et al. 2009	Sprague-Dawley rats exposed to inhalational FA or TiO_2 nanoparticles	Increased coronary arteriole tone, impaired FID, attenuated Ach and Ca(2+)
Lundbäck et al. 2009	12 healthy adults exposed to DE (350 μg/m^3) or FA for 1 hour during moderate exercise	AP, AIx, and Tr increased 10 min post DE-exposure, increased stiffness of the radial artery
Tamagawa et al. 2008	31 female New Zealand White rabbits exposed to intratrachael PM_{10} or saline for 5 days or 4 weeks	PM_{10} increased lung and activated macrophages, IL-6, and reduced Ach dilation of carotid artery
Peretz et al. 2008	27 adults exposed to Filtered Air and DE	DE decreased BAd with dose-dependent response, increased plasma ET-1
Rundell et al. 2007	PM exposure in 16 athletes during exercise in locations with high or low PM air concentrations	Increased vasoconstriction, reduced post-exercise FMD in brachial artery, reduction in re-oxygenation post-exercise in high PM, not low PM
Briet et al. 2007	40 white male nonsmokers	Small artery reactive hyperemia increased with $PM_{2.5}$ and PM_{10}
Törnqvist et al. 2007	15 healthy subjects exposed to diluted diesel exhaust or filtered air for 1 hour during intermittent exercise	A selective impairment of Ach-induced endothelium-dependent vasodilatation in forearm vessels
Frampton et al. 2006	40 healthy subjects and 16 subjects with asthma	Altered peripheral blood leukocyte and adhesion molecules expression, increased retention of leukocytes in the pulmonary vasculature in PM exposure
O'Neill et al. 2005	270 patients with or at risk of diabetes	Increased nitroglycerin-mediated reactivity, decreased vascular reactivity
Mills al. 2005	30 healthy men exposed to DE (300 μg/m3) or FA for 1 hr during intermittent exercise	DE attenuated vasodilation following bradykinin, Ach, sodium nitroprusside infusion. DE decreased tPA release following bradykinin
Nurkiewicz et al.,2004	Sprague-Dawley rats intratracheally exposed to saline, TiO_2 or ROFA.	ROFA increased PMNs, BAL albumin, BAL LDH
Brook et al. 2002	25 healthy adults exposed to PM or Filtered air	Increased brachial artery vasoconstriction

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Table 5.

Particulate Matter and Oxidative Stress: Literature Summary

Authors, Year	Methods	Main Findings
Jantzen et al. 2018	23 healthy elderly subjects	CD34+KDR+ late endothelial progenitor cells decreased by 48% in the blood
Li et al. 2017	Controlled human exposure study	$PM_{2.5}$ increased markers of oxidative stress, including serum malondialdehyde, iso-prostaglandin F2α, superoxide dismutase, and 8-hydroxy-2-deoxyguanosine
Zhang et al. 2016a	97 elderly subjects living in the Los Angeles area	Demonstrated associations among airway oxidative stress and inflammation with traffic-related air pollutants, ultrafine particles and transition metals
Zhang et al. 2016b	93 elderly subjects living in the Los Angeles area	Reactive hyperemia index inversely associated with traffic related pollutants and other mobile-source components, as well as oxidative potential of transition metals and $PM_{<2.5}$
Liu et al. 2015	Controlled human exposure study	Increased levels of urinary 8-OHdG in healthy nonsmoking adults exposed to coarse (2.5–10 μm) or ultrafine concentrated ambient particles
Wang et al. 2012	Human lung EC monolayer	PM induces marked increases in vascular permeability via ROS-mediated calcium leakage
Huang et al. 2012	125 Beijing participants in the during-Olympic Games period	Change in PM caused decrease in levels of airway inflammation and urinary 8-OHdG
Miller et al. 2009	Effects of DEP (10–100 microg/mL) in isolated rat aortic rings	DEP caused oxidative stress through oxygen-centered free radicals that reduce bioavailability of endothelium-derived NO
Hartz et al. 2008	Isolated rat brain capillaries exposed to DEPs	DEPs, alters blood-brain barrier function through oxidative stress and proinflammatory cytokine production
Sun et al. 2008	Sprague-Dawley rates exposed to $PM_{2.5}$	Upregulation of Rho/ROCK pathway, activated by reactive oxygen species, causes increased vascular tone
Nurkiewicz et al. 2006	Rats intratracheally indussed with residual oil fly ash (ROFA) or titanium dioxide	Impaired endothelium-dependent dilation, PMNL adhesion, MPO deposition, and oxidative stress
Taniyama et al. 2003	Review	ROS plays a central role in normal physiology, and contributes to vascular disease
Gurgueira et al. 2002	Rat model of short-term concentrated ambient particle exposure	Tissue-specific increases in superoxide dismutase and catalase activity
Bai et al. 2001	Human pulmonary artery endothelial cells exposed to diesel exhaust particles	Endothelial cell damage caused by DEP extracts is likely mediated by oxygen derived free radicals

Table 6.

Particulate Matter and Atherosclerotic Plaque Formation: Literature Summary

Authors, Year	Methods	Main Findings
Du et al. 2018	ApoE$^{-/-}$ mice fed normal or high-fat chow and exposed to $PM_{2.5}$ or filtered air for 8h/d, 7d/wk, for 16 wks.	$PM_{2.5}$ increased aortic root plaques and plaque area, ox-LDL, LDL-C, apoplipoprotein B, and serum and aortic CD36. Decreased HDL-C, apolipoprotein A1
Miller et al. 2017	Healthy humans exposed to gold nanoparticles for 2h during exercise. Carotid endarterectomy patients exposed to gold 2x for 2h before surgery	Gold in blood and urine, excised carotid plaques Particles in blood and liver, with the smallest particles in the highest quantities
Bell et al., 2017	MESA-Air participants	$PM_{2.5}$ decreased HDL particle number but not HDL cholesterol.
Cao et al. 2016	Review	Increased reactive oxygen species (ROS) or an adaptive response to oxidative stress in mediating particle-induced cell formation
Wang et al. 2016	4800 participants	Living < 150 m from major roadways increased CIMT, not CAC or AAC
Akintoye et al. 2016	Meta-analysis investigating the effect of $PM_{2.5}$	$PM_{2.5}$ increased CIMT, not arterial calcification or ABI
Kaufman et al. 2016	$PM_{2.5}$ and NO_x measured in subjects aged 45–84 years	$PM_{2.5}$ increased coronary calcification progression, no effect on CIMT
Ramanathan et al. 2016	Healthy participants	$PM_{2.5}$ significantly decreased the anti-oxidant capacity of HDL in participants with a higher pre-exposure anti-oxidant capacity
Keebaugh et al. 2015	ApoE-/- mice exposed to CAP for 5 hr/day, 4 days/wk for 8 weeks	Increased plaque area and lipid content in brachiocephalic artery, increase serum MDA, decreased HRV
Cao et al. 2015	Human THP-1 derived macrophages exposed to DEP	DEP increased intracellular reduced GSH, lipid droplet formation, and led to lysosomal dysfunction
Morales-Barcenas et al. 2015	Airway epithelial A549 cells exposed to PM_{10} from industrial zone (IZ) or commercial zone (CZ)	PM_{10} increased protease activity and invasiveness. CZ PM_{10} increased MMP-2 after 24 hr exposure
Su et al 2015	689 adults	$PM_{2.5}$, PM_{10}, NO_2, and NO_x increased subclinical atherosclerosis
Du et al. 2015	Human monocyte-derived macrophage and Chinese hamster ovary cell lines	Smaller HDL particles were the most efficient at removing cholesterol from macrophages.
Rao et al. 2014	ApoE$^{-/-}$ and LDLR$^{-/-}$ exposed to $PM_{2.5}$ or filtered air for 6 months	$PM_{2.5}$ increased 7-ketocholesterol in plasma and aortic plaques; increased CD36 in macrophages in plaques
Armijos et al. 2014	287 healthy children	Increased CIMT in children <100 meters from the nearest heavily trafficked road compared to those living ≥ 200 meters away
Gan et al. 2014	509 healthy subjects	No associations between TRAP and progression of carotid atherosclerosis
Li et al. 2013	LDLR$^{-/-}$ exposed to inhalational UFPs or FA for 5h/d, 3d/wk for 10 wks	Exposure to UFP decreased plasma HDL, paraoxonase activity, HDL anti-oxidant capacity. Increased ox-LDL, free oxidized fatty acids, triglycerides, TNF-alpha, plaque lesion, cross-sectional plaque area in aortic sinus
Chen et al. 2013	ApoE$^{-/-}$ exposed to PM or filtered air	Increased serum total cholesterol, LDL, TNF-alpha, C-reactive protein. Increased aortic plaque area and TNF-alpha and IL-6 in BAL of PM mice

Authors, Year	Methods	Main Findings
Toth et al. 2013	Review	Low HDL-C identifies patients at elevated risk, and much investigation suggests that HDL may play a variety of antiatherogenic roles
Li et al. 2013	Fat-fed low density lipoprotein receptor-null (LDLR$^{-/-}$) mice exposed to filtered air (FA) or UFPs for 10 weeks	UFP exposure promoted proatherogenic lipid metabolism and reduced HDL antioxidant capacity
Miller et al. 2013	ApoE−/− mice and wild-type mice exposed to (35 μL) DE or saline 2 days/wk for 4 wks.	DEP in both strains increased neutrophils in BAL and Nrf2 in liver
Wilker et al. 2013	380 elderly men	Black carbon increased CIMT
Lund et al. 2011	ApoE$^{-/-}$ mice exposed to inhalational filtered air or whole engine emissions	Increased ox-LDL, vascular ROS, MMP-9, macrophage infiltration, endothelin-1
Bai et al. 2011	ApoE−/− mice exposed to (200 mg/m3) PM2.5 or FA, 6h/day, 5 days/wk for 7wks.	Increased oxidative stress (iNOS, nitrotyrosine, CD36) and lipid and DNA oxidation in $PM_{2.5}$ mice
Kunzli et la. 2011	Review	CIMT is a useful candidate for cross-sectional and longitudinal studies investigating the role of air pollution in atherogenesis
Campen et al. 2010	ApoE−/− mice exposed to DE or FA for 6 h/day for 50 days.	DE increased MMP-9, ET-1 mRNA, collagen, and macrophages in DE vessels.
Tranfield et al. 2010	Watanabe heritable hyperlipidemic rabbits exposed to instilled (5 mg) PM10 or saline for 2 days/wk for 4 wks.	Ultrastructural plaque analysis showed increased foam cells, fragmented or absent dense ECM, increased endothelial-foam cell contact
Bauer et al. 2010	3,380 adults	$PM_{2.5}$ increased CIMT and atherosclerosis
Ying et al. 2009	ApoE$^{-/-}$ mice exposed to CAPs $PM_{2.5}$ or FA	Increased aortic expression of NADPH oxidase subunits, iNOS, superoxide generation, protein nitration
Floyd et al. 2009	ApoE-/- mice exposed to FA or CAPs for 6 h/day, 5 days/wk for 5 months	CAPs-induced changes to inflammation, proliferation, cell cycle, hematological system, and cardiovascular pathways
Yatera et al. 2008	Watanabe heritable hyperlipidemic rabbits exposed to intratracheal PM_{10} 2x/wk for 1 month	PM_{10} increased the number of monocytes in the endothelium over plaques, in plaques, and in the smooth muscle beneath plaques
Sun et al. 2008	Human bronchial epithelial cells, hSMCs, monocytes exposed $PM_{2.5}$ and $PM_{0.1}$. ApoE−/− exposed to PM2.5 or FA for 6 hr/day, 5 day/wk for 6 months	$PM_{2.5}$ and UFP increased TF protein. PM2.5 increased TF and macrophages in plaques
Araujo et al. 2008	ApoE−/− mice exposed to UFP, $PM_{2.5}$, or FA 5 hrs/ day, 3 days/wk for total of 75 hrs.	UFP increased the number and size of atherosclerotic lesions infiltrated w/ foam cells, reduced HDL's anti-inflammatory effect, and increased MDA and Nrf2 in the liver
Lund et al. 2007	ApoE-/- mice exposed by inhalation to FA, PM whole exhaust or filtered exhaust	Increased aortic MMP-3, MMP-7, and MMP-9 mRNA, tissue inhibitor of MMP-2, ET-1 and HO-1. ROS in arteries, not plasma, of PM exposed mice
Sun et al. 2005	28 ApoE−/− exposed to $PM_{2.5}$ or FA for 6 h/day, 5 days/wk for 6 mo.	$PM_{2.5}$ increased vasoconstriction to phenylephrine and serotonin, attenuated Ach-vasodilation, increased iNOS, macrophage infiltration, ROS, and 3-nitrotyrosine
Miyata et al. 2003	New Zealand White rabbits with abdominal aorta balloon injury followed by PM_{10} or saline exposure for 4 wks ± lovastatin(5mg/kg/day)	PM_{10} exposure accelerated balloon catheter induced plaque formation, increased intimal macrophages, and lipid accumulation

Abbreviations: AP: Augmentation Pressure, AIx: Augmentation Index, Tr: time to wave reflection, FMD: flow-mediated dilation, BP: blood pressure, NMD: endothelial-independent nitroglycerin-mediated dilatation, MVRI: microvascular responsiveness index, OC: organic carbon, EC: elemental carbon, TiO_2: titanium dioxide, SNP: sodium nitroprusside, FID: flow-induced dilation, ROFA: residual oil fly

ash, BAL: bronchoalveolar lavage, MPO: myeloperoxidase, hSMCs: human smooth muscle cells, TF: tissue factor, CIMT: carotid intima-media thickness, TRAP: traffic-related air pollution, ABI: ankle-brachial index, CAC: coronary artery calcification, AAC: abdominal aortic calcification, MDA: malondialdehyde, CRP: c-reactive protein, CK: creatine kinase