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REVIEW

Potential Biological Mediators of Myocardial and Vascular Complications of Air Pollution—A State-of-the-Art Review

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Ambient air pollution is recognised globally as a significant contributor to the burden of cardiovascular diseases. The evidence from both human and animal studies supporting the cardiovascular impact of exposure to air pollution has grown substantially, implicating numerous pathophysiological pathways and related signalling mediators. In this review, we summarise the list of activated mediators for each pathway that lead to myocardial and vascular injury in response to air pollutants. We performed a systematic search of multiple databases, including articles between 1990 and Jan 2022, summarising the evidence for activated pathways in response to each significant air pollutant. Particulate matter <2.5 μm ($PM_{2.5}$) was the most studied pollutant, followed by particulate matter between 2.5 μm–10 μm (PM_{10}), nitrogen dioxide (NO_2) and ozone (O_3). Key pathogenic pathways that emerged included activation of systemic and local inflammation, oxidative stress, endothelial dysfunction, and autonomic dysfunction. We looked at how potential mediators of each of these pathways were linked to both cardiovascular disease and air pollution and included the overlapping mediators. This review illustrates the complex relationship between air pollution and cardiovascular diseases, and discusses challenges in moving beyond associations, towards understanding causal contributions of specific pathways and markers that may inform us regarding an individual's exposure, response, and likely risk.

Keywords Air pollution • Particulate matter • Myocardial injury • Inflammation • Environmental health

Introduction

Public health efforts since the 1950s have resulted in an up to 80% reduction in the concentration of major air pollutants in megacities [1]. However, outdoor ambient air pollution remains a leading environmental cause of cardiovascular morbidity and mortality, making it a significant public health consideration for policymakers [2]. Particle matters with an aerodynamic diameter of less than 2.5 μm ($PM_{2.5}$), and between 2.5 μm–10 μm (PM_{10}), ozone (O_3) and nitrogen dioxide

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(NO_2) are amongst the major known hazardous air pollutants (HAP) that can impact cardiovascular health in the acute setting as well as chronic exposure.

In 2015 alone, exposure to $PM_{2.5}$ was found to be responsible for more than 4 million deaths, up from 3.5 million in 1990, putting it at the fifth highest ranking risk factor for mortality [3]. High-income countries comprised only 1% of deaths related to household air pollution but 12% of ambient air pollution-related mortality in that year. Other studies show direct causation on mortality and comorbidities, including a range of cardiovascular diseases [4–8], most notably coronary artery disease (CAD) [9–11], lung cancer [12], diabetes [13] and stroke [14], to name a few. In addition to health impacts, air pollution causes significant direct and indirect economic burdens globally [15]. Furthermore, the latest advice from the World Health Organization (WHO) advises that there is no safe level for $PM_{2.5}$ [2,16].

Studies focussing on the mechanism behind air pollution-related cardiovascular disease (CVD) since the 1980s have implicated the role of systemic and local inflammation, oxidative stress, vascular endothelial damage, plaque vulnerability, hypercoagulable state and autonomic dysfunction as some of the involved pathophysiological pathways. However, the exact mechanisms by which these pathways are activated remain a "hot" topic in environmental health studies. In this context, the role of cardio-respiratory interaction needs further research. The passage of smaller particulate matters from larger airways to alveoli and across the capillary bed to the systemic circulation is thought to cause local inflammation via local endothelial pathways and systemic inflammation by activation of airway receptors. However, little is known about the fate of micro-particulate matters in the bloodstream. Most of the biomarkers that are used for these studies are end-products of these processes, reflecting activity of these signalling pathways. Whilst they have been implicated in both cardiovascular disease processes and seen to be elevated in association with air pollution, the direct causal roles are less clear.

Biological mediators have a new-found home in the systems biology model of diseases. The concepts of exposome (the measure of all the exposures of an individual in a lifetime, and how these exposures relate to health) and pollutome (the totality of all forms of pollution that have the potential to harm human health) aim to complement these models by addressing the interaction between the environment and an individual's building blocks that results in diseases. It is therefore pertinent to have a summary of the available evidence for all the implicated biomarkers to pave the way for future research in this field.

Aims

For this review, we aimed to collect all the available data from human and animal studies for potential mediators involved in the pathogenesis of myocardial and vascular injuries and to categorise them based on their mechanism of action.

Method

Essential questions in this investigation before identifying potential biomarkers were:

1. *What are primary myocardial and vascular injuries attributed to acute or chronic air pollution exposure?*
2. *Which air pollutants are implicated in the pathogenesis of those pathologies?What are the primary mechanisms by which these air pollutants mediate their injury?*
3. *What are the mediators released after exposure to air pollutants that activate these pathological pathways that may act as markers of individual susceptibility and higher personal risk of cardiovascular complications?*

We examined all systematic reviews since 2015 to have the most recent summary of evidence for each sub-topic of interest and included relevant papers from 1990 on, since most technological advancements in detection and quantification of bio-mediators started in this period. Our choices of search engines were Google Scholar for its superior indexing and search algorithms, and PubMed for its greater number of indexed papers.

Review papers addressing the first question were summarised first to allow a more targeted search for the next steps. Identified mechanisms of injury were atherosclerosis formation and progression leading to coronary artery disease (CAD) and acute coronary syndrome (ACS), congestive cardiac failure (CCF), cardiomyopathy, and pulmonary hypertension (type 1, 2 and 3). To identify relevant HAPs (essential question 2), we used the individual results from the previous step along with the individual pollutant's name. A HAP was considered relevant if there was at least one review article or human study addressing that HAP—these included $PM_{2.5}$, PM_{10}, NO_2 and O_3. Finally, to generate the list of mediators that need to be included, we used the papers that were filtered in question 1 and question 2 and summarised the described pathways linking the identified HAPs to cardiovascular pathologies of interest. Our final list of pathophysiological pathways included systemic inflammation as the leading mechanism, along with local tissue inflammation, such as adipose tissue inflammation, that leads to the production of harmful adipokines, oxidative stress and mitochondrial dysfunction, endothelial dysfunction, impaired lipid metabolism, thrombogenesis, increased plaque vulnerability and autonomic dysfunction.

We then identified individual mediators linked to cardiovascular injury for each pathway by searching for the pathway combined with Boolean keywords + or AND, along with terms *cardiovascular disease, ischaemic heart disease, myocardial infarction, coronary artery disease, congestive cardiac failure, congestive heart failure, atherosclerosis, cardiomyopathy,* and *vascular disease*. Using this method allowed us to have a more comprehensive list of mediators to rule out, one by one, by performing inquiries in our elected search engines using individual mediators, with the keywords *Air Pollution, Particulate Matter 2.5, Particulate Matter 10, PM2.5, PM10,*

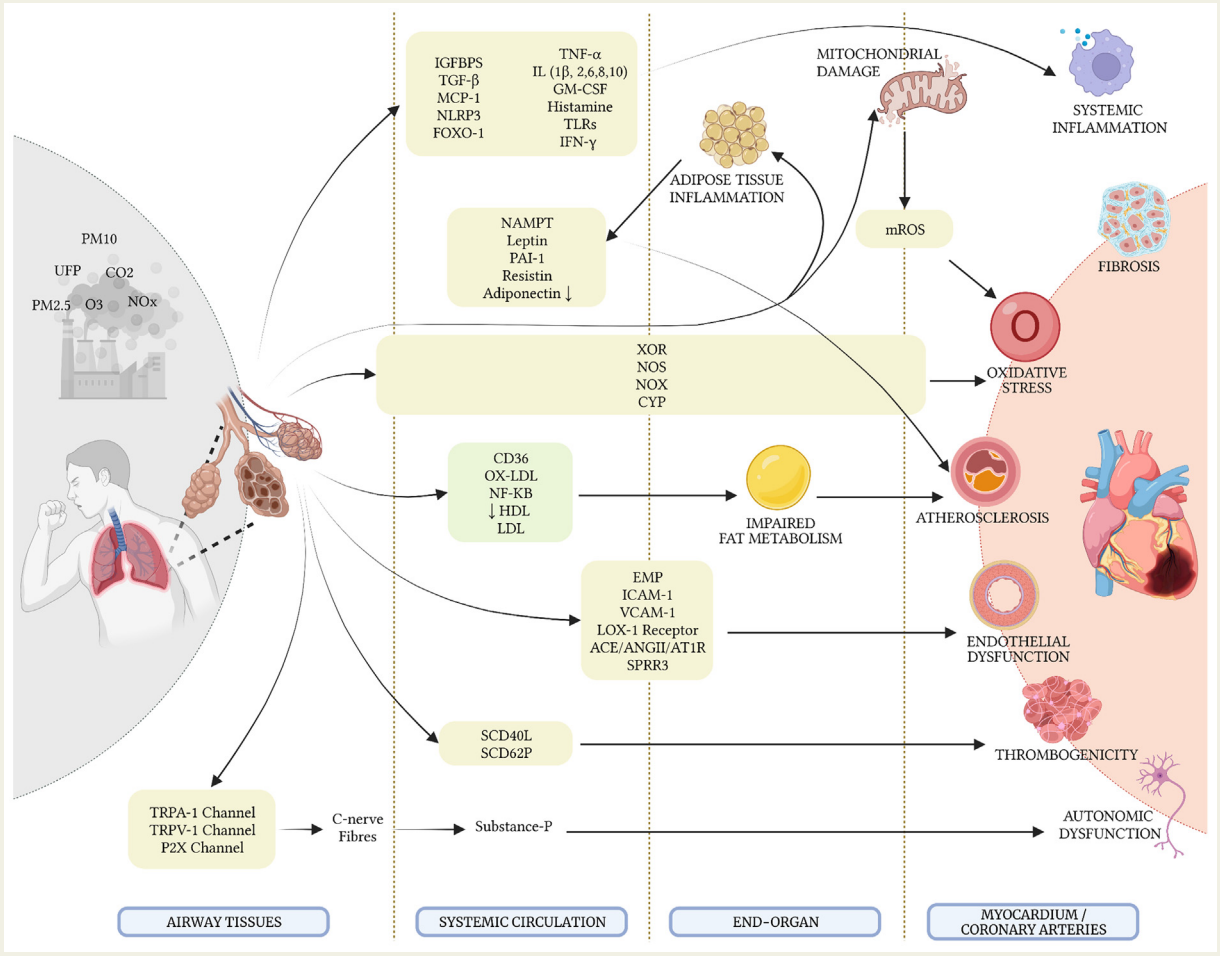

Figure 1 Potential biomarkers of myocardial and vascular complications of air pollution and their mechanisms of injury.

nitrogen dioxide, *carbon dioxide* and *ozone*. To better categorise the final set of mediators, we grouped them into inflammatory and non-inflammatory classes. We then grouped these papers based on individual bio-mediators or, in some instances, the covered pathways. Older papers that had been replaced by newer, more up-to-date evidence, and papers with similar findings were reviewed as a group, and papers that had the best evidence and were most up to date were kept.

This method was chosen to have a maximal screening potential. Potential sources of assessment bias, however, include our reliance on review articles as the initial screening step, which seemed to primarily focus on the effects of $PM_{2.5}$ and man-made sources of air pollution. Our complete search strategy is outlined in Supplementary material.

Results

Figure 1 outlines the potential biomarkers of myocardial and vascular complications of air pollution and their mechanism of injury.

Results, Part A: Inflammatory Mediators

1. Systemic Inflammation

The inflammatory response is triggered in response to tissue injuries as well as internal and external factors that get flagged as potentially harmful. These responses are classed as either acute or chronic, each with a specific set of mediators which result in cellular and vascular events. As shown in Table 1, air pollutants can result in the release of a range of mediators into the systemic circulation that can result in injury to the cardiovascular system.

2. Local Tissue Inflammation

HAP can induce local tissue inflammation via direct insult as well as indirectly by triggering the systemic inflammatory response. Besides inflammation of the lungs, that is the primary source of systemic cytokine release, the following tissues can also be inflamed following HAP exposure, further releasing harmful mediators:

Table 1 Potential air pollution induced systemic inflammatory mediators.

Mediator	Description	Triggers	Effect on CVD
Tumour Necrosis Factor-α (TNF-α)	An important pro-inflammatory cytokine released by monocytes and macrophages. It has been implicated in a range of autoimmune conditions such as rheumatoid arthritis (RA).	$PM_{2.5}$ [17] PM_{10} [18] O_3 [19] NO_2 [20]	CAD [21] CCF [22] Lipid metabolism, insulin resistance, endothelial dysfunction, ROS formation and hypercoagulable state [23]
Interleukin 1 beta (IL-1 β)	Part of the IL-1 family that is released systemically from monocytes, smooth muscle cells and endothelial cells in response to microbial products and endogenous triggers that act on IL-1 receptors.	$PM_{2.5}$ [24] PM_{10} [18] NO_2 [20] O_3 [25]	Atherogenesis by activating inflammasome-IL-1β pathway [26]
Interleukin-2 (IL-2)	Responsible for eliminating diseased cells by contributing to the inflammatory cascade via activating CD4 and CD8 T-cells. Also has a significant role in the resolution of inflammation.	Chronic HAP [27] ↑ NOx [28] ↓	CAD [29] Stronger association with stable angina than ACS [30]
Interleukin-6 (IL-6)	A pivotal multifunctional cytokine that triggers the release of many other downstream inflammatory cytokines and is the main stimulus for C-reactive protein (CRP) synthesis.	$PM_{2.5}$ [17] PM_{10} [18] O_3 [31] SO_2 [32] NO_2 [33]	CAD with the same weight as traditional risk factors such as HTN [33] Levels predictor of worse outcomes [34]
Interleukin-8 (IL-8)	A small cytokine that belongs to the CXC subfamily, which is released primarily from monocytes and macrophages, leading to the attraction of other inflammatory cells towards the inflammatory site as well as activation of monocytes and neutrophils. IL-8 has a central role in the inflammatory cascade at the site of coronary artery plaque formation [35].	$PM_{2.5}$ [36] UFP [37] PM_{10} [38] O_3 [31] Iron particles [39]	Inflammatory cascade at the site of coronary artery plaque formation [35]. Chemotactic effects on VSMC and inhibition of local TIMP-1 expression contributing to atherosclerosis formation [35].
Interleukin-10 (IL-10)	Anti-inflammatory cytokine by inhibiting inflammatory response from macrophages, antigen presentation and proliferation and inhibiting Th1 T cells.	$PM_{2.5}$ [40] ↓ NOx [28] ↓	Anti-atherogenic [41]
Granulocyte macrophage colony-stimulating factor (GM-CSF)	A multifunctional cytokine that controls all phases of the leukocyte life cycle from production to proliferation and differentiation.	PM_{10} [18] O_3 [42] NO_2 [43]	MI [44] Serum levels predictive of the severity of cardiac failure and myocardial remodelling [44]
Histamine		Diesel particles [45] $PM_{2.5}$ [46] O_3 [47]	Increase thrombogenicity [45]
Toll-like receptors (TLRs)	There are 13 TLRs recognised that are located on the plasma membrane or endolysosomal compartment, with the primary function of detecting 'danger signals' and activating a range of inflammatory mediators.		Cardiomyopathy, atherosclerosis, MI, and myocardial remodelling in CCF [48]

Table 1. (continued).

Mediator	Description	Triggers	Effect on CVD
Insulin-like growth factor binding proteins (IGFBPs)	Modulate insulin-like growth factors (IGF) binding to their receptors by binding to them and carrying them in plasma as a dimetric complex [49].	$PM_{2.5}$ [24]	CAD, IHD, and total mortality [49]
Interferon γ (IFN-γ)	A central cytokine in both innate and adaptive immunity, which, by activating Janus kinases (JAKs), modulates close to 2,300 human genes.	$PM_{2.5}$ [50] O_3 [51]	Atherosclerosis via formation of foam cells, VSM inflammation, the release of adhesion cells, and systemic inflammation [52]
Transforming growth factor beta (TGF-β)	A superfamily of more than 30 proteins involved in cellular growth and modulating different phases of cellular life, such as differentiation, proliferation, and apoptosis [53].	$PM_{2.5}$ [54]	Cardiac fibrosis formation via SMAD dependent and independent mechanisms [53]
Monocyte chemoattractant protein-1 (MCP-1)	A very potent chemokine that belongs to the C-C chemokine family and is released in response to a range of pro-inflammatory stimuli, such as oxidative stress and growth factor, which can result in the attraction of monocytes to sub-endothelium [55].	$PM_{2.5}$ [56]	Thrombogenicity, CAD and restenosis following balloon angioplasty [55]
NLRP3 inflammasome	NLRP3 belongs to the NOD-like receptor (NLR) family with a pyrin domain, which is involved in inflammasome formation, which in turn can initiate an inflammatory cascade [57].	$PM_{2.5}$ [58]	Atherosclerosis, IHD and cardiomyopathy [57]
PI3K/Akt/FOXO1 pathway	Forkhead transcription factors of the O class (FOXOs), consisting of four members, are expressed in most human tissues, and play a role in various cell cycle stages and inflammation, metabolism, and stress resistance [59].	$PM_{2.5}$ [60]	Ischaemia/reperfusion injury, cardiomyopathy, and insulin insensitivity [59]

Abbreviations: $PM_{2.5}$, particulate matter <2.5 μm; PM_{10}, particulate matter <10 μm; CAD, coronary artery disease; CCF, congestive cardiac failure; ROS, reactive oxygen species; HAP, hazardous air pollutant; IHD, ischaemic heart disease; ACS, acute coronary syndrome; HTN, hypertension; UFP, ultrafine particles; VSM, vascular smooth muscle; TIMP-1, tissue inhibitor matrix metalloproteinase 1; Th1, T helper 1; MI, myocardial infarction.

Adipose tissue inflammation

Long-term exposure to $PM_{2.5}$ can lead to adipose inflammation [61], leading to the release of adipokines into the circulation. The mechanism behind this effect is not established but may be secondary to systemic inflammation in a similar manner to that proposed to occur in patients with metabolic syndrome. $PM_{2.5}$ is known to alter mitochondrial activity and gene expression in brown adipose tissue (BAT) and white adipose tissue (WAT) differently, with more exaggerated changes seen in BAT—resulting in a functional mismatch and contributing to a range of metabolic syndrome features including insulin resistance and atherosclerosis [62].

Intestinal inflammation

Air pollution enters the gastrointestinal tract (GIT) via mucociliary clearance of inhaled air, and therefore can directly interact with the GIT epithelium to cause local, and subsequently systemic inflammation by forming reactive oxygen species (ROS) and pro-inflammatory cytokines [63].

Perivascular adipose tissue (PVAT) inflammation

PVAT involves adipocytes surrounding blood vessels and, in normal physiology, has a dominant anticontractile function, but in the pathophysiological state contributes to endothelial dysfunction, atherosclerosis and aortic aneurysm [64]. It is shown to be activated in mice exposed to $PM_{2.5}$, likely by ROS formation and inflammatory changes [64]. Acrolein is proposed as the primary mediator responsible for upregulation of PVAT and release of PVAT leptin following exposure to $PM_{2.5}$ [64].

These processes can result in release of mediators when triggered by HAP, as shown in Table 2.

Table 2 Potential air pollution induced local inflammatory mediators.

Mediator	Description	Triggers	Effect on CVD
Visfatin/nicotinamide phosphoribosyl transferase (NAMPT)	An intracellular and extracellular adipocytokine found in adipocytes, bone marrow, muscles, and the heart [65]. Visfatin has a role in releasing inflammatory cytokines, MMPs, and activating inflammatory signalling pathways [65].	$PM_{2.5}$ [66] PM_{10} [66]	Atherosclerosis progression by promoting inflammation and adhesion, vascular remodelling by VEGF modulation, the release of FGF-2 and MMPs and activation of several angiogenic signalling pathways [65]
Leptin		$PM_{2.5}$ [64]	Atherosclerosis by alteration in VSMC [64]
Plasminogen activator inhibitor-1 (PAI-1)	Sourced from inflamed adipose tissue, vascular endothelium and the liver that can be stored in platelets, making them resistant to thrombolysis [67]. PAI-1's secretion is stimulated by a range of cytokines, growth factors and angiotensin II and IV [67].	$PM_{2.5}$ [68] PM_{10} [68] Metal particles [69]	Atherosclerosis and CAD [67]
Resistin	An adipokine that has been shown to counteract insulin action leading to insulin resistance.	$PM_{2.5}$ [61]	Atherosclerosis, thrombus formation, angiogenesis, VSM cell function and altered endothelial function [70]
Adiponectin	The most abundant secreted factor by adipocytes, with levels declining following stimulation with insulin, and cytokines such as TNF-α and endothelin-1 increase with IGF-1 stimulation [71]. Adiponectin's level is declined with increased adipose tissue mass, and its function is opposite of that of leptin and resistin, making it an anti-inflammatory and anti-thrombotic agent [71].	$PM_{2.5}$ [72] ↓	Cardioprotective agent by controlling atherosclerotic pathways such as endothelial dysfunction, plaque initiation and progression [71]

Abbreviations: MMPs, matrix metalloproteinases; $PM_{2.5}$, particulate matter <2.5 μm; PM_{10}, particulate matter <10 μm; VEGF, vascular endothelial growth factor; FGF-2, fibroblast growth factor 2; VSMC, vascular smooth muscle cells; CAD, coronary artery disease; TNF-α, tumour necrosis factor alpha; IGF-1, insulin-like growth factor 1; VSM, vascular smooth muscle.

3. Oxidative Stress

Oxidative stress refers to the imbalance between the production of reactive oxygen species (ROS) and antioxidants, which play a central role in both local and systemic inflammation. The main active ROS are free radicals (O^-) in various forms such as O_2^-, OH^- and H_2O_2 (superoxide, hydroxyl, and hydrogen peroxide) [73]. ROS serve an essential role in vasodilation in controlled quantities. The different types of ROS differ from each other in terms of their production source and structure. These highly reactive components are controlled using various mechanisms collectively referred to as antioxidants. Failure of this control mechanism or excessive ROS production (endogenous or exogenous) results in an adverse reaction locally and systemically.

In oxidative stress, ROS themselves can be considered mediators that are released in response to exposure to toxins such as $PM_{2.5}$. Studies have shown that air pollution is a significant source of oxidative stress. $PM_{2.5}$ comprising metals (iron [Fe], copper [Cu]) and organic species (photochemically aged organics), have the highest oxidative potential (OP) even at moderate concentrations [74]. ROS can also interact with their surrounding lipids in the membrane,

resulting in lipid pre-oxidisation. This effect produces a range of compounds, such as hydroxyl fatty acids and oxidised cholesterol, eventually causing destruction and increased membrane permeability, which further promotes local and systemic inflammation [63]. Various mediators are implicated in HAP-induced oxidative stress, as shown in Table 3.

4. Mitochondrial Dysfunction

The role of mitochondrial disorders in acquired cardiovascular pathophysiology has become a subject of great activity owing to correlations seen in hereditary mitochondrial diseases and cardiovascular comorbidities. There are several ways that mitochondrial physiology can be perturbed: altered morphology, disrupted mitochondrial energetics, increased oxidative stress, dysregulation of apoptosis and autophagy, and via increased mitochondrial mutations [82].

Mitochondrial oxidative stress and DNA damage are shown to result in endothelial dysfunction [83] and various cardiac complications such as hypertension, atherosclerosis, and cardiomyopathy [84]. Mitochondrial DNA (mtDNA) damage has a role in innate immune response and inflammation [84] which can explain these cardiovascular complications [85]. More specifically, some of the pathophysiological processes attributed to cardiovascular injury include increased arterial pressure and vascular dysfunction [84], Incomplete degradation of mtDNA by autophagy [86] and accumulation of mtDNA–LL37 complexes in atherosclerotic plaques [87].

Exposure to air pollution, especially $PM_{2.5}$ and PM_{10}, result in mitochondrial damage resulting in several adverse cardiovascular outcomes such as reduced HRV [88]. This is owing to diverse mitochondrial functions in energy production, regulation of metabolism and homeostasis of elements such as iron and copper and even cellular death mechanisms [89]. Pathways leading to mitochondrial

Table 3 Potential air pollution induced oxidative stress mediators.

Mediator	Description	Triggers	Effect on CVD
Xanthine oxidoreductase (XOR)	Expressed as either xanthine dehydrogenase (XDH) or xanthine oxide (XO) which are responsible for the oxidation of xanthine to uric acid resulting in the influx of free radicals [73].	$PM_{2.5}$ [75]	Impaired myocardial energy production, especially in CCF [73]
Nitric oxide synthases (NOS)	Which consists of three known subtypes neuronal (nNOS), inducible (iNOS) and endothelial (eNOS), stimulates the production of NO both in the physiological state to maintain cardiovascular homeostasis but also in response to pathophysiological stimuli.	$PM_{2.5}$ [76] ↓ (Mainly eNOS)	Protective effect on the cardiovascular system and anti-thrombotic effect [77]
NADPH oxidase (NOX)	Constitutes seven members, utilise NADPH to donate electrons which results in the production of superoxide (O_2^-) or hydrogen peroxide (H_2O_2) [78].	$PM_{2.5}$ [79]	HTN, atherosclerosis, IHD and cardiac fibrosis [78]
Cytochrome P450 (CYP)	Primarily responsible for the peroxidation and oxidation of elements such as vitamins, steroids, and certain drugs. Outside its physiological role, CYP contributes to amino acid (AA) metabolism and ROS production.	$PM_{2.5}$ [80]	HTN, angiogenesis, atherosclerosis, CCF, arrhythmia and cardiomyopathy [81]

Abbreviations: $PM_{2.5}$, particulate matter <2.5 μm; CCF, congestive cardiac failure; NADPH, nicotinamide adenine dinucleotide phosphate; HTN, hypertension; IHD, ischaemic heart disease; AA, amino acid; ROS, reactive oxygen species.

Table 4 Potential air pollution induced mediators of mitochondrial dysfunction.

Mediator	Description	Triggers	Effect on CVD
Mitochondrial reactive oxygen species (m)	Raised ROS due to various internal or exogenous factors are shown to cause mtDNA damage [90,91].	$PM_{2.5}$ [88] PM_{10} [88]	Myositis and dilated cardiomyopathy [92] Atherosclerosis and VSM dysfunction [91,93]

Abbreviations: ROS, reactive oxygen species; mtDNA, mitochondrial DNA; $PM_{2.5}$, particulate matter <2.5 μm; PM_{10}, particulate matter <10 μm; VSM, vascular smooth muscle.

damage are currently poorly understood, and, at present, ROS are the central identified mediators following exposure to toxins such as air pollution, as shown in Table 4.

Results, Part B: Non-Inflammatory Mediators

5. Endothelial Dysfunction

Endothelial dysfunction has a critical role in developing atherosclerotic plaques as the initial step in this pathological cascade which is often followed by increased vascular permeability to lipoproteins, enhanced leucocyte adhesion, platelet aggregation, and the production of various inflammatory cytokines. Endothelial dysfunction is a result of various pathophysiological pathways, most notably: oxidative stress, inflammation, leucocyte adhesion and transmigration, apoptosis and cell death, endothelial NO synthase uncoupling, endothelial-to-mesenchymal transition, and endothelial cell senescence [94].

Acute exposure to $PM_{2.5}$ is shown to elevate the circulating von Willebrand factor (vWF) level, which directly measures endothelial injury [95]. Liang et al. [95] demonstrated that the effect of $PM_{2.5}$ on endothelial dysfunction is likely via inflammation and oxidative stress, whereas, in another study [96], direct cytotoxicity and autophagy were proposed as the likely mechanism. Air pollution mediated factors that can lead to endothelial dysfunction are show in Table 5.

6. Atherosclerotic Plaque Vulnerability

Atherosclerotic plaque rupture is considered the leading cause of myocardial infarction and ischaemic stroke. Plaque vulnerability is shown to be increased after exposure to HAPs, likely by upregulation of MMPs and TIMPs. Key mediators are metalloproteases and proteins that modulate these moieties, as shown in Table 6.

7. Thrombogenesis

High HAP levels are associated with increased prothrombogenicity markers, as shown in Table 7 [24]. Obese patients are shown to be primarily impacted by the prothrombogenic effect of $PM_{2.5}$, which is thought to be modulated by adipose inflammation leading to platelet activation and aggregation [112].

8. Autonomic Dysfunction

Autonomic dysregulation, which results from the accentuated sympathetic drive and diminished parasympathetic activity, is considered a major risk factor for adverse cardiovascular outcomes such as cardiac arrest and AMI [115]. Alterations in cardiac autonomic tone are thought to be the most immediate effects of exposure to air pollutants [116]. This is thought to be due to a shift from sympatho-inhibition to sympatho-excitation as evidenced by studies showing reduced high-frequency heart rate variability (HRV) [117] and the observed protective effect of β-adrenoceptor inhibitors on pollution-evoked CV events [118]. There is no study directly assessing autonomic nerve activity in response to air pollution, and most of our understanding of the pathophysiology is theoretical.

Inflammatory mediators

Inflammatory mediators can have a direct effect on modulation of autonomic system. These include:

- *Toll-like receptor 2 (TLR2) Methylation:* secondary to $PM_{2.5}$ is shown to result in activation of autonomic system [119].

Airway receptors

Airway receptors include sensors located throughout the upper and lower airways (C-nerve fibres, *Rapidly* adapting pulmonary receptors [RARs] and *Slowly* adapting pulmonary receptors [SARs]), designed to sense environmental irritants, such as cigarette smoke and air pollutants, leading to a range of reflexes such as coughing and dyspnoea [116].

Air pollution-induced mediators of C-nerve fibres activation are as follows:

- *Transient receptor potential ankyrin 1 (TRPA1) channel* is a small Ca^{2+}-permeant non-selective cation channel activated by cold exposure, environmental irritants, and reactive oxides [120]. Its activation results in inflammatory hyperalgesia and neurogenic inflammation, and, being located on nociceptive neurons, causes the perception of noxious stimuli [120]. Following exposure to diesel exhaust, these receptors are shown to increase cardiac arrhythmogenesis and autonomic activation [121].
- *Transient receptor potential vanilloid 1 (TRPV1) channel* is present on the nasal mucosa, trachea, bronchi, and alveoli, which senses toxins such as capsaicin, extracellular

Table 5 Potential air pollution induced mediators of endothelial dysfunction.

Mediator	Description	Triggers	Effect on CVD
Endothelial microparticles (EMP)	Result from endothelial shedding and are thought to have both beneficial and detrimental effects on the endothelium [97].	$PM_{2.5}$ [98]	Endothelial injury, inflammation, thrombosis, and angiogenesis [97]
Intercellular adhesion molecule 1 (ICAM-1)	Expressed on a range of cells, including cardiomyocyte, which is upregulated in response to cytokine, ROS, and apoptosis, amongst other stimuli [99]. As the name implies, it mediates the adhesion of circulating inflammatory molecules to the vascular wall and trans-endothelial migration to vascular intima.	$PM_{2.5}$ [100] PM_{10} [101] NO_2 [20]	Atherosclerosis and the progression of CAD [99]
Vascular adhesion molecule 1 (VCAM-1)	Belongs to the superfamily of immunoglobulins, expressed in the endothelium of blood vessels in most vital organs, including the brain and heart, induced by pro-inflammatory cytokines, and following expression leading to accumulation and transmigration of monocytes and other innate inflammatory cells [102].	$PM_{2.5}$ [100] PM_{10} [101]	Atherosclerosis, HTN, AF, IHD and HFpEF [102]
Lectin-like oxidised low-density lipoprotein 1 receptor (LOX-1 receptor)	A prominent scavenger receptor that is expressed on ECs, inflammatory cells and cardiomyocytes. LOX-1 receptors located on macrophages can bind to modified LDL (e.g., oxidised carbamylated or acetylated) and non-self or modified self-targets that result in uptake of the modified lipids. Similarly, in endothelial cells, they behave as sensors that can respond to external stimuli and alter their cellular phenotype from anti-inflammatory to pro-inflammatory. In the normal physiological state, these actions eliminate harmful or degraded substances. However, these responses can result in endothelial dysfunction in a pathophysiological state.	$PM_{2.5}$ [103]	Atherosclerosis [104]

Table 5. (continued).

Mediator	Description	Triggers	Effect on CVD
Angiotensin-converting enzyme/ angiotensin II/angiotensin type 1 receptor axis (ACE/ANGII/ AT1R)	Renin-angiotensin system (RAS) with the end-product of angiotensin II has long been identified as an important agent in the pathophysiology of cardiovascular diseases and cardiac remodelling. The development of angiotensin ACE inhibitors and angiotensin receptor blockers (ARBs) have revolutionised the management of hypertension, CCF and IHD [105].	$PM_{2.5}$ [106]	Cardiac remodelling, HTN, CCF and IHD
Small proline-rich repeat protein 3 (SPRR3)	Usually found in the foregut and oesophagus; however, it is also expressed in VSMCs of the atheroma of large arteries in a pathological state in response to mechanic cyclic stress [107].	$PM_{2.5}$ [108]	Cardiac fibrosis by augmentation of fibroblast proliferation [107]

Abbreviations: $PM_{2.5}$, particulate matter <2.5 μm; PM_{10}, particulate matter <10 μm; VSMCs, vascular smooth muscle cells; CCF, congestive cardiac failure; HTN, hypertension; IHD, ischaemic heart disease; AF, atrial fibrillation; HFpEF, heart failure with preserved ejection fraction; ECs, endothelial cells.

protons (released during tissue acidosis and ischaemia) as well as excess heat [122].

- *Purinergic P2X channel* receptors are present throughout the body with physiological roles such as neurotransmission, inflammation, and cell death [123]. In the lungs, subtypes of P2X receptors can be found on most microvascular endothelial cells.

Activation of C-nerve fibres result in production of substance P, which is also a potent biological mediator, as shown in Table 8.

Baroreceptors

Baroreceptors are stretch-sensitive sensors located in the carotid sinus and aortic arch to adjust blood pressure in response to alterations in systemic BP by inhibiting the sympathetic or activating the parasympathetic system [116]. Baroreflex desensitisation can result from chronic hypertension and CVD [132]. Exposure to major air pollutants such as SO_2 reduces baroreflex sensitivity (BRS). At the same time, many studies have also shown BP instability following exposure to air pollutants (lowered BP in the acute setting and hypertension in the long term), which can indirectly result in reduced BRS [116].

Table 6 Potential air pollution induced mediators of increased atherosclerotic plaque vulnerability.

Mediator	Description	Triggers	Effect on CVD
Matrix-degrading metalloproteinases (MMPS)	Present in macrophages, endothelial cells, and smooth muscle cells at low levels [109], playing an essential role in regulating inflammatory response and thrombogenesis following plaque rupture [110].	$PM_{2.5}$, NO_2, CO and SO_2 [24]	Alteration in vascular anatomy and atherosclerotic plaque vulnerability [24]
Tissue inhibitor of metalloproteinases (TIMPS)	The proteins responsible for modulating MMPs.	$PM_{2.5}$, NO_2, CO and SO_2 [24]	Serum level is associated with Framingham Risk Score and inversely with LV systolic function [111]

Abbreviations: $PM_{2.5}$, particulate matter <2.5 μm; PM_{10}, particulate matter <10 μm; CVD, cardiovascular disease; MMPs, matrix metalloproteinases; LV, left ventricle.

Table 7 **Potential air pollution induced thrombogenic mediators.**

Mediator	Description	Triggers	Effect on CVD
Soluble CD40 ligand (SCD40L)	A pro-inflammatory and pro-thrombotic protein that belongs to the superfamily of TNF superfamily with receptors on B cells. sCD40L is predominantly sourced from platelets and can enhance platelet activation and aggregation [113].	HAP [24]	Thrombus formation [113]
Soluble P-selectin (SCD62P)	A cell adhesion protein that belongs to the lectin family, which is stored in platelets and endothelial cells. Once activated, it gets translocated to the cell surface and released as a soluble form to circulation. Once the soluble form is bounded to its receptor PSGL-1, it starts a pro-coagulant cascade [114].	HAP [24]	Thrombus formation [114]

Abbreviations: HAP, hazardous air pollutants; TNF, tumour necrosis factors; CVD, cardiovascular disease; PSGL-1, P-selectin glycoprotein ligand 1.

Chemoreceptors

Chemoreceptors are located centrally in the brainstem and peripherally in the aorta and carotid bodies, maintaining homeostasis [116]. Carotid body chemoreceptors act as sensors for variations in O_2, CO_2, pH and temperature and activate sympathetic tone in response to hypoxia [116]. Thus far, no study has directly examined the effect of air pollution on carotid body chemoreceptors. However, given that there is evidence of hypoxia following exposure to air pollution, it is safe to conclude that these sensors play a role in air pollution-induced autonomic dysregulation [116].

9. Impaired Lipid Metabolism

An important site of lipid metabolism that is also impacted by exposure to air pollution is the intestine. The intestine is a crucial player in lipid metabolism by controlling dietary or biliary cholesterol absorption and synthesising endogenous cholesterol such as apolipoprotein A-1 (apoA-I) and high-density lipoprotein (HDL) via intestine enterocytes [63]. Recent evidence shows that air pollution can directly alter intestinal lipid metabolism by changes in lipid intestinal redox lipidome [63].

Another vital source of dysregulation in lipid metabolism is the liver. Air pollutants can result in lipid peroxidation leading to oxidation of a range of lipids, including low-density lipoprotein (LDL) and Apo [63]. The oxidisation of lipids via intestinal and hepatic routes has a range of adverse health impacts, such as diabetes, atherosclerosis, and systemic inflammation [63]. Air pollution induced mediators causing impaired lipid metabolism are shown in Table 9.

Table 8 **Activated airway receptors following exposure to HAP with the potential to cause cardiovascular damage.**

Mediator	Description	Triggers	Effect on CVD
Substance P (SP)	Widely expressed in both central and peripheral nervous systems with functions such as regulating pulmonary and cardiovascular function, emetic reflux, noxious stimuli, and modulating autonomic reflexes [124]. SP is also released by inflammatory cells [125]. Local SP is shown to result in coronary artery vasodilation by releasing NO [126] and have a protective effect against endothelial dysfunction [127]. In contrast, over the long term, elevated SP is shown to have a detrimental effect on the heart as it plays a vital role in cardiac mast cell activation [128]. Cardiac mast cell activation does so via three pathways: the release of pro-inflammatory mediators such as TNFα and MMPs; the release of renin; and the production of vascular endothelial growth factor (VEGF) [129].	O_3 [25,130]	Cardiac fibrosis and hypertrophy by upregulating Endothelin-1 [131]

Abbreviations: TNFα, tumour necrosis factor alpha; MMP, matrix metalloproteinases.

Table 9 Air pollution induced mediators causing impaired lipid metabolism.

Mediator	Description	Triggers	Effect on CVD
Fatty acid translocase (FAT; CD36)	A member of the scavenger receptor family that is expressed on endothelial cells (ECs), cardiomyocytes, and adipocytes amongst other tissues, which has a crucial role in immune regulation, platelet activation, and regulation of metabolism by regulating fatty acid (FA) uptake in ECs and myocardial tissue and FA metabolism in the liver [133]. CD36 is stimulated by insulin, hyperglycaemia, and hyperlipidaemia [133].	$PM_{2.5}$ [134] O_3 [135]	IHD, cardiomyopathy, cardiac hypertrophy, and atherosclerosis by altering myocardial energy supply and the activation of platelets. [133]
OX-LDL	Excessive ox-LDL stimulate the expression of the LOX-1 receptor, thereby reducing the protective autophagy response, leading to EC dysfunction [136].	$PM_{2.5}$ [137]	Atherosclerosis [136]
LR4/MYD88/NF-KB signalling pathway		$PM_{2.5}$ [138] O_3 [19]	Promote the transformation of macrophages into foam cells [138] Excessive expression of inflammatory factors such as TNF-α, CRP and IL-6 [19]
High-density lipoprotein (HDL)	A critical cardioprotective mediator with a primary anti-atherosclerotic function by reverse cholesterol transport and efflux of cholesterol from macrophages into lipid-free ApoA-I, which results in healthy NO synthesis [139].	$PM_{2.5}$ [139] ↓	HDL dysfunction is linked with CAD, atherosclerosis and increased cardiac mortality [139]
Low-density lipids (LDL)	In contrast to HDL, increased LDL levels are directly correlated with increased atherosclerosis burden and related CVD.	$PM_{2.5}$ [140]	Atherosclerosis [140]

Abbreviations: $PM_{2.5}$, particulate matter <2.5 μm; IHD, ischaemic heart disease; TNF-α, tumour necrosis factor alpha; CRP, C-reactive protein; IL-6, Interleukin 6; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CAD, coronary artery disease; CVD, cardiovascular disease.

10. Other Mediators

The emergence of new mediators that do not fall under any of the traditional pathogenic pathways is shining a new light in our understanding of the missing links between interaction of HAPs with airway tissues and adverse cardiovascular outcomes (Table 10).

Discussion

There is convergent evidence connecting CVD with acute and chronic exposure to HAP, identifying HAP as an independent CVD risk factor [147]. Through our advancements in household heating methods, we have seen an enormous reduction in mortality attributable to indoor air pollution. Despite this success, industrialisation has resulted in increases in large-scale ambient outdoor air pollution, meaning the impact of air pollution is no longer confined to the place of the pollutant's origin.

Advancements in molecular biology have enabled our understanding of the complex nature of air pollution—highlighting numerous pathways and mediators of myocardial and vascular injury. In this paper we have demonstrated that local and systemic inflammation get triggered in

Table 10 Novel mediators linking air pollution and cardiovascular injury.

Mediator	Description	Triggers	Effect on CVD
Aryl hydrocarbon receptor (AHR)	Plays a central role in regulating the toxicity of environmental pollutants, and their upregulation results in inflammation, oxidative stress, and lipid infiltration [141].	$PM_{2.5}$ [137]	Inflammation, oxidative stress, and lipid infiltration [141].
Gut microbiome	By far the largest reservoir of micro-organisms, containing 90% of the human body, which have myriad roles in the body's homeostasis, including their role in the immune system and cell-signalling processes [142].	HAP [143]	Associated with increased CVD comorbidities such as IHD and CAD
Stress hormones	Activation of the Hypothalamus-Pituitary-Adrenal (HPA) axis results in stress hormones, including glucocorticoids and catecholamines. These compounds result in the so-called "fight or flight" by modulating various body functions such as inflammation, metabolism, CNS function and cardiovascular function [144]. In a pathological state caused by excess production either due to continuous stress stimuli, abnormal stress response or malignant tumours, these excess stress hormones can result in metabolic syndrome, excess immune response, EC damage, and atherosclerosis [144].	$PM_{2.5}$ [145] O_3 [145]	HTN, AMI, and chronic CAD [146]

Abbreviations: $PM_{2.5}$, particulate matter <2.5 μm; HAP, hazardous air pollutants; HPA, hypothalamus-pituitary-adrenal; IHD, ischaemic heart disease; CAD, coronary artery disease; CNS, central nervous system; EC, endothelial cells; AMI, acute myocardial infarction; HTN, hypertension.

response to most HAPs via activation of cytokines such as interleukins and TNF-α. Inflammation is usually accompanied by oxidative stress and mitochondrial damage. In most scenarios, pro-atherosclerosis mechanisms, such as endothelial dysfunction, lipid metabolism dysfunction, and increased plaque vulnerability, are also activated. Other biological processes that influence the cardiovascular system, such as autonomic dysfunction and alteration of the gut microbiome, may also be triggered. By providing a big-picture view of the currently accepted HAP-related mediators, we can start to build a physiological framework of HAP activity *in vivo* beyond the alveoli. We can see that, not only is the widely hypothesised local and systemic inflammatory response indeed being activated, but also alternate non-inflammatory pathways, such as endothelial damage and autonomic dysfunction, are involved, and this may point toward a common, yet-to-be-discovered, 'pre-inflammatory' mechanism. The systems biology model put forward in this paper can also be used to improve our understanding of the other environmental triggers leading to CVD. It is noteworthy that the focus of most of the human studies used in this paper was short-term exposure to traffic-related air pollution (TRAP). As such, there is a knowledge gap in our understanding of how these proposed bio-mediators differ in response to other sources of air pollution, such as bush fires or sandstorms. Similarly, although, historically, most of our public health knowledge regarding morbidities and mortality attributable to air pollution comes from cohort studies of the long-term effects of HAPs, a great degree of further research needs to be done on long-term effects on mediators of pathophysiological pathways.

Future directions for researchers should also include examining common pathways for the mediators described in this paper in large-cohort studies. Further, by utilising

multiomics (a biological analysis approach in which the data sets are multiple "omes" such as the genome, proteome, transcriptome, epigenome, metabolome, and microbiome) technologies and novel machine-learning techniques, researchers can aim to expand our understanding of pathways leading to activation or deactivation of these mediators. The sub-molecular omic view of diseases, from genomics to metabolomics, equips us to understand 'pre-inflammatory' mechanisms that are common between various pathological states. This will be important for our future drug-discovery efforts. Finally, to identify vulnerable or resilient individuals, future studies need to utilise the latest air-quality monitoring technologies and especially high temporal resolution and granular resolution satellite-based data to design long-term assessment of participants' short-term HAP exposure. This will enable us to risk stratify patients based on their short-term exposomic profile rather than a large-scale long-term estimation of their exposure.

Beyond laying grounds for future directions of HAP-related research, this paper should also be seen as part of the series of 'wake-up call' publications in recent years aimed at policymakers and clinicians [15,148]. Public understanding of the dangers of inhaling HAPs tends to be centred around respiratory implications: the cardiovascular damage may supersede respiratory injuries in susceptible individuals, and this needs to be considered in public health policies, as well as in the day-to-day assessment and education of patients.

Conclusions

Despite many studies showing mediators of inflammation and vascular dysfunction in response to air pollution, we are far from being able to apply this to clinical decision making. Whilst we all see distinct individual differences in lung responses to air pollution, host cardiovascular response to air pollution is less evident. If a marker were shown to be causally involved and could be reliably measured as an integrated marker of exposure and host response, it may have potential as a risk measure that could guide management, both in regard to extra vigilance to avoid exposure, as well as more aggressive primary or secondary prevention strategies. Also, whilst all the above is seen to increase in response to air pollution, many are common mediators of inflammation, and the exact mechanisms are often not known. Is it particulates activating systemic factors in the lungs, or are particles carried in cells or vesicles to organs where damage is then observed (e.g., vasculature, heart)? Improved understanding of the activation points may provide insights to novel drug targets.

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Appendices

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