The Impact of Fine Particulate Matter 2.5 on the Cardiovascular System: A Review of the Invisible Killer

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Abstract: Air pollution exerts several deleterious effects on the cardiovascular system, with cardiovascular disease (CVD) accounting for 80% of all premature deaths caused by air pollution. Short-term exposure to particulate matter 2.5 (PM 2.5) leads to acute CVD-associated deaths and nonfatal events, whereas long-term exposure increases CVD-associated risk of death and reduces longevity. Here, we summarize published data illustrating how PM 2.5 may impact the cardiovascular system to provide information on the mechanisms by which it may contribute to CVDs. We provide an overview of PM 2.5, its associated health risks, global statistics, mechanistic underpinnings related to mitochondria, and hazardous biological effects. We elaborate on the association between PM 2.5 exposure and CVD development and examine preventive PM 2.5 exposure measures and future strategies for combating PM 2.5-related adverse health effects. The insights gained can provide critical guidelines for preventing pollution-related CVDs through governmental, societal, and personal measures, thereby benefitting humanity and slowing climate change.

Keywords: air pollution; particulate matter; cardiovascular disease; cardiovascular system; ambient; exposure; mitigation; mitochondria

1. Introduction

Air pollution refers to the release of pollutants into the atmosphere, which causes detrimental effects on living beings. Annually, more than 7 million people worldwide die prematurely due to air pollution, more than any other form of pollution [1,2]. As ranked by the Institute for Health Metrics and Evaluation in 2020, air pollution is the fourth leading cause of mortality among all metabolic and behavioral risk factors [1]. Moreover, recent World Health Organization (WHO) statistics showed that 9 out of 10 people breathe air that has pollution levels exceeding the WHO guidelines; therefore, these people are at an increased risk of noncommunicable diseases (NCDs) such as chronic obstructive pulmonary disease (COPD), cardiac diseases, lung cancer, and stroke. The premature mortality rate due to air pollution is three times greater than that caused by malaria, tuberculosis, and acquired immunodeficiency syndrome together and 15 times higher than that due to wars or other violent causes [3]. The mortality rate associated with air pollution in low- and middle-income countries is 100-fold that of high-income countries. During the past 20 years, heart disease has been the leading cause of death worldwide, accounting for...
40–60% of all premature deaths due to air pollution [4–6]. Air pollutants have been linked to endothelial dysfunction and vasoconstriction, blood pressure (BP) elevation, prothrombotic and coagulant changes, systemic inflammatory and oxidative stress responses, autonomic dysfunction, arrhythmias, and atherosclerosis [7].

It has been predicted that reducing air pollution to WHO air quality standards would increase life expectancy by 0.6 years [5,8]. However, the levels of air pollutants are continuously increasing in both developing countries and developed countries. This is mainly because the stringent air quality guidelines set by the WHO are far from being met, and many breaches in the regulations have been documented in urban areas [3]. According to the United States Environmental Protection Agency (US EPA), particulate matter (PM) is defined as “fine inhalable particles with diameters of generally ≤ 2.5 μm” [4]. Small PM (PM$_{2.5}$) is considered the most lethal fraction of air pollution, and it was the fifth leading risk factor for mortality in 2015 [6]. Concentrations of ambient PM$_{2.5}$ are measured in micrograms of PM per cubic meter of air (µg/m$^3$). When PM$_{2.5}$ is inhaled, it penetrates deep into the lower respiratory tract and reaches the blood and other organs via translocation through membrane receptors. Owing to the larger surface area of PM$_{2.5}$, adsorption of heavy metals, toxic agents, and organic materials is facilitated, thereby enabling the generation of reactive oxygen species (ROS) in the blood and lungs.

Approximately 18.6 million deaths were attributed to cardiovascular disease (CVD) in 2019 globally, including 957,000 deaths in the U.S. [9]. Although PM$_{2.5}$ is associated with a large number of NCDs, approximately half of these deaths are caused by its cardiovascular effects [4,10]. The detrimental effects of air pollution on the cardiovascular system (CVS) came to prominence in the early 1990s, and a markedly linear relationship between PM$_{2.5}$ levels and CVD-related mortality and morbidity was observed [11,12]. There is accumulating evidence that PM$_{2.5}$ exerts toxic effects on the CVS, with increased risk of arrhythmia, atherosclerosis, hypertension, myocardial infarction (MI), stroke, thrombosis, and heart failure exacerbation within hours to days of exposure in susceptible individuals [4]. Similar to PM$_{2.5}$, black carbon (BC), a common and potent contributor to PM$_{2.5}$ total mass, is also linked with cardiovascular effects [13]. Recently, several epidemiological and experimental studies have reported the adverse effects of air pollution on the heart and its vasculature; however, the underlying biomechanisms in cellular organelles remain largely elusive. Mitochondria are one of the major targets of environmental pollutants because of their involvement in xenobiotic metabolism, including air toxicants [14].

In this review, we present information on the current knowledge gaps between PM$_{2.5}$ and CVD systematically by evaluating literature findings, epidemiological studies, and clinical manifestations. Thus, a better understanding of the detrimental cardiovascular effects associated with exposure to PM$_{2.5}$ may be provided, thereby leading to improved risk assessments and potentially guiding the development of tailored interventions to mitigate those adverse effects. We herein present a review on the composition and sources of PM$_{2.5}$, related biological mechanisms, effects of PM$_{2.5}$ on mitochondria, and epidemiological studies on short- and long-term effects. We also specifically elaborate on the degree of evidence of the association of the effects of PM$_{2.5}$ and various CVDs. Lastly, we discuss several public and personal mitigation strategies related to exposure to air pollution and address future viewpoints.

2. Composition and Sources of Particulate Matter

Our body is exposed to many contaminants present in air, and hence, it needs to be protected. PM concentration is a common proxy indicator of air pollution. Inhalable PM includes ultrafine, fine, and coarse particles with aerodynamic diameter <0.1 µm, ≤ 2.5 µm (PM$_{2.5}$), and 2.5–10 µm (PM$_{2.5–10}$), respectively [4,15–17]. Typically, smaller PM fractions exert more effects, as they have a larger reactive surface area and can infiltrate deeply into the pulmonary alveoli and then potentially into the bloodstream. Even though inhaled PM$_{10}$ and PM$_{2.5}$ particles can penetrate through the lungs and enter the bloodstream, PM$_{2.5}$
poses a greater health risk than PM$_{10}$ [18]. Chronic exposure to PM increases the risk of developing cardiovascular and respiratory diseases, as well as lung cancer.

There are multiple and context-specific sources of air pollution. Three types of particles present in PM$_{2.5}$ are as follows: primary particles (elemental carbon), secondary particles (organic aerosols), and nitrate and sulfate particles. Primary PM$_{2.5}$ is directly emitted from both natural sources (aerosolized soil, dust storms, forest fires, pollen, molds, and volcanic eruptions) and anthropogenic activities (agriculture or waste incineration, biomass burning, burning of wood, crustal or road dust, cigarette smoke, cooking, construction, fossil fuel combustion, household heating, industry, mechanical wear, power plants, sea salt, and transportation) [19]. The formation of secondary PM$_{2.5}$ in the atmosphere occurs via the condensation of low-volatility products released through the chemical reactions of organic and inorganic precursors [20]. The chemicals emitted from automobile exhausts or coal combustion react with water vapor in the air and sunlight to form novel particles. Overall, PM$_{2.5}$ includes several elements (black carbon, organic carbon and sulfates), sea salt (sodium and chloride), and metal oxides (aluminum, magnesium, iron, potassium, silicone, titanium, and zinc) [21,22]. Notably, PM$_{2.5}$ derived from residual oil combustion and traffic sources is known to exert short-term effects on human health, whereas PM$_{2.5}$ generated from coal combustion is known to exert long-term adverse effects [23].

PM$_{2.5}$ composition varies with regard to the different chemical combinations of particles along with variable factors including regions, climate, and anthropogenic activities. Rural areas have high levels of crustal materials such as silicon and aluminum. Air pollution in urban areas has received the most attention owing to the high population density, greater traffic-related emissions, elevated levels of secondary aerosols (ammonium, nitrates, and sulfates), high combustion levels (elemental and organic carbon), and the increasing urbanization of societies globally. Industrialized areas account for high levels of trace elements including zinc, iron, and palladium [24].

3. Biological Pathways Linking PM$_{2.5}$ and CVD

Although a large body of evidence has improved our understanding of the biological mechanisms underlying air pollution-mediated cardiovascular effects, this topic remains to be fully elucidated [4,5,17,25,26]. The primary mechanisms through which PM$_{2.5}$ influences the incidence of cardiovascular events are intricate, multiple, and interdependent. PM inhalation stimulates extrapulmonary effects on the CVS through three biological pathways: (1) oxidative stress and systemic inflammation; (2) direct translocation into systemic circulation; and (3) perturbation of the autonomic nervous system (ANS) (Figure 1).

3.1. Oxidative Stress and Systemic Inflammation

Oxidative stress and systemic inflammation are the primary mechanisms by which PM$_{2.5}$ increases the risk of CVDs [22]. Inhaled air pollutants induce oxidative stress in various cell types of the respiratory tract and can be transmitted systemically, contributing to the activation of several effector mechanisms including inflammation [27,28]. Inhaled PM$_{2.5}$ triggers a variety of inflammatory mediators in the lungs, including pro-oxidative (ROS) and pro-inflammatory (tumor necrosis factor, interleukin [IL]-1β, IL-6, interferon-γ, and granulocyte macrophage colony-stimulating factor) initiators, vasoactive hormones (endothelin), and acute-phase reactants (C-reactive protein), which are released into the blood circulation [29,30]. Innate immune receptors, such as toll-like receptors (TLR2/4) and nucleotide oligomerization domain-like receptors, may be activated by a direct or indirect mechanism through secondary mediators, including ROS. Additionally, ion channels, including transient receptor potential (TRP) receptors such as TRPA1 and TRPV1, are activated by oxidative stress caused by combustion or soluble particles [31–33].
Figure 1. Biological pathways associated with particulate matter (PM) and cardiovascular disease (CVD). Primary signaling pathways through which inhaled PM can induce the incidence of cardiovascular events, eventually leading to cardiovascular morbidity and mortality. Adapted from Ref. [5].

Activated pulmonary endothelial cells release adhesion molecules, thereby leading to the binding and induction of leukocytes and platelets and resulting in the systemic activation of blood coagulation [34,35]. This finding is supported by reports from previous studies that showed associations between high levels of PM$_{2.5}$ and hypercoagulability markers and increased thrombin formation [35,36]. Furthermore, an ROS-activated pathway is involved in the PM-stimulated pro-inflammatory mechanism, which is linked to atherosclerosis, arrhythmias, MI, and vascular dysfunction [37]. PM$_{2.5}$, along with other gaseous co-pollutants such as ozone has also been shown to increase the effects of PM. It has been reported that when ozone gas levels increase from approximately 30 ppb to 100 ppb, the half-lives of antioxidants are reduced from days to hours, and the half-lives of surfactants are reduced from hours to minutes [38].
3.2. Direct Translocation into Systemic Circulation

Due to the small size and large surface area of PM$_{2.5}$, it can cross the pulmonary epithelium and reach the heart and other organs, causing adverse health effects. Preliminary studies substantiate that PM$_{2.5}$ and ultra-fine particles can translocate directly into the pulmonary and systemic circulations [39,40]. Inhaled PM$_{2.5}$ causes pulmonary inflammation that can spread to the circulatory system, resulting in abnormal hemostatic activity [41]. In a number of epidemiological studies, PM$_{2.5}$ exposure has been associated with venous thrombosis and reduced plasma clotting time [42]. Acute PM$_{2.5}$ exposure is linked to increased arterial stiffness [43] and blood pressure [44]. Acute thrombosis such as MI and stroke can be exacerbated by exposure to PM$_{2.5}$ [45].

3.3. Perturbation of the Autonomic Nervous System

In normal conditions, the rhythmic activity of the heart is regulated by the activity of autorhythmic cells in the sinoatrial node, which is controlled by the vagus nerve [46]. Acute exposure to PM$_{2.5}$ particles can perturb the ANS and increase the risk of arrhythmia and other cardiovascular events [47]. Heart rate (HR) and HR variability (HRV) are the two main factors associated with cardiac death in patients with heart failure. Controlled exposure studies in humans have shown alterations in BP and HRV [26], while studies in canine and mouse models [48,49] have shown the progression of hypertension upon stimulation of the central sympathetic nervous system by PM$_{2.5}$.

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4. PM$_{2.5}$ and Mitochondrial Dysfunction

Mitochondria are promising targets because of their role in the regulation of cell metabolism by the production of ATP, regulation of carbohydrate, lipid, and pyrimidine metabolism, ionic balance maintenance (calcium, copper, and iron homeostasis), regulation of apoptosis, and their function as a hub for several cardioprotective signaling molecules [14]. The mitochondria are also involved in the metabolism of xenobiotics (including environmental toxicants) with the aid of mitochondrial P450s, as they act as a primary source of free radicals upon toxicant exposure [54]. Previous studies have suggested that environmental toxicants can damage mitochondrial DNA (mtDNA) and alter mitochondrial gene expression [55]. Notably, mtDNA lacks the ability to repair DNA; therefore, it is more vulnerable to oxidative damage than nuclear DNA [56]. Mitochondria are considered the primary source of environmental toxicant accumulation owing to their high membrane lipid content. This entails the accumulation of a wide variety of compounds, including PM and polycyclic aromatic hydrocarbons [57].

The mitochondrial inner membrane harbors four multi-subunit electron transport chain (ETC) complexes (complexes I–IV), which are the machinery for generating membrane potential and hence ATP. ETC complexes transport electrons from both NADH and FADH2 to molecular oxygen to produce water, and hydrogen ions are pumped from the matrix towards the mitochondrial intramembrane space, forming the membrane potential and driving ATP synthesis with the aid of ATP synthase. PM$_{2.5}$-exposed rat cardiac fibers and vascular endothelial cells display abnormalities in the mitochondrial membrane ultrastructure, such as swollen and disordered cristae. PM$_{2.5}$ induces aberrant morphologies of mitochondria by dysregulating mitochondrial fission/fusion and size [1,58], indicating the failure of quality control in mitochondrial function [1,59]. Morphological defects in the mitochondrial membrane have a direct impact on the activities of its residents, such as ETC complexes. The PM$_{2.5}$-mediated reduction of ETC complex activity has been described in different cell types. Dysfunctional ETC complexes fail to maintain membrane potential, and reduction in membrane potential and ATP synthesis have been reported [60–62]. Opening of the mitochondrial permeability transition pore by PM$_{2.5}$ causes further reduction of membrane potential and ATP synthesis,
eventually leading to cell death. Mitochondrial dysfunction and subsequent cell death trigger inflammation in various tissues [63]. Recent evidence suggests that mitochondrial dysfunction plays an important role in PM$_{2.5}$-mediated inflammation responses [64–66]. The release of mtDNA and N-formyl peptides from dysfunctional mitochondria acts as a damage-associated molecular pattern and triggers inflammation. Increased ROS production by PM$_{2.5}$ is also directly related to the activity of ETC complexes. Dysfunctional ETC complexes slow down respiration and increase the pool of NADH in mitochondria, which enhances ROS generation [67,68].

Air pollutants mediate CVD by targeting mitochondria through either the inflammation-mediated pathway or the oxidative stress-induced pathway [14]. Mitochondrial membrane alterations mediated by air pollutants can affect the ETC complexes and their dynamic nature. In addition to xenobiotics, metal toxicants (cadmium, lead, manganese, and mercury) and certain chemicals (ethidium bromide, MPP+, and paraquat) accumulate in mitochondria [57,69]. A high number of mitochondria per cell has been reported, which can offset mitochondrial dysfunction or damage. However, the number and consequences differ depending on the type of cells or tissues involved. Because the heart possesses the highest mitochondrial content, even a moderate level of mitochondrial damage may cause adverse effects [14]. An increasing number of studies have shown the significance of mitochondria as a primary ROS source in air pollution-associated pathology. Excess production of mitochondrial ROS is often associated with several CVDs such as atherosclerosis, hypertension, MI, and myocardial ischemia-reperfusion injury [70–72]. A key summary of the investigational studies demonstrating the effects of PM$_{2.5}$ on mitochondria in the CVS is shown in Table 1.

Table 1. Key studies investigating the effects of PM$_{2.5}$ on mitochondria in the cardiovascular system.

| Study | Study Model, Pollutant and Year Published | Main Findings |
|-------|------------------------------------------|---------------|
| Aung et al. [73] | In vitro model (human aortic endothelial cells (HAEC) exposed to both fine (PM$_{1.8}$) and ultrafine particles (UFPs–PM$_{0.1}$)), 2011 | Gene responses involved in xenobiotic and oxidoreductase activities, inflammatory pathways, and transcription factors were affected. |
| Hu et al. [74] | In vitro model (HUVECs exposed to PM$_{2.5}$), 2016 | Decreased cell viability, increased LDH activity, increased ROS and MDA productions, inhibition of SOD activity, and increased levels of proinflammatory cytokines, cell adhesion molecules, and tissue factor. Upregulation of IL-6 dependent JAK1/STAT3 pathway. |
| Montiel-Dávalos et al. [75] | In vitro model (human umbilical vein endothelial cells (HUVEC) exposed to PM$_{2.5}$), 2010 | Increased production of reactive oxygen species (ROS) and nitric oxide (NO), and increased translocation of nuclear factor-kappa B (NF-κB) leading to apoptosis. |
| Sivakumar et al. [76] | In vitro model (H9c2 cardiomyocytes exposed to 100 µg/mL PM$_{2.5}$), 2021 | Augmented mitochondrial dysfunction and inactivation of PI3K/Akt signaling pathway (mitotoxicity). |
| Sivakumar et al. [77] | In vivo model (rat model of myocardial infarction (MI) exposed to PM$_{2.5}$), 2022 | Lowers mitochondrial endurance during cardiac recovery. |
| Sun et al. [78] | In vivo model (rats exposed to PM$_{2.5}$ or filtered air for 10 weeks), 2008 | Increase in mitochondrial superoxide production mediated by activation of Rho/ROCK pathway. |
| Wittkopp et al. [79] | Cohort study model (Elderly adults > 65 years with coronary artery disease—Measured hourly PM$_{2.5}$), 2013 | Toxic effects of air pollutants depend on the mitochondrial haplotype. Haplogroup H are more sensitive to air pollutants than haplogroup U. |
5. Epidemiological Studies on the Short- and Long-Term Effects of PM$_{2.5}$ in the CVS

The health of susceptible populations, including children, pregnant women, elderly individuals, and people with chronic diseases, can deteriorate even on low-pollution days. Epidemiological evidence demonstrates that exposure to PM$_{2.5}$ can cause serious health problems [80]. The impact of short-term exposure to air pollutants is temporary and ranges from simple discomfort, including irritation of the eyes, nose, skin, and throat, to breathing difficulties, cough, chest tightness, and wheezing, to more serious health effects such as asthma, COPD, lung and heart problems, frequent hospitalization, pneumonia, and respiratory illnesses [18]. Additionally, short-term exposure can trigger dizziness, headache, and nausea [18]. These health effects can be worsened by prolonged long-term exposure, which damages other body systems, including the neurological, reproductive, and respiratory systems (Figure 2). The long-term effects of PM last for years or are lifelong and can even induce different types of cancers and death [81].

*Figure 2*. Short- and long-term effects of PM$_{2.5}$ on human health. The inhalation of particulate matter (PM) can irritate the lining of the nasal cavity, thereby inducing runny nose and cough. Inhaled PM can also travel deep down the airways and enter the lungs, thus triggering inflammation and causing shortness of breath, as well as worsening preexisting respiratory diseases such as asthma, COPD, lung and heart problems, frequent hospitalization, pneumonia, and respiratory illnesses [18]. Additionally, short-term exposure can trigger dizziness, headache, and nausea [18]. These health effects can be worsened by prolonged long-term exposure, which damages other body systems, including the neurological, reproductive, and respiratory systems (Figure 2). The long-term effects of PM last for years or are lifelong and can even induce different types of cancers and death [81].

Several epidemiological studies have linked air pollution to several cardiovascular conditions [4], such as cardiac arrhythmia [82], coronary artery disease [83], cerebrovascular disease [84], heart failure [85], peripheral arterial disease (PAD) [86], and venous thromboembolism (VTE) [87]. In 1993, a pioneering study was conducted over a period of 14–16 years to assess the levels of air pollution in six major U.S. cities, where high levels of PM$_{2.5}$ exposure were linked to cardiovascular morbidity and mortality [11]. The American Heart Association writing group reported that short-term PM exposure leads
to acute cardiovascular morbidity and mortality, while long-term exposure could shorten life expectancy by a few years [88]. In general, PM$_{2.5}$ exposure leads to a high risk of arrhythmia, heart failure exacerbation, MI, and stroke within hours to days [4]. Numerous epidemiological studies on PM exposure using different experimental designs have been published (Table 2). Table 2 summarizes recent epidemiological studies reported during the years 2017–2021 showing sizeable associations between PM$_{2.5}$ exposure and cardiovascular-related morbidity and mortality. Recently, Zhang et al. [89] conducted a meta-analysis to examine the sex differences linked to IHD and stroke with long-term PM$_{2.5}$ exposure. The study identified that long-term PM$_{2.5}$ exposure in women was associated with an increased risk of IHD (relative risk (RR), 1.21; 95% confidence interval (CI), 1.15–1.27). The additional women-to-men ratio of RR (RRR) was 1.05 (95% CI, 1.02–1.08) per 10 $\mu$g/m$^3$ increment in PM$_{2.5}$ exposure. Wu et al. [90] conducted a time-series study to estimate the link between short-term PM$_{2.5}$ exposure and CVD-related hospitalizations in Lanzhou, China, and showed that short-term PM$_{2.5}$ exposure increased the hospitalizations for total CVD, especially IHD in male and elderly populations. Another recent open cohort study [91] was conducted to investigate the associations between long-term PM$_{2.5}$ exposure and cardiovascular events as well as CVD-specific mortality among hemodialysis patients in the U.S. A PM$_{2.5}$ level of 1 $\mu$g/m$^3$ was associated with an increased risk of cardiovascular events (1.02, 95% CI: 1.01, 1.02) and CVD-specific mortality (1.02, 95% CI: 1.02, 1.03).

Notably, studies on short-term exposure have assessed the cardiovascular consequences of PM$_{2.5}$ based on hourly or daily variations in pollutant concentrations, whereas studies on long-term exposure have investigated annual variations in pollutant concentrations. In general, epidemiological studies have examined blood and urine samples to identify mechanistic markers accountable for cardiovascular changes. However, the relative magnitudes of short- and long-term effects lack clarity owing to the use of different epidemiological methods and exposure errors.

Researchers have found substantial correlations between PM exposure and adverse effects on cardiac autonomic activity [92], electrical instability [93], and myocardial perfusion in panel and controlled-exposure studies [94,95]. HRV, a measure of cardiac function, has been associated with PM exposure, where deleterious changes have been observed [96,97]. In addition to HRV, PM$_{2.5}$ has been associated with changes in cardiac rhythm [98], cardiac ischemia [99], and severe arrhythmia [95]. Furthermore, a meta-analysis reported that a daily increase of 10 $\mu$g/m$^3$ in PM$_{2.5}$ exposure was linked to a 0.84% increase in cardiovascular-related deaths [100]. In addition to the aforementioned epidemiological studies, several others have also linked PM$_{2.5}$ exposure to the development of cardiovascular conditions.
Table 2. Epidemiological studies published in the last five years (2017–2021) investigating the effects of PM$_{2.5}$ on the cardiovascular system.

| Study and Year | Study Name | Study Period | Number of Participants | Age Range of Participants | Country, Region | PM$_{2.5}$, µg/m$^3$ (Mean or Range) | Outcome Types |
|---------------|------------|--------------|------------------------|---------------------------|-----------------|-----------------------------------|---------------|
| Achilleos et al. 2017 [101] | Meta-analysis (Pubmed and Web of Science) | 1996–July 2015 | 3851 records | All ages | Europe, U.S., West Pacific, Canada, and South America | 10 | Mortality: Cardiovascular disease (CVD) (0.80% (95% CI: 0.41, 1.20%). |
| Newell et al. 2017 [102] | Meta-analysis (PubMed, Web of Science, Embase, LILACS, Global Health, and Proquest) | Database inception–November 2016 | 85 records | ≥18 years | East Asia, Pacific region, Latin America, Caribbean, Europe, Central Asia, and (Middle East and North Africa) or Sub-Saharan Africa. | 10 | Mortality: CVD (0.47% (95% CI 0.34–0.61)). |
| Chen et al. 2017 [103] | China’s Disease Surveillance Points system (DSPS) | January 2013–December 2015 | 272 Chinese cities | >5 years | China | 10 | Mortality: CVD (0.27% (95% posterior interval (PI), 0.18–0.36)), coronary heart disease (0.30% (95% PI, 0.19–0.40)), Stroke: 0.23% (95% PI, 0.13–0.34), cardiopulmonary disease (CPD) (17.55 (95% PI, 12.25–22.86)). |
| Zhao et al. 2017 [104] | Meta-analysis (PubMed, and CNKI databases) | 2007–2017 | 30 records | All ages | China | 10 | Mortality: CVD (0.68%, 95% confidence interval (CI): 0.39–0.97%). |
| Amsalu et al. 2019 [105] | Beijing Public Health Information Center | January 2013–December 2017 | 460,938 admissions | 18–64 years and ≥65 years | China, Beijing | 10 | Mortality: CVD (0.30, 95% CI: 0.20, 0.39%), CHD (0.34, 95% CI: 0.22 to 0.45%), Atrial Fibrillation (AF) (0.29, 95% CI, 0.03 to 0.55%). |
| Tian et al. 2019 [106] | The urban employee basic medical insurance (UEBMI), urban resident basic medical insurance, and new rural cooperative medical scheme | January 2014–December 2017 | 8,834,533 hospital admissions | 18–64 years, 65–74 years, and ≥75 years | China | 10 | CVD (0.26% (95% CI 0.17% to 0.35%), Ischaemic heart disease (IHD) (0.31% (0.22% to 0.40%)), heart failure (0.27% (0.04% to 0.51%)), heart rhythm disturbances (HRD) (0.29% (0.12% to 0.46%)), ischaemic stroke (IS) (0.29% (0.18% to 0.40%). |
| Study and Year | Study Name | Study Period | Number of Participants | Age Range of Participants | Country, Region | PM$_{2.5}$, µg/m$^3$ (Mean or Range) | Outcome Types |
|---------------|------------|--------------|------------------------|--------------------------|----------------|---------------------------------|--------------|
| Wyatt et al. 2020 [107] | US Renal Data System (RDS) | 2008–2014 | 361,568 patients | NA | U.S. | CVD (1.8%, 95% CI 0.4% to 3.2%), dysrhythmia, conduction disorder (4.8% (95% CI 2.3% to 7.4%)), and heart failure (3.7% (95% CI 1.4% to 6.0%).) | |
| Qiu et al. 2020 [108] | Victim-crossover study of US New England Medicare participants | 2000–2012 | 532,154 individuals | >64 years | U.S. New England- (states of Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont) | CVD, acute myocardial infarction (AMI) (4.3% (95% CI: 2.2%, 6.4%)), and congestive heart failure (CHF) (3.9% (2.4%, 5.5%)), IS (2.6% (0.4%, 4.7%)). | |
| Dahlquist et al. 2020 [109] | Victim-crossover study of Stockholm | 2012–2013 and 2016–2018 | 8899 individuals | 75 years | Sweden-Stockholm | Acute AF. | |
| Farhadi et al. 2020 [110] | Meta-analysis (PubMed, Scopus, Web of Science, and Embase) | January 2000–January 2018 | 26 records | NA | NA | MI (relative risk (RR) = 1.02; 95% CI 1.01–1.03). | |
| Ren et al. 2020 [111] | Victim-crossover study of Shenyang, China | January 2014–December 2017 | 157,144 patients | 0–30 years, 31–60 years, and >60 years | China-Shenyang Liaoning | CVD. | |
| Zhou et al. 2021 [112] | Taiyuan Center for Disease Control and Prevention | January 2013–October 2015 | 50,782 patients | >65 years | China-Taiyuan | Mortality: CVD (0.51% (95% CI: 0.08, 0.94)), IHD (1.01% (95% CI: 0.53, 1.50)), MI (1.08% (95% CI: 0.34, 1.83)). | |
| Yue et al. 2021 [113] | Meta-analysis (PubMed, Embase, the Cochrane library and Web of Science) | 2015–2020 | 18 records | <65 years and >65 years | China, Sweden, Korea, U.S., Italy, Canada, Iran, Israel, Denmark | AF (1.01(95% CI 1.00–1.02) and 1.07 (1.04–1.10)). | |
| Kuzma et al. 2021 [114] | Victim-crossover study of Bialystok and Katowice in Poland, Europe | 2008–2017 | 9046 patients | 64–69 years | Europe-Poland | Incidence: STEMI (OR = 1.041, 95% CI = 1.020–1.073; P < 0.001, lag-1). | |
### Table 2. Cont.

| Study and Year | Study Name | Study Period | Number of Participants | Age Range of Participants | Country, Region | PM$_{2.5}$, µg/m$^3$ (Mean or Range) | Outcome Types |
|----------------|------------|--------------|------------------------|---------------------------|-----------------|-----------------------------------|---------------|
| Chen et al. 2021 [115] | Meta-analysis (PubMed, Embase, and Web of Science) | 2006–2019 | 13 studies | <65 years and ≥65 years | North America, Europe, and Asia | 10 | AF (ER = 23.2%, 95% CI = −9.3–67.5), (ER = 0.6, 95% CI = −3.9–5.4), (ER = 2.3, 95% CI = 0.1–5.2). |
| Badaloni et al. 2017 [116] | Rome Longitudinal Study (RoLS) | October 2001–December 2010 | 1,249,108 individuals | 30–44 years, 45–54 years, 55–64 years, 65–74 years, and > 75 years | Italy, Rome | 5 | Mortality: IHD, CVD (hazard ratio (HR) = 1.05; 95% CI: 1.02–1.08), (HR = 1.06; 95% CI: 1.01–1.11). |
| Jerrett et al. 2017 [117] | American Cancer Society Cancer Prevention Study II (CPS-II) | 1982–2004 | 668,629 participants | ≥30 years | U.S., Washington, DC, and Puerto Rico | 10 | Mortality: IHD. |
| Kim et al. 2017 [118] | National Health Insurance Service–National Sample Cohort (NHIS-NSC) | 2007–2013 | 1,025,340 individuals | ≥18 years | Korea-Seoul | 1 | Mortality: cardiovascular event (CE) (1.36 (95% confidence interval, 1.29–1.43)) and Incidence: Stroke. |
| Pinault et al. 2017 [119] | Canadian Census Health and Environment Cohort (CanCHEC) | 2000–2008 | 2,448,500 participants | 25–89 | Canada | 10 | Mortality: IHD (HR = 1.16; 95% CI: 1.13–1.20). |
| Pun et al. 2017 [120] | Medicare Beneficiaries | 2000–2008 | 52.9 million participants | 65–120 | U.S. | 10 | Mortality: CVD (RR = 1.56, 95% CI: 1.55, 1.57) |
| Qiu et al. 2017 [121] | Elderly Health Service of the Department of Health in Hong Kong | 1998–2001 | 66,820 individuals | ≥65 years | Hong Kong | 10 | Incident: Stroke (1.14 (95% CI 1.02–1.27). |
| Stockfelt et al. 2017 [122] | PPS cohort and the GOT-MONICA cohort | 1990–2011 | 10,350 participants | 25–64 years and 64–75 years | Sweden-Gothenburg | 5 | IHD (HR: 1.24 95% CI: 0.98–1.59) and Incident: Stroke (HR: 1.48; 95% CI: 0.88–2.49). |
| Study and Year | Study Name | Study Period | Number of Participants | Age Range of Participants | Country, Region | PM$_{2.5}$, µg/m$^3$ (Mean or Range) | Outcome Types |
|----------------|------------|--------------|------------------------|---------------------------|----------------|-----------------------------------|---------------|
| Turner et al. 2017 [123] | American Cancer Society Cancer Prevention Study-II | 1999–2008 | 429,406 participants | <40 years and 40–80 years | U.S., Columbia, Puerto Rico etc. | 11–15 | Mortality: CV (relative excess risk due to interaction (RERI) = 0.10, attributal proportion (AP) = 0.05, synergy index (S) = 1.11). |
| Yin et al. 2017 [124] | Disease Surveillance Points (DSPs), China | 1990–1991 | 189,793 participants | ≥40 years | China | 10 | Mortality: CVD (1.12 (1.10, 1.13)). |
| Cakmak et al. 2018 [125] | Canadian Census Health and Environment Cohort (CanCHEC) | 1991–2011 | 3.6 million participants | ≥25 years | Canada | 10 | Mortality: IHD (1.13; 95% CI 1.08, 1.19). |
| Gandini et al. 2018 [126] | Italian Longitudinal Study (ILS) | 1999–2000 | 140,011 individuals | >35 years | Italy | 10 | AMI (1.15 (1.12–1.18)) and Incidence: Stroke. |
| Loop et al. 2018 [127] | REasons for Geographic and Racial Differences in Stroke (REGARDS) cohort | 2003–2007 | 17,126 participants | ≥45 years | U.S. -Stroke Belt and Stroke Buckle | 2.7 | Mortality: CHD (0.94 (0.83–1.06)) and Non-fatal: AMI (0.85 (0.73–0.99)). |
| Parker et al. 2018 [128] | National Health Interview Survey (NHIS) | 1997 to 2009 | 657,238 participants | ≥25 years | U. S. | 10 | Mortality: Heart disease (HR, 1.16; 95% CI, 1.08–1.25). |
| Yitshak-Sade et al. 2018 [129] | Harvard School of Public Health Institutional Review Board | 2001–2011 | 2,015,660 participants | ≥65 years | U.S., New England | 2.3 | CVD (6.58% (5.90%; 7.26%)), and IS (0.82% (−0.68%; 2.35%)). |
| Bai et al. 2019 [130] | Ontario Population Health and Environment Cohort (ONPHEC) | 2001 to 2015 | 6,248,299 participants | 35–85 years | Canada-Ontario | 9.6 | Mortality: CHF (1.05 (95% CE 1.04–1.05)) and Incident: AMI (3%; 95% CE 2–3%). |
| Danesh Yazdi et al. 2019 [131] | Medicare and Medicaid Services denominator file | 2000–2012 | 11,084,660 individuals | ≥65 years | Southeastern United States-Florida, Alabama, Mississippi, Georgia, North Carolina, South Carolina, and Tennessee | 1 | AMI and Stroke. |
| Dirgawati et al. 2019 [132] | The Health in Men Study (HIMS) | Apr 1996–Jan 1999 | 12,203 participants | ≥65 years | Perth | 5 | Fatal: Stroke. |
| Study and Year | Study Name | Study Period | Number of Participants | Age Range of Participants | Country, Region | PM$_{2.5}$, µg/m$^3$ (Mean or Range) | Outcome Types |
|---------------|------------|--------------|------------------------|---------------------------|-----------------|-----------------------------------|---------------|
| Heritier et al. 2019 [133] | Swiss National Cohort (SNC) | Dec 2000–Dec 2008 | 7.28 million observations | >30 years | Switzerland | 10 | Mortality: AMI (1.034, 95% CI: 1.014–1.055). |
| Huang et al. 2019 [134] | China-PAR | 2000–2015 | 117,575 participants | <50 years >50 years | China | 10 | Incident: Stroke (13% (1.133, 1.09 to 1.17)). |
| Lim et al. 2019 [135] | National Institutes of Health–American Association for Retired Persons (NIH-AARP) | 1995–2011 | 548,845 participants | 50–71 years | U.S. states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and metropolitan areas (Atlanta, Georgia; Detroit, Michigan) | 10 | CVD (1.13; 95% CI, 1.08–1.18), IHD (HR, 1.16; 95% CI, 1.10–1.23). |
| Ljungman et al. 2019 [136] | Swedish cohorts (includes the Primary Prevention Study (PPS) and the Multinational Monitoring of Trends and Determinants in Cardiovascular Diseases (GOT-MONICA)) | Jan 1990–Dec 2011 | 114,758 individuals | 25–64 years | Sweden-Gothenburg, Stockholm, and Umea | 1.94 | Incident: IHD (6.5% (95% CI: −0.5, 14)). |
| Pope et al. 2019 [137] | National Health Interview Surveys (NHIS) | 1986–2014 | 1,599,329 participants | 18–84 years | U.S. | 10 | Mortality: CP (1.24 (95% CI: 1.20, 1.29)) and (1.23 (95% CI: 1.17, 1.29)). |
| Shin et al. 2019 [138] | Ontario Population Health and Environment Cohort (ONPHEC) | Apr 2001–Mar 2015 | 5,071,956 participants | 35–85 years | Canada-Ontario | 10 | AF: HR (95% CI): 1.03 (1.01, 1.04) and Incidence: Stroke (HR (95% CI): 1.05 (1.03, 1.07)). |
| Hayes et al. 2020 [139] | National Institutes of Health NIH-AARP | 2000–2005 | 565,477 participants | 50–71 years | U.S. states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and urban areas (Atlanta, GA, and Detroit, ML) | 10 | Mortality: IHD (HR 1.16; 95% CI 1.09–1.22) and Stroke (HR 1.14; CI 1.02–1.27). |
6. PM$_{2.5}$-Induced Risk of Cardiovascular Diseases

As discussed in Section 3, the pathophysiological mechanisms through which PM triggers cardiovascular events include the activation of oxidative stress/inflammation pathways, direct translocation into blood circulation, and autonomic imbalance. These alterations lead to subclinical CVDs (as shown in Figure 1) including atherosclerosis, coagulation, hypertension, myocardial remodeling, and thrombotic and non-thrombotic acute cardiovascular events such as heart failure, endothelial dysfunction, and arrhythmias [4,10], which are covered in the following sections.

6.1. Acute Coronary Syndrome and Myocardial Infarction

Acute coronary syndrome (ACS) is triggered by acute myocardial ischemia including unstable angina, ST-elevation MI (STEMI), and non-STEMI (NSTEMI) [140]. The link between exposure to PM$_{2.5}$ and ACS development has been demonstrated in several systematic reviews and meta-analyses. Case-crossover reports have shown that patients with STEMI have an increased risk of PM-induced ACS [141,142]. Similarly, another time-stratified case-crossover study demonstrated the risk of acute coronary events upon short-term exposure to PM$_{2.5}$, where excessive risk was observed in patients with preexisting coronary artery disease [143]. Furthermore, a PM$_{2.5}$-related risk of MI was evidenced for STEMI events and not NSTEMI events, where a 10 $\mu$g/m$^3$ elevation in concurrent-day PM$_{2.5}$ was linked to an 8–15% increased risk of STEMI [143]. In a European cohort study that included 100,166 participants, each 5-$\mu$g/m$^3$ increase in PM$_{2.5}$ was linked to an 18% increase in nonfatal acute coronary events [83]. In a systematic review of 26 studies, PM$_{2.5}$ exposure showed an increase in MI risk ranging from 5 to 17% per 10 $\mu$g/m$^3$ increase [144].

In a meta-analysis of 34 studies, the associations between short-term exposure to PM$_{2.5}$ and an increase in MI risk were evaluated [145]. In this study, a 2.5% increase in the risk of MI per 10 $\mu$g/m$^3$ elevation was observed [145]. It is also evident from population-based cohort studies that long-term PM$_{2.5}$ exposure substantially influences the survival of ACS and acute MI patients [146,147].

6.2. Arrhythmia

Cardiac arrhythmia is a group of conditions that trigger an abnormal heartbeat, and it is linked to a high incidence of CVD and mortality [148]. Several studies demonstrate that both high and low levels of PM$_{2.5}$ exposure induce an increased risk of cardiac arrhythmias. A meta-analysis showed that short-term exposure to PM$_{2.5}$ increases the incidence of arrhythmia hospitalization or mortality [149]. A multicenter longitudinal study assessed the effects of short-term PM$_{2.5}$ exposure in high-risk patients with implantable cardioverter-defibrillators (ICD) or cardiac resynchronization therapy defibrillators (ICD-CRT) and demonstrated an association between the prevalence of ventricular tachycardia and ventricular fibrillation [150]. Long-term exposure to PM increases the risk of ventricular arrhythmia. Two population-based cohort studies from Canada and South Korea showed a link between PM$_{2.5}$ and an increased incidence of atrial fibrillation (AF) [138,151]. Recently, in a large prospective cohort study, long-term exposure to PM$_{2.5}$ exposure was associated with right-bundle branch block and bradycardia among middle-aged Koreans [152]. Previously, a meta-analysis of four observational studies suggested that PM$_{2.5}$ was associated with a 0.89% increase in the AF risk per 10 $\mu$g/m$^3$ elevation [153]. Recently, a meta-analysis of 18 studies also demonstrated that both short- and long-term exposures to PM$_{2.5}$ had adverse effects on AF prevalence in the general population [113].

6.3. Cardiovascular Mortality

Several reports have suggested that both short- and long-term exposures to PM$_{2.5}$ are linked to an increase in cardiovascular mortality. Time-series analyses of hourly, daily, and monthly variations in PM$_{2.5}$ levels have identified the correlation between cardiovascular-related death and PM [4,15]. Low levels of daily exposure to PM$_{2.5}$ showed an increment in the risk of 0.3–1.0% cardiovascular mortality per 10 $\mu$g/m$^3$ increase in PM$_{2.5}$. High levels of
daily exposure to \( \text{PM}_{2.5} \) ranging from 39 to 177 \( \mu \text{g/m}^3 \) was associated with a 0.35% excess risk of cardiovascular mortality per 10 \( \mu \text{g/m}^3 \) increase in \( \text{PM}_{2.5} \) [154,155]. A meta-analysis identified that short-term exposure to \( \text{PM}_{2.5} \) (a daily increase of 10 \( \mu \text{g/m}^3 \)) was linked to a 0.84% surge in cardiovascular-related mortality [100]. Similarly, another quantitative systematic review demonstrated links between short-term exposure to nitrogen dioxide (daily increment of 10 \( \mu \text{g/m}^3 \)) and increases of 0.4–0.88% in deaths from CVD [156]. Long-term \( \text{PM}_{2.5} \) exposure (10 \( \mu \text{g/m}^3 \) increment in annual \( \text{PM} \) concentration) was linked to an 11% increase in cardiovascular-related deaths [157]. In a large cohort study of long-term \( \text{PM} \) exposure in the American population, a 15% increase in deaths due to ischemic heart disease (IHD) per 10 \( \mu \text{g/m}^3 \) increase in \( \text{PM}_{2.5} \) was observed [158]. Similarly, a Canadian national cohort study concluded that \( \text{PM}_{2.5} \) exposure at a very low concentration (mean, 8.7 \( \mu \text{g/m}^3 \)) increased cardiovascular-related mortality by 31% per 10 \( \mu \text{g/m}^3 \) elevation [159]. Furthermore, several studies in China reinforce the link between high levels of \( \text{PM}_{2.5} \) exposure and increased cardiovascular-related mortality [155,160]. According to a large-scale prospective study involving women, long-term exposure to traffic-related pollutants was strongly correlated with cardiovascular-related mortality. An increase in sudden cardiac deaths of 38% was observed in a population living within 50 m of a major roadway compared with those living beyond 500 m [161].

6.4. Heart Failure and Ischemic Heart Disease

Congestive heart failure (CHF) is a chronic and progressive syndrome in which the heart muscle becomes incapable of pumping sufficient blood to meet the body’s demand for blood and oxygen. A systematic review of 35 studies reported that short-term \( \text{PM}_{2.5} \) exposure increased the relative risk of hospitalization due to heart failure or mortality by 2.1% per 10 \( \mu \text{g/m}^3 \) elevation [85]. Similarly, a case-crossover study conducted in 26 large cities in China correlated short-term \( \text{PM}_{2.5} \) exposure to an increase in the risk of CHF hospitalization by 1.3% [162]. A large-scale population-based study in South Korea on healthy participants demonstrated that long-term exposure to \( \text{PM}_{2.5} \) increased with a hazard ratio of 1.44% per 1 \( \mu \text{g/m}^3 \) [118]. In addition, pollutants of \( \text{PM}_{2.5–10} \) were also significantly associated with an increased risk of cardiovascular failure. However, there was no evidence to determine whether patients with ischemic heart failure or patients with non-ischemic heart failure are more susceptible to air pollution.

6.5. Blood Pressure and Hypertension

A large body of evidence has shown that both short- and long-term exposure to \( \text{PM}_{2.5} \) could induce hypertension. Acute exposure to ambient \( \text{PM}_{2.5} \) (10 \( \mu \text{g/m}^3 \)) is associated with slight elevations in systolic and diastolic BP of 1–3 mmHg, while chronic exposure demonstrated elevated BP followed by the occurrence of incident hypertension [163,164]. In a systematic meta-analysis of 22 studies, long-term \( \text{PM}_{2.5} \) exposure showed a positive association between BP and an increase of 1.393 mmHg and 0.895 mmHg per 10 \( \mu \text{g/m}^3 \) elevation for systolic and diastolic BP, respectively [165]. Biological factors such as age and sex may influence the \( \text{PM}_{2.5} \)-related risk of hypertension. Previous studies have shown that youth may have a greater risk of PM-mediated hypertension than the elderly [166]. However, there are a few discrepancies in sex studies, where some show a higher influence of \( \text{PM}_{2.5} \) in men, while other reports demonstrate a higher influence in women [164,167–169]. Hence, studies that have shown sex differences in \( \text{PM}_{2.5} \) having impact on hypertension, are rare. Recently, a meta-analysis of 11 studies explored the association between long-term \( \text{PM}_{2.5} \) exposure and hypertension in women, where hazard ratios and odds ratios of 1.23 and 1.07, respectively, were obtained. Furthermore, subgroup analysis demonstrated that menopausal, non-white, and diabetic adults were more sensitive to \( \text{PM}_{2.5} \) exposure [170]. Randomized controlled studies on the effect of \( \text{PM}_{2.5} \) exposure on hypertension and vascular alterations have been well summarized elsewhere [26].
6.6. Vascular Dysfunction, Peripheral Arterial Disease, and Atherosclerosis

PM$_{2.5}$, a major risk factor for vascular endothelial injury, is regarded as an early predictor of atherosclerosis [171–173]. Recently, Hu et al. identified that PM$_{2.5}$ could induce endothelial injury and inflammation, causing endothelial dysfunction through NLRP3 inflammasome activation [174]. Both short- and long-term PM exposure have been associated with changes in endothelial function. Long-term exposure to PM$_{2.5}$ in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort [175] demonstrated relationships between PM exposure and changes in vascular function. Studies have shown that long-term exposure to PM is associated with reduced endothelial function by reducing the flow-mediated dilation of the brachial artery and vasoconstriction [175]. In addition to the above-mentioned reports, there are other studies that have shown an association between PM and endothelial dysfunction, which were well summarized in an earlier study [171]. However, studies on the association between PM and PAD are scarce. In a study among elderly populations, positive associations were observed between chronic and acute exposures to PM$_{2.5}$ and increased PAD hospitalization rates of 0.26% and 4.4%, respectively [176]. In a cross-sectional study conducted in Germany with 4544 participants, a 5th- to 95th-percentile increment upon long-term exposure to PM$_{2.5}$ was linked with high incidences of both low and high ankle-brachial indexes [177]. Several atherosclerosis biomarkers, including carotid intima-media thickness (CIMT), coronary artery calcium, and carotid plaques have been linked to air pollution, and a MESA-Air cohort study in the United States demonstrated that a 5-µg/m$^3$ elevation in long-term PM$_{2.5}$ exposure was linked to coronary artery calcification [178]. A meta-analysis including eight cross-sectional and three longitudinal epidemiological studies showed a positive correlation between CIMT and long-term exposure to PM$_{2.5}$ [179]. Recently, PM$_{2.5}$ was shown to promote the development of atherosclerotic plaques and plaque vulnerability through the TLR4 pathway [173].

6.7. Thrombosis and Coagulation

A large body of evidence supports the association between platelet function and PM exposure [4,180–183]. VTE, which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third leading vascular disease, affecting nearly 10 million people annually [184]. Although previous studies have linked PM exposure to VTE, studies on the relationship between PM$_{2.5}$ exposure and the development of DVT and PE remain scarce. Long-term exposure studies on PM$_{2.5}$ were linked to DVT and hypercoagulability [4]. Similarly, another study showed that long-term exposure to PM$_{2.5}$ enhanced the risk of increased platelet counts in men and women by 17% and 14%, respectively, indicating adverse effects on blood coagulability [180]. Kloog et al. showed that long- and short-term effects of PM$_{2.5}$ exposure on 453,413 DVT and 151,829 PE hospital admissions were associated with an increased risk of DVT (0.63% and 6.98% for short- and long-term exposure, respectively) and PE (0.38% and 2.67% for short- and long-term exposure, respectively) [185].

7. Strategies to Mitigate the Effects of PM$_{2.5}$ on Cardiovascular Disease

As of 2019, air pollution and climate change have been recognized by the WHO as top global environmental threats to human health. Recent refined modelling indicates that prior prediction models underestimated the health burden of air pollution and estimated that there were approximately nine million annual deaths due to air pollution globally [186]. More than 99% of deaths are due to household air pollution, and nearly 90% are due to ambient air pollution, occurring mostly in low- and middle-income countries, where people often burn solid fuels for cooking and heating. The sources of food derived from animals or plants also contribute to air pollution through ammonia, which is formed as a result of agricultural activities, animal farming, and food waste disposal. As awareness of air pollution increases worldwide, there is a need to provide evidence-based strategies to lessen its effects on health and the environment. Novel innovative and effective measures should be undertaken to tackle the formidable battle against air pollution at the global
level. Both public and personal strategies play critical roles in mitigating exposure to air pollution (Figure 3).

**Figure 3.** Local- and personal-level mitigation measures to reduce exposure to air pollution. The figure presents important elements related to reducing air pollution exposure and protecting respiratory and cardiovascular health. Sources contributing to both ambient and household air pollution are shown. Populations at high risk with exposure to air pollution include pregnant women, elderly individuals, children, newborns, and people with preexisting health conditions.

### 7.1. Societal and Governmental Mitigation Strategies

Ambient air pollution causes several million premature deaths per year, mainly due to exposure to small particle sizes of \(<2.5 \mu m\). In 2019, the State of Global Air reported that 40% of outdoor air pollution-related deaths were due to COPD, 30% of premature deaths were attributed to acute lower respiratory tract infections, 19% of deaths were attributed to lung cancer, 26% and 20% of deaths were attributed to stroke and IHD, respectively, 19% of deaths were linked to diabetes, and 20% were attributed to neonatal deaths. According to the WHO statistics, outdoor air pollution contributes to 4.2 million deaths annually, which are primarily due to cardiovascular and respiratory illnesses. To reduce outdoor air pollution, key policies that support air quality standards should be implemented such as energy-efficient housing, sustainable land use, agricultural incineration, better waste management, vehicle settings, emission management, improved road infrastructure, and transition to cleaner fuels, [187]. For example, the Clean Air Act program in the U.S. has estimated the prevention of more than 230,000 premature deaths associated with ambient PM by 2020. Such programs have lowered the levels of common air pollutants, including PM [135,188]. The air quality in the U.S. improved remarkably between 1990 and 2020, with the concentration of annual fine particles dropping by 41% [135]. A few major cities have already introduced policies aiming at reducing urban air pollution, such as bike sharing in Paris, congestion charging in London, and an environmental police force in Beijing.

To establish and enforce emission regulations, it is recommended that health care professionals and providers collaborate with governmental agencies and advocacy organizations. It is crucial for health care professionals to connect with patients through automated air pollution alert networks, including warnings through SMS, e-mail, or phones, such as the US EPA's AirNow network [127,136]. Furthermore, individuals are encouraged to plan their activities through news feeds, websites, and mobile apps or applications to reduce their exposure to air pollution. Additionally, transitioning to cleaner fuels may be economically and logistically difficult for some countries, although others are making progress. For example, to provide clean cooking gas to 50 million poor Indian households, the Indian Ministry of Health allocated USD 1.5 billion [189]. While achieving carbon net zero is difficult, certain actions could be implemented including the replacement of current transportation systems with green or sustainable transportation, such as zero-emission vehicles, fitting vehicles with more effective filters and combustion engines, and introducing...
hybrid or electric vehicles. In places where there is a lack of electricity or gaseous fuels, solid fuels can be replaced with highly efficient stoves, improved fuels, ventilation, and education [190]. Moreover, protecting the integrity of ecosystems improves the health of communities worldwide. Therefore, the expansion of green land is necessary to prevent biodiversity loss, especially in highly urbanized and polluted countries [188]. Developing countries, such as China and India, are taking effective measures to expand the greening pattern to tackle two interconnected global problems, namely, air pollution and global warming, simultaneously [191].

7.2. Personal Mitigation Strategies

Individuals should be educated to reduce their exposure to traffic while commuting [192]. Commuting during peak hours should be avoided, particularly when using major roadways. Car travel should be accompanied by customs such as keeping the windows closed, maintaining the internal air circulation system, and utilizing a good air filtration system in cars [4]. On high-pollution days, people are advised to avoid or limit outdoor activities, keep windows closed, and use central air conditioning and air filtration systems [193]. Maintenance of a clean air circulation system has been shown to reduce the risk of cardiovascular-related hospitalization [194]. Under elevated ambient pollution levels, individuals are encouraged to perform exercise regimens indoors or in parks. While outdoors, individuals are encouraged to wear protective air filter-based equipment, such as personal face masks, to reduce air pollution exposure. Owing to the time-consuming implementation of policies to improve air quality, pedestrians and bicyclists choose personal masks or other devices to mitigate air pollution risks. Preliminary studies on the use of N95 masks by healthy individuals and individuals with heart disease in China have shown a reduction in BP, indicating an effective strategy for mitigating the effects of exposure to air pollution [195,196]. Similarly, another study from China showed low BP in healthy individuals who wore N95 masks [197]. These studies substantiate the use of particle-filtering masks to mitigate the short-term effects of urban air pollution on CVS caused by PM. Even though N95 masks filter out all but 5% of the particles, harmful gases remain unfiltered. To overcome this limitation, N95 masks combined with activated charcoal should be used to reduce exposure to harmful gases.

Recently, it has been suggested that glutathione and citrate attenuate cytotoxicity induced by urban PM in microglia [198]. The combination of glutathione and citrate reduces the toxicity of PM exposed to cells through mechanisms such as ROS scavenging, organic acid supplementation in the tricarboxylic acid cycle, and chelating Ca$^{2+}$ ions. Further studies concerning the beneficial effects of glutathione and citrate are needed. A variety of dietary supplements, such as omega-3 polyunsaturated fatty acids, olive oil, and antioxidant vitamins have been shown to confer protection against autonomic and endothelial dysfunction and oxidative stress-induced reactions caused by air pollutants [199,200]. Individuals who are at a high risk of exposure to ambient air pollution could benefit from these dietary supplements. The most effective way to reduce indoor air pollution is to eliminate the burning of solid fuels. Access to cleaner fuels, such as liquefied petroleum gas, natural gas pipelines, and electric stoves, is critical for public health. Several studies have shown a positive association between the replacement of solid fuels with improved stoves and significant improvements in health outcomes [201–203]. Recently, two reviews have provided insights into personalized mitigation approaches for the reduction of exposure to air pollution in cardiovascular and respiratory health systems [154,204].

8. Conclusions and Future Perspectives

Outdoor and indoor pollution are recognized as major risk factors for premature mortality, morbidity, and decreased life expectancy, resulting in significant direct and indirect costs to society [3,205]. We have gained greater insights into the links between air pollution and cardiovascular-related morbidity and mortality through numerous epidemiological and experimental (in vitro and in vivo) findings. Improving air quality has led to a number
of public health benefits, including improved longevity, lower mortality, and improved pathological studies [3]. Given the associations between health risks and air pollution, developed countries have implemented several initiatives to alleviate the effects of air pollution. According to the United Nations Environment Program, five cities, Paris, Seoul, New York, Bogota, and Accra, are taking innovative steps such as banning cars, implementing ultra-low emission zones, using green transportation, increasing green space, and switching to gas or electric stoves to achieve clean air [206]. However, the harmful effects of PM$_{2.5}$ exposure on health necessitate more research efforts for gaining a deeper understanding of their pathogenic processes and development of useful tools for the prevention of primary and secondary diseases.

Accumulating evidence shows that PM affects not only the CVS but also the respiratory and central nervous systems. However, experimental and epidemiological evidence on PM$_{2.5}$ is limited. In light of this, it is essential to gather more information about the dire effects of PM$_{2.5}$ on sensitive populations. Moreover, it has been shown that the toxic effects of PM$_{2.5}$ vary depending on its source and composition. For example, some components, such as BC, nitrates, and organic matter, and some metals, such as nickel and vanadium, are considered more dangerous than others. Furthermore, studies have shown that effects on cardiovascular health vary with the composition of PM$_{2.5}$. For instance, some PM$_{2.5}$ metals have shown toxic effects on health, such as increased levels of inflammatory blood markers and a greater risk of coronary events [207,208]. Variations in PM$_{2.5}$ composition may also contribute to differences in findings among studies, and future research is needed to gain insights into the role of PM$_{2.5}$ components in cardiovascular health risks. Hence, it is necessary to design several epidemiological and experimental studies to address the role of each component of PM$_{2.5}$ and its associated adverse effects on health. Furthermore, more research efforts should focus on particles sized <100 nm, that is UFPs, which have been shown to exhibit more damaging effects on health. Because mitochondria are considered one of the primary targets for air pollutants, the further evaluation of mitochondrial epigenetics is necessary to thoroughly elucidate its biological mechanism and relevance in CVDs. Further investigations regarding the relationship between drug intake and air pollution are required. It would be interesting to evaluate whether widely prescribed drugs such as aspirin, β-blockers, and statins are associated with fewer cardiovascular events in comparison with non-prescribed groups who are equally exposed to high air pollution levels.

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**References**

1. Brauer, M.; Casadei, B.; Harrington, R.A.; Kovacs, R.; Sliwa, K.; WHF Air Pollution Expert Group. Taking a Stand Against Air Pollution—The Impact on Cardiovascular Disease: A Joint Opinion from the World Heart Federation, American College of Cardiology, American Heart Association, and the European Society of Cardiology. *Glob. Heart* 2021, *16*, 8. [CrossRef] [PubMed]
2. Burnett, R.; Chen, H.; Szyszkowicz, M.; Fann, N.; Hubbell, B.; Pope, C.A., 3rd; Apte, J.S.; Brauer, M.; Cohen, A.; Weichenthal, S.; et al. Global estimates of mortality associated with long-term exposure to outdoor fine particulate matter. *Proc. Natl. Acad. Sci. USA* 2018, *115*, 9592–9597. [CrossRef]
3. Mannucci, P.M.; Harari, S.; Franchini, M. Novel evidence for a greater burden of ambient air pollution on cardiovascular disease. *Haematologica* 2019, *104*, 2349–2357. [CrossRef] [PubMed]
4. Brook, R.D.; Rajagopalan, S.; Pope, C.A., 3rd; Brook, J.R.; Bhatnagar, A.; Diez-Roux, A.V.; Holguin, F.; Hong, Y.; Luepker, R.V.; Mittleman, M.A.; et al. Particulate Matter Air Pollution and Cardiovascular Disease: An update to the scientific statement from the american heart association. *Circulation* 2010, 121, 2331–2378. [CrossRef] [PubMed]

5. Miller, M.R.; Newby, D.E. Air pollution and cardiovascular disease: Car sick. *Cardiovasc. Res.* 2019, 116, 279–294. [CrossRef]

6. Cohen, A.J.; Brauer, M.; Burnett, R.; Anderson, H.R.; Frostad, J.; Ester, K.; Balakrishnan, K.; Brunekreef, B.; Dandona, L.; Dandona, R.; et al. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: An analysis of data from the Global Burden of Diseases Study 2015. *Lancet* 2017, 389, 1907–1918. [CrossRef]

7. Boogaard, H.; Walker, K.; Cohen, A.J. Air pollution: The emergence of a major global health risk factor. *Int. Health* 2019, 11, 417–421. [CrossRef] [PubMed]

8. Apte, J.S.; Brauer, M.; Cohen, A.J.; Ezzati, M.; Pope, C.A., III. Ambient PM2.5 Reduces Global and Regional Life Expectancy. *Environ. Sci. Technol. Lett.* 2018, 5, 546–551. [CrossRef]

9. Rajagopalan, S.; Landrigan, P.J. Pollution and the Heart. *N. Engl. J. Med.* 2021, 385, 1881–1892. [CrossRef] [PubMed]

10. Newby, D.E.; Mannucci, J.M.; Tell, G.S.; Baccarelli, A.; Brook, R.D.; Donaldson, K.; Forastiere, F.; Franchini, M.; Franco, O.; Graham, I.; et al. Expert position paper on air pollution and cardiovascular disease. *Eur. Heart J.* 2014, 36, 83–93. [CrossRef] [PubMed]

11. Dockery, D.W.; Pope, C.A., 3rd; Xu, X.; Spengler, J.D.; Ware, J.H.; Fay, M.E.; Ferris, B.G., Jr.; Speizer, F.E. An Association between Air Pollution and Mortality in Six U.S. Cities. *N. Engl. J. Med.* 1993, 329, 1753–1759. [CrossRef]

12. Miller, M.R. Oxidative stress and the cardiovascular effects of air pollution. *Free Radic. Biol. Med.* 2020, 151, 69–87. [CrossRef] [PubMed]

13. Bell, M.L.; Dominici, F.; Ebisu, K.; Zeger, S.L.; Samet, J.M. Spatial and Temporal Variation in PM2.5 Chemical Composition in the United States for Health Effects Studies. *Environ. Health Perspect.* 2007, 115, 989–995. [CrossRef] [PubMed]

14. Boovarahan, S.R.; Kurian, G.A. Mitochondrial dysfunction: A key player in the pathogenesis of cardiovascular diseases linked to air pollution. *Res. Environ. Health* 2018, 33, 111–122. [CrossRef]

15. Pope, C.A., 3rd; Dockery, D.W. Health Effects of Fine Particulate Air Pollution: Lines that Connect. *J. Air Waste Manag. Assoc.* 2006, 56, 709–742. [CrossRef] [PubMed]

16. Martinelli, N.; Olivieri, O.; Girelli, D. Air particulate matter and cardiovascular disease: A narrative review. *Eur. J. Intern. Med.* 2013, 24, 295–302. [CrossRef]

17. Bourdrel, T.; Bind, M.-A.; Bejot, Y.; Morel, O.; Argacha, J.-F. Cardiovascular effects of air pollution. *Arch. Cardiovasc. Dis.* 2017, 110, 634–642. [CrossRef]

18. Maniasalidis, I.; Stavropoulou, E.; Stavropoulos, A.; Bezirtzoglou, E. Environmental and Health Impacts of Air Pollution: A Review. *Front. Public Health* 2020, 8, 14. [CrossRef] [PubMed]

19. Ryoo, H.G.; Heo, J.; Kim, S.-Y. Source apportionment of PM10 and PM2.5 air pollution, and possible impacts of study characteristics in South Korea. *Environ. Pollut.* 2018, 240, 963–972. [CrossRef] [PubMed]

20. Weagle, C.L.; Snider, G.; Li, C.; van Donkelaar, A.; Philip, S.; Bissonnette, P.; Burke, J.; Jackson, J.; Latimer, R.; Stone, E.; et al. Global Sources of Fine Particulate Matter: Interpretation of PM2.5 Chemical Composition Observed by SPARTAN using a Global Chemical Transport Model. *Environ. Sci. Technol.* 2018, 52, 11670–11681. [CrossRef]

21. Masri, S.; Kang, C.-M.; Koutrakis, P. Composition and sources of fine and coarse particles collected during 2002-2010 in Boston, MA. *J. Air Waste Manag. Assoc.* 2015, 65, 287–297. [CrossRef] [PubMed]

22. Alexeeff, S.E.; Liao, N.S.; Liu, X.; Eeden, S.K.V.D.; Sidney, S. Long-Term PM2.5 Exposure and Risks of Ischemic Heart Disease and Stroke Events: Review and Meta-Analysis. *J. Am. Heart Assoc.* 2021, 10, e016890. [CrossRef] [PubMed]

23. Lippmann, M.; Chen, L.-C.; Gordon, T.; Ito, K.; Thurston, G.D. National Particle Component Toxicity (NPACT) Initiative: Integrated epidemiologic and toxicologic studies of the health effects of particulate matter components. *Res. Rep. Health Eff. Inst.* 2013, 5–13.

24. Kundu, S.; Stone, E.A. Composition and sources of fine particulate matter across urban and rural sites in the Midwestern United States. *Environ. Sci. Process. Impacts* 2014, 16, 1360–1370. [CrossRef] [PubMed]

25. Ohlwein, S.; Kappeler, R.; Joss, M.K.; Künzli, N.; Hoffmann, B. Health effects of ultrafine particles: A systematic literature review update of epidemiological evidence. *Int. J. Public Health* 2019, 64, 547–559. [CrossRef]

26. Rajagopalan, S.; Al-Kindi, S.G.; Brook, R.D. Air Pollution and Cardiovascular Disease. *J. Am. Coll. Cardiol.* 2018, 72, 2054–2070. [CrossRef] [PubMed]

27. Li, N.; Xia, T.; Nel, A.E. The role of oxidative stress in ambient particulate matter-induced lung diseases and its implications in the toxicity of engineered nanoparticles. *Free Radic. Biol. Med.* 2008, 44, 1689–1699. [CrossRef] [PubMed]

28. Rao, X.; Zhong, J.; Brook, R.D.; Rajagopalan, S. Effect of Particulate Matter Air Pollution on Cardiovascular Oxidative Stress Pathways. *Antioxid. Redox Signal.* 2018, 28, 797–818. [CrossRef] [PubMed]

29. van Eeden, S.F.; Tan, W.C.; Suwa, T.; Mukea, H.; Terashima, T.; Fujii, T.; Qui, D.; Vincent, R.; Hogg, J.C. Cytokines Involved in the Systemic Inflammatory Response Induced by Exposure to Particulate Matter Air Pollutants (PM10). *Am. J. Respir. Crit. Care Med.* 2001, 164, 826–830. [CrossRef]

30. Törnqvist, H.; Mills, N.; Gonzalez, M.G.M.; Miller, M.R.; Robinson, S.D.; Megson, I.; MacNee, W.; Donaldson, K.; Söderberg, S.; Newby, D.E.; et al. Persistent Endothelial Dysfunction in Humans after Diesel Exhaust Inhalation. *Am. J. Respir. Crit. Care Med.* 2007, 176, 395–400. [CrossRef] [PubMed]
31. Shoenfelt, J.; Mitkus, R.J.; Zeisler, R.; Spatz, R.O.; Powell, J.; Fenton, M.J.; Squibb, K.A.; Medvedev, A.E. Involvement of TLR2 and TLR4 in inflammatory immune responses induced by fine and coarse ambient air particulate matter. J. Leukoc. Biol. 2009, 86, 303–312. [CrossRef]

32. Becker, S.; Fenton, M.J.; Soukup, J.M. Involvement of Microbial Components and Toll-like Receptors 2 And 4 in Cytokine Responses to Air Pollution Particles. Am. J. Respir. Cell Mol. Biol. 2002, 27, 611–618. [CrossRef]

33. Milici, A.; Talavera, K. TRP Channels as Cellular Targets of Particulate Matter. Int. J. Mol. Sci. 2021, 22, 2783. [CrossRef]

34. Rückerl, R.; Iñal-Mulli, A.; Koenig, W.; Schneider, A.; Woelke, G.; Cyrys, J.; Heinrich, J.; Marder, V.; Frampton, M.; Wichmann, H.E.; et al. Air Pollution and Markers of Inflammation and Coagulation in Patients with Coronary Heart Disease. Am. J. Respir. Crit. Care Med. 2006, 173, 432–441. [CrossRef] [PubMed]

35. Baccarelli, A.; Zanobetti, A.; Martinelli, I.; Grillo, P.; Hou, L.; Giacomini, S.; Bonzini, M.; Lanzani, G.; Mannucci, P.M.; Bertazzi, P.A.; et al. Effects of exposure to air pollution on blood coagulation. J. Thromb. Haemost. 2007, 5, 252–260. [CrossRef] [PubMed]

36. Bonzini, M.; Tripodi, A.; Artoni, A.; Tarantini, L.; Marinelli, B.; Bertazzi, P.A.; Apostoli, P.; Baccarelli, A. Effects of inhalable particulate matter on blood coagulation. J. Thromb. Haemost. 2010, 8, 662–668. [CrossRef] [PubMed]

37. Gurgueira, S.A.; Lawrence, J.; Coull, B.; Murthy, G.G.K.; González-Flecha, B. Rapid increases in the steady-state concentration of reactive oxygen species in the lungs and heart after particulate air pollution inhalation. Environ. Health Perspect. 2002, 110, 749–755. [CrossRef] [PubMed]

38. Lakey, P.; Berkemeier, T.; Tong, H.-J.; Arangio, A.; Lucas, K.; Pöschl, U.; Shiraiwa, M. Chemical exposure-response relationship between air pollutants and reactive oxygen species in the human respiratory tract. Sci. Rep. 2016, 6, 32916. [CrossRef] [PubMed]

39. Nemmar, A.; Hoet, P.; Vanquickenborne, B.; Dinsdale, D.; Thomeer, M.; Hoylaerts, M.F.; Vanbilloen, H.; Mortelmans, L.; Nemery, B. Passage of Inhaled Particles Into the Blood Circulation in Humans. Circulation 2002, 105, 411–414. [CrossRef] [PubMed]

40. Nemmar, A.; Vanbilloen, H.; Hoet, P.H.M.; Verbruggen, A.; Nemery, B. Passage of Intratracheally Instilled Ultrafine Particles from the Lung into the Systemic Circulation in Hamster. Am. J. Respir. Crit. Care Med. 2001, 164, 1665–1668. [CrossRef] [PubMed]

41. Robertson, S.; Thomson, A.L.; Carter, R.; Stott, H.R.; Shaw, C.A.; Hadoke, P.W.F.; Newby, D.E.; Miller, M.R.; Gray, G.A. Pulmonary diesel particulate increases susceptibility to myocardial ischemia/reperfusion injury via activation of sensory TRPV1 and β1 adrenoreceptors. Part. Fibre Toxicol. 2014, 11, 12. [CrossRef] [PubMed]

42. Hazari, M.S.; Haykal-Coates, N.; Winsett, D.W.; Krantz, Q.T.; King, C.; Costa, D.L.; Farraj, A.K. TRPA1 and Sympathetic Activation Contribute to Increased Risk of Triggered Cardiac Arrhythmias in Hypertensive Rats Exposed to Diesel Exhaust. Environ. Health Perspect. 2011, 119, 951–957. [CrossRef] [PubMed]

43. Hajat, A.; Roux, A.V.D.; Castro-Diehl, C.; Cosselman, K.; Golden, S.H.; Hazlehurst, M.F.; Szprio, A.; Vedal, S.; Kaufman, J. The Association between Long-Term Air Pollution and Urinary Catecholamines: Evidence from the Multi-Ethnic Study of Atherosclerosis. Environ. Health Perspect. 2019, 127, 057007. [CrossRef] [PubMed]

44. Cederbaum, A.I. Molecular mechanisms of the microsomal mixed function oxidases and biological and pathological implications. Redox Biol. 2014, 4, 60–73. [CrossRef] [PubMed]
55. Byun, H.-M.; Panni, T.; Motta, V.; Hou, L.; Nordio, F.; Apostoli, P.; Bertazzi, P.A.; Baccarelli, A.A. Effects of airborne pollutants on mitochondrial DNA Methylation. Part. Fibre Toxicol. 2013, 10, 18. [CrossRef] [PubMed]

56. Stejković, G.; Makarova, A.V.; Wanrooij, P.; Forslund, J.; Burgers, P.M.; Wanrooij, S. Oxidative DNA damage stalls the human mitochondrial replisome. Sci. Rep. 2016, 6, 28942. [CrossRef]

57. Meyer, J.N.; Leung, M.C.K.; Rooney, J.P.; Sendoel, A.; Hengartner, M.O.; Kisby, G.E.; Bess, A.S. Mitochondria as a Target of Environmental Toxicants. Toxicol. Sci. 2013, 134, 1–17. [CrossRef]

58. Xu, Z.; Xu, X.; Zhong, M.; Hotchkiss, I.P.; Lewandowski, R.P.; Wagner, J.G.; Bramble, L.A.; Yang, Y.; Wang, A.; Harkema, J.R.; et al. Ambient particulate air pollution induces oxidative stress and alterations of mitochondria and gene expression in brown and white adipose tissues. Part. Fibre Toxicol. 2011, 8, 20. [CrossRef]

59. Chan, D.C. Mitochondrial Dynamics and Its Involvement in Disease. Annu. Rev. Pathol. 2020, 15, 235–259. [CrossRef]

60. Di Gregorio, I.; Busiello, R.A.; Burgos-Aceves, M.A.; Paoletti, M.; Paolella, G.; Lionetti, L. Environmental Pollutants Effect on Brown Adipose Tissue. Front. Physiol. 2019, 9, 1891. [CrossRef]

61. Marchini, T.; Magnani, N.; D’Annunzio, V.; Tasat, D.; Gelpi, R.; Alvarez, S.; Evelson, P. Impaired cardiac mitochondrial function and contractile reserve following an acute exposure to environmental particulate matter. Biochim. Biophys. Acta 2012, 1830, 2545–2552. [CrossRef] [PubMed]

62. Hiura, T.S.; Li, N.; Kaplan, R.; Horwitz, M.; Seagrawe, J.-C.; Nel, A.E. The Role of a Mitochondrial Pathway in the Induction of Apoptosis by Chemicals Extracted from Diesel Exhaust Particles. J. Immunol. 2000, 165, 2703–2711. [CrossRef] [PubMed]

63. West, A.P. Mitochondrial dysfunction as a trigger of innate immune responses and inflammation. Toxicology 2017, 391, 54–63. [CrossRef] [PubMed]

64. Walker, M.A.; Volpi, S.; Sims, K.B.; Walter, J.E.; Traggiai, E. Powering the Immune System: Mitochondria in Immune Function and Deficiency. J. Immunol. Res. 2014, 2014, 164309. [CrossRef] [PubMed]

65. Kapnick, S.M.; Pacheco, S.E.; McGuire, P. The emerging role of immune dysfunction in mitochondrial diseases as a paradigm for understanding immunometabolism. Metabolism 2018, 81, 97–112. [CrossRef] [PubMed]

66. Breda, C.N.D.S.; Davanzo, G.G.; Basso, P.J.; Câmara, N.O.S.; Moraes-Vieira, P.M.M. Mitochondria as central hub of the immune system. Redox Biol. 2019, 26, 101255. [CrossRef] [PubMed]

67. Murphy, M.P. How mitochondria produce reactive oxygen species. Biochem. J. 2009, 417, 1–13. [CrossRef] [PubMed]

68. Chattopadhyay, M.; Khemka, V.K.; Chatterjee, G.; Ganguly, A.; Mukhopadhyay, S.; Chakrabarti, S. Enhanced ROS production and oxidative damage in subcutaneous white adipose tissue mitochondria in obese and type 2 diabetes subjects. Mol. Cell. Biochem. 2014, 399, 95–103. [CrossRef] [PubMed]

69. Cochenné, H.M.; Murphy, M.P. Complex I Is the Major Site of Mitochondrial Superoxide Production by Paratquat. J. Biol. Chem. 2008, 283, 1786–1798. [CrossRef] [PubMed]

70. Kurian, G.A.; Philip, S.; Varghese, T. Effect of aqueous extract of the Desmodium gangeticum DC root in the severity of myocardial infarction. J. Ethnopharmacol. 2005, 97, 457–461. [CrossRef] [PubMed]

71. Mügge, A. The role of reactive oxygen species in atherosclerosis. Z Kardiol. 1998, 87, 851–864. [CrossRef] [PubMed]

72. Almeida, A.S.; Figueiredo-Pereira, C.; Vieira, H.L.A. Carbon monoxide and mitochondria-modulation of cell metabolism, redox response and cell death. Front. Physiol. 2015, 6, 33. [CrossRef] [PubMed]

73. Aung, H.H.; Lame, M.W.; Gohil, K.; He, G.; Denison, M.S.; Rutledge, J.C.; Wilson, D.W. Comparative gene responses to collected ambient particles in vivo: Endothelial responses. Physiol. Genom. 2011, 43, 917–929. [CrossRef] [PubMed]

74. Hu, H.; Wu, J.; Li, Q.; Asweto, C.; Feng, L.; Yang, X.; Duan, F.; Duan, J.; Sun, Z. Fine particulate matter induces vascular endothelial activation via IL-6 dependent JAK1/STAT3 signaling pathway. Toxicol. Res. 2016, 5, 946–953. [CrossRef]

75. Montiel-Dávalos, A.; Ibarra-Sánchez, M.D.J.; Ventura-Gallegos, J.L.; Alfaro-Moreno, E.; López-Marure, R. Oxidative stress and apoptosis are induced in human endothelial cells exposed to urban particulate matter. Toxicol. Vitro. 2010, 24, 135–141. [CrossRef]

76. Sivakumar, B.; Kurian, G.A. PM2.5 from diesel exhaust attenuated cytotoxicity in H9c2 cardiomyocytes subjected to ischemia reoxygenation by inducing mitotocicity. Drug Chem. Toxicol. 2021, 1–9. [CrossRef] [PubMed]

77. Sivakumar, B.; Kurian, G.A. PM2.5 Exposure Lowers Mitochondrial Endurance During Cardiac Recovery in a Rat Model of Myocardial Infarction. Cardiovasc. Toxicol. 2022, 22, 545–557. [CrossRef] [PubMed]

78. Sun, Q.; Yue, P.; Ying, Z.; Cardounel, A.J.; Brook, R.D.; Devlin, R.; Hwang, J.-S.; Zweier, J.L.; Chen, L.C.; Rajagopalan, S. Air Pollution Exposure Potentiates Hypertension Through Reactive Oxygen Species-Mediated Activation of Rho/ROCK. Arter. Thromb. Vasc. Biol. 2008, 28, 1760–1766. [CrossRef]

79. Wittkopp, S.; Stainer, N.; Tjoa, T.; Gillen, D.; Daher, N.; Shafer, M.; Schauer, J.J.; Sioutas, C.; Delfino, R.J. Mitochondrial Genetic Background Modifies the Relationship between Traffic-Related Air Pollution Exposure and Systemic Biomarkers of Inflammation. PLoS ONE 2013, 8, e64444. [CrossRef] [PubMed]

80. Lippmann, M. Toxicological and epidemiological studies of cardiovascular effects of ambient air fine particulate matter (PM2.5) and its chemical components: Coherence and public health implications. Crit. Rev. Toxicol. 2014, 44, 299–347. [CrossRef] [PubMed]

81. Nakano, T.; Otsuki, T. Environmental air pollutants and the risk of cancer. Gan Kagaku Ryoho. Cancer Chemother. 2013, 40, 1441–1445.

82. Watkins, A.; Danilewitz, M.; Kusha, M.; Massé, S.; Urch, B.; Quadros, K.; Sears, D.; Farid, T.; Nanthakumar, K. Air Pollution and Arrhythmic Risk: The Smog Is Yet to Clear. Can. J. Cardiol. 2013, 29, 734–741. [CrossRef] [PubMed]
83. Cesaroni, G.; Forastiere, F.; Stafoggia, M.; Andersen, Z.J.; Badaloni, C.; Beelen, R.; Caracciolo, B.; De Faire, U.; Erbel, R.; Eriksen, K.T.; et al. Long term exposure to ambient air pollution and incidence of acute coronary events: Prospective cohort study and meta-analysis in 11 European cohorts from the ESCAPE Project. *BMJ* 2013, 348, f7412. [CrossRef] [PubMed]

84. Stafoggia, M.; Cesaroni, G.; Peters, A.; Andersen, Z.J.; Badaloni, C.; Beelen, R.; Caracciolo, B.; Cyrys, J.; De Faire, U.; De Hoogh, K.; et al. Long-Term Exposure to Ambient Air Pollution and Incidence of Cerebrovascular Events: Results from 11 European Cohorts within the ESCAPE Project. *Environ. Health Perspect.* 2014, 122, 919–925. [CrossRef] [PubMed]

85. Shah, A.S.V.; Langrish, J.P.; Nair, H.; McAllister, D.A.; Hunter, A.L.; Donaldson, K.; Newby, D.E.; Mills, N.L. Global association of air pollution and heart failure: A systematic review and meta-analysis. *Lancet* 2013, 382, 1039–1048. [CrossRef]

86. Hoffmann, B.; Moebus, S.; Kröger, K.; Stang, A.; Möhlenkamp, S.; Dragano, N.; Schmermund, A.; Memmesheimer, M.; Erbel, R.; Jöckel, K.-H. Residential Exposure to Urban Air Pollution, Ankle–Brachial Index, and Peripheral Arterial Disease. *Epidemiology* 2009, 20, 280–288. [CrossRef]

87. Cesaroni, G.; Andersen, Z.J.; Badaloni, C.; Beelen, R.; Caracciolo, B.; Cyrys, J.; De Faire, U.; De Hoogh, K.; et al. Particulate air pollution and risk of ST-segment depression during repeated submaximal exercise tests among subjects with coronary heart disease: The Exposure and Risk Assessment for Fine and Ultrafine Particles in Ambient Air (ULTRA) study. *Thorax* 2004, 59, 526–531. [CrossRef] [PubMed]

88. Hoffmann, B.; Moebus, S.; Kröger, K.; Stang, A.; Möhlenkamp, S.; Dragano, N.; Schmermund, A.; Memmesheimer, M.; Erbel, R.; Jöckel, K.-H. Residential Exposure to Urban Air Pollution, Ankle–Brachial Index, and Peripheral Arterial Disease. *Epidemiology* 2009, 20, 280–288. [CrossRef]

89. Beelen, R.; Peters, A.; Stafoggia, M.; Cesaroni, G.; Badaloni, C.; Smeets, J.J.; Cyrys, J.; De Faire, U.; De Hoogh, K.; et al. Long-term exposure to particulate matter and incident cardiovascular disease: Results from 11 European ESCAPE Project cohorts. *Environ. Health Perspect.* 2014, 122, 919–925. [CrossRef] [PubMed]

90. Wu, T.; Yang, X.; Chu, A.; Xie, X.; Bai, M.; Peng, Y.; Zhang, Z. Acute effects of fine particulate matter (PM2.5) on hospital admissions for cardiovascular disease in Beijing, China: A time-series study. *Environ. Sci. Eur.* 2020, 32, 187. [CrossRef]

91. Xi, Y.; Richardson, D.; Kshirsagar, A.V.; Wade, T.J.; Flythe, J.E.; Whitel, S.A.; et al. Association Between Long-term Ambient PM2.5 Exposure and Cardiovascular Outcomes Among US Hemodialysis Patients. *Am. J. Kidney Dis.* 2022, 80, 134–143. [CrossRef]

92. Wu, T.; Yang, X.; Chu, A.; Xie, X.; Bai, M.; Peng, Y.; Zhang, Z. Acute effects of fine particulate matter (PM2.5) on hospital admissions for cardiovascular disease in Beijing, China: A time-series study. *Environ. Sci. Eur.* 2020, 32, 187. [CrossRef]

93. Sarnat, S.E.; Suh, H.H.; Coull, B.A.; Schwartz, J.; Stone, P.H.; Gold, D.R. Ambient particulate air pollution and cardiac arrhythmia in a panel of older adults in Steubenville, Ohio. *Occup. Environ. Med.* 2006, 63, 700–706. [CrossRef]

94. Mills, N.L.; Törnqvist, H.; Gonzalez, M.C.; Vink, E.; Robinson, S.D.; Söderberg, S.; Boon, N.A.; Donaldson, K.; Sandström, T.; Blomberg, A.; et al. Ischemic and Thrombotic Effects of Dilute Diesel-Exhaust Inhalation in Men with Coronary Heart Disease. *N. Engl. J. Med.* 2007, 357, 1075–1082. [CrossRef]

95. Folino, A.F.; Scapellato, M.L.; Canova, C.; Maestrelli, P.; Bertorelli, G.; Simonato, L.; Iliceto, S.; Lotti, M. Individual exposure to particulate matter and the short-term arrhythmic and autonomic profiles in patients with myocardial infarction. *Eur. Hear. J.* 2009, 30, 1614–1620. [CrossRef]

96. Chan, C.-C.; Chuang, K.-J.; Shiao, G.-M.; Lin, L.-Y. Personal Exposure to Submicrometer Particles and Heart Rate Variability in Human Subjects. *Environ. Health Perspect.* 2004, 112, 1063–1067. [CrossRef]

97. Wu, S.; Deng, F.; Niu, J.; Huang, Q.; Liu, Y.; Guo, X. Association of Heart Rate Variability in Taxi Drivers with Marked Changes in Particulate Air Pollution in Beijing in 2008. *Environ. Health Perspect.* 2010, 118, 87–91. [CrossRef] [PubMed]

98. Suh, H.H.; Zanobetti, A. Exposure Error Masks the Relationship Between Traffic-Related Air Pollution and Heart Rate Variability. *Environ. Health Perspect.* 2012, 120, 417–421. [CrossRef]

99. Hoffmann, B.; Moebus, S.; Kröger, K.; Stang, A.; Möhlenkamp, S.; Dragano, N.; Schmermund, A.; Memmesheimer, M.; Erbel, R.; Jöckel, K.-H. Residential Exposure to Urban Air Pollution, Ankle–Brachial Index, and Peripheral Arterial Disease. *Epidemiology* 2009, 20, 280–288. [CrossRef]

100. Atkinson, R.W.; Kang, S.; Anderson, H.R.; Mills, I.C.; Walton, H.A. Epidemiological time series studies of PM2.5 and daily mortality and hospital admissions: A systematic review and meta-analysis. *Thorax* 2014, 69, 660–665. [CrossRef]

101. Achilleos, S.; Kioumourtzoglou, M.-A.; Wu, C.-D.; Schwartz, J.D.; Koutrakis, P.; Papatheodorou, S.I. Acute effects of fine particulate matter constituents on mortality: A systematic review and meta-regression analysis. *Environ. Int.* 2017, 109, 89–100. [CrossRef] [PubMed]

102. Newell, K.; Kartsonaki, C.; Lam, K.B.H.; Kurmi, O.P. Cardiorespiratory health effects of particulate ambient air pollution exposure in low-income and middle-income countries: A systematic review and meta-analysis. *Lancet Planet. Health* 2017, 1, e368–e380. [CrossRef]

103. Chen, R.; Yin, P.; Meng, X.; Liu, C.; Wang, L.; Xu, X.; Ross, J.A.; Tse, L.A.; Zhao, Z.; Kan, H.; et al. Fine Particulate Air Pollution and Daily Mortality. A Nationwide Analysis in 272 Chinese Cities. *Am. J. Respir. Crit. Care Med.* 2017, 196, 73–81. [CrossRef] [PubMed]

104. Zhao, L.; Liang, H.-R.; Chen, F.-Y.; Chen, Z.; Guan, W.-J.; Li, J.-H. Association between air pollution and cardiovascular mortality in China: A systematic review and meta-analysis. *Oncotarget* 2017, 8, 66438–66448. [CrossRef] [PubMed]

105. Amsalum, E.; Wang, T.; Li, H.; Liu, Y.; Wang, A.; Liu, X.; Tao, L.; Luo, Y.; Zhang, F.; Yang, X.; et al. Acute effects of fine particulate matter (PM2.5) on hospital admissions for cardiovascular disease in Beijing, China: A time-series study. *Environ. Health* 2019, 18, 70. [CrossRef]
106. Tian, Y.; Liu, H.; Wu, Y.; Si, Y.; Song, J.; Cao, Y.; Li, M.; Wu, Y.; Wang, X.; Chen, L.; et al. Association between ambient fine particulate pollution and hospital admissions for cause specific cardiovascular disease: Time series study in 184 major Chinese cities. *BMJ* 2019, 367, l6572. [CrossRef]

107. Wyatt, L.H.; Xi, Y.; Kshirsagar, A.; Di, Q.; Ward-Caviness, C.; Wade, T.J.; Cascio, W.E.; Rappold, A.G. Association of short-term exposure to ambient PM2.5 with hospital admissions and 30-day readmissions in end-stage renal disease patients: Population-based retrospective cohort study. *BMJ Open* 2020, 10, e041177. [CrossRef] [PubMed]

108. Qiu, X.; Wei, Y.; Wang, Y.; Di, Q.; Sofer, T.; Abu Awad, Y.; Schwartz, J. Inverse probability weighted distributed lag effects of short-term exposure to PM2.5 and ozone on CVD hospitalizations in New England Medicare participants—Exploring the causal effects. *Environ. Res.* 2019, 182, 109095. [CrossRef]

109. Dahlquist, M.; Frykman, V.; Kemp-Gudmundsdottir, K.; Svennberg, E.; Wellenius, G.A.; Ljungman, P.L.S. Short-term associations between ambient air pollution and acute atrial fibrillation episodes. *Environ. Int.* 2020, 141, 105765. [CrossRef]

110. Farhadi, Z.; Gorgi, H.A.; Shabaninejad, H.; Delavar, M.A.; Torani, S. Association between PM2.5 and risk of hospitalization for myocardial infarction: A systematic review and a meta-analysis. *BMC Public Health* 2020, 20, 314. [CrossRef]

111. Ren, Q.; Li, S.; Xiao, C.; Zhang, J.; Lin, H.; Wang, S. The Impact of Air Pollution on Hospitalization for Cardiovascular and Cerebrovascular Disease in Shenyang, China. *Iran. J. Public Health* 2020, 49, 1476–1484. [CrossRef] [PubMed]

112. Zhou, H.; Geng, H.; Dong, C.; Bai, T. The short-term harvesting effects of ambient particulate matter on mortality in Taiyuan elderly residents: A time-series analysis with a generalized additive distributed lag model. *Ecotoxicol. Environ. Saf.* 2020, 207, 111235. [CrossRef] [PubMed]

113. Yue, C.; Yang, F.; Li, F.; Chen, Y. Association between air pollutants and atrial fibrillation in general population: A systematic review and meta-analysis. *Ecotoxicol. Environ. Saf.* 2020, 208, 111508. [CrossRef] [PubMed]

114. Kuzma, L.; Warhá, W.; Kralisz, P.; Kazmierski, M.; Bachórzewska-Gajewska, H.; Wojakowski, W.; Dobrzycki, S. Impact of short-term air pollution exposure on acute coronary syndrome in two cohorts of industrial and non-industrial areas: A time series regression with 6,000,000 person-years of follow-up (ACS—Air Pollution Study). *Environ. Res.* 2021, 197, 111154. [CrossRef]

115. Chen, M.; Zhao, J.; Zhuo, C.; Zheng, L. The Association Between Ambient Air Pollution and Atrial Fibrillation. *Int. Hear. J.* 2021, 62, 290–297. [CrossRef]

116. Badaloni, C.; Cesaroni, G.; Cerza, F.; Davoli, M.; Brunekreef, B.; Forastiere, F. Effects of long-term exposure to particulate matter and metal components on mortality in the Rome longitudinal study. *Environ. Int.* 2017, 109, 146–154. [CrossRef]

117. Jerrett, M.; Turner, M.C.; Beckerman, B.S.; Pope, C.A.; van Donkelaar, A.; Martin, R.V.; Serre, M.; Crouse, D.; Gapstur, S.M.; Krewski, D.; et al. Comparing the Health Effects of Ambient Particulate Matter Estimated Using Ground-Based versus Remote Sensing Exposure Estimates. *Environ. Health Perspect.* 2017, 125, 552–559. [CrossRef]

118. Kim, H.; Kim, J.; Kim, S.; Kang, S.-H.; Kim, H.-J.; Kim, H.; Heo, J.; Yi, S.-M.; Kim, K.; Youn, T.-J.; et al. Cardiovascular Effects of Long-Term Exposure to Air Pollution: A Population-Based Study With 900 845 Person-Years of Follow-up. *J. Am. Hear. Assoc.* 2017, 6, e007170. [CrossRef]

119. Pinault, L.L.; Weichenthal, S.; Crouse, D.L.; Brauer, M.; Erickson, A.; van Donkelaar, A.; Martin, R.V.; Hystad, P.; Chen, H.; Finès, P.; et al. Associations between fine particulate matter and mortality in the 2001 Canadian Census Health and Environment Cohort. *Environ. Res.* 2017, 159, 406–415. [CrossRef]

120. Pun, V.C.; Kazemparkouhi, F.; Manjourides, J.; Suh, H.H. Long-Term PM2.5 Exposure and Respiratory, Cancer, and Cardiovascular Mortality in Older US Adults. *Am. J. Epidemiol.* 2017, 186, 961–969. [CrossRef]

121. Qiu, H.; Sun, S.; Tsang, H.; Wong, C.-M.; Lee, R.S.-Y.; Schooling, C.M.; Tian, L. Fine particulate matter exposure and incidence of stroke. *Neurology* 2017, 88, 1709–1717. [CrossRef]

122. Stockfelt, L.; Andersson, E.M.; Molnár, P.; Gidhagen, L.; Segersson, D.; Rosengren, A.; Barregard, L.; Sallsten, G. Long-term effects of total and source-specific particulate air pollution on incident cardiovascular disease in Gothenburg, Sweden. *Environ. Res.* 2017, 158, 61–71. [CrossRef]

123. Turner, M.C.; Cohen, A.; Burnett, R.T.; Jerrett, M.; Diver, W.R.; Gapstur, S.M.; Krewski, D.; Samet, J.M.; Pope, C.A. Interactions between cigarette smoking and ambient PM2.5 for cardiovascular mortality. *Environ. Res.* 2017, 154, 304–310. [CrossRef]

124. Yin, P.; Brauer, M.; Cohen, A.; Burnett, R.T.; Liu, J.; Liu, Y.; Liang, R.; Wang, W.; Qi, J.; Wang, L.; et al. Long-term Fine Particulate Matter Exposure and Nonaccidental and Cause-specific Mortality in a Large National Cohort of Chinese Men. *Environ. Health Perspect.* 2017, 125, 117002. [CrossRef] [PubMed]

125. Cakmak, S.; Hebbern, C.; Pinault, L.; Lavigne, E.; Vanos, J.; Crouse, D.L.; Tjepkema, M. Associations between long-term PM2.5 and ozone exposure and mortality in the Canadian Census Health and Environment Cohort (CANCHEC), by spatial synoptic classification zone. *Environ. Int.* 2017, 111, 200–211. [CrossRef]

126. Gandini, M.; Scarinzi, C.; Bande, S.; Berti, G.; Carnà, P.; Ciancarella, L.; Costa, G.; Demaria, M.; Ghigo, S.; Piersanti, A.; et al. Long term effect of air pollution on incident hospital admissions: Results from the Italian Longitudinal Study within LIFE MED HISS project. *Environ. Int.* 2018, 121, 1087–1097. [CrossRef] [PubMed]

127. Loop, M.S.; McClure, L.A.; Levitan, E.B.; Al-Hamdan, M.Z.; Crosson, W.L.; Safford, M.M. Fine particulate matter and incident coronary heart disease in the REGARDS cohort. *Am. Hear. J.* 2018, 197, 94–102. [CrossRef] [PubMed]

128. Parker, J.D.; Kravets, N.; Vaidyanathan, A. Particulate Matter Air Pollution Exposure and Heart Disease Mortality Risks by Race and Ethnicity in the United States: 1997 to 2009 National Health Interview Survey With Mortality Follow-Up Through 2011. *Circulation* 2018, 137, 1688–1697. [CrossRef]
129. Yitshak-Sade, M.; Bobb, J.F.; Schwartz, J.D.; Kloog, I.; Zanobetti, A. The association between short and long-term exposure to PM2.5 and temperature and hospital admissions in New England and the synergistic effect of the short-term exposures. Sci. Total Environ. 2018, 639, 868–875. [CrossRef]

130. Bai, L.; Shin, S.; Burnett, R.T.; Kwong, J.C.; Hystad, P.; van Donkelaar, A.; Goldberg, M.S.; Lavigne, E.; Copes, R.; Martin, R.V.; et al. Exposure to ambient air pollution and the incidence of congestive heart failure and acute myocardial infarction: A population-based study of 5.1 million Canadian adults living in Ontario. Environ. Int. 2019, 132, 105004. [CrossRef]

131. Yazdi, M.D.; Wang, Y.; Di, Q.; Zanobetti, A.; Schwartz, J. Long-term exposure to PM2.5 and ozone and hospital admissions of Medicare participants in the Southeast USA. Environ. Int. 2019, 130, 104879. [CrossRef]

132. Dirgawati, M.; Hinwood, A.; Nedkoff, L.; Hankey, G.; Yeap, B.B.; Flicker, L.; Nieuwenhuijsen, M.; Brunekreef, B.; Heyworth, J. Long-term Exposure to Low Air Pollutant Concentrations and the Relationship with All-Cause Mortality and Stroke in Older Men. Epidemiology 2019, 30, S82–S89. [CrossRef] [PubMed]

133. Héritér, H.; Vienneau, D.; Foraster, M.; Eze, I.C.; Schaffner, E.; De Hoogh, K.; Thiesse, L.; Rudzik, F.; Habermacher, M.; Köpfli, M.; et al. A systematic analysis of mutual effects of transportation noise and air pollution exposure on myocardial infarction mortality: A nationwide cohort study in Switzerland. Eur. Hear. J. 2018, 40, 598–603. [CrossRef]

134. Huang, K.; Liang, F.; Yang, X.; Liu, F.; Li, J.; Xiao, Q.; Chen, J.; Liu, X.; Cao, J.; Shen, C.; et al. Long term exposure to ambient fine particulate matter and incidence of stroke: Prospective cohort study from the China-PAR project. BMJ 2019, 367, l6720. [CrossRef]

135. Lim, C.C.; Hayes, R.; Ahn, J.; Shao, Y.; Silverman, D.T.; Jones, R.R.; Thurston, G.D. Mediterranean Diet and the Association Between Air Pollution and Cardiovascular Disease Mortality Risk. Circulation 2019, 135, 1766–1775. [CrossRef]

136. Ljungman, P.L.S.; Andersson, N.; Stockfelt, L.; Andersson, E.M.; Sommar, J.N.; Eneroth, K.; Gidhagen, L.; Johansson, C.; Lager, A.; Leander, K.; et al. Long-Term Exposure to Particulate Air Pollution, Black Carbon, and Their Source Components in Relation to Ischemic Heart Disease and Stroke. Environ. Health Perspect. 2019, 127, 107012. [CrossRef]

137. Pope, C.A., 3rd; Lefler, J.S.; Ezzati, M.; Higbee, J.D.; Marshall, J.D.; Kim, S.-Y.; Bechle, M.; Gilliat, K.S.; Vernon, S.E.; Robinson, A.; et al. Mortality Risk and Fine Particulate Air Pollution in a Large, Representative Cohort of U.S. Adults. Environ. Health Perspect. 2019, 127, 077007. [CrossRef]

138. Shin, S.; Burnett, R.T.; Kwong, J.C.; Hystad, P.; Van Donkelaar, A.; Brook, J.R.; Goldberg, M.S.; Tu, K.; Copes, R.; Martin, R.V.; et al. Ambient Air Pollution and the Risk of Atrial Fibrillation and Stroke: A Population-Based Cohort Study. Environ. Health Perspect. 2019, 127, 087009. [CrossRef] [PubMed]

139. Hayes, R.B.; Lim, C.; Zhang, Y.; Cromar, K.; Shao, Y.; Reynolds, H.; Silverman, D.T.; Jones, R.R.; Park, Y.; Jerrrett, M.; et al. PM2.5 air pollution and cause-specific cardiovascular disease mortality. Int. J. Epidemiol. 2020, 49, 25–35. [CrossRef] [PubMed]

140. Meng, X.; Zhang, Y.; Yang, K.-Q.; Yang, Y.-K.; Zhou, X.-L. Potential Harmful Effects of PM2.5 on Occurrence and Progression of Acute Coronary Syndrome: Epidemiology, Mechanisms, and Prevention Measures. Int. J. Environ. Res. Public Health 2016, 13, 748. [CrossRef]

141. Gardner, B.; Ling, F.; Hopke, P.K.; Frampton, M.W.; Utell, M.J.; Zareba, W.; Cameron, S.J.; Chalupa, D.; Kane, C.; Kulandhaisamy, S.; et al. Ambient fine particulate air pollution triggers ST-elevation myocardial infarction, but not non-ST elevation myocardial infarction: A case-crossover study. Part. Fibre Toxicol. 2014, 11, 1. [CrossRef] [PubMed]

142. Zhang, Q.; Qi, W.; Yao, W.; Wang, M.; Chen, Y.; Zhou, Y. Ambient Particulate Matter (PM2.5/PM10) Exposure and Emergency Department Visits for Acute Myocardial Infarction in Chaoyang District, Beijing, China During 2014: A Case-Crossover Study. J. Epidemiol. 2016, 26, 538–545. [CrossRef]

143. PopeIII, C.A.; Muhlestein, J.B.; Anderson, J.L.; Cannon, J.B.; Hales, N.M.; Meredith, K.G.; Le, V.; Horne, B.D. Short-Term Exposure to Fine Particulate Air Pollution Is Preferentially Associated With the Risk of ST-Segment Elevation Acute Coronary Events. J. Am. Hear. Assoc. 2015, 4, e002506. [CrossRef] [PubMed]

144. Bhaskaran, K.; Hajat, S.; Haines, A.; Herrett, E.; Wilkinson, P.; Smeeth, L. Effects of air pollution on the incidence of myocardial infarction. Heart 2009, 95, 1746–1759. [CrossRef] [PubMed]

145. Mustafic, H.; Jabre, P.; Caussin, C.; Murad, M.H.; Escolano, S.; Tafflet, M.; Périer, M.-C.; Marjon, E.; Vernerey, D.; Empama, J.-P.; et al. Main air pollutants and myocardial infarction: A systematic review and meta-analysis. JAMA J. Am. Med Assoc. 2012, 307, 713–721. [CrossRef]

146. Chen, H.; Burnett, R.T.; Copes, R.; Kwong, J.C.; Villeneuve, P.; Goldberg, M.S.; Brook, R.D.; Van Donkelaar, A.; Jerrrett, M.; Martin, R.V.; et al. Ambient Fine Particulate Matter and Mortality among Survivors of Myocardial Infarction: Population-Based Cohort Study. Environ. Health Perspect. 2016, 124, 1421–1428. [CrossRef]

147. Tonne, C.; Wilkinson, P. Long-term exposure to air pollution is associated with survival following acute coronary syndrome. Eur. Hear. J. 2013, 34, 1306–1311. [CrossRef] [PubMed]

148. Dresen, W.F.; Ferguson, J.D. Ventricular Arrhythmias. Cardiol. Clin. 2018, 36, 129–139. [CrossRef]

149. Song, X.; Liu, Y.; Hu, Y.; Zhao, X.; Tian, J.; Ding, G.; Wang, S. Short-Term Exposure to Air Pollution and Cardiac Arrhythmia: A Meta-Analysis and Systematic Review. Int. J. Environ. Res. Public Health 2016, 13, 642. [CrossRef]

150. Folino, F.; Buja, G.; Zanotto, G.; Marras, E.; Allocca, G.; Vaccari, D.; Gasparini, G.; Bertaglia, E.; Zoppo, F.; Calzolari, V.; et al. Association between air pollution and ventricular arrhythmias in high-risk patients (ARIA study): A multicentre longitudinal study. Lancet Planet. Health 2017, 1, e58–e64. [CrossRef]
151. Kim, I.-S.; Yang, P.-S.; Lee, J.; Yu, H.T.; Kim, T.-H.; Uhm, J.-S.; Pak, H.-N.; Lee, M.-H.; Joung, B. Long-term exposure of fine particulate matter air pollution and incident atrial fibrillation in the general population: A nationwide cohort study. *Int. J. Cardiol.* 2019, 283, 178–183. [CrossRef] [PubMed]

152. Zhang, Z.; Kang, J.; Hong, Y.S.; Chang, Y.; Ryu, S.; Park, J.; Cho, J.; Guallar, E.; Shin, H.C.; Zhao, D. Long-Term Particulate Matter Exposure and Incidence of Arrhythmias: A Cohort Study. *J. Am. Heart. Assoc.* 2020, 9, e016885. [CrossRef] [PubMed]

153. Shao, Q.; Liu, T.; Korantzopoulos, P.; Zhang, Z.; Zhao, J.; Li, G. Association between air pollution and development of atrial fibrillation: A meta-analysis of observational studies. *Heart Lung.* 2016, 45, 557–562. [CrossRef] [PubMed]

154. Al-Kindi, S.G.; Brook, R.D.; Biswal, S.; Rajagopalan, S. Environmental determinants of cardiovascular disease: Lessons learned from air pollution. *Nat. Rev. Cardiol.* 2020, 17, 656–672. [CrossRef]

155. Lu, F.; Xu, D.; Cheng, Y.; Dong, S.; Guo, C.; Jiang, X.; Zheng, X. Systematic review and meta-analysis of the adverse health effects of ambient particulate matter on human health. *Environ. Pollut.* 2015, 194, 5–11. [CrossRef] [PubMed]

156. Mills, I.C.; Atkinson, R.W.; Kang, S.; Walton, H.; Anderson, H.R. Quantitative systematic review of the associations between short-term exposure to nitrogen dioxide and mortality and hospital admissions. *BMJ Open* 2015, 5, e006946. [CrossRef]

157. Hoek, G.; Krishnan, R.M.; Beelen, R.; Peters, A.; Ostro, B.; Brunekreef, B.; Kaufman, J.D. Long-term air pollution exposure and cardio-respiratory mortality: A review. *Environ. Health Perspect.* 2013, 12, 43. [CrossRef]

158. Krewski, D.; Jerrett, M.; Burnett, R.T.; Ma, R.; Hughes, E.; Shi, Y.; Turner, M.C.; Pope, C.A., 3rd; Thurston, G.; Calle, E.E.; et al. Extended follow-up and spatial analysis of the American Cancer Society study linking particulate air pollution and mortality. *Res. Rep. Health Eff. Inst.* 2009, 5–114. discussion 115–136.

159. Crouse, D.L.; Peters, P.A.; Van Donkelaar, A.; Goldberg, M.S.; Villeneuve, P.J.; Brion, O.; Khan, S.; Atari, D.O.; Jerrett, M.; Pope, C.A.; et al. Risk of Nonaccidental and Cardiovascular Mortality in Relation to Long-term Exposure to Low Concentrations of Fine Particulate Matter: A Canadian National-Level Cohort Study. *Environ. Health Perspect.* 2012, 120, 708–714. [CrossRef] [PubMed]

160. Xie, W.; Li, G.; Zhao, D.; Xie, X.; Wei, Z.; Wang, W.; Wang, M.; Li, G.; Liu, W.; Sun, J.; et al. Relationship between fine particulate air pollution and ischaemic heart disease morbidity and mortality. *Heart* 2015, 101, 257–263. [CrossRef]

161. Hart, J.E.; Chiueu, S.E.; Laden, F.; Albert, C.M. Roadway proximity and risk of sudden cardiac death in women. *Circulation* 2014, 130, 1474–1482. [CrossRef] [PubMed]

162. Liu, H.; Tian, Y.; Song, J.; Cao, Y.; Xiang, X.; Huang, C.; Li, M.; Hu, Y. Effect of Ambient Air Pollution on Hospitalization for Heart Failure in 26 of China’s Largest Cities. *Am. J. Cardiol.* 2018, 121, 628–633. [CrossRef] [PubMed]

163. Cai, Y.; Zhang, B.; Ke, W.; Feng, B.; Lin, H.; Xiao, J.; Zeng, W.; Li, X.; Tao, J.; Yang, Z.; et al. Associations of Short-term and Long-term Exposure to Ambient Air Pollutants With Hypertension. *Hypertension* 2016, 68, 62–70. [CrossRef] [PubMed]

164. Yang, B.-Y.; Qian, Z.; Howard, S.W.; Vaughan, M.G.; Fan, S.-J.; Liu, K.-K.; Dong, G.-H. Global association between ambient air pollution and blood pressure: A systematic review and meta-analysis. *Environ. Pollut.* 2018, 235, 576–588. [CrossRef] [PubMed]

165. Liang, R.; Zhang, B.; Zhao, X.; Ruan, Y.; Lian, H.; Fan, Z. Effect of exposure to PM2.5 on blood pressure. *J. Hypertens.* 2014, 32, 2130–2140, discussion 2141. [CrossRef]

166. Thillaippan, N.B.; Chakraborty, P.; Hasan, G.; Taylor, C.W. IP3 receptors and Ca2+ entry. *Biochim. Biophys. Acta Mol. Cell Res.* 2015, 1858, 1092–1100. [CrossRef]

167. Lin, H.; Guo, Y.; Zheng, Y.; Di, Q.; Liu, T.; Xiao, J.; Li, X.; Zeng, W.; Cummings-Vaughn, L.A.; Howard, S.W.; et al. Long-term Effects of Ambient PM2.5 on Hypertension and Blood Pressure and Attributable Risk Among Older Chinese Adults. *Hypertension* 2017, 69, 806–812. [CrossRef] [PubMed]

168. Zhang, Z.; Guo, C.; Lau, A.K.; Chan, T.-C.; Chuang, Y.C.; Lin, C.; Jiang, W.K.; Yeoh, E.-K.; Tam, T.; Woo, K.S.; et al. Long-term Exposure to Fine Particulate Matter, Blood Pressure, and Incident Hypertension in Taiwanese Adults. *Environ. Health Perspect.* 2015, 126, 017008. [CrossRef]

169. Wu, Y.; Ye, Z.; Fang, Y. Spatial analysis of the effects of PM2.5 on hypertension among the middle-aged and elderly people in China. *Int. J. Environ. Health Res.* 2019, 31, 729–740. [CrossRef]

170. Ma, Y.; Sun, M.; Liang, Q.; Lau, A.K.; Chen, T.; Duan, J.; Sun, Z. The relationship between long-term exposure to PM2.5 and hypertension in women: A meta-analysis. *Environ. Pollut.* 2020, 266, 114192. [CrossRef] [PubMed]

171. Liang, S.; Zhang, J.; Ning, R.; Du, Z.; Liu, J.; Batibawa, J.W.; Duan, J.; Sun, Z. The critical role of endothelial function in fine particulate matter-induced atherosclerosis. *Part. Fibre Toxicol.* 2020, 17, 61. [CrossRef] [PubMed]

172. Montone, R.A.; Camilli, M.; Russo, M.; Termite, C.; La Vecchia, G.; Iannaccone, G.; Rinaldi, R.; Gurgoglione, F.; Del Buono, M.G.; Sanna, T.; et al. Air Pollution and Coronary Plaque Vulnerability and Instability. *JACC: Cardiovasc. Imaging* 2021, 15, 325–342. [CrossRef] [PubMed]

173. Geng, J.; Liu, H.; Ge, P.; Hu, T.; Zhang, Y.; Yang, J.; Xu, B.; Wang, B.; Xie, J. PM2.5 promotes plaque vulnerability at different stages of atherosclerosis and the formation of foam cells via TLR4/MyD88/NFkB pathway. *Ecotoxicol. Environ. Saf.* 2019, 176, 76–84. [CrossRef] [PubMed]

174. Hu, T.; Zhu, P.; Liu, Y.; Zhu, H.; Geng, J.; Wang, B.; Yuan, G.; Peng, Y.; Xu, B. PM2.5 induces endothelial dysfunction via activating NLRP3 inflammasome. *Environ. Toxicol.* 2021, 36, 1886–1893. [CrossRef]

175. Krishnan, R.M.; Adar, S.D.; Sziro, A.A.; Jorgensen, N.W.; Van Hee, V.C.; Barr, R.G.; O’Neill, M.S.; Herrington, D.M.; Polak, J.F.; Kaufman, J.D. Vascular Responses to Long-term Exposure to Fine Particulate Matter. *J. Am. Coll. Cardiol.* 2012, 60, 2158–2166. [CrossRef] [PubMed]
176. Kloog, I. Fine particulate matter (PM2.5) association with peripheral artery disease admissions in northeastern United States. *Int. J. Environ. Health Res.* 2016, 26, 572–577. [CrossRef]

177. Zhang, S.; Wolf, K.; Breitner, S.; Kronenberg, F.; Stafoggia, M.; Peters, A.; Schneider, A. Long-term effects of air pollution on ankle-brachial index. *Environ. Int.* 2018, 118, 17–25. [CrossRef]

178. Kaufman, J.D.; Adar, S.D.; Barr, R.G.; Budoff, M.; Burke, G.L.; Curl, C.L.; Daviglus, M.L.; Roux, A.V.D.; Gassett, A.J.; Jacobs, D.R.; et al. Association between air pollution and coronary artery calcification within six metropolitan areas in the USA (the Multi-Ethnic Study of Atherosclerosis and Air Pollution): A longitudinal cohort study. *Lancet* 2016, 388, 696–704. [CrossRef]

179. Provost, E.B.; Madhلوم, N.; Panis, L.I.; De Boever, P.; Nawrot, T.S. Carotid Intima-Media Thickness, a Marker of Subclinical Atherosclerosis, and Particulate Air Pollution Exposure: The Meta-Analytical Evidence. *PLoS ONE* 2015, 10, e0127014. [CrossRef]

180. Zhang, Z.; Chan, T.-C.; Guo, C.; Chang, L.-Y.; Lin, C.; Chuang, Y.C.; Jiang, W.K.; Ho, K.F.; Tam, T.; Woo, K.S.; et al. Long-term exposure to ambient particulate matter (PM2.5) is associated with platelet counts in adults. *Environ. Pollut.* 2018, 240, 432–439. [CrossRef]

181. Robertson, S.; Miller, M.R. Ambient air pollution and thrombosis. *Part. Fibre Toxicol.* 2018, 15, 1–16. [CrossRef] [PubMed]

182. Franchini, M.; Mengoli, C.; Cruciani, M.; Bonfanti, C.; Mannucci, P.M. Association between particulate air pollution and venous thromboembolism: A systematic literature review. *Eur. J. Intern. Med.* 2015, 27, 10–13. [CrossRef] [PubMed]

183. Fonggodri, K.; Chamnancharun, S.; Desakorn, V.; Thanachartwet, V.; Sahassananda, D.; Rojnuckarin, P.; Umemura, T. Particulate Matter 2.5 and Hematological Disorders From Dust to Diseases: A Systematic Review of Available Evidence. *Front. Med.* 2021, 8, 692008. [CrossRef]

184. Khan, F.; Tritschler, T.; Kahn, S.R.; Rodger, M.A. Venous thromboembolism. *Lancet* 2021, 398, 64–77. [CrossRef]

185. Kloog, I.; Zanobetti, A.; Nordio, F.; Coull, B.A.; Baccarelli, A.A.; Schwartz, J. Effects of airborne fine particles (PM<sub>2.5</sub>) on deep vein thrombosis admissions in the northeastern United States. *J. Thromb. Haemost.* 2015, 13, 768–774. [CrossRef]

186. Fuller, R.; Landrigan, P.J.; Balakrishnan, K.; Bathan, G.; Bose-O'Reilly, S.; Brauer, M.; Caravanos, J.; Chiles, T.; Cohen, A.; Corra, L.; et al. Pollution and health: A progress update. *Lancet Planet Health.* 2022, 6, e535–e547. [CrossRef]

187. Hadley, M.B.; Baumgartner, J.; Vedanthan, R. Developing a Clinical Approach to Air Pollution and Cardiovascular Health. *Circulation* 2018, 137, 725–742. [CrossRef]

188. Franchini, M.; Mannucci, P.M. Mitigation of air pollution by greenness: A narrative review. *Eur. J. Intern. Med.* 2018, 55, 1–5. [CrossRef] [PubMed]

189. Sagar, A.; Balakrishnan, K.; Guttikunda, S.; Roychowdhury, A.; Smith, K.R. India Leads the Way: A Health-Centered Strategy for Air Pollution. *Environ. Health Perspect.* 2016, 124, A116–A117. [CrossRef]

190. Ezzati, M.; Baumgartner, J.C. Household energy and health: Where next for research and practice? *Lancet* 2016, 389, 130–132. [CrossRef]

191. Chen, C.; Park, T.; Wang, X.; Piao, S.; Xu, B.; Chaturvedi, R.K.; Fuchs, R.; Brovkin, V.; Clais, P.; Fensholt, R.; et al. China and India lead in greening of the world through land-use management. *Nat. Sustain.* 2019, 2, 122–129. [CrossRef] [PubMed]

192. Adar, S.D.; Kaufman, J. Cardiovascular Disease and Air Pollutants: Evaluating and Improving Epidemiological Data Implicating Traffic Exposure. * Inhal. Toxicol.* 2007, 19, 135–149. [CrossRef] [PubMed]

193. Chen, R.; Zhao, A.; Chen, H.; Zhao, Z.; Cai, J.; Wang, C.; Yang, C.; Li, H.; Xu, X.; Ha, S.; et al. Cardiopulmonary Benefits of Reducing Indoor Particles of Outdoor Origin. *J. Am. Coll. Cardiol.* 2015, 65, 2279–2287. [CrossRef]

194. Bell, M.L.; Ebisu, K.; Peng, R.D.; Dominici, F. Adverse Health Effects of Particulate Air Pollution. *Epidemiology* 2009, 20, 682–686. [CrossRef]

195. Langrish, J.P.; Mills, N.L.; Chan, J.K.; Leseman, D.L.; Aitken, R.J.; Fokkens, P.H.; Cassee, F.R.; Li, J.; Donaldson, K.; Newby, D.E.; et al. Beneficial cardiovascular effects of reducing exposure to particulate air pollution using a simple facemask. *Part. Fibre Toxicol.* 2009, 6, 8. [CrossRef] [PubMed]

196. Langrish, J.P.; Li, X.; Wang, S.; Lee, M.M.Y.; Barnes, G.D.; Miller, M.R.; Cassee, F.R.; Boon, N.A.; Donaldson, K.; Li, J.; et al. Reducing Personal Exposure to Particulate Air Pollution Improves Cardiovascular Health in Patients with Coronary Heart Disease. *Environ. Health Perspect.* 2012, 120, 367–372. [CrossRef]

197. Shi, J.; Lin, Z.; Chen, R.; Wang, C.; Yang, C.; Cai, J.; Lin, J.; Xu, X.; Ross, J.A.; Zhao, Z.; et al. Cardiovascular Benefits of Wearing Particulate-Filtering Respirators: A Randomized Crossover Trial. *Environ. Health Perspect.* 2017, 125, 175–180. [CrossRef]

198. Shin, T.H.; Manavalan, B.; Lee, D.Y.; Basith, S.; Seo, C.; Paik, M.J.; Kim, S.W.; Seo, H.; Lee, J.Y.; Kim, J.Y.; et al. Silica-coated magnetic-nanoparticle-induced cytotoxicity is reduced in microglia by glutathione and citrate identified using integrated omics. *Part. Fibre Toxicol.* 2021, 18, 42. [CrossRef]

199. Romieu, I.; Castro-Giner, F.; Künzli, N.; Sunyer, J. Air pollution, oxidative stress and dietary supplementation: A review. *Eur. Respir. J.* 2008, 31, 179–197. [CrossRef]

200. Tong, H.; Rappold, A.; Diaz-Sanchez, D.; Steck, S.E.; Bernsten, J.; Cascio, W.E.; Devlin, R.B.; Samet, J.M. Omega-3 Fatty Acid Supplementation Appears to Attenuate Particulate Air Pollution–Induced Cardiac Effects and Lipid Changes in Healthy Middle-Aged Adults. *Environ. Health Perspect.* 2012, 120, 952–957. [CrossRef]

201. McCracken, J.P.; Smith, K.R.; Diaz, A.; Mittleman, M.; Schwartz, J. Chimney Stove Intervention to Reduce Long-term Wood Smoke Exposure Lowers Blood Pressure among Guatemalan Women. *Environ. Health Perspect.* 2007, 115, 996–1001. [CrossRef] [PubMed]
202. McCracken, J.; Smith, K.R.; Stone, P.; Díaz, A.; Arana, B.; Schwartz, J. Intervention to Lower Household Wood Smoke Exposure in Guatemala Reduces ST-Segment Depression on Electrocardiograms. Environ. Health Perspect. 2011, 119, 1562–1568. [CrossRef] [PubMed]

203. Bräuner, E.V.; Forchhammer, L.; Møller, P.; Barregard, L.; Gunnarsen, L.; Afshari, A.; Wåhlin, P.; Glasius, M.; Dragsted, L.O.; Basu, S.; et al. Indoor Particles Affect Vascular Function in the Aged. Am. J. Respir. Crit. Care Med. 2008, 177, 419–425. [CrossRef] [PubMed]

204. Carlsten, C.; Salvi, S.; Wong, G.; Chung, K.F. Personal strategies to minimise effects of air pollution on respiratory health: Advice for providers, patients and the public. Eur. Respir. J. 2020, 55, 1902056. [CrossRef] [PubMed]

205. GBD 2017 DALYs; Hale Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018, 392, 1859–1922. [CrossRef]

206. These Five Cities are Taking Aim at Air Pollution. Available online: https://www.unep.org/news-and-stories/story/these-five-cities-are-taking-aim-air-pollution (accessed on 20 September 2021).

207. Niu, J.; Liberda, E.N.; Qu, S.; Guo, X.; Li, X.; Zhang, J.; Meng, J.; Yan, B.; Li, N.; Zhong, M.; et al. The Role of Metal Components in the Cardiovascular Effects of PM2.5. PLoS ONE 2013, 8, e83782. [CrossRef] [PubMed]

208. Wolf, K.; Stafoggia, M.; Cesaroni, G.; Andersen, Z.J.; Beelen, R.; Galassi, C.; Hennig, F.; Migliore, E.; Penell, J.; Ricceri, F.; et al. Long-term Exposure to Particulate Matter Constituents and the Incidence of Coronary Events in 11 European Cohorts. Epidemiology 2015, 26, 565–574. [CrossRef]