Review article

Impact of the environmental pollution on cardiovascular diseases: From epidemiological to molecular evidence

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ABSTRACT

Environmental pollution poses a significant threat to human health, particularly concerning its impact on cardiovascular diseases (CVDs). This review synthesizes epidemiological and molecular evidence to elucidate the intricate relationship between environmental pollutants and CVDs. Epidemiological studies highlight the association between exposure to air, water, and soil pollutants and increased CVD risk, including hypertension, coronary artery disease, and stroke. Furthermore, molecular investigations unravel the underlying mechanisms linking pollutant exposure to CVD pathogenesis, such as oxidative stress, inflammation, endothelial dysfunction, and autonomic imbalance. Understanding these molecular pathways is crucial for developing targeted interventions and policy strategies to mitigate the adverse effects of environmental pollution on cardiovascular health. By integrating epidemiological and molecular evidence, this review provides insights into the complex interplay between environmental factors and CVDs, emphasizing the urgent need for comprehensive preventive measures and environmental policies to safeguard public health.

1. Introduction

Environmental pollutants emerged as a likely threat issue for cardiovascular disease (CVD), presenting a growing concern for global public health [1]. Natural contamination is characterized as the roundabout or coordinate modification of the natural, thermal, physical, or radioactive properties of any medium in such a way as to make a danger or potential risk to human wellbeing or to the

wellbeing, security, or welfare of any living species [2]. In fact, there is a dynamic equilibrium between genes and environment, where each term of the equation affects and is influenced by the other. The effects of the environment on the genes are, in short, termed adaptation and allows each species to survive, adapt or select distinct genetic traits. These adaptations (or even mutations) are, conversely, essential of life, without which there would have been no evolution. Here we concentrate on the rapid effects of the environmental pollution According to this, one in six deaths is estimated to be linked to environmental pollution causes [3]. CVDs are the driving cause of mortality and a major donor to dreariness and inability in around the world. Unfortunately, their incidence is on the rise globally, with the estimated number of CVD-related deaths rising from approximately 12.1 million in 1990 to 19.8 million in 2022 - a notable 18.71 % increase over the past decade [4].

Numerous studies have provided compelling evidence linking pollution to an increased risk of CVDs such as heart attacks, strokes, and hypertension [5–7]. Air pollution, in particular, has been extensively studied and shown to have a significant impact on cardiovascular health [8,9]. Pollutants from burning fossil fuels, automobile exhaust, and industrial processes, such as fine particulate matter, nitrogen dioxide, and sulfur dioxide, can cause endothelial dysfunction, oxidative stress, and inflammation—all of which are linked to the onset and course of cardiovascular disease (CVD).

Numerous mechanisms exist via which pollution impacts cardiovascular health. In addition to air pollution, toxins such industrial chemicals, insecticides, and heavy metals can harm the heart [1]. These pollutants can also pollute water and soil. By ingestion, inhalation, or skin contact, these pollutants can enter the body and have systemic effects that aid in the pathophysiology of cardiovascular disorders.

Selective people are more vulnerable to the adverse effects of pollution on cardiovascular health. These include individuals with pre-existing heart conditions, the elderly, children, and those living in socioeconomically disadvantaged areas with higher exposure to pollutants [1]. Addressing health disparities and protecting vulnerable populations from pollution-related cardiovascular risks are important considerations in public health interventions.

Despite the growing body of evidence linking pollution to CVDs, several challenges exist in addressing this issue. These include the complex nature of pollution sources and their interactions, as well as the lack of comprehensive data in certain regions. Additionally, attributing specific cardiovascular events solely to pollution exposure can be challenging due to confounding factors and individual variability in susceptibility.

To address pollution-related cardiovascular risks, a comprehensive approach is imperative. In this scenario, the concept of the exposome represents a paradigm shift in understanding the complex relationship between environmental exposures and health outcomes, including CVDs [10,11]. Introduced by Christopher P. Wild in 2005 [12], the exposome encompasses the totality of environmental exposures, including chemical, physical, and biological agents, as well as social and lifestyle factors, that an individual encounters throughout their life. Unlike traditional approaches that focus on single pollutants or isolated risk factors, the exposome considers the cumulative and synergistic effects of multiple exposures over time, providing a more comprehensive framework for investigating environmental determinants of human diseases. However, assessing exposures and their impact on the internal environment using omics techniques and functional assays presents significant challenges, and studies linking exposure data, omics results, and health outcomes remain relatively uncommon. A promising approach for evaluating the impact of the exposome on cardiovascular diseases (CVDs) was introduced by Wada et al. [13]. The authors developed a multitrait Bayesian variable selection model to address the complexity of exposure profiles and their relationship to cardiometabolic health, considering sets of complementary exposures and traits. By integrating this model with conditional independence networks, the study identified a subset of six closely correlated traits (BMI, waist circumference, triglycerides, HDL-C, systolic blood pressure, and diastolic blood pressure) and selected groups of exposures that cooperatively predicted cardiometabolic health outcomes. The approach was further complemented by single-trait analyses, which facilitated the identification of exposures uniquely tied to specific traits and those consistently associated across multiple traits. This innovative methodology lays the foundation for large-scale cohort studies, offering a path forward to bridge the current research gap on the effects of environmental pollution on CVDs. Indeed, it is mandatory to deepen our comprehension of the underlying molecular mechanisms by which pollution impacts cardiovascular health and to develop effective preventive and therapeutic interventions.

This narrative review reports and discusses the most recent data regarding the relationship between CVDs and environmental pollution, also laying the groundwork for developing global strategies aimed at reducing the impact of pollution on CVDs. This includes implementing stricter environmental regulations to reduce pollutant emissions, promoting clean energy sources and sustainable transportation systems, and adopting urban planning strategies that prioritize environmental health. Public education and awareness campaigns are also crucial for empowering individuals to take preventive measures and advocate for policy changes.

2. Toxic metals as cardiovascular risk factors

Because of the increasing levels of environmental pollution, toxic metals accumulation in environment have spread so these compounds are quite common in everyday life. Toxic metals include heavy metals and other induvial metals or metal compounds which can negatively affect public health. The primary sources of heavy metals, including lead (Pb), cadmium (Cd), and mercury (Hg), are coal burning, gold mining, and the manufacture of metals and cement [14]. Toxic metal exposure generally results from industrial activity, which may expose workers to these metals, but the main cause is the release of these metals into the environment. Toxic metals could be dispersed into the air, soil, and water, resulting in widespread contamination and various sources of exposure [15]. As cardiovascular diseases and related deaths representing the first health issue worldwide [16], it's essential to determine how these toxic compounds could activate pathological mechanisms within the cardiovascular system. Among toxic metals, Pb, Hg and Cd have been deeply investigated for their possible role in the development of CVDs. However, for other toxic metals, there are some findings

suggesting a possible role in promoting dysfunction in the cardiovascular system. Evaluation, control and monitoring of these environmental processes is quite complex and possibly required the definition of an ideal "epigenetic score meter" [17], where exogenous epigenetic information could give quantitative measures of disease risk.

2.1. Epidemiological evidence

Several epidemiological studies correlated toxic metals exposure with pathological cardiovascular conditions. In the Strong Heart Study, a large population-based prospective cohort study, long term exposure to Cd has been evaluated through its urinary levels in American Indian communities [18]. This analysis highlighted that high levels of urinary Cd were associated with increased CV mortality and increased incidence of cardiovascular diseases. Urinary levels of Cd have also been positively correlated to cardiac infarction/injury score and subclinical myocardial injury [19]. In line with this, the data analysis from US survey on 33,994 individuals between the periods of 1988–1994 showed that urinary levels of Cd are linearly associated with cardiac infarction/injury score and subclinical myocardial injury, in a population with no atherosclerosis or chronic kidney disease. Interestingly, dose-dependent exposure to Cd promotes vascular diseases from low to high grade severity, mainly coronary artery disease and peripheral artery disease [20]. The correlation between cadmium and CVD events has been confirmed also in the Korean population, through a cross-sectional study on 20–59 aged people (approximately 10,000) [21]. In that study, blood levels of Cd, which are more elevated in smokers in comparison to non-smokers, has been associated to stroke and hypertension. Strong correlations between Cd exposure and cardiovascular events are supported by the population-based Malmö Diet and Cancer study (MDC) [22]. By measuring levels of Cd within the blood, authors proved that it promotes carotid plaque vulnerability and, both as direct consequence and independently, promote ischemic stroke. Both blood Cd and Pb were associated with increased incidence of resistant hypertension, as evidenced in the study on 1999–2018 National Health and Nutrition Examination Survey (NHANES) data [23]. These two metals have been associated with functional changes of heart's activity [24]. In fact, environmental exposure to Pb and Cd and their presence in urine has been positively associated with systolic left ventricular disfunction in a population living in Cd contaminated territories. Likewise, independent studies have associated blood levels of both Cd and Pb with dyslipidaemia, which could promote atherogenic events and lead to a cardiovascular impairment [25,26].

Air pollutants can be any other environmental supply of publicity to poisonous metals. In the Healthy Volunteer Natural Relocation (HVNR) Study [27] numerous PM2.5 metallic constituents, inclusive of Pb and As had been definitely related to variation in blood pressure, especially systolic, diastolic and pulse pressure. Toxic metals could impair cardiovascular functions also through an indirect effect. Methylmercury is a neurotoxic metal compound which could be involved in the modulation of cardiac activity by regulating sympathetic and parasympathetic system as emerged from a prospective study of a Faroese birth cohort [28]. Here, the authors demonstrate that exposure to methylmercury at intrauterine levels could impair cardiovascular function during childhood and adolescence. his impairment occurs primarily through dysregulation of the cardiac autonomic system, which has significant consequences on blood pressure and heart rate. They demonstrated that Hg could take part to atherogenic processes. Specifically, chronic Hg exposure has been strictly associated to cardiovascular pathological events, such as dyslipidaemia and acute myocardial infarction by analysing lipid profile and genetic alterations in a cohort of Amazonian riverine people [29].

Aluminium (Al) is a well-known toxic metal [20–32] which could play a negative effect on cardiovascular system, mainly due to work overexposure. In 2022, a study on workers of an electrolytic Al plant in China measured plasma Al concentrations by inductively coupled plasma mass spectrometry and correlate these measures with blood pressure [33]. They found that the prevalence of hypertension increased significantly together with Al plasma levels. An adverse effect on heart function and contractility after Al chronic exposure has been detected in a 20-year-old patient with no prior history of cardiovascular clinical conditions, who developed recurrent ventricular tachycardia [34]. In addition, a likely affiliation among Al exposure and an increased chance of mortality from CVDs came out from an investigation on cohorts of patients who worked in gold miners or exposed to electric arc furnace [35,36].

The growing body of evidence linking the exposure to antimony (Sb) to adverse health outcomes. Sb, a toxic metal commonly found in industrial emissions, electronics, and flame retardants, has been increasingly investigated for its potential health risks [37]. The association between Sb exposure and CVDs, as observed in several epidemiological studies, underscores its potential role in exacerbating cardiovascular conditions, particularly in populations with specific cardiovascular risk factors. In this context, the Danish case-cohort study [38] is significant because it focuses on a relatively healthy subgroup—never-smokers—thereby isolating Sb exposure as a more direct factor in the development of acute myocardial infarction (AMI) and heart failure. The positive trend between urinary Sb concentrations and increased rates of AMI and heart failure provides compelling evidence that this metal might contribute to the pathophysiology of specific CVDs. This suggests that even low-level, chronic exposure to environmental Sb can be considered as a risk for CVDs. Noteworthy, the Sb exposure and its urine concentration seem to associate with an increased risk of death from various causes including CVDs [39].

Relatively little is known about the effects of Tungsten (W) on health. Exposure to tungsten can occur through drinking water, food, air pollution, and indoor dust [40]. Urinary levels of W may be associated with CVD mortality related to stroke [41]. Through its interaction with Molibdenum (Mo), which plays an essential role as cofactors as several cellular enzymes, it could increase CVDs incidence depending on Mo levels [42]. Together with Cd and Uranium, high levels of urinary W may promote incident CVD and all-cause mortality risk [43].

2.2. Molecular mechanisms

The molecular mechanisms which underlying CVD impairment are primarily due to toxic metals include several processes, such as

inflammation, oxidative stress, endothelial dysfunction, epigenetic modification, alteration of lipid metabolism and direct cardiotoxicity. Oxidative stress and inflammation represent the main and well-known mechanisms which are activated in cells after toxic metals exposure [44].

Chronic exposure to Cd may activate pathological processes, including oxidative stress and inflammation. Urinary levels of Cd have been positively associated with an increase in levels of gamma glutamyl transferase, C-reactive protein, and alkaline phosphatase, known biomarkers for oxidative stress and inflammation, thereby promoting several diseases, including cardiovascular disease (CVD) [45]. Experimental evidence suggests a role for Hg as an important contributor to oxidative stress damage in the cardiovascular system. Acute exposure to Hg after a single intraperitoneal injection in mice, determine a reduction of many enzymes, in terms of expression and activity, required in cardioprotective metabolism of arachidonic acid as those of Cyp450 family and soluble epoxide hydrolase. The impairment of these enzymes significantly increases the cardiovascular risk [46].

On the other hand, assessment of circulating lipids, oxidative stress, and genotoxicity after chronic Hg exposure in wild-type C57BL/6J mice and APOE knockout mice indicated that APOE knockout animals exhibited little effect. More toxic than wildlife to methyl-Hg poisoning. However, Hg contributes to marked chromosomal alterations, increased oxidative stress, and dyslipidemia [47]. Concerning the alteration of lipid metabolism due to toxic metals, chronic exposure to low Cd in C57BL/6J mice can change myocardial lipid profile, promoting the expression of pro-inflammatory lipid, such as ceramides, and leading to myocardial inflammation and morphological damages [48]. A prospective study on a Chinese population, collected data from 2018 to 2019 in Shiyan People's Hospital in Hubei Province and found that urinary Cd was associated with an altered lipid metabolism [49]. Indeed, reduced HDL levels and elevated risk of dyslipidaemia has been found. Furthermore, urinary Cd has been related to one CpG locus named, which could partially mediate the dyslipidaemia state promoted by Cd.

Endothelial dysfunction is one of the initiating mechanisms which could lead to atherosclerosis. There are evidences which connect toxic metals to endothelial dysfunction. Markers of this process are represented by plasma soluble cell adhesion molecules, such as sVCAMI-I and sICAM-I [50,51], also related to cardiovascular damage and diseases. A study conducted in Kosovo on a population from 1985 to 1998 evaluated blood levels of Pb and correlated them with blood pressure and endothelial dysfunction markers. The study found a significant association between concurrent Pb exposure and sVCAM-1 levels in men, while in women, there was a correlation between concurrent Pb exposure and sICAM-1 levels [52]. Similarly, As has emerged as a toxic metal that may play a role in endothelial dysfunction. Indeed, the effects of long-term exposure to As from drinking water may promote vascular inflammation and endothelial dysfunction, as indicated by time-dependent increases in sICAM-I and sVCAM- I, suggests a potential mechanism for the association between As exposure and cardiovascular disease [53]. Another study showed that As is able to induce endothelial cell damage, through the activation of autophagy [54]. Indeed, As upregulates autophagy in rat aortic arch endothelium, activating AMPKα in As-induced endothelial dysfunction by regulating mTORC1/p70S6K/ULK1. Toxic metals in PM 2.5 can also cause endothelial damage, promote mobilization of endothelial progenitor cells from bone marrow to peripheral blood, and inhibit signaling events triggered by VEGF [55]. Cardiotoxicity, related to morphological and functional impairment of the heart, has been related mainly to Cd and Pb. The underlying molecular mechanisms are diverse. In the cardiac system of mice, Cd exposure leads to morphological impairment of the myocardium, which is related to damaged sarcomeres and myofibrils [56]. Moreover, exposure to Cd lead to increased expression of metalloproteinases (MMP) 2 and 14, which can promote myocardial fibrosis and focal necrosis. In the arterial system, cadmium
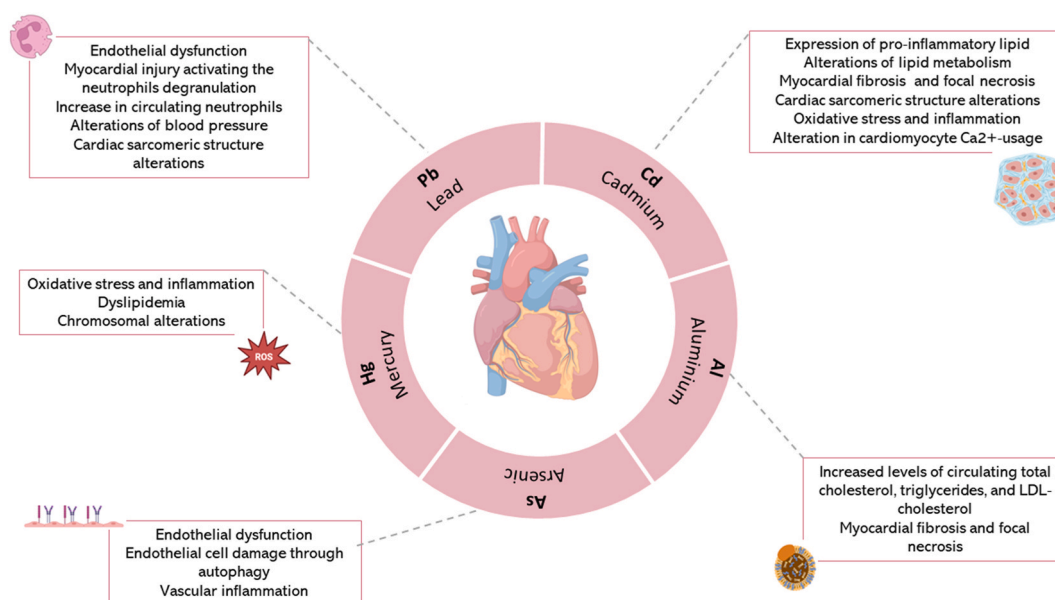
Fig. 1. Main morphological and cellular/metabolic changes within the cardiovascular system related to toxic metals exposure. The activation of these processes could promote several CVD, from vascular conditions, such as hypertension and atherosclerosis, to myocardial infarction.

damages the endothelium and media of the aorta and reduces the viability of human aortic smooth muscle cells. Another evidence from an *in vivo* study indicate that Cd exposure promote alteration of cardiac structure and reduces left ventricular ejection fraction and fractional shortening in male hearts [57]. To understand this phenomenon, by looking at isolated cardiomyocytes, it has been demonstrated that Cd induced alteration in cardiomyocyte $Ca2+$-usage and decreased SERCA2a expression and PLB phosphorylation. Cardiotoxic mechanisms are initiated also by Pb, but through different process. It has been demonstrated that Pb exposure in mice promote early myocardial injury, activating the process of degranulation in the neutrophil, as indicated by increased levels of d myeloperoxidase and neutrophil elastase in the serum of Pb-exposed mice, as well as the increase of neutrophils in extracellular supernatant following exposure [58]. Furthermore, a study on mice indicates that exposure to low doses of Lead (Pb), early in life has significant and lasting negative effects on myocardial structure and mitochondrial function [59]. This damage represents a persistent hazard to exposed mice, also in adult age, leading to a predisposition for developing CVDs, such as AngII-induced heart failure. Significant cardiotoxic effects has been found in experimental model exposed to Al. In rats, Al exposure induce histological alterations, such as cardiac fibrosis with foci of necrosis around the vessels and disarrangement of cardiomyocyte nucleus, which also impair the contractile function, as indicated by changes in electrocardiogram (ECG) [60]. Noteworthy, increased levels of circulating total cholesterol, triglycerides, and LDL-cholesterol have been also associated to Al exposure for three weeks in albino mice [61].

Beyond cardiotoxic effect, there are some epigenetic modifications which could activated pathological pathways related to cardiovascular events. These modifications could be promoted by some toxic metals. DNA methylation could be analysed in order to find epigenetic features which could be related to some pathological events, or, in case of toxic metals, to the exposure to these metals and its consecutive risk for cardiovascular events. For example, genome-wide DNA methylation data from the Strong Heart Study (1989-199) were studied, finding certain epigenetic biomarkers in the tibia and blood to be associated with increased risk of death from cardiovascular disease, likely reflecting the cardiovascular effects of cumulative and recent Pb exposure [62]. Data from the same study, allowed to detect also some epigenetic signature of As exposure, detectable in blood [63]. Indeed, the authors found differential methylation of CpG sites annotated to genes which are involved in As activated processes related to CVD risk.

Taken together, these data highlight how toxic metals can activate a variety of mechanisms that lead to CVD damage (Fig. 1), with the development of associated diseases and death [64]. The raising information supports the global effort that must be made to reduce the input of these pollutants into the environment as much as possible, to minimize their exposure and human diseases related risk [65, 66].

3. Particulate matter air pollution and cardiovascular disease

3.1. Airborne pollutants

The greatest environmental risk factor for health is thought to be air pollution. Nearly every person on the planet is affected by outdoor air pollution. 99 % of people on the planet, according to World Health Organization (WHO) data from 2019, stayed in areas where air quality standards were not known [67]. The main pollutants are particulate matter (PM), nitrogen oxides (NO_x), sulfur dioxide (SO_2), carbon monoxide (CO) - mainly released from coal burning and diesel fuel combustion - and Ground-level ozone (O_3), a secondary pollutant which is created when sunlight catalyses the reaction between volatile organic compounds (VOCs) and nitrogen oxides [68].

Indoor air pollution, although historically less investigated, is a recognized global concern and contributes significantly to the health burden associated with airborne pollutants. The primary agents are PMs along with VOCs and Volatile Inorganic Compounds (VICs) [69].

PM is a mixture of liquid droplets and solids emitted into the atmosphere, these particles include coarse PM with diameters between 2.5 and 10 μm (PM10), fine PM with diameters less than or equal to 2.5 μm (PM2.5), and ultra-fine PM with diameters less than 1 μm (PM1) and less than 0.1 μm (PM0.1) [70].

3.2. Epidemiological evidence

A campaign conduced in China showed that PM $\leq$ 1 exhibits a stronger correlation with CVD. Specifically, there was a 0.29 % increased risk of CVD for every 10 μg/m3 increase in PM1, which is 21 % more than the risk linked to PM2.5 (0.24 %) [71]. Furthermore, in 2019, Yang et al. performed a study on 24,845 people from 33 towns in Northeastern China, ages 18 to 74, which revealed that long-term exposure to PM1 was strongly connected with CVD, especially in men and the elderly [72].

Until now, PM $\leq$ 1 may have a greater propensity to deposit within the lungs and circulatory system compared to larger particles (PM2.5 and PM10) [71] and physicochemical characteristics, such as a potentially more toxic chemical structure and a higher surface area to mass ratio could set it apart from PM2.5 [72].

PM10 is typically trapped by the upper respiratory tract and expelled with mucus secretion, while PM2.5 can reach the lung's respiratory membrane, interact with alveolar macrophages, and enter the bloodstream, acting systemically [67,73,74]. Exposure to rising PM2.5 levels, both short- [75,76] and long-term [67], is connected to an overall increase in mortality. American College of Cardiology, World Heart Federation, European Society of Cardiology and American Heart Association together released a statement in 2021 that provided evidence of the impact of airborne pollution on CVD, particularly linking PM to stroke and ischemic heart disease [77]. As mentioned earlier, most of the world population is continuously subjected to air pollution. However, vulnerable populations, defined by sociodemographic variables, suffer the most from it [78]. PM, particularly PM2.5, is composed of black carbon, sulfur-containing particles, metal oxides (iron, zinc, silicon, calcium, titanium, aluminum, potassium), organic carbon, debris from

wildfires and volcanic eruptions, as well as pollutants associated with urban vehicle emissions [79,80]. Coarse particles (PM10) primarily localize in the upper respiratory tract (trachea and bronchi) due to their size and can be more easily removed by the mucous layer in the tracheobronchial system. Instead, fine particles (PM2.5) are able to enter the lower respiratory tract, where, at the level of lung alveoli, they promote the activation of macrophages and epithelial cells that release pro-inflammatory cytokines. All of this leads to vascular damage and systemic inflammation, factors underlying the onset of chronic diseases, including CVDs [79,80]. Each 10 $\mu g/m^3$ increase in chronic PM2.5 exposure raises the risk of CVD by 10 % [81].

According to an estimate by WHO, Air pollution causes 4.2 million premature deaths worldwide each year, with a specific reference to the year 2019 indicating that 37 % of premature deaths are linked to stroke and ischemic heart disease [82]. Different studies have shown that atmospheric PM is involved in several mechanisms, such as dyslipidemia, inflammation, oxidative stress, metabolic disfunction and epigenetic changes, which play a role in vascular dysfunction and progression of atherosclerosis [83].

The effects of PM 0.1 on cardiovascular health are still an emerging area of research, and much remains to be understood about its specific biological mechanisms. Nevertheless, the evidence linking both occupational and environmental exposure to PM 0.1 with adverse cardiovascular outcomes underscores the need for stricter regulatory standards and improved air quality monitoring. In particular, it is known that prolonged occupational exposure particulate matter during work was associated with CVD risk markers, such as increase concentrations of homocysteine, resting pulse and decrease of HDL concentrations [84] while exposure to environmental PM 0.1 has been associated with small decrease in systolic and diastolic blood pressure [85].

Key concepts about PM exposure are listed in Box 1.

3.3. Underlying molecular mechanisms

The impact of PM on the alteration of lipid profile is characterized by increased levels of several biomarkers, such as TC, TG and LDL-C against the reduction of HDL-C, which is one of the most important protective factors in CVD [86]. PM 2.5 is associated with increase of lipid peroxidation, oxidation of LDL-C (ox-LDL) that is exacerbated by Reactive Oxygen Species (ROS) [87,88], glutathione activity [89,90] and promote vascular inflammation [91].

LDL particles enter the extracellular matrix via the arterial wall and undergo oxidation. These oxidized particles then stimulate an immune response and local inflammation.

Macrophages are recruited and phagocytose LDL by utilizing the LDLR receptor, resulting in the formation of foam cells and the release of cytokines that intensify the immune cascade reaction. This, in turn, prompts the movement of smooth muscle cells towards the intima. Smooth muscle cells then proliferate and produce extracellular matrix as a result [86]. Moreover, the generation of pro-inflammatory aldehydes like malondialdehyde (MDA), which stimulates macrophages and promotes the development of atherosclerotic plaques, is determined by lipid peroxides [79,91]. In 2019, McGuinn et al. carried out a study on a cohort of cardiac catheterization patients who were exposed to long-term PM2.5 and found increases in different lipoprotein concentrations, such as LDL-C or LDL-P, which can contribute to CVD pathogenesis [92].

Although changes in lipid profiles play a role in CVD, low-grade inflammation and oxidative stress are the most important in the potential molecular mechanism of atmospheric PM [86]. These two factors are closely linked because oxidative stress commonly reaches its peak, leading to tissue injury and inflammation [83]. In reaction to PM2.5, alveolar macrophages seem to coordinate the inflammatory response both locally and systemically, exacerbating CVD. Toll-like receptors (TLR), NOD-like receptors (NLR), and the scavenger receptor CD36 are the Pattern Recognition Receptors (PRRs) involved in this process. PM 2.5 and PM 2-5-generated oxidation products activate these receptors, promoting the release of pro-inflammatory cytokines and chemokines. Furthermore, PM2.5 is enabled to initiate the NLRP3 inflammasome that release inflammatory markers, such as IL 1α, IL-1β, TNF-α, IL-6, IL-8, IL-17, IL-18, CCL2 (MCP-1), CCL3 (MIP-1α), GM-CSF and COX-2 [86,93]. In addition, PM 2.5 increases the production of reactive oxygen and nitrogen species (ROS/RNS) by NADPH oxidases (NOX) and nitric oxide synthases (NOS); in fact in the downstream process increased production of oxidants is driven by Nuclear Factor kappa B (NF-kB) signaling pathway, leading to the activation of pro-inflammatory genes [93]. Liang et al. investigated in 2019 how the JNK/P53 pathway is involved in the development of deep vein thrombosis and disseminated intravascular coagulation, as a result of the inflammatory response induced by PM 2.5 [94–97]. Long-term exposure to PM2.5 enhances vasoconstriction and increases the release of several vasoconstrictors, such as C-reactive protein (CRP), TNF-α, IL-1β, prostaglandin E2 and endothelin-1 [80]. Oxidative stress and inflammation, from the Fenton reaction to the regulation of ferroptosis

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Box 1
Key points of PM exposure.

Key Points-References.

- Air pollution is recognized as the most significant environmental health risk factor. Nearly every individual on the planet is impacted by outdoor air pollution - [67].
- PM is a mixture of carbon, sulfates, metal oxides, and urban pollutants, leads to inflammation and vascular damage, increasing cardiovascular disease risk by 10 % for every 10 $\mu g/m^3$ rise in exposure - [79,81].
- PM can be divided in two main groups based on the dimension of the particles: PM2.5 and PM10 - [67].

driven by PM exposure, are implicated as risk factors for some CVD (atherosclerosis, stroke, hypertrophy, and vascular remodeling) [80].

Another aspect implicated in CVD burden are epigenetic changes [98]; in fact, it is thought that environmental exposure is a crucial factor in the modulation of gene expression. Solute carrier family members (SLC) regulate metals transporting, including toxic elements, from intracellular to extracellular environments, in both directions and some of them may reach the nucleus where they could interact with histones and chromatine. PM may affect DNA methylation, non-coding RNA, miRNAs expression, histone modification and chromosome remodeling [99]. A methylome-wide association study (MWAS) was conducted by Gondalia et al. on a cohort from the Atherosclerosis Risk in Communities and the Women's Health Initiative. The findings have demonstrated the correlation between three cytosine-phosphate-guanine (CpG) sites where DNA methylation occurs and PM exposure; the genes MATN4, ARPP21, and CFTR are implicated in CVD. Specifically, there was a positive association found between the methylation of cg19004594 (exon of MATN4) and the 28-day mean PM10 concentrations, which may have contributed to cardiac remodeling [100]. Finally, evidence reveals that PM-mediated chronic inflammation may induce immunosenescence through telomere shortening. These processes deregulate transcription and increase the level of some cytokines (TNF-α, IL-6) in circulation and the rate of atherogenesis; however, the function of the telomere in inflammation is just beginning to emerge [83]. A "methylation profile scores" has been hypothesized to evaluate these parameters [101]. Still, scientists have not yet quantified epigenetic measures that reflect the pace of environmental toxicity on human health, and tested whether "methylation profile scores" are appropriate predictors of CVD. At the end, the impact of genetics on susceptibility to air pollution could potentially elucidate variations in the effects of air pollution on individuals, who are affected by CVD [86]. Key concepts about the molecular mechanisms related to PM exposure toxicity in CVDs are listed in Box 2. The main molecules involved in PM exposure-related CVD toxicity are showed in Table 1.

4. Nitrogen oxides (NO$_X$) and ground-level ozone (O$_3$)

Air pollution is a mixture of PM and various oxidant gases, which are ozone (O$_3$), sulfur dioxide (SO$_2$), nitrogen dioxide (NO$_2$) and carbon monoxide (CO) [93]. Other components like sulfates and organic carbon, that originate from fossil fuel combustion, play an important role as CV risk factor and are associated with unhealthy effects [112,113]; however, NO$_2$ and O$_3$ are considered the major gaseous pollutants in the air.

While NO$_2$ is a ubiquitous urban pollutant, typical of vehicle emissions, and is associated with cardiovascular disease (CVD) and other health outcomes, O$_3$ is a secondary pollutant that develops through photochemical processes in the atmosphere occurring downwind from newly generated emission sources. O$_3$ undergoes chemical reduction by fresh NO$_x$ and hydrocarbons [114].

Tang et al. carried out a study on a large individual (4,276,989) in Jiangsu, China. According to their findings, NO$_2$ concentrations often increase in the winter months, most likely as a result of increased combustion. On the other hand, during the warm seasons, O$_3$ concentrations usually show increased levels because heat and sunlight promote the synthesis of O$_3$ from precursor pollutants. Additionally, the impact of air pollution was influenced by different features such as gender, age, and season. Women and individuals aged over 75 exhibit a major sensitivity to these pollutants [116]. However, different investigations revealed that an increase of 10 ppb in NO$_2$ exposures gave an additional CVD risk of 1.76 for men, compared to 1.29 for women [115].

Both NO$_2$ and O$_3$ are free radical species in general, and their capacity for oxidation can cause cell damage and aid in the formation of CVD. Because of these factors, the WHO developed air quality standards in 2021, with short-term exposure thresholds for NO$_2$ and O$_3$ being 13.30 ppb (25 μg/m3) and 50 ppb (100 μg/m3), respectively [110,116].

In particular, these two gases intensify the oxidative stress action mediated by PM2.5 through the alteration of the lung's barrier, promoting a better transit of air PM above the lung [83]. In fact, Weichenthal et al. showed a strong correlation between fine air PM and CV mortality for ppb of O$_x$ beyond the threshold. This observation can be explained by the fact that inflammatory mediators and/or PM2.5 components must first exit the lungs and enter the systemic circulation in order to affect CV health. It's possible that this process occurs more rapidly at elevated O$_x$ concentrations, potentially due to increased lung permeability as previously mentioned [117]. Despite the potential involvement of inflammatory and oxidative stress responses in the lungs, which could impact other tissues like the CV system, there is a lack of the specific mechanism that directly connected O$_3$ air pollution to the worsening of CVD [83].

Box 2
Key points of molecular mechanisms related to PM exposure toxicity in CVDs.

Key Points.

- Changes in lipid profiles, low-grade inflammation and oxidative stress are key factors in the potential molecular mechanisms of atmospheric particulate matter in the developement of CVD - [86].
- Macrophages, activated by oxidized LDL and lipid peroxides, form foam cells and release cytokines, promoting plaque development - [86].
- PM-induced inflammation and oxidative stress release pro-inflammatory factors and vasoconstrictors, linking PM exposure to heightened cardiovascular disease risk - [93,99].
- Epigenetic changes induced by PM, such as DNA methylation, contribute to CVD - [100].

Table 1
Main molecules involved in PM exposure-related CVD toxicity.

Molecules	Biological function	Pathway	References
MDA	Malondialdehyde, a pro-inflammatory aldehyde, is a product of lipid peroxides, which activates macrophages that can lead the development of atherosclerotic plaques and CVD disease.	Inflammation	[79,91]
IL-1α IL-1β	Pro-inflammatory cytokines called interleukin-1 alpha and beta play a role in the development, advancement, and complications of atherosclerosis and heart failure.	Inflammation	[102]
TNF-α	Pro-inflammatory cytokine tumor necrosis factor-alpha is involved in the transcriptional control of the NLRP3 inflammasome through NF-kB signaling.	Inflammation	[93]
IL-6	Pro-inflammatory cytokine interleukin-6 leads to oxidative stress and inflammation, both of which worsen CVD.	Inflammation and oxidative stress	[103]
IL-8	Neutrophils are drawn to and activated by the chemoattractant cytokine interleukin-8 in inflammatory areas.	Inflammation	[104]
IL-17	Pro-inflammatory cytokine interleukin-17 works on heart cells and arteries, causing thrombosis, coagulation, and inflammation.	Inflammation	[105]
IL-18	The NLRP3 inflammasome, a key player in the inflammatory cascade, activates interleukin-18, a pleiotropic pro-inflammatory cytokine. Its expression might be connected to vulnerability and the advancement of atherosclerotic plaque.	Inflammation	[106]
CCL2 (MCP-1)	Chemokine ligand 2, often referred to as monocyte chemoattractant protein-1, is a key player in the inflammatory process because it either draws in or increases the expression of other inflammatory cells. Monocyte migration is brought on by MCP-1, which also causes endothelial activation and dysfunction.	Inflammation	[107]
CCL3 (MIP-1α)	The chemotactic chemokine Macrophage Inflammatory Protein-1 Alpha is released by macrophages. It is secreted by activated platelets and plays a role in drawing leukocytes to the site of atherothrombosis.	Inflammation	[108]
GM-CSF	Granulocyte macrophage colony stimulating factor is a cytokine that is known to cause inflammation. The main cause of this activity is its function as a growth and differentiation factor for populations of macrophages and granulocytes.	Inflammation	[109]
COX-2	Prostaglandins that mediate pain and promote inflammation are produced by cyclooxygenase-2, which is expressed in response to growth and inflammatory stimuli.	Inflammation	[110]
NF-kB	Nuclear factor kappa-light-chain-enhancer of activated B cells is a cytoplasmic dimeric transcription factor that forms a complex with I-κB to keep NF-κB inactive and prevent its translocation to the nucleus. It is triggered by cytokines and endotoxins, which causes the production of genes that code for chemokines and cytokines. It's possible that NF-κB is essential for atherosclerosis and CVDs.	Inflammation	[111]
PGE2	Prostaglandins are created during an inflammatory response and are derived from arachidonic acid. PGE2 can influence both pro- and anti-inflammatory reactions, depending on the tissues involved.	Inflammation	[112]
CRP	C-reactive protein is released during inflammatory pathway and is considered a non specific biomarker of this process. CRP promote endothelial cells disfunction and is involved in the development of unstable plaques.	Inflammation	[113
ET-1	A powerful vasoconstrictor and mitogen, endothelin-1 is composed of 21 amino acids. ET-1 is crucial for the regulation of vascular tone and vasoconstriction in the vascular system.	Inflammation	[114]

In some epidemiological studies it has been discovered a relationship between air PM and metabolic syndrome (MetS) and this correlation is more consistent for NO_2 exposures. MetS is regarded a significant public health challenge since promotes CVD [118].

Currently, few studies have directly assessed the impact of various pollutants on cardiovascular disease (CVD). Insufficient multi-pollutant datasets at the incredibly fine spatial scales required to account for the spatial variation in some pollutants, such as NO_2 and O_3, are partially to blame for this [115]. Key concepts about the relationship about NO_x and O_3 and CVDs are listed in Box 3. Table 2 reported the main oxidant gases in air pollution and their effect of CVD.

5. Organic pollutants

More than 20 years ago the Stockholm Convention on Persistent Organic Pollutants (POPs) was introduced with the specific aim of

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Box 3
Key points of Nitrogen oxides (NO_x) and ground-level Ozone (O_3) and CVD.

Key Points.

- Air pollution includes particulate matter (PM) and various oxidant gases; NO_2 and O_3 are the primary gaseous pollutants [114, 119].
- Elevated exposure to NO_2 and O_3 increases CVD risk. Moreover, these gases intensify oxidative stress caused by PM2.5, potentially affecting CV health - [83].
- Some epidemiological studies have shown the relationship between NO_2 exposures and metabolic syndrome, which promotes CVD - [118].

Table 2

Principal pro-oxidative gases in air pollution and their role in CVDs.

Gases	Characteristics	References
NO_2	Nitrogen and oxygen combine to generate NO_2, an atmospheric gas pollution, when fossil fuels like coal, oil, methane gas, or diesel are heated to high temperatures. Additionally, NO_2 can be generated indoors through the combustion of materials like wood or gas. NO_2 is among the six prevalent air pollutants subject to national air quality standards.	[120]
O_3	O_3 is a secondary air pollutant; NO2 and other nitrogen oxides present in the ambient air contribute to catalyze chemical reactions leading to the formation of ozone. It is constantly created in the upper atmosphere when solar UV radiation interacts with atmospheric oxygen.	[115,121]
SO_2	The primary sources of SO_2 in the atmosphere are power plant combustion of coal and oil as well as copper smelting. In the natural world, volcanic eruptions can release it into the atmosphere.	[122]
CO	The incomplete reaction of fuel and air results in the formation of CO, an urban gas. It is mostly caused by emissions from fossil fuel-powered engines, such as those found in cars and other non-road vehicles. In cities with dense traffic, there are higher CO levels.	[123]

protecting humans and the environment from POPs.

POPs are carbon-based compounds with toxic activity capable of persisting intact for a long period of time, to disperse widely in the environment, to accumulate in organisms [124]. Yet, for the afore mentioned persistency of those compounds, they still represent a global concern. Long term exposure to POPs has been linked with cancer as well as reproductive, immune, neurobehavioral and endocrine disorders [4]. POPs have been recognized to interact with fat metabolism and several studies linked long term exposure to increased circulating levels of triglycerides, cholesterol and atherosclerosis [125].

More generally, lifestyle and genetic variables, including chemical stresses, are associated with the development and outcome of CVDs. Among these, POPs play a significant role. Specifically, polycyclic aromatic hydrocarbons (PAH), per- and polyfluoroalkyl substances (PFAS), organochlorine pesticides (OCPs), dioxin-like polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs) are strongly correlated with the occurrence of inflammatory disorders [126]. In fact, epidemiological studies indicate that the interaction with particles from combustion may increase the risk of CVD, in particular thrombosis, myocardial infarction, atherosclerosis and hypertension [127].

Since POPs are the main group of chemical stressors, their presence in the air together with PM and gaseous pollutants rise the risk of several chronic diseases [126].

In urban areas, diesel exhaust particles (DEP) are widely present and come from exposure to traffic derived PM. In fact, many of the biological effects of DEP are linked to soluble organic chemicals attached to the carbon core of the particles. It appears that these lipophilic and semi-lipophilic compounds separated from DEP, passed through alveolar epithelial cells, and caused pro-inflammatory reactions in endothelial cells, which facilitated the development of atherosclerosis and vascular dysfunction. It is commonly recognized that the aryl hydrocarbon receptor (AhR) can be bound by lipophilic substances that are separated from DEP and PAHs, possibly leading to the activation of genes linked to inflammation [128]. Classic pathways are triggered when ligand-activated AhR dimersizes with AhR nuclear translocator (ARNT) and attaches itself to xenobiotic response elements (XREs) in target gene promotor regions, like CYP1A1/CYP1B1 cytochrome P450 enzymes. When different CYP-enzymes break down PAHs from DEP, they can produce ROS, which have the ability to cause inflammation and the production of cytokines that promote inflammation. By interacting with the NF-kB, AhR may also contribute to the spread of inflammatory signals via non-classical pathways [127].

Furthermore, lipophilic chemicals from DEP induce a significant upregulation of pro-inflammatory elements, such as IL-1α, IL-1β, cyclooxygenase-2 (COX-2), metalloproteinase-1 (MMP-1). Cox-2 is found in inflamed blood vessels and exhibits high expression in atherosclerotic lesions, where it has the potential to generate high quantities of prostanoids and prostaglandin E2 (PGE2). PGE2 can then promote MMP expression, which can lead to tissue degradation and the instability of atherosclerotic plaques [128].

Similarly to lipophilic chemical detached from DEP, PAHs, which result from the incomplete burning of organic materials, such as coal, fossil fuels, tobacco smoke, and different industrial processes, have the potential to damage DNA. It is established that DNA damage in both circulation and vessel-wall cells is associated with atherosclerosis, however more studies are required to improve CVD prevention and treatment [127].

Another group of POPs are PCBs, which are collected in organisms through dietary intake. In mammals, the liver assumes a vital role as the primary location for the initial distribution of PCBs due to its perfusion levels. The primary reservoir for PCBs is the adipose tissue, which has the greatest PCB tissue-to-blood partition coefficient because of PCBs' lipophilic properties [126]. According to the Agency for Toxic Substances and Disease Registry (ATSDR), considering immune toxicity endpoints, the minimal toxic dose (Minimal Risk Levels, MRL) for those who are exposed to PCBs orally and over time is 20 ng/kg/day [129]. PCB126, one of the most common PCB metabolites, induces inflammation in macrophages and directs monocytes towards an M1-like phenotype via the AhR and nuclear factor kappa-B (NF-κB) pathways. This therefore resulted in the activation of oxidative stress-sensitive indicators such heme oxygenase 1 (HMOX1) and NADPH quinone dehydrogenase 1 (NQO1), as well as inflammatory factors like tumor necrosis factor alpha (TNFα) and interleukin-1 beta (IL-1β) [130,131]. In particular, exposure to PCB126 results in elevated levels of plasma inflammatory markers, including plasminogen activator inhibitor-1 (PAI-1), intercellular adhesion molecule-1 (ICAM-1) and trimethylamine N-oxide (TMAO) [132]. An initial approach to highlight the connection between increased plasma levels of TMAO and the onset of coronary artery disease was investigated by Petriello et al. in a study conducted on mice in 2016 [133]. In general, TMAO contributes to foam cell formation, triggering platelet activation, and promoting vascular inflammation [134].

Another PCB metabolite, PCB29-pQ, may activate the RIPK1/3-MLKL pathway via a ROS-dependent mechanism, therefore contributing to the MAPK–NF–κB inflammatory cascade. The necrotic core of plaques is formed by the activation of macrophage-derived foam cells, which in turn accelerates the production of inflammatory cytokines [135]. Additionally, PCB29-pQ has the

potential to induce the polarization of macrophages/monocytes towards CD163 positive macrophages, serving as a potential stimulant for the acceleration of atherosclerosis through the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway [136].

Through the food chain, also PFAS can accumulate in the blood and tissues of human organisms, since are produced by many industrial and consumer products. Specifically, exposure to PFAS has been connected, both *in vitro* and *ex vivo*, to modifications in plasma membrane fluidity, altered Calcium signaling, and an increased platelet reactivity to agonist. The incorporation of PFAS leads to an elevation in various platelet functional responses, including microvesicle release, experimental thrombus formation, adhesion and aggregation. These results offer mechanistic evidence in favor of the theory that platelet-centered mechanisms could contribute to the higher frequency of CV events seen in individuals who have been exposed to PFAS over an extended period of time [137]. The health implications of exposure to PFASs have raised global concerns. Recent evidence indicates an association between PFASs exposure and inflammatory diseases, including metabolic dysfunctions such as CVD [138].

The toxicity of POPs unfolds through interactions among multiple organs such as the intestine, liver, vascular system, brain and immune system, contributing to the onset of various inflammatory disorders. Future studies should aim for a more comprehensive understanding of multi-organ interactions, providing more meaningful insights into toxicity mechanisms and potential intervention strategies [139].

Key concepts about the relationship about POPs exposure and CVDs are listed in Box 4.

Table 3 reported the main POPs involved in human diseases.

6. Conclusions

In light of the data presented in this review, exposure to environmental pollution should be considered a risk factor for CVDs. However, studies aimed at identifying the presence of pollutants directly in tissue and correlating them with the patient clinical outcome will be indispensable to verify whether exposure to pollution should be considered as an independent cardiovascular risk factor for CVDs or as a condition capable of increasing the risk of other known factors such as hypertension, diabetes, obesity and smoke habit [144–151]. Multidisciplinary approaches, including histology, electron microscopy [152–154], spectrometric analysis [155] and multiomics investigations [156,157], are needed to explore in fact the intricate relationship among pollutants exposure, pollutants bioaccumulation and clinical outcome.

In this scenario, oxidative stress, inflammation, and endothelial dysfunction have been proposed as biological link between environmental pollutants exposure and CVDs development.

According to data from the annual economic burden of CVD (2018–2019) [158], in the United States, it is estimated at \$407.3 billion, encompassing direct and indirect costs, including lost future productivity attributed to premature CVD mortality. Therefore, addressing environmental pollution not only improves public health but also leads to significant cost savings in healthcare expenditures [159,160]. This reallocation of resources can enhance access to care for patients and contribute to overall healthcare system sustainability.

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Not applicable.

Box 4
Key points of Persistent Organic Pollutants (POPs) and CVD.

Key Points- References.

- Long-term exposure to POPs is associated with increased levels of triglycerides, cholesterol, and atherosclerosis. PCBs, OCPs, PAHs, PFASs, and PBDEs are linked to inflammatory disorders and CVD - [126,127].
- In urban areas lipophilic chemicals from DEP and PAHs may activate inflammatory pathways and induce DNA damage, further exacerbating CVD risk - [128].
- PCBs accumulate in adipose tissue, leading to inflammation and oxidative stress are implicated in vascular inflammation and atherosclerosis progression - [130.
- PFASs, accumulated through food intake, alter platelet function and calcium signaling, potentially increasing CV event occurrence - [137].

Table 3
Impact of primary Persistent Organic Pollutants exposure on health.

POPs	Characteristics	References
PCBs	Dioxin-like polychlorinated biphenyls are toxic chemicals that persist in the environment and accumulate in the food chain. PCB126 is one of the most common PCB metabolites and exposure to it results in elevated levels of plasma inflammatory markers. Another PCB metabolite, PCB29-pQ may participate in the MAPK–NF–κB inflammatory pathway.	[130,1352]
OCPs	Synthetic pesticides recognized for their high toxicity, slow disintegration, and bioaccumulation are called organochlorine pesticides, and they are widely used in both agriculture and the chemical industry.	[140]
PAHs	A class of chemical molecules known as polycyclic aromatic hydrocarbons is created through incomplete combustion or high pressure procedures. They consist only of carbon and hydrogen, formed from three or more fused benzene rings. Photooxidation and degradation of PAHs can yield simpler compounds.	[141]
PFAS	Per- and polyfluoroalkyl are a class of chemicals that persist in the environment and exposure in people can be related to inflammatory disorders; exposure may happen by using products that contain PFAS.	[142]
PBDEs	Polybrominated diphenyl ethers represent a group of chemical substances incorporated into specific manufactured items to decrease the risk of product combustion. These substances have the potential to penetrate into the air, water, and soil during their manufacturing process, or to be released from the products containing them, especially upon breakage. Certain PBDEs have the capacity to accumulate in fish and mammals through ingestion of contaminated food or water.	[143]
DEP	The most prevalent urban outdoor air pollutants are diesel exhaust particles, which are a combination of carbon particles, organic compounds, heavy metals, and free radicals. Specifically, a lipophilic compound that has separated from DEP may cause damage to DNA, pass past alveolar epithelial cells, and cause endothelial cells to react in a pro-inflammatory manner. Consequently, this leads to the development of atherosclerosis and vascular dysfunction.	[127,128]

Compliance with ethical norms

Not applicable.

Consent for publication

Not applicable.

CRediT authorship contribution statement

Manuel Scimeca: Writing – original draft, Funding acquisition, Conceptualization. **Valeria Palumbo:** Writing – original draft. **Erica Giacobbi:** Writing – review & editing. **Francesca Servadei:** Writing – review & editing. **Stefano Casciardi:** Writing – review & editing. **Elena Cornella:** Writing – original draft. **Federica Cerbara:** Writing – original draft. **Gabriele Rotondaro:** Writing – original draft. **Christian Seghetti:** Writing – original draft. **Maria Paola Scioli:** Writing – original draft. **Manuela Montanaro:** Writing – review & editing. **Francesco Barillà:** Writing – review & editing. **Renata Sisto:** Writing – review & editing. **Gerry Melino:** Writing – original draft, Funding acquisition, Conceptualization. **Alessandro Mauriello:** Writing – original draft, Funding acquisition, Conceptualization. **Rita Bonfiglio:** Writing – original draft, Conceptualization.

Declaration of competing interest

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