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Review article

# Pollution from fine particulate matter and atherosclerosis: A narrative review

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ABSTRACT

According to the WHO, the entire global population is exposed to air pollution levels higher than recommended for health preservation. Air pollution is a complex mixture of nano- to micro-sized particles and gaseous components that poses a major global threat to public health. Among the most important air pollutants, causal associations have been established between particulate matter (PM), mainly < 2.5 μm, and cardiovascular diseases (CVD), *i.e.*, hypertension, coronary artery disease, ischemic stroke, congestive heart failure, arrhythmias as well as total cardiovascular mortality. Aim of this narrative review is to describe and critically discuss the proatherogenic effects of $PM_{2.5}$ that have been attributed to many direct or indirect effects comprising endothelial dysfunction, a chronic low-grade inflammatory state, increased production of reactive oxygen species, mitochondrial dysfunction and activation of metalloproteases, all leading to unstable arterial plaques. Higher concentrations of air pollutants are associated with the presence of vulnerable plaques and plaque ruptures witnessing coronary artery instability. Air pollution is often disregarded as a CVD risk factor, in spite of the fact that it is one of the main modifiable factors relevant for prevention and management of CVD. Thus, not only structural actions should be taken in order to mitigate emissions, but health professionals should also take care to counsel patients on the risks of air pollution.

## 1. Introduction

In the growing number of disabilities and deaths due to atherothrombotic cardiovascular disease (CVD), air pollution is emerging as an important player in determining the risk of events (Rajagopalan and Landrigan 2021). Several clinical manifestations of CVD have been associated with air pollution, involving the arterial more than the venous circulation (Newby et al. 2015). This makes environmental pollution the largest cause of premature avoidable death and disability (Landrigan et al. 2018; Newman et al. 2020), being globally responsible for up to 8.8 million deaths (11.6 % of all deaths) (Collaborators 2020; Lelieveld et al. 2020). In Europe, air pollution reduces mean life expectancy by approximately 2.2 years, with an attributable mortality incidence rate of 133/100 000 per year (Lelieveld et al. 2019).

Air pollution is a complex mixture of nano- to micro-sized particles and gaseous substances. Particulate matter (PM) of various sizes [< 10 μm ($PM_{10}$), between 2.5 and 10 μm (coarse PM), < 2.5 μm ($PM_{2.5}$; fine particles) and < 0.1 μm ($PM_{0.1}$; ultrafine)] as well as gaseous components ($NO_2$ and ozone) are the most important pollutants in urban areas (Munzel et al. 2018). Gases have an array of adverse effects on health, but the largest body of evidence pertains to $PM_{2.5}$, as a major environmental threat to global public health (Al-Kindi et al. 2020; Chen and Hoek 2020; Cohen et al. 2017; Collaborators 2020; Pye et al. 2021).

Although the undisputed role of air pollution on CVD has led to a number of reports showing an increased mortality from cardiovascular atherothrombotic disease and other major CVDs (Bowe et al. 2019; Fuller et al. 2022; Kupcikova et al. 2021; Landrigan et al. 2018; Mannucci and Ancona 2021; Newby et al. 2015), a definite unifying mechanism is still missing (Bevan et al. 2021). At least two hypotheses stand: a) $PM_{2.5}$ are small enough to deposit in the small airways of the lungs generating a local inflammatory response but also entering the systemic circulation, b) PM exposure stimulates the release of extracellular vesicles which contribute to the local and systemic effects of PM exposure (Eckhardt et al. 2022). Air pollutants also impact the selective loading of

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extracellular vesicle cargoes including microRNA and proteins, which modify the cellular function in recipient cells. Accordingly, pollutant-induced extracellular vesicles may contribute to a pro-inflammatory, pro-oxidative and pro-thrombotic milieu (Chiaradia et al. 2021; Eckhardt et al. 2022). Extracellular vesicles are small lipid-bilayer membrane components released by most cellular types that exert pivotal and multifaceted roles in intercellular communication processes, with key effects on cell survival, endothelial homeostasis, inflammation, neoangiogenesis and thrombogenesis. Extracellular vesicles actively participate in each step of the onset and progression of atherosclerosis, and also to thrombus formation that leads to atherothrombotic CVD (Badimon et al. 2022; Macchi et al. 2021b) (Fig. 1).

Within this framework, considering that the CVD risk burden is associated with the progression of coronary atherosclerosis (Han et al. 2020), hereto we describe the link between $PM_{2.5}$ exposure and atherosclerosis as a consequence of the mechanistic interplay between lipoproteins, endothelial activation, neutrophil attraction to the endothelium, extravasation and lipid uptake (de Bont et al. 2022).

***Research Strategy.*** By using pubmed.gov, CM and MR screened original articles, *meta*-analyses and narrative reviews. Studies were excluded if they were non-English language records. The terms air pollution, particulate matter ($PM_{10}$), fine particulate matter ($PM_{2.5}$), oxidative potential, chemical composition of fine particulate matter were matched with such terms as cardiovascular diseases, ischemic heart disease and atherosclerosis. Upon a first screening, we considered the articles related to arterial stiffness, coronary artery calcium score, carotid intima media thickness, endothelium, inflammation-related atherosclerosis, lipoproteins, plaque and subclinical atherosclerosis. Relative to clinical studies, the search for literature comprised observational, retrospective, and prospective studies.

**Table 1**
Recommended 2021 WHO Global Air Quality Guidelines levels.

| Pollutant | Average time | 2021 AQGs |
|---|---|---|
| $PM_{2.5}$ (μg/m$^3$) | Annual | 5 |
| | 24-hour | 15 |
| $PM_{10}$ (μg/m$^3$) | Annual | 15 |
| | 24-hour | 45 |
| $O_3$ (μg/m$^3$) | Peak season | 60 |
| | 8-hour | 100 |
| $NO_2$ (μg/m$^3$) | Annual | 10 |
| | 24-hour | 25 |
| $SO_2$ (μg/m$^3$) | 24-hour | 40 |
| CO (mg/m$^3$) | 24-hour | 4 |

Annual and peak season represents long-term exposure, 24 and 8 h represent short-term exposure. AQGs, Air Quality Guidelines levels.

## 2. $PM_{2.5}$ exposure and CVD risk

The most recent World Health Organization (WHO) Air Quality Guideline recommends that annual average $PM_{2.5}$ should not exceed 5 μg/m$^3$, and that daily levels should not exceed 15 μg/m$^3$ (Table 1) (WHO Air quality guidelines 2021). These limits were reduced in part because of the WHO-commissioned systematic reviews (Perez Velasco and Jarosinska 2022) which suggested that there was a potential increased risk of mortality even in areas where $PM_{2.5}$ is below the previous WHO limits (annual average 10 μg/m$^3$, while 24-hour exposures should not exceed 25 μg/m$^3$ more than 3 times a year). On January 2023, the US Environment Protection Agency (EPA) proposed to revise the primary (health-based) annual $PM_{2.5}$ standard from the current level of 12.0 μg/m$^3$ to within the range of 9.0 to 10.0 μg/m$^3$ (Agency 2023).

The relationship between PM and CVD risk stands across a range of exposures, with neither lower nor upper limits for effect changes (Burnett et al. 2018; Mannucci 2022). At the end of 2019, the EPA stated that

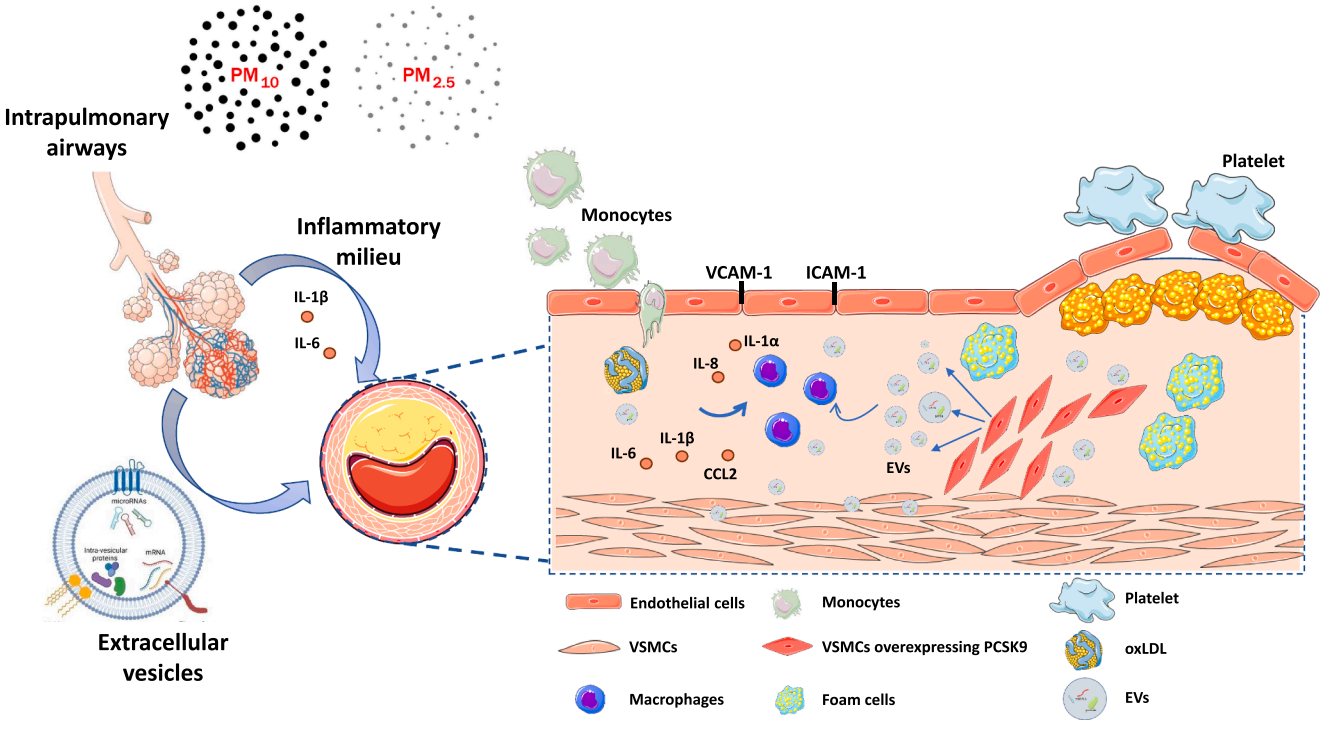


**Fig. 1.** Schematic representation of the liaison between PM exposure and atheroma formation. Exposure to PM provides a scenario of chronic low-level inflammation which arises in the lungs and enters the blood circulation. PM also favours the release from lung macrophages of extracellular vesicles with inflammatory properties. CCL2, C-C Motif Chemokine Ligand 2; EVs, extracellular vesicles; ICAM, Intercellular adhesion molecule 1; IL, interleukin; oxLDL, Oxidized Low-density lipoprotein; VCAM, Vascular cell adhesion molecule 1.

there is a causal relationship between CVD and both short- and long-term $PM_{2.5}$ exposure (Agency 2019). The 2021 Joint Opinion document stemming from such authorities as the World Heart Federation, American and European Societies of Cardiology recommends that patients at high risk of CVD should be encouraged to avoid long-term exposure to high levels of ambient air pollution, and that in regions where people sustain long-term exposure to high levels, CVD risk screening programmes should be considered (Brauer et al., 2021). Overall, it should be borne in mind that living in areas where air pollution is prominent impacts negatively on health (Munzel et al. 2020).

Effects of air pollution have been documented both in the short term (*e.g.*, exacerbations of disease leading to premature mortality or hospital admissions), and in the long term (including cardiovascular, respiratory, metabolic, psychiatric and birth outcomes) (Bazyar et al. 2019). Short-term exposure to air pollution increases the risk of myocardial infarction, stroke, heart failure, arrhythmia and sudden death, each of them by ≈1 % to 2 % for every 10 μg/m$^3$ $PM_{2.5}$ rise (Rajagopalan et al. 2020). The analysis of as many as 154,810 acute hospitalizations for CVD showed a relative risk of 0.97 % (0.67–1.27 %) for total CVD admissions per each 10 μg/m$^3$ increase of $PM_{2.5}$ at lag 0–5 (average of 6 days after admission). This indicates an early effect on the day of exposure (Stafoggia et al. 2022). A time-stratified case-crossover study including 1,292,880 patients hospitalized in China for acute coronary syndrome (ACS) showed that transient exposure to such air pollutants as $PM_{2.5}$, $NO_2$, $SO_2$, or CO (but not ozone) may trigger the onset of ACS, even at concentrations below the most recent WHO air quality guidelines (Chen et al., 2022b). According to a most recent *meta*-analysis in which relative risks (RRs) per 10 μg/m$^3$ increase in air pollutant concentrations have been used as effect estimates, short-term exposure to $PM_{2.5}$ is also associated to all-cause and CVD mortality (Orellano et al. 2020) (Table 2).

Concerning annual exposure, each 10 μg/m$^3$ increase in $PM_{2.5}$ is associated with a 15 % relative increase of deaths due to coronary artery disease (CAD; hazard ratio (HR), 1.15, 95 %CI 1.11–1.20) (Krewski et al. 2009). Another study confirmed a 11 % increase (95 %CI 6–16 %) in CVD mortality rate for each 10 μg/m$^3$ rise in $PM_{2.5}$ (Hoek et al. 2013). These findings are in line with a population-based study on 900,845 person-years, with an HR of 1.36 (95 %CI 1.29 – 1.43) for each 1 μg/m$^3$ increment (Kim et al. 2017) and with a *meta*-analysis reporting an increase of ischemic heart disease and stroke events each 10 μg/m$^3$ rise in long-term $PM_{2.5}$ exposure (Alexeeff et al. 2021). A further *meta*-analysis of 18 prospective studies, comprising 7,300,591 individuals (followed for a median of 9 years) concluded that when compared to a low long-term exposure to $PM_{2.5}$, a rise in exposure to $PM_{2.5}$ increases CVD (HR 1.09; 95 %CI 1.00–1.18) and CVD mortality (HR 1.12; 95 %CI 1.07–1.18) (Krittanawong et al. 2023).

Of note, the conclusion of the importance to reduce the levels of $PM_{2.5}$ below the current regulatory standard (at least in USA) came from a retrospective study on 3.7 million adults highlighting that moderate $PM_{2.5}$ concentrations (10 to 11.9 μg/m$^3$) were associated with increased risks of incident acute myocardial infarction (6 %), ischemic heart disease mortality (7 %) compared with low concentrations (≤8 μg/m$^3$) (Alexeeff et al. 2023).

Mechanistically, long-term $PM_{2.5}$ exposure may enhance CVD risk through plaque progression, whereas short-term exposure appears to trigger acute plaque rupture (Munzel et al. 2021a) (Table 2). However, these associations can be modified by exposure to cold and dry air, warm temperatures, sunlight intensity and humidity (Klompmaker et al. 2021). In more humid conditions, the size of particles increases by moisture absorption (Davis et al. 2016), while a rise in temperature affects the chemical properties of air pollution mixture.

Most of the evidence from epidemiological studies stems from high-income countries, notwithstanding that, compared to low-, middle-income countries, exposure to air pollution is substantially lower in high-income countries. The analysis of the PURE study (Prospective Urban and Rural Epidemiology) comprising 157,436 individuals of whom 140,030 resident in middle- and low-income countries, showed that each 10 μg/m$^3$ increase of $PM_{2.5}$ was associated with a raised risk of CVD (HR 1.05; 95 %CI 1.03–1.07), myocardial infarction (HR 1.03; 95 %CI 1.00–1.05), stroke (HR 1.07; 95 %CI 1.04–1.10) and total CVD mortality (Hystad et al. 2020). The increased risk was observed across the entire range of $PM_{2.5}$ levels, spanning from 6 μg/m$^3$ in Vancouver (Canada) to as much as 140 μg/m$^3$ in Jaipur (India) (Table 2).

The PURE study also tried to uncover the paucity of data on the association between pollution exposure and the incidence of CVDs in women compared to men. The HRs for the composite of major cardiovascular events (CVD deaths, myocardial infraction, stroke and heart failure) were 1.24 (95 % 1.06 – 1.46) in women *vs* 0.97 (95 %CI 0.84–1.12) in men, with a women-to-men ratio for HRs equal to 1.28 (95 %CI 1.05–1.56) (Walli-Attaei et al. 2022). Women, who are typically responsible for household chores such as cooking and collecting firewood, bear the greatest health burden from the use of polluting fuels and devices for lighting and heating homes (Balmes 2019b; Manfrini and Bugiardini 2022). Relative to $PM_{2.5}$ exposure, an excess risk of ischemic heart disease or stroke in women came from an analysis of 63.7 million individuals. The quantitative estimation of women-to-men ratio for relative risk showed that women had a 5 % greater risk of ischemic heart disease per 10 μg/m$^3$ increase of $PM_{2.5}$. Conversely, no sex differences were found for stroke (Zhang et al. 2022). Relative to this latter, a 15-year follow-up analysis of 155,410 postmenopausal women without previous cerebrovascular disease showed that long-term exposure to $PM_{2.5}$ was associated with a significant increase of cerebrovascular events [HR 2.14 (95 %CI 1.87–2.44)] comparing the top (greater than 13.6 μg/m$^3$) *vs* bottom (<9.9 μg/m$^3$) quartiles of $PM_{2.5}$ (Kulick et al. 2023).

**Table 2**
Impact of particulate matter exposure on cardiovascular disease mortality.

| | Cardiovascular disease mortality |
|---|---|
| **Short term $PM_{2.5}$** | RR = 1.01 (95 %CI 1.01–1.02) for each 10 μg/m$^3$ daily increase (Fajersztajn et al. 2017)<br>RR = 1.0092 (95 %CI 1.0061–1.0123) (Orellano et al. 2020) |
| **Short term $PM_{2.5\text{-}10}$** | A 10 μg/m$^3$ increase on lag 0–1 day was associated to 0.43 % (95 % CI, 0.15 % − 0.71 %) increased risk (Liu et al., 2022a) |
| **Long term exposure $PM_{2.5}$** | HR = 1.15 (95 %CI 1.11–1.20) for each incremental 10 μg/m$^3$ (Krewski et al. 2009)<br>RR = 1.12 (95 %CI 1.08–1.15) for each incremental 10 μg/m$^3$ (Pope et al. 2004)<br>RR = 1.11 (95 %CI 1.06–1.16) for each incremental 10 μg/m$^3$ (Hoek et al. 2013)<br>RR = 1.11 (95 %CI 1.07–1.15) for each incremental 10 μg/m$^3$ (Yang et al., 2019a)<br>HR = 1.03 (95 %CI 1.00 − 1·05) for each incremental 10 μg/m$^3$. For this study, HR was 1.05 (95 %CI 1.03–1.07) for CVD, 1.03 (95 %CI 1.00–1.05) for MI, and 1.07 (95 %CI 1.04–1.10) for stroke (Hystad et al. 2020)<br>HR = 1.08 (95 %CI 1.03–1.13) for each incremental 10 μg/m$^3$ (Alexeeff et al. 2023) |
| **Long term exposure $PM_{10}$** | RR = 1.09 (95 % CI 1.02–1.16) for each incremental 10 μg/m$^3$ (Yang et al. 2019a) |

CVD, cardiovascular disease; HR, hazard ratio; MI, myocardial infarction; RR, relative risk.

### 2.1. $PM_{2.5}$ constituents and their sources on CVD risk

$PM_{2.5}$ is a complex and dynamic mixture of organic and inorganic components and thus it is a limitation to consider all particle mass concentrations as equally harmful. Indeed, not all particles affect health equally. Combustion source categories, particle number concentration, surface area, content of transition metals, organics, sulfate and nitrate as well as the oxidative potential have been proposed as metrics to reflect the adverse PM effects on health (Chen et al. 2022a; Daellenbach et al. 2020). The analysis of the US Medicare population database showed that $PM_{2.5}$ stemming from biomass combustion has a smaller impact on all-cause mortality than $PM_{2.5}$ from fossil fuel combustion sources (namely, coal burning and traffic-derived $PM_{2.5}$) (Kazemiparkouhi et al. 2022; Wang et al., 2022b). Specifically, the HR for CVD mortality was 1.15 (95 %CI 1.13–1.16) for coal-related $PM_{2.5}$, 1.12 (95 %CI 1.11–1.14) for traffic-related sources, 1.01 (95 %CI 1.01–1.01) for metal-related $PM_{2.5}$ and 1.06 (95 %CI 1.05–1.06) for soil-related $PM_{2.5}$ (Kazemiparkouhi et al. 2022). Among causes of CVD deaths, HRs were generally higher for ischemic heart disease, cerebrovascular disease, and pneumonia. Data of the California Teachers Study cohort (Ostro et al. 2015; Ostro et al. 2010) showed that multiple sources (on-road and off-road gasoline and diesel, high sulfur fuel combustion) and constituents (elemental carbon, organic carbon, $SO_4^{2-}$, $NO^{3-}$, Fe, K, Si, Zn, Cu) were associated with ischemic heart disease mortality. The impact on ischemic heart disease was confirmed in a US nationwide population of 445,860 adults followed from 1982 to 2004 for vital status and causes of death. The strongest health benefit in terms of ischemic heart disease was achieved through reduction of fossil fuel combustion exposures, especially from coal-burning sources. Conversely, $PM_{2.5}$ from both wind-blown soil and biomass combustion was not associated with ischemic heart disease mortality (Thurston et al. 2016).

A time-stratified case-crossover study on 93,344 individuals demonstrated that among men (not women), $PM_{2.5}$ mass concentrations were associated with acute cardiovascular outcomes when the proportion of both metals and sulfur were elevated (Weichenthal et al. 2021). In this scenario, combined transition metal and sulfur content can influence the oxidative potential of $PM_{2.5}$ because sulfate plays a key role in producing highly acidic fine aerosols capable of dissolving primary transition metals that contribute to the aerosol oxidative potential (Fang et al. 2017). Organic carbon, nitrate and sulfate have been consistently associated with different biomarkers of acute cardiovascular risk (*i.e.*, hs-CRP, fibrinogen, platelet count, von Willebrand factor) (Strak et al. 2013). Thus, the integration of information on major chemical components into conventional approaches that consider $PM_{2.5}$ alone should improve the risk prediction for cardiovascular mortality (Chen et al. 2020).

Finally, whether acidity matters remains an issue (Thurston et al. 2022). The role of acidity in enhancing particle toxicity was recognized since the Great Smog in London in 1952. The presence of $NH_3$ in the air reduces the acidity of ambient particles and acidity mobilizes toxic transition metals, inducing oxidative stress. Conversely, sulfate plays a key role in producing highly acidic fine aerosols capable of dissolving primary transition metals that contribute to the aerosol oxidative potential (Fang et al. 2017). This concept is of crucial importance if we consider that the oxidative potential of outdoor $PM_{2.5}$ is associated with acute cardiovascular events, a morbidity enhanced by exposure to transition metals and acidic sulfate. In a national case-crossover study, an OR of 1.07 (95 %CI 1.04–1.10) per 10 $\mu g/m^3$ was observed for cardiovascular events when copper and sulfur were above the median (Weichenthal et al. 2021).

## 3. From subclinical atherosclerosis to plaque instability

Atherosclerosis is an umbrella term describing the formation in the arterial wall of fibrofatty lesions that cause morbidity and mortality worldwide. Atherosclerosis is characterized by the retention of modified lipoproteins in the arterial wall, a burden initiated by inflow of atherogenic lipoproteins that activates resident macrophages and recruits monocyte-derived cells (Libby et al. 2019). Advances in cardiovascular imaging provided valuable insights for the development and evolution of atherothrombotic CAD, focused on the clinical significance of the atherosclerotic plaque, and how this relates in both symptomatic and asymptomatic subjects to the future risk of progression and changes induced by therapies (Tuzcu et al. 2001). Various invasive and non-invasive imaging modalities allow to detect early and subclinical atherosclerotic lesions, as well as to examine the natural history of these lesions in relation to plaque progression and instability, considering that plaque progression is uniformly demonstrated to be the key step between nonobstructive subclinical atherosclerosis and acute atherothrombotic events (Ahmadi et al. 2019).

### 3.1. Inflammation and metalloproteases

Experimental and clinical evidence clearly implicates low-grade chronic inflammation in atherogenesis and its thrombotic complications (Libby 2017). Atherosclerosis is a lipid- driven inflammatory disease of the arterial intima in which the balance of pro-inflammatory and anti-inflammatory mechanisms dictates clinical outcomes (Back et al. 2019). The pulmonary oxidative stress following PM inhalation may spill into the systemic circulation such inflammatory mediators as cytokines exacerbating plaque instability (Miller et al. 2017). Cytokines, a class of proteins that mediate inflammation and modulate immunity, contribute critically to atherosclerosis, as well as to other diseases sustained by low grade, chronic inflammation (Libby 2012).

Epidemiological studies have shown that an increased risk of CVD is associated with raised levels of interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α) and cell adhesion molecules (Mostafavi et al. 2015), as well as of such acute phase reactants as serum amyloid A (Wong et al. 2019) and high sensitivity C reactive protein (hsCRP) (Ridker et al. 2000). Although not specifically related to the atherosclerotic process, hsCRP is a useful biomarker to improve the classification of patients at low or moderate risk of CVD (Yousuf et al. 2013). By means of $^{18}$F-FDG-PET/CT imaging, it has been shown that, over a median period of 4.1 years, annual average exposure to $PM_{2.5}$ was associated with a higher risk of major adverse cardiac events (MACE; HR = 1.40; 95 %CI 1.13–1.73), an effect due to a rise in both leukopoietic activity and arterial inflammation, that collectively account for approximately one third of the relationship between $PM_{2.5}$ exposure and MACE (Abohashem et al. 2021) (Table 3).

A detailed evaluation of biomarkers affecting plaque vulnerability was carried out in the frame of the AIRCHD study (Air Pollution and Cardiovascular Dysfunctions in Healthy Adults Living in Beijing), which showed that a 2-year exposure to high $PM_{2.5}$ levels (91.8 ± 63.8 $\mu g/m^3$) raised circulating biomarkers of plaque vulnerability (*e.g.,* the matrix metalloproteinases (MMPs)-1, −2, −3, −7, −8, and −9) from 8.6 % to 141.4 % (Xu et al., 2019) (Table 3). A significant association was also found with the decrease of TIMP (tissue inhibitors of MMP, TIMP-1 and 2), as well as with elevations in systemic inflammatory markers, *i.e.*, IL1-β, CRP, MIP-1α/β (macrophage inflammatory protein 1 α/β), sRAGE (soluble receptor for advanced glycation end products) and IGFBP (insulin like growth factor – binding protein-1 and −3). Hypercoagulability was documented by a shortened prothrombin time and by increases of sCD40L (soluble CD40 ligand), sCD62P (soluble P-selectin) and fibrinogen/fibrin degradation products (Xu et al. 2019). For each 10 $\mu g/m^3$ increase in the short-term exposure to ambient $PM_{2.5}$ there was a rise of 2.43 % for PAI-1 (plasminogen activator inhibitor-1), 1.08 %, for von Willebrand factor (vWF) and 1.14 % for sP-selectin (soluble P-selectin) (Wang et al., 2022a). Furthermore, among the markers of plaque instability, the sCD40 ligand, derived largely from activated platelets, can trigger an inflammatory reaction in vascular endothelial cells (Henn et al. 1998). Indeed, dysfunction of the endothelial lining of lesion-prone areas of the arterial vasculature is an important contributor to the

mechanisms of atherothrombotic CVD (Gimbrone and Garcia-Cardena 2016). By these mechanisms $PM_{2.5}$ may induce epithelial-mesenchymal transition (EMT), a pathological process associated with changes in cell morphology, clearly evident after $PM_{2.5}$ exposure (Li et al. 2018; Peng et al. 2022). $PM_{2.5}$ exposure also elicits a marked rise of MMP-2, and MMP9 and ICAM-1 and reduces TIMP-1 and TIMP-2 (Lin et al. 2022). On the whole, by affecting inflammatory mediators and such enzymes as metalloproteases that directly act on the vascular structure, exposure to PM may be responsible for raised plaque instability (Loftus et al. 2000). However, the lack of appropriate animal models of unstable plaque limits the mechanistic understanding of the triggered events (Bevan et al. 2021). In this scenario, it is worth mentioning that exposure of apoE-null male mice to ambient ultrafine particles enhanced atherosclerosis via the promotion of systemic prooxidant and proinflammatory effects (Araujo et al. 2008).

### 3.2. Coronary artery calcium score

The coronary artery calcium (CAC) score is a measure of coronary calcification that can be visualized by cardiac computer tomography (CT) (Perrone-Filardi et al. 2011), which was more frequently employed after CAC scores higher than zero were found to be associated with a higher risk of CVD events (Greenland et al. 2018; Hollenberg et al. 2022). In a large US study on 6,795 participants aged 45–84 years enrolled in the Multiethnic Study of Atherosclerosis and Air Pollution (MESA air) CT scans were carried out in six metropolitan areas at repeated intervals in order to detect progression of CAC (Kaufman et al. 2016). Every 5 μg $PM_{2.5}$ /$m^3$ increment led to a CAC progression of 4.1 AU per year. A somewhat stronger association between $PM_{2.5}$ and CAC progression was found in hypertensive individuals and in those older than 65 years. These findings on aging and hypertension suggest a synergistic association between air pollutants and these strong risk factors for atherosclerosis progression.

A Chinese study focused on CAC measurements in individuals with suspected CAD and an elevated AU score (mean 91.4). In this prospective, population-based, cross-sectional study comprising 8867 consecutive cases between 25 and 92 years of age, exposure to $PM_{2.5}$ was independently associated with increases in CAC scores of 27.2 % for each 30 μg/$m^3$ increase in $PM_{2.5}$ (Wang et al. 2019b). Associations were stronger among males, older people and patients with diabetes. Similar findings were obtained in an Australian cohort of 606 healthy participants, 16 % of whom with high CAC scores (≥100) and 4 % with very high scores (≥400) (Huynh et al. 2021). Against a median annual $PM_{2.5}$ of 6.9 μg/$m^3$, exposure to higher concentrations was associated with greater odds of high or very high CAC scores.

Among 5070 participants of the Gothenburg cohort of the Swedish CArdioPulmonary bioImage Study (SCAPIS), long-term residential mean exposure to air pollution ($PM_{2.5}$, $PM_{10}$, and $PM_{coarse}$) was not associated with a positive or high CAC score. No association was also found when the analysis was restricted to individuals with bilateral carotid artery plaques. In this study, mean PM exposure was relatively low, with long-term average values below the Swedish national guidelines but above the new WHO limit of 5 μg/$m^3$ annual mean $PM_{2.5}$. However, a tendency towards a stronger association between PM exposure and high CAC scores was found in current and former smokers compared to never-smokers, in patients with diabetes or on lipid lowering medications (Kilbo Edlund et al. 2022).

These findings lend some support to the gradual development of atherosclerosis as a modifiable pathway between chronic exposure to traffic-related PM and cardiovascular morbidity and mortality even at low exposure levels. A positive association was described in an observational, retrospective cohort study of 31,279 adult residents in Seoul. Analyses were stratified according to either the cumulative amount of $PM_{2.5}$ exposure or the average concentration of $PM_{2.5}$. During a follow-up of 53 months, the CAC score increased by 30.8 AU per year under a $PM_{2.5}$ concentration of 24.9 μg/$m^3$ and these changes correlated with the cumulative amount of $PM_{2.5}$ exposure. Notably, after adjustment for significant parameters associated with CAC progression (age, sex, obesity, current smoking, family history of CVD, hypertension, diabetes mellitus, hypercholesterolemia, use of statin, high blood urea), the cumulative amount of $PM_{2.5}$ exposure was significantly associated with CAC progression (OR 1.09, for every 100 μg/$m^3$ increase) (Lee et al.

**Table 3**
Particulate matter-driven changes in the frame of atheroma formation.

| | Population | Major findings | Author/year |
|---|---|---|---|
| Atherosclerotic inflammation | 503 individuals without cardiovascular disease | Increased leukopoietic activity (β = 0.129; 95 %CI 0.042–0.215) and arterial inflammation (β = 0.088; 95 %CI 0.006–0.171) according to continuous annual $PM_{2.5}$ exposure. | (Abohashem et al. 2021) |
| Plaque vulnerability | 73 healthy adults followed from 2014 to 2016 | MMPs-1, −2, −3, −7, −8, and −9 increased from 8.6 % (95 %CI 0.1–17.8) to 141.4 % (95 %CI 111.8–171.0) according to interquartile range increases in $PM_{2.5}$ concentrations. | (Xu et al. 2019) |
| Coagulation biomarkers | Meta-analysis comprising 8555 individuals | Every 10 μg/$m^3$ increase in short-term exposure to ambient $PM_{2.5}$ raised PAI-1 by 2.43 % (95 %CI 0.59–4.29), vWF by 1.08 % (95 %CI: 0.21–1.96) and sP-selectin by 1.14 % (95 %CI: 0.59–1.68). | (Wang et al. 2022a) |
| Coronary artery calcium score | Prospective 10-year cohort study (6795 participants) | Coronary calcium progressed by 4.1 Agatston units per year (95 %CI 1.4–6.8) each 5 μg $PM_{2.5}$/$m^3$ increase. | (Kaufman et al. 2016) |
| Coronary artery calcium score | 8867 consecutive individuals with suspected coronary artery disease | $PM_{2.5}$ was independently associated with increases in CAC scores of 27.2 % (95 %CI 10.8–46.1) for each 30 μg/$m^3$ increase in $PM_{2.5}$ (annual mean daily monitoring). Odds ratio (OR) for detectable CAC (AU ≥ 0) and severe CAC (AU ≤ 400) were 1.28 (95 %CI 1.13–1.45) and 1.59 (95 %CI 1.20–2.12), respectively. | (Wang et al. 2019b) |
| Coronary artery calcium score | 606 asymptomatic adults (Australia, during 2017–2018) | Exposure to higher $PM_{2.5}$ (per μg/$m^3$) was significantly associated with greater odds of having high CAC (OR 1.20, 95 % CI 1.02–1.43) and very high CAC (OR 1.55, 95 % CI 1.05–2.29). | (Huynh et al. 2021) |
| Coronary artery calcium score | Observational, retrospective cohort study of 3127 consecutive adults | CAC scores increased by 30.8 Agatston units per-year with exposure to a median $PM_{2.5}$ concentration 24.9 μg/$m^3$ and tended to increase with the cumulative amount of $PM_{2.5}$ exposure. | (Lee et al. 2022) |
| Carotid intima media thickness | A prospective cohort study with 5660 participants | Living at a residence with a 2.5 μg/$m^3$ higher concentration (inter-quartile range) during the follow-up period was associated with a 5.0 mm/y (95 %CI 2.6–7.4 mm/y) faster change in IMT over time. | (Adar et al. 2013) |

(continued on next page)

**Table 3** (*continued*)

| | Population | Major findings | Author/year |
|---|---|---|---|
| Carotid intima media thickness | Meta-analysis comprising 18,349 participants | An increase of 5 μg/m$^3$ $PM_{2.5}$ was associated with a 1.66 % (95 %CI: 0.86–2.46) thicker CIMT, namely, an average increase of 12.1 μm. | (Provost et al. 2015) |
| Carotid intima media thickness | 8867 consecutive patients with suspected coronary artery disease | Over a period of 10 years (2000 and 2010), c-IMT increased on average by 12 μm per year. | (Wang et al. 2019b) |
| Carotid intima media thickness | 789 subjects aged 12–30 years who lived in the Taipei metropolis | Interquartile range increases in $PM_{2.5}$ (8.2 μg/m$^3$) were associated with 0.46 % (95 % CI: 0.02–0.90) higher c-IMT. | (Chen et al. 2022c) |
| Carotid intima media thickness | 363 adolescents | At birth, $PM_{2.5}$ exposure was associated with a 6.23 μm (95 %CI 0.15–12.3) higher c-IMT per interquartile range increase in $PM_{2.5}$ absorbance in the 10th quantile of c-IMT. | (Peralta et al. 2022) |
| Plaque morphology | 364 individuals undergoing serial CCTA (≥2 follow-up) | 1 μg/m$^3$ increase in residential concentration of $PM_{2.5}$ led to:<br>- HR of 1.24 (95 %CI 1.10–1.40) for dense calcified CV<br>- HR of 1.28 (95 %CI 1.15–1.44) for fibrous CV<br>- HR of 1.41 (95 %CI 1.23–1.61) for fibrofatty<br>- HR of 1.55 (95 %CI 1.22–1.97) for necrotic core CV | (Yang et al., 2019b) |
| Plaque morphology | 126 patients with ACS undergoing OCT imaging were retrospectively selected | $PM_{2.5}$ was associated with:<br>- plaque rupture, OR: 1.194 (95 %CI 1.036–1.377)<br>- presence of thin-cap fibroatheroma, OR: 1.161 (95 %CI 1.024–1.317)<br>- macrophage infiltrates, OR: 1.479 (95 %CI 1.244–1.760) | (Montone et al. 2022) |
| Coronary vasomotor disorders | 287 patient undergoing coronary angiography and intracoronary provocation test | Independent predictors of a positive provocation test: OR of 4.568 (95 %CI 2.758–7.566) for $PM_{2.5}$ and OR of 1.676 (95 %CI 1.056–2.662) for $PM_{10}$.<br>Independent predictors of MINOCA in patients with positive provocation tests: OR of 11.458 (95 %CI 4.308–30.476) for $PM_{2.5}$ and OR of 3.625 (95 %CI 1.701–7.726) for $PM_{10}$. | (Camilli et al. 2022) |
| Arterial Stiffness | Longitudinal repeated-measure study was conducted among 247,640 participants | PWV increasing by 3.03 % (95 %CI 0.53 – 5.58) for an interquartile range elevation of 37 μg/m$^3$ $PM_{2.5}$ over a lag 0–7 day. | (Hu et al. 2022) |
| Lipids | Cross-sectional study (6587 patients) | Each 10 μg/m$^3$ increase of $PM_{2.5}$ was associated with a rise in TC by 0.92 % (95 %CI: 0.64–1.20), in LDL-C by 3.04 % (95 %CI 2.61 – 3.47) and in TG by 2.23 % (95 %CI 1.44–3.02). HDL-C was reduced by 2.03 % (95 %CI 1.69–2.37). | (McGuinn et al. 2019) |
| Lipids | 2289 midlife women enrolled in the longitudinal Study | Each 3 μg/m$^3$ increase of annual $PM_{2.5}$ exposure led to a decrement in HDL-C of 0.7 % (1.4 %, 0.1 %) and in apolipoprotein A1 of 0.6 % (1.1 %, 0.1 %). Lipoprotein(a) was increased by 3.8 % (1.0, 6.6) | (Wu et al. 2019) |
| Lipids | 12,778 conscripted Korean soldiers undergoing health check-ups | A 10 μg/m$^3$ increase in $PM_{2.5}$ exposure was associated with a 0.66 % reduction of HDL-C (95 %CI − 1.21, −0.10) | (Kim et al. 2022) |

ACS, acute coronary syndrome; CAC, coronary artery calcium score; CCTA, coronary computed tomographic angiography; c-IMT, carotid intima media thickness; CVD, cardiovascular disease; HDL, high-density lipoprotein; HR, hazard ratio; MINOCA, Myocardial infarction with nonobstructive coronary arteries; MMP, metalloproteases; OCT, optical computed tomography; OR, odds ratio; PAI, plasminogen activator inhibitor-1; PM, particulate matter; PWV, pulse wave velocity; TC, total cholesterol; TG: triglycerides; sP-selectin, soluble P selectin; vWF, Von Willebrand factor.

2022). These findings confirm that exposure to particulate air pollutants is one of the major risk factors for the development of atherothrombotic CVD and particularly CAD (Huynh et al. 2021). The CAC score provides findings indicative of raised cardiovascular risk, particularly upon long PM exposure, although direct imaging and characterization of plaque phenotype and vulnerability would help to better differentiate exposure effects from cardiovascular risks in vulnerable individuals (Table 3).

### 3.3. Carotid intima media thickness

The association of particulate and traffic-related pollutants with baseline levels as well as progression of the carotid intima media thickness (c-IMT) has been the object of numerous investigations. This marker of atherogenesis (Kunzli et al. 2011) provides a sensitive approach in order to investigate early lifetime risk of disease progression (Bauer et al., 2010). Large observational studies and atherosclerosis regression trials of lipid-modifying medications established that the IMT of the carotid and femoral arteries are valid surrogate markers for the progression of atherosclerotic disease (de Groot et al. 2004).

Pertaining to $PM_{2.5}$, the most important drawback in order to evaluate the association with c-IMT is the heterogeneity of the available data. In the context of a *meta-analysis*, of the 42 initially identified articles only six cross-sectional studies and three longitudinal studies could be included in the analysis. Overall, mean exposure to $PM_{2.5}$ ranged from 4.1 to 20.8 μg/m$^3$ and the average c-IMT was 0.73 mm (SD 0.14). An increase of 5 μg/m$^3$ $PM_{2.5}$ was associated with a 1.66 % (95 % CI 0.86–2.46) thicker c-IMT, which corresponds to an average increase of 12.1 μm (Provost et al. 2015).

The Testing Response on Youth (TROY) Study of 861 college students was based on self-administered questionnaires in order to collect information on health and sociodemographic characteristics. Residential addresses were geocoded and used to assign cumulative estimation of air pollution exposure on the basis of the data derived from the U.S. Environmental Protection Agency's Air Quality System database (Breton et al. 2012). No association was found between $PM_{10}$, $PM_{2.5}$ and ozone exposure with 7.8-μm and 10.1 μm c-IMT thickening, in childhood or elementary school children respectively. In line with these findings, data from the Atherosclerosis Risk in Young Adults study showed no association between air pollution and c-IMT (Lenters et al. 2010). Similar conclusions were reached by the Multiethnic Study of Atherosclerosis and Air Pollution (MESA air). In this prospective cohort study, over a period of 10 years from 2000 to 2010, c-IMT increased on average by 12 μm per year. However, the estimate for the effect on c-IMT of a 5 μg/m$^3$ higher long-term exposure to $PM_{2.5}$ provided a non-statistically significant value of −0.9 μm per year (95 %CI from −3 to 1.3 (Kaufman et al. 2016). In this framework, it is worth emphasizing that although hypercholesterolemia, hypertension, obesity and smoking at a young age increase the risk of atherosclerosis later in life, exposure to environmental toxicants is associated with higher c-IMT in adolescents and young adults (Lin et al. 2016). The analysis of 789 subjects who lived in the Taipei metropolitan area concluded that long-term exposure to $PM_{2.5}$ was associated with subclinical atherosclerosis in a young population (aged 12–30). Those who were more vulnerable to air pollution-related atherosclerosis were young adults, females, and non-smokers,

non-hypertensive, or nonhyperglycemic subjects (Chen et al. 2022c). In 363 adolescents participating in the Dutch PIAMA birth cohort (Prevention and Incidence of Asthma and Mite Allergy), $PM_{2.5}$ exposure at birth was significantly associated with a 6.23 μm (95 %CI 0.15–12.3) higher c-IMT per interquartile range increase in $PM_{2.5}$ (Peralta et al. 2022) (Table 3). Overall, it can be speculated that the mechanisms by which air pollution accelerates atherosclerosis is unrelated to intima-media thickness, that is more likely to be a marker of arterial injury than of atherosclerosis *per se*.

### 3.4. Plaque morphology

The link between air pollution and increased risk of coronary events was disentangled by Montone et al (Montone et al. 2022), who showed that exposure to high concentrations of pollutants is associated with features of vulnerable plaque and plaque rupture as the mechanisms of coronary instability. Among 126 patients with CVD, exposure to high levels of $PM_{2.5}$ was independently associated with plaque rupture (odds ratio (OR): 1.19; 95 %CI 1.03 to 1.37), the presence of thin-cap fibroatheroma (OR 1.16; 95 %CI 1.02–1.31) and macrophage infiltrates (OR 1.47; 95 %CI 1.24–1.760) at the culprit site. These findings are in line with those evaluating the composition of coronary plaques by coronary computed tomography (Yang et al., 2019b) (Table 3). At the mechanistic level, an enhanced systemic as well as plaque inflammatory activation may explain these findings and indeed $PM_{2.5}$, among other pollutants, was positively associated with hsCRP (Montone et al. 2022).

All in all, thin-cap fibroatheroma is the most frequent cause of fatal coronary events, being the primary type of plaque at the site of rupture. This parameter can be evaluated by optical computed tomography (OCT) which allows the quantification of fibrous cap thickness and accumulation of both lipid and macrophages. These changes may be the consequence of sustained systemic but also focal inflammatory conditions resulting from environmental pollution (Nicholls and Shaw 2022). Indeed, preclinical and clinical evidence have shown a short-term bone marrow response to air pollution exposure (Brook et al. 2010). High levels of PM can stimulate the bone marrow to enhance the release of neutrophils, band cells and monocytes into the circulation, which causes a cellular inflammatory response (Tan et al. 2000).

## 4. Vascular function

A major predictor of adverse CVD events, particularly in subjects with no apparent disease, is endothelial dysfunction. Impaired endothelial function, as assessed by reduced flow mediated dilatation (FMD), is a progressive but reversible expression of atherogenesis, although with controversial prognostic value (Vita 2011). A number of studies attempted to identify susceptible individuals potentially amenable to endothelium-targeted interventions. An imbalance in vasomotor tone and/or related prohypertensive response may trigger ischemic cardiac events and contribute to the risk of heart failure and stroke. A 2-hour exposure to high ambient $PM_{2.5}$ plus ozone increases diastolic blood pressure and triggers vasoconstriction in healthy adults (Brook et al. 2002). Moreover, $PM_{2.5}$ but not ozone significantly decreased FMD as early as 24 h after particle exposures (Brook et al. 2009).

### 4.1. Vascular dysfunction

Vascular mechanisms regulating vasodilation are controlled by two independent mechanisms: nitric oxide (NO), derived from the endothelial nitric oxide synthase (eNOS) and the peptide ET-1 (Lerman and Zeiher 2005). The balance of these mediators, vasodilator (NO) and vasoconstrictor (ET-1), is responsible for endothelial dysfunction. While NO is generally the end-product of the conversion of such stable molecules as $NO_2$ and $O_2$ (Murray 2016), a large fraction of this substance comes from a denitrification process, produced by microorganisms that reduce nitrate to nitrite, with NO finally escaping into the air. Thus, NO production occurs mainly in vascular tissues and eNOS regulates vasodilation. Exposure to diesel exhaust markedly impairs NO-mediated vasomotor function by raising endothelial oxidative stress (Wauters et al. 2013). In a human model, NO-mediated skin vasodilation decreased from 466 ± 164 % to 29 ± 12.35 % upon exposure to diesel exhaust (Wauters et al. 2013). This may be the consequence of a raised $PM_{2.5}$ inhalation impairing NO mediated vasodilation (Mills et al. 2005).

In the context of coronary vasomotor disorders in patients with nonobstructive CAD, data relative to 287 consecutive patients who underwent coronary angiography and intracoronary provocation test showed that PM was an independent predictor of MINOCA (myocardial infarction with nonobstructive coronary arteries) in those with positive provocation tests. Namely, OR was 11.458 (95 %CI 4.308 – 30.476) in the case of $PM_{2.5}$ and 3.625 (95 %CI 1.701 – 7.726) in the case of $PM_{10}$ (Camilli et al. 2022) (Table 3).

The vascular identification of the endothelin peptide ET-1 followed the recognition that the endothelium-derived relaxing factor NO is antagonized on the vascular wall, thus maintaining vascular homeostasis (Yanagisawa et al. 1988). ET-1 has two isoforms, ET-2 and ET-3, each with a role in vascular responses (77), the predominant ET-1 having larger vasoconstrictive effect (Luscher and Barton 2000). ET-1 is a 21-aminoacid peptide produced by cleavage of pro-ET-1 by the specific endothelin converting enzyme ETE-1. In addition to the endothelium (the most common source) ET-1 can be also produced by vascular smooth muscle cells, cardiomyocytes, macrophages and other cells. Upregulation of the ET-1 gene is induced by reactive oxygen species (ROS), angiotensin-2, cytokines, TNFα, interleukins, insulin and a number of other factors including cold temperatures (Chen and Sun, 2006). ET-1 is present at low concentrations (pg/ml) in plasma of healthy individuals, thus reflecting its role in homeostasis regulation and the need of its binding to two G-protein coupled receptors (ET-A and ET-B). Vasoconstrictive responses are mainly transmitted by ET-A (Bremnes et al. 2000). Furthermore, a rise of ET-1 inhibits eNOS and the production of NO, thus being responsible for endothelial dysfunction with the related general promotion and development of CVD (Finch and Conklin 2016).

In spite of the significant evidence linking ET-1 to CVD risk, only few studies evaluated the relationship between air pollution and circulating levels of ET-1. In a study of children exposed to $PM_{2.5}$ in Mexico City and in neighbouring areas taken as controls, exposure to elevated $PM_{2.5}$ levels in the previous 7 days was associated with a rise of ET-1 levels (Calderon-Garciduenas et al. 2007) together with an elevated pulmonary arterial pressure. In the presence of high exposure to $PM_{2.5}$ there was a positive correlation between higher ET-1 levels and inflammatory markers (Calderon-Garciduenas et al. 2008). The association between ET-1 mediated pathways following pollution exposure also appears to be associated with matrix metalloproteinase (MMP) 9 expression and activity (Lund et al. 2009).

Another approach was based upon the evaluation of ET-A receptor antagonism during exposure to diesel exhaust (Verhaar et al. 1998). In view of the activity of the ET-A receptor antagonist PQ123 on NO vascular release, it was hypothesized that diesel exhaust inhalation might lead to reduced NO bioavailability rather than to a rise of ET-1 (Langrish et al. 2009).Exposure of this pollutant in animals is associated with raised ET-1 levels. In rats a short exposure to diesel exhaust leads to a coronary vasoconstrictive response to ET-1 (Cherng et al. 2009), as well as to an increased mRNA expression of the ET-A receptor (Kodavanti et al. 2011). In rabbits, $PM_{10}$ exposure significantly raised plasma ET-1 levels (Miyata et al. 2013). All these results cumulatively indicate that in nearly all the tested animal models an array of well designed exposure experiments consistently showed that pollutants increase ET-1 or its receptors.

Balance between vasodilator and vasoconstrictor inputs has a crucial role in maintaining optimal vascular homeostasis. Experimental evidence supports an effect of PM on endothelial function in both conduit and resistance vessels, including the coronary circulation. As a

consequence of chronic PM exposure, endothelial dysfunction may lead to persistent hypertension (Munzel et al. 2018).

### 4.2. Arterial stiffness

Systemic conduit arteries normally exert a powerful cushioning function, which assures nearly steady flow to the microvasculature despite intermittent left ventricular cardiac ejection. This cushioning function becomes impaired in the presence of large artery stiffening, leading to multiple consequences with a major impact on cardiovascular health. A compliant aorta does buffer excess pulsatility caused by intermittent left ventricular ejection and also exhibits a slow pulse wave velocity (PWV), which allows pulse wave reflections to reach the heart during diastole, thus increasing diastolic coronary perfusion pressure with no systolic ventricular load (Chirinos et al. 2019). Arterial stiffness can be measured at different arterial segments or sites. These include segmental carotid-femoral pulse wave velocity (cfPWV), local carotid, femoral or brachial artery stiffness. cfPWV is measured as the time taken for the arterial pulse to propagate from the carotid to the femoral artery. Propagation time is measured variously from the foot of the waveform or the point of maximum upslope (Millasseau et al. 2005; Ruscica et al. 2017; Van Bortel et al. 2012). The clinical value of carotid-femoral-PWV is generally included in the reclassification of CVD risk.

A limited number of studies evaluated the effect of short-term air pollution exposure on measures of arterial stiffness (Mitchell et al. 2010). In the Framingham Heart Study, long- and short-term air pollution exposure and its association with arterial stiffness were evaluated with linear regressions by using long-term residential $PM_{2.5}$ and proximity to roadway. Living closer to a major roadway was associated with higher arterial stiffness [0.11 m/s higher cfPWV (95 %CI 0.01 – 0.22) living $< 50$ m *vs* $400 \leq 1000$ m], thus suggesting that pollutant mixtures rather than $PM_{2.5}$ may affect arterial stiffness. No association was found between arterial stiffness measures and exposure to short- or long-term levels of $PM_{2.5}$ (Ljungman et al. 2018). Further, no associations were found in a longitudinal study evaluating the relationship between 48-hour personal exposures to $PM_{2.5}$ and haemodynamic parameters, including the cfPWV (Baumgartner et al. 2018). A similar conclusion was reached in a study focused on the comparison of two sites in London, the western end of Oxford Street where traffic is restricted to buses and taxicabs mainly powered by diesel, and the nearby, traffic-free Hyde Park (Sinharay et al. 2018). Other data were reported in the frame of a longitudinal study in 15 Chinese cities comprising 247,640 people exposed to an average daily $PM_{2.5}$ concentration as high as 48 $\mu g/m^3$. For an interquartile range elevation of 37 $\mu g/m^3$ $PM_{2.5}$ over a lag 0–7 day, there was a 3.03 % rise in PWV (Hu et al. 2022) (Table 3).

In this complex scenario, it can be inferred that the positive association stands for people with risk factors for CVD. A secondary analysis of the SPRINT (Systolic BP Intervention Trial) study, in which moderate to high-risk patients with hypertension were enrolled, found a significant association between $PM_{2.5}$ and PWV after controlling for baseline characteristics. Specifically, higher progression over 3 years in PWV was found in individuals living in areas with $PM_{2.5}$ levels above the National Ambient Air Quality Standards (12 $\mu g/m^3$) (Al-Kindi et al. 2022).

## 5. Blood lipids

Because lipids are stablished risk factors for atherothrombotic CVD, a special attention has been paid to the lipid/air pollution relationship (Collaborators 2018). While there is clear evidence for an association between air pollution and an abnormal lipid profile in animal models (Ge et al. 2017), human data have often been heterogeneous, because alterations in blood lipids are indeed dependent upon such multiple factors as the socioeconomic status and the degree of indoor- and outdoor-physical activity (Andersen et al. 2015). Other drawbacks confounding this association may be attributed to differences in study populations, air pollution levels, modelling of exposure duration, exposure accuracy and outcome measurements (Kim et al. 2022). Strong associations with higher total cholesterol (TC) and lower high-density lipoprotein cholesterol (HDL-C) were reported by Wang et al (Wang et al. 2021). Elevated $PM_{2.5}$ was associated with 0.92 %, 2.23 % and 3.04 % rises in TC, triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C) respectively, and 2.03 % reduction of HDL-C levels. Interestingly, part of the effect of PM on TG content, at least in the case of diesel exhaust, was mediated by an altered total, mitochondrial and ATP-linked oxygen consumption rate rather than to an increased lipogenesis (Yin et al. 2019).

Among middle-aged American women, annual $PM_{2.5}$ levels were associated with lower HDL-C but not with TC, TG, and LDL-C (Wu et al. 2019). In a rural Chinese population (Mao et al. 2020), 3-year exposure to air pollutants ($PM_{2.5}$, $PM_{10}$ and $NO_2$) led to similar findings. Each 1 $\mu g/m^3$ increase of $PM_{2.5}$ was associated with a 0.10 % increase in TC, 0.63 % rise of LDL-C and with a 2.93 % reduction in TG and 0.49 % in HDL-C. A rise of 5.7 %, 4.0 % and 3.8 % for the odds for hypercholesterolemia, hyperbetalipoproteinaemia and hypoalphalipoproteinemia was also found. The potential for pollutants to affect peroxisome proliferator activated receptor activity in the liver may be an additional reason for blood lipid changes (Contreras et al. 2013).

A few lipid fractions mediate per se arterial damage as well as atherosclerosis development. This is the case of sphingolipids. Mainly produced by hepatocytes and transported in blood by lipoproteins (Iqbal et al. 2017), sphingolipids are intermediate regulators of apolipoprotein (apo)B-containing lipoprotein metabolism (Shanbhogue and Hannun 2020). They derive from sphingosine and ceramides, the direct precursors of the major cellular sphingolipids, and levels of ceramides and sphingomyelin in plasma are predictors of CVD events (Hilvo et al. 2020). Considering the potential of sphingolipids to act as intermediates of the atherogenic effects elicited by $PM_{2.5}$ (*e.g.*, in the presence of elevated apoB levels), the SCOPE prospective investigation (Study Comparing the Cardiometabolic and Respiratory effects of Air Pollution Exposure) evaluated whether or not short-term (up to 14 days) to medium-term (30 days) exposure of healthy individuals to $PM_{2.5}$ increased apoB-containing lipoproteins, and also whether this effect could be mediated by sphingolipids (Xu et al. 2022). Increased levels of sphingolipids did indeed mediate a positive association between 14-day and 30-day $PM_{2.5}$ average levels and non-HDL-C level but not LDL-C levels. These findings indicate that sphingolipid metabolism mediates the proatherogenic effects of exposure to $PM_{2.5}$, and that the significance of these lipid mediators in eliciting arterial changes may pave the way to novel approaches for CVD prevention (Xu et al. 2022).

Among basic, lipid-related mechanisms of tissue damage, the importance of proprotein convertase subtilisin/kexin type 9 (PCSK9) is well established. Besides being one of the major regulators of the LDL receptor, PCSK9 plays direct roles in atherothrombosis (Greco et al. 2022; Macchi et al. 2021a). An Italian study on 500 individuals with obesity demonstrated that $PM_{10}$ is positively associated to PCSK9 levels, the latter being in turn positively related with the Framingham Risk Score (Macchi et al. 2019) (Table 3). Overall, there is a general consensus that PM affects lipoproteins leading to an increase in the atherogenic fractions as well as to a reduction of HDL. Accumulating evidence has reported that HDL function can be impaired leading to a reduction in its cholesterol efflux capacity, antioxidant and anti-inflammatory potential, and its ability to promote the release of NO (Ossoli et al. 2022).

## 6. Aerosols and radioactivity carrying particles

Organic aerosol can be responsible for adverse health outcomes exceeding, on a molar basis, those of $PM_{2.5}$ (Gold and Mittleman 2013; Pye et al. 2021). Aerosol particles cool the climate by scattering solar radiation and acting as cloud condensation nuclei. Higher temperatures resulting from increased greenhouse gas levels lead to increased biogenic secondary organic aerosol and cloud condensation nuclei

concentrations that in turn generate a negative climate feedback mechanism (Yli-Juuti et al. 2021). Aside from the harmful effects of these pollutants (Al-Kindi et al. 2020), secondary organic aerosols derive from anthropogenic and natural emissions, suggesting that in the next future they may become a predominant environmental pollutant, owing to the presence of such anthropogenic volatile organic oxidative compounds as monoterpenes and isoprene (Pye et al. 2019; Pye et al. 2021). Interest has been raised by the possible harm related to the environmental exposure to fine particles carrying radioactivity, most commonly radon isotopes, that decay to α, β and γ radiation emitting progenies. $PM_{2.5}$ acting as a particle radioactivity vector can penetrate deeply into the lung and enter the circulation, with an ensuing continued decay (Kamiya et al. 2015). In a very recent investigation carried out in Massachusetts on cardiovascular and all-cause mortality, significant associations were detected between gross β-activity, $PM_{2.5}$ and mortality causes (Dong et al. 2022). The highest associations were found for myocardial infarction [(rate ratio (RR) 1.16; 95 %CI 1.08 – 1.24)] and stroke (RR 1.11; 95 %CI 1.04 – 1.18) with a significant positive interaction between $PM_{2.5}$ and gross β activity.

## 7. Future perspectives and mitigation strategies

Because air pollution is one of few major modifiable risk factors relevant to the prevention and management of CVD, it is the time for action in order to tackle the ominous consequences of PM exposure. Thus, not only health professionals should counsel their patients on the risks of air pollution, but stronger actions should be globally taken to mitigate emissions (Brauer et al., 2021) (Fig. 2). In this context, it must be understood whether there is a net benefit or harm to cardiovascular health when physical activity is performed in polluted air (Hahad et al. 2021). Yet, patients with a history of CVD or pulmonary disease should definitely limit outdoor activities when air quality is poor (Rajagopalan and Landrigan 2021). Second, wearing a FFP2 face mask rather than surgical and home-made tea cloth masks represents an effective tool to reduce $PM_{2.5}$ exposure (Cherrie et al. 2018). Third, deciphering the human exposome is a novel way to improve health and reduce the overall burden of disease. As highlighted by Munzel (Munzel et al. 2021b), the COVID-19 pandemic may be an opportunity to build better and more sustainable societies and cities. In this context, the European Green Deal is a comprehensive road map striving to make the EU countries more resource-efficient and sustainable, and also a great opportunity to make cities carbon–neutral, more liveable and healthier through better urban and transport planning and more greenness (Bereziartua et al. 2022; Mannucci 2022). An increase in green space exposure was significantly associated with 2–3 % lower odds of CVD mortality (OR 0.97, 95 %CI 0.96–1 0.99), ischemic heart disease mortality (OR 0.98, 95 %CI 0.96 – 1.00), cerebrovascular disease mortality (OR 0.98, 95 %CI 0.97 – 1.00), and stroke incidence/prevalence (OR 0.98, 95 %CI 0.96 – 0.99) (Liu et al., 2022b). In line with this evidence, among 75,975 participants of the CMEC (China Multi-Ethnic Cohort) study, each interquartile increase in Enhanced Vegetation Index ($EVI_{500m}$) reduced the CVD risk of the moderate-risk group by 4 % (OR 0.96 0.94, 0.98) and of the high-risk group by 8 % (OR 0.92, 95 %CI 0.90–0.96]) (Yu et al. 2023). Overall, although cardiometabolic risk factors (*e.g.*, diabetes mellitus, hypertension, and hyperlipidaemia) may partly mediate the greenness to heart disease relationships (Wang et al. 2019a), potential mechanisms by which green space can affect cardiovascular health are through stress reduction, mental health improvement and by promoting physical activity (Balmes 2019a).

## 8. Conclusions

Air pollution is not a new but is often an ignored CVD risk factor. The positive association between the atherosclerotic process and exposure to an array of air pollutants is now supported by a number of experimental and clinical studies (Montone et al. 2023). Nearly all deaths attributable

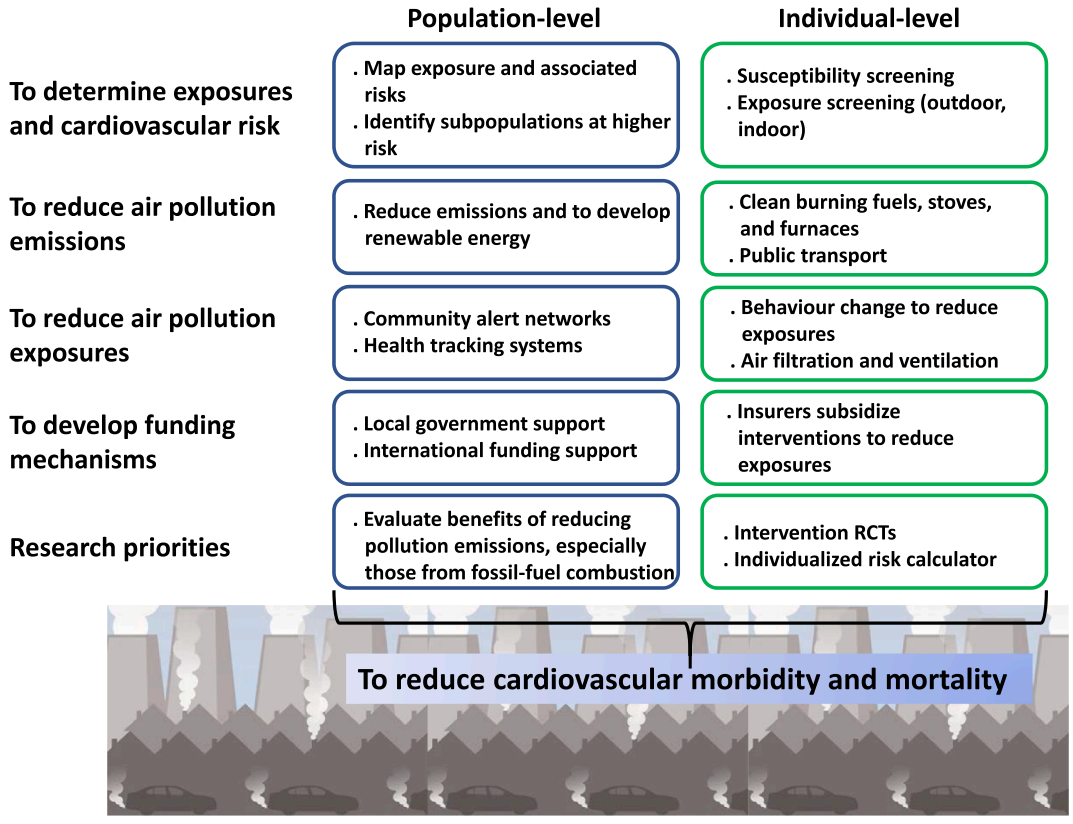


**Fig. 2.** Conceptual diagram proposing a combined population-level and individual-level approach to mitigate air exposures and protecting cardiovascular health. Adapted with permission of Springer Nature (Hadley et al. 2018).

to air pollution are associated with ambient concentrations below the current standards, a finding that suggests that more stringent $PM_{2.5}$ air quality standards may further reduce the global death toll associated with air pollution (Bowe et al. 2019). This concept becomes more important when race and social class are taken into consideration, considering that racial/ethnic minorities and lower-income groups are at a higher risk of death from exposure to $PM_{2.5}$ than other population/income groups (Bowe et al. 2019; Jbaily et al. 2022; Josey et al. 2023). Considering also that the particles we breathe have different sources and compositions and thus varying health implications per unit mass, it should be pointed out that fossil-fuel combustions appears to be more strongly associated with mortality from CVD (Thurston 2022). Noteworthy, beside the evaluation of $PM_{2.5}$ mass, exposure to such secondary inorganic $PM_{2.5}$ components as sulfate, nitrate and ammonium leads to higher all cause and CVD mortality (Raaschou-Nielsen et al. 2023). Mechanistically speaking, PM (especially $PM_{2.5}$) enhances plaque instability by increasing inflammatory mediators and metalloproteases that directly act on the vascular structures as well as by increasing the atherogenic lipoprotein fractions and by reducing HDL. High levels of PM can stimulate the bone marrow to enhance the release of neutrophils and monocytes into the circulation, which causes a cellular inflammatory response. On the clinical standpoint of view, the CAC score provides findings indicative of raised cardiovascular risk, particularly upon long PM exposure whereas this latter seems unrelated to c-IMT, that is more likely to be a marker of arterial injury than of atherosclerosis *per se*.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

No data was used for the research described in the article.

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