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THE CARDIOVASCULAR SYSTEM AS POTENTIAL TARGET OF AIR POLLUTION – REVIEW OF RECENT EVIDENCE

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Introduction: Air pollution has emerged as a significant contributor to morbidity and mortality worldwide. The World Health Organization attributes approximately 4.2 million deaths annually to ambient air pollution, with cardiovascular diseases (CVD), strokes, and chronic respiratory conditions being the most commonly associated causes. This review consolidates recent evidence on how air pollution, particularly exposure to microparticles, affects the cardiovascular system.

Methodology: A systematic search on PubMed was conducted, retrieving 52 reviews published in the last decade, which focused on air pollution and its cardiovascular effects. After excluding studies biased by location or unrelated to the topic, 20 reviews were selected for analysis. The reviews were synthesized based on short- and long-term cardiovascular outcomes associated with air pollutants, including particulate matter (PM2.5, PM10), NO2, SO2, and CO.

Results: Consistent associations were found between short-term air pollution exposure and increased risk of cardiovascular morbidity and mortality. Increases in PM2.5 were linked to a 2.58-fold rise in cardiovascular morbidity within 24 hours. The risk of myocardial infarction, high blood pressure, stroke, and heart failure also showed significant associations with various air pollutants. However, evidence was inconsistent regarding ultrafine particles and cardiovascular mortality. Meta-analyses of randomized controlled trials suggested that air quality improvement through indoor filtration systems reduced systolic blood pressure, but outdoor respirator usage showed limited cardiovascular benefits.

Conclusions: While the relationship between air pollution and cardiovascular diseases is evident, further research is needed to address inconsistencies and enhance our understanding of specific pollutants' effects. Efforts to reduce air pollution could significantly lower cardiovascular risk, especially in vulnerable populations.

Keywords: air pollution, cardiac diseases, morbidity, mortality.

INTRODUCTION

Air pollution has been described, in the recent years, as an important cause of morbidity and mortality in the modern society. The World Health Organization (WHO) has reported around 4.2 million deaths per year that can be attributed to ambient air pollution. Among the causes of these deaths, the most frequently reported were cardiac disease, strokes, chronic pulmonary diseases such as COPD (chronic obstructive pulmonary disease) and pulmonary cancer. Moreover, WHO estimates that about 25% of the total burden of ischemic heart disease.

Air pollution encompasses the environmental exposure (both indoor or outdoor) to a large range of molecular hazards in the form of gases, particulates, vapors or dusts. The outdoor pollution is mainly produced by exhaust from motor vehicles, industrial or agricultural processes, break-down of plastic materials and other waste generated by human activities and rarely by natural events, such as volcanic eruptions or wild fires. Fuel combustion, cigarette smoking, improper ventilation systems, materials used for construction or refurbishments, cleaning agents are common sources of indoor pollution in households. As for the occupational settings, exposure to microparticles is a well-defined hazard, responsible for many work-related diseases such as pneumoconiosis, occupational bronchitis and asthma, hypersensitivity pneumonitis, byssinosis and lung cancer among others.

WHO defines the short-term air quality level as "a high percentile of the distribution of daily values, for example the 99th percentiles equivalent to three to four days a year exceeding this value" [1] of the microparticles.

The specific element in the definition of the microparticles is the very small size, under 100 μm. Their large surface-to volume ratio allows them to transport a variety of pollutants and microorganisms. The human blood contains both exogenous and endogenous particles. They have in common a spherical structure and the capacity to interact directly or indirectly with various target cells. Some endogenous microparticles have physiological roles and act as signals between cells, but others might contribute to autoimmunity, inflammation, cellular growth or extracellular matrix deposition [2].

Environmental microparticles are divided in inhalable particles (aerodynamic diameter ≤ 10 μm) and respirable (aerodynamic diameter ≤ 2.5 μm) and ultrafine particles (aerodynamic diameter ≤ 0.1 μm). The inhalable fraction is retained in the upper and medium size respiratory airways. The most important for the systemic affects are the respirable and the ultrafine ones which are able to penetrate in the deep lung and pass through the lung interstitium in the pulmonary capillaries. Their distribution and clearance kinetics is unknown[3], but cardiovascular system is one of their targets[4]. In the last decades, the awareness about this consequence of air pollution materialized in thousands of publications on this topic. Therefore, this article will present the results of the most recent systematic reviews related to the effects triggered by the exogenous microparticles on the cardio-vascular system.

MATERIAL AND METHOD

A PubMed search was conducted for systematic reviews published in the last 10 years, using as key words: air pollution OR microparticles AND cardiovascular AND cardiac. The search was restricted to articles published in English. Fifty-two records were retrieved, from which we excluded the ones specifically dedicated to one country, to avoid biases found on single-area studies[5]. Two authors screened the titles and abstracts to eliminate the ones which were out of scope. Finally, 20 systematic reviews were selected for synthetizing their results According to their main objective, the systematic reviews focused on mechanistic studies, or long-term effects were excluded (Table 1). Those publications which shown data on short- and long-term effects in a distinctive way, were included for the short-term data.

RESULTS

As an overall remark, all publications underlined that different studies had their own definition of short term air pollution, which had to be standardized in the meta-analysis for proper comparison. In general, the increment was expressed as 10 μg/m^3 increase for solid microparticles and in 10 ppb for gazes, except for CO, for which 0.1 ppm increase was recorded. Some metanalysis reported also the delay, as lag-time (lagT), between the increment in air pollution and the outcome. The lagT was expressed in hours or days, depending on the review and/or the pollutant which have been analyzed.

In the following lines we will synthetize the findings of the metanalysis, according to the outcomes which were analyzed. The specific meta-indicators which have been estimated by these meta-analyses are summarized in Table 1.

Table 1

Main results of the meta-analysis

	Type of air polution or intervention	Specific outcome	Targeted population	Main results	Ref
1	CO, SO_2, NO_2, $PM_{2.5}$,PM_{10}, O_3	Stroke (all forms)	General population	RR per: 1 ppm increment in CO = 10 ppb increment in SO_2 = 1.019 (1.011–1.027) 10 ppb increment in NO_2 = 1.001 (1.000–1.002) 10 ppb increment in O_3 = 1.014 (1.009–1.019) 10 μg/m^3 increase in $PM2_{.5}$ = 1.011 (1.011 to 1.012)	Shah AS, 2015
2	Per 10 μg/m^3 increase in $PM_{2.5}$ or PM_{10}	Specific forms of stroke; total cerebrovascular diseases, ischemic stroke, hemorraghic stroke	General population	RR total cerebrovascular disease mortality: $PM_{2.5}$ =1.014 (1.009–1.01) PM_{10} = 1.005 (1.003–1.007) No statistically significant increase if data were analyzed by for hospitalizations* No studies were specifically focused on different types of stroke	Wang Y, 2014

Table 1 (continued)

3	Per 10 μg/m^3 increase in $PM_{2.5}$	HRV	Healthy or patients < or ≥ 40 years old	Overall HRV changes: SDNN :− 0.92% change (− 1.26%, − 0.59%); less in healthy invidualus, no difference for age rMSSD :− 1.47% change (− 2.17%, − 0.77%); larger decrease among healthy population than in patients; larger decrase in people ≥ 40 years old HF: − 2.17% change (− 3.24%, − 1.10%); the decrease of HF in patient was smaller in healthy population; greater decreased in people ≥ 40 years old LF − 1.52% change (− 2.50%, − 0.54%); a greater effect in healthy population and in in people ≥ 40 years old	Niu Z, 2020
4	Increase of 10,000 particles/cm^3 in UFP	HRV	Healthy people	increase in UFP after 6h of exposure: SDNN decreases by 4.0% [7.1%, −0.9%] 5RMSSD decrease by 4.7% (69.1%, 0.0%)	Zhang S, 2022
5	UFP/quasi-UFP particles	Cardiovasc. mortality Hypertension HRV		In7consistent association, no met8a-analysis for the cardi9ovascular mortality. Relation between UFP/quasi UFP was maintained after adjustment to other pollutants. Consistent association with the alteration of HRV indicators	Ohlwein S,, 2019
6	Carbon black	Cardiovasc. mortality		Cardiovasc. mortality: RR = 1.006 [1.003–1.009] No changes in sensitivity analysis	Zhu X, 2023
7	Per 10 ppb increase in O_3	HRV	General population	Increase in O_3: SDNN: −1.11% (−1.35%, −0.87%) RMSSD: −3.26% (−5.42%, −1.09%) HF: −3.01% (−4.66%, −1.35%) LF: −2.14% (−3.83%, −0.45%).	Zong Z, 2022
8	Per 10 μg/m^3 increase in $PM_{2.5}$	HRV	Older adults (average age ≥ 50 years	SDNN: –0.39% (0.72%, 0.06%) RMSSD: –1.20% (2.17%–0.23%)* LF: –2.31% (3.85%, 0.77%) HF: –1.87% (3.45%–0.29%)	Wang F. 2020
9	High temperature and air polution: 10 μg/m^3 increase for particulate matters, 0.1 ppm for CO, and 10 ppb for other gaseous pollutants.	Excess risk in: CVD morbidity MI morbidity Out of hospital cardiac arrest	Not specified	ER of cardiovascular morbidity within 3 h after exposure to: $PM_{2.5}$ = 2.65% (1.00%–4.34%) $PM_{10-2.5}$ = 0.31% (0.02%–0.59%) O_3: 1.42% (0.14%–2.73%) CO: 0.41% (0.01%–0.81%) ER for MI morbidity during the first 6h of exposure to: $PM_{2.5}$ = 3.97% (1.69%–6.30%) PM_{10} = 1.53% (0.69%–2.38%) NO_2 = 2.07% (1.09%–3.06%) ER for OHCA during the first 12h of the onset of the exposure to: CO = 1.03% (0.21%–1.86% ER for OHCA during the first 24h of the onset of the exposure to: $PM_{2.5}$ = 4.86% (0.75%–9.14%) O_3 = 0.39% (0.03%–0.75%)	Wu K, 2022
10	CO exposure	MI	General population	1 mg/m^3 increase: Risk ratio =1.052, (1.017–1.089)*	Lee, 2020
11	Air pollution	High blood pressure	Not specified	ORs for high blood pressure for: $PM_{2.5}$ =1.10 (1.06–1.13) PM_{10}=1.06 (1.02–1.10) NO_2 =1.0 (1.02–1.08) SO_2 =1.10 (1.02–1.18) O_3 =1.05 (0.98–1.12)	Yang, 2018
12	$PM_{2.5}$ reduction of 20.9 μg/m^3 (average) after indoor air filters	High blood pressure	Non smoking participants	exposure classified as low, if < 10 μg/m^3; high, if 10–35 μg/m^3; extreme, if > 35 μg/m^3; mean SBP reduction = −3.94 mmHg (−7.00,−0.89); a difference in mean DBP: −0.95mmHg (−2.81, 0.91)	Walzer, 2020

Table 1 (continued)

13	Wildfire				
14	Per 1 ppm increase in CO, per 10 ppm increase in NO_2, SO_2 or O_3, per 10 mg/m3 increase in $PM_{2.5}$	Atrial fibrillation		All pollutant increment was significantly associated to atrial fibrillation RR for CO = 1.006 (1.002–1.011) RR for NO_2 =1.012 (1.007–1.017) RR for SO_2 =1.010 (1.006–1.013) RR for $PM_{2.5}$ =1.009 (1.002–1.016) RR for O_3 =1.011 (1.002–1.019)	Shao Q, 2016
15	Per 10 μg/m^3 increase $PM_{2.5}$	Atrial fibrillation	Older adults (≥ 55 years old)	OR =1.11, (1.03–1.19) pooled %-change =1.01% (0.14%–1.88%)	Wang F, 2021
16	Wildfire, $PM_{2.5}$ increase compared to non wildfire days	Cardiovascular morbidity	Older adults ≥ 65 years old	RR= 1.05(1.09–1.21)	Barros B,
17	Per 10-μg/m^3 increment of $PM_{2.5}$ or PM_{10},	Heart failure	Adult population	For $PM_{2.5}$ RR=1.018 (1.011, 1.025) For PM_{10} RR=1.016 (1.011, 1.020)	Jia, 2023
18	Indor air filters intervention to reduce $PM_{2.5}$ concentration	Blood pressure RHI	General population	Mean difference Systolic BP: –2.28 (–3.92, –0.64) Diastolic BP: –0.35 (–1.52, –0.83) Pulse pressure: –0.86 (–2.07, 2.37) RHI = 0.10 (–0.04. 024)	Xia X, 2021
19	Intervention: personal-level indoor air cleaners and wearing respirator outdoors	Blood pressure RHI HRV	General population, except occupational exposure	Personal indoor air cleaners SBP: 2.01% decrease (0.50%, 3.52%) DBP:–1.03 (–3.01–0.96) RHI: 3.04% increase (–2.65%, 8.74%) SDNN: –0.71(–3.85–2.43) Wearing respirator outdoors HRV: increases in SDNN =2.20%, (0.54%, 3.86%), rMMSD = 6.46% (4.28, 8.63), LF= 1.28% (–2.15–4.72), HF = 18.84%(14.21, 23.48) SBP = – 0.63 mmHg (–0.39, 1.66) DBP= –0.05 (–0.59, 0.48)	Liu S, 2022
20	Interventional: wearing particulate filtering respirators	Blood pressure HRV	General population, randomized controled studies	Effects on BP parameters: SBP: mean difference = –0.78 mmHg (95% CI: –2.06, 0.50) DBP: mean difference = –0.49 mmHg (95%CI: –1.37, 0.38) MAP: mean difference mean difference – 1.1 mmHg (95%CI: –2.13, 0.01) Effects on HRVparameters: mean increase in HF= 38.92 ms^2 [(95% CI: 1.07, 76.77) mean increase in LF: 31.58 ms^2 [(95% CI: −34.04, 97.2 reduction in the ratio of LF to HF = −0.14 [(95% CI: −0.27, 0.00) no statistically significant difference in SDNN, rMSSD, pNN50 and HR	Faridi, 2022

Overall cardiovascular morbidity and mortality

The overall cardiovascular impact was assessed in relation to different pollutants. The more prominent excess risk of morbidity was related to $PM_{2.5}$ = 2.58 (95%CI = 1.14, 4.05) within the 24h after the 10 μg/m^3 increase. There lagT for the peak of the excess risk was a different for different pollutants: 13–24 h for $PM_{2.5}$ and PM_{10}, 0–3h for O_3, 0–6h for SO_2 and NO_2 and 0–12h for CO[6]. The relation remains stable after adjustment to wind speed, air pressure, public holidays or influenza. Due to the low number of studies reporting temperature, no pooled data were obtained for this parameter.

The level of carbon black is part of the $PM_{2.5}$ microparticles and reflects the contribution of combustion to air pollution. All 8 studies included in another metanalysis were consistent with a relative risk increase of cardiovascular mortality. However, the quality of the studies was considered low to moderate[7].

In contrast with the results related to carbon black, the cardiovascular mortality related to ultrafine particles showed inconsistent results. From the 6 articles selected for the systematic review performed by Ohlwein S. *et al*.[8], positive associations were found only in half of the studies; 2 studies showed no effect and 1 reported a negative association. One study collected data about $PM_{2.5}$, particle number concentration (PNC) of ultrafine particles and NO_2. In this study, mortality related per an interquartile range increase of PNC raised by 8.8% (95%CI: 2.7 –15.29) after 5 days, more significantly for the size ranges of the ultrafine microparticles with 30–50 nm, 50–100 nm diameter, for females and elderly (age ≥75years). It was noted that adjustment for NO_2 led to a decrease in effect estimates, causing loss of significance of the association, which was confirmed also in another research [9].

Wildfire is a source of $PM_{2.5}$, NO_2, SO_2, volatile organic compounds, CO. A metanalysis including studies from different continents, revealed a high morbidity for all cardiovascular diseases on people ≥ 65 years old. The estimation of the higher risk, was, however, based on a large heterogenicity of the studies[10] .

Disease specific morbidity and/or mortality

Myocardial infarction

The risk of acute coronary event was consistently found at higher rates in 2 metanalyses[11,12]. Interestingly, in both analysis the time lag association was shorter for $PM_{2.5}$, PM_{10} and NO_2 and longer for CO. For example, Lee et al. emphasized that a positive association was maintained for 3 days after the initial increase in CO. The in-depth analysis in both metanalysis revealed the heterogenicity of the studies and possible confounding of the risk estimation; therefore, the quality of evidence was considered moderate for CO. For $PM_{2.5}$, PM_{10} and NO_2 the association seemed to be more robust, as it was maintained after adjustments for wind speed, air pressure or public holidays.

The risk of myocardial infarction was not increased after exposure to particles generated by wildfire (OR = 0.99, 95%CI = 0.96–1.02) in US population-based studies[10].

High blood pressure

The majority of 12 studies found increases of at least one measure of blood pressure after exposure to ultrafine particles[8], with various lag periods. Studies which performed adjustment to other pollutants confirmed the independent influence of ultrafine particles. In another meta-analysis, short-term exposures to SO_2, PM_{10}, $PM_{2.5}$, SO_2, NO_2 were also significantly associated with hypertension, particularly in men. Distinction for systolic and diastolic blood pressure showed less robust association in the sensitivity analysis. The relation was stronger in studies reporting high level of pollution[13], but due to the heterogenicity and the publication biases, the quality of evidence was considered of low confidence.

Several metanalyses have focused on the efficacy of indoor air purification or personal protective measures against microparticles on blood pressure parameters. This improvement in indoor air quality significantly reduced the systolic blood pressure. In the studies included in this metanalysis, the particulate matter concentration was reduced, on average, by 56% (with a range between 40%–82%). The amelioration of the blood pressure parameters became significant only if the analysis was restricted to the randomized controlled studies (RCT): the mean difference of the PP after interventions in RCT was –1.56 [95%CI: –2.98, –0.15] mmHg and of the RHI was 0.13 (95% CI: 0.01, 0.25) units[14]. Similar results emerged from other aggregated data from 10 RCT which showed that, after a median 13.5 days of usage of indoor filters, a significant reduction of mean systolic blood pressure was obtained, which was not influenced by age, initial level of particulate exposure, or follow up duration[15].

Distinction between indoor portable air cleaners and wearing a respirator outdoors has been analyzed. The authors found significantly beneficial changes in systolic blood pressure, even without any apparent improvement on the reactive hyperemia index or reduction in inflammation and oxidative stress biomarkers with the usage of personal air cleaners indoor. For the outdoor respirators no improvement was noticed[16].

In another meta-analysis performed on 8 RCT, wearing particulate filtering respirators did not improved systolic, diastolic blood pressure. The reduction in mean arterial pressure was marginally statistically significant. Even non reaching the statistically significance threshold, when the analysis was restricted to the studies including older population (>60 years old), the effect was better[17]. There was a high heterogenicity in the design of these studies: the demographics of the populations were different (age, gender, geographical area), the duration of wearing the

particulate filtering respirators had a large variation (from 2 to 48h), the masks were recommended in different situations (indoor, outdoor, indoor and outdoor). Even if so heterogenous in design, none of the publications recorded a statistically significant lowering of the BP measures. Few studies reported a minimal education of the participants on wearing the respirators, the adherence to the intervention, the efficacy of the masks, and none of them controlled with sham masks.

Stroke

Stroke was the main topic of two meta-analysis and both provided data to support a higher risk after exposure to air pollution. They complement each other, as they quantified this risk in different ways. The first differentiated the risk according to different pollutants (CO, SO_2, NO_2, $PM_{2.5}$, PM_{10})[18] and the second intended to differentiate between the types of strokes (total cerebrovascular disease, ischemic stroke/transient ischemic attack and hemorrhagic stroke) [19]. The results regarding $PM_{2.5}$ were similar in both studies. An increase in NO_2 revealed a consistent association with both ischemic and hemorrhagic stroke in several studies. The higher effect was in the first day of the pollution, diminishing in the following days[18]. Unfortunately, the review which targeted to find if there is any specificity between exposure to particulate matter and cerebrovascular outcome (ischemic or hemorrhagic) did not retrieve any article with this objective and no epidemiological conclusion could be found on the specific lesions related to microparticles on the cerebral circulation.

The systematic review analyzing the exposure to wildfire microparticles did not find a higher risk for cerebrovascular diseases[10].

Atrial fibrillation

There are not many studies focused on this outcome, but the results showed a significant positive association with increment in all main gaseous pollutants (CO, NO_2, SO_2 and O_3)[20] in a population with a mean age of 59 years old. The population-attributable risk was 0.60 (0.20–1.09) for C), 1.19 (0.70–1.67) for NO_2, 0.99 (0.60–1.28) for SO_2, 1.09 (0.20–1.86) for O_3, and 0.89 (0.20–1.57) for $PM_{2.5}$. Similar results were found also in association with $PM_{2.5}$, for patients older than 50 years[21]. The ORs were higher in high quality studies, when the variation in $PM_{2.5}$ was ≥ 25 μg/m^3 and in research conducted in Asia and North America. The OR was less than 1 in the European countries.

In what concerns exposure to microparticles increase during wildfire accidents, current data is not supporting a higher risk of arrythmias in general[10].

Heart failure

The risk of heart failure increases during the first day of exposure to air pollution, and gradually decreases to in the following days of one week[22]. For the majority of pollutants, the risk was maintained during the two-three days, except for O_3, for which the lag 0–6 was the only one associated with a statistically significant risk. Apparently, it is not the case after wild fire exposure[10].

Disfunction of the autonomic system

The disfunction of the autonomic system is generally assessed by the heart rate variability (HRV) indices. Various pollutants induced significant changes after short term increase: $PM_{2.5}$[23], ultrafine particles[24], O_3[25]. The overall associations were stronger in regions with higher levels of $PM_{2.5}$[26]. The differences were most significant in healthy individuals[23,24] most probably explained as a result of the beta-blockers prescribed for patients. Elders seems to be more sensitive for HRV modifications in relation to microparticle inhalation[23]. In older adults, the relation was stronger for LF than for other HRV indicators[26]. Although important, the time lag was not evaluated in all metanalysis; after exposure to ultrafine particles, the more prominent effect had a lagT of 6h[24], with a large variation between investigators (5min to 95h)[8]. This might be explained by the interference with other pollutants, such as $PM_{2.5}$ and NO_2, which decreases the risk estimate[8].

Using indoor personal respirators modestly decreased the SDNN, without a statistical significance. On the contrary outdoor respirators significantly increased the SDNN, but were considered to have a moderate to high overall risk of bias. Therefore, the quality of evidence was graded as very low[16].

In the RCT comparison described above[17], the HRV was associated with better mean HF and LF parameters but no effect on SDNN, rMSSD pNN50 or HR. As already mentioned, due to the limitations of the studies included in the analysis, these results should be cautiously interpreted.

DISCUSSION

In this article, we gathered the most significant data coming up from meta-analysis, about the relation between short term air pollution and cardiovascular diseases. Even if not conclusive, these studies showed that the morbidity and mortality of the overall and of some specific cardiovascular diseases are influenced by air pollution. It is worth mentioning that they are supported by the higher risk of heart failure in low- or middle-income countries compared to high income countries, which may be at least partially attributed to lower pollutant levels in[1] and the beneficial result of the interventions aimed to reduce the exposure. However, the conclusions raised by almost all authors were that the evidence is moderate. There are several explanations for this conclusion. First, is the heterogenicity of study design of the initial reports included in the meta-analysis: a) the definition of air pollution is not the same in different studies; b) the confounders are not always analyzed; c) the interaction between different air pollutants is rarely taken into consideration; d) the lag time for the measured outcome is variable. Despite the standardization efforts done for the meta-analysis scope, these elements contribute to the lack of coherence between different studies. Second, exposure measured at one point could not reflect the real exposure of the individuals. For example, distinction between outdoor and indoor in not always possible, because, depending on the concrete weather circumstances, outdoor pollutants could even concentrate indoor[1]. An effort has been done to standardize the methods of exposure evaluation, but further steps need to be taken. Third, comorbidities were rarely considered, although defining the most susceptible populations is critical for tertiary prevention. In general, older age and preexistent cardiac disorders increased the power of the association, but also other medical conditions, such as chronic respiratory diseases or disorders with chronic, pro-inflammatory status, should be assessed.

Meanwhile, a vast literature accumulates on the mechanisms of cardiovascular toxicity of air pollution. One of the widely accepted theories is the oxidative stress supported by important studies, derived from the Framingham Offspring cohort. For example, a positive relation between $PM_{2.5}$ and sulphates exposure and the level of urinary creatinine indexed 8-epi-$PGF_{2\alpha}$, were found[27,28]. Moreover, $PM_{2.5}$ levels and black carbon levels were positively associated with myeloperoxidase (MPO) levels. These 2 compounds (MPO and 8-epi-$PGF_{2\alpha}$) are involved in reactive oxygen species production and in lipid peroxidation, which can lead to platelet activation, endothelial dysfunction and unstable plaques[29]. However, there are also reports about a negative correlation between $PM_{2.5}$, black carbon, NO_x and plasma fibrinogen levels, while other studies found absolutely no association between air pollutants and plasma fibrinogen levels[30].

Recent studies describe the direct effects of air pollutants on the endothelium: superoxide reacts with NO radicals, producing an even more highly reactive intermediate, the peroxynitrite ($ONOO^-$). The peroxynitrite is a cytotoxic compound which can participate in redox reactions with many types of biological molecules, such as proteins or nucleic acids. It also possesses vasoconstricting effects, increasing vascular stiffness and potentially increasing blood pressure. Moreover, it causes eNOS uncoupling and nitration of tyrosine amino acids from prostacyclin synthases and manganese superoxide dismutases, inactivating these enzymes which have important antioxidative effects[31,32]. Another mechanism of endothelial dysfunction is the increased von Willebrand factor circulating levels during a short term increased $PM_{2.5}$ concentration. Von Willebrand factor is an independent predictor of adverse clinical outcome in patients with cardiovascular disease and is associated with increased platelet activation[33]. In fact, prothrombotic biomarkers were found after exposure to particulate matter-bound metals[34,35].

Indirect effects were also described. $PM_{2.5}$ exposure can lead to sympathetic nervous system activation and inflammation in the hypothalamus, especially in blood pressure regulating regions, increasing vascular tonus and blood pressure. A suggested mechanism of neurogenic inflammations involves the $TRPA_1$ receptors in airways sensory neurons which detect particulate matter and induce central nervous system inflammation mediated by IKKβ (inhibitor of nuclear factor kappa-B kinase subunit β)[36–39]. Several authors have described cytokines imbalance as mechanisms of system inflammation associated with air pollution, with increased concentration of proinflammatory cytokines such as: tumor necrosis factor α (TNF-α), monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein 1α (MIP-1α) and adhesion proteins slICAM-1 and sVCAM-1. Simultaneously, the level of some anti-inflammatory

molecules, such as epidermal growth factor (EGF) or the soluble CD40 ligand (sCD40L) was reduced, according to some authors, leading to a proinflammatory status of the organism[40–43].

The increased sympathetic activity plays an important role in triggering various acute cardiovascular diseases, such as sudden cardiac death by acute arrhythmias. Sympathetic activity can trigger ectopic depolarization nodes in the heart, which can lead to acute or chronic tachyarrhythmias. This can also explain the increased risk of cardiac events while commuting in traffic[44–46].

Experimental research showed that epigenetic changes might occur in healthy individuals exposed for short time (24h) to $PM_{2.5}$.[47]. There is evidence that epigenetic modifications play a critical role in regulating processes like coagulation, anticoagulation, fibrinolysis, and cellular adhesion during thrombus formation, underscoring the intricate molecular mechanisms involved in thrombotic disorders[48]. For example, a meta-analysis on the CpG methylation[49] highlighted that the methylation of the cg03636183 near F2R like thrombin or trypsin receptor 3 (F2RL3) site was indeed linked to coronary heart disease and myocardial infarction in several studies, among which one was related to welding fumes[50]. The *F2RL3* product is thrombin protease-activated receptor 4 (PAR-4) and its overexpression induced by methylation would explain enhanced activation of platelets in response to thrombin generated at the site of tissue injury, with negative vascular consequences[51] Epigenetic mechanism induced by exposure to $PM_{2.5}$ increased the ACE expression[52], impaired the oxidative status through methylation of mitochondrial DNA and[53], methylation of Toll-like receptor 2 (*TLR-2*), and *ICAM-1*[54].

The association between air pollution and cardiovascular diseases pose real problems on the exercise recommendation, which is now largely accepted in cardiovascular diseases. In this respect, a systematic review underlined that benefits of exercise overcome the risk, but also that the expected benefits might be reduced if exercise is performed in polluted environments[55].

CONCLUSIONS

Current medical literature supports a relation between air pollution and the cardiovascular diseases incidence and severity. Better designed studies should overcome the limits of our epidemiological data, and give more evidence about this relation with specific cardiovascular diseases, also taking into account the potentially synergic effect of different pollutants. As there are many reasons to endorse the mechanistic relation, sustained efforts to reduce air pollution should be considered.

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