Physical Activity in Polluted Air and Cardiovascular Health

Subjects: Cardiac & Cardiovascular Systems
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Both exposure to higher levels of polluted air and physical inactivity are crucial risk factors for the development and progression of major noncommunicable diseases and, in particular, of cardiovascular disease. While regular physical activity is well known to improve general health, it may also increase the uptake and deposit of air pollutants in the lungs/airways and circulation, due to increased breathing frequency and minute ventilation, thus increasing the risk of cardiovascular disease.

Keywords: air pollution ; physical activity ; cardiovascular disease ; inflammation ; oxidative stress ; antioxidant defense

1. Introduction

Physical inactivity is among the leading risk factors for major noncommunicable diseases, including cardiometabolic disease and cancer. The beneficial health effects of physical activity are well known, with further positive impacts on mental health, quality of life, cognitive function, and healthy weight [1]. On a global scale, more than every fourth adult is insufficiently physically active, which means that they do not achieve the minimum recommended level of 150 min of moderate intensity or 75 min of vigorous intensity physical activity per week, as indicated by recent data from Guthold et al. [2]. Environmental factors, such as air pollution, heavy metals, pesticides, and traffic noise, are increasingly recognized as endocrine disruptors that contribute to cardiometabolic diseases such as metabolic syndrome and type 2 diabetes [3][4][5][6]. Likewise, the World Health Organization (WHO) concludes that air pollution is a major contributor to the global burden of disease, with 9 out of 10 people worldwide breathing polluted air, exceeding the WHO guideline values for ambient air quality [7]. Both air pollution and physical inactivity were demonstrated to cause excess deaths from noncommunicable diseases, including cardiovascular disease, respiratory disease (mainly induced by air pollution), type 2 diabetes, and certain types of cancers [8]. Especially, the risk for diabetes is largely increased in areas with polluted air [9][10], with a central role for low grade inflammation and altered lipid metabolism by air pollution constituents [11]. For comparison, WHO estimated that ambient air pollution was associated with 4.2 million deaths in 2016 [12], while insufficient physical activity accounted for 3.2 million deaths for the same year [13]. Of note, we recently used a novel hazard ratio function, the estimate of the Global Exposure-Mortality Model (GEMM), to reveal 8.79 million global premature deaths in 2019, as well as 790,000 excess deaths per year in Europe, attributable to air pollution, thus greatly exceeding the calculations from WHO [14]. The interplay between air pollution and physical activity and the joint effects on health outcomes constitute an emerging area of investigation with important public health implications. For instance, higher air pollution may interfere with physical activity behavior, as it could create a barrier for doing physical activity that is, importantly, not restricted to outdoor environments as outdoor and indoor environments are fundamentally connected [8]. These circumstances lead to a key question—should physical activity be encouraged in areas with polluted air? While regular physical activity is in general regarded to improve somatic and mental health, it may also influence the uptake and deposit of air pollutants in the lungs and airways due to increased breathing frequency and minute ventilation, thus increasing the risk of several noncommunicable diseases, mainly from cardiorespiratory origin [15].

2. Pathomechanisms of Air Pollution with Focus on Oxidative Stress and Inflammation

Oxidative stress and inflammation represent the common denominator of the adverse cardiorespiratory health effects of air pollution. Recent evidence from human and animal studies suggests that exposure to multiple air pollutants may have the potential to increase systemic oxidative stress and inflammation, both relevant to mediating disease risk (reviewed in [16][17]). However, understanding the complete picture of underlying pathomechanisms is still ongoing, and complex interactions with other risk and lifestyle factors, such as physical activity, are very likely. As shown in **Table 1**, the short and long-term impacts of air pollution constituents on various markers of oxidative stress and inflammation are supported

by a number of recent clinical studies. Exemplarily, Liu et al. evidenced a positive association between polycyclic aromatic hydrocarbons (PAHs) and levels of malondialdehyde in a panel study of 40 chronic obstructive pulmonary disease patients and 75 healthy controls, which was even more pronounced in subjects with impaired lung function [18]. Nassan et al. performed a mass spectrometry based metabolomic profiling of plasma samples among 456 men, to show that acute and chronic exposures to fine particulate matter ($PM_{2.5}$) were related to metabolic pathways involved in inflammation, oxidative stress, immunity, and nucleic acid damage and repair [19]. These observations can be mechanistically explained, at least in part, by air pollution induced mitochondrial damage and dysfunction, as reviewed in [20]. Abohashem et al. demonstrated that higher $PM_{2.5}$ exposure was associated with an increase in major adverse cardiovascular events, and that this was mediated by an increase in leucopoietic activity and arterial inflammation [21]. These results are not restricted to adult populations, as indicated by a recent study from Mann et al. that indicates that acute increases in traffic related air pollutants were associated with 8-isoprostane levels in 299 children (aged 6–8) [22]. Likewise, adolescents (n = 100) were demonstrated to be a susceptible group, by showing that exposure to multiple air pollutants was related to markers of oxidative stress, acute inflammation, altered hemostasis, endothelial dysfunction, monocyte enrichment, and high blood pressure [23]. In a larger cohort of 3996 subjects, Li et al. found acute increases in $PM_{2.5}$ and sulfate to be associated with increased C-reactive protein levels, which was also true for nitrogen dioxide (NO_2) in the case of interleukin (IL)-6, and for black carbon (BC), sulfate, and ozone (O_3) in the case of tumor necrosis factor receptor 2 [24]. Conversely, BC, sulfate, and NO_x were negatively associated with fibrinogen, and sulfate was negatively associated with tumor necrosis factor (TNF)-α levels.

Cell culture exposures suffer from often unrealistic interaction between certain cell types and air pollution constituents, and controlled human exposure studies are hard to perform due to ethical concerns. This makes the use of animal models an indispensable tool in probing the mechanisms of air pollution induced pathology. For a long time, O_3 was the main focus of air pollution research, with its effects on human health being well characterized [25] and only recently has $PM_{2.5}$ taken its place. Other gaseous constituents, such as NO_2 and sulfur dioxide (SO_2), also play a prominent role in the air pollution induced pathology, but receive less attention [26][27].

O_3 is still an important contributor to air pollution and there is a large body of literature dedicated to its effects on health. One of the main ways in which O_3 influences the onset and progression of cardiovascular disease is through oxidative stress and inflammation. A study in mice found that O_3 exposure modulated vascular tone regulation and increased oxidant stress and mitochondrial DNA damage [28]. Authors have also observed a larger increase in atherosclerotic plaques in ApoE−/− mice exposed to O_3, pointing to a proinflammatory phenotype. Endothelial dysfunction due to O_3 exposure was also observed to be CD36 dependent, as a study showed that vasorelaxation by acetylcholine was not impaired in CD36−/− mice [29]. The same study demonstrated an increase in the number of lung macrophages and neutrophils after O_3 exposure in wild type mice. In diabetes prone mice, O_3 exposure not only impaired insulin response but also caused systemic inflammation that was observed through the elevation of interferon (IFN)-γ, TNF-α, and IL-12 in visceral adipose tissue [30]. Expression of oxidative stress related genes, such as Cox4 and Nrf2, was also increased. Interestingly, a study on a successive O_3 and carbon black particles exposure revealed that heart rate and heart rate variability were both changed in mice exposed to O_3 and then carbon black particles, but not in mice exposed to clean air and then carbon black alone, indicating that O_3 is a major contributor to air pollution induced cardiovascular disease [31].

PM, especially $PM_{2.5}$, is now known to influence the onset and progression of cardiovascular disease, mainly through oxidative stress and inflammation pathways [32]. Exposure of mice to $PM_{2.5}$ was shown to increase the number of circulating monocytes and their infiltration into the vasculature [33]. The same study found that inflammation markers such as TNF-α and monocyte chemoattractant protein 1 (MCP-1) were upregulated in the lung tissue, together with markers of lipid peroxidation, and that nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) was activated in the aorta. More evidence that NADPH oxidase is a major contributor to oxidative stress was demonstrated in a study where superoxide production was increased in rat aortic rings after exposure to $PM_{2.5}$, but the effect was abolished after inhibition of NADPH oxidase [34]. Endothelial function, a potent early prognostic functional parameter for later cardiovascular events [35][36][37], is partly dependent on the ability of eNOS to produce nitric oxide (NO), and the presence of superoxide radical is detrimental to the NO signaling, because NO and O_2^- react to produce peroxynitrite ($ONOO^-$) [38][39]. It was shown that 3-nitrotyrosine, a marker of protein nitration by $ONOO^-$, was elevated in the thoracic aorta of ApoE−/− mice exposed to concentrated ambient PM [40]. PM can also impair NO signaling through the uncoupling of eNOS, as was shown in a study where rats were exposed to diesel PM [41]. Oxidative stress in the aorta as a result of PM exposure was normalized after treatment with BH4, an eNOS cofactor. A decrease in eNOS, accompanied by oxidative stress and an increase in Mn-SOD, was also observed in the pulmonary artery of $PM_{2.5}$ exposed rats [42]. Inflammation in the mesenteric arteries, as defined by increased expression of TNF-α, IL-6, MCP-1, E-selectin, and vascular cell adhesion molecule 1 (VCAM-1), was observed after the concentrated ambient PM exposure of ApoE−/− mice [43]. Progression of atherosclerosis through the accumulation of oxidized lipids and the infiltration of immune cells was associated with $PM_{2.5}$

exposure in ApoE−/− mice [44]. Accumulation of oxidized lipids such as 7-ketocholesterol was suggested to be CD36 mediated. In most of the above mentioned studies, endothelial function, as measured by the endothelium dependent relaxation of isolated aortic rings, was impaired. Interestingly, a study on rats showed significant impairment of endothelial function after the instillation of ambient PM, but not after the instillation of carbon black or TiO_2 particles, suggesting that the complex composition of ambient PM is responsible for the observed cardiovascular effects [45]. An overview of the mechanisms by which air pollution confers negative cardiovascular effects is presented in **Figure 1**.

Table 1. Human studies on the association of inflammation and/or oxidative stress with air pollution.

First Author/Year	Population/Cohort	Air Pollutants	Major Outcomes	Ref.
Liu, 2021	40 chronic obstructive pulmonary disease patients and 75 controls	PAHs	A one fold increase in hydroxylated PAHs was associated with a 4.1–15.1% elevation of malondialdehyde, which was stronger in subjects with impaired lung function.	[18]
Abohashem, 2021	503 subjects without cardiovascular disease	$PM_{2.5}$	Higher $PM_{2.5}$ was associated with increased risk for major adverse cardiovascular events, mediated by an increase in leucopoietic activity and arterial inflammation.	[21]
Ni, 2021	740 subjects	$PM_{2.5}$	Acute increases in $PM_{2.5}$ were associated with increased soluble lectin like oxidized LDL receptor-1, but not with nitrite.	[46]
Nassan, 2021	456 men	$PM_{2.5}$ species	Acute increases in $PM_{2.5}$ species were associated with metabolic pathways involved in inflammation, oxidative stress, immunity, and nucleic acid damage and repair.	[19]
Mann, 2021	299 children	Traffic related air pollutants (sum of PAH456, NO_2, elemental carbon, $PM_{2.5}$)	Acute increases in traffic related air pollutants were associated with 8-isoprostane.	[22]
Prunicki, 2020	100 subjects	$PM_{2.5}$, NO, NO_2, CO, PAHs	Air pollutants were associated with oxidative stress, acute inflammation, altered hemostasis, endothelial dysfunction, monocyte enrichment, and diastolic blood pressure.	[23]
Riggs, 2020	100 subjects	$PM_{2.5}$	A 10 μg/m^3 increase in $PM_{2.5}$ was associated with a 12.4% decrease in reactive hyperemia index (95% CI −21.0–−2.7). Increased $PM_{2.5}$ was associated with elevated F-2 isoprostane metabolite, angiopoietin 1, vascular endothelial growth factor, placental growth factor, intracellular adhesion molecule-1, and matrix metalloproteinase-9 as well as reduced vascular adhesion molecule-1.	[47]

First Author/Year	Population/Cohort	Air Pollutants	Major Outcomes	Ref.
Li, 2019	73 subjects	$PM_{2.5}$, BC, NO_2, CO	Increases in air pollutants were associated with reductions in circulating high density lipoprotein cholesterol and apolipoprotein A-I, as well as elevations in HDL oxidation index, oxidized LDL, malondialdehyde, and C-reactive protein.	[48]
Lin, 2019	26 subjects	PAHs	Increases in 5-, 12-, and 15-hydroxyeicosatetraenoic acid, as well as 9- and 13-hydroxyoctadecadienoic acid, were observed. Decreases in paraoxonase and arylesterase, as well increases in C-reactive protein and fibrinogen, were observed.	[49]
Balmes, 2019	87 subjects	O_3	Acute O_3 exposure did not alter C-reactive protein, monocyte–platelet conjugates, and microparticle associated tissue factor activity, whereas increases in endothelin-1 and decreases in nitrotyrosine were observed.	[50]
Han, 2019	60 subjects with prediabetes and 60 healthy subjects	$PM_{2.5}$	Acute exposure to $PM_{2.5}$ resulted in increased exhaled NO, white blood cells, neutrophils, interleukin-1α, and glycated hemoglobin. Compared to healthy subjects, prediabetic subjects displayed pronounced $PM_{2.5}$ associated systemic inflammation, elevated systolic and diastolic blood pressure, impaired endothelial function, and elevated fasting glucose.	[51]
Xia, 2019	215 pregnant women	$PM_{2.5}$	Acute increases in $PM_{2.5}$ and lead constituent were associated with endothelial dysfunction (increased endothelin-1, E-selectin, and intracellular adhesion molecule-1) and inflammation (increased interleukin-1β, interleukin-6, tumor necrosis factor-α). Endothelial dysfunction and elevated inflammation were partially mediated by the effect of $PM_{2.5}$ and lead constituent on blood pressure.	[52]
Li, 2019	3820 subjects	$PM_{2.5}$, BC, O_3, sulfate, NO_X	Negative associations of acute $PM_{2.5}$ and BC with P-selectin, of O_3 with monocyte chemoattractant protein 1, and of sulfate and NO_x with osteoprotegerin were found.	[53]
Li, 2017	3996 subjects	$PM_{2.5}$, sulfate, NO_x, BC, O_3	Acute increases in $PM_{2.5}$ and sulfate were associated with increased C-reactive protein, which was also true for NO_x in case of interleukin-6 and for BC, sulfate, and O_3 in case of tumor necrosis factor receptor 2. Conversely, BC, sulfate, and NO_x were negatively associated with fibrinogen, and sulfate was negatively associated with tumor necrosis factor α.	[24]

First Author/Year	Population/Cohort	Air Pollutants	Major Outcomes	Ref.
Mirowsky, 2017	13 subjects with coronary artery disease	O_3	Per acute IQR increase in O_3, changes in tissue plasminogen factor (6.6%, 95% CI 0.4–13.2), plasminogen activator inhibitor-1 (40.5%, 95% CI 8.7–81.6), neutrophils (8.7%, 95% CI 1.5–16.4), monocytes (10.2%, 95% CI 1.0–20.1), interleukin-6 (15.9%, 95% CI 3.6–29.6), large artery elasticity index (−19.5%, 95% CI −34.0–−1.7), and the baseline diameter of the brachial artery (−2.5%, 95% CI −5.0–0.1) were observed.	[54]
Pope 3rd, 2016	24 subjects	$PM_{2.5}$	Episodic increases in $PM_{2.5}$ were associated with increased endothelial cell apoptosis, an anti-angiogenic plasma profile, and elevated circulating monocytes, and T, but not B, lymphocytes.	[55]
Wu, 2016	89 subjects	$PM_{2.5}$, NO_2	Acute increases in $PM_{2.5}$ were associated with brachial–ankle pulse wave velocity, whereas no association was found for NO_2. NO_2 was associated with increased C-reactive protein.	[56]

PAHs: polycyclic aromatic hydrocarbons, $PM_{(diameter\ size)}$: particulate matter, NO_2: nitrogen dioxide, NO: nitric oxide, CO: carbon monoxide, BC: black carbon, O_3: ozone, NO_x: nitrogen oxides, IQR: interquartile range, CI: confidence interval.

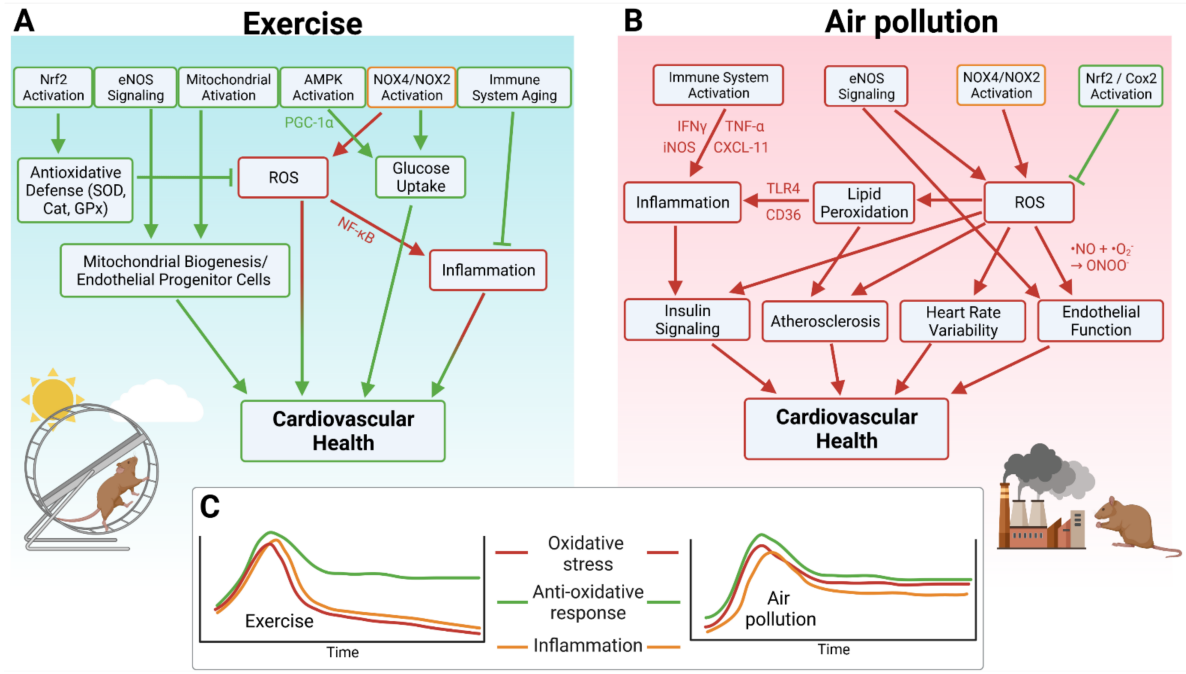

Figure 1. (**A**) Major pathways by which exercise improves cardiovascular health as inferred from animal studies. (**B**) Major pathways by which air pollution negatively influences cardiovascular health. (**C**) Chronic versus acute exposure to exercise or air pollution. Oxidative stress and inflammation are acutely elevated during both exercise and air pollution exposure, but decrease after exercise and remain high after air pollution. Antioxidative defense also increases acutely following either exercise or air pollution exposure, but remains high in both scenarios, resulting in a long-term benefit of exercise. Created with BioRender.com, accessed on 4 November 2021.

3. Key Mechanisms of Antioxidant and Anti-Inflammatory Effects of

Physical Activity

While there is a general consensus that regular physical activity can improve cardiorespiratory fitness and health, and contribute to the prevention of disease, it is important to note that different types and contexts of physical activity may result in differential health effects. These relationships may strongly depend on sociodemographic characteristics (e.g., age, sex, and socioeconomic status), settings (e.g., leisure time physical activity, commuting, and sports), types (e.g., anaerobic/strength or aerobic/endurance activities), extent of physical activity (intensity, frequency, and duration), and overall fitness level and health status [57]. Several studies have investigated these differential health effects induced by different modes of physical activity. In the German Gutenberg Health study (*n* = 12,650), Arnold et al. recently demonstrated arterial stiffness (measured by stiffness index), a well established marker of cardiovascular disease risk that is fundamentally influenced by oxidative stress and inflammatory processes, to be favorably associated with sports related endurance activities, but also with active commuting [58]. Conversely, physical activities associated with intense work, such as heavy occupational activity, were shown to be associated with higher arterial stiffness. Of special importance is that the combination of both engaging in endurance training and having lower arterial stiffness (below median) resulted in decreased risk of all-cause mortality over a follow up period of eight years. In line with this, a prospective study of 723 subjects showed that sports and habitual activities possessed beneficial effects on physical fitness (13 motor performance tests) and health status (physician diagnosis concerning orthopedics, neurology, and cardiovascular system) [57]. In contrast, comparable amounts of work related activities did not substantially influence physical fitness or health status. On a mechanistic level, leisure time physical activities seem also to be accompanied by improved antioxidant defense and immune response [59]. In support of this, the beneficial impact of daily walking and gait on oxidative stress levels and inflammation was shown in patients with peripheral artery disease [60][61]. In further studies, leisure time physical activities were found to be inversely related to levels of inflammation, such as C-reactive protein, plasma fibrinogen, white blood cell count, and adhesion molecules [62][63][64][65]. In a more recent randomized controlled trial, the acute oxidative stress response following different types of activities, i.e., anaerobic, aerobic, and combined, were compared in healthy untrained young males [66]. The results revealed that aerobic, anaerobic, as well as combined activities may have the potential to acutely increase oxidative stress (in the sense of beneficial eustress [67][68]) and antioxidant responses, with a differential pattern of results related to the intensity and the duration of the physical activity.

Understanding of the relationship between exercise, oxidative stress, and antioxidant capacity has been cultivated over decades of study. Aerobic cellular metabolism produces free radicals as a byproduct of ATP synthesis that are, in normal conditions, detoxified by robust physiological defenses before serious damage to proteins, lipids, and DNA occurs [69]. Detoxification by antioxidant systems (e.g., the Nrf2 controlled gene pathway, the glutathione system, and nonenzymatic antioxidants) is essential to the life of the organism [69][70]. Despite the obvious benefits in cardiorespiratory and metabolic health, muscular exercise has long been known to cause the formation of reactive oxygen species (ROS), which initially seems somewhat incongruent to the well documented benefits to health. In 1978, markers of lipid peroxidation in the form of expired pentane were detected following 60 min of exercise [71] and a year later in rats [72]. Other studies later determined that vitamin E appeared to be important in protecting cellular membranes from the damage incurred by the greater oxidative load caused by exercise [73][74].

While the findings of higher ROS burden in exercise are consistent, there are varying reports as to the source of these oxidants. Mitochondria have been quite intuitively indicated as the primary source of ROS during exercise, but others report that mitochondria may not be the primary source of ROS, and other enzymatic sources may be critical [75]. NADPH oxidases, a group of enzymes whose endogenous role is the production of superoxide, have also been reported to be active in exercise induced ROS production. NOX-4, an isozyme present in the myocardium and also in skeletal muscle fibers, was demonstrated to increase in expression in the mouse myocardium and also to trigger Nrf2 in response to exercise. Mice deficient in cardiomyocyte NOX-4 were reported to have decreased exercise performance [76]. NOX-2 is also expressed in skeletal muscle fibers, and loss of function studies indicate that it is likely the primary source of cytosolic ROS during exercise and also plays a role in exercise stimulated glucose metabolism [77]. Interestingly, another study indicated a somewhat tissue dependent role for both NOX-2 and NOX-4 in exercise, alongside the stimulation of antioxidant defenses [78]. Another ROS-producing enzyme found in the plasma membranes of skeletal muscle is xanthine oxidase, which has also been implicated as a source of ROS following exercise, as indicated by protection following inhibition by allopurinol [79]. Importantly, ROS generation and detoxification capacity appear to be highly tissue and stimulus dependent [80]. The contribution of multiple ROS sources to the “eustress” mechanism by physical exercise can be best explained by the crosstalk concept of different ROS sources via redox switches in the involved enzymatic pathways [81][82][83][84], in the case of exercise most likely initial formation of mitochondrial ROS leading to the cross activation of NADPH oxidases and xanthine oxidase to orchestrate the concert of harmful and beneficial redox signaling pathways [85][86].

In line with these findings of greater free radical formation, exercise appears to cause the upregulation of endogenous antioxidant enzymes, namely, mitochondrial superoxide dismutase (SOD) and catalase were reported to be increased by 37% in the muscles of rats following a running program [87]. Mice placed on a long term swim program (21 weeks, 1 h/d 5 d/w) also expressed higher levels of catalase, SOD, and glutathione peroxidase in the plasma, heart, and liver [88]. Importantly, these two studies (amongst many others, reviewed in [89]) demonstrate that the physiological response to exercise induced oxidant load is plastic and occurs acutely in response to ongoing exercise, but is also maintained at higher levels over the course of training, leading to an increase in basal nonexertion levels. Many other studies support these findings, where SOD1, SOD2, and glutathione peroxidase are increased in regularly trained muscles [90][91][92][93]. In addition, the activation of the AMP activated protein kinase (AMPK) is a feature of exercise beneficial health effects, with downstream activation of protective pathways based on PGC-1α, improved angiogenesis and mitochondrial biogenesis, thrombus stabilization, anti-inflammatory and antioxidant effects, prevention of smooth muscle cell proliferation, and endothelial cell apoptosis [94]. AMPK is required for exercise protective effects on endothelial function and a higher number of endothelial progenitor cells, as well as against vascular senescence [95].

Although it was initially believed that moderate to high intensity exercise leads to a suppression of the immune system, finer analysis and more current data suggest that exercise leads to a redistribution of immune cells into tissues, resulting in heightened immune surveillance and possibly delaying the aging of the immune system (reviewed in [96]). Leukocytes migrate into active muscle and there is a transient increase in the levels of cytokines produced by immune cells. The identity of these upregulated cytokines is not consistent across many studies, however, C-reactive protein, IL-6, and IL-10 appear to be amongst these. Notably, oxidative stress and inflammation are intimately tied. NF-κB is an important transcription factor involved in cytokine production and regulating the immune response to physiological stressors that is also redox sensitive [97], particularly to the redox status of glutathione-s-transferase [98]. As previously discussed, exercise causes an increase in ROS and a subsequent increase in antioxidant capacity, possibly linking these two mechanisms. An overview of the mechanisms by which exercise promotes cardiovascular health is shown in **Figure 2**. Taking all of these beneficial effects of exercise into account, it is not surprising that exercise was proposed as a powerful nonpharmacological intervention against several environmental and behavioral risk factors, such as noise exposure, smoking, and mental stress [99] but also against common complications during the aging process [100]. Besides exercise, intermittent fasting was also discussed as an efficient nonpharmacological intervention against disease development and progression, which may be also of interest for the present overview since intermittent fasting shares many features with physical exercise with respect to the underlying protective mechanisms [101]. It remains to be fully established whether the beneficial effects of exercise always dominate and prevent the harmful health effects of air pollution.

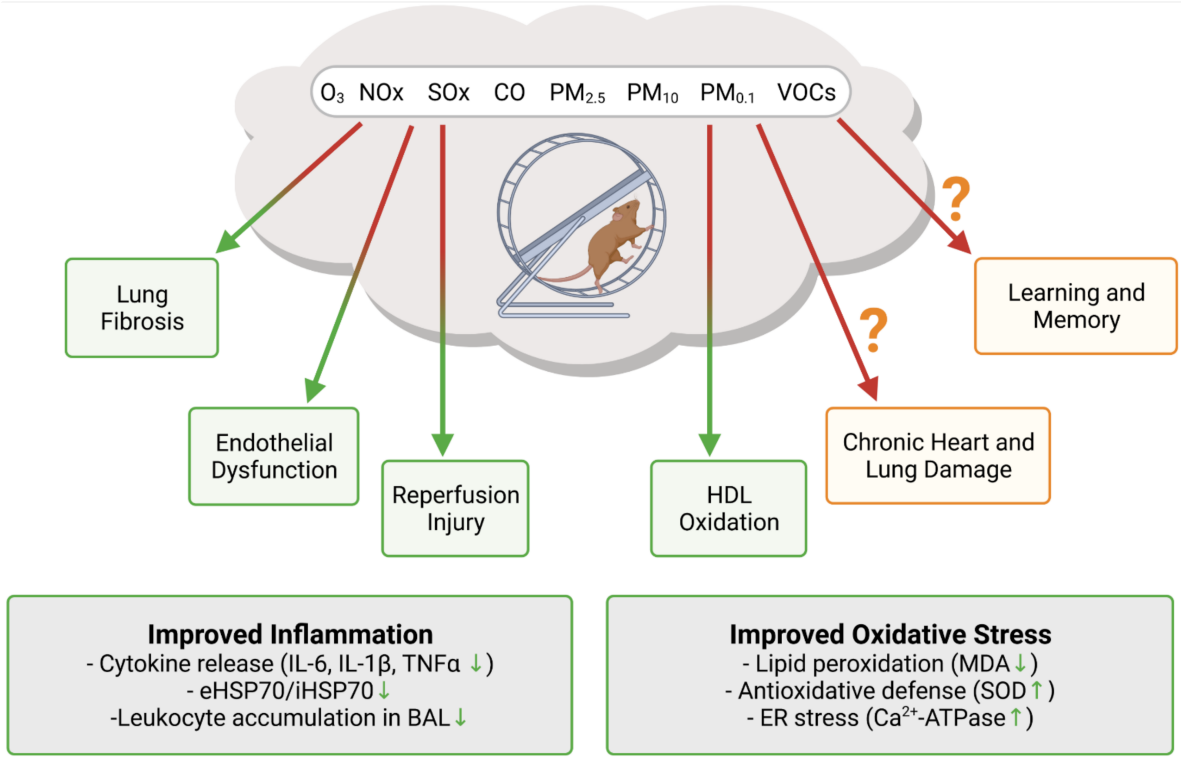

Figure 2. Insight into the synergistic effects of exercise and air pollution exposure from animal studies. Exercise was shown to offset air pollution mediated increase in oxidative stress and inflammation. It is still not clear if exercise in polluted air can ameliorate the detrimental effects of air pollution in the long term. Created with BioRender.com, accessed on 4 November 2021.

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