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Review

Pulmonary Effects Due to Physical Exercise in Polluted Air: Evidence from Studies Conducted on Healthy Humans

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Abstract: Physical inactivity has caused serious effects on the health of the population, having an impact on the quality of life and the cost of healthcare for many countries. This has motivated government and private institutions to promote regular physical activity, which, paradoxically, can involve health risks when it is carried out in areas with poor air quality. This review collects information from studies conducted on healthy humans related to the pulmonary effects caused by the practice of physical activity when there is poor air quality. In addition, several challenges related to the technological and educational areas, as well as to applied and basic research, have been identified to facilitate the rational practice of exercise in poor air quality conditions.

Keywords: air pollution; physical exercise; lungs

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1. Introduction

The increase in the world population and the use of polluting energy sources in the modern world have led to changes in the quality of the air we breathe. Pollutants floating in the air cause harmful effects on health, which have been extensively studied [1–3]. As a result of these studies, this type of pollution has been linked to cancer, cardiovascular disorders, acute pulmonary disorders (infections, acute bronchial obstruction), and chronic disorders (asthma, chronic obstructive pulmonary disease) [4]. According to data provided by the World Health Organization in 2018, about 90% of people are exposed to polluted air, particularly in poor or developing countries on all continents, which produce a total of around seven million deaths annually at a global level [5]. Although we breathe a mixture of substances in the air, on an individual level, it has been possible to individually identify some pollutants that cause health disorders, such as tropospheric ozone (O_3), particulate matter (PM_x), carbon monoxide (CO), nitrogen oxides (NO_x), and sulfur oxides (SO_x) [6,7]. These are usually concentrated in urban centers, and are mainly, though not exclusively, caused by activities typical of human beings, such as transport, heating, cooking, and agricultural and industrial activities [8].

Our bodies come into contact with atmospheric pollutants through the wide area of exposure of the lung tissue, making this organ particularly susceptible to damage from the components of the air we breathe, such as particulate matter, cigarette smoke, various gases, and pollen [9,10]. Consequently, this interaction will cause alterations in the functionality of this organ. The amount of polluting substances that reach the lungs during exercise will depend on both their concentration in the air and the magnitude of the pulmonary physiological phenomena typical of physical effort: bronchodilation, increased ventilation, mouth breathing, and increased diffusing capacity. This implies that, during exercise, a

higher load of tissue pollutants will be observed [11], which impacts deeper lung areas and may even be associated with a greater passage of these substances into the bloodstream, as in the case of gases and ultrafine particulate matter (Figure 1).

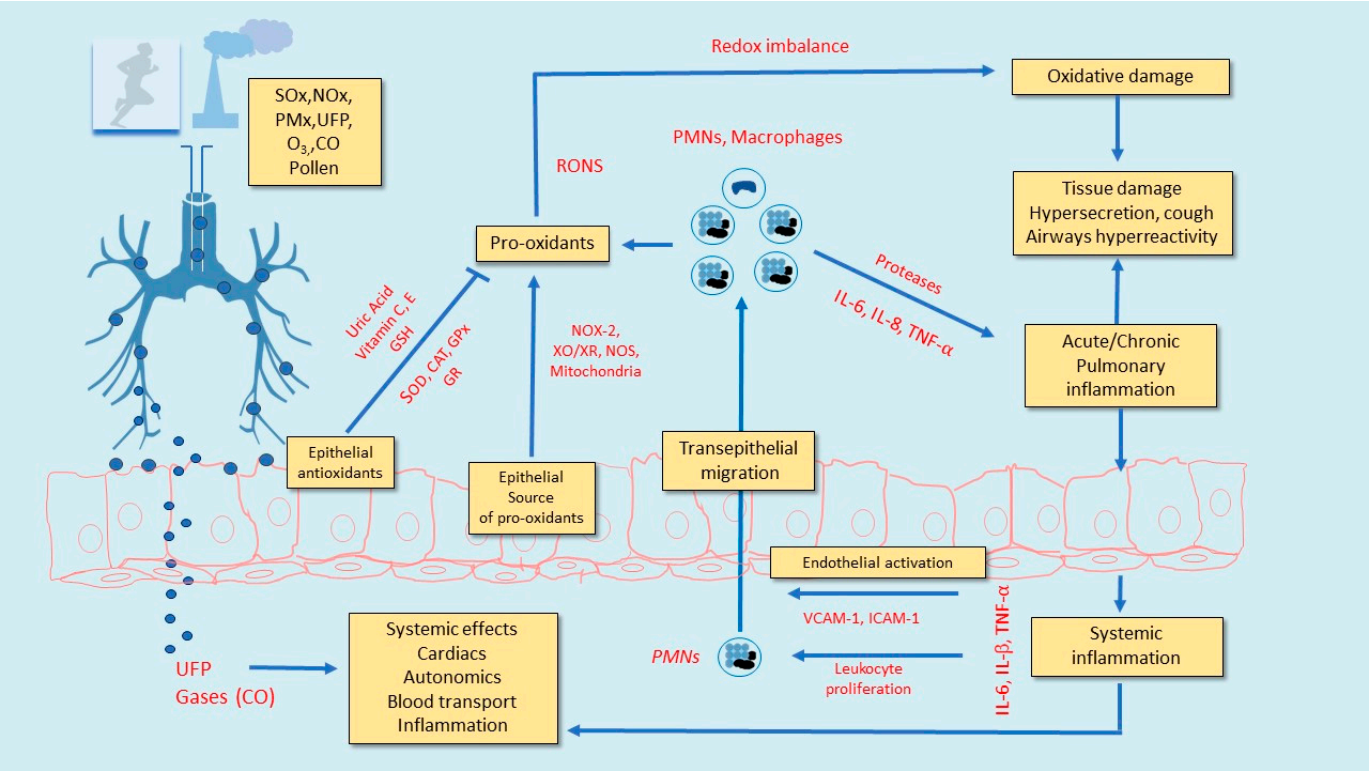

Figure 1. Systemic and localized effects at the lung level generated by air pollutants. SO_x = sulphur oxides; NO_x = nitrogen oxides; PM_x = particulate matter; UFP = ultrafine particles; SOD = superoxide dismutase; CAT = catalase; GP_x = glutathione peroxidase; GR = glutathione reductase; GSH = reduced glutathione RONS = reactive oxygen and nitrogen free radicals; NOX-2 = NADPH oxidase type 2; XO = xanthine oxidase; XR = xanthine reductase; NOS = nitric oxide synthase; PMNs = polymorphonuclear leukocytes. VCAM-1 = vascular cell adhesion molecule 1; ICAM-1 = intercellular adhesion molecule 1.

In consideration of the processes described, for some years now, the question has been what the pulmonary effects due to physical exercise in areas with poor air quality are, in the short and long term, both in healthy people and in those suffering from pathologies [12–15]. The issue is becoming relevant nowadays, since, in many countries with poor air quality, increased participation in outdoor sports activities, such as massive urban races and the use of bicycles, have been observed. In addition, there is little information about the effects and potential risks for the exposed population, as well as future measures to help to reduce exposure for both people who exercise and healthcare professionals. To address this matter, the interaction mechanisms and effects resulting from the contact between the air and lung tissue are presented in this study. In addition, some challenges in the field of research are described, and recommendations for the safe practice of physical exercise under these conditions are made. The papers used for this narrative review were original or review manuscripts, in which an exercise protocol under laboratory or field conditions was carried out, including the study of pulmonary function parameters, in the presence of air pollutants in healthy humans. The papers were mainly taken from the PubMed search engine, and there was no limitation regarding the year of publication.

2. Alteration of Ventilatory Function and Appearance/Exacerbation of Respiratory Symptoms during Physical Exercise with Polluted Air: Short- and Medium-Term Effects

By doing physical exercise in an environment with polluted air, increased airway resistance is induced. Initially, this was described in protocols that set O_3 at different concentrations [16–19]. Thus, in these studies, it is a common result to find lower values than those expected in forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), and forced mid-expiratory flow rate ($FEF_{25–75}$) [19,20]. Regarding the pollutant particles in suspension, particulate material less than 10 microns (PM_{10}) promotes the establishment of chronic lung function problems, mainly associated with decreased FEV_1 [21]. Likewise, $PM_{2.5}$ (<2.5 microns) has been related to a drop in FEV_1 and FVC in subjects who lived in the vicinity of a highway [22]. Physical exercise increases these effects as their intensity and duration increase as a consequence of the increased work of breathing. Minute ventilation, together with greater exposure to the pollutant, will determine their inhaled load in the airways [16,23,24]. Several authors have observed that, during moderate and maximum exercise in an environment contaminated with O_3, there are more symptoms, such as dyspnea, respiratory distress, and a feeling of tightness in the chest, which quickly lead to the cessation of exercise [25–28]. Several authors have shown an alteration in lung function parameters (FEV_1, FVC, and $FEF_{25–75}$) in both healthy trained and untrained subjects exposed to high concentrations of O_3 while performing physical exercise [15], with some of them even experiencing the effects a few hours after exercising [29]. Abnormal respiratory symptoms have also been observed after one hour of exercise and one hour of rest in an environment contaminated with PM_{10} and $PM_{2.5}$, however, no spirometric changes were found [21]. In another study, Brant et al. [30] observed decreased mucociliary clearance, decreased pH in the expired air, and increased symptoms of respiratory distress in motorcyclists who were chronically exposed to NO_2 during heavy traffic for 5–8 h a day, five days a week. Likewise, the practice of aerobic exercise in the open air at an average $PM_{2.5}$ concentration of 65.1 $\mu g/m^3$ over a period of five days also altered mucociliary clearance [31]. Yet, the study conducted by Kubesch et al. (2015) demonstrated improvements in lung function with physical exercise in a highly polluted environment; however, an acute pulmonary inflammatory effect was also observed [32]. Other studies on healthy subjects who performed strenuous long-duration exercise (between ~2–5 h) in a polluted environment ($PM_{2.5}$ and O_3) did not show deleterious effects on lung function parameters [33,34]. This should be interpreted with caution, since the systematization of this behavior, which constantly promotes an oxidative/inflammatory lung environment, could mean permanent lung damage in the future. Children are especially sensitive to contact with atmospheric pollutants, which leads to a higher rate of school absenteeism and an increase in high and low airway infections [35], and alters lung function, thereby increasing the probability of death [36]. Infant lungs show an incomplete respiratory tree where the pulmonary epithelium is being formed, which has been associated with greater permeability of this structure. Similarly, some studies have suggested that long-term exposure to air pollutants could potentially affect children's lung development [37–39]. Modification of lung function in children who are active in polluted air has been associated with high concentrations of O_3 [40], MP_{10}, NO_x, and CO [41]. McConell et al. [42] demonstrated that there was an association between the prevalence of asthma in children and prolonged and intense exercise done outdoors with high levels of O_3. In the case of adults, moderate exercise increases the amount of particulate material entering the lungs by 4.5 times versus resting [12], where similar results are expected for the other environmental pollutants. One group of subjects who can be particularly affected by polluted air is the group of amateur long-distance athletes (e.g., marathons, cross-country cycling). Thus, a group of cyclists exercised in open-top field chambers for dispensing O_3, showing a decrease in FEV_1 after moderate exercise for sixty minutes [24]. Furthermore, a group of cyclists in competition (75 min) increased their respiratory symptoms (wheezing, dyspnea) after inhaling a mixture of pollutants. Respiratory distress and spirometric alterations were correlated with the concentration of O_3 [43]. Korrick et al. [44] found

a decrease in FEV_1 and FVC in subjects who took prolonged walks in an environment with low levels of O_3 and particulate matter, demonstrating that the changes in lung function were caused by exercise, even with low levels of pollutants. Gong et al. [45] conducted an intermittent exercise protocol (two hours) in healthy subjects and subjects with asthma using an environmental test chamber with ultrafine particulate matter seven to eight times higher than average air levels in unpolluted areas. Thus, a decrease in arterial oxygen saturation and FEV_1 was observed the day after the test, with no differences between healthy subjects and subjects with asthma. A total of 23 studies evaluated the effect of O_3 on the decline of FEV_1, which were carried out under standardized conditions in a test chamber. Here, relationship models were observed in various conditions of O_3 concentration, exposure time, and minute ventilation; in addition, the thresholds for the appearance of the broncho-constrictor phenomenon were attained [46]. Kim et al. [47] observed a decline in FEV_1 in an exercise protocol at 0.06 ppm O_3 and stable ventilation of 35 L/min in six cycles of 50 min. The obstructive modification caused by O_3 is the result of a bronchoconstrictive response induced by a vagal reflex activated by irritation [48]. The release of acetylcholine (parasympathetic response) will increase the activation of the submucosal glands, leading to greater release of mucus [49]. The results found in relation to NO_2 on lung function have been variable; Bauer et al. [50] and Strand et al. [51] demonstrated a broncho-constrictor effect in asthmatics. Likewise, Kulstrunk and Bohini (1992) observed decreased FEV_1 after a maximal exercise test (~8 min) with high NO_2 levels was performed by healthy subjects [52]. However, Jorres et al. [53] did not observe any changes in FEV_1 after exercising for 1.5 h with 3 h of exposure to 1 ppm of NO_2. In relation to CO, due to its high diffusion capacity in the alveolar capillary membrane and its great affinity with carboxyhemoglobin (COHb), systemic effects have mainly been recognized in healthy subjects who exercise. Due to COHb, there will be less availability of hemoglobin to bind oxygen (hypoxemia), thus altering the transport capacity of this gas to active muscles [54] and limiting energy production and physical effort. Decreased physical performance in healthy subjects due to CO exposure alone was observed with maximum intensity exercise [55], but not when it was performed at submaximal intensity and a lower concentration of this gas [56].

All previously mentioned studies describe the short- and medium-term effects of exposure to air pollutants, with little evidence to clarify the long-term effects. However, subjects exposed for years to outdoor jobs on the streets, but who did not exert great physical effort, showed a decreased ability to perform physical work, as well as a decreased maximum voluntary ventilation (MVV) [57].

3. Lung Inflammation and Oxidative Stress Due to Exercise in Polluted Air

In the lung region, there is a complex microenvironment where the interaction of the cells of this organ (pneumocytes, endothelial cells, alveolar macrophages) and inflammatory cells (various types of leukocytes) from the bloodstream takes place. Due to the gas exchange function between the lungs and the environment, this tissue organization is constantly exposed to the action of pollutants present in the air. The interaction between lung tissue and air pollutants largely depends on the physical and chemical characteristics of the latter. In this way, some air pollutants will cause direct damage at the cellular level (O_3, SO_x, NO_x), others will be deposited in the airway (particulate matter), and some will diffuse through the alveolus capillary membrane into the bloodstream (ultrafine particulate matter and gases), as shown in Figure 1.

Lung inflammation and oxidative stress play an essential role in altering lung function with exposure to O_3, especially when exercising [58]. In this sense, the low solubility of O_3 in water suggests that the main interaction of this molecule will be with the surface of the epithelium, and, in particular, with the epithelial lining fluid. This contact will promote reactions with thiol groups (-SH), antioxidants (glutathione, ascorbic acid), and macromolecules (lipids, proteins, carbohydrates), among others found in the epithelial fluid, promoting an oxidative/inflammatory environment. A higher number of molecules

that are attracted due to the increased ventilatory flow induced by exercise will enhance these effects, especially for long-duration exercises (e.g., marathons). A study conducted by Kinney et al. [59] observed increases in lung inflammation markers with low levels of O_3 in the air during moderate exercise in a group of amateur runners. The predominance of this phenomenon occurred during the spring and summer seasons in comparison to the winter season. Both seasons are characterized by a higher production/concentration of ozone in the environment due to a higher level of ultraviolet radiation. The effect of the time of exposure to O_3 was also addressed by Aris et al. [60], who observed an increase in polymorphonuclear leukocytes (PMNs or neutrophils) 18 h after exposing healthy subjects and athletes to 0.20 ppm of O_3 during 4 h of moderate exercise. A study conducted by Gomes et al. (2011) showed a lung inflammatory/oxidative effect in subjects who ran 8 km in a hot environment (31 °C) with increased levels of O_3, but this was not the case in a cold environment (20 °C); nevertheless, no changes in lung function were observed in any environment [61]. This suggests that O_3 has a high capacity to promote inflammation and damage in the respiratory epithelium, affecting lung function, even more so when intense and long-term exercise is done. Other environmental factors, such as ambient temperature, must also be considered.

In the case of particulate matter, exposure to larger particles, such as PM_{10}, has also shown lung inflammatory effects [62,63]. However, the main target structures of the smallest particles ($PM_{2.5}$ and UFPs) will be the pulmonary vascular and cardiovascular components [64,65]. Some inflammatory responses against contamination are the infiltration of PMNs and macrophages that release proteases with degradative and pro-oxidant activity, favoring cell damage [9,11,66]. Depending on the degree of exposure, this phenomenon can occur on multiple occasions, and can even become a chronic process [39], similar to that seen in subjects who smoke [67]. In this way, it is necessary to detail these processes when exercising during exposure to a polluted environment. Ghio et al. [68] observed an increase in PMNs in the bronchial and alveolar fractions of bronchoalveolar lavage (BAL) after 1 h of intermittent light exercise in an environment with PM_{10} (23.1–311 $\mu g/m^3$) and $PM_{2.5}$ (47.2–206.7 $\mu g/m^3$). Larsson et al. [69], 14 h later, observed increases in alveolar macrophages and lymphocytes in BAL after one hour of light exercise in an environment with PM_{10} and $PM_{2.5}$. In asthmatics, Pietropaoli et al. [70] found increased macrophages in induced sputum when they performed two hours of intermittent exercise in an environment with ultrafine particulate matter (10 $\mu g/m^3$), unlike healthy subjects (10, 25, and 50 $\mu g/m^3$). A recent study highlighted the effect of outdoor endurance training as an immune protection factor against exposure to particulate matter by controlling lung inflammation in this group, but not in exposed sedentary subjects [71]. This reinforces the importance of controlling air quality, the type of exercise, and the level of physical condition in order to take advantage of its benefits and thus avoid the deleterious effects of pollution. Cavalcante de Sá et al. [31] observed higher pH values in the exhaled condensed air of athletes who ran (45 min/day for five days) in an unpolluted environment versus athletes who ran in a polluted environment with high $PM_{2.5}$. Some studies have focused on the pro-inflammatory effects of NO_2 [56,72,73]. Jorres et al. [53] found increases in pro-inflammatory mediators in BAL in asthmatics, but not in healthy subjects, after 1.5 h of exercising and 3 h of exposure to NO_2 (1 ppm). Devlin et al. [74] showed that light/moderate exercise for two hours at a concentration of 2 ppm of NO_2 increased the levels of PMNs, IL–6, and IL–8 in BAL after 24 h. The action of pro-oxidants released directly by PMNs or produced secondarily from reactions involving metals contained in particulate matter are a challenge for enzymatic (catalase, superoxide dismutase, and glutathione peroxidase) and non-enzymatic (glutathione, vitamins C, vitamin E, and uric acid) lung antioxidant defenses. If they are overcome by pro-oxidants, an imbalance called oxidative stress is established, causing damage to structural molecules, in which lipoperoxidation is the most studied phenomenon. The association between oxidative damage and the modification of lung function has previously been described and confirmed by observing the negative correlations between plasma lipoperoxidation and glutathione, each with

FEV_1, as well as the positive correlations between the activity of the enzyme glutathione peroxidase and FEV_1 [75]. Therefore, it is possible to think of a potential benefit on lung function in subjects exposed to polluted air [76–78] with the consumption of antioxidants in the diet (β-carotene, vitamins C and E), for example, through the consumption of fresh fruits and vegetables [79].

4. Recommendations to Consider When Prescribing Exercise in Areas with Low Air Quality

Our biological design requires us to perform physical activity to stay healthy. Thus, the study of physical exercise has been the concern of researchers from the most diverse disciplines of knowledge. In this regard, one of the most relevant results, which is derived from research in this area, indicates that low levels of physical activity are associated with obesity, metabolic diseases, cancer, cardiovascular diseases, stress, anxiety, and depression [80–83]. In addition, low levels of physical activity have an impact on the quality of life of the population [84,85], and may be the cause of economic losses [86]. Hence, countries should promote exercise, but they should also be responsible for ensuring that it is done in a safe environment. Exercising with polluted air will be a problem for the foreseeable future, particularly since the concentration of pollutants in the air in many cities in developing countries will continue to be high. Hence, it is important for health personnel and the general population to be aware of the effects of pollution on the lungs, and to know both the guidelines regarding potential preventive measures and the status of issues that are not yet resolved in the research arena. In relation to prevention matters, one of the first pillars of the exercise/polluted air interaction consists of efforts to reduce air pollution. Firstly, we must think that the result of a high concentration of pollutants is a multifactorial outcome, thus, it depends on geographical factors (location and design of urban centers), environmental factors (temperature, humidity, luminosity), and derivatives of human activity (population growth, energy matrix used in industry/means of transport). Regarding these determinants, there are few factors that can be changed in the short term; however, both state and private organizations can devise plans for the re-evaluation of air quality and emission standards. At the same time, programs of general environmental education focused on air quality can be created. One measure with a direct impact on those who exercise under these conditions is to reduce the load of pollutants they are exposed to. To address this objective, it is necessary to favor access to air quality information by establishing monitoring points in cities where there are none, and by increasing their number in cities where they already exist. In addition, it will be advantageous to increase the number of mobile stations at training points and during sporting events, such as massive urban races. Along this line, there is a challenge for technological innovation in order to reduce the size and costs of the monitoring units, or, ideally, for them to be individual devices. The information obtained from the monitoring should also be integrated into applications for smartphones that can suggest routes with better air quality at the time of exercising. In the same direction, the development of new technologies focused on physical measures to reduce the entry of pollutants into the airway is pending [87]. In this regard, the greater social tolerance to the use of masks in times of the COVID-19 pandemic must be an advantage [88]. Finally, the identification of pollutants that are typical of indoor sporting environments should be improved by promoting measures to transform them into healthy environments and by using technology for the development and installation of filters in these places [89].

Regarding the biological phenomena of this problem, from our review, we conclude that it is necessary to increase the number of studies conducted on humans in relation to the acute effect of exposure to polluted air, and particularly in relation to chronic changes, where the information is practically nil. Likewise, the most solid information on biological effects refers to the action of individual pollutants, and progress must be made in the study of the interaction between pollutants and the influence of environmental conditions, such as humidity and temperature. The above objective is essential to optimize current models of inhalation load exposure [90,91] and the recommendations arising from it in the future.

Another pending task in research is to improve and establish biological monitoring, which should be done by optimizing non-invasive methods (spirometric tests, analysis of expired air, and sputum analysis) and in ideal conditions carried out by the users themselves. One of the objectives of this biological monitoring is the monitoring of at-risk populations (patients with chronic lung diseases, professional athletes, urban long-distance runners or cyclists) and to carry out preventive interventions in these populations. Once these groups have been identified, targeted environmental education programs should be carried out. Another relevant aspect both for this group and for the general population is to optimize exercise planning and to be flexible regarding the time and place it will be done and its intensity, balancing this programming with the health objectives of the general population and competitive athletes. Finally, from the studies regarding the damage mechanisms, the dietary and pharmacological recommendations are alternative solutions, among which the maintenance of a healthy diet with an important content of antioxidants (fruits and vegetables) is noted, as well as the search for new strategies to complement these substances, since evidence has not shown any effectiveness in lung diseases [92]. From the perspective of pharmacological agents, the production and administration of anti-inflammatory agents focused on airway epithelial damage should be studied (a summary of the topics discussed in this chapter is presented in Figure 2).

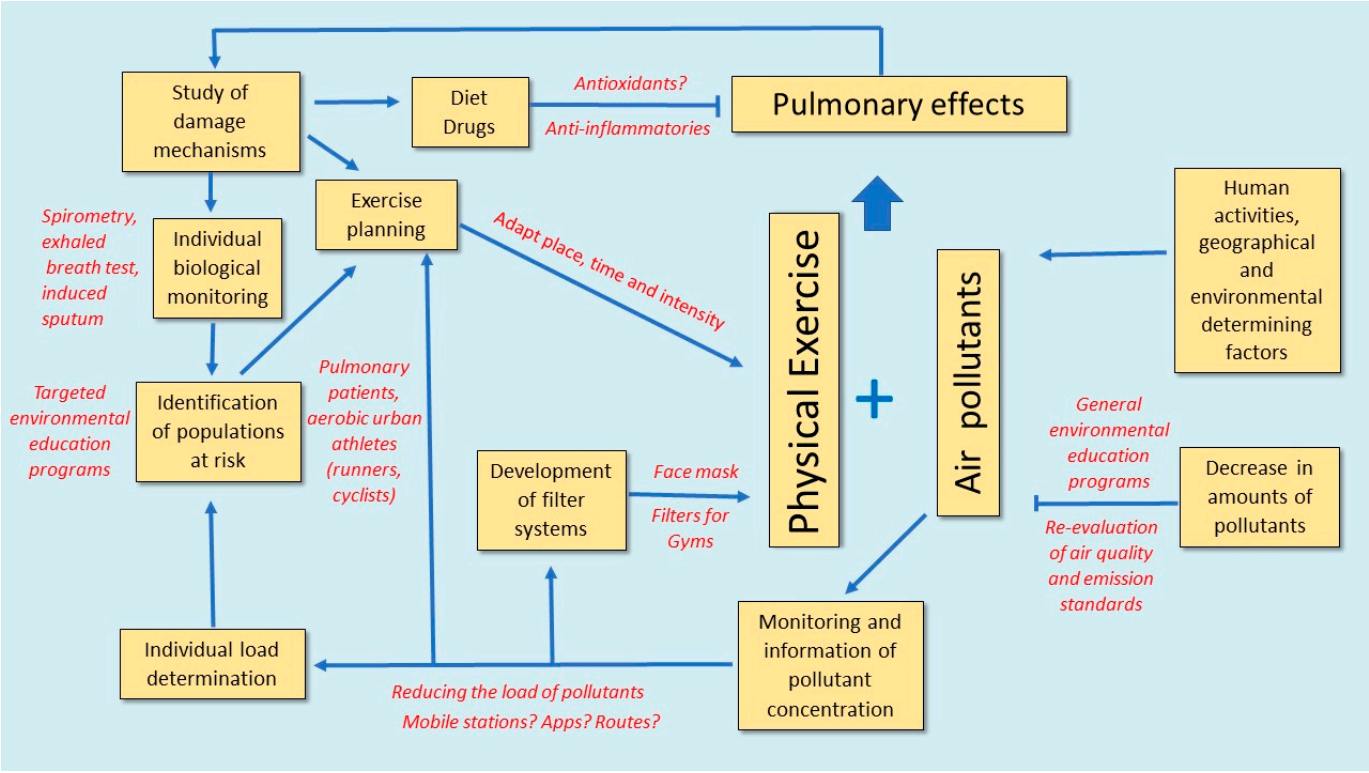

Figure 2. Overview of future goals and strategies to optimize the performance of exercise in polluted conditions.

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