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Environmental air pollution: respiratory effects

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ABSTRACT

Environmental air pollution is a major risk factor for morbidity and mortality worldwide. Environmental air pollution has a direct impact on human health, being responsible for an increase in the incidence of and number of deaths due to cardiopulmonary, neoplastic, and metabolic diseases; it also contributes to global warming and the consequent climate change associated with extreme events and environmental imbalances. In this review, we present articles that show the impact that exposure to different sources and types of air pollutants has on the respiratory system; we present the acute effects—such as increases in symptoms and in the number of emergency room visits, hospitalizations, and deaths—and the chronic effects—such as increases in the incidence of asthma, COPD, and lung cancer, as well as a rapid decline in lung function. The effects of air pollution in more susceptible populations and the effects associated with physical exercise in polluted environments are also presented and discussed. Finally, we present the major studies on the subject conducted in Brazil. Health care and disease prevention services should be aware of this important risk factor in order to counsel more susceptible individuals about protective measures that can facilitate their treatment, as well as promoting the adoption of environmental measures that contribute to the reduction of such emissions.

Keywords: Air pollution; Particulate matter; Respiratory tract diseases; Pulmonary disease, chronic obstructive; Asthma; Respiratory tract infections; Lung neoplasms.

INTRODUCTION

A major problem in the world today is air pollution, not only because of its impact on climate change but also because of its impact on public and individual health, being an important risk factor for increased morbidity and mortality.

Although exposure to air pollution has records that date back more than 20 centuries ago, until the well-known episodes of a sudden increase in pollutants that occurred in the Meuse Valley (Belgium, 1930), in Donora (Pennsylvania, USA, 1948), and above all in London (United Kingdom, 1952), studies on the effects of exposure to air pollutants were restricted to work environments and to exposure to toxic agents used in wars.(1) It was only from the mid-20th century onward that the subject began to be studied more and more,(2) with the first document on the effects of air pollution on health, prepared by the WHO and published in 1958, recommending that pollutant levels be reduced for health protection.(3,4)

Air pollution is estimated to have been responsible for approximately 5 million deaths worldwide in 2017, 70% of which being caused by outdoor environmental air pollution. Environmental and household air pollution jointly rank fifth among the five leading risk factors for death worldwide (Table 1).(5)

AIR POLLUTION AND ITS MAJOR SOURCES

The majority of emissions of pollutants are a result of human activity. Currently, the main sources of pollution in urban areas are motor vehicles and industries.(6) In some countries, including Brazil, the main source of environmental pollution originating from non-urban areas is the burning of biomass (sugarcane fields, pastures, savanna, and forests). Natural emissions, such as those from dust storms in large desert areas, those from accidental fires, and nitrogen oxides (NO_x) emissions from lightning, may contribute secondarily to the generation of air pollutants.(6,7)

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Pollutants are classified as either primary or secondary. Primary pollutants are those emitted directly into the atmosphere by industries, thermoelectric power plants, and motor vehicles powered by fuels. Primary pollutants include sulfur dioxide (SO_2); nitrogen oxides (NO_x: NO and NO_2); particulate matter (PM)—total suspended particles less than 10 µm in aerodynamic diameter (PM_{10}) and less than 2.5 µm in aerodynamic diameter ($PM_{2.5}$)—; and carbon monoxide (CO). In some countries, volatile organic compounds (VOCs) and metals are also monitored. Fine and ultrafine particles, since they have a higher surface/mass ratio and can be transferred to the systemic circulation, have a more marked effect.[8] Secondary pollutants are those formed from chemical reactions induced by NO_x-catalyzed photochemical oxidation of VOCs, which, in the presence of ultraviolet rays from sunlight, give rise to ozone.[9] Other secondary pollutants are formed through a process of nucleation and condensation of gaseous pollutants (NO_2 and SO_2) and acid mists, such as NO_x and secondary PM, formed by sulfates and nitrates.[1,7,10]

Exposure to air pollution varies widely across countries, regions, cities, and households. A study based on 2017 data estimates that 42% of people were exposed to fine PM ($PM_{2.5}$) above concentrations considered to be of minimal risk and 43% of those people were exposed to ozone worldwide.[5]

IMPACT ON HEALTH

Globally, most deaths and years of life lost due to premature death or lived with disability (disability-adjusted life years) that are secondary to air pollution exposure are a result of cardiopulmonary disease, lung cancer, or type 2 diabetes (Table 2).[5] A study using a novel approach[11] reported values that were higher than those calculated by the Global Burden of Disease (GBD) models[12]: an estimated 8.8 million deaths globally in 2015[11] versus 4.24 million.[12] In addition, the loss of life expectancy was reported to be 2.9 years worldwide in 2015.[13] In two of the aforementioned studies, the number of environmental air pollution-related deaths in 2015 in Brazil was estimated to be 52,300[12] and 102,000,[11] environmental air pollution being the ninth leading risk factor for mortality.[12]

Why and how air pollution has an impact on health: mechanisms involved in respiratory effects

The damage caused by particulate and gaseous pollutants depends on the inhaled concentration of

Table 1. Major risk factors for, and their impact on, morbidity and mortality worldwide in 2017 according to the Global Burden of Disease 2017 Risk Factor Collaborators.[5]

Risk factors	Deaths × 1,000 (95% CI)	DALYs × 1,000 (95% CI)	Global ranking
Diet (all causes)	10,900 (10,100-11,700)	255,000 (234,000-274,000)	1
Hypertension	10,400 (9,400-11,500)	218,000 (198,000-237,000)	2
Smoking (active + environmental + smokeless)	8,100 (7,800-8,420)	213,000 (201,000-227,000)	3
Elevated fasting blood glucose levels	6,530 (5,230-8,230)	171,000 (144,000-201,000)	4
Air pollution (total)	4,900 (4,400-5,400)	147,000 (132,000-162,000)	5
Environmental air pollution ($PM_{2.5}$)	2,940 (2,500-3,360)	83,000 (71,400-94,300)	
Environmental air pollution (ozone)	472 (177-768)	7,370 (2,740-12,000)	
Household air pollution	1,640 (1,400-1,930)	59,500 (50,800-68,900)	

$PM_{2.5}$: fine particulate matter < 2.5 µm in aerodynamic diameter; DALYs: disability-adjusted life years (the sum of the number of years of life lost due to premature death and the number of years lived with limitation/disability). In air pollution-related deaths and air pollution-related DALYs, the sum of the separate impacts of the pollutants is slightly higher than the sum of their combined impact.

Table 2. Estimates of deaths and disease burden associated with air pollution: global data for 2017 according to the Global Burden of Disease 2017 Risk Factor Collaborators.[5]

Pollutants and diseases	Environmental air pollution: $PM_{2.5}$		Household air pollution	
	Deaths × 1,000 (95% CI)	DALYs × 1,000 (95% CI)	Deaths × 1,000 (95% CI)	DALYs × 1,000 (95% CI)
COPD[a]	1,105 (583-1,606)	23,070 (13,040-32,800)	362 (248-482)	9,370 (6,480-12,400)
Ischemic heart disease	977 (839-1,120)	21,900 (18,900-25,400)	410 (344- 490)	10,200 (8,450-12,100)
Ischemic brain disease	445 (343-552)	10,510 (8,189-13,020)	231 (178-293)	5,761 (4,493-7,417)
Respiratory infections	433 (343-527)	18,500 (14,400-23,400)	459 (367-552)	25,900 (20,300-31,300)
Lung cancer	265 (183-351)	5,860 (4,050-7,730)	85 (60-113)	1,990 (1,410-2,640)
Type 2 diabetes	184 (123-227)	10,500 (6,700-13,900)	92 (63-113)	4,750 (3,110-6,190)
Cataracts	-	-	-	1,440 (732-2,250)
Total	3,412 (2,677-4,168)	147,000 (132,000-162,000)	1,640 (1,400-1,930)	59,500 (50,800-68,900)

$PM_{2.5}$: fine particulate matter < 2.5 µm in aerodynamic diameter; DALYs: disability-adjusted life years (the sum of the number of years of life lost due to premature death and the number of years lived with limitation/disability). [a]Ozone was responsible for 472,000 (95% CI: 177,000 to 768,000) deaths and 7.37 million (95% CI: 2.74 to 12.00 million) DALYs.

such pollutants, the defenses of the respiratory system, and the solubility of gaseous pollutants. The possible mechanisms involved in cardiorespiratory effects include inflammation and oxidative stress induced by reactive oxygen and nitrogen species (RONS) generated by inhaled pollutants.[14,15] Recent studies suggest a relevant role for inhaled environmentally persistent free radicals (EPFR) produced by combustion of catechols, phenols, and hydroquinones, which can remain in the air for up to 21 days.[16]

Chronic or acute inhalation of PM, O_3, and EPFR generates RONS, which trigger an inflammatory process and amplify it through the endogenous production of more RONS. If RONS production overcomes antioxidant defenses, there is activation of the mitogen-activated protein kinase (MAPK) complex, involved in the activation of nuclear transcription factors, such as NF-κB and AP-1, which stimulate the synthesis of RNA and the production of pro-inflammatory cytokines IL-8 and TNF-α, possibly inducing the formation of DNA adducts.[14,17] Air pollution has also been associated with epigenetic effects that, although potentially reversible without the occurrence of mutations, can produce changes in DNA expression, potentiating the inflammatory effects of pollutants.[8]

Air pollution has also been associated with reduced function of regulatory T lymphocytes, increased IgE levels, and increased production of CD4+ and CD8+ T lymphocytes, along with a greater Th2 response to stimuli by antigens in polluted environments, which would be associated with diseases such as rhinitis and asthma.[6,8]

Air pollution: respiratory effects

Air pollution is associated with various health effects, in addition to respiratory effects (Figure 1). Acute respiratory effects are those associated with recent exposure (hours or days), whereas chronic ones are a result of prolonged exposure, usually longer than 6 months.

With regard to acute effects, there is a consistent association between increased pollutant levels and increased numbers of emergency room visits, hospitalizations, and deaths, especially among

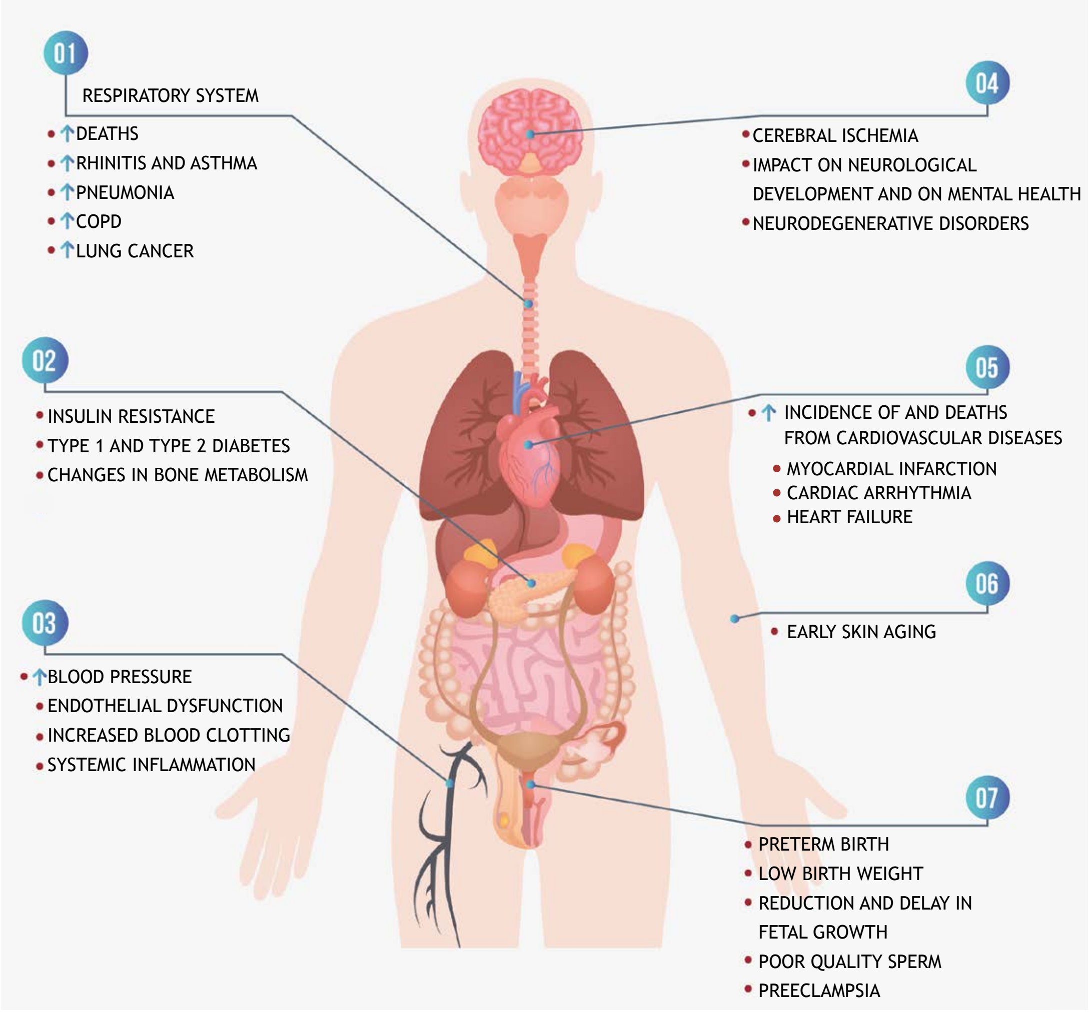

Figure 1. A representation of diseases and changes associated with air pollution. Adapted from Peters et al.[26]

individuals with chronic respiratory diseases, children, and elderly individuals.[18] A study involving 112 cities in the USA found a 1.68% increase in mortality due to respiratory disease for every 10 μg/m^3 increase in $PM_{2.5}$ concentration.[19] A systematic review and meta-analysis of 110 time-series studies conducted in several regions of the world revealed a 1.51% increase in mortality from respiratory diseases for every 10 μg/m^3 increase in $PM_{2.5}$ concentration.[20] In addition, a study conducted in Latin America[21] revealed a 2% increase in the risk of mortality from respiratory and cardiovascular diseases for every 10 μg/m^3 increase in $PM_{2.5}$ concentration, which is in line with the findings of studies conducted in Europe and North America.

The effects of chronic exposure have been associated with increased overall mortality from respiratory diseases, increased incidence of asthma and COPD, increased incidence of and mortality from lung cancer, reduced lung function, and a deficit in lung development during childhood.[22,23] One of the first studies on the subject, conducted in six major cities in the USA, revealed that the risk of death from cardiopulmonary diseases was 26% higher among individuals living in more polluted cities than among those living in less polluted cities.[24] These findings have been confirmed in other studies, including a prospective study involving 500,000 adults from all 50 U.S. states that revealed 9% and 18% increases in the risk of mortality from cardiopulmonary diseases and lung cancer, respectively, that were associated with a 10-μg/m^3 increase in $PM_{2.5}$ concentration.[25]

Pollution and rhinitis

A growing number of studies show an association between environmental air pollution and increased incidence and exacerbation of rhinitis. Authors suggest that genetic factors alone do not appear to be sufficient to justify the increase observed in the prevalence and exacerbation of allergic diseases, in particular, eczema, rhinitis and asthma. Exposure to PM_{10} and $PM_{2.5}$ appears as a factor that has a major impact in increasing the prevalence of these diseases, especially in children and adolescents.[6,27]

Pollution and asthma

Exposure to pollutants such as PM, NO_2, ozone, and carbon, as well as to motor vehicle traffic-related air pollution, is associated with a higher number of exacerbations, hospitalizations, and deaths in patients with asthma.[6,28,29]

One of the first studies evaluating the acute effects of air pollution, which involved 3,676 children from 12 locations in the state of California, USA,[30] showed that children with asthma who were exposed to NO_2, PM_{10}, and $PM_{2.5}$ had a higher prevalence of respiratory symptoms and a greater need for medication than did children without asthma. The most significant association was with exposure to NO_2, with a 2.7 times higher prevalence of symptoms for every 24 ppb increase in NO_2 concentration. A study conducted in Hubei province, China, with 4,454 individuals who died from asthma between 2013 and 2018 found increases of 7%, 9%, and 11% in mortality that were associated with $PM_{2.5}$, O_3, and NO_2, respectively.[31]

In recent years, studies have revealed that air pollution is also associated with an increased incidence of asthma, especially in children and adolescents,[6,23,32-34] with less robust data on adults.[35,36] One of the first prospective studies on the subject, also conducted in California, showed an association between chronic exposure to ozone and an increased incidence of asthma.[37] Another study evaluated the global incidence of air pollution-related asthma. For 2015, 4 milllion new cases of asthma (13% of global incidence) were estimated to be associated with exposure to NO_2 in children and young people under 18 years of age, 150,000 of which were in Brazil and Paraguay (aggregate data).[38] In adults, a study conducted in Australia showed that individuals exposed to NO_2 for at least 5 years and those living less than 200 m from a major road were at an increased risk of developing asthma and experiencing a marked decline in lung function.[39]

Pollution and COPD

Since the 1990s, epidemiological studies have shown an association between air pollution and acute respiratory events in individuals with COPD, with an increased number of exacerbations, emergency room visits, hospitalizations, and deaths.[40] One of the first studies on the subject, which evaluated hospitalizations secondary to COPD exacerbation that were associated with exposure to pollutants, found that, for every 10 μm/m^3 increase in PM_{10} concentration, there was a 2.5% increase in hospitalizations. A recent study[41] involving 303,887 individuals in the United Kingdom revealed that a 5 μg/m^3 increase in $PM_{2.5}$ concentration was associated with 83 mL and 62 mL reductions in FEV_1 and FVC, respectively, as well as with a 52% increase in COPD prevalence.

More recent studies suggest that exposure to pollutants is associated with an increased incidence of COPD.[23,41] A cohort study conducted in Norway involving 57,000 individuals found an 8% increase in COPD incidence that was associated with a 5.8 μg/m^3 increase in NO_2 concentration.[42] Another recently published cohort study,[43] involving 7,071 individuals in six U.S. metropolitan regions between 2000 and 2018, found an increased percentage of areas of pulmonary emphysema, as assessed by HRCT, that were associated with exposure to O_3, $PM_{2.5}$, NO_x, and carbon particles. A study analyzing 2017 data estimated that 1.1 million COPD deaths were attributable to air pollution worldwide,[5] representing 34.6% of all COPD deaths in that year.[44]

Pollution and lung function

In recent years, evidence has been accumulating on the effects of air pollution on lung function, confirming the findings of earlier studies.[45,46] The effects of air pollution appear to be more marked during the first years of life, including during the intrauterine period. Jedrychowski et al.[47] evaluated maternal exposure to $PM_{2.5}$ during the second trimester of pregnancy and found lower FEV_1 and FVC values (differences of 87 mL and 91 mL, respectively) at 5 years of age in children whose mothers had higher exposure to $PM_{2.5}$. In the city of Guangzhou, China, a study of highly polluted areas (an annual average PM_{10} concentration between 80 and 96 µg/m^3) showed that higher levels of pollution are associated with a reduction in the growth rate of $FEF_{25-75\%}$ and FEV_1 in boys.[48]

A prospective study[49] that followed children from age 10 to age 18 years in 12 cities in California found a reduction in the total growth of FEV_1 that was associated with $PM_{2.5}$, NO_2, acid vapor, and carbon particles. The proportion of young individuals who, at age 18 years, had an FEV_1 of less than 80% of the predicted value was 4.9 times higher (a prevalence of 7.9%) in the communities with the highest levels of $PM_{2.5}$ than in the communities with the lowest levels.

A study conducted in the city of São Paulo, Brazil, involving taxi drivers and traffic controllers revealed that exposure to high levels of $PM_{2.5}$ was associated with a nonsignificant reduction in FEV_1 and FVC, but there was a significant increase in $FEF_{25-75\%}$, suggesting possible interstitial changes due to exposure to polllutants.[50]

Pollution and respiratory infections

Exposure to air pollutants increases the risk of upper and lower airway infections. Exposure to PM was responsible for 433,000 deaths from respiratory infections globally in 2017, especially affecting children and elderly individuals.[5] A systematic review estimated a 12% increase in the risk of pneumonia in children for every annual average increase of 10 µg/m^3 in $PM_{2.5}$ concentration.[51] In line with this, a systematic review and meta-analysis using six European cohorts and involving 16,000 children showed an up to 30% increase in NO_2 exposure-related risk of pneumonia.[35]

Current studies suggest a possible contributing effect of air pollution on the spread of SARS-CoV-2 (COVID-19). A study conducted in Italy revealed that, in cities where the concentrations of air pollutants were higher before the epidemic, there was an accelerated spread of the virus, as well as a higher number of infected individuals, when compared with less polluted cities.[52,53] A recently published study that characterized, with the use of satellites, the global concentration of $PM_{2.5}$ and its anthropogenic fraction, estimated that exposure to PM would have contributed 15% (95% CI: 7-33%) to global COVID-19 mortality, being an important cofactor for increasing the risk of COVID-19 morbidity and mortality.[54,55]

Pollution and lung cancer

The International Agency for Research on Cancer considers environmental air pollution carcinogenic to humans, because it increases the risk of lung cancer.[56] Although a positive association has also been found between exposure to this type of pollution and bladder cancer, a causal relationship has yet to be established. According to global data,[5] an estimated 2.16 million new cases of lung cancer and 1.88 million lung cancer deaths occurred in 2017, lung cancer being the leading cause of cancer death among men and the third leading cause of cancer death among women. It is estimated that 14% (n = 265,000) of lung cancer deaths are attributable to environmental air pollution,[5] a proportion that ranges from 1% to 25% across countries. The mean risk for developing lung cancer ranges across studies from 20% to 30% for a 10 µg/m^3 increase in PM_{10} concentration and a 5 µg/m^3 increase in $PM_{2.5}$ concentration.[56,57]

Air pollution can induce genotoxic effects that include formation of DNA adducts, breaks in DNA strands, and damage to DNA bases due to oxidation, genetic mutations, chromosomal damage to somatic cells, gametic mutations, and oncogenic transformation. Molecular epidemiological studies in humans reveal associations between the frequencies of DNA damage (such as adducts in lymphocytes) and cytogenetic damage (such as chromosomal translocations and micronuclei) and exposures to PM and/or carcinogenic polycyclic aromatic hydrocarbons. Multiple proven effects lend plausibility to the association between air pollution and lung cancer development through a direct effect, as well as to tumor development via oxidative stress and persistent inflammation.[56]

Pollution and physical exercise

Low physical activity is an important risk factor for mortality and was associated with 1.26 million deaths in 2017. Regular mild- to moderate-intensity exercise contributes to reducing or delaying the onset of chronic diseases by up to 10 years.[58]

Exercising in air-polluted environments can have health consequences in susceptible populations, such as children, the elderly, and individuals with chronic diseases, as well as resulting in poorer physical performance in athletes.[59,60] A study conducted in communities with high ozone concentrations in California[61] found that the risk of developing asthma was 3.3 times higher in children playing three or more sports per week than in children playing no sports. Sports had no effect in cities with low ozone concentrations.

In healthy individuals, the respiratory effects of air pollution do not appear to be significant.[62] A study conducted in London, United Kingdom,[63] compared changes over time in lung function and sputum inflammatory markers in adults with asthma who walked for 2 h in a park and, on a separate occasion, along a busy traffic street. Participants with asthma showed a significant decline in lung function and an increase in inflammatory markers after walking along a busy traffic street.[63] A study with a similar design that compared healthy individuals, individuals with

COPD, and individuals with stable coronary disease revealed that, in all participants, walking for 2 h in a park led to an increase in lung function, an increase that was absent or reduced after walking along a busy traffic street.[59] Studies in humans[59] and studies using mathematical models[64,65] have shown that, for healthy individuals and even for individuals with chronic diseases, mild-to-moderate exercise in polluted environments, even where pollution levels are above the reference values recommended by the WHO,[7] has beneficial effects that override the effects of inhalation of an increased load of pollutants. Therefore, the balance of studies suggests that mild-to-moderate exercise is beneficial even in polluted places.[8,60,64,65]

Other pulmonary conditions

Recent studies have shown an association of exposure to air pollution with sleep apnea,[8] increased risk of bronchiolitis obliterans, increased risk of death in lung transplant recipients,[66] and increased risk of progression to interstitial lung disease.[67]

SUSCEPTIBLE/VULNERABLE POPULATIONS

Intrinsic and extrinsic factors increase the vulnerability and/or susceptibility of individuals to the adverse effects of air pollutants. In addition to age, having a preexisting chronic disease, such as asthma, COPD, pulmonary fibrosis, arrhythmias, hypertension, ischemic heart disease, diabetes, autoimmune diseases, and obesity, makes individuals more vulnerable.[8,68]

Individuals with poor socioeconomic status are most vulnerable, since they are likely to be exposed for longer periods on their way to work and tend to live closer to industrial areas. In addition, they live in overcrowded households, in areas without appropriate green spaces, and have diets poor in fruits and vegetables, which are rich in antioxidants.[8,68]

Pregnant women

Exposure to air pollutants during pregnancy can compromise fetal development and cause intrauterine growth restriction, prematurity, low birth weight, congenital anomalies, and intrauterine and perinatal death.[8,69]

Intense cell proliferation, physiological immaturity, accelerated organ development, and changes in metabolism increase the fetus' susceptibility to inhalation of air pollutants by the mother, and the mother in turn can have her respiratory system compromised by the action of pollutants, which can thereby affect the transport of oxygen and nutrients across the placenta. Exposure to high concentrations of PM is associated with placental inflammation, abnormal trophoblastic invasion, and decreased placental angiogenesis, impacting fetal development.[69]

Children

Worldwide, 93% of children live in environments in which air pollutant concentrations are above those recommended by the WHO.[70] The WHO estimates that one in every four deaths of children under 5 years of age is directly or indirectly related to environmental risks.[70] Global analyses for 2015 estimated the number of deaths from respiratory infections resulting from exposure to environmental air pollution among children aged 5 years or younger to be 727,000.[71] Children have higher minute ventilation and higher basal metabolic rates and engage in more physical activity than do adults, as well as spending more time outdoors.

The fact that children's immune system is not fully developed increases their susceptibility to respiratory infections.[8,70] Inside the womb, fetuses can be affected by pollutants inhaled by the mother, with can have health consequences in adulthood, such as an increased risk of asthma.[8,70,72]

Elderly individuals

The elderly population is growing because of increased life expectancy and steadily declining birth rates. In 2013, elderly individuals aged 80 years or older represented 14% of the world population.

Elderly individuals are susceptible to the adverse effects of exposure to air pollutants because they have a less efficient immune system (immunosenescence) and a progressive decline in lung function, which can lead to decreased exercise tolerance. Wu et al.,[73] in a study conducted in Beijing, China, observed a greater increase in hospitalizations for air pollution-related pneumonia in the elderly compared with younger age groups. A cohort study conducted in the USA[74] that used Medicare data showed that, between 2000 and 2012, acute exposures to fine PM and ozone during the warmest seasons of the year (spring and summer) were associated with an increased risk of all-cause mortality among elderly individuals. The same effect was observed even on days with concentrations below the air quality limits set by the U.S. Environmental Protection Agency.

Genetic susceptibility

The production of free radicals and the induction of inflammatory response by pollutants in the respiratory system can be neutralized by the antioxidant agents present in the aqueous layer lining the respiratory epithelium—glutathione S-transferase (GST), superoxide dismutase, catalase, tocopherol, ascorbic acid, and uric acid—which can prevent oxidative stress and represent the first line of defense against the adverse effects of pollutants. Polymorphisms in genes responsible for controlling oxidative stress (*NQO1*, *GSTM1*, and *GSTP1*) and in inflammatory genes (*TNF*) alter the presence and intensity of respiratory symptoms and change lung function and the risk of developing asthma in response to pollutants.[75]

Of the antioxidant agents present in the respiratory epithelium, the GST family is considered one of the most important, being represented by three major classes of enzymes: GSTM1; GSTP1; and GSTT1.[76]

Polymorphisms in genes encoding the enzymes of the GST family can change the expression or function of these enzymes in the lung tissue, resulting in different responses to inflammation and oxidative stress and, consequently, in increased susceptibility to the adverse effects of air pollutants.[76] A study conducted by Prado et al.[77] found a marked loss of lung function in sugarcane workers exposed to air pollution who had deletions in the *GSTM1* and *GSTT1* genes.

Studies have also revealed the epigenetic effect of exposure to PM, an effect that can override genetic susceptibility. Altered epigenetic regulation of white blood cells and various other tissue cells, especially PM-induced changes in DNA methylation, appears to contribute to the health effects associated with air pollution.[23]

BRAZIL: RELEVANT STUDIES ON THE EFFECTS OF AIR POLLUTION

Since the late 1970s, the effects of air pollutants, from both vehicular and industrial sources and from biomass burning, have been systematically studied in Brazil.

Air pollution from fossil fuel burning

Over the past 30 years, 170 studies on the subject conducted in Brazil have been published. From 1975 onward, the Air Pollution Experimental Laboratory of the University of São Paulo School of Medicine Department of Pathology, in the city of São Paulo, located in the state of São Paulo, Brazil, carried out experimental and epidemiological studies to assess the adverse effects of exposure to air pollutants. The first study exposed rats to the environmental air in the city of São Paulo and to the environmental air in the city of Atibaia, also located in the state of São Paulo and where the air, at the time, was considered cleaner. After 6 months of exposure, there were changes in mucus rheological properties, destruction of cilia, and, consequently, increased bacterial colonization of the respiratory epithelium, all of which led to the death of 50% of the rats exposed to the air in the city of São Paulo.[78] In parallel, using models from ecological time series studies, another study showed that daily increases in NO_x concentration were associated with increased mortality from respiratory diseases in children aged 5 years or younger in the city of São Paulo.[79] Another study by the group showed that lung autopsy samples from residents of the city of Guarulhos, located in the state of São Paulo and where pollution levels were high at the time of the study, presented more evidence of histopathologic damage than did those from residents of the cities of Ourinhos and Ribeirão Preto, also located in the state of São Paulo but where pollution levels were lower, even after controlling for smoking.[80]

In another study, mice were exposed to different concentrations of inhaled fine PM, and even those exposed to low concentrations showed oxidative stress, inflammation, and lung tissue damage.[81]

Ecological time series studies have shown associations between increased emergency room visits in children with respiratory diseases and increased air pollution[82]; between increased hospitalizations for respiratory diseases in children and adolescents and increased concentrations of PM_{10} and SO_2[83]; and between increased emergency room visits due to pneumonia and influenza,[84] as well as due to asthma and COPD[85,86] in adults and increased air pollution.

A study conducted on workers exposed to environmental air pollution in the city of São Paulo, located in the state of São Paulo, Brazil, revealed that, those with the highest level of exposure had a reduction in FVC compared with those with the lowest level of exposure.[50] Chart 1 summarizes the major studies on the respiratory impact of urban air pollution conducted in Brazil.

Air pollution from biomass burning

Over the past 20 years, studies conducted in Brazil have assessed the impacts that forest fires (especially in the Brazilian Amazon) and pre-harvest sugarcane burning (especially in the state of São Paulo) have on the health of the exposed population (Chart 2).

Studies conducted in urban areas located in sugarcane producing regions in the state of São Paulo have shown that, during the sugarcane burning season, there were increases in emergency room visits for inhalation therapy[87] and for pneumonia,[88] as well as an increase in hospitalizations of children and elderly individuals for all respiratory diseases,[89] specifically for asthma.[90] In Monte Aprazível, a town in the state of São Paulo, rhinitis prevalence increased and lung function decreased in children during the sugarcane burning season.[91] Another study revealed that, during manual harvesting of burnt cane, workers had exacerbated respiratory symptoms, reduced lung function, reduced antioxidant enzyme activity, and increased oxidative stress markers.[77] In another group of sugarcane workers, it was found that, during the sugarcane burning season, there were changes in mucus properties and impairment of nasal mucociliary clearance.[92]

Emissions from fires in the Amazon region can be transported long distances and, in addition to affecting the global climate,[93] can impact the health of children and the elderly.[94,95] Studies conducted in the state of Mato Grosso have shown that increased exposure to PM contributed to increased hospitalizations of children less than 5 years of age due to respiratory diseases[96] and to acute decreases in PEF.[97]

In an experimental study in mice, animals received repeated intranasal instillation of PM from different sources, and PM from biomass burning were found to be more toxic than PM from vehicular traffic.[98]

FINAL CONSIDERATIONS

Environmental air pollution affects billions of people every day worldwide, having a major impact on

Chart 1. Major studies on air pollution, predominantly from vehicular and industrial sources, and respiratory diseases conducted in Brazil.

Authors	Population and setting	Outcome	Exposure	Results
Sobral[(100)]	Children in the city of São Paulo, located in the state of São Paulo	Respiratory diseases	Air pollution	Increased respiratory diseases in more polluted areas
Saldiva et al.[(78)]	Rats in the cities of São Paulo and Atibaia, both located in the state of São Paulo	Changes in the mucociliary system	Environmental air in the two cities	Changes in the mucus and cilia and increased mortality from respiratory diseases in the city of São Paulo
Saldiva et al.[(79)]	Children aged 5 years or younger in the city of São Paulo	Mortality from respiratory diseases	Measured primary pollutants	An association between NOx and increased mortality
Saldiva et al.[(101)]	Elderly individuals > 65 years old in the greater metropolitan area of São Paulo	Mortality from respiratory diseases	PM_{10}, NO_x, SO_2, and CO	Increased deaths associated with increased air pollutant levels
Souza et al.[(80)]	Autopsy in individuals who died a violent death. Smokers in the city of Ourinhos (mean, 31 years) and nonsmokers in the city of Guarulhos (mean, 26 years), both located in the state of São Paulo	Lung histopathologic changes	Tobacco and air pollution	Comparison of lung injury between nonsmokers in the more polluted city (Guarulhos) and smokers in the less polluted city (Ourinhos)
Lin et al.[(82)]	Children and adolescents in the city São Paulo	Emergency room visits	Measured air pollutants	Increased visits associated with PM_{10} and O_3
Braga et al.[(83)]	Children aged 12 years or younger in the city of São Paulo	Hospitalizations for respiratory diseases	PM_{10}, SO_2, NO_2, CO, and O_3	An association between hospitalization and air pollutants
Braga et al.[(102)]	Individuals aged 19 years or younger in the city of São Paulo	Hospitalizations for respiratory diseases	PM_{10}, SO_2, NO_2, CO, and O_3	An increased risk in children ≤ 2 years and adolescents aged 14 to 19 years
Conceição et al.[(103)]	Children aged 5 years or younger in the city of São Paulo	Mortality from respiratory diseases	Primary and secondary pollutants	A mortality increase associated with increases in CO, SO_2, and PM_{10}
Martins et al.[(104)]	Elderly individuals in the city of São Paulo	Mortality from respiratory diseases	Primary and secondary pollutants	An association between PM_{10} and increased numbers of deaths; more deaths in those with a lower socioeconomic status
Mauad et al.[(105)]	Mice in the city of São Paulo	Lung development	Air pollution	Exposure to PM and decreases in inspiratory and expiratory lung volumes
Arbex et al.[(86)]	Adults and elderly individuals in the city of São Paulo	Emergency room visits	Air pollutants	Increased visits by elderly individuals and women
Riva et al.[(81)]	Mice (an experimental study)	Inflammatory changes in the lung	Inhaled fine PM	Low concentrations of $PM_{2.5}$ induce oxidative stress and inflammation in the lung.
Santos et al.[(50)]	Workers exposed to environmental air pollution	Lung function	Individual exposure to $PM_{2.5}$	Reduced FVC and increased $FEF_{25\text{-}75\%}$
Gouveia et al.[(106)]	Individuals of all ages and children less than 5 years old	Hospitalizations for respiratory diseases	PM_{10}	Increased hospitalizations in all age groups and in children less than 5 years old
de Barros Mendes Lopes et al.[(107)]	Mice: exposure during pregnancy and after birth (São Paulo)	Lung formation and growth	$PM_{2.5}$	Exposure leads to a reduced number of alveoli and impaired lung function in adult mice.

PM_{10}: particulate matter with an aerodynamic diameter less than 10 μm; $PM_{2.5}$: particulate matter with an aerodynamic diameter less than 2.5 μm; and NO_x: nitrogen oxides.

morbidity and mortality, as well as contributing to global warming.

The presence of chronic systemic diseases increases the susceptibility of individuals to the adverse effects of air pollutants, manifesting from mild forms of illness to death, which occurs in patients with increased susceptibility. Recent studies show that exposure to air pollutants can cause asthma, COPD, and lung

Chart 2. Major studies on air pollution, especially from biomass burning, and respiratory diseases conducted in Brazil.

Authors	Population and setting	Outcome	Exposure	Results
Arbex et al.[87]	Population in the city of Araraquara, located in the state of São Paulo	Use of medication by the population (inhalation therapy)	TSP	Increased visits for inhalation therapy during the sugarcane burning season
Cançado et al.[89]	Children and elderly individuals in the city of Piracicaba, located in the state of São Paulo	Hospitalization for respiratory disease	$PM_{2.5}$, PM_{10}	Increased hospitalizations on more polluted days; major effects during the sugarcane burning season
Arbex et al.[90]	Population in the city of Araraquara	Hospitalization for asthma	TSP	Increased hospitalizations on more polluted days and during the sugarcane burning season; a 50% increase in hospitalizations during the sugarcane burning season
do Carmo et al.[94]	Children and elderly individuals in Alta Floresta, a town in the state of Mato Grosso	Outpatient treatment for respiratory disease	$PM_{2.5}$ from forest burning	Increased visits by children but not by elderly individuals
Ignotti et al.[95]	Children and elderly individuals in microregions of the Brazilian Amazon	Hospitalization for respiratory disease	$PM_{2.5}$ > 80 µg/m^3	Increased hospitalizations in children and elderly individuals
Rodrigues et al.[108]	Elderly individuals in the Brazilian Amazon	Hospitalization for asthma	Dry season vs. wet season	Hospitalization rates are three times higher during the dry season than during the wet season.
Riguera et al.[91]	Schoolchildren aged 10 to 14 years in Monte Aprazível, a town in the state of São Paulo	Asthma and rhinitis symptoms, PEF	$PM_{2.5}$ and black carbon	Increased symptoms of asthma and rhinitis; a higher prevalence of rhinitis during the sugarcane burning season; decreased PEF
Goto et al.[92]	Sugarcane workers in Cerquilho, a town in the state of São Paulo	Mucociliary clearance	Sugarcane burning	Impaired clearance and changes in mucus properties
Prado et al.[77]	Sugarcane workers and residents of Mendonça, a town in the state of São Paulo	Lung function, respiratory symptoms, oxidative stress markers	Sugarcane burning	Reduced lung function, increased respiratory symptoms, and increased oxidative stress during the harvest season
Silva et al.[96]	Children and elderly individuals in the city of Cuiabá, located in the state of Mato Grosso	Hospitalization	$PM_{2.5}$	Increased hospitalizations in children but not in elderly individuals
Arbex et al.[88]	Population in the city of Araraquara	Emergency room visit for pneumonia	TSP	An increased effect of exposure during the sugarcane burning season
Jacobson et al.[97]	Schoolchildren aged 6 to 15 years in the city of Tangará da Serra, located in the state of Mato Grosso	Lung function	PM_{10} and $PM_{2.5}$	Decreases in PEF
Mazzoli-Rocha et al.[98]	Mice, cities of São Paulo and Araraquara, both located in the state of São Paulo	Lung resistance, lung elastance, and lung inflammation	Repeated instillation of PM	PM from sugarcane burning is more toxic than is PM from vehicular sources.
de Oliveira Alves et al.[109]	Lung cells, the Amazon region	Cell toxicity	PM during burning in the Amazon forest	Increased levels of reactive oxygen species, inflammatory cytokines, DNA damage, apoptosis, and necrosis

TSP: total suspended particles; PM_{10}: particulate matter with an aerodynamic diameter less than 10 µm; and $PM_{2.5}$: particulate matter with an aerodynamic diameter less than 2.5 µm.

cancer. Exposure of pregnant women to air pollutants has serious adverse effects on the fetus that, if not lethal, can result in compromised health in childhood, adolescence, adulthood, and old age. Regular physical exercise can contribute to minimizing the effects of air pollution.

The most effective measures for reducing the impact of air pollution on human health are those related to reducing emissions. Expansion of public transportation, the use of cleaner fuels in vehicles, industries, and households, as well as a change in building construction standards, which require a lot of energy, are feasible and necessary measures to reduce global warming and its direct effects on human health.[99] It is estimated that reducing emission levels to those recommended by the WHO and the Paris Agreement can lead to up to 60% decrease in pollution-related deaths annually.[11] In this context, physicians should be able to inform and advise the population about healthy eating habits, regular physical exercise, and chronic disease control. Physicians should also contribute to strengthening the necessary measures to reduce emissions in favor of environmental recovery. The current SARS-CoV-2 virus pandemic, which follows the SARS and MERS outbreaks in 2000 and 2012, respectively, shows that we cannot adopt a passive behavior regarding environmental imbalances caused by the way the planet is developed and occupied.

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