



REVIEW ARTICLE

Climate changes, air pollution and allergic diseases in childhood and adolescence



Marilyn Urrutia-Pereira ^a, Guillermo Guidos-Fogelbach ^b, Dirceu Solé ^{c,*}

^a Universidade Federal do Pampa, Departamento de Medicina, Pampa, RS, Brazil

^b Instituto Politécnico Nacional, Escuela Nacional de Medicina y Homeopatía, Postgraduate Department, Mexico City, Mexico

^c Universidade Federal de São Paulo, Escola Paulista de Medicina, Departamento de Pediatria, Divisão de Alergia, Imunologia Clínica e Reumatologia, São Paulo, SP, Brazil

Received 25 August 2021; accepted 8 October 2021

Available online 10 December 2021

KEYWORDS

Climate change;
Air pollution;
Asthma;
Allergic diseases;
Children;
Respiratory infections

Abstract

Objective: To analyze the impacts of climate change on the development of immature respiratory and immune systems in children.

Source of data: The authors of the present study performed a non-systematic review of English, Spanish, and Portuguese articles published in the last five years in databases such as PubMed, EMBASE, and SciELO. The terms used were air pollution OR climate changes OR smoke, AND children OR health.

Synthesis of data: The increase in the prevalence of some diseases, such as allergic ones, is attributed to the interactions between genetic potential and the environment. However, disordered growth combined with inadequate waste management has caused problems for the planet, such as heatwaves, droughts, forest fires, increased storms and floods, interference in food crops and their nutritional values, changes in the infectious disease pattern, and air pollution resulting from the continuous use of fossil fuels. Children, beings still in the development stage with immature respiratory and immune systems, are the primary victims of the climate crisis.

Conclusions: The authors documented that prenatal and postnatal exposure to ambient air pollutants will accelerate or worsen the morbidity and mortality of many health conditions, including allergic diseases. Ambient air pollutants change the microbiota, interfere with the immune response, and take direct action on the skin and respiratory epithelium, which facilitates the penetration of allergens. Understanding how the children and adolescent health and well-being are affected by climate change is an urgent matter.

© 2021 Sociedade Brasileira de Pediatria. Published by Elsevier Editora Ltda. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Study conducted at the Universidade Federal de São Paulo, São Paulo, SP, Brazil.

* Corresponding author.

E-mail: sole.dirceu@gmail.com (D. Solé).

Introduction

Climate change is one of the main concerns of humankind due to social, economic and health impacts on the

<https://doi.org/10.1016/j.jpmed.2021.10.005>

0021-7557/© 2021 Sociedade Brasileira de Pediatria. Published by Elsevier Editora Ltda. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

population.¹ Although air quality has improved in many regions in recent decades, levels of certain air pollutants still exceed those established by the World Health Organization (WHO) guidelines in most countries, 90% of people on Earth breathe polluted air.²

There is evidence that indicate an increase in the prevalence of some diseases, such as allergic ones, is attributed to the interactions between genetic potential and the environment. This review aimed to assess the relationship between exposure to climate change and pollution in the development and/or worsening of allergic diseases in children and adolescents.

Climate change and air pollution are closely related. The burning of fossil fuels is the main contributor to air pollution. Human activities and reliance on fossil fuels have led to increased concentrations of natural and anthropogenic greenhouse gas emissions. Climate change brings together heatwaves and drought, which facilitate forest fires, increased intensity of storms and floods, affecting crops and food quality, changes in the pattern of infectious diseases, and air pollution from the continuous use of fossil fuels. These changes can induce stress, mental problems, food-borne, water-borne, or vector-borne diseases, respiratory diseases, malnutrition, illnesses brought on by excessive heat poverty, and displacement.^{2,3}

Children, beings still in the development stage with immature respiratory, immune, and other systems, are the primary victims of the climate crisis.³ During the warmer season, they are generally exposed to higher temperatures for longer when playing outdoors, and because they are less able to maintain the ideal indoor temperature, they are at risk of experiencing thermal stress. As such, understanding how children and adolescent health and well-being could be affected by climate change is an urgent matter.⁴

It is impossible to predict the impact of climate change on future generations. However, the various adverse health outcomes from prenatal and postnatal exposure will likely have a combined effect that will accelerate or worsen morbidity and mortality of many health conditions, including allergic diseases.⁵

Environmental pollutants

Air pollutants can be classified as primary or secondary. Primary pollutants are emitted directly by sources such as CO, SO₂, and particulate matter (PM), while secondary pollutants form in the atmosphere due to chemical and physical reactions (O₃, NO₂, sulfates, and ultra-fine particulates).⁶ They can be classified as gaseous or PM, depending on their composition. O₃, nitrogen oxides (NO_x), CO, CO₂, volatile organic compounds (VOC), polycyclic aromatic hydrocarbons (PAH), and heavy metals are among the gaseous compounds.⁶

The PM (solid and liquid particles) can be subdivided by taking its aerodynamic diameter into account in: PM₁₀ (< 10 μm), PM_{2.5} (< 2.5 μm), and PM_{0.1} (ultra-fine particulates; < 0.1 μm).⁵ PM's gaseous compounds negatively affect the airways, and it has a significant impact on the respiratory system (Table 1).⁶

In the last decades, many countries have developed projects to reduce the emission of pollutants into the

atmosphere, where many of these have not been fulfilled or are in the early stages of implementation. As the case of developing countries that still need industrialization to grow are seeing air pollution levels increase. Thus, 80% of individuals living in urban areas are exposed to air pollution levels that exceed WHO guidelines.⁷ Table 2 shows the air quality standards in Brazil, according to the country's National Council for the Environment (CONAMA) – 2018.⁸

Household pollutants

The leading pollutants inside the home are released by burning solid fuels (SF) and tobacco smoke. It is thought that between 2.5 to 3 billion people in the world (about 50% of the world's population) and up to 90% of families living in rural areas use SF to cook, heat, and light their homes.⁹

Burning SF (biomass and coal) for heating and cooking is considered the dominant source of indoor air pollution in rural areas, a common practice given the lack of modern energy sources. The inefficient and incomplete burning of SF by using traditional methods (stoves and open fireplaces in environments without adequate ventilation) leads to higher levels of several pollutants: PAH, heavy metals, VOC, black carbon, PM, SO₂, CO, and NO.¹⁰ Incomplete SF combustion is one of the primary sources of intra-household PM and mainly releases fine and ultra-fine (<1 mm in diameter) particulates.¹⁰

Most cigarettes' basic components are tobacco, chemical additives, a filter, and paper packaging. Smokers are exposed to a toxic mixture of more than 7,000 chemicals and up of more than 60 known carcinogens compound when they inhale cigarette smoke (Table 3), and the United States Food and Drug Administration has listed 93 of them.¹¹

Besides the compounds found in tobacco leaves, artificial industrial additives are also incorporated to add flavor, reduce the irritation smoke causes in the respiratory tract, and enhance the effects of nicotine. Nicotine is considered a stimulant as it excites many brain cells. It is not as harmful as tar and CO, but it is addictive. The amount of nicotine varies depending on the cigarette, but the amount the smoker inhales is what matters. Smoking one cigarette results in the uptake of 1 to 2 mg of nicotine, which is reflected in mean arterial plasma concentrations of about 0.03 mg/L (30 ng/mL).¹¹

Health impact

Air pollutants exert their most harmful action on the respiratory system after inhalation. Both gaseous components (O₃, VOC, CO, and NO_x) and PM are well-established inflammatory stimuli to the mucosa of the respiratory tract. Depending on the aerodynamic diameter of PM, its action can occur at different points in the respiratory tract: PM₁₀ is deposited in the nasal cavity and central airways.

Exposure to air pollutants can increase the adaptive immune response of T helper type 2 (Th₂) and Th₁₇ lymphocytes as in asthma and disrupt the antiviral immune response.¹²

Table 1 Common air pollutants, sources, and health effects.^{5,6}

Pollutant	Source	Harmful Action
Particulate Matter PM	fuel burning ; (motor vehicles, marine vessels, aircraft, domestic heating, energy production, any other industrial burning – waste incineration, wood-burning stoves, and fireplaces) pollens and other bioaerosols ; traveling on dirt roads (mainly coarse particles); wind-dispersed dust (mainly coarse particles); surface tire abrasion (mainly coarse particles); construction work (mainly coarse particles); secondary formation by chemical reactions of fine particles	PM₁₀ – Trachea, bronchi, bronchioles PM_{2.5} – alveoli PM_{0.1} – Alveoli, lung tissue, blood Reduces mucociliary activity and alveolar macrophages Upper airway irritation Oxidative stress and pulmonary and systemic inflammation, Remodeling Chronic obstructive pulmonary disease, Can be carcinogenic
Gaseous Ozone (O₃)	not emitted directly from human resources ; arises from chemical reactions of volatile organic compounds in the atmospheric presence of sunlight	Trachea, bronchi, bronchioles, and alveoli Highly irritating photochemical oxidant Prolonged exposure injury, inflammation, and hyperreactivity
Nitrogen dioxide (NO₂)	thermal electricity generating stations ; motor vehicle exhaust ; other modes of transportation (airplanes, railways, maritime); ice resurfacing equipment, propane-powered forklifts ; gas stoves ; secondary formation by chemical reactions	Trachea, bronchi, bronchioles, and alveoli Irritant Affects mucosa, hyperreactivity, and greater susceptibility to infections
Sulfur dioxide (SO₂)	burning fuels containing sulfur (diesel); transportation (which burns residual fuel oil); sintering process used in powder metal casting	Trachea, bronchi, bronchioles, and alveoli Irritant Affects mucosa, hyperreactivity, and greater susceptibility to infections
Carbon monoxide (CO)	motor vehicle (especially during cold weather, in garages, and in traffic tunnels); home heating systems ; malfunctioning or poorly ventilated heating ovens ; wood-burning stoves ; ice resurfacing equipment	Alveoli, bloodstream Cell hypoxia cephalalgia associated with fetal death
Particulate and gaseous Air toxins (benzene, vinyl chloride, formaldehyde, mercury, arsenic)	fossil fuel combustion (motor vehicles); industrial process products/consumption activities (dry cleaning)	

Particle matter (PM)

The role of PM in understanding the damage of respiratory epithelial cells occurs via a toll-like receptor (TLR) 4 pattern recognition and/or TLR2 activation via NFκ-B signaling and NLRP3 inflammasome resulting in induced production of the pro-inflammatory mediators – interleukin (IL)-1a, IL-1b, IL-6, CXCL8, and colony-stimulating factor (GM-CSF).^{6,12} The PM_{10S} and PM_{2.5S} lead to the activation of the NLRP3 inflammasome via the production of reactive oxygen substances (ROS) and, consequently, alveolar macrophages, neutrophils, and dendritic cells.^{6,12} Once processed by dendritic cells, the antigens will be introduced to T lymphocytes and,

depending on co-stimulatory molecules released by dendritic cells, a Th₁- or Th₂-type immune response will be established. Thus, in short, PM will lead to airway inflammation (Figure 1).¹²

Additionally, exposure to fine particulate matter (PM_{2.5}) was linked to altered methylation of most CpG sites for the important immunoregulatory genes *FOXP3*, *IL-4*, *IL-10*, and *IFNγ*. Their dysregulation has a high potential to cause loss of epithelial barrier integrity, DNA damage, oxidative stress, mitochondrial damage, changes associated with pulmonary fibrosis.^{13,14} Exposure to PM, even subchronic, in mice leads to alterations in both the lung and intestinal microbiome (dysbiosis), leading to lung and intestine damage and

Table 2 Air quality standards in Brazil according to the National Environmental Council (CONAMA) – 2018.⁸

Air pollutant	Period of reference	Air quality reference standards				
		Intermediaries			Final	
		PI-1 mg/m ³	PI-2 mg/m ³	PI-3 mg/m ³	PF mg/m ³	ppm
PM ₁₀	24 hours	120	100	75	50	-
	Annual ^a	40	35	30	20	-
PM _{2.5}	24 hours	60	50	37	25	-
	Annual ^a	20	17	15	10	-
SO ₂	24 hours	125	50	30	20	-
	Annual ^a	40	30	20	-	-
NO ₂	1 hour ^b	260	240	220	200	-
	Annual ^a	60	50	45	40	-
O ₃	8 hours ^c	140	130	120	100	-
Smoke	24 hours	120	100	75	50	-
	Annual ^a	40	35	30	20	-
CO	8 hours ^c	-	-	-	-	9
TSP	24 hours	-	-	-	240	-
	Annual ^d	-	-	-	80	-
Pb ^e	Annual ^a	-	-	-	0,5	-

Ppm, part per million; PM₁₀, particulate matter with a diameter less than 10 μm; PM_{2.5}, particulate material with a diameter less than 2.5 μm; SO₂, sulfur dioxide; NO₂, nitrogen dioxide; O₃, ozone; CO, carbon monoxide; TSP, total suspended particles; Pb, lead.

^a Annual arithmetic mean.

^b Hourly average.

^c Maximum moving average obtained in the day.

^d Annual geometric mean.

^e Measured in TSP.

systemic inflammation impact the development of allergic disease over the lifespan.¹³⁻¹⁶

O₃ exposure's direct action on the respiratory epithelium induces the release of cytokines and arachidonic acid metabolites, the leukotrienes formed from the cyclooxygenase and lipoxygenase activity, which impairs mucociliary depuration and increases the production of free radicals.¹⁷

Climate change and microbiome

Climate change and environmental air pollution also determine changes in the environmental microbiota, which in turn is reflected in the infant's colonization and, consequently, in its microbiota: cutaneous, respiratory, intestinal, among others.¹⁸ This dysbiosis can be followed by significant

changes in the infant's immune system, such as altered TLR expressions, altered T-cell function, altered antiviral responses, and altered allergic sensitization.¹⁸ Many of these changes are believed to be due to epigenetic changes, acquired *in utero* and transmitted to subsequent offspring, and by co-exposure to allergenic and non-allergenic stimuli. The airway microbiota has acute and long-term effects on respiratory health, while the intestinal microbiota influences airway health indirectly through the gut-lung axis.¹⁸

The gastrointestinal tract can also be involved with air pollution, just like the respiratory and cardiovascular tracts, although there is controversy among researchers. Experimental studies with animals that received high doses of urban PM by gavage showed increased intestinal permeability due to loss of tight junctions between enterocytes, increased IL-6 expression, and apoptosis of colon epithelial cells. Prolonged exposure to PM₁₀, in addition to the previous alterations, determined alterations in the intestinal microbiota and in the homeostasis of fatty acids. Furthermore, PAHs, components of air pollutants, can significantly interfere in the balance between aryl hydrocarbon receptor (AhR) ligands derived from commensal bacteria in the gastrointestinal tract and from regulatory Th cells and epithelial Th₁₇,¹² a critical step for the onset of inflammatory bowel disease and food allergy.¹⁹

The action pollutants have on the cells of the immune system compromises the immune tolerance mechanisms and the antiviral and antibacterial defense mechanisms, making infections by respiratory agents more frequent (Table 4).¹²

Table 3 Main chemicals and chemical compounds identified as harmful and potentially harmful constituents in tobacco products and tobacco smoke.¹¹

Constituents	
Carbon monoxide	Arsenic
Hydrogen cyanide	Nickel
Benzene	Benzopyrene
Formaldehyde	Cadmium
Nicotine	Pesticide residues
Phenol	Acetone
Polycyclic hydrocarbons (PAHs)	Naphthalene
Tobacco-specific nitrosamines (TSNAs)	Phosphorus P4/P6

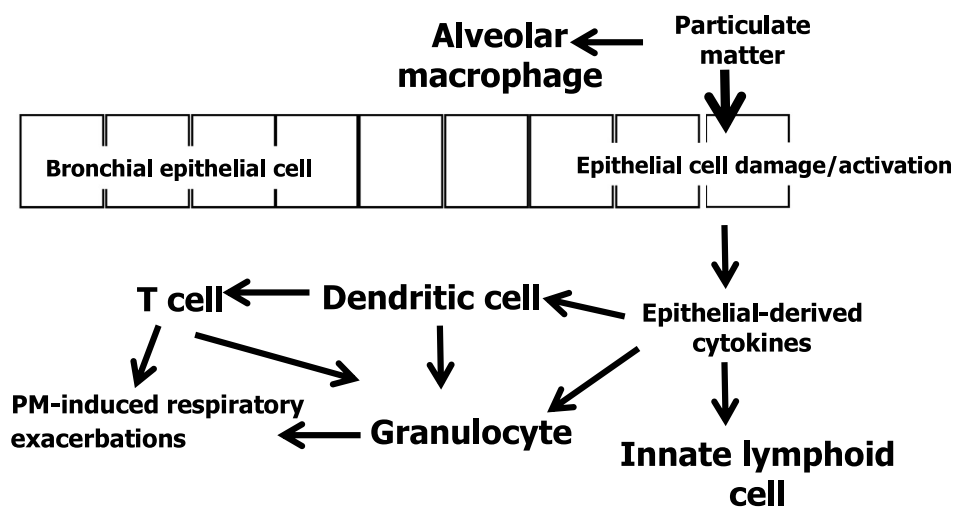


Figure 1 Interaction between particulate matter and immune system cells involved in respiratory tract homeostasis – Adapted from Glencross et al., 2020.¹²

Air Pollution and Respiratory or Allergic Diseases

Asthma

Genetic predisposition combined with environmental exposure to inhaled substances that affect the airways is the strongest risk factor for developing asthma. In recent years, robust epidemiological evidence has shown that air pollution not only affects patients with pre-existing asthma but can also act to initiate it.²⁰ Furthermore, a given individual subjected to the set of all exposures to the external environment from preconception onwards will suffer the consequences of these exposures at the cellular and organ level.²¹

Prenatal exposure

The impacts of exposure to air pollution during the prenatal period can affect organogenesis and the development of organs (i.e., the lungs), which can lead to long-term complications, affecting respiratory health in different manners.²²

Recent studies have shown the accumulation of black carbon on the fetal side of the placenta, suggesting that environmental particulates can be transported to the fetus and represents a potential mechanism that could

explain the detrimental health effects of pollution from early in life.²³

Exposure during pregnancy (24th to 36th weeks) at 2 µg/m³ or more than PM_{2.5} during the sacular phase of lung growth was associated with a 1.29-fold higher risk of asthma (95%CI: 1.06-1.58), current asthma (RR: 1.27; 95%CI: 1.04-1.54), but not current wheezing.^{24,25} Impaired lung development also contributes to infant mortality.²²⁻²⁶

Exposure to PM₁₀ from heavy road traffic during pregnancy was associated with significant reductions in lung function.²³ Maternal exposure to traffic-related NO₂, especially in the first trimester of pregnancy, has been associated with an increased risk of developing asthma, rhinitis, and eczema in children.²⁷

Components of cigarette smoke are potentially toxic to the developing fetus, including lead, nicotine, cotinine, cyanide, cadmium, mercury, CO, and PAH. CO reduces the fetus's supply of O₂, leading to hypoxia since it binds to hemoglobin with an affinity 200 times greater than O₂ and makes it difficult to release the O₂ to the cells. Chronic mild hypoxia of fetal tissue may persist for five to six hours after the mother has stopped smoking.²⁸

A recent meta-analysis evaluated the deleterious effects of exposure to tobacco smoke during pregnancy, associated

Table 4 Changes in immune tolerance and antimicrobial response due to air pollution.¹²

Dysregulation of immune tolerance	Dysregulation of antimicrobial and antiviral immunity
Stimulates epithelial cells and macrophages to produce pro-inflammatory cytokines and leukocyte-attracting chemokines	Increased number of macrophages with decreased phagocytic capacity
Adjuvant PM action increases the maturation of antigen-presenting cells and their expression of antigens	NO ₂ increases epithelial expression of ICAM-1 (respiratory virus receptor)
Suppression of regulatory T cell response by pro-inflammatory cytokines (such as IL-6)	Dysregulation of the production of IFN-γ by T cells
Protein oxidation leading to neoantigen formation	Development of a Th2-standard inflammatory environment, unsuitable for microbial airway infection

PM, particulate matter; NO₂, nitrogen dioxide; ICAM-1, intercellular adhesion molecule 1; IL-6, interleukin 6; IFN-γ, interferon gamma.

with harmful effects on the fetus and the newborn in the first two years of life.²⁹ Regarding the respiratory system, exposure during pregnancy and passive exposure after birth was associated with increased risk of wheezing in children under two years of age, higher frequency of respiratory tract infections in children under two years (including bronchiolitis, pneumonia, bronchitis, pulmonary tuberculosis, otitis media), and increased risk of developing asthma.²⁹ It is thought that at the epigenetic level, exposure to tobacco smoke during pregnancy may alter DNA methylation and messenger RNA expression in placental tissue, which may determine alterations in the expression of genes that affect the development of health conditions in the offspring.³⁰

Early life exposure

Exposure to PM has been associated with impaired lung function in children, documented by the decrease in peak expiratory flow rates and forced expiratory volume in the first second, especially among asthmatic children, and clinically externalized by the increase in the number of exacerbations, visits to emergency rooms, hospitalizations, and child deaths.^{31,32}

Exposure to PM₁₀ and NO₂ has been associated with reduced eosinophilic and neutrophilic inflammation of the respiratory mucosa in children with no wheezing. On the other hand, prolonged exposure to PM₁₀ has been associated with eosinophilic inflammation in children with wheezing, suggesting that it may contribute to developing asthma, inflammation, and promoting airway remodeling.³³

Passive exposure to tobacco smoke or nicotine-releasing devices has been associated with an increased risk of wheezing and asthma in children.²⁹

c) Pollution and allergic sensitization

The increase in global warming-related to climate change is associated in changes in pollen seasons, making them longer.³⁴ Scientific evidence shows that components of air pollution may also interact with airborne allergens and enhance the risk of atopic sensitization and exacerbation of symptoms in sensitized individuals. PM, O₃, CO₂, Diesel Exhaust Particles, SO₄, and NO_x have been shown to enable the release of pro-inflammatory mediators that can accelerate IgE-mediated sensitization and allergy of susceptible subjects. Additionally, air pollution has been shown to increase pollen allergenicity.^{35,36}

Although house dust mites (HDMs) and fungal spores are important sources of allergens inducing asthma and rhinitis, which are very sensitive to microenvironment modifications. Therefore, global or regional changes in temperature, humidity, air pollution, or other environmental conditions could modify natural HDMs and molds growth, survival, and allergen production.³⁷ Consequently, sensitization to HDMs and molds has increased in some regions of the world, especially in the subtropical and tropical areas.^{38,39} The synergistic effects between extreme heat and aeroallergens intensify the toxic effect of air pollutants, which in turn increases the allergenicity of aeroallergens.³⁹

Allergic rhinosinusitis

Environmental air pollution has been one of the causes indicated by the increased prevalence of allergic rhinosinusitis (AR). Norbäck et al. studies point out that prenatal exposure to high levels of NO₂ is associated with increased prevalence of AR in offspring.⁴⁰

Prenatal and postnatal exposure to elevated levels of NO₂ and PM₁₀ were associated with an increased prevalence of rhinitis and a lower frequency of wheezing remission. Having mold, humidity, and cockroaches in the home was associated with an increase in the prevalence of wheezing, and cooking using gas was associated with an increase in the appearance of rhinitis.⁴⁰

Exposure to indoor and outdoor allergens is a well-established risk factor for developing AR and more severe forms, especially indoor exposure.¹⁷ On the other hand, exposure to traffic-related air pollution (TRAP) for inducing oxidative stress and affecting the dendritic-T-cell epithelial cell axis towards a Th immune response₂ justifies the relationship between these types of exposure and the development of AR.⁴¹

Atopic dermatitis

Human skin acts as a protective biological shield against oxidant chemicals and air pollutants. As the largest organ in the body, it is constantly exposed to compounds in the surrounding environment. The evidence relates exposure to many environmental factors, either in high concentrations or for a long time, such as ultraviolet (UV) radiation, ambient air pollutants (PAH, VOC, MP, heavy metals, gas pollutants [CO, NO_x, SO₂, O₃]) and indoor air pollutants (consumption of solid fuels, tobacco smoke) to the loss of the barrier function exerted by the skin.^{42,43}

Damage to the skin barrier also appears to be closely related to increased production of reactive oxygen species (ROS), induction of oxidative stress, activation of the AhR, and inflammatory cytokines associated with precocious extrinsic aging and increased incidence of psoriasis, acne, atopic dermatitis, and skin cancer.^{42,43} VOCs have been associated with a higher prevalence of atopic dermatitis.⁴³

The mechanism by which air pollution contributes to the development and exacerbation of atopic dermatitis is still unknown. An experimental study on mice with atopic dermatitis documented an accentuation of the skin condition when exposed to ovalbumin and PM₁₀. There was an increase in clinical severity scores, transepithelial water loss, and epidermal thickness compared to the group without intervention. Several genes associated with cutaneous inflammation were detected for regulation. According to the authors, PM₁₀ induced/aggravated skin inflammation due to the differential expression of genes controlling the integrity of the skin barrier and immune response.⁴⁴

Eye allergy

Although the respiratory system is the main one affected by the harmful effects of air pollutants, the ocular surface is also affected because it is directly exposed to various environmental factors and pollutants, internal and external.⁴⁵ The dense innervations on the ocular surface are very sensitive to environmental chemicals, and only a thin teary film protects human eyes, often insufficient for preventing the

development of symptoms of conjunctivitis or dry eyes following exposure.⁴⁵

The correlation between exposure to high levels of O₃ and an increase in ambient temperature with the presentation pattern of the recent ocular allergy and an increase in its prevalence has been documented.⁴⁶

Besides affecting allergic diseases, the inflammatory response associated with air pollution may contribute to other conditions such as cardiovascular disease, hypertension, malignancy, Alzheimer's disease, dementia, cognitive impairment, and stroke.^{47,48}

Conclusions

The advances achieved in the Anthropocene period (from the 1950s onwards) have taken a heavy toll on us, given the climate changes it generated. These changes will undoubtedly have profound, acute, and long-term detrimental effects on children today and in the future. Pediatricians could play a relevant role in a series of actions, such as implementing and promoting educational strategies for children and their caregivers. As pediatricians, we have a moral responsibility to ensure the health of children today and those born in future generations.

Conflicts of interest

The authors declare no conflicts of interest.

References

- Di Cicco ME, Ferrante G, Amato D, Capizzi A, De Pieri C, Ferraro VA, et al. Climate change and childhood respiratory health: a call to action for paediatricians. *Int J Environ Res Public Health*. 2020;17:5344.
- Annesi-Maesano I, Maesano CN, Biagioni B, D'Amato G, Cecchi L. Call to action: air pollution, asthma, and allergy in the exposure era. *J Allergy Clin Immunol*. 2021;148:70–2.
- Pacheco SE. Catastrophic effects of climate change on children's health start before birth. *J Clin Invest*. 2020;130:562–4.
- Helldén D, Anderson C, Nilsson M, Ebi KL, Friberg P, Alfvén T. Climate change and child health: a scoping review and an expanded conceptual framework. *Lancet Planet Health*. 2021;5:e164–75.
- Akdis CA. Does the epithelial barrier hypothesis explain the increase in allergy, autoimmunity and other chronic conditions? *Nat Rev Immunol*. 2021;21:739–51.
- Goossens J, Jonckheere A-C, Dupont LJ, Bullens DM. Air pollution and the airways: lessons from a century of human urbanization. *Atmosphere*. 2021;12:898.
- World Health Organization (WHO). Air quality guidelines [cited 2021 June 1]. Available from: <https://www.who.int/publications/i/item/WHO-SDE-PHE-OEH-06.02>
- Conselho Nacional do Meio Ambiente (CONAMA). Resolução Nº 491, de 19 de novembro de 2018. Padrões de Qualidade do ar (Brasil). [cited 2021 June 1]. Available from: https://www.in.gov.br/materia/-/asset_publisher/Kujrw0TZC2Mb/content/id/51058895
- Rosário Filho NA, Urrutia-Pereira M, D'Amato G, Cecchi L, Anso-tegui IJ, Galán C, et al. Air pollution and indoor settings. *World Allergy Organ J*. 2021;14:100499.

- Ali MU, Yu Y, Yousaf B, Mujtaba Munir MA, Ullah S, Zheng C, et al. Health impacts of indoor air pollution from household solid fuel on children and women. *J Hazard Mat*. 2021; 416:126127.
- U.S. Food and Drug Administration. Products, ingredients & components cigarettes [cited 2021 June 1]. Available from: <https://www.fda.gov/tobacco-products/products-ingredients-components/cigarettes>
- Glencross DA, Ho TR, Camiña N, Hawrylowicz CM, Pfeffer PE. Air pollution and its effects on the immune system. *Free Radic Biol Med*. 2020;151:56–68.
- Auerbach A, Hernandez ML. The effect of environmental oxidative stress on airway inflammation. *Curr Opin Allergy Clin Immunol*. 2012;12:133–9.
- Prunicki M, Cauwenberghs N, Lee J, Zhou X, Movassagh H, Noth E, et al. Air pollution exposure is linked with methylation of immunoregulatory genes, altered immune cell profiles, and increased blood pressure in children. *Sci Rep*. 2021;11:4067.
- Brunst KJ, Leung YK, Ryan PH, Khurana Hershey GK, Levin L, et al. Forkhead box protein 3 (FOXP3) hypermethylation is associated with diesel exhaust exposure and risk for childhood asthma. *J Allergy Clin Immunol*. 2013;131. 592-4.e1-3.
- Nadeau K, McDonald-Hyman C, Noth EM, Pratt B, Hammond SK, Balmes J, et al. Ambient air pollution impairs regulatory T-cell function in asthma. *J Allergy Clin Immunol*. 2010;126. 845-52. e10.
- Naclerio R, Anso-tegui IJ, Bousquet J, Canonica GW, D'Amato G, Rosario N, et al. International expert consensus on the management of allergic rhinitis (AR) aggravated by air pollutants: impact of air pollution on patients with AR: current knowledge and future strategies. *World Allergy Organ J*. 2020;13:100106.
- Tang HH, Teo SM, Sly P, Holt PG, Inouye M. The intersect of genetics, environment, and microbiota in asthma—perspectives and challenges. *J Allergy Clin Immunol*. 2021;147:781–93.
- Eguiluz-Gracia I, Mathioudakis AG, Bartel S, Vijverberg SJ, Fuertes E, Comberiati P, et al. The need for clean air: the way air pollution and climate change affect allergic rhinitis and asthma. *Allergy*. 2020;75:2170–84.
- Bontinck A, Maes T, Joos G. Asthma and air pollution: recent insights in pathogenesis and clinical implications. *Curr Opin Pulm Med*. 2020;26:10–9.
- Annesi-Maesano I, Forastiere F, Balmes J, Garcia E, Harkema J, Holgate S, et al. The clear and persistent impact of air pollution on chronic respiratory diseases: a call for interventions. *Eur Resp J*. 2021;57:2002981.
- Korten I, Ramsey K, Latzin P. Air pollution during pregnancy and lung development in the child. *Paediatr Respir Rev*. 2017; 21:38–46.
- Bové H, Bongaerts E, Slenders E, Bijmens EM, Saenen ND, Gyse-laers W, et al. Ambient black carbon particles reach the fetal side of human placenta. *Nat Commun*. 2019;10:3866.
- Hazlehurst MF, Carroll KN, Loftus CT, Szpiro AA, Moore PE, Kaufman JD, et al. Maternal exposure to PM_{2.5} during pregnancy and asthma risk in early childhood: consideration of phases of fetal lung development. *Environ Epidemiol*. 2021;5:e130.
- Bettiol A, Gelain E, Milanese E, Asta F, Rusconi F. The first 1000 days of life: traffic-related air pollution and development of wheezing and asthma in childhood. A systematic review of birth cohort studies. *Environ Health*. 2021;17:46.
- Cai Y, Hansell AL, Granell R, Blangiardo M, Zottoli M, Fecht D, et al. Prenatal, early-life, and childhood exposure to air pollution and lung function: the ALSPAC cohort. *Am J Respir Crit Care Med*. 2020;202:112–23.
- Deng Q, Lu C, Li Y, Sundell J, Norbäck D. Exposure to outdoor air pollution during pregnancy and childhood asthma, allergic rhinitis, and eczema. *Environ Res*. 2016;150:119–27.

28. Brasil. Ministério da Saúde. Instituto nacional de câncer (INCA). Tabagismo passivo [cited 2021 June 1]. Available from <https://www.inca.gov.br/tabagismo/tabagismo-passivo>
29. Gould GS, Havard A, Lim LL. The Psanz smoking in pregnancy expert group, kumar R. exposure to tobacco, environmental tobacco smoke and nicotine in pregnancy: a pragmatic overview of reviews of maternal and child outcomes, effectiveness of interventions and barriers and facilitators to quitting. *Int J Environ Res Public Health*. 2020;17:2034.
30. Palma-Gudiel H, Cirera F, Crispi F, Eixarch E, Fananas L. The impact of prenatal insults on the human placental epigenome: a systematic review. *Neurotoxicology Teratol*. 2018;66:80–93.
31. Ward CJ. It's an ill wind: the effect of fine particulate air pollution on respiratory hospitalizations. *Can J Econ*. 2015;48:1694–732.
32. Liu L, Liu C, Chen R, Zhou Y, Meng X, Hong J, et al. Associations of short-term exposure to air pollution and emergency department visits for pediatric asthma in Shanghai. *China Chemosphere*. 2021;263:127856.
33. Bonato M, Gallo E, Bazzan E, Marson G, Zagolin L, Cosio MG, et al. Air pollution relates to airway pathology in wheezing children. *Ann Am Thorac Soc*. 2021 May 18. <https://doi.org/10.1513/AnnalsATS.202010-1321OC>. Epub ahead of print PMID: 34004126.
34. D'Amato G, Chong-Neto HJ, Monge Ortega OP, Vitale C, Ansotegui I, Rosario N, et al. The effects of climate change on respiratory allergy and asthma induced by pollen and mold allergens. *Allergy*. 2020;75:2219–28.
35. D'Amato M, Cecchi L, Annesi-Maesano I, D Amato G. News on climate change, air pollution, and allergic triggers of asthma. *J Investig Allergol Clin Immunol*. 2018;28:91–7.
36. Buters J, Prank M, Sofiev M, Pusch G, Albertini R, Annesi-Maesano I, et al. Variation of the group 5 grass pollen allergen content of airborne pollen in relation to geographic location and time in season. *J Allergy Clin Immunol*. 2015;136. 87-95.e6.
37. D'Amato G, Holgate ST, Pawankar R, Ledford DK, Cecchi L, Al-Ahmad M, et al. Meteorological conditions, climate change, new emerging factors, and asthma and related allergic disorders. A statement of the World Allergy Organization. *World Allergy Organ J*. 2015;8:25.
38. Acevedo N, Zakzuk J, Caraballo L. House dust mite allergy under changing environments. *Allergy Asthma Immunol Res*. 2019;11:450–69.
39. Deng SZ, Jalaludin BB, Antó JM, Hess JJ, Huang CR. Climate change, air pollution, and allergic respiratory diseases: a call to action for health professionals. *Chin Med J (Engl)*. 2020;133:1552–60.
40. Norbäck D, Lu C, Zhang Y, Li B, Zhao Z, Huang C, et al. Onset and remission of childhood wheeze and rhinitis across China - Associations with early life indoor and outdoor air pollution. *Environ Int*. 2019;123:61–9.
41. Liu G, Liu SX. Traffic-related air pollution and allergic rhinitis. *Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi*. 2018;32:153–6.
42. Abolhasani R, Araghi F, Tabary M, Aryannejad A, Mashinchi B, Robati RM. The impact of air pollution on skin and related disorders: a comprehensive review. *Dermatol Ther*. 2021;34:e14840.
43. Puri P, Nandar SK, Kathuria S, Ramesh V. Effects of air pollution on the skin: a review. *Indian J Dermatol Venereol Leprol*. 2017;83:415–23.
44. Woo YR, Park S-Y, Choi K, Hong FS, Kim S, Kim HS. Air pollution and atopic dermatitis (AD): the impact of particulate matter (PM₁₀) on an AD mouse-model. *Int J Mol Sci*. 2020;21:6079.
45. Latka P, Nowakowska D, Nowakowska K, Rejdak R. How air pollution affects the eyes a review. *Ophthalmol J*. 2018;3:58–62.
46. Das AV, Basu S. Environmental and air pollution factors affecting allergic eye disease in children and adolescents in India. *Int J Environ Res Public Health*. 2021;18:5611.
47. Calderón-Garcidueñas L, Engle R, Mora-Tiscareño A, Styner M, Gómez-Garza G, Zhu H, et al. Exposure to severe urban air pollution influences cognitive outcomes, brain volume and systemic inflammation in clinically healthy children. *Brain Cogn*. 2011;77:345–55.
48. Manisalidis I, Stavropoulou E, Stavropoulos A, Bezirtzoglou E. Environmental and health impacts of air pollution: a review. *Front Public Health*. 2020;8:14.