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ORIGINAL ARTICLE

Environmental pollutants and allergic sensitization: A systematic literature review

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Abstract

Background: Exposure to environmental pollutants has been associated with an increased risk of respiratory and allergic diseases.

Objective: To describe the interactions between common pollutants and the immune system and their association with allergic diseases.

Methods: A systematic literature review was conducted using PubMed, Clinical Key, Redalyc, MEDLINE, and SciELO for studies published between 2018 and 2024.

Results: Evidence shows that pollutants such as $PM_{2.5}$, PM_{10}, NO_2, CO, and ozone trigger oxidative stress, inflammatory responses, and epithelial damage, facilitating allergic sensitization, asthma, rhinitis, and dermatitis.

Conclusions: Exposure to environmental pollutants plays a key role in the development and exacerbation of allergic diseases, highlighting the need for preventive measures.

Key words: Allergies, Pollution, Pollutants, Rhinitis, Asthma, Contaminants

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Introduction

Air pollution is a mixture of solid, liquid, and gaseous particles from different sources, such as fuel combustion, factories, and exhaust emissions. The primary air pollutants include Particulate Matter (PM), O_3, NO_2, CO, and SO_2.[1] Air pollution has acquired great importance in recent years because it represents an essential risk to health and quality of life. A significant relationship has been found between exposure to air pollution and a high risk of developing different pathologies, in addition to increasing the risk of death, mainly from cardiovascular and respiratory causes, making it one of the leading causes of morbidity and mortality worldwide. According to the World Health Organization (WHO), 4.2 million premature deaths from cardiovascular, respiratory causes and cancer are attributable to air pollution, mainly particulate matter.[1–3] For this reason, the WHO has decided to develop guidelines to limit the world's population's exposure to these pollutants and thus reduce their harmful effects on health. However, in 2019 alone, approximately 99% of the world's population was estimated to live where the organization's air quality guidelines were not respected.[1] Exposure to air pollution,

mainly metals and PM, has been closely associated with toxic and harmful effects on the general population, with short- and long-term consequences such as cancer, immune and congenital defects, hormonal alterations, metabolic alterations; and specific organic pathologies such as cardiovascular, endocrine, respiratory, renal, reproductive and gastrointestinal pathologies through different pathogenic mechanisms, such as oxidative, inflammatory, carcinogenic and apoptotic effects.[1,4,5]

Objectives

The objective of this review was to analyze the interactions between the most common pollutants in ambient air and the immune system, including their contributions to the development of allergic responses and their influence on sensitization patterns. The biological and molecular mechanisms through which pollutants can trigger allergic responses will also be described. Finally, the public health implications of the findings are discussed.

Methodology

Intentional searches were conducted in the PubMed, Clinical Key, Redalyc, MEDLINE, and SciELO databases for keywords related to the topic in Spanish and English to select the material contributing to answering the research question. The article inclusion criteria were qualitative and quantitative articles in Spanish and English published between 2018 and 2024 that answered the research question. Review articles, articles whose scientific content was irrelevant, articles whose texts were only partially available, and those published after 2018 were excluded. A total of 45 articles were reviewed.

Environmental contaminants

Chrome

Chromium is present in occupational and consumer products as small molecular weight haptens and can induce hypersensitivity reactions such as allergic contact dermatitis. In fact, in a meta-analysis, Farzad Alinaghi et al.[6] determined the prevalence of chromium allergy in the general population to be 1.8% (95%CI: 1.3%-2.6%). In 2015, Europe, Regulation No. 301/2014 was implemented, limiting the use of chromium to a maximum level of 3 ppm, with the hope of reducing allergy cases.

In another meta-analysis by Farzad Alinaghi et al.,[7] analyzing the prevalence of metal contact allergy in metal workers, chromium was shown to have a prevalence of 8.5% (95%CI: 5.7%-11.9%). It was also found that the prevalence of contact allergy in non-European countries was more significant (14.8%).

Mercury

Mercury is a global and bioaccumulative pollutant generated through the aquatic food chain in its elemental and organic forms, so there is great concern about the effects of this metal on human health.[8] There is strong evidence of mercury immunotoxicity through inhibiting the immune response to infections, autoimmunity, immunosuppression, oxidative stress, and proinflammatory response. For example, Gardner et al.[9] reported that exposure of polymorphonuclear cells in vitro to subcytotoxic concentrations increases the production of proinflammatory cytokines.

A cohort study by Carrasco P. et al.[8] sought to evaluate the association between pre- and postnatal mercury exposure and allergy problems in preschoolers by measuring total mercury levels in the blood and hair of 4-year-old children. The limits of quantification for blood samples were 2.0 µg/L, whereas for hair samples, they were 0.01 µg/L. Respiratory symptoms and other environmental factors (such as exposure to tobacco smoke and diet) were analyzed via questionnaires administered to parents. Smoking during and after pregnancy was found to be a risk factor for wheezing. However, no statistically significant association was found between total mercury levels and allergy symptoms.

Nitrogen

In general, many existing meta-analyses show statistically significant effects of nitrogen on airway sensitivity in individuals with asthma. For example, Khreis et al.[10] conducted a meta-analysis that analyzed the association between traffic-related environmental pollutants, specifically NO_2, and the development of asthma. They reported a random effects risk of 1.05 (95%CI: 1.02, 1.07) per 4 µg/m^3 increase in nitrogen dioxide, indicating a 5% increase in the risk of developing asthma for every 4 µg/m^3 increase of this gas.

Numerous epidemiologic studies have consistently demonstrated associations between short-term ambient NO_2 exposure and exacerbation of asthma. This evidence is supported by positive associations observed in various studies linking short-term NO_2 exposures to increased hospital admissions and emergency department visits for asthma among both children and individuals of all ages.[11–15] An increase in airway sensitivity and an increase in airway sensitivity after 30 minutes of exposure to nitrogen in the range of 200 to 300 ppb was demonstrated.[16]

On the other hand, Ezzraty, V. et al.[17] investigated in a cross-sectional, randomized, double-blind study if repeated spikes of nitrogen at different realistic concentrations induced changes in airway inflammation in patients with asthma. The concentrations the research subjects were exposed to were designed to resemble as close as possible to those within an enclosed environment where combustion occurs during daily activities, e.g., cooking (200 to 600 ppm). Subjects were exposed at short 30-minute intervals: on the first day, one exposure was made, while on the following day, they were exposed twice (separated by 1 hour), and two weeks elapsed between the first and the second exposure. Thus, they found that repeated short exposures to nitrogen without exposure to allergens increased eosinophilic airway inflammation in participants with intermittent asthma without inducing any change in lung function.

Kun Han et al.[18] conducted a meta-analysis on traffic-related organic and inorganic air pollution and the risk of childhood asthma development. They aimed to clarify the potential associations between traffic-related pollutants (nitrogen, benzene, among others) and asthma during childhood (0 to 18 years). They found a statistically significant association in all the patients, especially for benzene (OR 1.21, 95%CI: 1.12-1.31, $P < 0.00001$).

In a randomized, cross-sectional, triple-blind clinical trial by Gent J. et al.,[19] they studied whether reduced exposure to indoor nitrogen or fine particulate matter reduces symptoms among children with persistent asthma. They recruited 126 children aged 5 to 11 years with persistent asthma living in homes with gas stoves, which had nitrogen levels of 15 ppb or more in the U.S. cities of Connecticut and Massachusetts. They participated in an intervention involving three air cleaners configured to reduce nitrogen via simulated particulate filtration and actual nitrogen scrubbing, particulate filtration, and control consisting of simulated particulate filtration. The air purifiers were randomly assigned to 5-week treatment periods using a three-arm crossover design. Although nitrogen-reducing treatment did not decrease asthma morbidity compared with control, there was a 1.8 symptom day reduction of 14 in particle-reducing treatment compared with control.

The European Mechanisms for Allergy Development (MeDALL) collaborative, in its work on air pollution and IgE sensitization in 4 European birth cohorts, revealed that air pollution was not consistently associated with IgE sensitization to any common allergen extract until the age of 16 years. However, allergen-specific analyses suggested increased risks of sensitization to birch. Some of the previously published cohort-specific results indicated that exposure to air pollution was related to pollen sensitization between 4 and 6 years of age, while in another cohort, associations between exposure to nitrogen at birth and specific sensitization were limited to food allergens.[20]

Finally, in their meta-analysis on environmental pollution exposure and the prevalence of allergic rhinitis during childhood, Qi-Yuan Zou et al.[21] reported that exposure to nitrogen and sulfur dioxide significantly increased the risk of allergic rhinitis.

Ozone

Ozone is made from the reaction of sunlight and vehicle exhaust products, such as nitrogen oxides, volatile organic compounds, carbon monoxide, and hydrocarbons.[22] The levels of inflammatory mediators are released in laboratory conditions and also in vitro, where bronchial epithelial cells release tumor necrosis alpha (TNF-α) and interleukins 6 and 8.[23,24]

Xing Li et al. (25) in their meta-analysis reported that asthma exacerbations are influenced by the concentration and time exposure of 1 hour or 8 hours daily to a maximum concentration; more ozone concentrations have been linked to an increased risk of asthma exacerbations. It is noteworthy that in the meta-analysis, the weather plays an important role in the exacerbation; warm seasons have more impact on asthma than cold seasons. On the other hand, Zheng et al.,[22] in their systematic review and meta-analysis, determined that several hours to seven days are considered as a short- term exposure to this pollutant, but the conclusion is not far from the previous study that we mentioned in this paragraph. Jantzen et al.[26] conducted a randomized, double-blind, cross-sectional study in which they exposed 23 subjects aged 62-72 years to clean air, house dust (at 275 mg/m^3 with a diameter of less than 2.5 mm), ozone at 100 ppb or a combination of dust and ozone. The combination of house dust and ozone was associated with a 48% decrease in $CD34^+KDR^+$ (Kinase Domain Receptor) late progenitor cells (EPCs) compared to cells exposed to clean air. Increased levels of reactive oxygen species and interleukin-8 were also found. This proves the inflammatory potential of house dust and the pulmonary oxidative stress induced by ozone. Therefore, the reduction of EPCs can be used as an indicator of cardiovascular risk.

PM

Xiaoxing Cui et al. investigated the association between particulate filtration in the bedroom (using a bedroom air filter) and changes in airway pathophysiology in children with asthma in a cross-sectional, double-blind study. They found that filtration improved airway mechanics by reducing airway resistance. Thus, they concluded that the internal filtration is a practical method for enhancing airflow in an asthmatic lung through improved airway mechanics and function and reduced inflammation.[27,28] On the other hand, in a meta-analysis, Lin Li et al.[29] reported that exposure to these pollutants significantly increased the risk of allergic rhinitis.

Sulfur dioxide

In their meta-analysis on the relationship between outdoor environmental pollutants and atopic dermatitis in adults, Hsiao Yu-Yu et al.[30] stated that the odds ratio (OR) for atopic dermatitis increases by 2.9% with every 10 $\mu g/m^3$ rise in sulfur dioxide (SO_2) exposure. It is important to note that Outdoor air pollutants such as SO_2 have detrimental impacts on adult atopic dermatitis, leading to its onset, increased severity, and exacerbation of symptoms, both in the short and long term. All pollutants and their effects are listed in **Table 1**.

Table 1. Contaminants and their associations.

Contaminant	Associations
Chrome	Contact dermatitis
Mercury	Inhibition of immune response, autoimmunity, immunosuppression, oxidative stress, proinflammatory response
Nitrogen	Exacerbations of asthma, eosinophilic inflammation, development of asthma in childhood, allergic rhinitis
Benzene	Development of asthma in childhood
Sulfur dioxide	Exacerbations of asthma, atopic dermatitis
Ozone	Exacerbations of asthma

Allergic sensitization pattern

How can exposure to pollutants impact predisposition to allergies?

Allergic sensitization, generally reported by specific immunoglobulin E (s-IgE) or skin testing, is a significant predictor of asthma, allergic rhinitis, and food allergy. In addition, polysensitization, as well as higher levels of s-IgE to any allergen, appears to be associated with severe and/or complex (comorbid) allergic disease.[31] Sensitization was defined as an s-IgE level greater than or equal to 0.35 KUA/L.[32]

The review focused on the associations between inflammatory and immune response genes and adverse respiratory outcomes following exposure to outdoor air pollution. Genetic variants, such as TNF-α, TLR4 (toll- like receptor 4), and TGFB1 (Transforming growth factor β1), were found to interact with pollutants like ozone, nitrogen dioxide, and particulate matter, affecting lung function and asthma risk. They highlighted the need for larger studies to confirm these findings, improve understanding of gene-environment interactions, and identify genetic determinants for targeted preventive measures and policies to limit pollution exposure. Standardization of exposure models, outcome measures, and consideration of epigenetic mechanisms were recommended for future research in this area.[20] The inner lining of the airways acts as a physical barrier that protects the submucosal tissues from harmful elements. This protective function relies on the integrity of the connections between cells, which include both tight junctions on top and adherens junctions below. When nasal epithelial cells are exposed in a controlled environment to $PM_{2.5}$, they may experience a decrease in the effectiveness of this barrier due to the reduction in the expression of certain binding proteins and the increase in the release of inflammatory cytokines such as IL-8, TIMP1 and Thymic Stromal Lymphopoietin (TSLP). This could increase the likelihood of rhinitis and rhinosinusitis in areas with high levels of $PM_{2.5}$ pollution.[33]

Infants and young children are more susceptible to the negative impacts of air pollution because their immune and respiratory systems are still developing. Additionally, they tend to spend more time outdoors and inhale approximately 50% more air per kilogram of body weight compared to adults, exposing them to relatively higher levels of environmental pollutants. As human lungs continue to develop from the intrauterine period to early adulthood, this more intense exposure to pollutants may increase children's vulnerability to the adverse effects of air pollution.[32]

How can pollutants influence allergic sensitization?

PM constitutes an airborne contaminant composed of a diverse array of tiny solid and liquid particles, encompassing both organic and inorganic materials, as well as substances originating from natural and human-made sources.[34] **Figure 1**. illustrates the inflammatory effects of PM_{10} on airway epithelial cells, including its role in recruiting immune cells through CXCL1 and IL-6 pathways.

The most relevant to health is PM with a diameter of 10 microns or less (PM_{10}, $PM_{2.5}$), which can penetrate deep into the lungs and induce surface reactions and defense cells. Most of these pollutants are the product of burning fossil fuels, but their composition may vary according to their source. The WHO air quality guidelines recommend a maximum exposure of 20 μg/m^3 for PM_{10} and a maximum exposure of 10 μg/m^3 for $PM_{2.5}$ based on evidence of the health effects of exposure to ambient air pollution. **Table 2** further explains the values established by the WHO on pollutant-based air quality criteria.[35,36]

In a 2021 meta-analysis, Nelson et al.[37] evaluated the most common pollutants in Latin American countries (PM_{10}, NO_2, O_3, and $PM_{2.5}$) and their effect on allergic rhinitis. The article revealed that the probability that a person exposed to pollutants would suffer rhinitis was 43% greater than that of a nonexposed person and that the likelihood that a child/adolescent exposed to pollutants would suffer allergic rhinitis was 36% greater than that of a nonexposed person. However, the authors clarify that the data should be interpreted cautiously, as the results were derived from different populations and the meta-analysis had considerable heterogeneity. In addition, some studies had a moderate risk of bias.

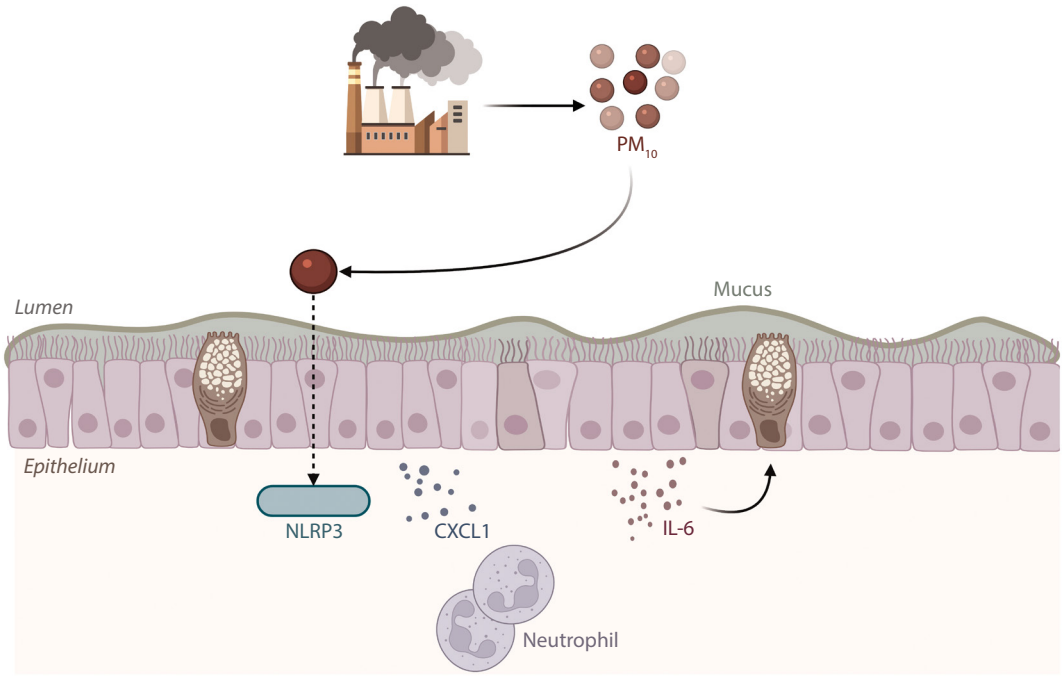

Figure 1. PM_{10} upregulates the expression of NLRP3 by airway epithelial cells, wich release CXCL1 and IL-6. CXCL1 contributes to the recruitment of neutrophils from the bloodstream and IL-6 promotes mucus secretion.

Table 2. Air quality criteria based on pollutants.

Contaminant	Average Time	WHO Recommended Value
$PM_{2.5}$	Annual	5 µg/m³
	24 hours (99th perc)	15 µg/m³
PM_{10}	Annual	15 µg/m³
	24 hours (99th perc)	45 µg/m³
O_3	High season	60 µg/m³ (8-hour daily max average, 6 months)
	8 hours (99th perc)	100 µg/m³
NO_2	Annual	10 µg/m³
	24 hours (99th perc)	25 µg/m³
SO_2	24 hours (99th perc)	40 µg/m³
CO	24 hours (99th perc)	4 mg/m³

Footnotes: [a] = 99th percentile (3–4 exceedance days/year); [b] = High season: six consecutive months with highest O_3 moving average; WHO reference: WHO global air quality guidelines, 2021.

Exposure to oxidizing air pollutants (O_3 and NO_2), but not $PM_{2.5}$, was associated with an increased risk of asthma (17%) and eczema (7%) in children. In multipollutant models, exposure to NO_2 and O_3 in the first three years of life showed a similar trend toward an increased incidence of asthma, allergic rhinitis, and eczema.

In addition to the contaminants mentioned at the beginning of this article, there are also persistent organic pollutants (POPs), which are lipophilic synthetic compounds that persist in the environment and bioaccumulate along the food chain in human and animal fatty tissues; additionally, they include a wide range of compounds, such as polychlorinated biphenyls (PCBs), non-dioxin-like polychlorinated biphenyls (ndl-PCBs), dioxins, dichlorodiphenyldichloroethylene (DDE), dichlorodiphenyltrichloroethane (DDT), hexachlorobenzene (HCB), and many other chemicals.[36]

In a meta-analysis, Gascón et al.[36] evaluated the adverse effects of early POP exposure on respiratory health, allergies, and the immune system in infancy, childhood, and adolescence. They concluded that POPs can negatively influence the development of the immune and respiratory systems. However, the scientific evidence for many of the exposure–outcome associations evaluated in this review is inadequate, mainly because of the small number of studies and the heterogeneity between studies in exposure and outcome assessment. Despite these findings, there were two interesting findings in this meta-analysis. The first and most important finding was that PCB exposure and ndl-PCBs during childhood/adolescence are not associated with allergic manifestations and asthma symptoms, i.e., several good-quality studies agree that they are not associated. Second, several good-quality independent studies have reported that prenatal DDE/DDT exposure predisposes individuals to allergic manifestations and asthma symptoms, but the evidence is not sufficiently conclusive.

In another meta-analysis, Melén et al.[20] investigated associations of air pollution exposure at birth. The combined results of the four birth cohort studies showed no overall association between exposure to the air pollution components studied and any allergic sensitization up to the age of 16 years. However, in analyses based on specific IgE antibodies against allergen extracts, an increased risk of sensitization to birch pollen with exposure to NO_2. In a subpopulation, the exposure to $PM_{2.5}$ at birth was related to IgE sensitization to major timothy grass allergen *Phleum pratense* (Phl p1) and the cat allergen *Felis domesticus* (Fel d 1).

The BAMSE and LISA/GINI studies, part of the MeDALL project, shed light on the intricate relationship between air pollution and the development of allergies. The BAMSE research initially suggested that traffic-related air pollution might trigger allergies in children up to eight years old. However, when we looked at older children, up to sixteen, this link was not as clear, hinting that air pollution's effects on allergies might change as children grow.

Instead, the LISA/GINI research did not show a strong connection between air pollution and allergy development in kids up to their teenage years.[36] This inconsistency suggests that the impact of air pollution on developing allergies is complex, possibly affected by when and how long children are exposed to pollution, the types of pollutants they encounter, and their own unique health susceptibilities. In essence, both sets of studies highlight that the relationship between air pollution and allergies is not straightforward and is influenced by various factors, including the child's age, the nature of the pollutants, and individual health characteristics.

It has been suggested that air pollution may increase the sensitivity of the airway epithelium to inhaled allergens. It has been shown that certain pollen allergens, such as the major birch pollen allergen *Betula verrucosa* (Bet v1) and the major grass pollen allergen *Lolium perenne* (Lol p1), can bind to small respirable particles, possibly enhancing the induction of respiratory allergies. However, pollutants may also contribute to enhanced allergic sensitization via other mechanisms. For example, exposure to air pollution strongly upregulates grass pollen allergen expression and thus may increase allergen loads during the pollen season. **Figure 2** depicts the interaction between pollen nitration caused by outdoor pollution and its role in asthma exacerbations. The finding that nitration of the major birch pollen allergen (Bet v1) enhances its immunogenicity and allergenic potential provides another possible mechanism by which pollution may increase allergic sensitization. This possibility is further supported by the altered morphology of pollen in contaminated areas.[37]

In the systematic review and meta-analysis conducted by Hsiao et al.,[30] evidence indicates that outdoor air pollutants are significantly associated with atopic dermatitis (AD) in adults, exerting both short-term and long-term effects. Long-term exposure to traffic-related air pollution and fine particulate matter ($PM_{2.5}$) is linked to increased prevalence and incidence of AD, with a notable odds ratio of 2.30 for incident AD per 10 μg/m^3 increase in $PM_{2.5}$ concentration. Short-term exposure, particularly to particulate matter less than 10 micrometers in diameter (PM_{10}) and SO_2, has been found to exacerbate AD symptoms, with an immediate excess risk of 2.9% per 10 μg/m^3 increase in SO_2. These findings underscore the detrimental impact of air pollutants on AD, emphasizing their significance in both the development and exacerbation of this condition in adults. Therefore, the role of air pollution should be considered in the management and treatment strategies for AD, highlighting the need for policies aimed at reducing air pollutant levels to mitigate the burden of this chronic skin disease.

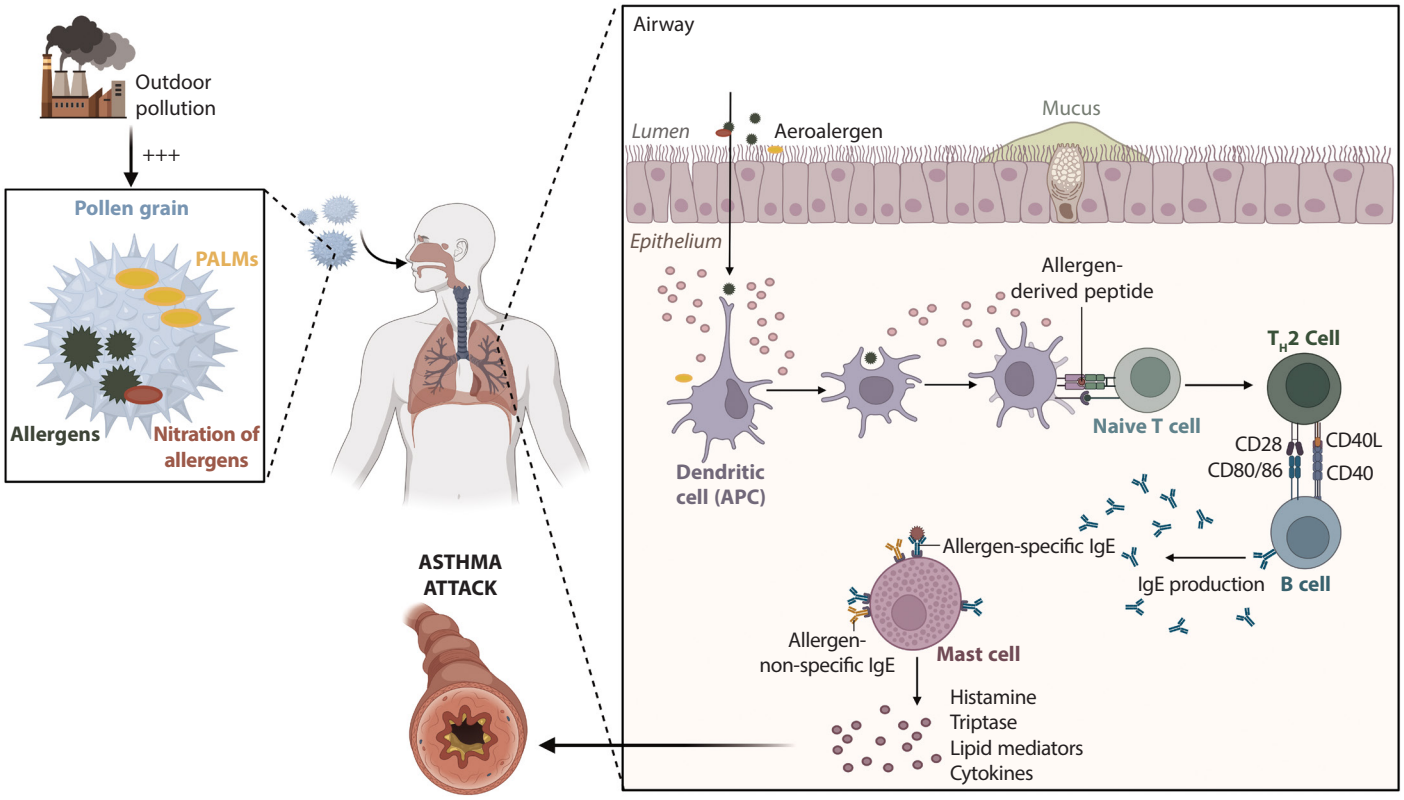

Figure 2. Outdoor pollution increases the production of pollen grains by plants, the amount of both allergens and PALMs per pollen grain, and favors the nitration of aeroallergens by pollutants like nitrogen oxides. Morover, global warming prolonges the periods where allergenic plants bloom.

The airway epithelial cells, when in contact with allergens, secrete pro-inflammatory mediators. On the other hand when a dendritic cell encounters an allergen it results on IgE sensitizations, wich are enhanced by the higher availability of PALMs and nitrated allergens. Finally when a sensitized mast cell interacts with a specific allergen it induces the release of inflammatory mediators wich cause asthma attacks in pollen-allergic patients.

PALM: pollen-associated lipid mediato

Scientific evidence

A comprehensive study by Burte et al.[38] analyzed the correlation between exposure to environmental pollutants and the severity of rhinitis in two extensive European cohorts, revealing that individuals residing in areas with elevated levels of PM_{10} and $PM_{2.5}$ experienced high severity of rhinitis symptoms Interestingly, the impact of air pollution on rhinitis severity was more pronounced among participants without allergic sensitization, especially for NO_2 exposure. However, for $PM_{2.5}$, the increase in severity was evident regardless of allergic sensitization status, suggesting that PM can exacerbate nasal symptoms independent of underlying allergic conditions.

The authors classified the rhinitis severity score (range, 0-12) as low, mild, moderate, or high according to the symptoms reported. Higher exposure to PM_{10} (particles with a diameter equal to or less than 10 micrometers) was associated with greater severity of rhinitis. The adjusted odds ratios (with 95% confidence intervals) for a 10 $\mu g/m^3$ increase in PM_{10} concentration were as follows: Mild severity: 1.20 [0.88-1.64], moderate severity: 1.53 [1.07-2.19], and high severity: 1.72 [1.23-2.41]. Among patients with allergic sensitization, increased exposure to air pollution was associated with increased rhinitis severity score only for $PM_{2.5}$.

Yoo-Jin et al.[39] conducted a study with a total sample of 2,052 school-aged children to determine the prevalence of allergic rhinitis and allergen sensitization rates in the community using ISAAC surveys, allergy skin tests, and to determine the association of local indicators of air pollution and changes in sensitization to inhaled allergens with changes in the epidemiology of allergic rhinitis. Environmental pollutant data were measured by the Korea Environment Agency, and pollutant measurements were collected for particulate matter (particulate matter with a mean aerodynamic diameter ≤ 10 μm [PM_{10}], μg/m^3), sulfur dioxide (SO_2, ppm), nitrogen dioxide (NO_2, ppm), ozone (O_3, ppm), and carbon monoxide (CO, ppm). According to the results of this study, the incidence of allergic rhinitis symptoms and air pollution concentrations were significantly associated with the mean and maximum values of PM_{10}, SO_2, and NO_3. A significant positive correlation was observed between the incidence of seasonal allergic rhinitis symptoms in spring and autumn and the mean and maximum diurnal concentrations of PM_{10} in those seasons. The correlation coefficients were 0.705 (p = 0.023) and 0.770 (p = 0.009), respectively. The mean CO concentrations were significantly positively correlated with the incidence of seasonal allergic rhinitis symptoms. The correlation coefficients were 0.835 (p = 0.003), 0.736 (p = 0.015) and 0.822 (p = 0.004).

Kuo et al.[40] conducted a time-stratified case-crossover study and conditional logistic regression analysis to explore the associations between asthma hospitalization risks in children and air pollutant levels ($PM_{2.5}$, PM_{10}, O_3, SO_2, NO_2) prior to hospitalization, focusing on a population of 2090 children aged 0-15 years from Taipei and Kaohsiung, Taiwan. Utilizing each subject as their own control, the study accounted for individual characteristics like age, sex, and lifestyle, analyzing hospitalization days against control days from the same month and weekday. The analysis, managed using Impala Hadoop and performed in R, indicated variable effects by age and season, with ORs and 95%CIs calculated for pollutant levels around hospitalization days. Specifically, O_3 was positively associated with asthma admissions in the 0-6 age group in Taipei, while in Kaohsiung, SO_2 and PM_{10} showed positive associations in the 0-6 and 7-12 age groups. Seasonally, NO_2's impact on asthma admissions was notably significant in Kaohsiung during autumn, with a marked effect on day three delays. These findings highlight the nuanced relationship between air pollution and childhood asthma, which varies with age, pollutants, and seasonal conditions, emphasizing the necessity for customized intervention strategies to mitigate air quality's impact on childhood asthma.

In addition, Hou et al.[41] studied a population of 34,544 people with suspected allergies according to IgE test results and demographic characteristics at the First Affiliated Hospital of Guangzhou Medical University between August 2012 and September 2019. In this population, 99 specific allergens were tested according to clinical diagnosis. Logistic regression was used to assess the effects of CO, NO_2, and $PM_{2.5}$ exposure on the risk of sensitization to specific inhalant/food allergens. Generalized additive models with multivariate adjustments were used to model the exposure–response relationship. Stratified analyses were performed to estimate the reliability of the correlations in various subgroups. Elevated levels of NO_2 significantly increase the risk of inhaled allergies. Stratified analyses illustrated associations between CO, particulate matter ($PM_{2.5}$), and NO_2 concentrations at 2-4 days (lag 2-4) prior to hospitalization and sensitization to inhaled allergic molecules. Exposure–response curves indicated increasing risks with increasing CO and $PM_{2.5}$ concentrations, particularly for house dust mite- and dog dander-specific molecules. Quantitative analyses revealed a significant correlation between CO concentrations and $PM_{2.5}$ concentrations (lag 2-4) and the risk of inhaled allergies, with the 95% adjusted OR (confidence interval, CI) increasing by 8% (95%CI, 2%-15%) for each 0.2 mg/m^3 increase in CO levels and increasing by 8% (95%CI, 2%-13%) for each 16.3 mg/m^3 increase in $PM_{2.5}$ concentration. The associations were strongest in the < 18 years group but appeared to have no significant differences according to sex. Taken together, the results of the present study suggested that there was a strong correlation between exposure to air pollutants, particularly CO and $PM_{2.5}$, and the risk of sensitization to specific inhaled allergens, with variations observed between age groups, pollutants and time periods.

Underlying mechanisms

In human populations, robust epidemiological evidence suggests that exposure to heightened levels of air pollution during early life stages correlates with reduced lung function throughout childhood. However, the long-term implications for asthma incidence remain largely unexplored in subsequent studies. The impact of air pollution on developing individuals begins as early as fetal development and may even extend further through potential epigenetic alterations inherited across generations.[42] The following mechanisms we are about to delve into revolve around ubiquitous contaminants frequently encountered in our environment.

Possible biological and molecular mechanisms by which pollutants may trigger allergic responses

One of the main mechanisms through which air pollutants cause cellular toxicity is the induction of oxidative stress, and one of the commonalities among air pollutant components (gaseous and particulate) is their ability to stimulate cellular and extracellular production of reactive oxygen species (ROS) and nitrogen (N).[43]

Effects of contamination on early stages of development

In murine models, fetal exposure to pollution has important effects on embryonic lung development. In a study by Mendes et al.[43] on BALB/c mice and their offspring exposed to urban air pollution ($PM_{2.5}$) from São Paulo, Brazil, on the basis of the effects on lung development, it was found that prenatal and early postnatal exposure to $PM_{2.5}$ leads to increased lung elastance and decreased alveolar counts in adult mice. While fetal lung structures are not affected, transcriptomic changes indicate alterations in the regulation of DNA damage, inflammation and cell proliferation. This study identified specific genes, such as *SOX8*, *ANGPTL4* and *GAS1*, with validated differential expression in the pseudoglandular stage of lung development, highlighting the molecular impact of air pollution on lung development. Furthermore, gestational exposure to environmental pollution has been associated with a possible increase in respiratory and cardiovascular morbidity and mortality, the development of diabetes mellitus and neurological diseases in newborns and children, but mainly with complications during delivery.

Diesel

Diesel (DE) is a type of fuel that exacerbates asthma, mainly through diesel exhaust particle (DLP) components such as polycyclic aromatic hydrocarbons (PAHs), sulfate, nitrate, metals and other trace elements.[44] These cytokines stimulate Th2 lymphocytes and promote the secretion of IL-4, IL-5, IL-9 and IL-13.[44-47]

The information that biodiesel (BD), a triglyceride-based alternative to diesel, results in less smoke, PM, CO, and hydrocarbon (HC) emissions, but more NO_2 emissions. Biodiesel's renewable, nontoxic, and eco-friendly attributes contribute to these emission reductions, offering a sustainable alternative to conventional diesel. The significant decrease in PM, CO, and HC emissions is attributed to the more complete combustion facilitated by biodiesel's higher oxygen content. However, this same oxygen enrichment, alongside the altered combustion temperature dynamics, leads to increased NO_2 emissions. Thus, while biodiesel presents environmental advantages in terms of lower overall pollutants, its impact on NO_2 emissions highlights a trade-off that is important to consider in the broader context of its use as an alternative fuel.[46]

Despite being more environmentally friendly, BD-treated mice presented higher levels of chemokines and cytokines in their lung tissue than did acute DE-treated mice. Timmerman found that mice sensitized to house dust mites (HDM) presented elevated IgG1 levels, increased lung elastance, eosinophilia and elevated TSLP expression after allergen exposure, suggesting that BD may modulate the immune system toward Th2-type inflammation.[44,47]

Pathogen recognition receptors (PRRs) are expressed mainly on epithelial and dendritic cells. These receptors can be stimulated by allergens such as HDMs (which bind to TLR4), which activate dendritic cells via cytokines produced by airway structural cells such as TSLP, granulocyte–monocyte colony–stimulating factor (GM-CSF), IL-25 and IL-33 and promote a Th2 response.[48]

IL-4 is the characteristic cytokine of Th2 cells, as it plays a key role in B-cell signaling to induce the switch to IgG1/IgE production.[49]

Mercury

Mercury (Hg) is a profoundly hazardous heavy metal that bioaccumulates in food chains and persists in circulation for long periods after release. Both natural and human-induced sources contribute to the presence of Hg, which can travel considerable distances in the atmosphere. Hg exist in several forms, each with different sources of exposure, target organs and toxicity levels. Of particular concern are organic methylmercury compounds, which pose the greatest risk to human health, as they accumulate in the food chain, especially in large predatory fish, causing severe and irreversible damage to the central nervous system, even at low concentrations.[50]

Although a conclusive relationship between asthma and Hg exposure has not been established, studies in children have shown conflicting results. Blood Hg concentrations have been found to be associated with some cases but not others. Hg body burden may be correlated with acute atopic eczema and total IgE levels in children.[39] Similarly, a study by Park and Kim with 1990 adult participants in Korea revealed a high correlation between high blood Hg levels and the incidence of atopic dermatitis.[51]

Polycyclic aromatic hydrocarbons (PAHs)

Polycyclic Aromatic Hydrocarbons (PAHs) Fine particles carrying PAHs can penetrate the lungs, causing inflammation and affecting respiratory health. Epidemiological studies suggest that PAH exposure and air pollutant concentrations are associated with the occurrence of allergic and nonallergic asthma. Increased asthma symptoms, exacerbation risks, and decreased lung function are also observed, although current evidence remains relatively limited. Multiple mechanisms, including inflammation, immunoglobulin E (IgE)-mediated reactions, mast cells, eosinophils, oxidative stress, and epithelial and endothelial cell dysfunction, likely contribute to these processes. The risk of asthma appears related to the duration and dose of chronic PAH exposure, which inflames the respiratory epithelium and contributes to diseases like cancer. PAHs are pervasive in daily life, primarily through tobacco for smokers and diet for nonsmokers, such as cereals and meats, compounded by air pollution from motor vehicles. As PAHs typically exist in complex pollutant mixtures, assessing individual exposure is challenging. Methods such as dietary questionnaires and urine tests for PAH biomarkers have shown promise; for instance, individuals consuming more meat test positive for these markers.[52,53]

Tobacco smoke, a major PAH source, contains high levels of benzo[a]pyrene (BP) and 3-methylcholanthrene, both with significant carcinogenic potential. Exposure occurs predominantly via inhalation, producing active metabolites that bind to DNA and cause mutations in oncogenes like P53. Alterations in P53 disrupt cell cycle regulation and apoptosis, driving cancer progression. Similar mechanisms occur with the consumption of grilled or smoked meats, further increasing exposure.

PAHs are metabolized by cytochrome P450 enzymes (CYP1A1 and CYP1B1), producing harmful metabolites that cause DNA damage and mutations essential for cancer development. Chronic PAH exposure exacerbates this damage and induces epigenetic changes, such as tumor suppressor gene methylation.[54]

At the cellular level, PAHs activate inflammatory pathways, including NF-κB, leading to the release of cytokines like IL-6, IL-8, and TNF-α. These cytokines recruit neutrophils and eosinophils, driving persistent inflammation. Tobacco smoke also disrupts immune cell function, causing hyperreactive neutrophils to release excessive reactive oxygen species and proteases, resulting in lung tissue damage and chronic inflammation. In asthma, PAHs alter eosinophil activity, disrupting typical inflammatory responses.

Chronic PAH exposure and tobacco smoke induce airway remodeling, including mucous cell hyperplasia, thickened basement membranes, and increased bronchial smooth muscle. These changes lead to airflow obstruction and persistent respiratory symptoms, further contributing to the pathophysiology of asthma and other chronic diseases.[55]

Particulate matter (PM)

PM is classified according to its diameter and settling velocity in the airways as fine (PM < 2.5 μm), ultrafine (PM < 0.1 μm) or coarse (PM < 10 μm). Damage is related to the amount and duration of PM exposure, which results in cell apoptosis via different mechanisms. Depending on the size of the molecule, exposure to PM is associated with damage and necrosis of the pulmonary epithelium. In contrast, chronic exposure to PM < 2.5 μm is necessary to cause damage that impacts the patient's quality of life. The minimum exposure to 5 days of PM 2.5-10 μm at a density of 10 $\mu g/m^3$ is associated with a risk of death from SARS at a relative risk of 1.06, 0.74, and 1.22, respectively.[56]

However, in the described mechanism, necrosis is mediated by the receptor-interacting protein 1 and 3 complexes (RIP1 and RIP3), which increases the production of reactive oxygen species, promotes cellular DNA damage, and induces the activation of poly-ADP-ribose polymerase-1 (PARP-1), which interferes with the regular activity of mitochondria, decreasing ATP production. At moderate exposure, the damage is related to autophagy produced by signals that inhibit mTOR, which produces phosphatidyl inositol 13 kinase (III P13K-Beclin 1). Finally, low exposure to these molecules is associated with apoptosis mediated by the activation of caspase three via extrinsic and intrinsic pathways; in addition, there is an increase in p53 expression due to direct DNA damage, which triggers apoptosis.[57–59]

When inhaled, coarse particles (PM < 10) tend to be deposited only in the upper airways. In contrast, fine and ultrafine particles can pass through the respiratory endothelium and navigate to the systemic circulation. In addition, other environmental pollutants are present in this group of underlying mechanisms, such as arsenic, which is highly associated with asthma, once breathed in, tiny particles settle in the bronchi and alveoli, where they are engulfed by macrophages, which are the main sites where harm occurs. The mechanisms by which these particles act are not yet well established, but among the effects caused by these particles are chronic inflammation, increased apoptosis, loss of nasal epithelial integrity, loss of homeostasis in the immune system, and aggravation of allergic inflammation by activation of M2 macrophages followed by a Th2-mediated response.

The lung is the main organ affected by ultrafine particles since, due to their size, they quickly access the lung surface and spread to other distal organs through the lung vasculature. These particles, unlike fine particles, cause damage after chronic exposure. In addition to their ability to spread quickly and cause damage to other organs, they trigger inflammation in the lung and inflammatory mediator release, such as reactive oxygen species, to different body organs, such as the heart and brain.[60–62]

In general, these particles' production of apoptosis and inflammation is closely related to the exacerbation of respiratory symptoms and allergic sensitization when interacting with other allergens in the environment, triggering more severe allergic responses in previously sensitized individuals.[63]

The mechanisms underlying the effects of $PM_{2.5}$ pollution have not been entirely determined. Still, there is a fundamental mechanism that can help explain the development of cardiopulmonary diseases caused by pollution. An alteration in iron homeostasis has been observed by forming complexes that capture the iron in the cell. In response to this reduction, the body will try to obtain iron by producing superoxide to increase the secretion of ferroportin, which will move iron through the cell as a compensatory mechanism; however, this process will not be sufficient to achieve homeostasis, which will expose the epithelial tissue of the lung, heart, and blood vessels to lesions.[64,65]

Arsenic

Chronic exposure to arsenic significantly impacts respiratory health by enhancing Th2-mediated immune responses, which are critical in the pathogenesis of allergic asthma. Studies highlight that arsenic exposure upregulates interleukins such as IL-4, IL-5, and IL-13, leading to increased periostin expression. Periostin, an extracellular matrix protein, supports the adhesion and activation of inflammatory cells, exacerbating respiratory symptoms and airway inflammation. Notably, periostin may serve as a biomarker for inflammation, offering predictive insights into the risk and severity of asthma in individuals exposed to arsenic. Understanding the role of arsenic

in altering immune responses and periostin's involvement provides essential insights for developing targeted interventions to mitigate its adverse health effects on respiratory conditions.[66,67]

Pesticides Chronic exposure to pesticides has been linked to a range of severe health issues such as cancer, neurotoxicity, infertility, miscarriages, and allergies, with workplace exposure particularly noted as a primary risk area. These substances not only cause direct toxicity but also modulate the immune system by fostering Th2-type inflammation. This immune response involves $CD4^+$ T lymphocytes that recruit eosinophils and produce interleukins like IL-4, IL-5, and IL-13, leading to conditions like asthma, allergic rhinitis, and atopic dermatitis. Similarly, chronic exposure to arsenic from contaminated water sources has been shown to impair lung function and exacerbate respiratory symptoms, primarily through Th2-mediated allergic asthma.

Arsenic exposure disrupts cellular iron homeostasis, forming complexes that sequester iron and induce compensatory mechanisms like increased ferroportin expression, which fails to restore balance and leads to significant lung and cardiovascular inflammation. Both pesticides and arsenic illustrate the complex ways environmental pollutants impact human health via immune system interactions and cellular disruptions. Monitoring levels of specific markers like periostin in individuals exposed to these toxins can provide insights into the severity of airway inflammation and potential asthma exacerbation. This approach underscores the importance of understanding environmental exposures' mechanistic impacts to develop targeted interventions and preventive measures aiming to mitigate these pollutants' adverse health effects.[68]

Biomarkers: Periostin and Emerging Indicators

Periostin is a systemic biomarker linked to Th2-driven inflammation in allergic and respiratory diseases, including asthma. Regulated by IL-4 and IL-13, periostin expression reflects key inflammatory processes such as eosinophilia and IgE synthesis.[69] Recent evidence indicates that pesticides like parathion and methoxychlor exacerbate Th2 inflammation by increasing IL-4 and IL-13, suggesting a potential rise in periostin levels in pesticide-exposed asthmatic patients.[70]

Despite these associations, periostin's lack of specificity limits its utility in pinpointing exacerbation triggers. It is elevated in various conditions, including allergic rhinitis, pulmonary fibrosis, and certain cancers.[71] Organophosphates, such as parathion, worsen asthma but lack direct evidence linking them to periostin increases.[72]

Clinically, periostin correlates with bronchial hyperreactivity and FeNO levels but not overall lung function, reinforcing its role as an inflammation marker with debated utility.[73] Elevated serum periostin is associated with higher exacerbation risk in moderate asthma,[74] but further studies are needed to validate its predictive value and clarify its role in pesticide-related exacerbations.

While periostin shows potential as a marker for Th2 inflammation and asthma exacerbation risk, its current application is limited by a lack of specificity and causal evidence. Future research should explore its role in environmental triggers, particularly pesticide exposure.

Interaction with Other Contaminants

Pesticide exposure rarely occurs in isolation; individuals are often simultaneously exposed to other environmental pollutants such as particulate matter (PM_{10}, $PM_{2.5}$), reactive gases like NO_2 and O_3, and heavy metals such as arsenic. These combined exposures create complex interactions that amplify harmful effects on health, particularly in respiratory and allergic diseases.

Fine particulate matter ($PM_{2.5}$) can penetrate deeply into the respiratory tract and act as a carrier for pesticides at the cellular level, increasing their toxicity. Both pesticides and pollutants like arsenic and NO_2 promote Th2-type inflammation, marked by elevated IL-4, IL-5, and IL-13, which exacerbates conditions such as asthma and allergic rhinitis. Additionally, arsenic disrupts cellular iron homeostasis, increasing oxidative stress and pulmonary inflammation, further worsening the effects of pesticide exposure.[75–77]

O_3 amplifies oxidative damage in the respiratory tract when combined with dust particles and pesticides. Similarly, NO_2 impairs respiratory epithelial barrier function, making it more susceptible to inflammation and allergens carried by $PM_{2.5}$ and PM_{10}.[25,26] These interactions highlight how pollutants collectively intensify inflammation and respiratory symptoms, particularly in sensitized individuals or those with preexisting conditions.

The cumulative impact of pesticides and other environmental pollutants underscores the need for an integrated approach in research and environmental policies. Regulations should address multiple pollutants simultaneously to mitigate their synergistic effects on respiratory and allergic diseases, with preventive measures targeting combined exposures.

Impact of Oxidative Stress

Chronic oxidative stress from environmental exposures, including pollutants, deregulates the immune system and exacerbates the severity of allergic conditions. A systematic review and meta-analysis by Bassu et al.[78] highlighted reduced serum paraoxonase-1 (PON-1) activity in asthma patients. PON-1, a critical antioxidant defense enzyme, was significantly lower in asthmatic individuals (SMD = −1.58; 95%CI −2.53 to −0.63; p = 0.001), indicating impaired antioxidant defenses in this population.

Environmental exposures, such as e-cigarette use, are consistently linked to respiratory disorders, including asthma and COPD. Wills et al.[79] reported that e-cigarettes disrupt immune gene expression and ciliary function while inducing oxidative stress and cytotoxicity in pulmonary membranes. These mechanisms increase susceptibility to infection and chronic respiratory diseases, with age-specific impacts on asthma and COPD risk.

At the cellular level, oxidative stress plays a crucial role in anaphylaxis. Piotin et al.[80] described how mitochondrial oxidative dysfunction, particularly in cardiomyocytes, drives mast cell degranulation, a key process in anaphylaxis. Antigen stimulation increases ROS production via NADPH oxidases and mitochondria, promoting mast cell activation. Morphological mitochondrial changes and translocation to exocytic sites were observed during degranulation, and antioxidant administration reduced ROS levels and mast cell degranulation. These findings emphasize oxidative stress and mitochondrial function as therapeutic targets in anaphylaxis. Further evidence links environmental pollution to inflammation and oxidative stress in respiratory pathways. Percival et al.[81] examined exhaled nitric oxide (eNO) in infants of asthmatic mothers, identifying associations between postnatal air pollution exposure (e.g., ozone, NO_2, $PM_{2.5}$) and increased eNO. Pollutants induce nitric oxide synthase-2 (NOS2) expression and epigenetic modifications in NOS2, NOS3, ARG1, and ARG2, altering nitric oxide metabolism. The Breathing for Life Trial demonstrated that infants of asthmatic mothers exhibit reduced lung function at six weeks, potentially due to inflammatory responses in the placenta and cord blood lymphoid cells linked to maternal pollutant exposure. Collectively, these findings underscore the systemic effects of oxidative stress in exacerbating allergic and respiratory conditions mediated through immune dysregulation, mitochondrial dysfunction, and pollutant-induced inflammation.

Public health impact

Recent studies have reaffirmed the critical health risks associated with particulate matter (PM), particularly $PM_{2.5}$ and PM_{10}. The finer particles, $PM_{2.5}$, are particularly detrimental due to their ability to penetrate deep into lung tissue and even enter the bloodstream, leading to systemic inflammatory responses, increased blood pressure, and decreased lung function. These particles are most strongly associated with adverse health effects following even short exposure periods. The main constituents of $PM_{2.5}$ include metals, organic debris, and crustal elements, which contribute to its high reactivity and toxicity.

PM_{10}, while larger and impacting primarily the upper respiratory tract, also poses significant health risks. Chronic exposure to $PM_{2.5}$, in particular, is associated with long-term respiratory tract diseases such as asthma, chronic obstructive pulmonary disease (COPD), and allergic rhinitis. It has been documented that long-term exposure can destroy the ciliary epithelium in the lungs, leading to increased secretion of MUC5AC, a mucin protein associated with these chronic conditions.

Global studies, including a comprehensive analysis in 205 cities, have demonstrated a robust correlation between short-term exposure to $PM_{2.5–10}$ and increased mortality from respiratory and cardiovascular diseases. These studies highlight the urgent need for regulatory frameworks and public health initiatives to mitigate exposure to these harmful particles. The consistent findings across various regions underline the pervasive threat posed by $PM_{2.5}$ to public health, emphasizing the necessity for continued research and policy action to address the impacts of air pollution.[75]

Pediatrics

One of the primary challenges that we need to address is the upsurge in the cases of allergic rhinitis. Carbon dioxide has a significant relationship with the incidence of this disease compared to that in adults. A study by the Department of Otorhinolaryngology of the Hospital of Hangzhou[61] demonstrated that exposure to 100 parts per million of carbon dioxide daily increases the relative risk of suffering allergic rhinitis in children younger than one-year-old. Pediatric children are highly susceptible to the negative effects of inhaling pollutants due to their young age, lower weight, and immature cellular development. As a result, the impact of pollutant inhalation is particularly significant in this population.

Physiologically, the pediatric population breathes 50% more air per kilogram of body weight. In addition, children under six years of age have immature pulmonary epithelium facilitating the crossing of toxins and pollutants through the epithelial barrier; ultimately, they have an immature immune system at birth, which may explain why pediatric children have a greater predisposition to contracting allergic rhinitis due to pollutants than adults in whom the process can take longer.[76]

Clinically, the diagnosis of allergic rhinitis in children goes unnoticed most of the time during the first level of care contact. This problem lies in long-term exposure to allergens such as pollutants and poor diagnosis of the disease, which can cause more severe damage to the upper and lower respiratory tract and lead to serious complications such as asthma and sinusitis.[77,82]

Adults

In the adult population, both short-term and long-term effects do not vary compared to those in the infant population. Atopic dermatitis is the most common cause of dermatitis because the epithelial barrier function of the skin is more easily impaired, allowing the penetration of allergens and microorganisms such as *Staphylococcus aureus*. $PM_{2.5}$ pollutants are entirely associated with the incidence of atopic dermatitis in adults and are the leading cause of allergic sensitization in the long term; however, in the short-term, atopic dermatitis was associated with exposure to SO_2 immediately after exposure (day 0) and O_3 with exacerbations after the fourth day of exposure. SO_2 is the most common allergen sensitizer related to atopic dermatitis, while $PM_{2.5}$ is strongly associated with allergic rhinitis due to deposition in the upper and lower respiratory tracts.[30]

Conclusions

Environmental pollution is an issue of utmost importance today since, in addition to the changes that have impacted our planet, a strong association was found between environmental pollutants and the effects of various cellular processes, resulting in an exacerbation and increased morbidity and mortality of mainly allergic and atopic diseases but also other diseases, such as cardiovascular, endocrine and neurological diseases.

Several mechanisms through which environmental pollutants, after high exposure in quantity and frequency, cause direct damage to cellular processes, the main ones being the production of reactive oxygen species, damage to genetic material, release of inflammatory molecules, and induction of cellular apoptosis, have been demonstrated.

Promoting research on this topic is imperative since the progressive increase in environmental pollution will force us to propose strategies to treat and prevent diseases exacerbated by the components of these pollutants.

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Conflicts of Interest

The authors declare no conflict of interest.

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