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The need for clean air: The way air pollution and climate change affect allergic rhinitis and asthma

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Abstract

Air pollution and climate change have a significant impact on human health and well-being and contribute to the onset and aggravation of allergic rhinitis and asthma among other chronic respiratory diseases. In Westernized countries, households have experienced a process of increasing insulation and individuals tend to spend most of their time indoors. These sequelae implicate a high exposure to indoor allergens (house dust mites, pets, molds, etc), tobacco smoke, and other pollutants, which have an impact on respiratory health. Outdoor air pollution derived from traffic and other human activities not only has a direct negative effect on human health but also enhances the allergenicity of some plants and contributes to global warming.

Eguiluz-Gracia and Mathioudakis are equally contributed to this work.

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Climate change modifies the availability and distribution of plant- and fungal-derived allergens and increases the frequency of extreme climate events. This review summarizes the effects of indoor air pollution, outdoor air pollution, and subsequent climate change on asthma and allergic rhinitis in children and adults and addresses the policy adjustments and lifestyle changes required to mitigate their deleterious effects.

KEYWORDS
allergic rhinitis, asthma, climate change., environment, pollution

1 | INTRODUCTION

Since the beginning of the industrial revolution, Western countries experienced an explosive process of urbanization, which dramatically affected environmental exposures. Following this trend, many low-to-middle income countries are undergoing similar processes. Consequently, >90% of the population lives in places where air quality does not meet the recommendations of the *World Health Organization* (WHO).[1] The *European Environmental Agency* reported that most urban dwellers were exposed to concentrations of fine particulate matter ($PM_{2.5}$) and particulate matter of ≤10 mm in diameter (PM_{10}) above WHO recommendations (74% and 42%, respectively).[2] Importantly, air pollution is currently one of the leading causes of premature death in the world.[3,4]

Allergic rhinitis (AR) and asthma share many pathophysiological links[5,6] and are among the commonest respiratory conditions,[7,8] with their increasing prevalence mirroring the rise in Westernized lifestyle worldwide.[9] Because the airways represent one of the major boundaries of the body, environmental exposures (collectively termed "the exposome")[10] greatly affect the homeostasis of the respiratory mucosae. Importantly, climate and urban dwelling (with its associated decrease in biodiversity) significantly determine the exposome composition.[11] Among the exposome components, pollutants, microbes, and allergens have a substantial impact on health.[12]

Several policy changes could help reduce the deleterious components of the exposome and minimize their effects on respiratory health.[2] Of note, some policy measures have already proven effective at decreasing the burden of air pollution–related diseases (e.g., restrictions on tobacco smoking in public places).[13]

This narrative review summarizes the latest insights regarding the effects of indoor and outdoor pollution and climate change on AR and asthma, and addresses the policy adjustments required to mitigate their effects. To this end, we identified relevant articles published during the period 2014-2019, together with several previous key studies related to the topic.

2 | INDOOR AIR POLLUTION

Most individuals in Westernized countries spend ~80% of their time indoors,[14,15] demonstrating the importance of indoor air quality. The composition of indoor air is affected by several factors including outdoor pollutants, the quality/quantity of ventilation, indoor allergens, and activities such as smoking, heating, and cooking.[16]

2.1 | Second-hand exposure to tobacco smoke

2.1.1 | Epidemiological evidence

Tobacco smoke contains at least 4500 toxic chemical compounds, including PM, oxidative gases, heavy metals, and at least 50 carcinogens.[17] Tobacco smoke poses significant health risks to nonsmokers who inhale the smoke in various microenvironments, such as households or workplaces (second-hand smoke (SHS) exposure). Recently, the pyro-synthesis and cigarette combustion related to domestic smoking were identified as key phenomena increasing the levels of PM and toxic chemical agents in households.[18]

Second-hand smoke exposure during pregnancy and infancy is associated with asthma onset, poor asthma control, and more severe exacerbations during childhood,[19-21] among other chronic conditions.[22] Prenatal and postnatal SHS exposure was linked to a 21%-85% increase in the risk of asthma in children, with the highest effect observed among children exposed to tobacco smoke during the first two years of life.[20,23] More recently, a study of five European birth cohorts (n = 10 860) showed that maternal smoking during infancy correlated with a 15% (95%CI: 0%-31%) increase in the risk of asthma in children.[24] Interestingly, SHS exposure might induce epigenetic changes with transgenerational repercussions on asthma onset,[25] which would imply a very long-term effect of tobacco smoking on respiratory health. The immaturity of the immune and respiratory systems of children and their larger air volume per weight kilogram inhaled as compared to adults might explain the high sensitivity to tobacco smoke during childhood.[26] The initial studies conducted by the *European Community Respiratory Health Survey* (ECRHS) in different European countries did not reach a definitive conclusion regarding the role of SHS exposure on asthma in adults.[27] Conversely, later studies suggested a higher risk of adult-onset asthma in patients exposed to tobacco smoke,[28,29] together with a slightly lower risk of seasonal AR.[29] Similarly, a recent study from the ECRHS found associations between SHS exposure and physician-diagnosed asthma and poorer asthma control in adults, yet no effect was observed on the lung function.[30]

2.1.2 | Tobacco smoke alters airway microbiota

Similar to the gut,[31,32] the respiratory tract of healthy humans is colonized by a variety of different bacteria, viruses, and fungi.[33] This colonization may shift in response to changes in the local environment (e.g., tobacco smoke), potentially inducing a long-lasting state of bacterial dysbiosis.[34] A study reported that the pharyngeal microbiota of individuals exposed to tobacco smoke was richer in species, such as *Porphyromonas*, *Neisseria*, and *Gemella*, compared to nonexposed subjects, but the authors failed to identify significant changes in the microbiota recovered from bronchoalveolar lavage samples.[35] Various tobacco smoke compounds can directly affect the airway microbiota (e.g., enhanced biofilm formation by *Staphylococcus aureus*[36]), and cigarettes themselves carry bacteria and fungi, including several human pathogens (Figure 1).[37] Furthermore, tobacco smoke upregulates the airway mucus production, impairs the mucociliary clearance, and induces low-grade inflammation within the lungs, collectively changing the micro-environmental conditions of the niche, which might affect the local microbiota.[38] These changes might eventually promote airway remodeling.[39,40]

Many chronic lung diseases, including asthma and bronchiectasis, have been associated with an altered respiratory microbiota.[34,41-43] The asthmatic bronchus with chronic inflammation and increased mucus production represents an ecological niche different from that of a healthy bronchus.[34] However, it is still unclear whether the bacterial dysbiosis is a cause or a consequence of the disease.[44] In this regard, the diverse compositions of the airway microbiota correlate with the concentration of inflammatory cytokines in murine lungs, suggesting that changes in the microbiota can also modulate the host's inflammatory status.[45]

2.2 | Other sources of indoor air pollution

Other agents, such as nitrogen dioxide (NO_2), carbon monoxide (CO), or some volatile organic compounds (VOC) (e.g., formaldehyde), are also main indoor pollutants.[46,47]

Indoor NO_2 is mainly generated by gas-fueled cooking and heating appliances, and the levels in European households can be as high as 2500 µg/m^3.[48] On the other hand, the *Towards Healthy Air in Dwellings in Europe* (THADE) project reported that the mean concentration of indoor NO_2 in Europe ranged from 10-15 µg/m^3 in Scandinavia to 65 µg/m^3 in Poland.[49] Numerous studies have reported positive associations between indoor NO_2 and the presence/aggravation of asthma symptoms in children.[16,50] Some VOCs generated from sources like building materials or consumer products (cleaning products, cosmetics, air fresheners, etc) act as indoor air pollutants.[51] A systematic review from 2015 reported only weak evidence relating exposure to this type of VOCs to the onset of asthma and AR, as well as to the aggravation of asthma/AR symptoms in both children and adults.[52]

The use of solid fuel (e.g., coal) for cooking and heating does not only remain a source of indoor pollution in developing countries, but is still a common practice for residential heating in many Western households.[53] Exposure to the smoke generated by this biomass has

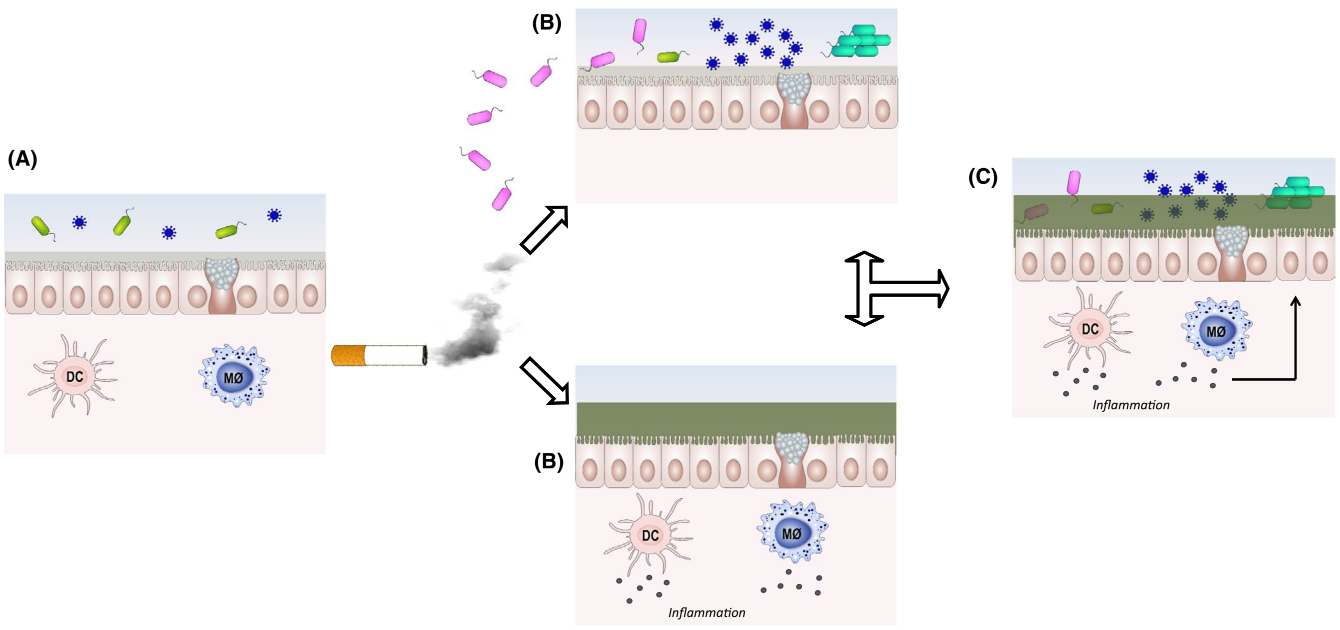

FIGURE 1 Tobacco smoke as driver of microbial dysbiosis in the airways: A, During homeostasis, there is a symbiosis between the airway microbiota and the stromal and immune cells of the respiratory epithelium; B, Tobacco smoke carries different microbes that can colonize the airways, and also promotes several changes in the resident microbiota such as the formation of biofilms by *Staphylococcus aureus*; C, Tobacco smoke upregulates mucus production, impairs the mucociliary clearance, and induces low-grade inflammation in the airway mucosa; C, The interaction between the effects of tobacco smoke on airway microbiota and respiratory epithelium further alters the ecological niche, promotes the outgrowth of certain species, and ultimately affects the microbial balance

been linked to several respiratory conditions in both adults and children,[54] but robust evidence is still lacking to support a causative role in the case of adult or pediatric asthma.

Indoor allergens from furry pets, molds, and house dust mites (HDM) also influence the quality of indoor air. Sensitization to furry animals is detected in up to 15% of the population[55] with a high degree of cross-reactivity among the different species. Moreover, HDM are the most common triggers of airway allergy, as up to 50% of asthmatics are sensitized to them.[56] Recent data suggest that in children with wheezing episodes, sensitization to HDM is associated with greater bronchial inflammation and reduced lung function.[57] Importantly, indoor allergens induce more severe phenotypes of airway allergy than outdoor seasonal allergens.[58-60] Additionally, dampness is present in 10%-15% of households, which can lead to mold or cockroach colonization and subsequent allergic sensitization of the residents.[61,62] Beyond allergic mechanisms, molds can promote inflammation of the upper and lower airways through several metabolites like glucans or mycotoxins.[63]

In addition to residential environments, indoor air quality in nonresidential buildings (e.g., schools) plays an important role in respiratory health.[64-66] The *Schools Indoor Pollution and Health: Observatory Network in Europe* (SINPHONIE) project, funded by the European Parliament, assessed indoor air exposure in schools in 23 countries.[67] The study found that $PM_{2.5}$, some VOCs (e.g., formaldehyde), radon, and allergens (especially molds) were commonly present.[67] Moreover, the *Health Effects of School Environment* (HESE) project [68] reported that 78% and 66% of children attending schools in Norway, Sweden, Denmark, France, and Italy were exposed to PM_{10} over 50 μg/m^3 and to carbon dioxide (CO_2) over 1000 ppm, respectively. Another study from the HESE project investigating the burden of fungi showed that the number of viable molds in indoor air exceeded the maximum standard of 300 cfu/m^3 in 33% of participating classrooms.[69] Very recently, these findings were confirmed in a study conducted in Southern Italy.[70] Importantly, this work observed that the concentration of elements from industrial emission was significantly higher in schools located in urban/industrial areas as compared to rural areas,[70] implying that the penetration of outdoor pollutants further deteriorates the quality of indoor air.

Table 1 summarizes the main effects of indoor pollution on AR and asthma.

3 | OUTDOOR AIR POLLUTION

3.1 | Epidemiological evidence

Various epidemiological studies have demonstrated that long-term exposure to outdoor air pollution (e.g., from traffic, industry) negatively affects respiratory health.[71] A multicenter study in

TABLE 1 Consequences of indoor air pollution over allergic rhinitis and asthma

Indoor Air Pollution (effects amplified by the amount of time spent indoors and the isolation of buildings)	
Environmental factors	**Health outcomes**
Second-hand tobacco smoke	
During perinatal period	1. Higher prevalence of asthma, poorer asthma control, and more severe asthma exacerbations during childhood[19-24] 2. Potential epigenetic changes with transgenerational repercussions[25]
During adulthood	1. Possibly higher asthma prevalence[28-30] 2. Possibly lower prevalence of allergic rhinitis[29]
Lifelong	Alteration of airway microbiota/bacterial dysbiosis[34]
NO_2 from gas-fueled cooking and heating	Higher prevalence and exacerbation rate of asthma during childhood (16. 50)
Volatile organic compounds from building materials and consumer products	Possibly higher prevalence and exacerbation rate of allergic rhinitis and asthma in both children and adults[52]
Indoor allergens	
Lifelong	1. Increased sensitization rates to house dust mites, molds, and allergens from furry animals [55,56] 2. More severe phenotypes of allergic rhinitis and asthma, as compared to those induced by outdoor allergens [58-60]
During childhood	Higher bronchial inflammation and reduced lung function in sensitized children with wheezing episodes[57]
Colonization of the households by molds and cockroaches due to dampness	1. Higher sensitization rate to dampness-related allergens[61,62] 2. Airway inflammation due to allergy-independent mechanisms (glucans, mycotoxins, etc)[63]

five European birth cohorts (conducted as part of the *European Study of Cohorts for Air Pollution Effects*, ESCAPE project) showed that exposure to PM and nitrogen oxides was associated with poor lung function in school-age children.[72] An early analysis of the ESCAPE project did not find a statistically significant association between air pollution and the development of asthma up to the school age.[73] However, the re-analysis of these cohorts when the study individuals were 14-16 years old revealed associations between asthma incidence and NO_2 (OR 1.13, 95% CI: 1.02-1.25) and $PM_{2.5}$ (OR 1.29, 95% CI: 1.00-1.66) exposure. The associations were particularly strong in the case of asthma diagnosed after the school age.[74] A recent meta-analysis of observational epidemiological studies published between 1999 and 2016 showed an association between traffic pollution and childhood asthma, with an OR ranging from 1.03 (95%CI: 1.01-1.05) to 1.08 (95%CI: 1.03-1.14) depending on the type of pollutant analyzed.[75] Other large studies have also reported similar links between outdoor pollution and childhood asthma.[76,77]

The ESCAPE project also analyzed five European adult cohorts (overall ~7500 participants) and found that higher exposure to nitrogen monoxide (NO), NO_2, and PM_{10} from traffic was associated with decreased lung function during adulthood.[78] A very recent study within the ESCAPE framework also found associations between decreased lung function and $PM_{2.5}$ exposure in adults, with stronger effects observed for males.[79] Another work within the ESCAPE project found suggestive (but nonsignificant) evidence that long-term exposure to NO_2, PM_{10}, and $PM_{2.5}$ was associated with higher asthma incidence in adults.[80] Interestingly, a recent analysis of data from three large European cohort studies (with > 600 000 participants) showed that long-term PM_{10} exposure was significantly associated with a 12.8% increase in lifetime asthma prevalence.[81] Furthermore, several studies have confirmed the association between outdoor pollution and asthma exacerbations.[82] Notably, a study from the *Improving Knowledge and Communication for Decision Making on Air Pollution and Health in Europe* (APHEKOM) network, which analyzed data from 10 European cities, showed that air pollution was accountable for up to 15% of all asthma exacerbations.[83]

Regarding rhinitis, the urban dwelling has been related to a higher risk of AR as compared to the suburban dwelling.[84] Nevertheless, studies assessing the effect of air pollution on rhinitis onset have yielded inconsistent results in both children [85] and [86] adults, which contrasts with the large body of evidence relating air pollution to asthma.

Besides outdoor pollution from traffic, industry, energy production, heating, etc, emissions from livestock farming include specific pollutants such as organic dust, toxins from microorganisms, and gases like ammonia or methane.[87] These agents also influence the respiratory system either directly or through their role as precursors of other polluting particles. A large-scale population-based

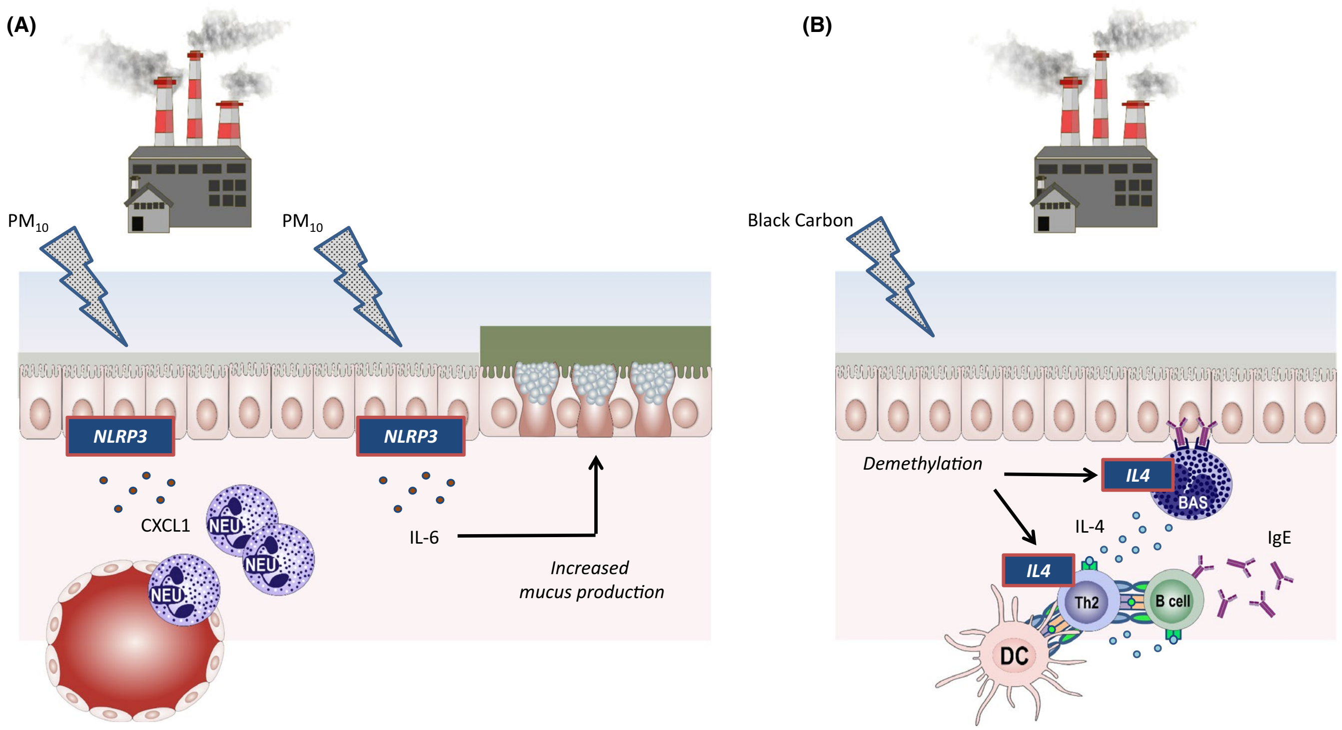

FIGURE 2 Innate and adaptive immune effects of outdoor pollution on respiratory epithelium: A, PM_{10} upregulates the expression of NLRP3 by airway epithelial cells (AEC). AECs in turn release CXCL1, which contributes to the recruitment of neutrophils from the bloodstream. AECs also release IL-6, which promotes mucus secretion: B, Black carbon induces the methylation and the expression of the *IL-4* gene in different immune cells in the respiratory epithelium. Increased levels of IL-4 promote both mucosal Th2 cell priming and local IgE production by IgE + B cells. *NRLP3: nucleotide-binding domain, leucine-rich repeat protein 3*

study including ~2000 Dutch rural dwellers recently showed that increased levels of livestock-related air pollution were associated with decreased lung function, even in nonfarming individuals.[87]

3.2 | Environmental-human interactions

The respiratory epithelium is composed of a pseudostratified layer of ciliated airway epithelial cells (AECs) intermingled with mucus-producing goblet cells.[88,89] A recent study compared the response of primary murine and human AECs to either traffic-derived or ambient (collected in Sidney metropolitan area) $PM_{2.5}$ and PM_{10}.[90] Noteworthy, ambient PM_{10} induced a stronger secretion of IL-6 and CXCL1 by AECs, an effect attributed to the higher content of iron-rich particles from geological origin, as compared to traffic-derived PM_{10}. Importantly, PM_{10}-mediated secretion of cytokines is dependent on the *nucleotide-binding domain, leucine-rich repeat protein 3* (NLRP-3), a component of the inflammasome.[91] The PM_{10}-mediated activation of the inflammasome induced profound innate immune effects in mouse models of allergic asthma, but was dispensable for PM_{10}-facilitated allergen sensitization.[91] This finding indicates that PM_{10} activates distinct inflammatory pathways, which might independently contribute to asthma pathogenesis.

Primary AECs from patients with severe asthma released more cytokines when exposed to PM or diesel exhaust (DE) compared to those from healthy subjects [92] or patients with less severe asthma phenotypes.[89] This observation might explain how pollutant-induced epithelial insults[93,94] can trigger asthma exacerbations.[83] Nevertheless, segmental allergen challenges in atopic subjects exposed to either DE or filtered air did not induce a different release of inflammatory mediators.[89,95] This finding suggests that the adjuvant effect might rely on repetitive exposures. A recent mouse study[96] compared the effects of a two-hour exposure to DE or to the allegedly less toxic biodiesel (BD). Both exhaust products induced cardiovascular and pulmonary inflammation, while only BD generated an increase of neutrophils in bronchoalveolar lavage.

The environment acts on the genome inducing epigenetic changes, which function as important effectors of external insults. Epigenetic modification induces alterations in the DNA structure leading to changes in gene expression and inducing downstream disease.[97] Two recent studies analyzing pediatric populations from New York city showed a relationship between black carbon exposure and relevant epigenetic changes in immune genes.[98,99] In a study analyzing samples from the oral mucosa, individuals with higher black carbon exposure had lower DNA methylation levels in the *IL-4* gene, possibly leading to higher expression.[99] This effect was even more significant in IgE-sensitized children[99] (Figure 2).

Importantly, most experimental studies apply pollutants in water solutions. This approach specifically selects for water-soluble components and modifies their chemical properties and interaction with AECs. This fact partly hampers the translation of the results from experimental settings to naturally occurring diseases. Moreover, in many studies, AECs are cultured submerged and in monolayers, which does not reflect their natural physiology. Therefore, experimental designs using primary AECs grown at the air-liquid interface are required to investigate the real effect of PM or DE exposures on AEC responses in health and disease.

3.3 | Environment-environment interactions

Some air pollutants do not only have a direct effect on the respiratory system but also interact with plants and fungi to enhance the production and allergenicity of pollen, like ragweed or cypress,[100,101] and of fungal spores.[102] For example, ragweed in an urban area with high CO_2 concentrations grew faster and flowered earlier and more intensely, which leaded to the production of more pollen, as compared to ragweed grown in rural areas.[103] Recently, it has been shown that pollutants can also promote the release of allergens via direct cell damage.[104] Pollen grains and fungal spores contain several bioactive compounds, which may exert pro-inflammatory and pro-allergic effects.[105,106] Recent data suggest that several pollen-associated lipid mediators (PALMs) activate Th2 cells to promote IgE synthesis in vitro.[107] Importantly, the pollen collected next to roads with heavy traffic released higher amounts of PALMs.[104] Similarly, a study carried out in Germany showed that birch trees exposed to higher concentrations of ozone produced more birch allergen (Bet v1) and PALMs per pollen grain than ozone-free trees.[108] Importantly, the skin prick test performed with an allergenic extract obtained from the highly exposed trees induced a significantly larger wheal diameter in birch pollen-AR patients as compared to the less exposed trees[108] (Figure 3).

Pollutants can also induce the oxidation or nitration of allergens, leading to changes in their conformation or stability. These chemical modifications enhance their immunogenicity and affect their interaction with receptors on immune cells.[11,104] Several studies have shown that nitrated fungal spores[109] and nitrated pollen from birch, ragweed, and hornbeam[108,110-112] have increased T cell–stimulatory and IgE-inducing capacity. Therefore, it is tempting to speculate that nitration by air pollutants plays a role in the IgE sensitization to allergens.[105]

However, the clinical significance of these phenomena remains unclear.[113] Epidemiological studies are largely limited by their inability to quantify individual exposure to air pollutants and allergens on a population scale. A French study including 36 397 AR patients found no effect of air pollution on the association between airborne pollen concentrations and rhinitis severity.[114] Conversely, a study in eleven Canadian cities showed an interaction effect of air pollution on the risk of asthma-related hospitalizations and the burden of pollen grains and fungal spores.[115] These findings have been recently confirmed in a study conducted in Belgium, which reported a synergistic effect of ozone, PM_{10} and pollen exposure on the risk of asthma-related hospitalizations.[116]

Table 2 summarizes the main effects of outdoor pollution on AR and asthma.

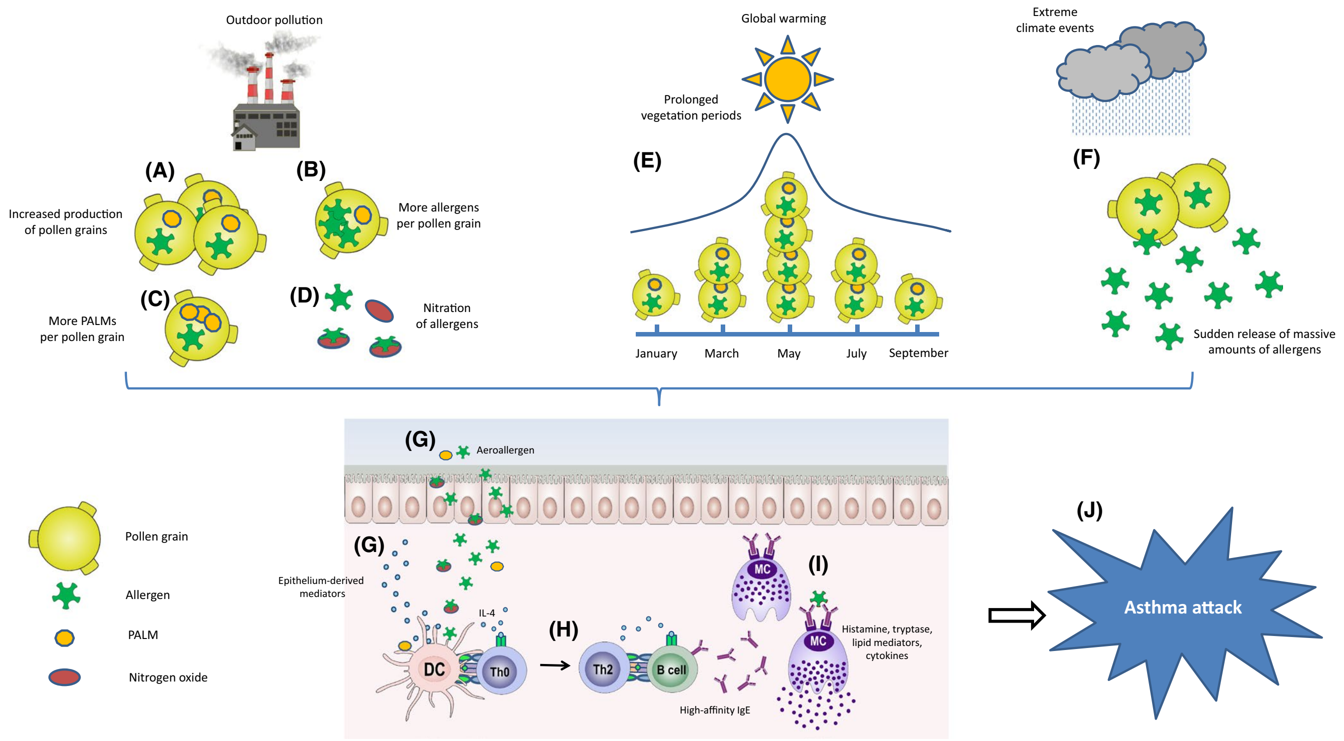

FIGURE 3 Effect of outdoor pollution and climate change over allergenic plant species: Outdoor pollution increases the amount of pollen grains produced by plants (A), and the amount of both allergens (B) and PALMs (C) per pollen grain. Moreover, aeroallergens can become chemically modified by outdoor pollutants like nitrogen oxides (D). The global warming induces prolonged vegetation periods of allergenic plants (E), and extreme climate events like thunderstorms, which provoke the sudden release of massive amounts of allergens to the atmosphere (F). All these effects result on a higher availability of aeroallergens, and they increase the chances of interaction between the allergens and the stromal and immune cells of the airway mucosa. The interaction of native and nitrated allergens with airway epithelial cells can result on the release of pro-inflammatory mediators (G), whereas allergen interaction with dendritic cells can result on IgE sensitizations (H). The chances of sensitization are further increased by the higher availability of PALMs and nitrated allergens (G). Moreover, allergen interaction with sensitized mast cells can induce the release of inflammatory mediators (I), ultimately inducing the onset of asthma attacks in pollen-allergic patients (J). *PALM: pollen-associated lipid mediator*

4 | CLIMATE CHANGE

4.1 | Climate change and aeroallergens

Air pollution and climate change are closely interlinked. Nowadays, the vast majority of global energy is derived from fossil fuels whose burning generates huge amounts of CO_2, methane, black carbon, nitrogen oxides, and sulfate aerosols.[117] Some of these pollutants (e.g., CO_2) are naturally occurring greenhouse gases, which persist for long periods in the atmosphere. Other agents (e.g., methane or black carbon) have shorter lifetimes but also contribute to climate change.[118] Greenhouse gases help keep the earth warm by absorbing the sun's energy and by redirecting it back to the earth's surface.[117] However, an overabundance of greenhouse gases traps an excessive amount of heat in the atmosphere and ultimately accounts for global warming.[119]

Global warming alters local vegetation patterns and speeds up the growth rate and phenology of plants, leading to increases in airborne pollen concentrations[100,120] and changes in the geographical spread of plants.[121,122] In this regard, climate change was associated with increased duration of the ragweed pollen season in different studies conducted in North America and Europe.[123-125] Changes in atmospheric humidity and precipitation also very likely affect the growth and distribution of fungi, yet this aspect remains uninvestigated.[126] The interactions of these changes with the photoperiod will modify the migration pattern of some plants and fungi.[127] Unlike air pollution,[108] global warming has not been related to date to enhanced allergenicity of plants.[100]

The effects of climate change on allergenic plants and fungi[128-130] are likely to continue in the future. A long-term prediction of these changes is challenging given the many variable factors, although computation efforts are currently ongoing.[121,131,132] A process-based model of weed growth, plant competition, and population dynamics predicted that ragweed might spread to Northern European countries.[121] Ragweed is a native species in North America, but is now rapidly invading several European areas.[121] The colonization of geographical areas by new species will likely induce respiratory symptoms by both de novo sensitizations and cross-reactivity with pre-existing species.[133,134]

TABLE 2 Consequences of outdoor air pollution over allergic rhinitis and asthma

Outdoor Air Pollution	
Environmental factors	**Health outcomes**
Pollution from traffic and industry (PM_{10}, $PM_{2.5}$, NO, NO_2, etc)	
During childhood	Higher asthma prevalence after the school age[74-77]
During adulthood	Possibly higher asthma prevalence[80,81]
Lifelong	1. Poorer lung function[72,78,79] 2. Higher rate of asthma exacerbations (82. 83) 3. Conflicting results on AR onset[85,86]
Livestock farming (organic dust, toxins form microorganisms, gases like ammonia and methane, etc)	Decreased lung function[87]
Black carbon	Possibly epigenetic changes leading to increased type two inflammation in children[99]
Interaction between air pollutants (PM_{10}, nitrogen oxides) and allergens (pollen, fungal spores, etc)	
Production of more pollen, more allergens per pollen grain, and more PALMs per pollen grain[100-104,108]	1. Potentially, facilitation of IgE sensitization against aeroallergens[104,107] 2. Higher rate of asthma-related hospitalizations[115,116]
Release of allergens via direct cell damage[104]	
Nitration of allergens[109-112]	

Abbreviation: PALM, pollen-associated lipid mediator.

4.2 | Climate change as an inducer of respiratory and allergic diseases

There is no doubt that climate change causes or exacerbates respiratory diseases.[135-139] The most important effects of climate change on respiratory health are described below (also summarized in Table 3):

1. The higher temperatures and increased frequency of heatwaves amplify the exacerbation rate, morbidity, and mortality of respiratory diseases.[140-143] The extent of this association usually parallels the pollution levels of local air.[144]
2. The seasonality and severity of AR and asthma are affected by the growth patterns of allergenic species,[145-148] which can act synergistically with air pollutants.[149] Global warming might also alter the species dominating distinct ecological niches.[150]
3. Climate change is expected to alter the pattern of respiratory tract infections.[151,152]
4. Intensive rain and flooding induce dampness and mold proliferation in affected households,[61,153] thus influencing the quality of indoor air.
5. Extreme climate events are the cause of specific phenomena like thunderstorm-related asthma episodes.[153,154] During these episodes, a large number of patients experience asthmatic symptoms during the initial 20-30 minutes of a large-scale thunderstorm, providing that it occurs during the allergen season and induces a cold outflow.[155] This phenomenon arises from a sudden release of massive amounts of aeroallergens,[154] and a causative role for pollen allergy is suspected.[156] Numerous case studies of thunderstorm-related asthma have been documented,[61] the largest of which took place in Melbourne (Australia) on November 21, 2016 (~4000 patients presented at hospitals with respiratory symptoms).[156,157]

Besides the direct effects of global warming on the airways, the altered levels of aeroallergens account from many of the effects of climate change on respiratory health. As climate change will also influence the amount and type of pollutants in the air, which themselves interact with aeroallergens,[138] the individual and/or combined effects of these environmental parameters on respiratory health are very difficult to predict.

5 | INTERVENTIONS TO MODIFY AIR POLLUTION AND CLIMATE CHANGE

5.1 | Policy changes

Policy changes are the most effective measures to decrease pollution.[158,159] While actions of individual citizens can mitigate air pollution only to a small extent,[160] larger lifestyle changes at the population level mainly result from policy interventions. For example, many countries have implemented smoke-free legislation to protect the population, particularly children in public places. A recent meta-analysis of 35 pediatric studies showed that enforcement of smoke-free policies was significantly associated with a 9.8% (95%CI: 3%-16%) and 18.5% (95%CI: 4.2%-32.8%) reduction of hospital admissions due to asthma attacks and lower respiratory tract infections, respectively.[13] These associations tended to be stronger in regions with more comprehensive smoke-free laws, indicating that stringent smoke-free policies are necessary to gain maximum health benefits.

The replacement of fossil fuels by renewable energy sources and commitment to a complete phaseout of coal power by the industry represent necessary milestones in the roadmap for a more environmentally friendly economy.[161,162] Over the past decade, the implementation of the European Union (EU) environmental policy framework contributed substantially to decreasing the emissions of many air pollutants and improving air quality across Europe.[163] The EU recently released an updated version of the *environmental performance standards for large combustion plants*, which set stricter emission ranges for NO, NO_2, sulfur dioxide, PM, and mercury from power plants.[164] A recent *National Emission Ceiling Directive* was also released as a measure to reduce emissions from different sectors.[165]

TABLE 3 Consequences of climate change and global warming over allergic rhinitis and asthma

Environmental changes	Health outcomes
More frequent extreme climate events	
Heatwaves, wildfires, higher temperatures, etc	Amplification of exacerbation rate, morbidity, and mortality of respiratory diseases.[140-143]
Intensive rain and flooding	Dampness in affected households with subsequent proliferation of molds and cockroaches.[61,153] See the consequences of the deterioration of indoor air quality in Table 1.
Thunderstorms	Increase in asthma exacerbations and hospitalizations following thunderstorm-related asthma episodes[153-157]
More intense and more prolonged pollen seasons.[100,120,123-125] Possibly similar changes for other allergens (e.g., fungi).	Increase in the severity and alteration of the seasonality of symptoms of allergic rhinitis and asthma [145-148]
Alteration of the local vegetation patterns with changes in the geographical spread[122] and migration of plants[127] Colonization of geographical areas by new species [121] with alteration of the species dominating distinct ecological niches.[150] Possibly, similar changes for fungi.[126]	Increased prevalence and severity of allergic rhinitis and asthma due to both de novo sensitizations and cross-reactivity with pre-existing species[133,134]
Possibly changes in the growth pattern and distribution of pathogenic microorganisms.[151]	Possibly changes in the pattern of respiratory tract infections

Nevertheless, a recent report from the *European Economic Area* showed that a large proportion of European citizens and ecosystems are still exposed to concentrations of air pollutants exceeding the legal limit values of the EU and the guideline values of the WHO (Table 4).[2] Renewable energy sources currently account for 24% of total electricity generated,[166] illustrating the long way to go before fossil fuels can be replaced. Government investment in clean energy should come together with policies incenting suppliers into a timely transition out of existing fossil-based infrastructure.[166]

At a local level, greenhouse-gas emissions can be reduced by shifting from private motorized transport to more sustainable modalities, such as public transport, cycling, and walking. There is evidence that having good cycling infrastructure integrated with public transport, training of both cyclists and motorists, and making driving costly can promote cycling.[166] Local authorities could also incentivize the population to shift to sustainable electric vehicles by introducing ownership tax exemptions and additional advantages such as waivers on fees (e.g., plug-in charging station or parking spots). Studies evaluating the effect of nearby green areas on respiratory health have yielded inconsistent results,[167] possibly due to the complex interactions between global warming, vegetation, and air pollution. Recent studies using the methodology recommended by the *Coordination of Information on the Environment* (CORINE) program have yielded conflicting results, indicating either a beneficial impact of greenness on general health,[168] or an increased risk of wheezing, asthma, and AR in children exposed to green spaces, especially coniferous forests.[169] Until future studies shed more light on this issue, it seems reasonable that city development plans include green spaces with diverse and nonallergenic species.[170,171]

The *European Academy of Allergy and Clinical Immunology* (EAACI)/*European Federation for Allergy and Airways Diseases Patients' Associations* (EFA) Interest Group on Allergy and Asthma at the European Parliament recently launched a call to increase the awareness about asthma and promote the legal changes required to decrease the burden of air pollution.[172,173]

5.2 | Lifestyle adjustments

Various lifestyle adjustments can mitigate air pollution and climate change and indirectly decrease the onset and progression of respiratory diseases. The avoidance of individual motorized transportation constitutes a simple and basic approach. Exercising outdoors is also recommended, as its benefits are expected to exceed the negative impacts of exposure to outdoor allergens and pollutants, at least in most European cities.[174,175] However, limiting the time spent outdoors during the pollen season (for pollen-allergic patients)[176] and during high traffic hours or warm days is a reasonable approach. Air quality alerts, pollen calendars, and allergy diaries, among other mobile health tools, can help plan outdoor activities, and control and monitor symptoms.[177,178] Besides mobility, livestock to provide meat for human consumption is among the main causes of CO_2 production. Therefore, reduction of meat consumption, together with limiting trips made by air traffic, and increasing the use of recyclable materials, are also meaningful measures to reduce CO_2 emissions.

Adequate and regular ventilation of the living spaces and the filtration of indoor air can prevent mold growth and reduce indoor NO_2 concentrations. Moreover, preventing dampness

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TABLE 4 Percentage of the urban population in the EU-28 exposed to air pollutant concentrations above the EU limit or target values and above the WHO air quality guidelines (AQGs)

Pollutant	EU reference value	Exposure estimate (%)	WHO AQG	Exposure estimate (%)
$PM_{2.5}$	Year (25)	7-8	Year (10)	82-85
PM_{10}	Day (50)	16-20	Year (20)	50-62
O_2	8-h (120)	7-30	8-h (100)	95-98
NO_2	Year (40)	7-9	Year (40)	7-9
BaP	Year (1)	20-25	Year (0.12) RL	85-91
SO_2	Day (125)	<1	Day (20)	20-38
Key	<5%	5%-50%	50%-75%	>75%

Note: Minimum and maximum values observed between 2013 and 2015. The comparison is made for the most stringent EU limit or target values set for the protection of human health. As the WHO has not set AQGs for benzo(a)pyrene (BaP), the reference level in the table was estimated assuming WHO unit risk for lung cancer for PAH mixtures and an acceptable risk of additional lifetime cancer risk of approximately 1 in 100 000. Estimated reference levels are given between parentheses and in $\mu g/m^3$, except for BaP, which is given in ng/m^3. This table was modified and reproduced with permission from the European Environmental Agency Report No 13/2017. Air quality in Europe—2017 report. Available from: https://www.eea.europa.eu/publications/air-quality-in-europe-2017 (assessed: July 2018).

and limiting the number of carpets can decrease the burden of HDMs and molds.[179] Nevertheless, in areas with a high burden of HDMs, these strategies are often insufficient, as emphasized by international guidelines and consensus documents on AR and asthma.[180-182] Moreover, individuals with an atopic predisposition should carefully consider the choice of keeping a pet.[179,183] In this regard, a large epidemiological survey identified exposure to cat during the first year of life as an independent risk factor for AR and asthma presence during school age.[184]

6 | CONCLUSION

Given the explosive global rise in urbanization, industrial production, aviation, road traffic, etc, the preservation of good air quality will become increasingly challenging. This narrative review summarizes the current literature about the potential effects of air pollution and climate change on AR and asthma. Although a formal meta-analysis was outside the scope of this review, and there were several difficulties for direct comparisons of the studies due to methodological differences, several conclusions could be made.

1. The evidence relating passive smoking and exposure to traffic-related pollution (including NO_2 and $PM_{2.5}$) to childhood asthma is currently robust, whereas the link with exposure to smoke from biomass and deleterious VOCs seems weaker.
2. Although the relationship between air pollution and adult-onset asthma has been uncertain for years, recent data suggest that passive smoking and traffic pollutants might be related to asthma development in adults.
3. The relationship between air pollution and AR onset seems less conclusive as compared to asthma in both children and adults.
4. The mechanisms for how pollutants induce respiratory disease are varied. Recent evidence indicates that epigenetic changes in the respiratory epithelium and the alteration of airway microbiota might account for some of the effects of $PM_{2.5}$ and tobacco smoke, respectively.
5. Exposure to indoor and outdoor allergens is a well-established risk factor for the development of AR and asthma in both adults and children, with indoor allergens inducing more severe phenotypes of airway allergy.
6. The capacity of outdoor pollutants to increase the allergenicity and immunogenicity of aeroallergens has been shown in vitro, but the clinical implications of these phenomena require further analysis.
7. Unlike pollutants, climate change affects pollen grains and fungal spores by increasing their availability rather than altering their chemical structure. Some of the deleterious effects of climate change on respiratory health are likely to arise from this increased availability.

As a key message, we can conclude that the detrimental effects of air pollution and climate change on human health are greatly preventable through timely implementation of adequate legislations. Governments need to adopt effective and evidence-based regulations, as political interventions are the only way to achieve large improvements at the population level. All these efforts are crucial steps in the pathway to clean air, and ultimately, to the prevention and reduction of AR, asthma, and other chronic respiratory conditions.

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CONFLICTS OF INTEREST

Apart from academic affiliations, ZD acts as Executive and Scientific Medical Director at a phase I/II pharmacological unit (QPS-NL), which performs clinical studies for pharmaceutical companies. In the past 3 years, ZD received honoraria, consultancy and speaker fees from Astrazeneca, ALK, Aquilon, Boehringer Ingelheim, CSL, HAL Allergy, MSD, Sanofi-Genzyme. The remaining authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

IEG and AM coordinated the work and designed the structure of the review. SB, SJHV, EF, PC, YSC, and PVT reviewed the literature, wrote the manuscript, and prepared the figures and tables. IEG, AM, ZD, JV, CG, and BH critically reviewed and finalized the manuscript.

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