

The Association Between Ambient Air Pollution and Allergic Rhinitis Inception and Control

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Abstract

Purpose of review The prevalence of allergic rhinitis as well as other allergic diseases has been increasing for at least five decades. A possible cause of this increase could be the exposure of genetically predisposed individuals to a constantly changing indoor and outdoor environment. Two of the changes strongly implicated in the sensitization process and in the triggering of symptoms of allergic diseases are air pollution and global warming induced by climate change, factors which are closely related to each other.

Recent findings Environmental pollutants may act on a developing immune and respiratory system, which increases the possibility of a negative impact on the structural and functional maturation of the respiratory system, and on the immune response in children. The increase in allergic respiratory diseases appears to be related with an increase in the atmospheric concentration of gases and respirable particulate matter.

Summary This article summarizes the main consequences of the complex relationship that exists between allergic rhinitis, environmental pollution, and climate change and presents some potential measures aiming at modifying some aspects of this intriguing relationship to achieve a clinical benefit in patients suffering from allergic diseases, especially allergic rhinitis.

Introduction

The term “exposome” was proposed by Wild to encompass human environmental non-genetic exposures, from conception onwards, complementing the genome [1]. It was developed to draw attention to the need for better and more complete comprehension of environmental exposure data, in order to balance the investment, tools, and knowledge in genetics [2•]. Within the exposome, three overlapping domains have been described: (1) a general external environment to include factors such as the urban environment, climate factors, social capital, and stress; (2) a specific external environment with specific allergens, contaminants, diet, physical activity, tobacco, infections, and other, and (3) an internal environment to include internal biological factors such as metabolic factors, gut microflora, inflammation, oxidative stress, and other [3].

The changes currently taking place in the atmosphere and climate, including global warming induced by human activities, have a significant impact on the biosphere and the human environment. Experimental and epidemiological studies have shown a positive correlation between climate change, air pollution, and the incidence of respiratory allergic diseases [4–7]. In last decades, a significant increase in the prevalence of allergic respiratory diseases and bronchial asthma has been observed.

In particular, allergic rhinitis (AR) is among the most common diseases worldwide and usually persists throughout life [8]. The prevalence of AR has been estimated to be approximately 2 to 25% in children [8, 9] and more than 40% in adults [8, 10]. It has increased in prevalence over the past 20 years, affecting approximately 17 to 28.5% of the adult population in Europe [11], i.e., more than 40–50 million people in the USA and over 500 million worldwide [12, 13]. This upward trend cannot be explained only by genetic factors which play a significant role in the development of asthma and allergic diseases, but also by changes that have taken place in the environment. Therefore, it is expected that any intervention that can be done to improve the environment would benefit the general population at large and patients with allergic rhinitis. It could reduce the possibility of developing allergic diseases, facilitate treatment, and improve the quality of life of these patients. Common symptoms of allergic rhinitis include sneezing, a runny, stuffy, itchy nose, coughing, a sore or scratchy throat, itchy watery eyes, frequent headaches, eczema-type symptoms, and excessive fatigue.

In this article, we will discuss three important aspects of the exposome, such as environmental pollution, climate change, and exposure to inhalant allergens.

Air pollution and allergic respiratory diseases

According to the World Health Organization (WHO), air pollution is the contamination of the indoor or outdoor environments by any chemical, physical, or biological agent that modifies the natural characteristics of the atmosphere.

Household combustion devices, motor vehicles, industrial facilities, and forest fires are common sources of air pollution. Pollutants of major public health concern include particulate matter, carbon monoxide, ozone, nitrogen dioxide, and sulfur dioxide.

Outdoor and indoor air pollution may cause respiratory and other diseases, which may be fatal [14]. Exposure to indoor and outdoor environmental pollutants has gained relevance as a serious public health problem due to an increase in the industrial activity, especially in developed countries, and changes in lifestyle [15••]. They can affect the health of adults and children, the latter group being particularly vulnerable to their action [16, 17]. Environmental pollutants may act on a developing immune and respiratory system, which increases the possibility of a negative impact on the structural and functional maturation of the respiratory system, and the immune response of children [17, 18].

The effects of pollutants on human health, and especially children, will depend on the type of pollutant, size, concentration, and solubility, the time of exposure, the ability to react with other pollutants and generate more toxic substances and the age at first, or consequent exposures, and individual susceptibility [17–19]. Pollutants interact with the immune system and induce pro-inflammatory epigenetic changes, which may cause, trigger, or aggravate numerous diseases [15••].

The impact of environmental pollution on health is produced by multiple pathogenic mechanisms, which include the generation of oxidative stress, changes in immunomodulation, systemic inflammation, and epigenetic alterations [19, 20, 21•, 22]. Several studies suggest that air pollution facilitates allergic sensitization in predisposed individuals [23–27]. For instance, laboratory studies have shown that diesel exhaust particles, nitrogen dioxide (NO₂), and ozone (O₃) can intensify the response of the airways to inhaled allergens and, therefore, a smaller amount of allergens could be needed to trigger a reaction [21•].

The increase in allergic respiratory diseases appears to be paralleled by an increase in the atmospheric concentration of gases and respirable particulate matter (Table 1). Many studies worldwide have shown positive and significant correlations between air pollution, particularly with vehicle and industrial emissions and increased risk of AR [29, 30].

NO₂ pollution [29, 31] and O₃ [30] in industrial areas were positively associated with AR in children and air pollutants such as PM₁₀, PM_{2.5}, O₃, CO, NO, NO₂, and SO₂ had a positive correlation with the incidence of AR, when compared with meteorological factors [32]. Several studies have also demonstrated that air pollution can promote and exaggerate response to allergens in the nasal cavity by increasing the allergenicity and bioavailability of airborne pollen allergens [28•]. There is also data that supports a direct relationship between air pollution and AR. One study provides evidence of a significant association between ambient particulate pollutants (PM_{2.5} and PM₁₀, which are usually present in high concentrations) and the prevalence of AR in Northeastern China [33].

Climate change, air pollution, and allergic respiratory diseases

There seems to be an overlap between air quality and climate change. Climate change is defined as a significant and lasting change in local or global climate

Table 1. Possible relationship between components of air pollution and allergens in inducing respiratory allergy [28]

Air pollution may be responsible for the following:
• Interaction with pollen grains, leading to increased release of allergens with modified antigenicity
• Interaction with microscopic allergen-carrying particles released by plants. These particles are able to reach the lower airways in inhaled air, inducing asthma in predisposed individuals.
• An inflammatory effect on the airways of susceptible individuals, with increased epithelial permeability, easier penetration of pollen allergens in the mucosa, and easier interaction with cells of the immune system. There is also evidence that predisposed individuals have increased airway reactivity induced by air pollution and increased bronchial responsiveness to inhaled pollen allergens.
• An adjuvant immunologic effect on IgE synthesis in atopic individuals, as already shown with diesel exhaust particles

patterns. The causes can be natural, such as variations in the energy received from the sun, volcanic eruptions, ocean circulations, biological processes, and others, or originated by various human activities, for example, through the emission of CO₂ and other greenhouse gases that trap heat, or an alteration in the use of large land areas.

The term “greenhouse effect” refers to the retention of heat from the sun in the Earth’s atmosphere by a layer of gases in the atmosphere. According to NASA, our planet has been heating up at an accelerated pace over the past decades. Climate experts predict that temperatures will continue to rise [34]. This phenomenon has been observed since the end of the nineteenth century. In this period, and since reliable measurements have been made, an increase of approximately 0.8 °C has been registered, two thirds of which has occurred since 1980 [35]. The main cause of this warming is the increase of greenhouse gases that result from human activities, such as the burning of fossil fuels (coal, gasoline, natural gas, and oil) and deforestation. The industrialized world has caused a 30% increase in the concentration of these gases since the last century, when, without human action, nature was responsible for balancing emissions.

Extreme heat is one of the most important causes of climate-related mortality, worldwide. Climate change has produced more frequent and intense heat waves and this trend is expected to increase during the coming decades [36]. It has also conditioned an increase in the frequency of cardiorespiratory attacks due to high concentrations of O₃ at ground level, changes in the frequency of respiratory diseases due to transboundary (long-range) environmental pollution, and altered distribution of allergens and some vectors of infectious diseases [5].

There are several potential influences of global climate changes on different aeroallergens, especially on pollens. The increase in CO₂ and other greenhouse gases, added to the rise in temperature and other climatic changes, has modified exposure to pollens due to, at least, some of the factors listed in Table 2 [37••]. Climate change has a direct influence on the abundance and properties for plants and on fungi emitting aeroallergens [38–41]. The complex interrelationship between ambient pollution, climate change, and aeroallergens is summarized in Fig. 1 [42].

The combination of genetic susceptibility and increased environmental pollution, which favors allergic sensitization, increases organ hyperreactivity and can act as a trigger of respiratory symptoms. In addition to the climatic change that conditions an increase in the production and allergenicity of the pollens, genetic susceptibility and increased environmental pollution constitutes a harmful association which affects health in general and respiratory diseases in particular [43, 44].

Table 2. Modifications in exposure to pollen allergens caused by climate changes [37]

- Increase and acceleration of plant growth
- Increase in pollen production of each plant
- Increase in the amount of proteins contained in the pollen grain (and therefore antigens)
- Alteration of the distribution of species (populations previously not exposed to certain pollens ow they are)
- Early start of plant growth, early start of pollination, and consequently, prolongation of the pollen season

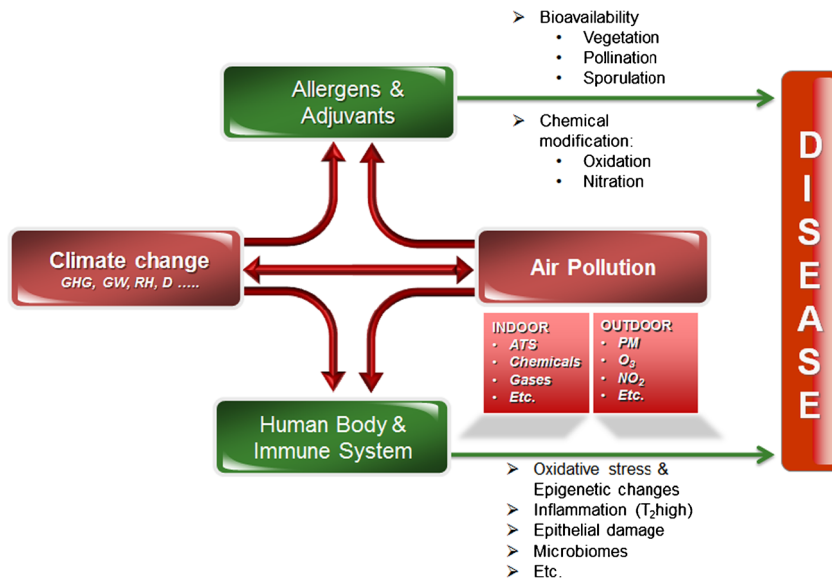


Fig. 1. Interplay between air pollution, climate change, and aeroallergens (Modified from Reinmuth-Selzle K et al. [42]). PM, particulate matter; NO₂, nitrogen dioxides; O₃, ozone; ATS, ambient tobacco smoke; GHG, greenhouse gases; GW, global warming; RH, relative humidity; D, drought

There is some evidence that climatic factors may indirectly contribute to an increase in the severity of AR symptoms through its effects on air pollution, pollen allergens, and mold spores, but not necessarily an increase in the prevalence of AR [45]. A recent analysis reported that regional differences in the prevalence of AR in the USA were related to a variety of climate factors, including humidity, drought, heat, and precipitation [46]. Some association between changes in climate over time and AR prevalence trends were also found. Upperman et al. observed a modest, but significant, association between exposures to extreme heat events and hay fever prevalence. These findings were more pronounced for extreme heat events taking place in the springtime [47]. Therefore, more studies are needed to determine which role, if any, climate factors may play in the development of AR.

Aeroallergens

Aeroallergens most frequently involved in the etiology of asthma and perennial allergic rhinitis are found in homes, or workplaces, while allergens associated with seasonal allergic symptoms come mainly from the outdoor environment.

Main indoor aeroallergens

There is a significant increase in allergic sensitization and clinical symptoms in westernized countries. This fact is related to several possibilities, including (a) an increase in the time (which can exceed 90%) that humans spend inside of homes, or buildings; (b) a decrease in the natural ventilation rate in modern buildings, with the consequent increase in the concentration of indoor allergens; (c) the modification of the environmental temperature and humidity by

heating, which produces ideal conditions for the growth of mites throughout the year; (d) the use of carpets and upholstered furniture which create ideal habitats for mites and are reservoirs of indoor allergens; (e) a greater presence of pets inside the homes; and (f) the diet.

In recent years, greater attention has been paid to the role of indoor allergens as a cause of sensitization and allergic respiratory diseases. Allergenic substances can be found in most familiar and occupational environments. The presence of carpets and structural and technological changes, such as heating, cooling, and humidification in homes, have made them more efficient and more comfortable for tenants. All these changes have provided an ideal habitat for dust mites, pets, cockroaches, and mold and bacteria in air conditioning ducts. All these sources of allergens play an important role in the sensitization process of the inhabitants of a home, in particular, those with a genetic predisposition for atopy. The adjuvant effect of some bacterial products, such as endotoxins, may also be important. It is important to note that exposure to all these indoor allergens may occur at the same time, thus increasing the risk for sensitization.

House dust is the main reservoir of indoor allergens. It is composed of organic and inorganic matter and includes plant and synthetic fibers, fungal spores and mycelia, bacteria, pollen grains, insects and insect feces, mammalian epithelia, and mites and mite feces. The term “indoor allergen” is applied to a variety of allergens, which are found inside human dwellings. Indoor allergens are by-products of living organisms such as cats, dogs, and other pets, as well as insects, molds, bacteria, and mites. Immunochemical methods have been developed to identify and estimate their concentrations in air and in settled household dust [48, 49]. These techniques help in the understanding of the natural distribution of allergens in the air and settled dust and can determine the concentrations that are associated with sensitization, or allergic respiratory symptoms.

House dust mites are the main source of indoor allergens throughout the world and especially in tropical and subtropical countries. Although the existence of mites in the environmental dust and its possible association with the development of asthma were known since the beginning of the century, it is not until 1967 that these arthropods could be identified as the main source of house dust allergens [50].

Main outdoor aeroallergens

Airborne pollen and fungal spores are the most important allergens in the outdoor environment. The importance of each species is a direct consequence of the phytogeographic conditions of each region. In this sense, it is important to mention that over the last decades, many studies [24, 37•, 44, 51–57] have shown changes in production, dispersion, and allergen content of pollen and spores. The nature of these changes may be different in different regions and even plant and mold species. There is increasing evidence that these changes could be due to the previously mentioned increasing in air pollution and the climate change.

Opportunities for intervention to reduce the burden of AR

Strategies tending to reduce exposure to environmental pollutants

A series of strategies tending to reduce exposure to environmental pollutants have been suggested by scientists. The health implications of combined

exposures to different pollutant sources have also been pinpointed [58, 59]. The current air quality standards were established decades ago, according to the knowledge available at that time about the direct effects of each pollutant acting, separately, on the general population.

However, more recent studies have focused on combined exposures of air pollutants with aeroallergens. The evidence in risk groups (i.e., children, the elderly, and patients with respiratory diseases) shows a distinct potentiation of effects, inferring a health impact more important than previously supposed. It seems now very appropriate to evaluate the costs of the etiological culprit attributable to air pollution in the wide range of factors affecting allergic diseases. Allergic patients constitute a sentinel group. The increase in prevalence and worsening health status is warning us about the need to act through corrective environmental measures (primary prevention). The costs of allergic diseases and other diseases, triggered or aggravated by air pollution, are enormous and increasing.

To conduct local environmental impact assessment studies seems mandatory. The data emanating from studies in cities of developed countries cannot always be extrapolated to other regions. Local studies are required to know how pollution by transport affects our population, if the current regulations are suitable for everyone, and what are the best fuel options, among other issues [60].

Transportation, fuel, and public health issues must be integrated in a multidisciplinary basis. Transport and fuel policies have a huge impact on public health. Unfortunately to date, they have been undervalued [61]. It is the countries undeniable responsibility to integrate them, to ensure the health of the population, and to prevent disease.

Political action on mobile sources based on health and environment should be promoted. Actions aimed at reducing air pollution from mobile sources such as the control of vehicle emissions (exhaust pipes), the use of public transport, cycling, and walking should be encouraged [62]. The use of the particular automotive park should be discouraged by the implementation of better transportation options. Surface traffic must be orderly and fluid. The replacement of tetraethyl lead in fuels, the use of catalytic converters, and the addition of biodiesel to fossil fuel are important but still insufficient advances. Political action on fixed sources (industries, garbage burning, thermoelectric power plants) based on health and environment is mandatory before it is too late.

The contributions from the different scientific societies dedicated to different respiratory diseases, to the development of environmental epidemiology, and to prevention are also necessary.

The re-evaluation of "permitted limits" of environmental contaminants is warranted. For example, Shwartz J et al., [63] looking at 13 years' worth of data from more than 13 million elderly people living in the Southeastern US, found that for each $1 \mu\text{g m}^{-3}$ (roughly 10%) increase in the annual average concentration of $\text{PM}_{2.5}$ in the air in a particular region, mortality risk rose by 2%. The risk showed up even in areas where $\text{PM}_{2.5}$ levels were below current EPA limits. They found that if particle concentrations could be reduced by about 10%, it would lower the death rates of people age 65 and older in the Southeastern US, saving 7000 to 10,000 lives per year.

It is evident that greater collaboration and a joined-up approach from governments and governmental departments consisting of representatives across Health, Transport, Environment, and Education departments are needed.

Environmental control of indoor allergens

Environmental control measures have become increasingly allergen specific. This field has benefited notably from the progress that has taken place in recent years in the knowledge of the characteristics of indoor allergens and their distribution in the environment. The admission of mite allergic asthmatic patients to a hospital, where mite allergen levels were low, produces a significant reduction in patients' bronchial hyperresponsiveness, and therefore, environmental control using a combination of effective measures can be used to prevent and treat allergic respiratory diseases. However, each home is different, and allergen levels can vary from room to room. Therefore, recommendations on environmental control techniques to be used are incomplete and may be less effective, if a previous investigation of the patient's environment is not carried out [64••, 65–68].

Environmental control of mites and their allergens

Here, we summarize the main strategies for abatement mite allergens [69–71]

- Reduction of environmental humidity

Maintaining relative environmental humidity below 50% is one of the logical recommendations for reducing mite populations, since it is the main limiting factor for its development. It is important to keep the relative humidity at approximately 50% constantly (or for most part of the day). In tropical and coastal regions, it is necessary to use high efficiency dehumidifiers, or air conditioning units, to reach these levels of humidity.

- Use of covers impermeable to allergens

The use of impermeable covers in mattresses and beds is one of the most effective ways to reduce exposure to allergens, and their use is therefore highly recommended. However, recent studies indicate that the use of impermeable covers as the only control strategy to reduce exposure to mite allergens seems to be clinically ineffective for the routine management of asthma in adults. It is also necessary to evaluate the quality of the material used in these covers since fabrics with micropores seem to produce greater reduction in exposure to allergens than polyurethane-covered fabrics. Encasings should be used in combination with other strategies, such as the removal of carpets in the bedroom.

- Vacuum cleaning

Carpets, upholstery, curtains, and other textile materials are the ideal habitat for house mites, so their presence is not recommended in homes of asthmatic individuals. Vacuuming upholstered furniture significantly reduces mite allergen levels. However, studies on the effect of vacuum cleaning on these materials indicate that only 10% of all live mites can be removed. Therefore, to vacuum clean in the absence of other measures provides only a transient decrease in the population of mites. It has been recommended to use vacuum cleaners with suitable filters (HEPA or similar), or with special bags of greater thickness to avoid the dispersion of allergens.

- Washing, drying, and dry cleaning of the bed linen

The washing of blankets, covers, and bedding at temperatures above 50 °C, weekly, eliminates mites and effectively reduces their allergens. Washing at

lower temperatures does not eliminate mites although it reduces their allergens. In dryers, the temperature must be maintained above 55 °C for at least 10 min.

- Freezing of toys and small cloth objects

Freezing clothes or small cloth items (stuffed animals, for example) for 24 h is an effective method of eliminating mites. Also, in cold climates, you can leave the bed clothes outside for a night.

- Air filtering

Particles of dust mites which are associated with mite allergens are not found in large quantities in the air. Therefore, the use of air filters does not greatly affect the levels of allergens in suspension.

- Acaricidal products

Different chemical substances have been used to control mites. Generally, these products have demonstrated their effectiveness under laboratory conditions. However, their effectiveness in housing varies considerably. A problem is the fact that acaricides act against live mites, but not against their allergens, which makes the problems persist, if a rigorous cleaning is not carried out. Benzyl benzoate is the most important and the most widely marketed. It is necessary to perform repeated treatments to observe a reduction in the levels of allergens, although not always this decrease is lasting and of sufficient entity to produce a clinical improvement.

Tannic acid is a protein denaturing agent, so it only affects allergens, and has no effect on mites and their growth. As in the case of benzyl benzoate, its effects are not lasting. The joint use of the two products improves the effectiveness of the treatment.

Control of cockroaches

All measures to control cockroaches must be carried out after a detailed inspection in which species, possible food sources, and shelters can be identified. An adequate control of cockroaches, and their allergens, requires physical prevention measures to prevent the entry and growth of cockroaches [72–74]. There are several presentations of insecticides (aerosol, powder, gel, baits...) but the best methods are the use of gels and baits. If the chemical treatment is successful, a reduction in the number of insects is observed in a couple of weeks, being effective for about 6 months. In the case of growth regulators, which affect the development and behavior of the insect, it is common to find high numbers of cockroaches in the following days, but its insecticidal effect lasts longer. All chemical treatment must be accompanied by hygiene measures, which will facilitate the action of insecticides and hinder the settlement of new populations. The most indicated thing to do is to use a vacuum cleaner to clean the inaccessible places, while the floor and walls of the kitchen (and the rest of the house) should be washed with detergent to eliminate the allergens. The bedroom, curtains, and clothing should also be cleaned. Some studies on the effectiveness of methods for environmental control of cockroach show that it is easier to eliminate insects than to reduce allergen levels through aspiration and that the reduction of allergens by successive

aspirations may not be enough to keep them below the levels that cause symptoms. A recent study concluded that the reduction of cockroach allergens can be achieved by combining measures such as education of people, application of insecticides, and professional cleaning of houses.

Control allergens of pets

So far, there are no definitive works that show a significant clinical improvement after environmental control or to have removed the animal [75–77]. The simplest method in the case of patients allergic to cats is the exclusion of the animal from the home. It must also be kept in mind that once the source of the allergens has disappeared, allergen levels may decrease slowly, due to their characteristics and their ease of transportation through the air. Therefore, it is recommended to replace carpets, upholstered furniture, and other reservoirs. It is also recommended to change the mattress or use covers impermeable to allergens. However, there are many people who are not willing to part with their pet, so the following environmental measures have been suggested:

- Washing of pets is a method that allows allergen levels to be reduced very quickly; however, they return quickly to the initial levels, making it necessary to wash twice a week, so it is not advisable. However, frequent washing of objects in contact with the pet is recommended.
- Restrict the presence of the pet to a certain area of the house and avoid, at least, entering the bedroom.
- Remove carpets and other reservoirs. If you are not willing, choose carpets that do not retain allergens and allow them to be vacuumed. Short pile, low density hair carpets, with fibers covered with fluorocarbons (Teflon) and high fiber density per filament, are the most suitable
- Daily aspiration of possible reservoirs
- Use waterproof mattress covers and pillows.
- The use of chemical products such as tannic acid allows reducing the levels of allergens very quickly; however, as in the case of washing, the levels quickly rise again.

Control of indoor molds

Humidity is the main factor in the growth of fungi; therefore, the management of this parameter will directly affect the levels of mold allergens. It is advisable to keep the relative humidity below 50%, avoid accumulations of water, reduce the number of plants inside the house, use air conditioner during the months of higher relative humidity (summer) and heat all the rooms during the winter, do not spread wet clothes inside the home, or eventually use dehumidifiers where necessary [78, 79]. Remediating buildings damaged by dampness and mold for preventing or reducing respiratory tract symptoms is another very good strategy to achieve that goal [80].

Conclusions

According to the WHO, air pollution is the largest environmental risk factor for human disease. They estimate that in 2012, around 1 in 8 deaths

worldwide was due to exposure to air pollution. A recent analysis also confirms that 92% of the world's population lives in places where air quality levels exceed WHO limits. One of the central problems is that most clinicians ignore this fact or directly and simply deny it. Nearly 30 years ago, Alexander Leaf, MD, drew a bold analogy. Changes brewing in climate and the environment, he wrote, may be just as harmful to human health as nuclear war [81]. Leaf, the former chief of medicine at Massachusetts General Hospital in Boston, acknowledged in a 1989 *New England Journal of Medicine* essay [82] that climate change was not in most physicians' purview. Even so, he advised clinicians that dealing with the related health threats "becomes our special burden."

The American Academy of Allergy Asthma and Immunology (AAAAI) recently assessed their members' knowledge, attitudes, and experiences with climate change and health in collaboration with George Mason University in a survey of the membership. Although a majority of respondents (81%) think that human-caused climate change is happening, only 22% indicated that climate change is relevant to direct patient care "a great deal" [83].

Finally and as mentioned previously, the indoor environment is also important in the development of symptoms of allergic rhinitis. Home environmental intervention for the prevention or control of allergic and respiratory diseases is as important as thinking about long-term measures to control air pollution or reduce climate change, both generated mostly by human activity. The control of exposure and the eradication of allergens in the environment require lasting and effective measures so that the clinical effect can be evident. One of the main problems for this lies in the adherence or compliance with the recommendations of these measures by patients since, as has been seen, it is not only about allergen-specific measures, but also many times to reduce the levels of allergens can include modifications of the house, control of moisture sources, control of pets and insects, and improvements in the ventilation of the house, among others.

All of the above is in reference to the specific external environment domain of the "exposome." Regarding the general external environment, it is clear that it depends mainly on state policies tending to modify behaviors and actions both of the individual (recycling of organic material, use of biodegradable products, etc.), and of the general (emission control of gases, promote the development of non-polluting energies, active control of both the construction of "healthy" homes, the use of pesticides, the emission of gases by industrial activity, etc.). These holistic changes in lifestyle will have an impact on the global health of the human being and not only on patients with allergic rhinitis.

Compliance with Ethical Standards

Conflict of Interest

Ledit R. F. Arduso declares that he has no conflict of interest.

Enrique Fernández-Caldas declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance
- Of major importance

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