Climate change and its impact on allergic rhinitis and other allergic respiratory diseases

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Purpose of review
To discuss current evidence of global climate change and its implications for allergic rhinitis and other allergic respiratory diseases.

Recent findings
Global climate change is evidenced by increasing average earth temperature, increasing anthropogenic greenhouse gas levels, and elevated pollen levels. Pollutants of interest include carbon dioxide (CO_2), ozone (O_3), and nitrous oxide (NO_2) because they can enhance the allergic response and lead to increased symptoms of allergic respiratory diseases. Heightened CO_2 levels stimulate pollen production via photosynthesis and increased growth in multiple plant species investigated. Although worsened air quality appears to increase prevalence of allergic rhinitis, the effects of increased temperature are less certain. The findings of increased aeroallergen levels likely contribute to increases in presentation of allergic diseases, although more healthcare impact studies are necessary.

Summary
Although recent literature indicates and strongly supports changes in temperature, pollution levels, and aeroallergen levels, more longitudinal epidemiologic surveillance of allergic diseases in relation to climate change as well as pathophysiologic studies on changing aeroallergen effects on allergic diseases are needed.

Keywords
allergen, allergic rhinitis, climate change, nonallergic rhinitis, pollen, temperature

INTRODUCTION

Allergic rhinitis is the most common manifestation of atopic diseases, with prevalence rates increasing by about 3.5% each decade and an estimate of 15–25% afflicted in Europe [1]. In the USA, patients with allergic rhinitis average more than three physician visits per year, nine prescriptions filled per year, and $1500 of additional healthcare expenses per year compared with similar patients without this diagnosis [2]. When only pediatric patients are considered, asthma is the most common chronic disease and affects 6.7 million (9.1%) children in the USA [3]. As allergic respiratory conditions are results of interactions between susceptible patient populations and their environments, global changes in weather and seasonal patterns are expected to affect the future prevalence, severity, presentation, and management of these conditions.

Important data substantiating global climate change continues to accumulate, with near unanimous professional consensus that greenhouse gas emissions secondary to human activity and global industrialization are already altering and will continue to alter our planet's climate. The earth's temperature is increasing, as evidenced by rising sea levels, melting glaciers, retreating sea ice in the Arctic, and diminished snow cover in the northern hemisphere. The Intergovernmental Panel on Climate Change (IPCC) predicts a 1.4–5.8°C change in the average world temperature by 2100 [4,5]. This increase in temperature is expected to be greater at higher latitudes and over land.

This review will focus on recent evidence of global climate change and its anticipated effect on allergic rhinitis and other allergic respiratory

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KEY POINTS

- We live in a dynamic environment with increasing average earth temperature, increasing anthropogenic greenhouse gas levels, and elevated pollen levels that have been recorded in recent decades.
- These changes in the climate are expected to alter the presentation and epidemiology of allergic rhinitis and other allergic respiratory diseases.
- Increased pollutant levels such as carbon dioxide (CO_2), ozone (O_3), and nitrous oxide (NO_2) enhance the allergic response, whereas higher CO_2 concentrations lead to higher biomass of potential pollen-producing plant species.
- More recent studies suggest a correlation between pollution and allergen levels with increased patient symptoms and disease incidence, but more healthcare impact studies are still needed.

diseases. We also examine the pathophysiology of allergic respiratory diseases with emphasis on allergic rhinitis in light of changes in the global climate.

PATHOPHYSIOLOGY OF ALLERGIC RHINITIS: THE CLASSICAL PATHWAYS

The classical pathways of allergic rhinitis require repeated exposures to an antigen to which the body shows abnormal hypersensitivity in the form of production of allergen-specific immunoglobulin E (IgE). Type 2 helper T cells play a central role in this pathogenesis, eventually leading to a Gell and Coombs type I immediate hypersensitivity reaction upon allergen exposure in addition to other inflammatory cascades [6]. IgE-dependent activation of mast cells and tissue eosinophilia occur after cross-linking of adjacent IgE molecules on mast cell surfaces by the allergen. Mast cell degranulation releases histamines, tryptase, and leukotrienes, leading to vasodilation, increased vascular permeability, afferent nerve stimulation, and increased secretions (Fig. 1) [7]. The late phase response of this reaction includes T-cell recruitment and tissue eosinophilia secondary to increased interleukin (IL)-5 production. IgE, IL-5, and eosinophilic cationic protein have all been found at higher levels compared with controls in allergic rhinitis [8].

ALTERNATIVE PATHOPHYSIOLOGY OF ALLERGIC RHINITIS

There is significant evidence for a contribution of sensory nerves to symptoms of allergic rhinitis. An inherent neuronal hyperexcitability has been observed secondary to increased levels of sensory sodium channels in allergic rhinitis as well as nonallergic rhinitis compared with controls [9]. Sensory nerves can also be activated via inflammatory mediators, and nerve fibers may also release neuropeptides that lead to vascular dilatation [10]. Substance P, vasoactive intestinal polypeptide (VIP), and calcitonin gene-related peptide are neurotransmitters that lead to dilation of nasal mucosa and protein extravasation. More specifically, substance P is released upon activation of nociceptive C-fibers within the nasal mucosa and has also been shown to induce histamine release *in vitro* at higher levels among allergic rhinitis individuals compared with nonallergic patients [11]. VIP is released along with acetylcholine by parasympathetic nerves and may regulate acetylcholine release and augment glandular secretory response [12].

O'Hanlon *et al.* evaluated levels of specific neuronal markers PGP 9.5 (nerve marker protein gene product 9.5), substance P, capsaicin receptor TRPV1 (transient receptor potential cation channel subfamily V member 1), and nerve growth factor (NGF) among 23 patients with allergic rhinitis and 17 controls [10]. They reported higher numbers of nerve fibers in mucosal epithelium, subepithelium, and deeper mucosal glands and blood vessel regions as stained by PGP 9.5 among patients with allergic rhinitis. Significantly higher levels of substance P and NGF immunoreactivity were also found in inferior turbinate biopsies among patients with allergic rhinitis. TRPV1 epithelial fiber counts were higher in rhinitis, but the difference was not statistically significant. Nasal sensitivity testing using graded monofilaments correlated with the degree of nerve staining. The findings of this study are congruent with the report by Gawlik and DuBuske [13] of increased substance P and bradykinin levels from nasal lavage after nasal allergen provocation compared with controls. Substance P was found to maintain a greater increase than bradykinin in the late phase response in this work.

The contribution of VIP to allergic rhinitis has also been studied, with high levels of VIP and its receptors found in nasal mucosa of patients with this condition [12,14,15]. Kim *et al.* [15] recently evaluated VIP downstream receptors VPAC1R and VPAF2R via mRNA collection and western blot analysis, revealing that both mRNA and protein levels were significantly increased in nasal mucosa among perennial allergic rhinitis patients compared with control patients undergoing augmentation rhinoplasty. Immunohistochemistry was also performed to demonstrate that these receptors are localized to epithelium, infiltrating inflammatory cells, endothelium, and submucosal glandular cells

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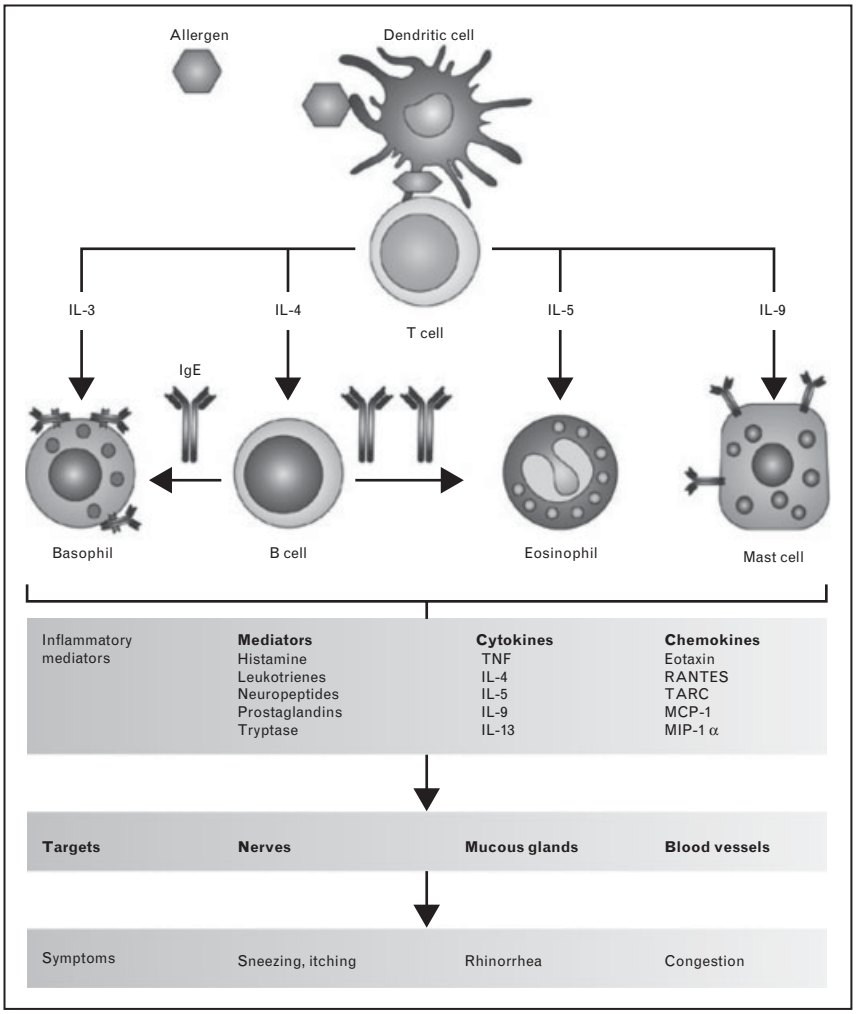

FIGURE 1. Classical pathways of allergic rhinitis. Reproduced with permission from [7]. IL, interleukin; MIP, macrophage inflammatory proteins; MCP, monocyte chemoattractant protein; RANTES, Regulated upon Activation Normal T-cell Expressed and Secreted; TARC, thymus and activation regulated chemokine; TNF, tumor necrosis factor.

in patients with allergic rhinitis. Such data suggest a functional abnormality and imbalance of neuronal regulation in allergic rhinitis.

EVIDENCE OF GLOBAL CLIMATE CHANGE: CHANGES IN AIR QUALITY

There is compelling evidence that the global climate continues to evolve, leading to environmental factors that will affect the host antigen response based on both classical and neuronal pathways of allergy. Changes in overall air quality and pollution have become a major concern in recent years, with record setting levels of anthropogenic greenhouse gas recorded [16].

Concentrations of carbon dioxide (CO_2), the most important anthropogenic greenhouse gas, have increased from a preindustrial value of 280 parts per million to 379 parts per million in 2005 [16]. The growth rate of CO_2 at 1.9 parts per million per year between the years 1995 and 2005 is alarmingly more rapid than any period in years past since continuous direct atmospheric measurements were initiated. The elevated CO_2 levels are also far above any natural range over the past 650 000 years as determined from ice cores. About 75% of CO_2 emissions are produced by fossil fuel burning, with most of the rest stemming from land use and deforestation [17].

Similarly, an increase in nitrous dioxide (NO_2) levels has consistently been recorded. With an approximately constant growth rate since 1980, NO_2 was measured at 319 parts per billion in 2005 compared with preindustrial values of about 270 parts per billion [16]. NO_2 is a marker of agricultural byproducts as well as vehicle-generated air pollution. It is a precursor of photochemical smog and is generated by burning of fossil-derived fuels in outdoor air in urban and industrial regions. Combined with ultraviolet radiation and oxygen, ozone

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(O_3) is formed as an additional air pollutant (Fig. 2) [18].

O_3 and NO_2 exposure enhances the airway response to inhaled allergens among atopic individuals, with enhancement of airway inflammation from both immediate and late-phase responses [18,19]. Exposure to these pollutants is linked to childhood respiratory illness, exacerbations of asthma, increased emergency department visits, and hospitalizations for asthma [20,21,22▪], perhaps because inflammatory cells and mediators, such as IL-6, IL-8, RANTES (Regulated upon Activation Normal T-cell Expressed and Secreted, also known as chemokine ligand 5 or CCL5), and granulocyte macrophage colony-stimulating factor are known to increase with O_3 exposure [17,23]. Among patients with seasonal allergic rhinitis, exposure to these pollutants increases eosinophil cationic protein in nasal lavage specimens 4 h after allergen challenge [19]. Such data suggest that the air pollutants O_3 and NO_2 may 'prime' eosinophils for subsequent activation by allergen in the susceptible patient. These findings are consistent with a study by de Marco *et al.* [24], who analyzed the impact of climate and NO_2 on prevalence of asthma and allergic rhinitis in Italy and found a moderate increase in asthma attacks, chest tightness, and wheezing among areas with higher NO_2 levels after adjustment for climate. A higher incidence of allergic rhinitis was also reported with rising levels of outdoor NO_2 exposure in this study. The effect of ground-level O_3 was modeled by Sheffield *et al.* [22▪] to predict the future rates of pediatric asthma-related emergency department visits in New York City. Their analysis predicts an increase in regional summer O_3-related asthma emergency department visits of 7.3% by the 2020s.

In an attempt to correlate air pollution levels with hay fever and sinusitis complaints, Bhattacharyya [25] compared air quality data from the Environmental Protection Agency with disease data from the National Health interview Survey. Kidney failure, a condition with no expected correlation with air quality, was used as the control group. The pollutants studied were carbon monoxide (CO, parts per million), nitrous dioxide (NO_2, parts per million), sulfur dioxide (SO_2, parts per million), and particulate matter (μg/l). This cross-sectional study showed that levels of pollutants in the USA have steadily declined for all parameters investigated in the years 1997–2006 except particulate matter, which decreased and then leveled off. The evidence points toward declining prevalence of both hay fever and sinusitis as well, with stronger regression coefficients for CO, NO_2, SO_2, and particulate matter compared with the kidney failure control population. Other studies have linked mucosal inflammation to air pollutant emission secondary to Type 2 helper T cell (humoral immune response) pathway shunting [26] and an enhanced IgE response with heightened airway reactivity [18,27] that is likely related to neuronal regulation.

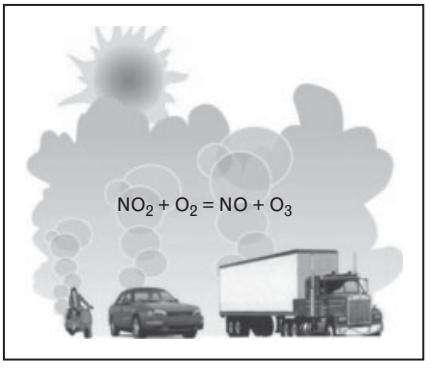

FIGURE 2. Production of ozone pollutant. Reproduced with permission from [18].

CHANGES IN TEMPERATURE AND AEROALLERGENS

The climate changes around the globe are also manifested by rising temperatures and shifts in aeroallergen seasons and concentrations.

An unusual 0.5°C rise in average earth temperature since the mid-1970 s [5] has been observed and is substantially attributable to the rise in anthropogenic increase in greenhouse gases, as previously mentioned. There is evidence that pollen (in this case birch pollen allergen) grown at higher temperatures results in significantly stronger allergenicity based on SDS-PAGE and IgE immunoblotting experiments [28]. Bhattacharyya [29] studied the influence of annual temperature on prevalence of otolaryngologic respiratory diseases between 1998 and 2006. Average annual temperature statistics were obtained from National Climatic Data Center, and disease prevalence of hay fever, sinusitis, and chronic bronchitis were investigated from the National Health Interview Survey using jaw/face pain as a control group. Regression analysis demonstrated a statistically significant correlation between rising temperature and sinusitis complaints, but no association with disease prevalence of hay fever, chronic bronchitis, or jaw pain was found. A limiting factor of this study is the small magnitude of variation in average temperature across the years studied, but the variations are significant by meteorological standards. In contrast, Kim *et al.* [30▪] recently reported on their study of changes in springtime temperature in Korea as it relates to hospital visits among patients with tree pollen

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allergy. This retrospective study found positive correlation between increases in minimum temperatures in March with tree pollen counts and with patient visit numbers.

Although the influence of rising temperatures on healthcare and allergic disease prevalence may be equivocal, environmental impact studies are more convincing. Outdoor fungal species such as *Cladosporium* have been reported to exist in increased atmospheric concentrations with increased temperature and humidity [31▪▪]. Corden and Millington [32] examined long-term trends of *Alternaria* spore concentrations in Derby, UK, recording both seasonal concentrations and start dates. A prolonged season over time was shown, and *Alternaria* spore concentrations increased during the study period. Corden and Millington related the trend to an earlier seasonal start date and increased winter and early spring temperatures locally. Other taxa on the rise include *Juniperus*, *Quereus*, *Carya*, and *Betula* in North America [33]. In Japan, the *Cryptomeria japonica* (Japanese cedar) pollen season has advanced from mid-March to February between 1983 and 1998 [34]. An increase in total pollen count was significantly associated with the mean temperature from July in the previous year, and the duration of pollen season was clearly linked to total pollen counts.

The pollen season has also lengthened for some ragweed species, and this change is mostly secondary to earlier start dates as well [31▪▪,35,36]. In one study from Poland, *Artemisia* pollen levels positively correlate with daily temperature and inversely correlate with relative humidity [37]. In addition to the positive effects of temperature and precipitation on ragweed pollen levels, increases in CO_2 levels also stimulate pollen production via photosynthesis and increased growth [36,38]. This was best quantified experimentally in a study by Ziska and Caulfield [38], who showed that total biomass and total pollen production per plant of common ragweed increased significantly with increased experimental CO_2 levels. Ziska *et al.* [36] later compared the impact of climatic change on pollen production of common ragweed between urban and rural environments in Maryland, USA. As expected, average daily values of CO_2 concentration and air temperature within an urban environment were 20–31% and 1.8–2.0°C higher than those at a rural site. The measured ragweed grew faster, flowered earlier, and produced substantially greater biomass and ragweed pollen at urban locations in contrast to rural locations. A separate study performed in Quebec, Canada reports a significant association between pollen levels and rates of medical consultations for allergic rhinitis [39], suggesting that increased pollen allergen in the air may indeed lead to more disease, as would be predicted based on classical IgE-mediated pathways. Frei and Gassner [40] suggested a causal relationship between pollen levels and hay fever prevalence in Switzerland. It is noted that not all studies have found increases in specific aeroallergen levels, as this investigation found a significant rise in birch and grass pollen concentration until 1990 with slight decrease in levels thereafter. Table 1 [22▪,25,29,30▪,36] provides a summary of the most pertinent studies discussed.

CONCLUSION

The current level of evidence supporting climate change and its effect on the dynamic environment is strong. These changes include increasing temperature, increasing anthropogenic greenhouse gas

Table 1. Summary of most recent studies and their results

Author	Parameter studied	Results
Sheffield *et al.* [22▪]	O_3	O_3 levels will increase and predict 7.3% increase in regional summer O_3-related asthma emergency department visits for children in New York City by 2020s
Bhattacharyya [25]	CO, NO_2, SO_2, and particulate matter	Prevalence of hay fever correlates positively with all pollutant levels studied
Bhattacharyya [29]	Temperature	Temperature has positive regression with sinusitis but not with allergic rhinitis
Ziska *et al.* [36]	CO_2 and temperature	Faster growth, earlier season, greater biomass of ragweed in urban environment in which temperatures and CO_2 levels are higher
Kim *et al.* [30▪]	Temperature, birch pollen level	Minimum temperature in spring correlates with increased pollen levels and increased hospital visits for tree pollen allergic patients (adjusted OR = 1.14)

OR, odds ratio.

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levels, and subsequent increase in aeroallergen levels for some species studied. Such alterations in nature are expected to lead to evolutionary changes in the presentation, incidence, and seasonality of allergic rhinitis and other allergic respiratory diseases. Air pollution has already been shown to worsen severity and incidence of allergic respiratory disease, but the effects of other parameters such as temperature and aeroallergen levels are less certain because of a paucity of healthcare impact studies compared with environmental studies. In addition, although the 'epidemic' of allergic disease in the past few decades can be putatively attributed to effects of environmental change on classical and alternative pathways of allergy, more studies on disease mechanisms directly affected by the changing climate are needed.

Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 218).

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