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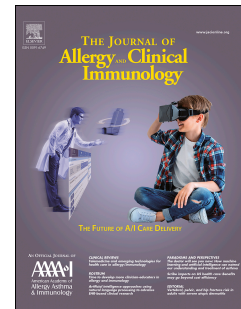
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The Climate Change Hypothesis for the Allergy Epidemic

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Abstract

The health consequences of climate change are being increasingly recognized. Herein, the climate change hypothesis is put forth as a substantial contributor to the growing global allergy epidemic. A call for deeper research and action on the impact of climate change on various aspects of allergic disease mechanisms, exacerbation, and prevalence is imperative.

Key Words

Allergy, climate change, hygiene hypothesis

Abbreviations

COVID-19	coronavirus disease 2019; public name for the virus or viral infection by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
O ₃	ozone
PM _{2.5}	particulate matter less than 2.5 micrometers
Th	T helper
U.S.A.	United States of America

Conflicts of Interest

M.E.R. is a consultant for Pulm One, Spoon Guru, ClostraBio, Serpin Pharm, Allakos, Celgene, Astra Zeneca, Adare/Ellodi Pharma, GlaxoSmith Kline, Guidepoint and Revolo Biotherapeutics and has an equity interest in the first five listed and royalties from reslizumab (Teva Pharmaceuticals), PEESV2 (Mapi Research Trust), and UpToDate. M.E.R. is an inventor of patents owned by Cincinnati Children's Hospital Medical Center.

Allergic diseases have reached epidemic proportions globally, affecting nearly 30% of the world's population. Originally inflicting the western population, the greatest trends in growth are now in low- and middle-income countries (1). Despite scientific focus and progress on these diseases, they are continuing to increase in prevalence, spectrum, and severity. Herein, we briefly consider causal factors responsible for allergic disease, including the hygiene hypothesis, and then put forth the climate change hypothesis as a contributor to the growing global allergy epidemic.

Although genetic predisposition is a contributing factor to disease susceptibility, the rise of these diseases has occurred too quickly to be explained by a genetic shift in the population, consistent with twin studies, thus implicating environmental or lifestyle changes. An increased exposure to allergens (e.g., house dust mite in centrally heated houses) has occurred, but these changes do not adequately explain the rise, especially as exposure to some allergens (e.g., home pets in early life) protects against the development of allergies. This lack of an adequately attributable cause to the allergy epidemic over the last half of century has led to the search for other factors that may explain the increased prevalence and evolving phenotypes of allergic disease in genetically predisposed individuals.

The *hygiene hypothesis* was first formulated in 1989 by the epidemiologist David P. Strachan, who found an inverse relationship between family size and development of allergic diseases (2). It was proposed that a lower incidence of infection in early childhood could be a cause of the rise in allergic diseases. Subsequently, the concept evolved into the broader notion that declining microbial exposure was a major causative factor for the increasing incidence of allergic diseases (3). A wide range of factors that might result in altered microbial exposure have been examined, such as clean food and water, sanitation, usage of antibiotics and vaccines, birth delivery modes

(e.g., usage of Caesarian section), and geographic migratory patterns (e.g., the move from farm to urban living). Strong support for the hygiene hypothesis has been derived from studies of the traditional lives of the Amish and Hutterites in the U.S.A., two populations that share genetic ancestry yet differ by only the Hutterites having significant rates of allergies (4). Although both populations are agricultural, only the Hutterites employ modern farming machinery. Mechanistically, it is now understood that bacteria and other pathogens trigger pattern recognition receptors (e.g., Toll-like receptors) on innate immune cells, which shift adaptive immunity into pathogen-protective T helper (Th) cells (e.g., Th1 and Th17 cells) and regulatory T cells rather than allergy-promoting Th2 responses. Indeed, the dust samples from the Amish population contained higher endotoxin levels and protected against the development of allergies in mice. Furthermore, it is now appreciated that allergic individuals harbor less diverse intestinal commensal flora than do non-allergic individuals, and this limited exposure may insufficiently prime the regulatory arm of the immune system to become tolerant to innocuous foreign antigens such as allergens (3).

Yet, the *hygiene hypothesis* has substantial limitations (5), such as the focus on hygiene rather than host-commensal microbe interactions, which are likely primary contributors to the development of allergy. Indeed, there is little convincing evidence that cleaning local or personal environments protects against allergies. Furthermore, improved hygiene over the past half century has not only been associated with a rise in allergic diseases, but also other chronic immunologic diseases, such as inflammatory bowel disease, multiple sclerosis, and rheumatoid arthritis, diseases associated with non-Th2 immunity (e.g., Th1, Th17, and/or Th23 responses). Importantly, on a societal level, the *hygiene hypothesis* could be used as a justification against anti-infectious disease measures (e.g., personal cleanliness and public sanitation efforts), including the usage of vaccination and

antibiotics, the two greatest medical breakthroughs of the last century. These concerns are particularly important and timely in view of the growing threat of emerging infectious diseases such as COVID-19. Taken together, though there are merits behind the *hygiene hypothesis*, there is now a timely and justified need for other parallel theories.

Climate change is a term used to describe human-induced global warming and its impacts on weather patterns. It is a ramification of expanding populations and the energy intensification required to keep up with sufficient food and energy needs. The main cause is the accumulation of greenhouse gases (mainly carbon dioxide and methane), which are a byproduct of burning fossil fuels. The resulting carbon dioxide absorbs infrared radiation (heat), causing enhanced surface temperature and resulting in *global warming* (6). Since the 1970s, the average temperatures have increased by approximately 2 °F (1 °C). Although this may seem small, there are greater fluxes in certain geographic locations (e.g., arctic regions), resulting in glacier recession, arctic ice melting, flooding, rises in sea levels, heat waves, wildfires, dispersal of plant and animal geographic ranges, disturbances in food supply, and increases in extreme weather conditions (7). The consequences of climate change are multifold, but its effect on human health are most substantial, already claiming the lives of millions of people per year (6), for example, from exacerbation of cardiovascular, infectious, and mental health diseases (8, 9). These health effects are not evenly distributed amongst different populations and geographic regions and more greatly impact vulnerable populations, including those with lower socioeconomic means (10). The development, morbidity, and mortality of allergic diseases are now appreciated as being impacted by *climate change*.

Climate change can invoke allergic diseases by a variety of mechanisms (Table 1), which have been recently reviewed (11). *Global warming* and related changes in rainfall patterns, hurricanes, and winds have modified many aspects of pollination, including its seasonality, timing of release, quantity, and geographic distribution (12). Indeed, peak concentrations of weed and tree pollens positively associate with temperature and precipitation changes, respectively (13). Furthermore, plants produce more pollen at high atmospheric levels of carbon dioxide. Pollens not only are allergen carriers, but also release lipid mediators that have pro-inflammatory and immunomodulatory effects on allergic responses. One of the consequences of climate change is the increased occurrence of extreme weather conditions, including thunderstorms (known to exacerbate asthma), flooding (resulting in a long-term increase in moisture and conditions that favor the growth of allergenic molds), prolonged heatwaves (causing several health issues, including increased time indoors and hence exposure to indoor allergens such as dust mites, cockroaches, and molds), and wildfires and dust storms that have the capacity to travel thousands of miles (both causing abrupt increases in PM_{2.5}). Wildfires promote natural air pollution due to generation of particulate matter of less than 2.5 micrometers (PM_{2.5}), carbon monoxide, polycyclic aromatic hydrocarbons, and semi-volatile and volatile organic compounds (7). The effect of thunderstorms on asthma exacerbations and deaths, especially during pollen season, is particularly notable. For example, on a single day in Melbourne, Australia, there were 9,000 subjects who needed emergency care for asthma and 10 died (14). The last decade has consistently recorded the highest yearly surface temperatures, draughts, floods, thunderstorms, and hurricanes, emphasizing the ever-growing threat from *climate change*.

It is now well appreciated that the by-products of burning fossil fuels are major components of air pollution, including ozone (O₃) and PM_{2.5}, and can have important effects on human health; for instance, the former directly induces bronchial hyperresponsiveness and the latter penetrates the lungs and is pro-inflammatory (15). What is less appreciated is that the consequences of climate change (e.g., wildfires, storms, heatwaves) increase sources of air pollution, promoting a feed-forward loop between air pollution and climate change (11). Experimentally, air pollution is a Th2-promoting adjuvant, and early life exposure increases sensitization to aeroallergens and food allergens, promotes eczema, and worsens asthma in humans and experimental models (16). Air pollution, particularly ozone, PM_{2.5} and diesel exhaust particles, increase the permeability of the respiratory tract, thereby facilitating penetration of allergens into the mucosa (14). Air pollution also decreases anti-viral host defense mechanisms (17). Indeed, long-term exposure to ozone contributes to increased respiratory disease mortality (18).

Taken together, it is undoubtable that the health impacts of *climate change* are impacting the allergy epidemic by a variety of cooperative mechanisms that are working together to accelerate disease development, severity, and spectrum. These impacts are currently shaping the immune system with relevant stimuli, such as the ability of PM_{2.5} and ozone to induce epigenetic programming of regulatory T cells (19) and modify mast cell activity (20), respectively, two cells critical in orchestrating allergic responses.

Although there are emerging data linking climate change to the allergy epidemic, further research is needed, particularly focused on the causal mechanisms and the interplay between air pollution and climate change. Given the high worldwide prevalence and the extraordinary cost of health

care services dedicated to allergic disease (more than \$100 billion per year), a call of attention to the climate change hypothesis as a substantial driver of the allergy epidemic is imperative. Health care professionals are in a special position to influence the *climate change* crisis, including by educating about its impact and the imperative to modify its course. The U.S.A. health sector is responsible for nearly 10% of national carbon emissions, stemming from building operations, such as energy usage, cooling, and heating (21). The World Health Organization emphasizes that climate change effects our ability to deliver safe and effective health care. Extreme weather will continue to cause hospital evacuations, power outages, and shortages of food and medical supplies. These overall strains on the systems reduce quality of care, patient outcomes, and exacerbate existing health problems, such as underlying allergic disease. The National Academy of Medicine is launching an Action Collaborative on Decarbonization of the U.S.A. Health Sector (22); this is a public-private partnership with multiple stakeholders (e.g., federal government, biomedical and pharmaceutical industries, hospitals, payers, and healthcare providers). Given the emerging evidence that *climate change* is an environmental contributor to allergic diseases, it is now time to complement the *hygiene hypothesis* with the *climate change* hypothesis, especially because there are actionable steps forward that will have tangible and timely personal, communal, and global benefits that will likely mitigate the impact of allergic diseases. As such, it is essential for allergists and immunologists and our professional organizations to promote a deeper understanding of the effect of climate change on various aspects of allergic disease, including its mechanisms, prevalence, and treatment.

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Table 1. Components of climate change and potential impact on allergic diseases

Global Warming	Modifies pollination (e.g., seasonality and distribution) Promotes extreme weather
Extreme Weather (Flooding, wildfires, thunderstorms, dust storms, heatwaves)	Increases growth of allergenic microorganisms (e.g., mold) Promotes asthma exacerbations Changes geographic spread of allergens Modifies housing patterns (e.g., crowding, indoor time, urban living) Causes emotional stress Increases air pollution
Air Pollution (e.g., O₃ and PM_{2.5})	Increases allergen sensitization (e.g., PM_{2.5} and other components are Th2 adjuvants) Increases bronchial hyperresponsiveness Stimulates respiratory inflammation Exacerbates asthma, rhinitis, and eczema