frontiers | Frontiers in Science

TYPE Frontiers in Science Lead Article
PUBLISHED 04 April 2024
DOI 10.3389/fsci.2024.1279192

OPEN ACCESS

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RECEIVED 17 August 2023
ACCEPTED 07 March 2024
PUBLISHED 04 April 2024

CITATION
Agache I, Akdis C, Akdis M, Al-Hemoud A, Annesi-Maesano I, Balmes J, Cecchi L, Damialis A, Haahtela T, Haber AL, Hart JE, Jutel M, Mitamura Y, Mmbaga BT, Oh J-W, Ostadtaghizadeh A, Pawankar R, Prunicki M, Renz H, Rice MB, Filho NAR, Sampath V, Skevaki C, Thien F, Traidl-Hoffmann C, Wong GWK and Nadeau KC. Immune-mediated disease caused by climate change-associated environmental hazards: mitigation and adaptation. *Front Sci* (2024) 2:1279192. doi: 10.3389/fsci.2024.1279192

Immune-mediated disease caused by climate change-associated environmental hazards: mitigation and adaptation

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10.3389/fsci.2024.1279192

Abstract

Global warming and climate change have increased the pollen burden and the frequency and intensity of wildfires, sand and dust storms, thunderstorms, and heatwaves—with concomitant increases in air pollution, heat stress, and flooding. These environmental stressors alter the human exposome and trigger complex immune responses. In parallel, pollutants, allergens, and other environmental factors increase the risks of skin and mucosal barrier disruption and microbial dysbiosis, while a loss of biodiversity and reduced exposure to microbial diversity impairs tolerogenic immune development. The resulting immune dysregulation is contributing to an increase in immune-mediated diseases such as asthma and other allergic diseases, autoimmune diseases, and cancer. It is now abundantly clear that multisectoral, multidisciplinary, and transborder efforts based on Planetary Health and One Health approaches (which consider the dependence of human health on the environment and natural ecosystems) are urgently needed to adapt to and mitigate the effects of climate change. Key actions include reducing emissions and improving air quality (through reduced fossil fuel use), providing safe housing (e.g., improving weatherization), improving diets (i.e., quality and diversity) and agricultural practices, and increasing environmental biodiversity and green spaces. There is also a pressing need for collaborative, multidisciplinary research to better understand the pathophysiology of immune diseases in the context of climate change. New data science techniques, biomarkers, and economic models should be used to measure the impact of climate change on immune health and disease, to inform mitigation and adaptation efforts, and to evaluate their effectiveness. Justice, equity, diversity, and inclusion (JEDI) considerations should be integral to these efforts to address disparities in the impact of climate change.

KEYWORDS

air pollution, immune diseases, allergy, asthma, biodiversity, climate change, mitigation, pollen

Key points

- Climate change is driving an increase in immune-mediated diseases such as asthma, allergies, autoimmune diseases, and cancers.
- Anthropogenically driven increases in pollen, wildfires, sand and dust storms, thunderstorms, and heatwaves—with concomitant increases in air pollution, heat stress, and flooding—are altering the human exposome and worsening human health.
- Multilevel, multisectoral adaptation and mitigation actions are vital to reduce emissions and improve air quality, provide safe housing, improve diets and agricultural practices, and increase environmental biodiversity and peoples' exposure to natural environments.
- New biomarkers, data science approaches, and economic models are vital to better measure the impact of climate change on health.
- Mitigation and adaptation efforts need to be global, equitable, and recognize that the health of the planet is integrally connected to human health.

Introduction

Increased anthropogenic activity, including deforestation, urbanization, modern agricultural practices, manufacture of synthetic chemicals, overuse of fertilizers and antibiotics, and the use of fossil fuels and biomass for energy, have altered Earth's environment. Global temperatures and the frequency and severity of climate change events such as heatwaves, wildfires, sand and dust storms (SDSs), and thunderstorms have all increased over recent decades (1). These events further increase global warming.

For example, wildfires release large amounts of greenhouse gases (GHGs) further contributing to air pollution and global warming, and accelerating the vicious climate feedback loop. Climate change events lead to increases in pollen burden, air pollution, flooding, and heat stress, which physically, chemically, and biologically alter the human exposome (i.e., the cumulative environmental exposures encountered by an individual in a lifetime). Wider environmental determinants of health are also affected by climate change, including biodiversity loss and access to nutritious food, clean drinking water, and secure shelter (Figure 1).

Humans have evolved an immune system to protect against environmental assaults and maintain health. The epithelial barriers of the gut, lungs, and skin are the body's first line of defense. Immune cells within the epithelial layer determine the extent of the

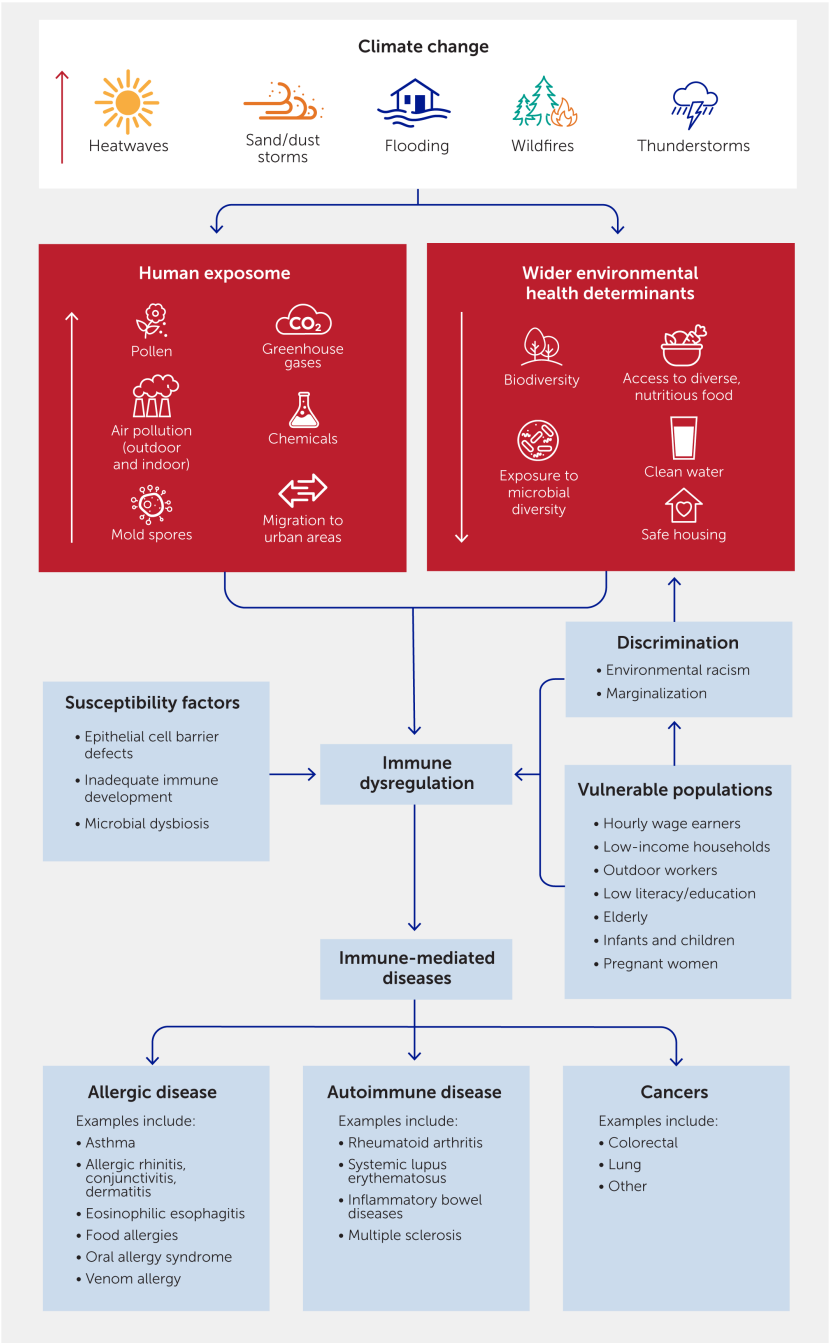

FIGURE 1
Effects of climate change-related events on immune dysregulation and human health through immune-mediated conditions. Climate change increases the frequency and severity of various types of events that affect the human exposome (the totality of a person's lifetime exposures). The resulting immune dysregulation can cause a variety of immune-mediated conditions such as allergies, asthma, autoimmune diseases, and cancers. These risks are increased by susceptibility factors in individuals and within vulnerable populations.

threat posed by foreign invaders and mount a response. However, overreaction and hypersensitivity of the immune system leads to immune dysregulation, which can result in allergic diseases, autoimmune diseases, and cancer—conditions whose prevalence rates have increased in recent decades (2–4). In recent decades, increased urbanization, antibiotic use, and exposure to toxic chemicals—coupled with decreased exposure to biodiverse environments, less diverse diets, and a lack of physical activity—have created conditions that increase the risks of skin and mucosal barrier disruption, microbial dysbiosis, and immune dysregulation in populations globally (5). The epithelial barrier hypothesis proposes that increases in exposure to air pollutants and other toxic substances in the air, water, and foodstuffs (such as detergents, household cleaners, food emulsifiers, preservatives, pesticides, and microplastics) damage the epithelial barrier. This damage increases the penetration of allergens and microbes, leading to increases in pro-inflammatory reactions (6). A defective epithelial barrier has been demonstrated in asthma and allergic diseases (7). In addition, gut barrier defects and microbial dysbiosis have been demonstrated in many allergic and autoimmune diseases and cancers (8, 9). In parallel, a loss of biodiversity and limited exposure to microbial diversity increasingly impair tolerogenic immune development.

Major allergic diseases include allergic asthma, allergic rhinitis, atopic dermatitis, and food allergy. The estimated prevalence of allergies varies by age group, allergy type, geographical region, and season, and has changed over time. Methodological differences between studies can explain some of the observed variance in rates. However, the consensus is that, overall, there has been an upward trend in the prevalence of asthma and allergies (10–14). These diseases have a serious impact on individuals' quality of life and incur substantial direct healthcare costs and indirect socioeconomic costs (15). Based on Global Cancer Observatory (GLOBOCAN) and World Health Organization (WHO) sources, cancer is a leading and increasing cause of mortality and morbidity worldwide. Globally, cancer caused approximately 10 million deaths in 2020, and it is the first or second leading cause of death in many countries (16, 17). The incidence of cancer in adults aged 50 years or younger has increased worldwide since the 1900s (18) and cancer risk has been linked to environmental factors such as air pollution (19, 20). Autoimmune diseases include rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel diseases (such as ulcerative colitis and Crohn's disease), and multiple sclerosis. The overall prevalence of autoimmunity is estimated to be approximately 3–5% in the general population. The incidence and prevalence of autoimmune diseases vary with age, gender, and ethnicity, with women being more at risk than men (21). These diverse conditions also incur a vast and rising disease burden globally (22) and accumulating evidence links their incidence to pollution (23).

Without mitigation of the environmental risk factors driven by climate change, further increases in allergic diseases, autoimmune diseases, and cancers are expected (24, 25). Global temperatures are 1.1°C higher than during prehistorical times and future global warming is projected to span a range from 1.4°C to 4.4°C by 2100, depending on different GHG emissions scenarios (26). The magnitude of the increase depends on the extent of human interventions aiming at (i) the reduction of fossil fuel use; (ii) the implementation of eco-friendly sustainable practices; and (iii) enforcing equitable socioeconomic factors. With the recognition of the imminent threats to health and the need for global cooperation, the 2015 Paris Agreement signed at the United Nations Climate Conference (COP) 21 aims to limit global warming to well below 2°C and as close to 1.5°C as possible by promoting transitions toward low-emission and climate-resilient development (27). Nevertheless, even an optimistic projected global temperature increase of 1.5°C will have major consequences for human health, including immune-mediated diseases. Many studies have shown that the adverse effects of climate change on disease risk are higher among those of a lower socioeconomic status, those of younger or older age, and those with comorbid diseases such as cardiovascular diseases, asthma, or other atopic diseases (28).

In this article, we review the links between climate change, environmental exposures, and immune dysregulation and its associated diseases. We then recommend adaptation and mitigation solutions to reduce the impact of climate change on human health via these conditions.

Inflammatory versus tolerogenic responses in allergy

Climate change-associated exposures can trigger a complex array of inflammatory or tolerogenic responses (Figure 2). In healthy individuals, the immune system mediates a tolerogenic response upon encountering common innocuous environmental factors. During immune dysregulation, the immune system mounts an inflammatory response, even to innocuous environmental factors or healthy cells in the body. The mechanisms involved in allergic reactions to pollen, food, or insect allergens are those best understood.

A defective epithelial barrier permits the entry of allergens, leading to the release of pro-inflammatory epithelium-derived cytokines such as interleukin (IL)-25, IL-33, and thymic stromal lymphopoietin (TSLP). These cytokines further prompt dendritic cells to transform naïve T helper (Th) cells into Th2 cells, which release pro-inflammatory cytokines such as IL-4, IL-5, IL-9, and IL-13. Epithelial cytokines also activate type 2 innate lymphoid cells (ILC2s) which also release pro-inflammatory cytokines IL-5 and IL-13. These cytokines favor B cell class switching to immunoglobulin (Ig)E. Allergic sensitization occurs when IgE binds to the high-affinity IgE receptor FcεR1 on mast cells. In these individuals, subsequent exposure to allergens favors IgE cross-links and the release of preformed and de novo–synthesized pro-inflammatory mediators, such as histamine, prostaglandins, leukotrienes, and other cytokines. In allergies, these proinflammatory mediators enhance vascular permeability, smooth muscle contraction, and eosinophilic infiltration, resulting in symptoms of bronchoconstriction.

The immune system also mediates tolerogenic mechanisms. Here, naïve Th cells are transformed into tolerogenic regulatory T cells (Tregs) rather than inflammatory Th2 cells. Tregs favor B cell isotype class switching to IgA and IgG4, both of which block

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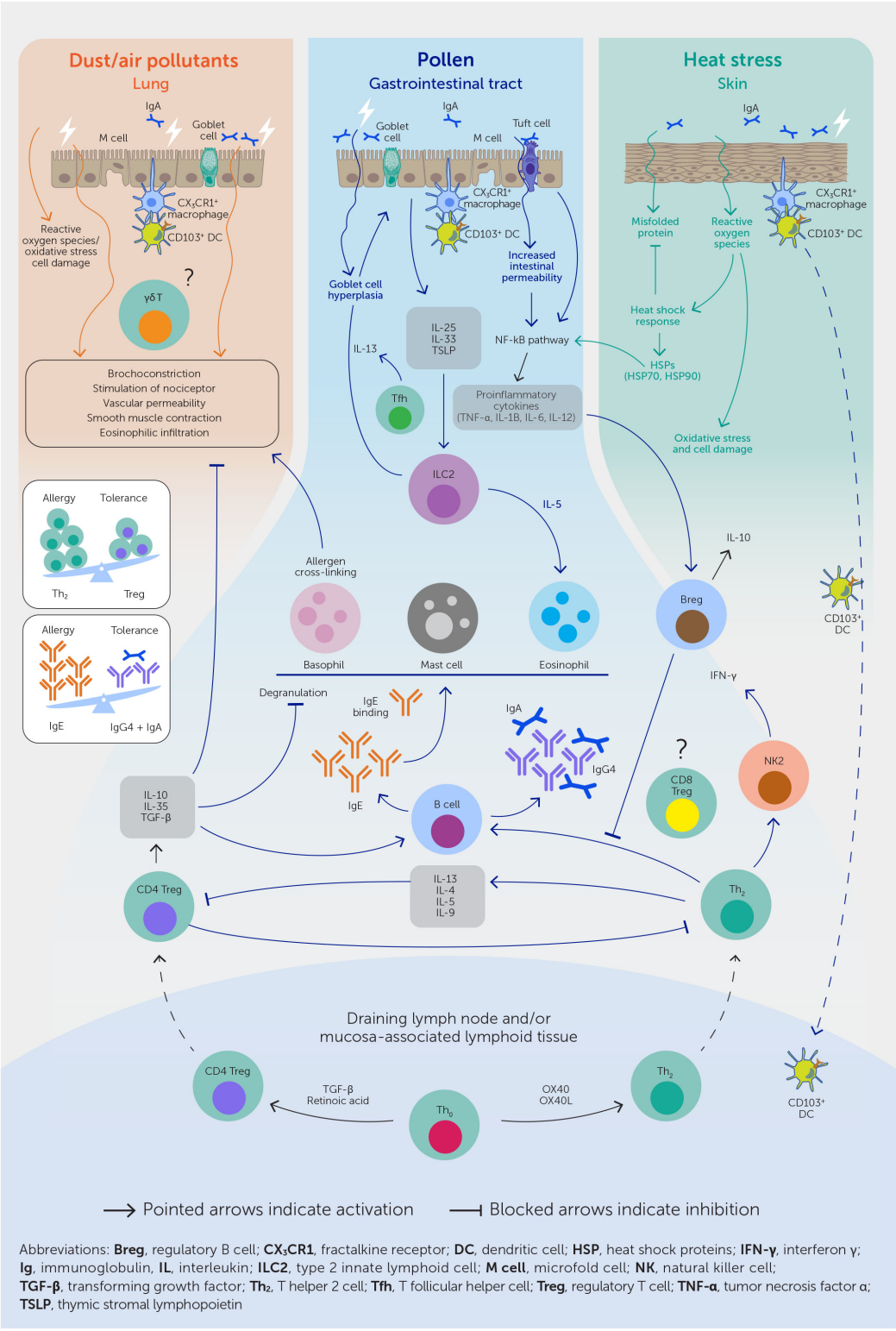

Abbreviations: **Breg**, regulatory B cell; **CX$_3$CR1**, fractalkine receptor; **DC**, dendritic cell; **HSP**, heat shock proteins; **IFN-γ**, interferon γ; **Ig**, immunoglobulin, **IL**, interleukin; **ILC2**, type 2 innate lymphoid cell; **M cell**, microfold cell; **NK**, natural killer cell; **TGF-β**, transforming growth factor; **Th$_2$**, T helper 2 cell; **Tfh**, T follicular helper cell; **Treg**, regulatory T cell; **TNF-α**, tumor necrosis factor α; **TSLP**, thymic stromal lymphopoietin

FIGURE 2
Climate change-associated exposures, such as pollen, air pollutants, and heat stress, trigger complex pathways mediating both inflammatory and tolerogenic responses. Penetration of allergens, pollutants, and other environmental stressors via a defective epithelial barrier leads to the release of pro-inflammatory cytokines such as interleukin (IL)-25, IL-33, and thymic stromal lymphopoietin (TSLP) and the skewing of T helper (Th) naïve cells to Th2 cells. Th2 cells mediate a pro-inflammatory cascade through cytokines IL-4, IL-5, IL-9, and IL-13, leading to a B cell isotype class switching to immunoglobulin (Ig)E. IgE bound to mast cells and basophils cross-link on subsequent allergen exposure, leading to the release of pro-inflammatory mediators such as histamine and prostaglandins. In allergies, these lead to enhanced vascular permeability, smooth muscle contraction, and eosinophilic infiltration, resulting in symptoms of bronchoconstriction. Heat stress and air pollutants work synergistically to mediate these pro-inflammatory effects. The immune system also actively mediates tolerogenic effects to commonplace environmental agents. Here, naïve Th cells are transformed into regulatory T cells (Tregs) which favor B cell isotype class switching to anti-inflammatory IgA and IgG4.

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Th2 inflammatory responses (29). The environmental factors hypothesized to increase the likelihood of inflammatory rather than tolerogenic responses include microbial and epithelial barrier dysregulation, increased hygiene, early life avoidance of allergens, refined diet, and air pollution (30).

Climate change, pollen, and asthma

Changes in land use and climate, such as rising temperatures and nitrogen oxides (NOx), ozone (O_3), and carbon dioxide (CO_2) levels, have led to increased pollen quantity, quality, allergenicity, and duration of the pollen season (Table 1, Figure 3) (38, 41). In one study, the production of allergenic pollen by ragweed increased by 61% when CO_2 concentrations were doubled (42). Greenhouse and field studies indicate that pollen concentrations are correlated with temperature and some estimates suggest that pollen concentrations may increase by 200% by the end of the century (37). Most pollen types have shifted toward earlier times of the year for pollen outputs (e.g., ragweed), possibly aggravating the burden on pollen-allergic patients (37, 38). Nitrogen dioxide (NO_2) and O_3 have also been shown to damage *Platanus* pollen cell membranes, increase the concentration of the *Platanus* pollen allergen a 3 released into the atmosphere, and alter its protein structure via nitrification and oxidation—enhancing its immunogenicity and stability (43).

The intensification of pollen exposure has important implications for public health. Increased allergenicity of pollen results in more severe symptoms in allergic individuals (32). There is increasing evidence correlating high pollen levels (especially grass pollen) with higher rates of asthma exacerbations and associated emergency department visits and hospitalization (44–46).

Furthermore, pollen is also affected by thunderstorms, leading to a phenomenon called thunderstorm asthma (TA) characterized by severe asthma attacks and asthma-related deaths in patients with allergic rhinitis. First described nearly 40 years ago, TA has been reported in North America, Europe, the Middle East, and Australia. TA events result from a complex interaction of environmental and individual susceptibility factors (47). Environmental factors include high concentrations of an aeroallergen and rain and moisture that rupture pollen grains and fungal spores, leading to the release of fine allergen-bearing starch granules that are <2.5 μm in size (48).

TABLE 1 Overview of the environmental factors influencing the allergenicity, abundance, and seasonality of aeroallergens (airborne pollen and fungal spores).

Aeroallergen traits	Aeroallergen functional group and most implicated taxa	Environmental factors			Reference
		Temperature	CO_2	O_3	
Higher allergenicity					
	Molds				
	Alternaria		↑		(31)
	Cladosporium		↔		(31)
	Pollen				
	Ambrosia		↔	↑	(32, 33)
Higher abundance					
	Molds				
	Alternaria	↑			(34)
			↑		(31)
	Cladosporium	↑			(34)
			↔		(31)
	Pollen				
	Alnus, *Ambrosia*, *Cupressaceae*, *Platanus*, Poaceae, *Quercus*	↑			(35–37)
Earlier season start					
	Pollen				
	Alnus, *Betula*, Cupressaceae, *Fraxinus*, *Platanus*, Poaceae, *Quercus* *Epicoccum* *Ambrosia*	↑			(35, 37, 38)

Abbreviations: **CO_2**, carbon dioxide; **O_3**, ozone.
The aeroallergen traits are sorted by functional group, namely molds and pollen. The direction of the arrow indicates if the change is parallel or opposite. Gaps indicate either no significant relationships or a lack of data.

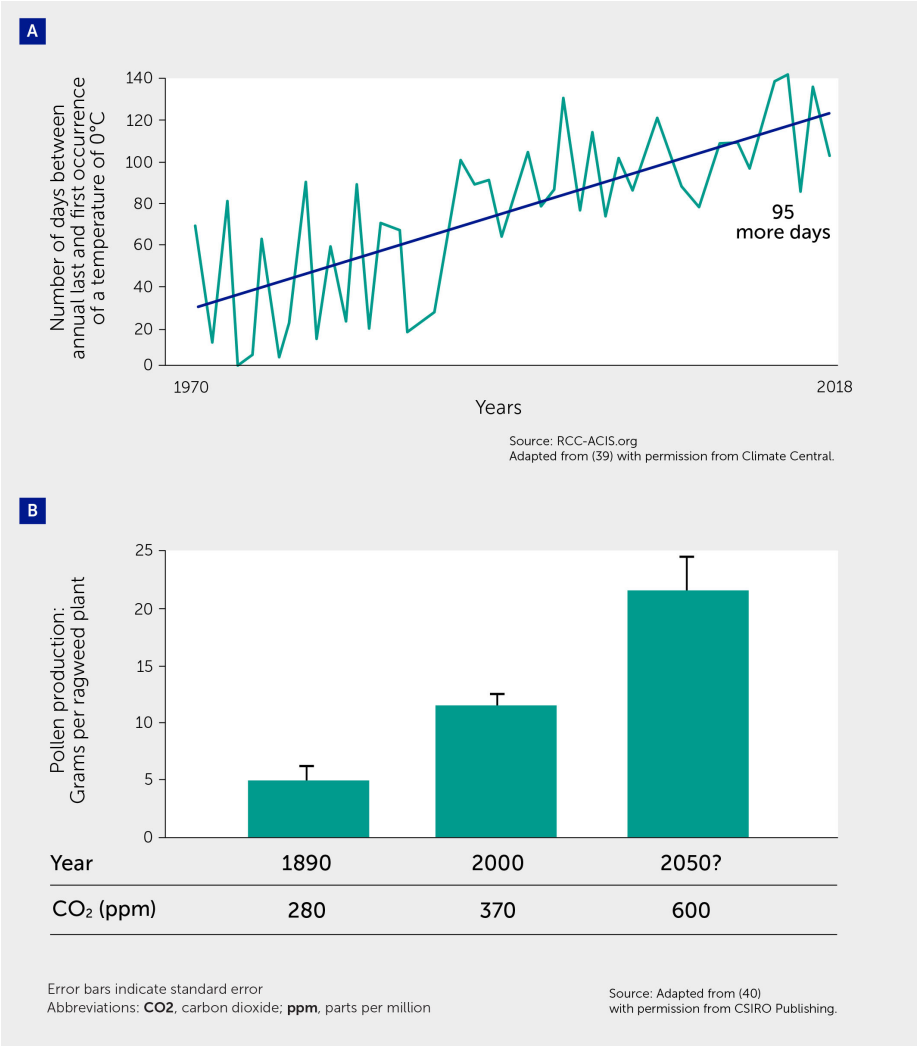

FIGURE 3
Climate change effects on pollen. **(A)** Global warming is causing longer growing seasons, which in turn leads to longer allergy seasons that start earlier in spring and last later into autumn. The figure shows data from 201 cities in the United States, plotting the number of days between the annual last and first occurrence of a temperature of 0°C (32°F), i.e., the first and last freezes of the year, over time—indicating a lengthening of the growing season. Adapted from (39) with permission from Climate Central. **(B)** Pollen concentrations increase with increases in atmospheric carbon dioxide (CO_2). Figure shows pollen production in common ragweed grown at pre-industrial CO_2 concentrations (280 ppm), current concentrations (370 ppm) and a projected 21st century concentration (600 ppm). Error bars indicate the standard error. The Student–Newman–Keuls test was used to determine differences among the CO_2 treatments at the 0.05 significance level. Adapted from (40) with permission from CSIRO Publishing.

Individual susceptibility factors include (i) pre-sensitization to seasonal aeroallergens; (ii) history of seasonal allergic rhinitis; and (iii) low rates of inhaled corticosteroid use in patients with allergic asthma (49). TA is also associated with fungal spores, such as *Alternaria*, whose proliferation is increased by floods and storms (47).

Air pollution

The 2019 Global Burden of Disease (GBD) study found that air pollution (outdoor and indoor) is estimated to contribute to about 10% of all noncommunicable disease deaths and is among the top three risk factors for death, with the burden of deaths predominantly in Asia and Africa (50, 51). The Lancet Commission on Pollution and Health linked air pollution to multiple adverse health conditions in children, including low birth weight; noncommunicable diseases such as asthma, cancer, and chronic obstructive pulmonary disease (COPD); and neurodevelopmental disorders (52, 53).

Global warming contributes to air pollution via increases in GHGs and other pollutants released by wildfires and SDSs, with important implications for immune and non-immune diseases (54–61).

Air pollution impacts both the innate and adaptive immune function in various ways (62) (Figure 2). Adaptive T cells such as CD8+ T and CD4+ T cells (Tregs, Th1, and Th2) are altered as are innate immune cells such as innate lymphoid cells type 2 (ILC2), dendritic cells, toll-like receptors (TLRs) and natural killer (NK) cells (63). A study found that ozone-oxidized black carbon caused

necroptosis in macrophages, increased levels of reactive oxygen species (ROS), and the expression of inflammatory factors and chemokines (64). Recently, age-related declines in immune function were linked to the accumulation of inhaled atmospheric particulate matter (PM) specifically contained within lung macrophages, which exhibited decreased activation, phagocytic capacity, and altered cytokine production. PM also disrupted the structures of B cell follicles and lymphatic drainage in lung-associated lymph nodes (65). Exposure to wildfire smoke and traffic-related air pollution has been associated with the activation of arylhydrocarbon receptors, toll-like receptors, and nuclear factor (NF)-κB signaling, and the upregulation of pro-inflammatory cytokines such as IL-22 (66). Firefighters have increased IL-6 and IL-12 and decreased IL-10 in their serum 12 hours after exposure to a wildfire (67). The activation of NLRP3 inflammasome and pyroptosis by environmental pollutants has been correlated to numerous diseases (68, 69). For example, perfluoroalkyl substance pollutants have been shown to activate the innate immune system through the absent in melanoma 2 (AIM2) inflammasome (70). In another study, the inflammasome was shown to be activated by micro- and nanoplastics, which are increasingly found in the air (71).

Chronic inflammation, including that triggered by air pollution, also promotes cancer progression. Inflammatory cytokines such as IL-6, TNF-α, and granulocyte macrophage colony-stimulating factor are mediated by air pollution, resulting in low-grade, chronic inflammation (72, 73). Low-grade inflammation fuels tumor progression by enabling immune evasion, angiogenesis, and metastatic dissemination. Air pollutants also mediate oxidative stress, which is characterized by an increase in ROS (74). Exposure to PM with an aerodynamic diameter of ≤2.5 mm ($PM_{2.5}$) was found to promote lung cancer by acting on cells that harbor pre-existing oncogenic mutations in healthy lung tissue (75). The discovery of immune checkpoint proteins, such as programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) and cytotoxic T-lymphocyte associated protein 4 (CTLA-4), represents a significant breakthrough in the field of cancer immunotherapy (76).

Ambient outdoor air pollution

Globally, 7.8% of all deaths in 2019 were attributed to outdoor air pollution, with this fraction exceeding 12% in some countries (Figure 4) (77).

Evidence suggests that exposure to numerous ambient air pollutants (e.g., PM, O_3, NOx) is related to the incidence and exacerbation of asthma in both children and adults (78–82). A systematic review and meta-analysis of 67 studies found that short-term daily exposure to O_3, NO_2, and sulfur dioxide (SO_2) was associated with increased emergency room visits and hospital admissions for asthma exacerbations. The pooled relative risk (RR) per 10 μg/m^3 increase of ambient mean 24-hour concentrations was 1.008 [95% confidence interval (CI) 1.005–1.011)] for O_3, 1.014 (95% CI 1.008–1.020) NO_2, and 1.010 (95% CI 1.001–1.020) for SO_2 (83). Another review evaluating 84 studies also concluded that short-term exposure (lag0 and lag1 exposure patterns) to outdoor pollutants increased asthma exacerbation risk (84). Other meta-analyses and systemic reviews have found an association between prenatal exposure to pollutants and the risk of asthma and wheezing in children (85, 86). A review conducted by the Health Effects Institute in the United States found that each 10 μg/m^3 increase in NO_2 was associated with a RR of asthma of 1.05 in children (12 studies) and 1.10 in adults (seven studies). Among children, each 5 μg/m^3 increase in $PM_{2.5}$ was associated with a relative risk of 1.33 (five studies). Similar effects were observed for associations with asthma prevalence among children (21 studies) (87). Another systematic literature review found compelling evidence that exposure to $PM_{2.5}$, PM with an aerodynamic diameter of ≤10 mm (PM_{10}), and NO_2 contributes to the risk of asthma development in childhood (88). Inhaled $PM_{2.5}$ are especially damaging to developing lungs as they are small enough to enter lung tissues (89). Exposure to O_3 has also been associated with new-onset asthma and is a well-established trigger for asthma exacerbations. Ambient air pollution is also associated with other respiratory diseases such as COPD. Analysis of data from the large UK Biobank showed that ambient air pollution exposure was associated with lower lung function and increased COPD prevalence (90).

Air pollution is also associated with cancer and autoimmune disease. In 2017, it was estimated that 14% of total lung cancers could be attributed to air pollution (91). A recent systematic review and meta-analysis found that exposure to $PM_{2.5}$ was associated with an increased risk of colorectal cancer: the odds ratios (OR) for incidence and mortality were 1.18 (95% CI 1.09–1.28) and 1.21 (95% CI 1.09–1.35), respectively. The risks of incidence and mortality were higher in the United States than in other countries studied (20). The International Agency for Research on Cancer (IARC) has classified outdoor air pollution as a Group 1 carcinogen (19).

A population-based cohort study found that every 10 μg/m^3 increase in PM_{10} was associated with an incremental 7% risk of developing an autoimmune disease. Exposure to PM_{10} at >30 μg/m^3 and $PM_{2.5}$ at >20 μg/m^3 was associated with a 12% and 13% higher risk of autoimmune disease, respectively (23). A study in Canada showed a link between fine PM and systemic autoimmune rheumatic diseases (SARDS) and found that the adjusted hazard ratio for SARDS related to one interquartile range increase in $PM_{2.5}$ (3.97 μg/m^3) was 1.12 (95% CI 1.08–1.15) (92).

Wildfires

Wildfires affect millions of people worldwide, causing a high incidence of attributable deaths from suffocation or injuries. Wildfires are growing in size and frequency as a result of climate change (93). Hundreds of thousands of hectares of forests and buildings/homes are destroyed worldwide each year by fire or human activities. These fires release large quantities of CO_2, carbon monoxide, and PM into the atmosphere. Indeed, wildfires are estimated to contribute at least 25% of the PM in the atmosphere (94, 95). The resulting increase in ambient pollution risks a range of health issues, including respiratory diseases, as detailed in the previous section. Specifically, exposure to wildfire

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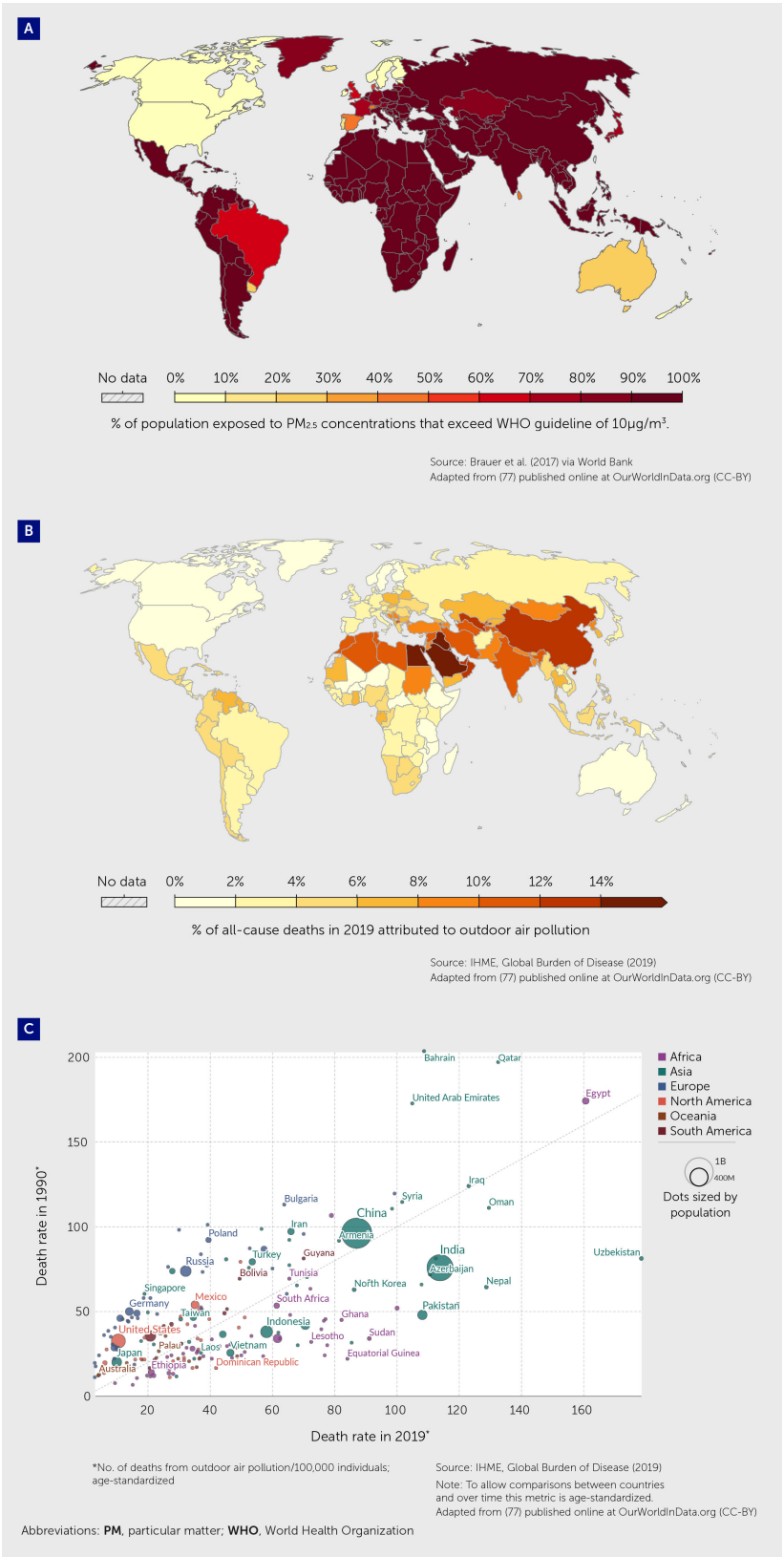

FIGURE 4
Contribution of air pollution to mortality rates globally. **(A)** Percentage of the population in 2017 exposed to mean annual ambient outdoor concentrations of particulate matter ($PM_{2.5}$) that exceed 10 µg/m^3/year, the guideline value recommended by the World Health Organization as the lower end of the range of concentrations over which adverse health effects due to $PM_{2.5}$ exposure have been observed adapted from (77). **(B)** Percentage of deaths in 2019, from any cause, attributed to outdoor air pollution (from ambient particulate matter and ozone) as a risk factor adapted from (77). **(C)** Age-standardized death rates from outdoor air pollution (number of deaths per 100,000 individuals) in 1990 and 2019 adapted from (77).

smoke has been shown to increase key pro-inflammatory markers, such as C-reactive protein (CRP) and IL-1β, which can worsen asthma and allergic disorders (96). Other studies have linked wildfires with increases in conjunctivitis (97).

In the United States, $PM_{2.5}$ from wildfires have been detected at levels 10- to 15-fold higher than the 24-hour standard (35 $\mu g/m^3$) even 1000 km away from the source (98). Decreases in respiratory peak flow rate have been documented 1 year after wildfire events (99). There was a significant increase in the use of dermatology clinics in San Francisco (~290 km downwind) for the treatment of atopic dermatitis and itch for a 2-week period during and after the Camp Fire in northern California in 2018 (100).

Sand and dust storms

The "global dust belt" refers to regions stretching from the Sahara Desert to the Gobi Desert in China and Mongolia. Globally, approximately 50% and 40% of all dust particles (≤20 μm in diameter) are from northern Africa and Asia, respectively. The remainder are from North America and the southern hemisphere (101).

SDSs can spread thousands of kilometers away from their origin: Saharan dust frequently reaches Europe and even North and South America. Asian dust is transported across the Pacific into North America. The long-term effects of drought, scarce vegetation, and human exploitation and land use, as well as variations in precipitation, temperature, and wind speed, are critical parameters in the context of climate change and its impact on dust emission and spread (102).

SDSs have a significant impact on hospital admissions for respiratory diseases such as asthma (103). Exposure to $PM_{2.5}$ and PM_{10} during SDS outbreaks has been associated with respiratory and allergic diseases (104). Airborne dust can stay suspended in the air for days following SDS events. SDSs can also carry pollen, fungal spores, bacteria, and viruses, leading to respiratory infections, asthma, and allergies. Many microorganisms and pathogens can survive long-range transport by SDSs. For example in the southwestern United States, complex interactions between drought, heat, and increases in dust conditions have led to increased incidence of coccidiomycosis infections (105).

Indoor air pollution

Indoor sources of air pollution include cooking and heating with biomass such as coal and firewood, use of candles and incense sticks, cigarette smoke, volatile organic compounds (VOCs) from cleaning and other consumer products, molds, dust mites, and animal dander. Indoor air pollution contributed to 4.1% of global deaths in 2019, with the highest death rates among low-income countries (Figure 5).

Many forms of indoor pollution can impair human health. For example, NO_2, which is generated by cooking and heating with gas, has been associated with an increased risk of asthma in children (107). A systematic review and meta-analysis estimated a 1.8-fold increase in pneumonia risk in young children due to exposure to unprocessed solid fuels (108). A systematic review of the effect of indoor PM and VOCs found that high VOCs were associated with upper airway and asthma symptoms in those with pre-existing lung disease (109). With decreased use of solid fuels and increased use of clean fuels for cooking, these rates have been decreasing since the 1990s and are expected to decrease further (102). Climate change has also led to increased flooding and extreme rainfall, which increases dampness in poorly weatherized homes, leading to indoor mold proliferation. Mold spores are indoor pollutants of concern as they increase asthma severity (110). A study observed a significant association between household mold and increased

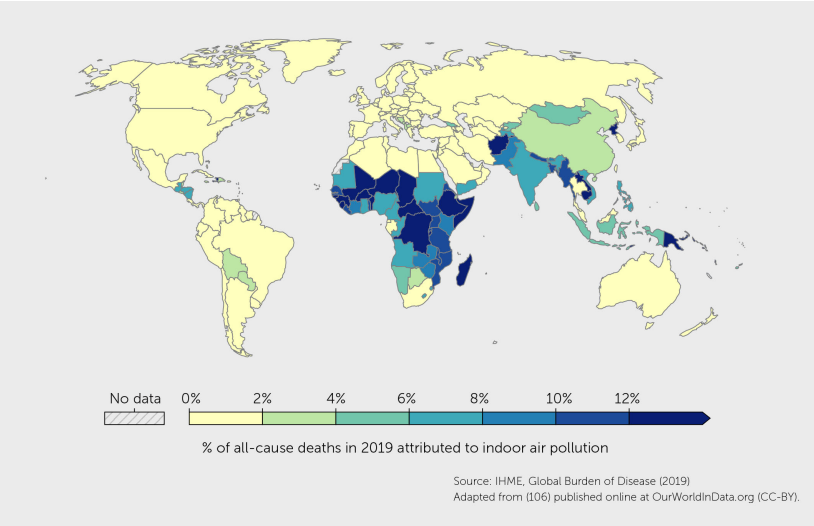

FIGURE 5
Percentage of deaths in 2019, from any cause, attributed to indoor air pollution (from burning solid fuels) as a risk factor (106).

prevalence of asthma (OR = 2.399). Similarly, another study in China found that mold odor was associated with asthma (OR = 1.90) (111, 112).

Heat stress

Climate change is also increasing global temperatures, with increases in the severity and frequency of heatwaves and the associated morbidity and mortality (113).

During heat stress, high levels of ROS are released (Figure 2). ROS induce oxidative damage and degradation of biomolecules (e.g., proteins, lipids, carbohydrates, and DNA) leading to cellular death, while also increasing the production of heat shock proteins (HSPs), antioxidants, other metabolites, anti-inflammatory cytokines, and stress granules that mitigate the effects of heat stress (114) (115). There is increasing evidence that HSPs can influence the immune system, mediating both pro-inflammatory and anti-inflammatory pathways. For example, HSP70-B29, a bacterial HSP70-derived peptide, has been shown to induce HSP-specific Tregs that suppress arthritis by cross-recognition of their mammalian HSP70 homologs (116). However, HSPs have also been demonstrated to induce the release of pro-inflammatory cytokines such as IL-6 and IL-1 through the NF-kB pathway (117, 118). In primary human keratinocytes and mice, HSP90 inhibition robustly suppressed 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced inflammation by targeting key pro-inflammatory cytokines and signaling pathways, suggesting it may be a potential topical treatment option for immune-mediated skin disease beyond psoriasis (119).

Heat stress has various direct and indirect effects on health and well-being. For example, a study in Australia found a significant increase in childhood asthma emergency department admissions during heatwaves (defined as three consecutive days of extreme heat). Male children and those aged 0–4 years were the most vulnerable (120). In China, exposure to ambient air pollution and high temperatures were independently and jointly associated with asthma risk in early childhood (121). Other direct effects of heat stress include cramps, stroke, increases in cardiovascular disease, and mental health conditions (122). Heat has been shown to cause ventricular-dependent changes that may undermine cardiac health, energy homeostasis, and function (123). Elderly individuals and those with comorbid conditions are at particular risk from heat stress (124).

Heat stress also indirectly affects health outcomes through disruption caused to infrastructures (e.g., power, water, and transport) and via increases in workplace injuries and drownings. Higher temperatures also increase the occurrence of harmful marine algal blooms that release toxins, and food and waterborne diseases (125).

Urban/rural environments and migration patterns

Climate change exacerbates shortages of food and water, which have led to human migration from rural to urban areas or from low- and middle-income countries to affluent countries. The United Nations predicts that close to 70% of the world's population will live in urban areas by 2050 (126). These migration patterns are associated with increases in asthma and allergy in individuals displaced from a rural environment to a more crowded urban area. Rural areas have higher microbial diversity and exposure to animals, both of which are protective against allergy and asthma. However, migration also exposes individuals to new pollutants and allergens. A study in Brazil found that rural-to-urban migration contributes to the high burden of asthma in urban migrants (127).

The built environment, which encompasses all manufactured or modified structures that provide people with living, working, and recreational spaces, is a critical determinant of allergy and asthma (128) owing to higher levels of indoor pollutants and allergens (129). Climate change is exerting changes in built environments that are expected to drive immune-mediated disease. For example, increased temperatures lead to a lower quality of indoor air. Flooding events result in increased urban indoor dampness, humidity, and mold levels (110). An increase in temperate zones is expected to lead to an increase in rodent populations (130), a matter of concern because mouse allergen is also a critical driver of childhood asthma disparities (131).

Food and water safety

Global warming and climate change have substantially endangered food safety for humans and domestic animals. Chemical pollutants contained in foods, such as emulsifiers, coloring agents, and preservatives, can disrupt the epithelial barrier that protects against asthma and allergies (132). Residual detergents found after rinsing foods also damage lung tissue, as shown in human bronchial cell cultures (133). Dioxins and toxic metals such as lead, cadmium, and mercury found in contaminated water are also highly toxic and can lead to decreases in immunity (134, 135).

Biodiversity loss

The human body is an ecosystem or "holobiont"—a concept describing the host (animal or plant) as a community of species linked to other ecosystems and subject to continuous evolutionary pressure (136). Functioning ecosystems provide essential benefits to humanity (137)—sometimes referred to as ecosystem services. Biodiversity (the variety of life including genes, species, and ecosystems) is a key factor in maintaining a healthy and functioning ecosystem and for human health (138). Climate change, habitat destruction, and intensive land use have led to a startling loss of biodiversity, including microbial species (137, 139). Millions of species worldwide could face extinction as a result of climate change in the next few decades (140, 141).

Biodiversity loss associated with climate change can have a huge impact on human health, both directly (through disruption in the food supply or via emerging infectious diseases) and

indirectly (by degrading ecosystem health and ecosystem services) (142).

In particular, exposure to a greater diversity of microbes is thought to be a key factor driving the early immune system away from the development of asthma and allergies (143). Maternal exposure to stables during pregnancy, for example, has been found to be associated with increased TNF-alpha and IFN-gamma levels in newborns (144).

Mental stress

Climate change is associated with increased mental health burden and stress (145). In individuals with persistent emotional stress and greater negative moods, allergy flares are more frequent (146). The stress hormones, including glucocorticoids, epinephrine, and norepinephrine, are thought to be involved in psychological stress-induced asthma exacerbation (147). A study of 763 Japanese mother-child pairs used 12 specific behavioral patterns as stress indicators and found that maternal chronic irritation and anger were associated with the risk of childhood asthma (148). In adolescents, stressors such as poverty, neighborhood stress, and school stress were individual predictors of emergency department visits for asthma (149). In 2021, a survey of children and young adults in 10 countries found that there was widespread climate anxiety and dissatisfaction with government responses to climate change (150).

Mitigation and adaptation to manage the effects of climate change on immune diseases

We have outlined the complex effects that climate change is having on environmental exposures that in turn cause immune dysregulation and its associated diseases, including asthma, allergies, autoimmune diseases, and cancers (Figure 1). Research into the pathophysiology of immune-mediated diseases has provided a greater understanding of their mechanisms and has led to the development of novel drugs (151). However, in addition to this individualized treatment approach, multisectoral, multidisciplinary, and multilevel efforts are urgently needed to mitigate and adapt to the effects of climate change-related exposures (Figure 6).

Mitigation refers to primary preventions intended to cut or prevent the emission of greenhouse gases (e.g., using an electric car or electrifying a housing unit) thus limiting the magnitude of future warming. Adaptation is a form of secondary prevention intended to reduce vulnerability to climate change impacts, such as going to cooling centers during heat stress (e.g., see www.marinhhs.org/cooling-centers) or using a filter in a home to decrease asthma and allergies (152).

Implementing Planetary Health and One Health approaches

Planetary Health has been defined as "the health of human civilization and the state of the natural systems on which it depends" (153). Planetary Health directs attention to the extensive degradation of our planet for the benefit of humans. The concept focuses on better balancing human needs with the health of Earth's ecosystems to promote sustainability and protect the health and well-being of future generations. Reversing the degradation of the planet's ecosystem will require collaborations between multiple disciplines and sectors in order to alter practices and policies at every level, from global to local, and drive sustainable solutions. One Health, an interdisciplinary approach stressing the interconnectedness of the health of humans, animals, and the environment, is an important approach for better planetary and human health (154, 155).

Environmental health professionals, specifically those specializing in asthma and allergy, can play an essential role in education, communication, and advocacy on climate change mitigation and adaptation measures. For example, the connection between climate change and asthma and allergy was emphasized during the 2008–2018 Finnish Allergy Programme (156). In the city of Lahti, the European Union Green Capital 2021, Natural Step to Health, a 2022–2032 Regional Health and Environment Programme focuses on asthma and allergy as one of the areas of interest (157). The goals also include mitigation of climate change and nature loss. In this program, a "Planetary Health Physician" connects the healthcare and environment sector to improve citizens' diet (e.g., in day-care), physical exercise/mobility, housing environment, and nature connectedness (158), in the spirit of Planetary Health (153).

Reducing emissions and improving air quality

Widespread and fast action to reduce short-lived climate pollutants (SLCP; e.g., methane, hydrofluorocarbons, and black carbon) emissions has the potential to reduce global warming by as much as 0.6°C over the next few decades (159). At the community level, this can be achieved through actions targeting the reduction of air pollution emissions from agricultural activities, fossil fuel, waste management, household energy, industrial production, transport, cooling, and refrigeration. SLCP reduction will be beneficial for health. For example, reducing methane emissions by 40% by 2030 could prevent an estimated 540,000 emergency room visits globally from asthma (160). Investments to increase the usage of public transportation by expanding networks and lowering or eliminating fares, incentives for greater use of electric vehicles, and increasing pollution taxes can also improve air quality (161).

In the United States, Congress established much of the basic structure of the Clean Air Act in 1970 and made major revisions in

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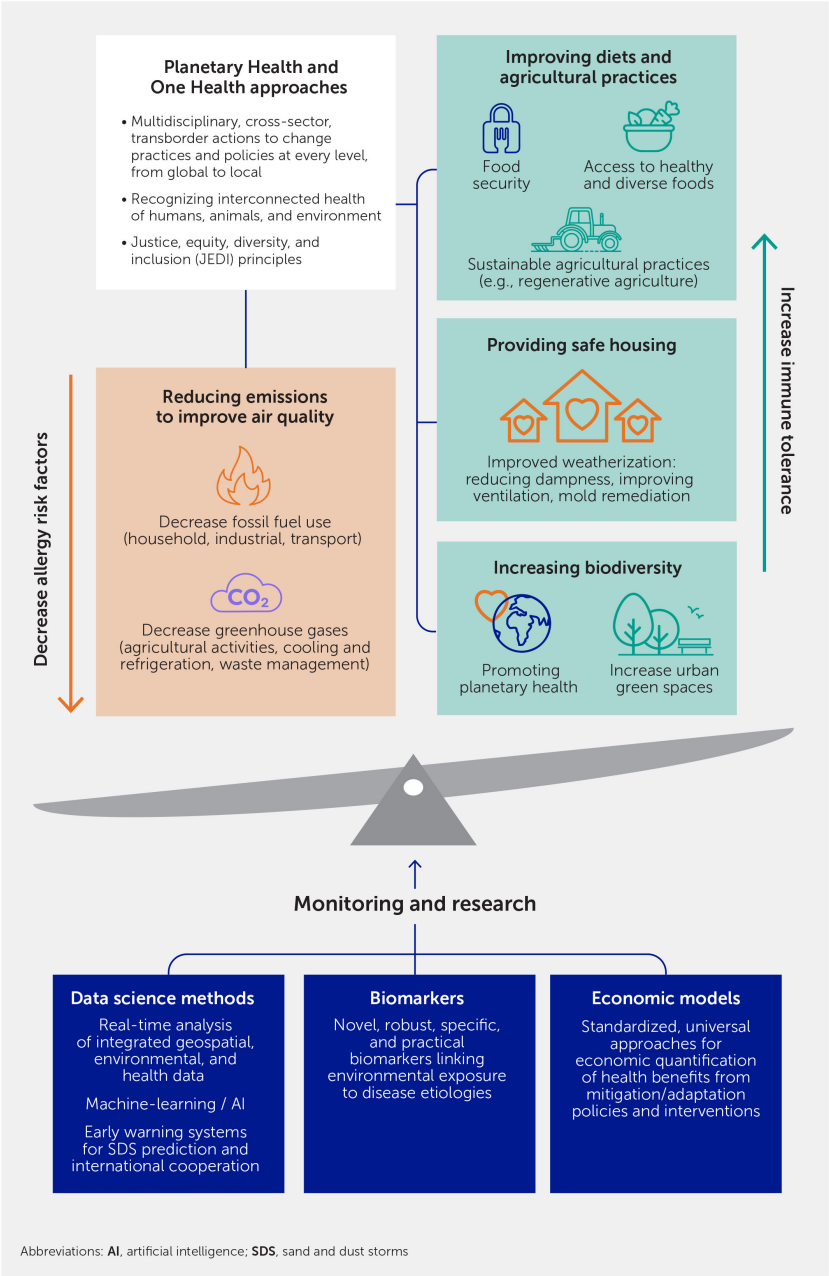

FIGURE 6
Mitigation and adaption actions to address increases in immune-mediated diseases associated with the exposome effects of climate change.

1977 and 1990 (162). Policies based on the Clean Air Act have led to decreases in air pollutant concentrations in southern California. Among children in southern California, decreases in ambient NO_2 and $PM_{2.5}$ between 1993 and 2014 were significantly associated with lower asthma incidence (163). A reduction in NO_2 of 4.3 parts per billion reduced the risk of incident asthma by 20%.

The air quality, health, and economic benefits of emission reductions from 2002–2011 in the eastern United States were estimated for the month of July 2011. During this extremely hot month, these actions were estimated to have prevented 10–15 O_3 exceedance days in the Ohio River Valley and 5–10 exceedance days in the United States mid-Atlantic region, saving 160–800 lives in the eastern United States and US$1.3–6.5 billion. Emission reductions were also estimated to have avoided 950 hospital admissions for respiratory symptoms, 370 hospital admissions for pneumonia, 570 emergency room visits for asthma symptoms, 922,020 minor restricted activity days, and 430,240 symptoms of asthma exacerbation (164). Therefore, surveillance of the impact of changes in air pollution on asthma and allergies would be useful in informing local and national government policies for managing environmental health risks. It would also allow systematic monitoring of the health impacts of policy decisions and plans implemented.

Emission reduction policies implemented in Seoul in 2007 also resulted in cleaner air, with significant decreases in PM_{10} (–17%) and NO_2 (–5%) in the period 2008–2011 compared with 2003–2007. It was estimated that the policy prevented 500,000 (11.3%) hospital visits for asthma in the total population and 320,000 (15.5%) in the younger population during this period (165).

Improving air quality can have even more rapid and substantial health benefits. In 1996, in preparation for the Olympics, the city of Atlanta implemented a 17-day alternative transportation strategy involving 24-hour public transportation. Within a month, there was a 42% reduction in children seeking medical care for asthma and a 19% decrease in hospitalizations for asthma (166). This suggests that air quality policies can benefit asthma and allergy clinical outcomes within a month of their implementation and that these markers (across all age groups) could be used to monitor policy effectiveness (Table 2).

Providing safe housing

Housing is one of the central determinants of exposure to indoor asthma risk factors. Children living in historically marginalized urban homes near areas of high air pollution have higher rates of asthma and more severe and uncontrolled asthma (177–179). Consistently, there is strong evidence that improved weatherization (i.e., ventilation and mold remediation) decreases the risk of respiratory disease outcomes (129). However, the current provision of housing through for-profit markets creates barriers for large segments of the population, particularly racial and ethnic minorities, and working-class communities more generally, to access safe living conditions (180). Climate change worsens air quality and exacerbates indoor dampness and mold, thereby potentially widening existing race and class disparities in housing quality and concomitant asthma burden. Existing public housing stocks require repair, upgrade, and expansion to address this urgent threat. Randomized controlled trials provide strong evidence of the respiratory health benefits of high-quality public housing (181). Modeling studies estimate that repairing New York City's public housing units would reduce asthma rates by a quarter among their 350,000 residents (182). In the private market, increases in regulatory health code requirements are needed, particularly with respect to mold remediation. An emerging evidence base is showing that proactive inspections are effective in this regard (183), particularly if informed by leading indicators of unhealthy or unsafe conditions (184).

Improving diets and agricultural practices

Asthma and allergies can be worsened by poor nutrition or inadequate diet interventions. Indeed, diversity in dietary proteins early in life has been shown to reduce the risk of asthma and allergies (185). Exploratory data suggest that improvements in diet quality could help reduce the inflammatory status among individuals with poorly controlled asthma (186). Dietary factors are also important in the development of food allergies, eosinophilic esophagitis, and other disorders resulting from chronic inflammation, such as autoimmune diseases and cancer. Therefore, focusing on food security, access to healthy foods, and diversity of food choices is important for the prevention of immune-mediated diseases.

The EAT-Lancet Commission on healthy diets from sustainable food systems established that global food production should stay within 5 Gt of CO_2 equivalent per year from food systems by 2050 (187, 188). The commission recommended a healthy, plant-forward diet, high in whole grains, legumes, vegetables, fruits, and healthy fats with a very modest amount of animal protein—about 300 calories worth, or only 12% of the reference intake of 2,500 calories/day. The inclusion of a wide variety of plant-based proteins (including nuts) in the diet, especially in early life, can also help prevent asthma and allergies by developing immune tolerance (30, 189). Understanding how these revised diets will enable better control of an inflamed immune system, improve microbiota, and enhance overall health will be important for the future.

Agricultural practices need to be overhauled to become more sustainable. For example, regenerative agriculture is a holistic land-management practice that aims to sequester carbon in the soil while improving soil health, crop yields, water resilience, and nutrient density. It advocates for, among other practices, the use of cover crops, reducing tilling, rotating crops, spreading compost (as well as super-compost "inoculants"), and moving away from synthetic fertilizers, pesticides, herbicides, and factory farming (190).

Increasing biodiversity and exposure to natural environments

Growing up in a biodiverse environment is one of the strongest and most consistent protective factors against the development of asthma and related atopic conditions (191). According to the available evidence, it is highly probable that we could develop safe and effective primary preventive regimens for asthma and allergy by developing better practices for planetary health and promoting biodiversity and exposure to natural environments.

Indeed, green spaces can reduce all-cause mortality (192). In Toronto, a study found that green space structures can protect individuals aged 0–19 years from a high risk of developing asthma, and this direct protective effect can be enhanced by high tree diversity (193). Among adults residing in the five largest urban areas in Belgium, higher exposure to increased residential green space was associated with lower rates of non-accidental and respiratory mortality (194). In Metro Vancouver, a population-based birth cohort study found that increased exposure to residential greenspace might improve childhood development by reducing the adverse developmental effects of traffic-related exposures, especially NO_2 air pollution (195).

Importantly, many greening practices are being established in cities worldwide to mitigate climate change effects (196). Planting trees and native plant species is an important part of creating better means to sequester carbon and reduce temperatures and CO_2. Asthma and allergy experts should be included in policy and city planning discussions to promote biodiversity and reduce

10.3389/fsci.2024.1279192

TABLE 2 Effects of climate change mitigation on asthma and allergies.

Intervention	Location/ time period	Pollutants	Health effects
Policies based on the Clean Air Act (163)	California, USA 1993–2014 3 cohorts (1993–2001, 1996–2004, and 2006–2014)	Median changes in community-level annual mean concentration among 9 communities from 1993–2006 were: −8.9 ppb for O_3 −4.3 ppb for NO_2 −4.0 μg/m^3 for PM_{10} −8.1 μg/m^3 for $PM_{2.5}$	$PM_{2.5}$: IRR was 0.81 for a median reduction of 8.1 μg/m^3 NO_2: IRR for asthma was 0.80 for a median reduction of 4.3 ppb
2007 emission reduction policies (165)	Seoul, South Korea 2008–2011	Decreases in PM_{10} (−17%) and NO_2 (5%) in the period 2008–2011 versus 2003–2007	Policy estimated to have prevented 500,000 (11.3%) and 320,000 (15.5%) hospital visits cases for asthma in the total and younger populations, respectively
2001 automobile NOx/PM laws (167)	Japan 1997–2000 (control) and 2001–2009 (policy intervention period)	Annual rates of decrease in air pollution in areas with PM law enforcement were 2.0- and 2.5-fold higher for NO_2 and suspended PM, respectively, versus non-enforcement areas	Decreases in the prevalence of pediatric asthma: NO_2: 0.118% per 1 ppb Suspended PM: 0.050% per 1 μg/m^3
Closure and reopening of a steel mill (168)	Utah, USA April 1985–February 1988	Decreases in PM_{10} during mill closure	24-hour PM_{10} >150mg/m^3 was associated with a 3-fold increase in hospital admissions (pneumonia, pleurisy, bronchitis, and asthma) in children; in adults, the increase in admissions was 44%
17-day "alternative transportation strategy" for the Olympic games (169)	Atlanta, USA Summer 1996	23% decrease in peak morning traffic	19% decrease in hospitalizations for asthma observed 4 weeks after peak weekday morning traffic counts decreased
Regulations driven by the 1990 Clean Air Act Amendments (170)	Atlanta, USA 1999–2013	Electricity generating unit NO_x and SO_2 emissions in the southeast decreased by 82% and 83%, respectively, between 1999 and 2013 Mobile-source emissions controls led to estimated decreases in Atlanta-area pollutant emissions of 61–93%, depending on the pollutant	Policies were estimated to prevent 16.5% of asthma emergency department visits between 2012–2013
Factory emission and travel restrictions (171, 172)	Beijing, China 2008 Olympics	40% and 7.3% decreases in $PM_{2.5}$ and O_3, respectively, observed during the Olympic period (August 8–September 20) versus baseline (June 1–June 30)	40% decrease in asthma events observed during the Olympic period versus baseline Peak expiratory flow levels increased in 78% of participants during the Olympics versus baseline Peak expiratory flow levels decreased in 80% of participants in the post-Olympic period versus Olympic period
Installation of a non-polluting, more effective home heater before winter in homes of children with asthma (173)	New Zealand. End of winter 2005 (baseline) and winter 2006 (follow-up)	Lower NO_2 levels measured in the living rooms of intervention households versus controls: 8.5 μg/m^3 vs 15.7 μg/m^3, respectively	Compared with children in the control group, children in the intervention group had 0.40 fewer visits to a doctor for asthma and 0.25 fewer visits to a pharmacist for asthma
Unflued gas heaters (control group), flued heaters (intervention group) in schools (174)	Australia 2000	Mean concentrations of NO_2 were 1.8-fold higher and mean concentrations of formaldehyde were 9.4 ppb higher during exposure to unflued gas versus flued gas heaters	Exposure to unflued gas heaters was associated with increased cough reported in the evening (OR = 1.16) and wheeze reported in the morning (OR = 1.38) Association with wheeze greater in atopic subjects
Unflued gas heaters (control group), flued gas/electric heaters (intervention group) in schools (175)	Australia 2000	NO_2 levels of 15.5 ppb and 47.0 ppb in the intervention and control schools, respectively	Difficulty breathing during the day (RR = 0.41) and night (RR = 0.32), chest tightness during the day (RR = 0.45), and daytime asthma attacks (RR = 0.39) were significantly reduced in the intervention group
Indoor HEPA filtration (176)	Cincinnati, USA October 2015–August 2017	Statistically significant reductions observed for $PM_{2.5}$ and black carbon pre- and post-HEPA	Participants with poorly controlled asthma and lower QoL scores at baseline showed significant improvements in asthma control (from 1.3 to 0.9; P = 0.003) and QoL (from 4.9 to 5.5; P = 0.02)

Abbreviations: **HEPA**, high-efficiency particulate air; **IRR**, incidence rate ratio; **OR**, odds ratio; **O_3**, ozone; **NO_2**, nitrogen dioxide; **NOx**, nitrogen oxides; **PM**, particulate matter; **ppb**, parts per billion; **QoL**, quality of life; **RR**, relative risk; **SO_2**, sulfur dioxide.

allergenicity. In fact, with proper planning and the inclusion of native dioecious plant species, it is possible to reduce major allergen spread (197).

Monitoring and research: data science, biomarkers, and economics

There is a pressing need for collaborative, multidisciplinary research to better understand the pathophysiology of immune diseases in the context of climate change. Moreover, the development and broad implementation of new data science techniques, biomarkers, and economic models are critical for measuring the impact of climate change on immune health and disease, informing the design of mitigation and adaptation policies and interventions, and evaluating their effectiveness.

Data science methods

Real-time analysis of integrated geospatial, environmental, and health data and the application of machine-learning techniques to better understand environmental-human interactions are currently some of the most important challenges in understanding the impact of global climate change on human health and disease. Big data analyses and artificial intelligence can be utilized to decipher the complex, multidimensional relationships between diverse parameters in the cause of diseases, with special attention to vulnerable populations, chronicity of cumulative effects over a lifetime, and multiple simultaneous exposures. The results of these studies are instrumental for the development of health resilience measures such as forecasting, adaptation of disease management, and prevention of noncommunicable diseases to manage climate change scenarios. The Integrated Clinical and Environmental Exposures Service (ICEES) provides regulation-compliant open access to electronic health record data that have been integrated with environmental exposure data, as well as analytic tools to explore the integrated data. Results suggest that the open-source ICEES can be used to replicate and extend published findings on factors that influence asthma exacerbations (198–200). The National Institutes of Health (NIH) is now looking to establish the Center for Exposome Research Coordination to accelerate precision environmental health. It aims to build upon the effort supported by the European Union to further extend, expedite, and coordinate exposome research efforts on a global scale (201). Another important program by the NIH is the Environmental Influences on Child Health Outcomes (ECHO) Program. ECHO combines observational and intervention research to answer important questions about how influences on early human development—even before birth—affect us throughout our lives and across generations. ECHO focuses on five pediatric health outcome areas: pre-, peri- and postnatal; upper and lower airways; obesity; neurodevelopment; and positive health, such as happiness and a sense of well-being (201). Examples of other exposome projects that have been established include the EU-funded Human Early-Life Exposome (HELIX) and the Health and Environment-wide Associations based on Large population Surveys (HEALS) (202). Big data monitoring methods are being used to evaluate air quality trends and vehicle traffic dynamics and monitor river water quality and wildfire pollutant composition (203–205). Big datasets and analytics that integrate statistics, computer science, biomedicine, and public health are being developed that can assist with understanding the complex dynamics between the environment and health.

Biomarkers

Biomarkers can provide evidence of exposure to pollutants, associate them with disease etiologies, and provide necessary data to inform policy decisions. For example, one study measured urinary concentrations of nine hydroxylated metabolites of polycyclic aromatic hydrocarbons (OH-PAHs) to assess wildland fire smoke exposure in wildland firefighters. Post-shift concentrations of OH-PAHs were 83–323% higher compared with pre-shift concentrations. Additionally, the increase in 4-hydroxy-phenanthrene urinary concentration was marginally associated with work shift exposure to $PM_{2.5}$ and significantly associated with levoglucosan, a marker of wildland fire or vegetative biomass smoke. These results suggest that OH-PAHs, especially 4-hydroxy-phenanthrene, may be useful biomarkers of wildland fire smoke exposure (206). Another urinary marker, 1-hydroxypyrene, has been associated with occupational exposure to polycyclic aromatic hydrocarbons (PAHs) from urban pollution (207).

Recent studies have correlated CRP with air pollution, suggesting that low-grade inflammation may be a causative factor for the adverse health effects associated with exposure to air pollution. In a study by Prunicki et al, individuals exposed to wildfire smoke from the El Portal wildfire in California in 2014 had increased levels of the proinflammatory markers, CRP and IL-1β, compared with non-smoke exposed controls (96). A large population-based cohort study in the United Kingdom found that CRP levels were positively associated with NO, NO_2, and $PM_{2.5}$ (208). Similarly, short-term exposure to air pollution was associated with higher serum high-sensitivity CRP levels in adult residents of two urban areas in northern France (209). A metabolomics study identified lysophosphatidylcholine (LysoPC) P-20:0 and LysoPC P-18:1(9z), two products of phospholipid catabolism, as potential biomarkers of $PM_{2.5}$ exposure (210).

Cancer biomarkers have also been associated with air pollution. For example, research in western China suggests that the lung cancer markers, cytokeratin 19 fragment (CYFRA211) and nerve-specific enolase (NSE), could be used as biomarkers for exposure to certain air pollutants (211).

While numerous studies have found associations between environmental exposures and biomarkers, robust, specific, and practical biomarkers are still lacking. In the future, omic approaches may provide comprehensive molecular signatures that can better assess the impact of climate change on disease development and progression. For example, a study found differences in metabolic profiles and alterations in the skin microbiome of women from polluted and less polluted cities (212). Omics has the potential to elucidate pathophysiological

mechanisms and to facilitate patient stratification, disease prognosis, and prediction of treatment efficacy (213).

Economic models of climate change interventions

The adverse health consequences of climate change are significantly mitigated by policies that reduce GHG emissions, decreasing health burdens and healthcare costs.

In the United States, federal agencies have relied on a common damage function, the "social cost of GHG emissions" to economically quantify the societal benefits or harms of decreasing or increasing GHG emissions (214). From 2008 to 2022, this damage function did not fully consider the health effects of climate change beyond diarrhea and malaria morbidity and mortality (215). As a result, United States federal agencies have historically underestimated the social benefits of climate mitigation (216). In fact, the London School of Hygiene and Tropical Medicine and others have recently estimated that by achieving net zero in 16 major cities worldwide, 20,000 cases of childhood asthma, representing a quarter of the current asthma cases in these cities, could be avoided annually (217). Such interventions also offer a good economic return on investment: for every US$1 spent on climate mitigation, at least US$3 is saved from health benefits, largely through a reduction of diseases such as asthma and allergies (88, 218). Peer-reviewed cost-benefit analyses of policies and scenarios to reduce GHG emissions have generally concluded that the immediate health benefits of cleaner air (such as reduced asthma and allergy) outweigh the implementation costs of these interventions (219–221).

Standardized, universal approaches to quantify the health benefits of reducing GHG emissions in economic terms are urgently needed to i) motivate and guide climate policies around the world and ii) promote actions to decrease the public health burden of allergies and improve respiratory health.

Conclusion

Climate change presents an existential threat to the health of humans, animals, and the entire ecosystem. The changing exposome has led to an increased risk of major diseases associated with immune dysregulation, including asthma, allergies, cancers, and autoimmune diseases. While progress has been made in the development of therapeutic options to treat these disorders, these approaches are inadequate to meet the challenges posed by climate change.

We must fully recognize that planetary health is the basis of human health. Individuals, organizations, and nations need to work toward systematically mitigating the health effects of climate change, adapting to these changes, and promoting planetary health to improve immune health and decrease the immense burden of immune-mediated disease. Fundamentally, there is an urgent need to develop and implement sustainable practices and reduce the use of fossil fuels to benefit planetary health for succeeding generations. We suggest more collaborative research on the impact of climate change and policies for climate change mitigation on asthma and allergy outcomes.

Socioeconomically disadvantaged groups, such as immigrants with limited language proficiency, communities of color, indigenous groups, and outdoor workers on daily wages, face the brunt of the impact of climate change because of poor housing infrastructure, proximity to highly polluted areas, or poor access to medical care. Children, pregnant women, the elderly, individuals with preexisting conditions, and people with disabilities are also at greater risk from the adverse health effects of climate change. Justice, equity, diversity, and inclusion (JEDI) considerations should be integral within climate adaptation planning to address existing disparities exacerbated by climate change.

Statements

Author contributions

IA: Visualization, Writing – original draft, Writing – review & editing. MA: Visualization, Writing – original draft, Writing – review & editing. CA: Visualization, Writing – original draft, Writing – review & editing. AA-H: Visualization, Writing – original draft, Writing – review & editing. IA-M: Visualization, Writing – original draft, Writing – review & editing. JB: Visualization, Writing – original draft, Writing – review & editing. LC: Visualization, Writing – original draft, Writing – review & editing. AD: Visualization, Writing – original draft, Writing – review & editing. TH: Visualization, Writing – original draft, Writing – review & editing. AH: Visualization, Writing – original draft, Writing – review & editing. JH: Visualization, Writing – original draft, Writing – review & editing. MJ: Visualization, Writing – original draft, Writing – review & editing. YM: Visualization, Writing – original draft, Writing – review & editing. BM: Visualization, Writing – original draft, Writing – review & editing. J-WO: Visualization, Writing – original draft, Writing – review & editing. AO: Visualization, Writing – original draft, Writing – review & editing. RP: Visualization, Writing – original draft, Writing – review & editing. MJ: Visualization, Writing – original draft, Writing – review & editing. HR: Visualization, Writing – original draft, Writing – review & editing. MR: Writing – original draft, Writing – review & editing, Visualization. NR: Visualization, Writing – original draft, Writing – review & editing. VS: Visualization, Writing – original draft, Writing – review & editing. CS: Visualization, Writing – original draft, Writing – review & editing. FT: Visualization, Writing – original draft, Writing – review & editing. CT-H: Visualization, Writing – original draft, Writing – review & editing. GW: Visualization, Writing – original draft, Writing – review & editing. KN: Visualization, Writing – original draft, Writing – review & editing.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article.

CA receives grants from the Swiss National Science Foundation, European Union (EU CURE), Novartis Research Institutes (Basel, Switzerland), Stanford University (Redwood City, CA, USA), and SciBase, Stockholm.

IA-M has received grants from EU and national public grants and has received support for attending the 2022 European Respiratory Society meeting in Barcelona from the society (€600).

TH has received honoraria for lecturing at Orion Pharma.

JEH receives grants from NIH/NIEHS P30 ES000002.

HR is supported by the German Lung Center (DZL) and the Universities Giessen and Marburg Lung Center (UGLMC), the MIRACUM Consortium of the Medical Informatics Initiative, the Stiftung Pathobiochemistry and DAAD and GIZ Hospital Partnership Programme. HR has received grants from the German Center for Lung Disease (DZL German Lung Center, no. 82DZL00502) and Universities Giessen and Marburg Lung Center (UGML).

MBR reports grants from the NIH and fees from the Conservation Law Foundation.

NARF received payment or honorarium from Sanofi, AstraZeneca, AbbVie, Novartis, Viatris, Chiesi, and Glenmark.

CS is supported by the Universities Giessen and Marburg Lung Center (UGMLC), the German Center for Lung Research (DZL), University Hospital Giessen and Marburg (UKGM) research funding according to article 2, section 3 cooperation agreement, and the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation)-SFB 1021 (Project Number 197785619), KFO 309 (Project Number 284237345), and SK 317/1-1 (Project Number 428518790) as well as by the Foundation for Pathobiochemistry and Molecular Diagnostics.

GWKW received funding support from TS Lo Foundation, Hong Kong Research Grant Council Grant No. 14119320, and National Natural Science Foundation of China.

KCN was funded by C-CHANGE and the following NIH grants: P01HL152953, R01 ES032253, U01AI147462, U19AI167903, P01AI153559, and U19AI104209.

The funders had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Conflict of interest

IA is Chair EAACI Guidelines on environmental science for allergic diseases and asthma and Deputy Editor of *Allergy*.

CA is chair of the European Academy of Allergy and Clinical Immunology Guidelines on Environmental Science in Allergic diseases and Asthma and is Editor-in-Chief of *Allergy*.

JB is the Physician Member of the California Air Resources Board a component agency of Cal/EPA.

CS receives consultancy and research funding, Bencard Allergie and Thermo Fisher Scientific; Research Funding, Mead Johnson Nutrition (MJN).

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The authors AD, RP, NARF, CS and KCN declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

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