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Elsevier Inc.
2024

Skevaki, C, Nadeau, K C, Rothenberg, M E, Alahmad, B, Mmbaga, B T, Masenga, G G, Sampath, V, Christiani, D C, Haahtela, T & Renz, H 2024, 'Impact of climate change on immune responses and barrier defense', Journal of Allergy and Clinical Immunology, vol. 153, no. 5, pp. 1194-1205. https://doi.org/10.1016/j.jaci.2024.01.016

http://hdl.handle.net/10138/575276
10.1016/j.jaci.2024.01.016

Review article

Impact of climate change on immune responses and barrier defense

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Climate change is not just jeopardizing the health of our planet but is also increasingly affecting our immune health. There is an expanding body of evidence that climate-related exposures such as air pollution, heat, wildfires, extreme weather events, and biodiversity loss significantly disrupt the functioning of the human immune system. These exposures manifest in a broad range of stimuli, including antigens, allergens, heat stress, pollutants, microbiota changes, and other toxic substances. Such exposures pose a direct and indirect threat to our body's primary line of defense, the epithelial barrier, affecting its physical integrity and functional efficacy. Furthermore, these climate-related environmental stressors can hyperstimulate the innate immune system and influence adaptive immunity —notably, in terms of developing and preserving immune tolerance. The loss or failure of immune tolerance can instigate a wide spectrum of noncommunicable diseases such as autoimmune conditions, allergy, respiratory illnesses, metabolic diseases, obesity, and others. As new evidence unfolds, there is a need for additional research in climate change and immunology that covers diverse environments in different global settings and uses modern biologic and epidemiologic tools. (J Allergy Clin Immunol 2024;153:1194-205.)

Key words: *Climate change, immune responses, noncommunicable diseases, innate immunity, adaptive immunity, inflammation, heat waves, wildfires, allergies, autoimmunities, biodiversity*

The Intergovernmental Panel on Climate Change (IPCC), in its latest sixth series of assessments, the Sixth Assessment Report of the Intergovernmental Panel on Climate Change (also known as the Sixth Assessment Report or AR6), established that climate change is harming the health of global populations.[1] The continued rise of global temperatures owing to anthropogenic fossil fuel emissions will result in a warmer atmosphere and oceans, which will disrupt the balance of nature and Earth's climate system. In fact, even if all anthropogenic emissions were to abruptly stop today, the global temperatures would continue to rise by about 0.5°C in the next decade.[2] There is increasing evidence that a warming climate with extreme meteorologic and atmospheric conditions (eg, temperature, humidity, water vapor pressure, precipitation, wind speed) can create an environment favorable to synthesis of and increases in the concentrations of particulate matter (PM) and ground-level ozone (O_3), in a phenomenon known as weather-related or climate penalty.[3,4] The pathways through which climate and health interact are complex and interdependent. Previous studies and reviews have explored the multiple pathways, health impacts, and drivers of today's climate change and its future.[5-9]

Climate-related exposures and climate-sensitive outcomes are listed in Table I. The World Meteorological Organization estimates that 50% of all disasters between 1979 and 2019 were attributed to weather, climate, and water extremes. For example, extreme weather conditions such as floods and storms disrupt infrastructures and health care delivery, which indirectly results in exacerbation of diseases among flood-stricken populations, not to mention the direct risks of injuries and drowning.[10] Similarly, extreme heat and heat waves are increasing in frequency, duration, and magnitude. Between 2000 and 2019, more than 5 million deaths each year were attributable to nonoptimal temperatures worldwide.[11] Heat also induces severe droughts and wildfires. Droughts disturb livelihoods and deteriorate both water quality and water quantity. Wildfires and their associated toxic smoke contain particulate and gaseous air pollutants that increase the risk of death and hospitalization—especially deaths and hospitalizations due to cardiovascular and respiratory causes.[12,13] An analysis of more than 60 million deaths around the world found that 0.62% of all-cause deaths annually (95% CI = 0.48-0.75) were attributable to the acute impacts of wildfire-related fine particles.[13] A warming climate has significant consequences for

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Received for publication June 29, 2023; revised January 16, 2024; accepted for publication January 18, 2024.

Available online February 2, 2024.

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0091-6749

https://doi.org/10.1016/j.jaci.2024.01.016

Abbreviations used
AhR: Aryl hydrocarbon receptor
AHR: Airway hyperresponsiveness
COPD: Chronic obstructive pulmonary disease
DEP: Diesel exhaust particle
miRNA: MicroRNA
NCD: Noncommunicable disease
NF-κB: Nuclear factor-κB
NLRP3: NLR family pyrin domain containing 3
PM: Particulate matter
$PM_{2.5}$: Particulate matter smaller than 2.5 μm
PM_{10}: Particulate matter smaller than 10 μm
ROS: Reactive oxygen species
TLR: Toll-like receptor
Treg: Regulatory T

infectious agents. An extended warm season expands the geographic range of ticks and alters vector ecology.[14,15] Climate projections warn of future epidemics of vector-borne diseases such as Dengue fever, malaria, leishmaniosis, and others.[16] By 2070, the population at risk of Dengue fever and malaria might increase by up to 4.7 additional billion people relative to 1970-1999.[17] Enteropathogens (eg, nontyphoidal *Salmonella*, *Vibrio cholerae*, rotavirus) will also have more favorable warmer water and food to proliferate and remain infective.[18] Elsewhere, food production is projected to be severely reduced.[19] Similarly, there is evidence of a reduced biodiversity of aquatic species and reduced seafood yield.[20] Global food availability per person could decrease by 3.2% by 2050, resulting in hundreds of thousands of excess deaths due to malnutrition and weight-related factors.[21]

More research on how climate change events and related exposures modify the immune system is now being conducted. The impact of climate change on allergens and allergic respiratory diseases is an important example in this regard.[22-26] Allergens and pollens are expected to increase in concentration and allergenicity while also circulating longer as a result of climate change. Global warming is associated with increased length of the pollen season, altered geographic distribution of pollen, and increases in pollen concentration and allergenicity.[27-31] Evidence now shows that the flowering period is being extended because of early onset of warm days in the spring. In North America, the intensity of pollen concentration has increased by 21% annually in the past 30 years.[27] Compared with 30 years ago, the allergenic pollen season is now starting an average of 20 days earlier and lasting an average of 8 days longer.[27] An important mechanism underlying this process is the increase in concentrations of carbon dioxide (CO_2) in the atmosphere, which is accelerating plant growth; boosting pollen production and pollen potency; accelerating the onset, length, and duration of the pollen season; and allowing the emergence of new pollen species. Doubling of atmospheric CO_2 increases ragweed pollen production by more than 60%,[32-38] which in sensitized individuals triggers the development of T_H2 cell inflammation with allergen-specific IgE production as well as eosinophil and mast cell activation.

Ragweed plants were exposed to climate change conditions with increasing CO_2 concentrations in a greenhouse. Analysis of the differentially expressed transcripts clearly demonstrated that the levels of several allergen-encoding ragweed proteins (*Ambrosia artemisifolia*) have increased in response to elevated CO_2 levels and drought stress. In addition, transcripts in coding allergenic proteins in other plants were also identified.[39] Moreover, with the rise in temperature due to climate change, the pollen season for some taxa in some regions starts earlier, lasts longer, and is more intense.[40]

This will lead to more *de novo* allergies and/or to aggravation of already-existing allergic diseases. In addition, intrusions of water into houses following extreme precipitation events lead to fungal growth and molds, increasing the risk of respiratory allergic diseases.[41] For example, following Hurricane Katrina, dust collected in New Orleans homes had significant presence of mycotoxins such as *Aspergillus*, *Cladosporium*, *Mycelia sterile,* and *Penicillium*.[42] The increase in molds in air dust may play a role in the development of adult-onset asthma via increased IgE sensitization to *Aspergillus* and *Cladosporium* species.[43] Global warming has also been associated with altered animal population dynamics owing to changes in reproduction and enhanced mortality.[44] Similarly, there is evidence of excess deaths in exposed Subarctic populations during cold spells and heat waves.[45]

In this article, we highlight the current state of evidence regarding the effects of climate-related exposures on the immune system, namely, air pollution (particulate and gaseous), extreme heat, extreme weather events, and biodiversity loss (Fig 1).

TABLE I. Exposures and health outcomes related to climate change

Climate-related exposures
- Extreme weather events (eg, floods, storms)
- Heat and heat wave
- Cold spells
- Droughts
- Wildfires
- Thunderstorms
- Air pollutants (particulate and gaseous)
- Vector ecology changes
- Enteropathogens
- Allergens
- Food and water scarcity
Climate-sensitive health outcomes*
- Injury
- Heat-related illness
- Respiratory illness
- Cardiovascular diseases
- Water-borne diseases
- Food-borne diseases
- Vector-borne diseases
- Zoonoses
- Malnutrition
- NCDs
- Mental health

*Adopted from the World Health Organization (see https://www.who.int/news-room/fact-sheets/detail/climate-change-and-health).

CLIMATE CHANGE–RELATED ENVIRONMENTAL EXPOSURES AND CONSEQUENCES FOR THE IMMUNE SYSTEM

PM

Air pollution is a complex mixture of gaseous and solid constituents that vary temporally and spatially. Inhalable and

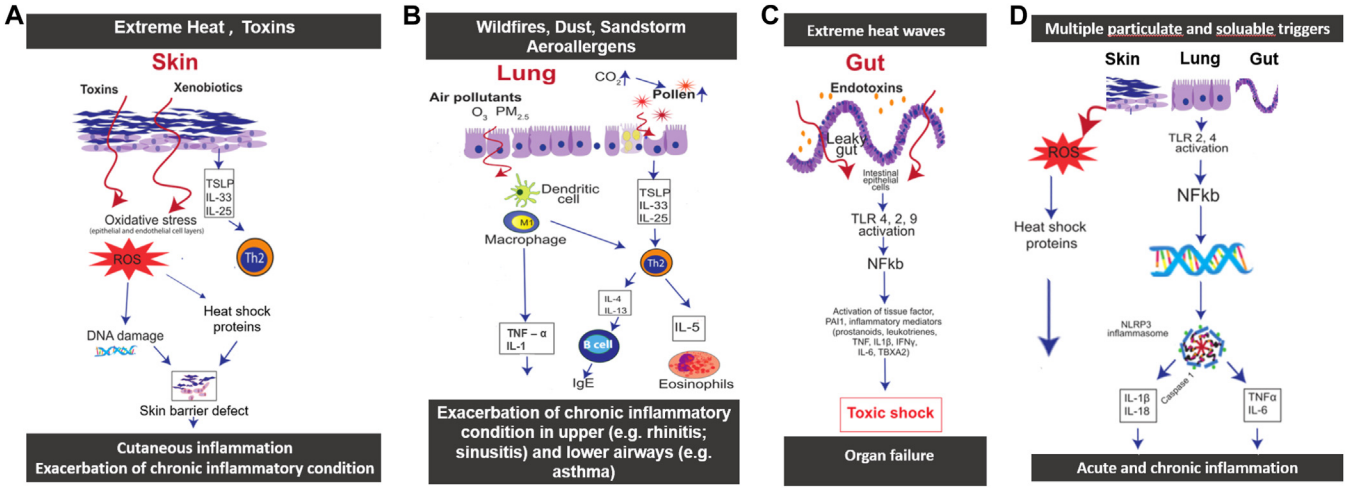

FIG 1. Climate change triggers events such as wild fires, increased dust exposure, sandstorms, increased exposure to aeroallergens and extreme heat waves (*top row*) that affect the integrity and function of the epithelial barrier. **A-C,** Shown are cellular and molecular events observed after cutaneous exposures (**A**), upper and lower airway function (**B**), and gut mucosa (**C**). **D,** The main signaling pathways leading to acute inflammatory responses at all barriers.

fine PM with aerodynamic diameters less than 10 μm and 2.5 μm (PM_{10} and $PM_{2.5}$), respectively, are some of the most common components of air pollution. The deposition of particles in different parts of the respiratory tract depends on their size (specifically, their aerodynamic diameter). Large particles (>5 μm) tend to deposit mainly in the upper (nasal) and large airways (trachea). Small particles (<2 μm) deposit mainly in the alveolar region, whereas particles in the size range from 2 μm to 5 μm deposit preferentially in the central and small airways. The smallest (<1 μm) can reach alveoli and may not be cleared. The precise proportion of disposition by size can vary, depending on particle size distribution in the ambient environment, individual physiologic factors such as tidal and minute volume, and presence of respiratory disease.

$PM_{2.5}$, which is arguably the most studied air pollutant, consists of toxic metals, crustal elements, carbon species, sulfates, and nitrates. $PM_{2.5}$ can disrupt epithelial barriers by degrading tight junction proteins; downregulating claudin-1, occludin, and E-cadherin; and impairing barrier function.[46,47] The process by which $PM_{2.5}$ consistently triggers these alterations remains unclear. However, these changes have been substantiated in both *in vivo* and *in vitro* studies. *In vitro* experiments point toward a direct mechanism,[48] whereas *in vivo* studies suggest that the induction of dysbiosis might be implicated. Genome-wide transcriptomic analysis following $PM_{2.5}$ exposure in keratinocytes has identified upregulated expression of genes involved in cholesterol metabolism as the most dominant functional pathway. Increased skin cholesterol level is associated with inflammatory skin diseases such as atopic dermatitis and can decrease skin barrier by disrupting the function of sebum.[49] Indeed, nasal and sinus biopsy samples taken during periods of exposure to high levels of air pollution demonstrate damaged epithelial barrier.[48] Moreover, PM activates epithelial Toll-like receptors (TLRs) (ie, TLR2 and/or TLR 4), resulting in nuclear factor-κB (NF-κB) and NLR family pyrin domain containing 3 (NLRP3) inflammasome signaling and production of proinflammatory mediators, including IL-1α, IL-1β, IL-6, C-X-C motif chemokine 8 (CXCL8), and GM-CSF.[50-57] These responses are seen both *in vitro* and following diesel exhaust particle (DEP) exposure in mice and even in human inhalation studies. Interestingly, compared with ragweed challenge alone, nasal challenge of ragweed-sensitized individuals with ragweed in the presence or absence of DEPs has demonstrated that DEPs increase ragweed-specific IgE, epsilon-mRNA splicing, decreased levels of type 1 cytokines, and increased levels of type 2 cytokines (Fig 2).[54] In addition, activation of the NLRP3 inflammasome by $PM_{2.5}$ and PM_{10} leads to the production of ROSs and, consequently, accumulation of activated inflammatory cells, including macrophages, neutrophils, and dendritic cells in murine models of lung inflammation induced by a variety of stimuli, including LPS and cigarette smoke.[58-62] More recently, it has been acknowledged that $PM_{2.5}$ increases the expression of angiotensin-converting enzyme 2, the epithelial cell receptor for severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2), and thus, coronavirus 2019 (COVID-19) virus susceptibility.[47]

At least in mice, increased signaling through the aryl hydrocarbon receptor (AhR) and increased reactive oxygen species (ROS) production is induced, which further accelerates the inflammatory response, as demonstrated in a murine model of asthma following exposure to the DEP constituent benzo(a) pyrene.[63] Activation of AhR by a variety of ligands, including constituents of PM such as polycyclic aromatic compounds, induces a conserved transcriptional responses in microsomal cytochrome P450–detoxifying enzymes and unique transcriptional responses in different cell types.[64] For example, AhR activation increases the number of regulatory T (Treg) cells *in vivo*, resulting in immunosuppression. This occurs through multiple mechanisms, including direct transactivation, epigenetic control of Foxp3 transcription, and modulation of dendritic cells.[64] In T_H17 cells, AhR induces the transcription factor Aiolos, which has been shown to silence IL-2 expression and attenuate IL-2–dependent suppression of T_H17 cell differentiation.[65] In patients with preexisting chronic airway and lung diseases (eg, asthma and chronic obstructive pulmonary disease [COPD]), these

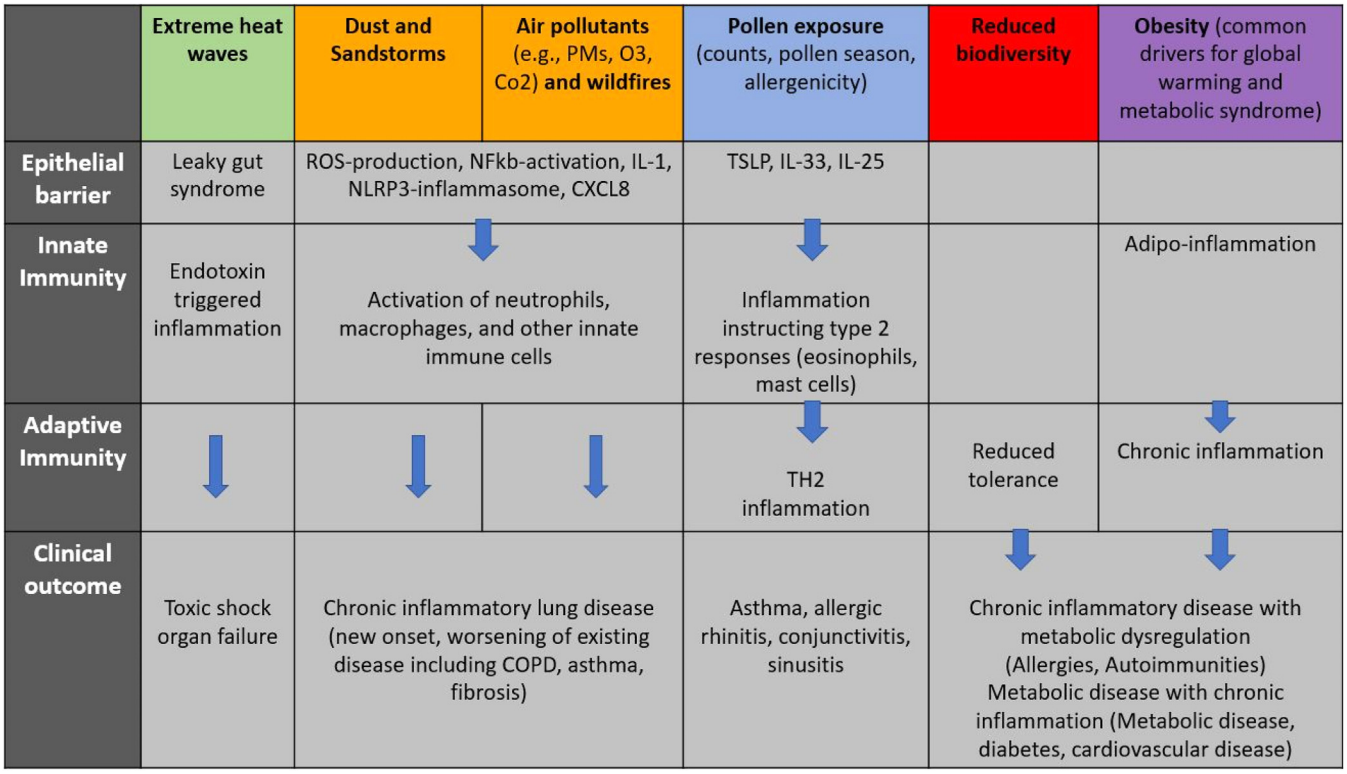

FIG 2. Major effects of climate changes with an impact on immunity and inflammation. The interaction between epithelial barrier, innate immunity, adaptive immunity, and clinical outcome.

pathways trigger further activation and recruitment of eosinophils and augment T_H2 cell–mediated inflammation. $PM_{2.5}$ causes alterations in ATP, characterized by an increase in extracellular ATP and a decrease in intracellular ATP, which is involved in triggering the NLRP3 inflammasome.[66] Additionally, exposure to fine PM in children living in an urban environment was associated with modified methylation of 5'–C–phosphate–G–3' (CpG) sites in important immunoregulatory genes, including *IL4*, *IL10*, and *IFNG*.[67] Notably, similar changes to methylation status of immune genes has been observed in pregnant women and may affect health outcomes for the mother and birth outcomes.[68] Particulate pollution disrupts the normal expression and function of structural proteins such as cytokeratin, and filaggrin. $PM_{2.5}$ exposure also is associated with an increase in lysosomal membrane permeability, lipid peroxidation, and FOXP3 methylation, the latter affecting Treg cells.[69]

One of the prominent components of $PM_{2.5}$ is black carbon, which is produced by incomplete combustion of fuel. In humans, exposure to black carbon has been shown to increase oxidative stress and induce the expression of IL-1β in human nasal epithelial cells, which likely exacerbate allergic rhinitis and asthma.[70,71] Nanoparticles and ultrafine particles present in air pollution can pass through the alveolocapillary membrane and enter the systemic circulation. They can then directly stimulate epithelial cells, macrophages, and fibroblasts to secrete proinflammatory and profibrotic mediators. Some nanoparticles generated from combusted fossil fuels have the capacity to destroy phospholipid membranes, endothelial cell junctions, and lysosomal membranes by interacting with lipid-rich structures, resulting in epithelial cell death.[46] They also disrupt the integrity of the epithelial barrier by altering cell junctions, inducing proinflammatory cytokines and causing mitochondrial and lysosomal dysfunction.[46]

Several components of traffic-related air pollution have also been associated with decreases in (gene-specific and/or average) DNA methylation, among other epigenetic changes. As an example, air pollution affects DNA methylation of FOXP3, which in turn controls the differentiation and activity of Treg cells, thus potentially having a role in diseases such as asthma,[72,73] eczema, or even aeroallergen sensitization.[74] Such changes have also been described in pregnancy and across all ages, although whether it is the cumulative exposure and associated changes or effects early in life that are most impactful remains unclear. Increased exposure to $PM_{2.5}$ during the seventh to 17th gestational weeks was significantly associated with an increased risk of childhood eczema, particularly among children who were not breast-fed or exposed to prenatal environmental tobacco smoke.[75] Changes to DNA methylation have also been proposed as a potential connection between particulate exposure and perinatal stress.[76] In the Normative Aging Study, DNA methylation profiling showed that short-term air pollution exposure, temperature, and relative humidity are associated with relative leukocyte proportions.[77] Micro-RNAs (miRNAs) have recently emerged as additional important players in the mechanisms behind our response to toxicants. Altered miRNA levels have been detected in various cells (eg, bronchial epithelial cells) and tissues (eg, human placental tissue) following exposure to heavy metals in $PM_{2.5}$.[78-82] In this context, specific upregulated or downregulated miRNAs were connected to enhanced inflammatory responses, disturbed

lung ventilation, and impaired cell survival and cell cycle progression. Such evidence has offered a mechanistic understanding of particulate exposure–mediated predisposition to COPD.

DEPs

DEPs may upregulate inducible bronchus-associated lymphoid tissue formation, with subsequent excessive production of proinflammatory mediators, generation of autoreactive T cells, and high citrullination levels in the lung.[83,84] Moreover, DEPs, and carbonaceous PM in general, may trigger a T-cell switch to an increased T_H17 cell–to–Treg cell ratio via the AhR.[85,86] One study that used both cell culture techniques and *in vivo* experiments in mice found that polycyclic aromatic hydrocarbons in PM act directly on AhRs in these T cells.[86] Air pollutants specifically regulate the production of IL-17, IL-21, and IL-22, which in turn influences the T_H1 cell–to–T_H17 ratio and stimulates the development of autoimmunity. IL-17 also plays an important role in O_3-induced inflammation, lung injury, and airway hyperresponsiveness (AHR).[87,88] AhR activation by DEPs mediates upregulation of IL-33, IL-25, and thymic stromal lymphopoietin (TSLP) with T_H2 cell activation, as shown in primary bronchial epithelial cells of patients with asthma.[89] In a mouse model of severe steroid resistant asthma, IL-33 contributed to a DEP-mediated increase in T_H2 cell inflammation and AHR via pathogenic IL-5^+IL17A^+CD4^+ effector T cells.[90] In accordance with epidemiologic evidence regarding triggering of respiratory symptoms, the data also indicate that DEPs activate T cells in asthmatic patients but not in controls.[91] Protein phosphate 4 is important in maintaining the baseline epithelial barrier integrity and is implicated in DEP-induced disruption and alarmin release.[92]

O_3

Ground-level (tropospheric) O_3 is an air pollutant that forms when sunlight reacts with nitrogen oxides and volatile organic compounds, which are emitted by cars, power plants, and various industrial emissions. It is often referred to as a ground-level "smog" (not to be confused with the stratospheric O_3, which is located in an outside layer that is approximately 10 to 50 km above the Earth's surface).

A warming climate has been shown to increase the concentrations of ground-level O_3. In a study conducted in the United States between 1994 and 2012, during which time temperature increased and wind speed decreased in most US regions), weather-related 8-hour maximum O_3 concentrations were found to increase by 0.18 ppb per year in the warm season (May-October) and 0.07 ppb per year in the cold season (November-April).[4] It was estimated that in the United States, this climate penalty for O_3 could be associated with 290 excess deaths (95% CI = 80-510) every year.[4] There is increasing evidence that a warming climate with extreme meteorologic and atmospheric conditions (eg, temperature, humidity, water vapor pressure, precipitation, wind speed) can create an environment favorable to synthesis and increasing concentrations of PM and ground-level O_3 in a phenomenon known as weather-related or climate penalty.[3,4] Ground-level O_3 passes through the lower respiratory tract and even into the capillary endothelium, leading to cell stress, desquamation, cell death by oxidative damage via ROSs, changes in gene methylation patterns, and production of proatopic cytokines such as IL-33.[93-95] As such, O_3 can potentate exacerbations and loss of control for preexisting respiratory diseases.[96,97] Acute exposure to high levels of O_3 triggers a predominantly neutrophilic inflammation.[98] Following chronic exposure, O_3 induces collagen deposition in epithelial and subepithelial areas, causing peribronchial fibrosis.[99] O_3 treatment of patients with multiple sclerosis leads to an increase in Treg cell numbers, Foxp3 expression, IL-10 and TGF-β levels.[100]

O_3 exposure leads to increased levels of intracellular ROSs, resulting in the activation of NF-κB–dependent pathways, including mitogen-activated protein kinase phosphatase 1 (MKP1), p38 mitogen-activated protein kinase (MAPK), human hypoxia-inducible factor 1-α (HIF-1α,), and others.[101] Consequently, a broad spectrum of proinflammatory genes are expressed and trigger the recruitment and activation of innate immune cells, including eosinophils, macrophages, and neutrophils. This is paralleled by mitochondrial ROS production, resulting in mitochondrial dysfunction and activation of the NLRP3 inflammasome.[96,97] At that stage, the proinflammatory pathways merge and synergize. Another important pathway is the increase in cell death via apoptotic and nonapoptotic mechanisms. In parallel, multiple genetic modifications such as histone acetylation and DNA methylation in genes linked to these proinflammatory pathways can occur.[102,103] Furthermore, exposure to O_3, PM, and NO_2 may affect different stages of the viral life cycle.[104] This has important clinical implications because viral infections are the main drivers of asthma and COPD exacerbations. In a murine model of O_3-induced asthma, the lncRNA PVT1-miR-15a-5p/miR-29c-3p-PI3K-Akt-mToR axis was implicated by promoting airway smooth muscle cell proliferation and T_H1 cell–T_H2 cell imbalance.[105]

Inhalation of O_3 may also worsen asthma by impairing glucocorticoid responsiveness, as well as in other ways.[106-108] O_3-induced oxidative stress leads to associated neutrophilic airway inflammation, which in turn is poorly controlled by glucocorticosteroids.[109] Specifically, O_3 inhalation generates ROS-induced release of alarmins through lipid peroxidation and immune cell activation. Some of these cytokines and chemokines activate the retinoic acid–related orphan receptor γt (RORγt) signaling pathway, leading to mRNA activation of the *IL-17A* and *IL-22* genes and subsequent neutrophil activation, which perpetuate ROS release. Proinflammatory signaling activates NF-κB, which inhibits expression and function of glucocorticoid receptors through inhibition of glucocorticoid receptor nuclear translocation, steric hindrance of nGRE binding, and interference with transcription factor tethering. Animal data implicate endogenous glucocorticoids in the regulation of pulmonary macrophages to O_3.[110]

Extreme heat

Endotoxins stimulate massive innate immune activation with increased levels of IL-6, TNF-α, and IL-1.[111-113] Many studies of heat stress have been conducted in mice or in livestock such as broiler chickens and cattle; in humans, these studies have been conducted primarily under exertional heat stress conditions.[114-116] A firm link between sustained environmental heat and elevated systemic levels of proinflammatory cytokines, together with neutrophil activation and activation of the clotting system, are seen during sustained heat waves, especially during the 2003 heat wave in Paris.[117,118] This activation may lead to

multiorgan failure.[119] In parallel, anti-inflammatory pathways are also activated, with the production of IL-1Ra, IL-10, and soluble TNF receptors together with the production of certain heat shock proteins.[113,119,120] However, from a clinical perspective, these anti-inflammatory pathways do not necessarily outweigh the proinflammatory activation seen under such conditions. In broiler chickens, heat exposure under experimental conditions[121] resulted in cell injury and expression of heat shock proteins. Furthermore, animals exposed to long periods of heat stress have decreased immunity, increased infections, and increased inflammation, such as gastrointestinal disease and defects in their epithelial barrier. Epidemiologic studies in humans have shown increased mortality and morbidity during hot days.[11] One study estimated that almost one-third of heat-related deaths can be attributed to anthropogenic climate change, and increased mortality from heat is evident on every continent.[122]

Wildfires

Wildfire activity has been enhanced in recent years and is expected to continue to increase as climate change progresses. Because of the ensuing rising temperatures, prolonged periods of drought, and altered rainfall and meteorology, climate change creates conditions favorable for wildfires. The impact of wildfires on human health is multidimensional and far-reaching. Although the immediate physical threat of fires is obvious—burns, injuries, displaced populations and destroyed homes—wildfire smoke can travel hundreds or even thousands of miles, affecting air quality across many regions. Wildfire smoke is a heterogeneous mixture of coarse, fine, and ultrafine particles; volatile organic compounds; heavy metals; and hazardous and gaseous air pollutants.[123] Although there are many chemical components in wildfire smoke, PM of various sizes stands out as a major component.[123,124] It has been shown that wildfire can exacerbate chronic heart and lung diseases, leading to increased hospital admissions and even premature deaths.[13] Lung function has been found to be compromised among individuals exposed to wildfire smoke.[125] Although there is evidence for an association between wildfires and asthma exacerbations, the literature is less consistent in terms of associations with COPD exacerbations. In a retrospective study in children, investigators have found an increase in Foxp3 methylation associated with wildfires,[126] which is consistent with findings of prior air pollution studies.[127,128] In the same study,[126] a reduction in number of proinflammatory T_H1 cells was also associated with wildfire exposure.

Thunderstorms and sandstorms

Thunderstorms have been connected with enhanced asthma exacerbations and hospital admissions.[129] Indeed, thunderstorms, and lightning in particular, can generate subpollen particles and lead to enhanced PM concentrations in the atmosphere, which exacerbates allergic manifestations in sensitized individuals. Exposure to extract from *Alternaria fungus* in ryegrass-sensitized individuals may enhance the type 2 lung inflammatory response, possibly through T_H2 cell recruitment and expansion of group 2 innate lymphoid cells. This may be a potential cause of thunderstorm-related asthma.[130] *Alternaria alternata* sensitivity is a predictor of epidemic asthma among patients with seasonal asthma and grass pollen allergy and thus plays a role in thunderstorm-related asthma.[131]

In arid conditions, strong winds can blow dust or sand across large distances. These dust storms carry airborne pollutants from natural and anthropogenic sources as well as biologic particulates such as pollens and fungi. With more frequent droughts, the frequency and severity of sandstorms are increasing. The impact on pulmonary inflammation has been best studied following Asian sandstorm events in mice or rats.[132] Increased production of proinflammatory mediators such as IL-12, monocyte chemotactic protein-1 (MCP-1), macrophage inflammatory protein-1α (MIP-1α), TNF-α, keratinocyte chemoattractant, and others has been observed in bronchoalveolar lavage fluid in mice that were exposed to Asian sand dust intratracheally.[133] This has been linked to activation of the NLRP3 inflammasome through signaling via TLRs (eg, TLR2) in alveolar macrophages. Rapid mediator release by basophils and mast cells has also been observed. It enhances production of inflammatory mediators by tissue-resident eosinophils. Maturation and activation of bone marrow–derived antigen-presenting cells have been reported as well, indicating that depending on the magnitude of the responses, local activation of innate immune cells may also exert systemic effects.

CLIMATE CHANGE AND BIODIVERSITY

Biodiversity encompasses both structural and functional variety of life.[134] How to reliably measure biodiversity is under constant debate, and consensus is lacking. In 2015, the World Health Organization reported the dependence of human health on biodiversity emphasizing the close interaction with climate change.[135] Climate change is affecting macrodiversity, including the biogeographic distribution of animal species and plants,[136] which is reflected in microdiversity. Air, soil, and water pollution also contributes to the loss of microbial diversity.[137] Nature loss is an alarming megatrend that is interconnected with global warming and its consequences.[138,139] In California, the level of diversity has been reduced over time to 20% of the original level of biodiversity.[140] Human activities are the major drivers for both climate change and nature loss.

The number of microbes in the body exceeds the number of human cells.[141] The body is protected by 2 nested layers of biodiversity, consisting of microbes residing in the wider environment and those in the body.[142] As the inner biodiversity determines the immunoregulatory circuits, everyday practices—what people eat, drink, breathe, and touch—matter. Housing environments are surrogate markers of the lifestyle. Rich environmental biodiversity around homes has been shown to protect adolescents against allergy.[143]

In green environments, the air contains not only variable microbial elements,[144] but also biogenic volatile organic compounds supporting health.[145] In a recent observational study, a high concentration of monoterpenes in the air decreased anxiety symptoms.[146] The biogenic volatile organic compounds affect cellular metabolism and autophagy by removing unnecessary or dysfunctional material.[147]

Immunologic resilience and exposome

Resilience of the immune system depends on environmental exposure and epigenetic adaptation throughout life.

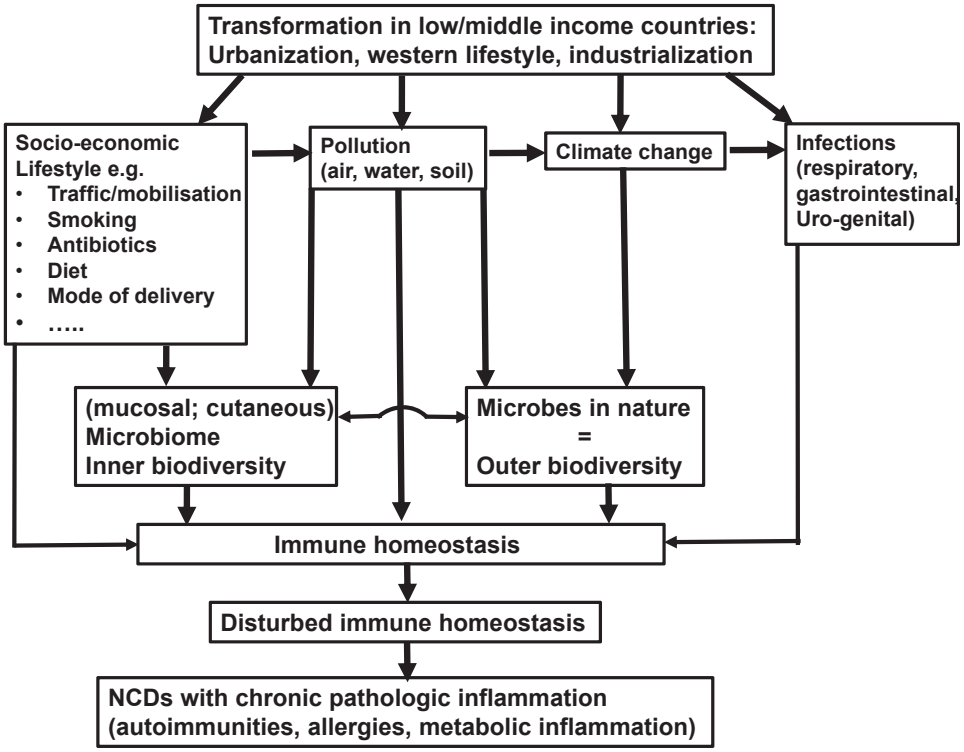

FIG 3. Transformation concept linking processes triggered by socioeconomic changes in low-income and lower middle-income countries with climate change, biodiversity, changes in microbial diversity, and the development of chronic inflammation.

The epigenetic DNA methylation, histone modifications, and function of small and long noncoding RNAs play a central role in mediating environmental effects.[148] Bacterial products such as peptidoglycans and short-chain fatty acids modify immune reactivity of both myeloid[149] and epithelial[150] cells through epigenetic programming. Artificial intelligence and machine learning have recently been presented as tools to explore the complex causality models of the environmental factors, the exposome.[151]

Urbanization, lifestyle, and prospects

In 2050, more than 70% of the human populations will live in cities, thus being disconnected from wider nature.[152] Improved hygiene standards have reduced not just infections but also immune-protective microbes and parasites—"old friends."[153] Likewise, the Western type of diet[154,155] and unnecessary antibiotic use (particularly in infancy), together with delivery by caesarean section, compromise microbial diversity.[156] Overall, microbial dysbiosis, immunologic imbalance, and low-grade inflammation pose a risk for asthma, allergy, and other noncommunicable diseases (NCDs).[157,158]

More mechanistic data are required to conceptualize connections between societal development, climate change, biodiversity loss, and human disease (Fig 3). Nonetheless, public health interventions emphasizing allergy health and immune tolerance have already slowed down the epidemic and helped patients.[159] Biodiversity interventions are on the way and have already given promising results (eg, applying forest floor and sod to a day care yard enhanced immune regulation and commensal microbiota in children).[160]

CLIMATE CHANGE AND IMPACT ON OBESITY AND METABOLIC DISEASES

A bidirectional relationship exists between adiposity and global warming. As atmospheric temperatures rise, individuals typically experience reduced adaptive thermogenesis and become less physically active while concurrently increasing their carbon footprint.[161-164] In parallel, lower agricultural yields, particularly in tropical regions, are a consequence of global warming, leading to a decrease in protein and micronutrient content of plant foods.[165] As a result, with a lower variety of healthy foods, the quality of diets is reduced. Furthermore, increased global energy prices also increase the prices of (healthy) basic foods. This series of events results in a shift toward the consumption of processed foods and beverages high in fat, sugar, and sodium.[161] The pathophysiologic consequences of these dramatic changes are at least 2-fold; on the one hand, undernutrition occurs in early life, and on the other hand, obesity develops later in life. Early-life undernutrition can be considered a predictor for the development of NCDs later in life, a concept originally described as the "Barker hypothesis,"[166] or the early origin of adult disease. Numerous epidemiologic studies support the Barker hypothesis; they include the follow-up study of underweight neonates and infants born during the hunger winter of 1944-1945, which showed development of numerous NCDs, including obesity, type 2 diabetes, cardiovascular disease, and many others. Obesity, too, is associated with a chronic inflammatory response originating in the adipose tissue, which is commonly termed *metaflammation*.[167] Metaflammation has been shown to be a risk for other NCDs in other organs, such as the liver, lung, and heart.[168,169] However, the clinical and pathophysiologic outcomes of today's global warming will be observed over the coming decades.

TABLE II. Future research needs

Climate change stressors	Research framework for Immunology	Example approaches to advance immunologic understanding
General	Cumulative stressors on the immune system over a lifetime; Mixture analyses of multiple events at a given time	Use tools such as the following to test for immune changes: single-cell omics, transcriptomics, AbSeq, CITE Seq, CyToF, EpiTOF, proteomics with inflammation panels, metabolomics specific to immune changes, epigenetic studies specific to immune activation pathways (eg, MethylSeq targeted to immune signatures), clinical biomarkers available in big databases
Extreme weather events	Effects of extreme weather events such as floods, hurricanes, extreme precipitation and others on overall immune system function	Conduct population-level observational health studies after a weather event (eg, before vs after a flood)
Air pollution	Effects of mixed air pollutants on the immune system	Study the immune injury from exposure to air pollutants and ultrafine particles
Extreme heat	Effects of heat stress on the immune system	Conduct observational and interventional studies in humans exposed to single and multiple heat events
Environmental degradation/ displacement/stress	Effects of stress and PTSD on the immune system from climate change events	Assess stress indices and their contribution to individual immune response in children and adults
Water and food supply shortages	Effects of climate-driven reduction in crop yields, destruction of livestock, and interference with the transport of food on the immune system	Define patterns of immune changes due to malnutrition and weight-related issues in children and adults, especially in low- and middle-income countries
Water quality	Effects of toxic metals and enteropathogens on the immune system	Identify vulnerable populations that are exposed to poor water quality
Allergens	Effects of increased allergens and extended pollen seasons on the immune system	Define immune changes by using systems biology approaches and immune markers in plasma and in cells
Vector ecology	Effects of increased geographic spread of vector borne diseases on the immune system	Define mechanisms and pathways of vector and parasite biology and immunologic interactions that drive disease or improve prevention
Greenness and other contextual exposures	Effects of low neighborhood and residential greenness on the immune system	Implement greening and natural environment exposures to improve natural immune tolerance or understand immune changes over time from neighborhood-level interventions

AbSeq, Simultaneous protein expression and RNASeq; *CITE Seq*, cellular indexing of transcriptomes and epitopes by sequencing; *CyToF*, cytometry by time of flight; *EpiTOF*, epigenetic landscape profiling using cytometry by time of flight; *MethylSeq*, bisulfite DNA methylation sequencing; *PTSD*, posttraumatic stress disorder.

CONCLUSION

In conclusion, climate change and the activation of innate immune responses are closely connected. Many effects of climate change directly or indirectly trigger the activation of innate immune cells, including neutrophils, eosinophils, monocytes, basophils, and mast cells. Numerous particulate and nonparticulate triggers stimulate overlapping pathways and effector responses, many of which synergize with NF-κB–dependent pathways and activate the NLRP3 inflammasome to trigger acute inflammatory responses. Furthermore, at least some of these effects result in aggravation and/or *de novo* induction of chronic inflammatory diseases, including allergies and autoimmune conditions. Future studies should strive to provide additional data regarding the mechanistic relationships between climate change and innate immune activation.

In our thorough analysis of the literature on climate change and health, there is a clear bias toward inhaled exposures. Indeed, this can be observed in the context of wild fires, air pollution (particulate and gaseous), and airborne allergens. This also suggests that there is an urgent need to increase our knowledge of how climate change affects other exposures as well (eg, direct cutaneous exposures or through the gastrointestinal tract or genitourinary tract) (Fig 2). Furthermore, we need studies that go beyond statistical associations to establish a cause-effect relationship. Intervention and environmental studies are urgently needed to address this gap.

The immune system is highly sensitive to environmental stressors associated with climate change. Certain events (eg, pollution, harmful microbiota, and toxicants) may interfere with immune tolerance or prevent it from occurring. Fig 2 depicts the interface between the epithelium and the immune system on one hand and the effects of climate change and associated events on the other hand. The development and maintenance of immune tolerance is critical; loss or failure of tolerance can result in disorders such as autoimmunity, allergy, respiratory illnesses, and others.

Overall, the synthesis of study findings in this review reveals key pieces of evidence highlighting the negative influence of climate change and related events on various aspects of immune functioning. Ideally, future studies should include relatable animal and human experiments with sufficient and adequate controls (placebo controls, controls of external conditions, and positive and negative control groups). These studies should also quantify dose-response relationships of exposures over time, especially in vulnerable populations. To ensure reproducibility of outcomes, results and data should be consolidated, harmonized, and validated with a global cohort. Alongside improving the rigor of study designs, there is a need to expand the field to accommodate larger group sizes and diverse environments, as well as to use more in-depth, state-of-the art analytic methods such as immune systems biology, next-generation sequencing, and big data technologies (Table II).

DISCLOSURE STATEMENT

C.S. is supported by the Universities Giessen and Marburg Lung Center (UGMLC); the German Center for Lung Research (DZL); University Hospital Giessen and Marburg research funding according to an Article 2, Section 3 cooperation agreement; the Deutsche Forschungsgemeinschaft (German Research Foundation [DFG])-SFB 1021 (project no. 197785619), KFO 309 (project no. 284237345), and SK 317/1-1 (project no. 428518790); and the Foundation for Pathobiochemistry and Molecular Diagnostics. H.R. is supported by the DZL and the UGLMC, the MIRACUM Consortium of the Medical Informatics Initiative, the Stiftung Pathobiochemistry and DAAD and GIZ Hospital Partnership Programme, the DFG, and the BMBF. K.C.N. is funded by the National Heart, Lung and Blood Institute (grant P01 HL152953, serving as principal investigator [PI]); the National Institute of Environmental Health Sciences (grants R21 ES03304901 and R01 ES032253-01, serving as PI for both); the National Institute of Allergy and Infectious Diseases (grant U01 AI147462-01A1, serving as PI); the Sean N. Parker Center for Allergy and Asthma Research; the Binn Family Foundation; and the San Francisco Firefighters Foundation in Cancer Research.

Disclosure of potential conflict of interest: C. Skevaki reports consultancy and research funding from Bencard Allergie. H. Renz reports speakers honoraria from Allergopharma, Novartis, ThermoFisher, Danone, Bencard, and Stallergenes, as well as consulting fees from Sterna-Biologicals (of which he is cofounder); in addition he is an associate editor of the *Journal of Allergy and Clinical Immunology*. The rest of the authors declare that they have no relevant conflicts of interest.

We would like to thank Silke Trier and Verena Schraub for the secretarial assistance.

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