Review article

Climate change and epigenetic biomarkers in allergic and airway diseases

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Human epigenetic variation is associated with both environmental exposures and allergic diseases and can potentially serve as a biomarker connecting climate change with allergy and airway diseases. In this narrative review, we summarize recent human epigenetic studies examining exposure to temperature, precipitation, extreme weather events, and malnutrition to discuss findings as they relate to allergic and airway diseases. Temperature has been the most widely studied exposure, with the studies implicating both short-term and long-term exposures with epigenetic alterations and epigenetic aging. Few studies have examined natural disasters or extreme weather events. The studies available have reported differential DNA methylation of multiple genes and pathways, some of which were previously associated with asthma or allergy. Few studies have integrated climate-related events, epigenetic biomarkers, and allergic disease together. Prospective longitudinal studies are needed along with the collection of target tissues beyond blood samples, such as nasal and skin cells. Finally, global collaboration to increase diverse representation of study participants, particularly those most affected by climate injustice, as well as strengthen replication, validation, and harmonization of measurements will be needed to elucidate the impacts of climate change on the human epigenome. (J Allergy Clin Immunol 2023;152:1060-72.)

Key words: *Climate change, epigenetics, epigenomics, DNA methylation, temperature, precipitation, extreme weather, malnutrition, epigenetic clocks, atopic disease, allergy, atopy*

Abbreviations used
CpG: Cytosine-phosphate-guanine dinucleotide
DMR: Differentially methylated region
EAA: Epigenetic age acceleration
EWAS: Epigenome-wide association study
$PM_{2.5}$: Particulate matter less than 2.5 μm in diameter
Treg: Regulatory T

The climate crisis is one of the greatest threats to humanity, with significant impacts on allergic, immunologic, and respiratory health.[1-5] The primary driver of climate change is the global production and consumption of fossil fuels—coal, crude oil, and natural gas—which emit greenhouse gasses, such as carbon monoxide and methane.[1,6] The average surface temperature of the planet has risen since preindustrial times largely because of fossil fuel use, and it is predicted to continue increasing unless immediate global efforts to reduce fossil fuel use take place. As a result, there have been changing precipitation patterns, increased frequency of natural disasters like wildfires and hurricanes, and alterations in land use patterns.[6-8] Global warming and the burning of fossil fuels are also associated with increased air and water pollution and increased UV radiation exposure.[9-11] These climatic and environmental changes to our planet have been linked to increases in risk for a wide range of human health outcomes, including heat stroke, vector-borne illnesses, cardiopulmonary diseases, malnutrition, and psychiatric conditions.[12,13] Relevant to allergy, changing atmospheric conditions in some regions, particularly increased temperature and precipitation, may lead to the spread of new pollen sources and increased intensity and duration of pollen generation.[4,14,15] Therefore, more extreme climatic conditions could lead to an increase in the burden of allergic diseases.

The epigenome lies at the intersection between environmental risk factors and human diseases. Epigenetic alterations refer to changes in gene expression that are not directly related to variation in the underlying genetic code. They allow us to better characterize early biomarkers of impact from environmental exposures and their connection to human health.[16,17] Epigenetic marks are tissue and cell type specific, which can yield insights into underlying changes and responses in specific organs. In epidemiologic studies, once DNA is extracted (often from a mixed population of cells in a human subject), methylation can be measured after bisulfite treatment using sequencing or microarrays (eg, the 450K or 850K/EPIC Illumina arrays [Illumina, San Diego, Calif]). The most commonly studied epigenetic modification in human studies is DNA methylation of cytosine nucleotides (cytosine-phosphate-guanine dinucleotide [CpG] sites).[16,17] Analytic strategies can include epigenome-wide analysis, candidate

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TABLE I. Description of the strategy used to search for recent articles

Parameter	Details
Dates of search	January 1, 2000, to August 1, 2023
Databases	PubMed, EMBASE, and Web of Science
Search terms	"epigenetics," "epigenome," "methylome," "DNA methylation," "histone," "non-coding RNA," "temperature," "thermal," "global warming," "climate," "radiation," "humidity," "hurricane," "flooding," "heat," "wildfires," "extreme weather," "extreme temperature," "heat wave," "blizzard," "thunderstorm," "tornado," "malnutrition," "famine"

gene approaches, testing of epigenetic biomarkers of aging, immune or cell type composition estimation, and identification of exposure biomarkers (eg, smoking) and epigenetic biomarkers of health.[18] These methodologies have been used in studies of allergic diseases, highlighting potential biologic pathways of disease development for environmental risk factors[19-22] and immunologic components of biologic aging.[23,24]

Harnessing the power of epigenetic biomarkers in the field of allergy and immunology can provide insights into how changing and extreme climatic conditions affect human health. Although temperature, humidity, and precipitation have been examined in human epigenetic studies less commonly than air pollution has,[19,25] research using plant and animal models have shown that these climatic factors affect DNA methylation and gene expression in multiple ways.[26-30] The most recent systematic review regarding climate and human epigenetic modifications was conducted in 2020; it identified 15 genes with methylation status associated with temperature, including genes associated with asthma (eg, *TLR2* and *NOS2*).[31] However, it did not examine other climatic factors. The objective of this article is to provide the first review of studies investigating epigenetic mechanisms related to multiple climatic factors, including temperature, humidity, and precipitation, and climate change-associated exposures, such as natural disasters and malnutrition, as well as how they may relate to allergic diseases. We also discuss strengths, challenges, and opportunities for future research on this topic.

METHODS

For this narrative review, we conducted an online search for original research articles published on the topic of epigenetics and climatic exposures. This search included multiple epigenetic mechanisms, including DNA methylation, histone modifications, and non-coding RNAs, as well as various environmental exposures related to climate and climate change, such as temperature, precipitation, and natural disasters. The search was performed in 3 databases—PubMed, Web of Science, and EMBASE—for articles published between January 1, 2000, and August 1, 2023, by using a combination of Medical Subject Headings (MeSH) terms that are listed in Table I. The findings from relevant articles from this search are discussed in the following sections organized by environmental exposure, and we provide interpretation regarding their connections to allergic and immunologic outcomes. Data on epigenetic markers and/or associated gene annotations related to climate exposures were extracted from studies, when available, and included in Table E1 (in the Online Repository at www.jacionline.org). For the section on temperature, we focused on recently published studies that were not evaluated in the most recent systematic review on this topic, which was published in 2020.[31] Although air pollution is a major cause of climate change, studies regarding direct associations of air pollution and DNA methylation were excluded from this review because they have previously been reviewed extensively.[25,32,33]

BACKGROUND ON ENVIRONMENTAL EPIGENETICS AND ALLERGY

The goal of environmental epigenetic studies is to investigate how and when environmental exposures contribute to epigenetic variation, which can affect the prevalence, incidence, and severity of human diseases. It is important to note that environmental exposures, including climate-related factors, at different stages of life (such as *in utero*, early childhood, and adulthood), can differentially affect the epigenome and to also note that genetic variation can also play a role in affecting variability of DNA methylation.[34] In particular, *in utero* exposure is a susceptible window, as epigenetic programming of cells, organs, and tissues is established during this period.[35] Additionally, ancestry-specific methylation quantitative trait loci (meQTL) support the inclusion of ancestrally diverse and multiethnic populations in epigenetic studies. Epigenetic modifications can also reflect disease progression, so the longitudinal collection of samples is key to distinguishing biomarkers of exposure from biomarkers of disease that might be characterized in cross-sectional studies (Fig 1).

There are several methodologies that are used in environmental epigenetics research, and we have defined commonly used terms found in this review and in the literature listed in Table II. The first step involves the extraction of DNA from a population of cells from specific tissues, such as whole blood, the skin, or nasal or bronchial epithelium. Once the DNA is processed, it can be analyzed by using a variety of methods, including methylation arrays.[36] The 450K and 850K EPIC BeadChips have commonly been used in epigenome-wide association studies (EWASs) to systematically measure the methylation of CpG sites across the human genome in large epidemiologic cohorts.[37] Then, several statistical and bioinformatic approaches are used to test for associations between methylation status of CpG sites and phenotypes and/or exposures of interest. The most common approach is to test each CpG individually across all DNA methylation measurements, often referred to as a differentially methylated position. This approach can be complemented by testing entire regions, defined by proximity or correlation structure, referred to as a differentially methylated region (DMR) with multiple CpGs. This technique has been used to systematically assess the relationship between multiple different environmental exposures, asthma, and allergic diseases.[38] A more targeted approach involves selecting certain genes *a priori* (eg, using specific primers or an array specific for a panel of genes related to inflammation) and analyzing methylation of the relevant CpG sites. An example of this approach is the study of how farm milk exposure contributed to increased methylation of *FOXP3* in regulatory T (Treg) cells, which was associated with decreased atopic sensitization

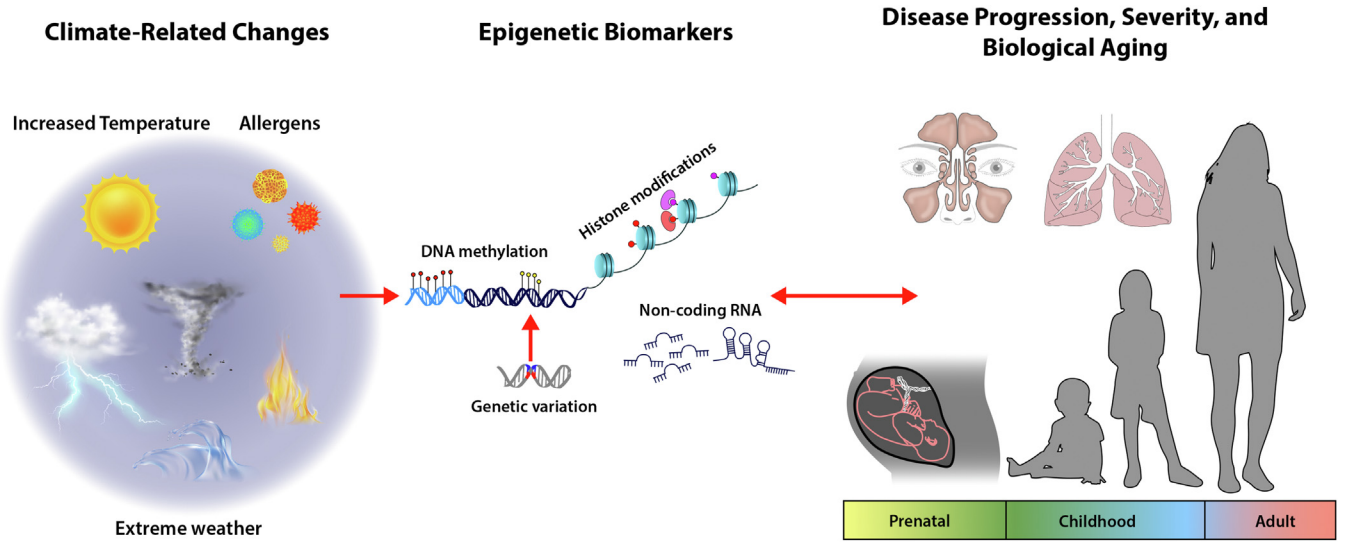

FIG 1. Conceptual framework for human epigenetic studies related to climate change, extreme weather events, and events aggravated by extreme weather and their relationship with allergic disease.

TABLE II. Definition of common terms used in epigenetics research

Term	Definition
EWAS	A comprehensive genome-wide testing of epigenetic marks and how they are associated with phenotypes or exposures of interest
CpG site	DNA dinucleotides of cytosine followed by guanine in which the cytosine nucleotide may have a methyl group added by DNA methyltransferase, which can alter gene transcription
DMR	An entire genomic region composed of multiple CpG sites with differential DNA methylation across samples
Non-coding RNAs	Functional molecules of RNA that are not translated to proteins but can affect gene expression and protein functioning
Epigenetic clocks	Statistical calculators that use methylation data at certain CpG sites to derive an epigenetic age, which is a marker of biologic aging that is correlated with morbidity and mortality
EAA	Deviations between epigenetic and chronologic age calculated as the residuals from when each DNA methylation clock output is regressed on the chronologic age of each participant
meQTLs	Single-nucleotide polymorphisms associated with DNA methylation variation of a CpG site

meQTL, Methylation quantitative trait locus.

and asthma in childhood.[39] A newer methodology is the use of epigenetic clocks, which are DNA methylation biomarkers of biologic aging found to be predictors of morbidity and mortality.[40] These biomarkers estimate an epigenetic age that is predictive of an individual's chronologic age. Deviation between both measures is referred to as epigenetic age acceleration (EAA), which is a strong risk factor for mortality and morbidity (including due to allergic diseases) and shown to be influenced by environmental factors. For example, 1 study found that cigarette smoking is associated with increased EAA among adults,[41] and another showed that greater EAA in childhood is associated with higher odds of having atopy and food allergen sensitization.[23]

Most environmental epigenetics studies on allergy and asthma have focused on cigarette smoke and air pollution as common exposures of interest. Although their results have been discordant, many EWASs have found that these exposures are frequently associated with differential methylation of CpG sites near or in the promoters of *AHRR*, *FOXP3,* and *IL4*.[33,42,43] This is relevant because DNA methylation in these regions could influence gene expression, as shown in studies of smoking and *AHRR* methylation.[44,45] These findings have emerged mostly from cross-sectional study designs, which are limited because the timing of exposure and disease development and the directionality of DNA methylation variability are less clear. Nonetheless, new methodologic advancements in the field of environmental epigenetics show promise for elucidating the relationship between climatic factors and allergic diseases to improve disease prevention and treatment.

Epidemiologic studies on climate change and epigenetics have focused on extreme weather events, temperature, and factors aggravated by climate change, such as famine and drought. These factors have frequently been tested for cross-sectional associations with DNA methylation isolated from leukocytes. In the following sections, we discuss studies from our search and place their results in the context of allergic and airway diseases. We found 1 study that examined microRNAs (miRNAs) as the epigenetic outcome of interest, whereas the rest of the studies measured DNA methylation; none of them investigated histone modifications.

TEMPERATURE

Mechanisms linking temperature to allergy and immunologic diseases

Exposures to high temperature, both chronic and acute, are associated with increased morbidity and mortality, and various epigenetic research methodologies have been used to investigate

TABLE III. Summary of epigenetic studies on temperature and precipitation

Study title	Authors (y)	Location	Population	Exposure	Epigenetic end point	Key finding(s)
Temperature						
EWAS of Short-Term Temperature Fluctuations Based on Within-Sibship Analyses in Australian Females	Wu et al (2023)	Australia	Adult female twins and their sisters in the AMDTSS	Short-term changes in temperature	DNA methylation (EWAS) of peripheral leukocytes analyzed with the 450K BeadChip	- Temperature changes were associated with differential methylation of 14 CpGs and 70 DMRs mapping to 68 genes linked to human diseases
Associations between Medium- and Long-Term Exposure to Air Temperature and EAA	Ni et al (2023)	Augsburg, Germany	KORA	Land surface temperature (medium-term: 4 wk and 8 wk; long-term: 365 d)	Epigenetic aging biomarkers: Horvath, Hannum, PhenoAge, GrimAge, and Skin and Blood clocks	- Medium-term exposures to high but not low temperature increased Horvath EAA, Hannum EAA, GrimAge EAA, and Skin-Blood EAA - Higher annual average temperature was associated with increased Horvath EAA, Hannum EAA, Pheno EAA, GrimAge EAA, and Skin and Blood EAA
Intermediate and Long-Term Exposure to Air Pollution and Temperature and the Extracellular MicroRNA Profile of Participants in the NAS	Yazdi et al (2023)	Boston, Mass	Adult men living around Boston who use medical services at the Veterans Affairs Hospital and are part of the NAS	Intermediate and long-term exposure to temperature	MicroRNAs found extracellularly in whole blood samples that were processed and sequenced	- Increased intermediate and long-term exposures to temperature were associated with levels of several extracellular miRNAs with clinical correlates to respiratory and cardiovascular diseases
Short-Term Air Pollution and Temperature Exposure and Changes in the Extracellular MicroRNA Profile of NAS Participants	Yazdi et al (2023)	Boston, Mass	Adult men living around Boston who use medical services at the Veterans Affairs Hospital and are part of the NAS	Short-term exposure to temperature	MicroRNAs found extracellularly in whole blood samples that were processed and sequenced	- In most cases, increased mean temperature was positively associated with extracellular microRNA levels, many of which were associated with inflammation, disease development, and fatty acid metabolism - Longer-term changes in temperature may affect changes in microRNA profiles more than short-term changes in temperature do
Weather and Birth Weight: Different Roles of Maternal and Neonatal *GPR61* Promoter Methylation	Yuan et al (2022)	Zhengzhou, China	Pregnant women who delivered in 2010-2012 and their newborns	Mean temperature and temperature range	Candidate gene methylation analysis of the *GPR61* promoter in peripheral leukocytes in maternal and umbilical cord blood	- There was a positive association between daily temperature range and *GPR61* methylation in maternal and cord blood that was linked to greater birth weight

(Continued)

TABLE III. *(Continued)*

Study title	Authors (y)	Location	Population	Exposure	Epigenetic end point	Key finding(s)
						- Maternal *GPR61* methylation modified associations between temperature and birth weight
Ambient Temperature and Genome-wide DNA Methylation: A Twin and Family Study in Australia	Xu (2021)	Australia	Adult female twins and their sisters in the AMDTSS	Mean temperature (short-, medium-, and long-term exposure)	DNA methylation (EWAS) of peripheral leukocytes analyzed with the 450K BeadChip	- Temperature was associated with differential methylation of 31 CpGs and 82 DMRs mapping to 85 genes linked to chronic diseases, including asthma
The Role of Maternal Methylation in the Association between Prenatal Meteorologic Conditions and Neonatal H19/H19-DMR Methylation	Yang (2020)	Zhengzhou, China	Pregnant women who delivered in 2010-2012 and their newborns	Minimum, mean, and maximum temperature	Candidate gene methylation analysis of the *H19* promoter and *H19*-DMR in peripheral leukocytes in maternal and umbilical cord blood	- Neonatal and maternal *H19* and *H19*-DMR methylation were negatively associated with temperature in the first trimester and positively associated with temperature in the third trimester
Precipitation						
Epigenetic Mechanisms Underlying the Association between Maternal Climate Stress and Child Growth: Characterizing Severe Drought and Its Impact on a Kenyan Community Engaging in a Climate Change-Sensitive Livelihood	Straight et al (2022)	Kenya, Africa	Children of exposed women	Severe drought in 2008-2009	DNA methylation (EWAS) from saliva analyzed with the Epic BeadChip	- 16 differentially methylated CpG sites were found, and most related to immunologic and metabolic pathways - There was an association between drought exposure and child body weight through cg03771070 methylation
Weather and Birth Weight: Different Roles of Maternal and Neonatal *GPR61* Promoter Methylation	Yuan et al (2022)	Houzhai, China	Pregnant women who delivered in 2010-2012 and their newborns	24-h precipitation	Candidate gene methylation analysis of the *GPR61* promoter in peripheral leukocytes in maternal and umbilical cord blood	- There was a positive association between precipitation and *GPR61* methylation in maternal and cord blood that was linked to greater birth weight - Maternal *GPR61* methylation modified associations between precipitation and birth weight

AMDTSS, Australian Mammographic Density Twins and Sisters Study; *KORA*, Cooperative Health Research in the Region of Augsburg; *NAS*, Normative Aging Study.

this relationship (Table III).[46] There might be several pathways linking temperature fluctuations to allergic disease (Table IV). For example, extreme heat might affect airway responsiveness by activating certain transient receptor potential cation channels and stimulating cholinergic reflex pathways.[47] Additionally, increased membrane fluidity and disruption of transmembrane structural proteins can increase risk for an inflammatory response. Regarding temperature-related epigenetic alterations, a systematic review of studies published before 2020 summarized results from 7 research articles and identified 15 candidate genes[31]; in the following sections, we discuss findings from more recent studies on this topic.

Recent epigenetic studies on temperature

Recently, more studies have been published to quantify temperature exposure and its impacts on the epigenome of humans. For example, an EWAS of blood cells from Australian women

TABLE IV. Biologic pathways connecting components of climate change with risk for allergic diseases

Climate change component	Mechanisms related to risk for allergic diseases
Increased temperature	1. Faster plant growth and prolonged pollen generation seasons lead to increased pollen quantity and allergenicity 2. There is increased membrane fluidity owing to redirected blood flow to the periphery and disruption of transmembrane structural proteins, which then increases risk for an inflammatory response 3. Extreme heat can affect airway responsiveness by activating certain transient receptor potential cation channels and stimulating cholinergic reflex pathways
Increased precipitation and hurricanes	1. Rainfall can cause atmospheric pollen grains to release large quantities of various small allergens that can be inhaled to exacerbate asthma and allergic rhinitis 2. Rising air moisture after storms and flooding can increase indoor and outdoor mold growth, including allergenic genera such as *Alternaria*, *Aspergillus*, and *Cladosporium*
More intense and frequent wildfires	1. Wildfire smoke contains air pollutants that can interact with the respiratory epithelium to directly cause inflammation and bronchoconstriction 2. These air pollutants also increase permeability of the respiratory tract and skin to facilitate penetration of allergens in people with asthma and atopic dermatitis 3. Air pollutants can adhere to pollen grains to change their morphology and allergenic potential
Disrupted food and water systems	1. Exposure to heavy metals such as arsenic and other water pollutants can trigger a proinflammatory response 2. Lower nutritional content of crops owing to increased atmospheric carbon dioxide levels could alter immune system functioning 3. Forced migration due to food and water insecurity exposes humans to new environmental allergens and infectious vectors, potentially increasing risk for food-related and other allergic reactions

showed associations between whole blood methylation and short-term temperature fluctuations. A total of 14 differentially methylated CpGs and 70 DMRs were associated with short-term temperature fluctuations. Of note, the most statistically significant CpG that had higher DNA methylation relative to temperature was annotated to the *KCNK4* gene.[48] This gene has been shown to be hypomethylated in blood samples for patients who achieved complete remission of asthma, defined as no use of asthma medications, no asthma symptoms, no airway hyperresponsiveness, and normal lung function at a recent clinic visit; however, this study did not examine the role of temperature.[49] In another study from Australia, ambient temperature ranging from the previous day to a year from sample collection was associated with differential methylation of 31 CpGs and 82 DMRs with biologic pathways enriched for asthma and eczema-associated genes, such as *NIPAL1* and *PHF11*.[50] In the Normative Aging Study of male veterans from the Greater Boston Area, short-term, intermediate, and long-term temperature exposures were associated with several miRNAs derived from extracellular vesicles, including some implicated in respiratory diseases.[51,52] In a birth cohort from China using a candidate gene approach, maternal whole blood and cord blood DNA methylation of the *GPR61* gene was associated with prenatal temperature and humidity exposure, with evidence that cord blood *GPR61* methylation mediated associations between prenatal exposure to temperature and humidity and birth weight.[53] Another study of a birth cohort in China reported differential methylation of the *H19* promoter in cord blood associated with prenatal temperature and humidity exposure.[54] These findings provide evidence that exposure to high temperature, both chronic and short-term and at different points of the life course, influences DNA methylation in leukocytes and miRNAs, as examined in 1 study.

Finally, there has been 1 study published on temperature and epigenetic aging. A study from the Cooperative Health Research in the Region of Augsburg (KORA) in Germany reported acceleration of multiple epigenetic aging clocks (Horvath, Hannum, GrimAge, and Skin-Blood) associated with medium-term (4-week and 8-week) exposure to high but not low temperature.[55] Additionally, higher average annual temperature was associated with increased EAA of those same epigenetic aging biomarkers and the PhenoAge epigenetic clock. These findings are relevant because acceleration of certain clocks, including PhenoAge and GrimAge, captures risk of all-cause mortality and disease morbidity, such as lower airway diseases and poor lung function.[56-58] In this study, higher annual temperature associations for select epigenetic aging markers were stronger for females, obese participants, and participants with cardiovascular disease. These findings are relevant to allergic disease, as acceleration of epigenetic aging biomarkers, particularly the Horvath clock, has been associated with asthma and allergic sensitization in children.[23,24] Overall, among DNA methylation studies on temperature, there is heterogeneity with respect to study design, temperature range and measurements, and epigenetic approaches and biomarkers tested.

PRECIPITATION

Mechanisms linking precipitation to allergy and immunologic diseases

Climate change is associated with increased extreme precipitation and flooding, as well as with more severe drought in many parts of the world, owing to changes in the hydrologic cycle.[59] One result of these climatic changes is increased exposure to molds, dust mite allergens, bacteria, and microbial toxins in both indoor and outdoor settings, which can trigger asthma exacerbations through both allergic and nonallergic mechanisms.[2,4] In addition, heavy precipitation and thunderstorms have been associated with severe asthma exacerbations and deaths in patients with pollen allergy.[60-63] The likely mechanism is that rainwater interacts with pollen to release a high concentration of smaller, more allergenic components that trigger asthma and allergic rhinitis, especially at the start of a storm (Table IV).[4,5]

Recent epigenetic studies on precipitation

Both extremes of precipitation exposure—drought and heavy rainfall—have been shown to affect DNA methylation (Table III). For example, in an EWAS conducted in Africa with children

whose mothers were exposed to severe drought, 16 CpG sites in saliva samples were found to be differentially methylated between exposed and unexposed participants.[64] In this study, 7 CpGs were hypermethylated and 9 were hypomethylated; some were related to genes involved with metabolism and immune function, such as *INFG*, which encodes for the IFN-γ cytokine that likely contributes to asthma pathogenesis.[65] Another study examining DNA methylation of the G protein–coupled receptor 61 (*GPR61*) promoter in newborns and their mothers found that increased exposure to precipitation during pregnancy was associated with greater *GPR61* methylation in maternal and cord blood samples, which affected birth weight.[53] The evidence supporting a relationship between precipitation exposure and DNA methylation alterations is further bolstered by an EWAS on exposure to Hurricane Maria, which is discussed in the following section.[66]

EXTREME WEATHER EVENTS

Climate change is associated with greater frequency and intensity of extreme weather events due to warmer temperatures; persisting drought conditions; and changes in sea level, ocean currents, and wind patterns. Examples of extreme weather events include wildfires, hurricanes, tropical cyclones, and heat waves, which have been increasing around the world, posing a global threat to public health.[8] Many of these events have been linked to allergic disease pathogenesis and other health outcomes in epidemiologic studies (Table IV). For example, exposure to air pollution from wildfires has been shown to increase risk for asthma[67] and atopic dermatitis,[68,69] and extreme heat events in the United States have increased the odds of experiencing seasonal allergic rhinitis.[70]

Recent epigenetic studies on wildfires

We found 2 human studies that examined the impacts of wildfires on the epigenome (Table V). An EWAS performed with adult women in Australia assessed 3-year average wildfire- and non–wildfire-related exposure to particulate matter less than 2.5 μm in diameter ($PM_{2.5}$).[71] In adjusted analyses, the researchers reported 26 CpGs that were significantly differentially methylated for wildfire-related $PM_{2.5}$; most of them were hypomethylated and did not overlap with findings for non–wildfire-related $PM_{2.5}$. They also found 33 significant DMRs for wildfire-related $PM_{2.5}$ with no overlap for non–wildfire-related $PM_{2.5}$. These epigenetic alterations for wildfire air pollution exposure mapped to 47 genes that are related to inflammation, carcinogenesis, and immune dysregulation, including *HLA-DQB1*, which is at a locus associated with asthma,[72] and *LRRC43*, which is associated with eczema and allergy.[73] In a smaller study of children aged 7 to 8 years in California, researchers reported that compared with individuals exposed to prescribed burns (ie, intentional burning of land primarily for forest management and wildfire hazard reduction), participants exposed to wildfires had greater methylation of the promoter region of *FOXP3*, which is expected to be associated with decreased gene expression.[74] This result is consistent with the findings of other studies of ambient air pollution exposure[75] and suggests a mechanism by which exposure to wildfire smoke affects allergic disease, as decreased FoxP3 level impairs the function of Treg cells, which play important roles in sustaining immune tolerance to allergens. Although both of the aforementioned studies examined DNA methylation in blood cells, long-term differential methylation and expression of genes related to inflammation have also been found in nasal epithelium cells of rhesus macaques exposed to wildfire smoke.[76]

Epigenetic studies of storms

Regarding cyclones, a study in Puerto Rico examined the epigenetic impacts of Hurricane Maria in 2017 on children who were exposed prenatally or conceived within 3 months after the hurricane (Table V).[66] There were 47 significant differentially methylated CpGs associated with all hurricane-related variables, including stress, and 30 of them (almost all of which were hypermethylated) were associated with gestational stage at the time of the hurricane. The researchers reported that the most biologically relevant site was the probe near the sepiapterin reductase (*SPR*) gene, as it is located in a CpG island and close to the gene's transcription start site in an open chromatin region. The gene is involved in the production of tetrahydrobiopterin, a metabolite that can affect T-cell–mediated autoimmunity and allergic inflammation.[77] The greatest mean methylation level changes occurred with hurricane exposure during weeks 20 to 25 of gestation, suggesting a prenatal period with increased susceptibility to epigenetic alteration. Other studies have found that exposure to Superstorm Sandy was associated with alterations in placental gene expression, which may be due to epigenetic modifications.[78,79] No human epigenetic studies were found for other extreme weather events such as heat waves and tornadoes.

MALNUTRITION

Undernutrition, obesity, and climate change are 3 conditions that affect countries worldwide and constitute a syndemic (ie, interacting at the same time, having synergistic effects on each other, and having similar underlying drivers).[80,81] Climate change has contributed to food insecurity through several pathways, including crop failures, destruction of agricultural property due to extreme weather, increased vector-borne diseases, and civil unrest, and it is predicted to lead to the malnourishment of 25 million more children globally by 2050.[80] Malnutrition has several effects on the human body, including impaired muscle and immune function (Table IV) as well as cardiopulmonary, gastrointestinal, and psychosocial impacts.[82] Although the literature on diet and epigenetic modifications is quite expansive, we focus here on discussing a diverse set of recent epigenetic studies of undernutrition and hunger (Table V).

Epigenetic studies on nutritional status and famine

Studies examining exposure to malnutrition associated with periods of famine or in rural communities and epigenetic alterations later in life have found mixed results. Early-life exposure to malnutrition and adversity among adult participants raised in a rural area in Mexico was associated with 160 hypermethylated CpG sites and 55 hypomethylated CpG sites in peripheral leukocytes.[83] Many of these sites were annotated to pathways pertaining to biologic regulation, neurocognition, and developmental processes. This study also provided evidence that EAA, which was calculated by using 4 different epigenetic clocks, is affected by nutritional status, which is in alignment with the findings of existing studies.[84,85] On the other hand, a larger EWAS conducted with blood samples from adult

TABLE V. Summary of epigenetic studies on extreme weather events and malnutrition

Study title	Authors (y)	Location	Population	Exposure	Epigenetic end point	Key finding(s)
Extreme weather events						
Wildfire-Related $PM_{2.5}$ and DNA Methylation: An Australian Twin and Family Study	Xu et al (2023)	Australia	Adult female twins and their sisters in the AMDTSS	Long-term exposure to wildfire-related $PM_{2.5}$	DNA methylation of peripheral leukocytes analyzed with the 450K BeadChip (EWAS and 7 metrics of global DNA methylation)	- Exposure was associated with differential methylation of 26 CpGs and 33 DMRs mapping to 47 genes, which did not overlap with non–wildfire-related air pollution results - There was a negative, but not significant, association with wildfire $PM_{2.5}$ and the 7 global methylation measures
The Impact of Prescribed Fire versus Wildfire on the Immune and Cardiovascular Systems of Children	Prunicki et al (2019)	Fresno, Calif	Children aged 7-8 years	Several air pollutants comprising wildfire air pollution	Candidate gene methylation analysis of the *Foxp3*, *IL4*, *IL10*, and *IFNγ* genes in peripheral leukocytes	- There was increased methylation of the Foxp3 promoter region postwildfire exposure
Pre- and Perinatal Hurricane Exposure Alters DNA Methylation Patterns in Children	Kello et al (2023)	Puerto Rico	Children who were prenatally exposed to Hurricane Maria or conceived within 3 months after the disaster: Project HELiOS	Hurricane Maria	DNA methylation of peripheral leukocytes analyzed with the EPIC BeadChip (EWAS)	- There was differential methylation of 47 CpGs: several hypermethylated sites associated with stage of gestation at the time of hurricane impact (biggest differences at gestation wk 20-25) - 1 significant DMR was found in association with the timing of the hurricane and is annotated to the *LLRC39* gene
Malnutrition						
Obesity-Associated Vitamin D Deficiency Correlates with Adipose Tissue DNA Hypomethylation, Inflammation, and Vascular Dysfunction	Mirza et al (2022)	Chicago, Ill	Premenopausal women with obesity	Vitamin D deficiency	Global DNA methylation in adipose tissue samples measured with the 5-mC DNA kit and targeted methylation analysis of 94 inflammatory genes with the EpiTect Methyl II PCR Array	- There was decreased global DNA methylation associated with vitamin D deficiency - More severe vitamin D deficiency was associated with greater hypomethylation of the promoters of the majority (70%) of inflammatory genes in the array
Vitamin D Supplementation Is Associated with Slower Epigenetic Aging	Vetter et al (2022)	Berlin, Germany	Adults in the BASE-II study and GendAge study	Vitamin D supplementation	5 epigenetic clocks: 7-CpG, Horvath, Hannum, PhenoAge, and GrimAge	- Treatment with vitamin D supplementation in deficient individuals was associated with 2.6-y lower 7-CpG age acceleration and 1.3-y lower Horvath age acceleration

(Continued)

TABLE V. *(Continued)*

Study title	Authors (y)	Location	Population	Exposure	Epigenetic end point	Key finding(s)
DNA Methylation Profile of a Rural Cohort Exposed to Early Adversity and Malnutrition: An Exploratory Analysis	Gomez-Verjan et al (2022)	Tlaltizapan, Mexico	Adults who experienced malnutrition and adversity early in life and healthy middle-class elders as controls	Early-life malnutrition and adversity in a rural region	DNA methylation of peripheral leukocytes analyzed with the EPIC BeadChip (EWAS) and 4 epigenetic clocks: Horvath, Hannum, PhenoAge, and GrimAge	- Early-life malnutrition and adversity was associated with 160 hypermethylated CpG sites and 55 hypomethylated CpG sites, many of which pertain to metabolic and neurocognitive pathways - There were differential epigenetic aging profiles based on malnutrition exposure
Childhood Exposure to Hunger: Associations with Health Outcomes in Later Life and Epigenetic Markers	Perna et al (2020)	Saarland, Germany	Adults who experienced hunger during the German famine (1945-1948) earlier in life who are part of the ESTHER study	Early-life exposure to hunger	DNA methylation of peripheral leukocytes analyzed with the 450K BeadChip (EWAS)	- Although 12 CpGs had a raw *P* value less than .05 associated with childhood hunger, no CpGs achieved epigenome-wide significance after multiple testing correction
Early-Life Exposure to Severe Famine Is Associated with Higher Methylation Level in the *IGF2* Gene and Higher Total Cholesterol in Late Adulthood: The GRECF Study	Shen et al (2019)	Anhui and Jiangxi, China	Adults in the GRECF study who experienced the famine while an infant or fetus and those born afterward	Chinese Great Famine in 1959-1961	Candidate gene methylation analysis of the *IGF2* gene in peripheral leukocytes in blood	- There was a positive association between famine exposure and DNA methylation of the CpG1 site of the *IGF2* gene and *IGF2* DMR - Each unit increase in methylation of the CpG1 site was associated with a 1.09-unit increase in total serum cholesterol level
DNA Methylation Signatures Link Prenatal Famine Exposure to Growth and Metabolism	Tobi et al (2014)	The Netherlands	Adults who experienced hunger during the Hunger Winter (1944-1945) earlier in life	Prenatal exposure to hunger during the Hunger Winter	Testing of differential methylation of 28 genomic annotations in whole blood samples	- 181 regions were identified as prenatal malnutrition-associated DMRs, most of which were hypermethylated, occurred in gene bodies, and displayed intermediate DNA methylation levels - There were differences in methylation patterns based on gestational timing of exposure

AMDTSS, Australian Mammographic Density Twins and Sisters Study; *BASE-II*, Berlin Aging Study II; *ESTHER*, Epidemiologische Studie zu Chancen der Verhütung, Früherkennung und optimierten Therapie chronischer Erkrankungen in der älteren Bevölkerung; *GRECF*, Genomic Research of the Chinese Famine; *HELiOS*, Hurricane Exposures and Long-term Infant Outcomes Study.

participants who experienced early-life exposure to hunger during the German famine (1945-1948) found no differentially methylated CpG sites after multiple testing correction.[86] The authors suggest that this finding may be attributable to limitations of statistical power, lack of detail regarding the severity of hunger episodes, and small methylation changes that may have been reversed by adulthood. However, 1 targeted gene study that examined early-life exposure to the Chinese Great Famine (1959-1961) found positive associations with *IGF2* gene methylation.[87] This is consistent with findings from a study of the Dutch Hunger Winter (1944-1945) that reported altered DNA methylation of *IGF2* among individuals prenatally exposed to famine.[88] Of note, increased IGF2 levels have a protective effect and lead to enhanced Treg cell function and IL-10 expression, so if hypermethylation of this gene as a result of malnutrition leads to decreased IGF2 levels, this may increase risk for food allergy and asthma. A comprehensive testing of the epigenome among the Dutch Hunger Winter subjects prenatally exposed to famine found 181

DMRs.[89] One of the genes found to have a DMR associated with prenatal malnutrition in this study is *CPT1A*, which may be associated with asthma, as another study found that this gene is overexpressed in T_H2 cells in patients with asthma versus in controls.[90]

Epigenetic studies on vitamin D

One specific example of how rising temperatures from climate change may affect nutrition is through increasing risk for vitamin D deficiency as a result of heat-related regulation of cortisol release.[91] A few studies of vitamin D deficiency have shown associations with DNA methylation and EAA. One study reported that vitamin D deficiency was associated with hypomethylation in adipocytes for the majority of promoters for the 94 inflammatory genes measured within this study.[92] The existing literature suggests both that vitamin D deficiency affects the methylome and that the resulting epigenetic alterations reciprocally affect vitamin D metabolism. In addition, a recent study on EAA among adults in Germany found that vitamin D levels affected EAA, as supplementation was associated with slower epigenetic aging: 2.6 years for a 7-CpG custom epigenetic clock and 1.3 years for the Horvath epigenetic clock.[93] Overall, more studies are needed to examine the epigenetic changes associated specifically with the ongoing and future changes in malnutrition within and across populations globally that are due to climate change.

DISCUSSION AND CONCLUSIONS

Currently, there is a limited body of scientific literature focusing on direct climate-related epigenetic impacts, such as from precipitation or extreme weather events. Temperature exposure has been the most widely studied weather-related variable. Other phenomena such as malnutrition or famine from historical events, which are expected to worsen in some areas of the world owing to climate change, have been characterized, but not as a direct result of climate change. Many studies using candidate gene approaches or epigenome-wide testing of peripheral blood leukocytes have reported multiple associations between climate factors and DNA methylation. These findings provide some support for the connection between climate change–associated epigenetic changes at loci previously associated with allergic diseases, including asthma, eczema, and allergic rhinitis. Studies are limited in longitudinal follow-up and lack integration between climate-related changes, epigenetic biomarkers, and phenotyping of allergic disease. Most epigenetic studies have examined leukocyte-isolated DNA methylation, which is relevant for allergy but could miss important biologic implications for other allergic diseases.

The changing climate will pose multiple health hazards, including increases in allergic disease incidence and severity in the near and distant future.[94] Although immediate morbidity and mortality following an extreme weather event are concerning, the long-term consequences might be larger. For example, mortality rates following Hurricane Maria in Puerto Rico remained elevated for a year afterward.[95] Epigenetic biomarkers might serve as promising tools to survey, monitor, and evaluate the impacts of climate change in global populations. Although epigenetic studies have systematically surveyed allergic disease associations and found positive results, few studies have linked environmental exposures to allergic diseases prospectively.[38] Similarly, not many epigenetic studies on extreme weather events, high temperature, and climate-related dietary impacts have incorporated subsequent measures of allergic diseases within the same study design, so the current evidence remains limited. To advance the field, it will be key to leverage epigenetic biomarkers of extreme weather events in the context of allergy and atopy—ideally with large prospective epidemiologic cohorts following these events and incorporating biomarkers of exposure and detailed ascertainment of allergic disease. Both study design and timing of data collection are critical because epigenetic alterations can serve as both biomarkers of exposure or disease and intermediates of disease progression that can be used to target therapies or monitor progression.[38] In this context, epigenetic marks, such as DNA methylation changes, can be passengers or drivers of observed associations. Careful design of longitudinal studies along with novel causal inference methods can help elucidate relationships.

Studies related to climate change and extreme weather events with epigenetic biomarkers have been limited, and all but one have investigated DNA methylation. The most widely studied meteorologic condition thus far has been temperature,[31] likely reflecting the availability of spatial data to estimate exposure. However, there is a lack of studies tracking personal exposure measures that might vary substantially throughout time, day, and season. We have identified a critical need to improve personal exposure measures of temperature, particle exposure, and diet associated with climatic and extreme weather events. Future work should characterize personalized measurements. This includes, for example, methods for measuring internal core temperature among some of the most vulnerable, including farm and construction workers. In this manner, epigenetic studies examining climate change may help elucidate mechanisms underlying climate injustice and allergic disease prevalence based on the disproportionate exposure to harmful climatic factors across populations.[96] Among the temperature studies, differential methylation of multiple genes implicated in either asthma or inflammation have been reported. Future work should characterize epigenetic biomarkers that might respond rapidly to extreme heat (eg, during a heat wave) compared with those that might be altered as a result of long-term exposure (eg, among farm workers). This will help characterize biologic pathways associated with acute and chronic exposure. Although epigenetic findings might be influenced by other population characteristics, biomarkers of epigenetic aging might serve as more consistent overall epigenetic indicators of the impact of climate on health, given their robust link to morbidity and mortality.

Like most other epigenetic studies, those related to climate change have been limited to mostly peripheral blood cells. Epigenetic marks are tissue and organ specific, which poses both a challenge but also an opportunity to elucidate organ-specific effects. Increasing the collection and use of target tissues for epigenetic studies beyond leukocytes, such as through collecting nasal or skin cells, will facilitate the testing of more complex and direct hypotheses by capturing early biomarkers of allergic diseases. Although collecting target tissues such as lung samples to study airway disease is not always feasible, surrogate tissues such as nasal cells can provide unique biologic insight compared with that provided by blood-based studies for allergic diseases.[24] Target tissues that might be accessible for study vary based on the setting. For example, skin cells are very relevant for atopic dermatitis[97] and nasal cells are very relevant for airway

disease and asthma.[24] These tissues are relevant to studying the effects of wildfires, for example, whereas leukocyte-isolated DNA might serve as a common source of inflammatory cells relevant for studying multiple climatic exposures. It is likely that the most sensitive tissue is dependent on the type of exposure, route of exposure, and systemic or localized effects in the body. Therefore, these factors need to be carefully considered in study design.

Another important limitation of extreme weather events is the collection of data, samples, and weather information in a timely manner following these events. Very few epigenetic studies have looked at extreme weather events directly. Given that there are many indirect and direct pathways that might operate from these events on the epigenome (eg, dietary changes, medical care access, drinking water quality, power outages, and extreme psychologic stress), there is a need to better characterize specific exposure pathways related to extreme weather events. Existing frameworks have proposed multiple causal pathways for climate-related changes to affect health.[1,13] Specificity on the causal pathway associated with epigenetic changes could lead to higher reproducibility of results and the development of sensitive biomarkers. One aspect of importance is the emerging understanding of the impact of climate change on mental health,[98] especially because psychologic stress plays a pathologic role in the development of allergic diseases.[99,100] This pathway should be carefully examined in epigenetic studies of extreme weather events and natural disasters.

Additionally, emerging evidence points at alterations in biologic aging estimated by epigenetic clocks related to climate change events, particularly temperature and diet. The 1 study linking temperature to EAA also reported stronger effects for females, obese participants, and individuals with cardiovascular disease,[55] which highlights susceptible populations that might be disproportionately affected by climate-related changes.

Heterogeneity of exposure assessment, timing, and measurement have precluded the replication of climate-related epigenetic biomarkers across cohorts. A global collaborative network to increase diverse representation of study participants and support replication efforts and the harmonization of measurements and power will be needed to elucidate the impacts of climate change on the human epigenome. Despite these challenges, the evidence suggests that epigenetic marks are influenced by climate exposures and could serve as biomarkers of allergic disease. Additionally, with strong prospective study designs, high-quality exposure ascertainment, and precise measurement of target tissues, epigenetics research can help elucidate mechanisms through which climate change affects atopic and airway diseases.

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