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Commentary

Use, limitations, and future directions of mixtures approaches to understand the health impacts of weather- and climate change-related exposures, an under-studied aspect of the exposome

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Abstract

The exposome concept aims to account for the comprehensive and cumulative effects of physical, chemical, biological, and psychosocial influences on biological systems. To date, limited exposome research has explicitly included climate change-related exposures. We define these exposures as those that will intensify with climate change, including direct effects like extreme heat, tropical cyclones, wildfires, downstream effects like air pollution, power outages, and limited or contaminated food and water supplies. These climate change-related exposures can occur individually or simultaneously. Here, we discuss the concept of a climate mixture, defined as three or more simultaneous climate change-related exposures, in the context of the exposome. In a motivating climate mixture example, we consider the impact of a co-occurring tropical cyclone, power outage, and flooding on respiratory hospitalizations. We identify current gaps and future directions for assessing the effect of climate mixtures on health. Mixtures methods allow us to incorporate climate mixtures into exposomics.

Keywords: mixtures; health; climate change; exposome

Background

The exposome concept integrates a large number of external exposures across various contexts (eg, ecosystems, lifestyle, social, physical-chemical) to investigate their cumulative impact on internal biological processes that potentially manifest as adverse health outcomes.[1] This framework can readily incorporate various environmental exposures (eg, air pollution, water contamination). Climate change-related exposures and their subsequent hazards are also a pressing environmental concern. Broadly, we define these exposures to be direct environmental exposures which will intensify with climate change. Climate change-related exposures include direct impacts on weather such as extreme heat, tropical cyclones, and wildfires, among others. Climate change also encompasses exposures such as as air pollution, power outages,[2] and contaminated or limited food[3] and water[4,5] supplies. Climate change can have additional downstream consequences that can largely impact health largely through changes in social factors and infrastructure. In theory, the exposome also includes climate change-related events; however, there has been limited exposome research that incorporates these exposures, despite their demonstrated impacts on health.[6] Individually, climate change-related events (eg, heat waves) can directly threaten an individual's health by taxing psychosocial, cardiovascular, respiratory, and other biological processes,[7,8] or by coalescing with other dimensions of the exposome. For example, a heat wave can interact with low household income or poor quality housing to worsen health.[6,9]

Climate change endangers population health by increasing the frequency, geographic range, and intensity of natural hazard such as tropical cyclones,[10] wildfires,[11] extreme heat,[12] floods,[13] and drought,[14] among others, that precipitate downstream events such as power outages[15] or displacement.[16] Instead of being isolated events,[6] climate-related exposures may occur simultaneously. Climate change will further increase the likelihood of co-occurring events.[17,18] Extreme heat, drought, and wildfire, for example, may occur at the same time and location. These exposures can also be causally inter-related and be part of feedback loops. For instance, extreme heat and drought can facilitate dry environments that increase risk of wildfires. These interdependencies complicate investigating the role of multiple climate change-related exposures on biological responses. However, complex relationships commonly occur among all environmental exposures; this issue, therefore, is not limited to the role of climate change-related exposures in the exposome. The exposome concept can aid researchers in understanding the health effects

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of simultaneous climate-related exposures. It provides a framework to better summarize all exposures affecting health, which we extend to include climate-related exposures. Here, we discuss considerations, methods, and gaps and future directions for applying the exposome framework to characterize a mixture of climate change-related exposures in health analyses. Our discussion may align more with environmental epidemiology's focus on hypothesis-driven research than with exposome research's emphasis on discovery, both approaches are needed to understand the impacts of climate mixtures on adverse health outcomes and biological processes.

Recently, the field of analyzing mixtures exposures has advanced rapidly, and numerous methods have been adapted from other fields or developed to evaluate multiple exposures in health studies. Techniques include least absolute shrinkage and selection operator (LASSO) and Bayesian kernel machine (BKMR) regressions.[19-21] Extending the field to include climate change-related exposures, however, requires additional considerations, due to the unique characteristics of mixtures of climate change-related exposures. Each mixtures method has been designed to address a specific research question(s) such as characterizing exposure patterns, identifying the most toxic mixture components, and estimating the overall effect of exposure to the entire mixture.[19,22,23] Environmental health studies have traditionally leveraged these techniques to better understand the health impacts of complex mixtures in the context of various chemical and non-chemical stressors including phthalates,[24,25] pesticides,[26] air pollution,[21] and sociodemographic factors.[27,28] Before using mixtures methods to consider exposure patterns, independent effects, and cumulative impacts, one must first consider the ways in which climate change-related disasters differ from more traditional exposures. The concept of a climate mixture is still in its nascent stages, but for our purposes, we define a climate mixture as at least three co-occurring climate change-related exposures.

Climate change-related exposures versus previously studied exposures in mixtures analyses

One important consideration is that not all climate change-related exposures occur in the same place or time. Traditionally, environmental epidemiology conceptualizes mixtures to involve exposures that individuals or communities continuously experience. For example, although the composition of an air pollution mixture varies seasonally and regionally, individuals are always exposed to a collection of pollutants simultaneously. On the other hand, individual climate change-related exposures may occur transiently and lack distinctive spatial and temporal patterns (Figure 1). Though climate change is facilitating unexpected extreme weather events such as a hurricane near California,[29] the tropical cyclone season in the United States spans June through November and mostly affects the coastal eastern United States.[30] Wildfires in the western United States, a growing problem as climate change drives drier, warmer environmental conditions,[31,32] predominantly take place from July through October. Electrical power outages in the United States occur throughout the year but vary by time of day, season, and region.[33] Certain climate mixture combinations such as wildfire disasters co-occurring with snowstorms would be unlikely to exist owing to the current spatial and temporal patterns of individual climate change-related exposures. Therefore, researchers interested in questions about climate mixtures should keep in mind positivity violations[34] where certain exposures have a zero probability of occurring or co-occurring in specific locations. For studies that require a comparison group, researchers should also carefully consider which populations would be appropriate as control groups.

Because exposomics strives to capture the comprehensive and cumulative effects of physical, chemical, biological, and psychosocial influences on biological systems across the human lifespan, identifying the long-term effects of climate mixtures on health is key.[35,36] For questions examining long-term health impacts, researchers should recognize that climate change-related exposures and chemicals exhibit different distribution patterns across time. Research on climate change-related exposures has predominantly focused on acute outcomes (eg, within days, weeks, or months of exposure), as defining long-term exposure to climate mixtures poses challenges. Longer contexts with long-term exposures and their respective chronic effects on population health involve additional complexity, including the definition of long-term exposures and selection of appropriate health outcomes.[19] Characterizing long-term exposures to chemical mixtures has typically been done by averaging concentrations over an extended period, such as annual averages over several years or maximal values across months. However, doing so for climate change-related exposures is not always appropriate. Some climate change-related exposures, such as tropical cyclones and wildfires, have distinct temporal patterns, and researchers must define long-term exposures for events with a sharp, irregular, and discontinuous pattern across time. For example, a prior study conceptualized wildfire fine particle ($PM_{2.5}$) exposure across 15 years using 5 definitions considering varying temporal units (weeks Versus continuous days Versus year), wildfire $PM_{2.5}$

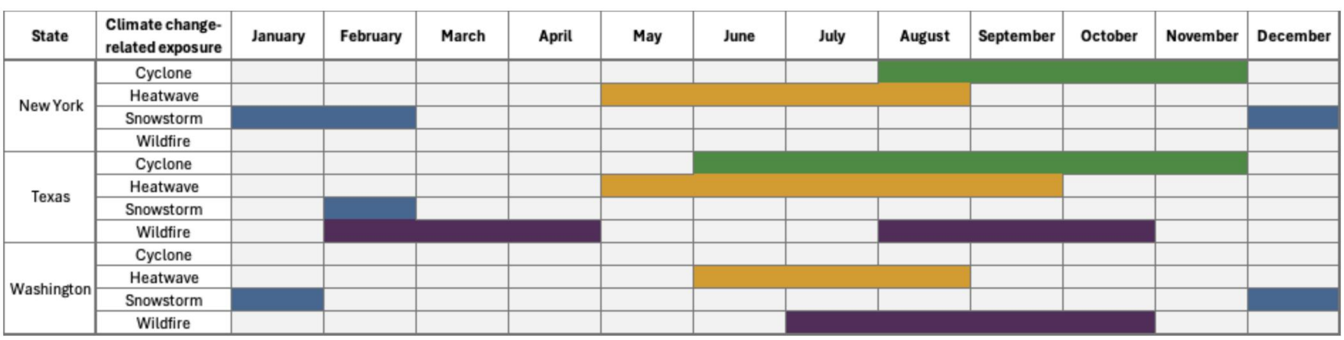

Figure 1. Example of how climate change-related exposures can be spatially and temporally misaligned. The colors—green, yellow, blue, and purple—represent the potential presence of a climate change-related exposure in a particular state-month, while grey represents the potential absence. As this is intended to be an illustrative example of climate change-related exposures, we determined the state-month presence of each climate change-related exposure based on likely geographic and seasonal trends.

thresholds (>5 $\mu g/m^3$ versus >0 $\mu g/m^3$), and aggregation methods (cumulative weeks Versus averages across years).[37] Given the varying ways to define long-term wildfire $PM_{2.5}$, researchers must think through which exposure definition is more biologically plausible and relevant for which health outcomes. The lack of standardized approaches for measuring long-term exposure to wildfire $PM_{2.5}$ applies to other climate-related exposures as well. When investigating the long-term health impacts of climate-related mixtures, researchers must grapple with defining exposure for those with irregular temporal patterns and decide on the most relevant health outcome(s).

Methods and examples for addressing research questions about multiple climate-exposures

Estimating the health impacts of climate mixtures is crucial for incorporating climate change-related exposures to exposome research. We briefly present research questions about multiple co-occurring climate change-related exposures, discussing the importance and relevance of these questions, established methods that can be used to answer them, and potential methodological limitations. This discussion will focus on hypothesis-driven techniques to methodologically address climate mixtures, an important step towards expanding the implementation of exposome research to include climate change-related exposures. Throughout the paper, we will use the following example: the climate mixture comprises a tropical cyclone event, power outages, and flooding, and the health outcome is respiratory hospitalizations. Respiratory hospitalizations are extracted from administrative health data that are often used in health studies and can cover large geographic regions (eg, states, entire US), ensuring adequate variability in macro-level climate change-related exposures. Studies have found that tropical cyclones are associated with respiratory hospitalizations.[38] One potential pathway, for example, is that tropical cyclones result in power outages, and the loss of electricity may prompt individuals who are reliant on electricity-dependent medical equipment to seek healthcare services.[38-40] Flooding can expose individuals to contaminated water and microbes (eg, bacteria, mold), which can increase risk for acute respiratory infections.[41] Our examples center on short-term exposure and acute respiratory hospitalizations. Certain methods cannot be used for all study designs (eg, BKMR is not appropriate for case-control studies or time-series with aggregated outcome data), but as our goal centers on climate mixtures and mixture methods, we will focus on illustrating the ways in which mixtures methods can be applied to such exposures.

We use this example to illustrate specific concepts and considerations for analyses of climate mixtures. We note that the methods we present below are not an exhaustive list of methods to analyze climate mixtures exposure in health models; rather, we present some examples of existing and widely used methods in environmental epidemiology that can be used to answer specific research questions about exposure to climate mixtures (Figure 2). In addition, many of the methods we present could be used to answer different research questions about climate mixtures. However, to discuss multiple methods, we only include each method in one research question category. Our climate mixture example is not fully generalizable to other climate combinations, but our discussion of concepts and considerations can be applied to future research.

The methods we described above are commonly used in environmental epidemiology applications. Nonetheless, we recognize that other methods may exist, such as sequence and life course analyses, or need to be developed to address some of the aforementioned limitations. Using these methods to incorporate climate change-related exposures in exposome research should be considered in future research, both in simulations and real-life data studies.

What are the independent effects of exposures to individual threats in a climate mixture?

Disentangling independent effects and quantifying the relative health impacts of each climate change-related exposure in a climate mixture can inform policies and interventions to prepare for specific climate threats. To this end, researchers may be interested in identifying which exposure(s) is the most "important" in associations with respiratory hospitalizations. Penalized methods determine which exposures in a mixture are most predictive of an outcome, and techniques such as the LASSO[19,23,42] can be used to determine which of the climate change-related exposures (tropical cyclones, flooding, or power outages) are most important by retaining variables with the greatest predictive importance based on an estimated penalty. This approach is useful for identifying the most important climate change-related exposure (s) in a climate mixture.

Non-penalized techniques that are not formulaically constrained (eg, minimizing the sum of absolute coefficient values in the case of LASSO) to identify the most harmful exposures in a climate mixture include Bayesian kernel machine regression (BKMR). Previous exposome studies have leveraged BKMR,[43-45] but to our knowledge none has applied the method in a climate context. BKMR uses a kernel function to estimate the independent exposure-response relationships between individual mixture components and a continuous or binary outcome but only allows for continuous exposures.[46,47] Because several climate change-related exposures are often conceptualized as binary in line with disaster classification and planning (eg, exposed Versus not exposed to a tropical cyclone) or categorical (no, minor, moderate, or severe flooding), the current BKMR formulation may require modification for estimating associations with climate change-related exposures in a larger mixture for these types of variables. As the field of analytic mixtures methods frequently changes, our examples are non-exhaustive. Recent techniques such as the Bayesian multiple index model (BMIM),[48] which can evaluate complex relationships while offering interpretability, can also be applied to climate mixture questions.

What are the cumulative effects of exposure to a mixture of multiple climate change-related exposures?

Given that the goal of exposomics is to estimate the health effects of all environmental exposures, therefore including climate change-related exposures, estimating joint effects for an entire climate mixture is particularly important. This information can guide emergency response and preparedness strategies to minimize health-related consequences by allocating resources and support for groups most likely to experience the worst outcomes. Using our example, researchers may want to know the combined effects of a tropical cyclone, flooding, and power outage on respiratory hospitalizations instead of identifying the most concerning exposure. However, the cumulative effect of this climate mixture may not be the sum of each exposure's independent effects. Power outages and flooding can be mediators between tropical cyclones and respiratory hospitalizations, so tropical cyclones may have direct and indirect effects on the

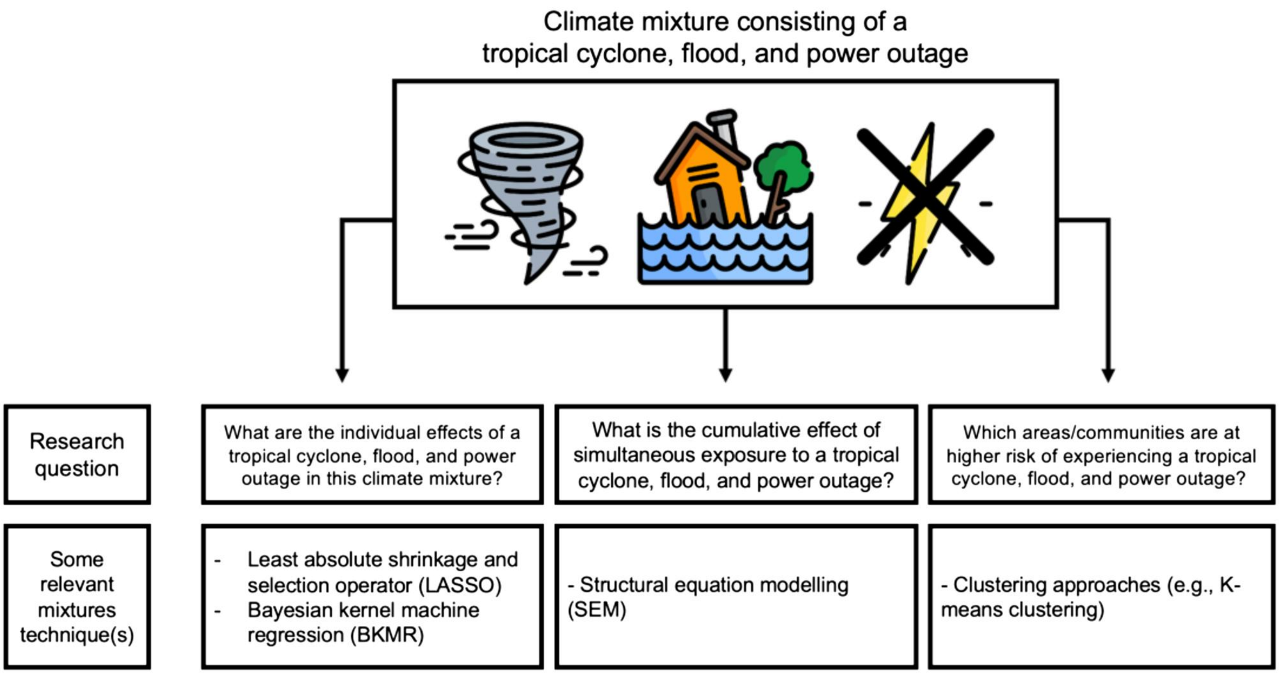

Figure 2. Visualization of the climate mixture with various research questions that can incorporate mixture techniques. Techniques presented here are common in environmental epidemiology. These are non-exhaustive examples of analytic approaches for research involving mixtures or how to incorporate climate change-related exposures in the field of exposomics analyses.

outcome. Estimating the cumulative effects of the mixture thus needs to account for such relationships. Structural equation modelling (SEM) as a framework can estimate overall effects of such complex mixtures.[23,49] Starting off with a user-specified model driven by theory, the SEM approach estimates the relationships and effects of latent (ie, unobserved) variables (in this case the effect of the "climate mixture" of interest). The estimated overall effect includes both the direct and indirect effects of tropical cyclones. Because SEM allows for complex relationships among climate change-related exposures, researchers can incorporate the potential mediators, power outages and flooding, in the estimation of the association between the tropical cyclone exposure and health outcomes, in our example respiratory hospitalizations. The total effect, then, would include the indirect effects of the tropical cyclones through flooding and power outages. The SEM framework can incorporate both continuous and categorical variables, so it allows for a more diverse array of climate change-related exposure conceptualizations compared to other approaches that are built for continuous exposures.

Which areas/communities are at higher risk of experiencing climate mixtures?

Pattern recognition techniques can be adapted and used to determine groups that are more exposed to climate mixtures or experience worse health effects. Such information is crucial for targeted emergency preparedness and mitigation strategies to protect human health. Tropical cyclones, flooding, and power outages affect many communities, and researchers may want to characterize the profiles of communities either likely to be exposed to this specific climate mixture or to identify the communities experiencing worse health outcomes after exposure. Generally, clustering approaches are techniques that identify distinct groups, maximizing homogeneity within groups and heterogeneity between groups.[50] In our example, groups could refer to counties experiencing different combinations or levels of tropical cyclones, flooding, and power outages. K-means clustering[51] is one method that could iteratively group counties into partitions with distinct patterns to tropical cyclones, flooding, and power outages; based off the groupings, researchers could identify the distinct climate mixture characteristics of county group members. Counties clustered together with high exposure to this climate mixture could for example share geographic similarities such as closer proximity to a coastline.[52] If the study aim is to evaluate which of these counties with high exposure face worse health outcomes, researchers could use the identified clusters and estimate cluster-specific effects for respiratory hospitalizations in our example. Clustering methods like k-means require the researcher to decide the number of groupings, so input from experts can inform the appropriate number and interpretation of groupings.

Methodological research considerations and gaps in assessing climate mixtures

Studies can apply mixtures methods to examine multiple co-occurring climate change-related exposures, but a few methodological gaps remain that limit the types of research questions and objectives we can investigate. As previously discussed, certain climate mixture combinations violate the positivity assumption across time and/or space, as not all climate change-related exposures can occur at the same time or place. Thus, creating a standardized exposure index across larger geographic regions (eg, the United States) to understand cumulative exposure is challenging. For instance, tropical cyclones in the United States almost always occur in geographically distinct areas, while extreme heat and snowstorms happen in separate seasons. Researchers have challenges when comparing cumulative exposure to a global set of climate mixture combinations across time and/or space. Instead, they should consider localizing their questions and analyses. For example, researchers may want to focus on creating an exposure index for areas in the Southeast with exposures in our previous examples (hurricanes, floods, and power outages) or for locations across Southern California with wildfire disaster, drought, and power outages.

Positivity violations limit the types of research questions that can be asked, while current practices to define and measure long-term health effects of multiple simultaneous exposures pose challenges. Given that climate change has and will exacerbate related exposures, it is essential to consider long-term health studies. Methodologically, there are not yet standard or widely used metrics to assess long-term climate change-related exposures. Such metrics could capture different exposure domains such as duration, intensity, and frequency,[27] so researchers should consider which metric is most appropriate for their research question and health outcome of interest. Earlier, we provided an example of how long-term wildfire smoke measures can drastically vary across years depending on how the metric is originally operationalized, but these quandaries and decisions also apply to other climate change-related exposures. Long-term exposures to the events in our previous example (tropical cyclones, flooding, power outages) can vary (Table 1). The ways in which we define long-term exposures to climate events and mixtures may capture different pathways, resulting in different estimated health effects. For example, specific parameterizations might be more appropriate for one exposure than another. Peak wildfire $PM_{2.5}$ in a year could be most strongly related to asthma exacerbation while the number of total weeks exposed to any wildfire $PM_{2.5}$ might be most predictive of asthma onset.

Another challenge to assessing long-term climate change-related exposures is the dearth of historic and present-day data. Some climate change-related exposures, such as those related to temperature (eg, heat waves, extreme cold), have measures as early as 1895[53] and today, there are robust measures with high spatiotemporal resolution, such as the hourly measures at a 1 km^2 resolution level.[54] For power outages, the Department of Energy records power outage events that affected more than 50,000 customers or resulted in a 300-megawatt loss,[55] but there is a lack of available data on smaller scale outages, hindering investigations of power outage-related health impacts. There have been growing efforts to assess small-scale outages,[33,56] and data on all types of power outages will be useful for future health research. Recent studies have leveraged data from 2001 at a spatial unit containing ∼11,000 electrical customers updated every 30min, but such studies have so far been conducted using data from New York State.[39] Spatial or temporal misalignment among individual climate change-related exposures in a climate mixture due to data limitations may make it impossible to chronicle trends for long-term climate exposure mixtures and characterize their chronic health impacts.

Table 1. Examples of long-term conceptualizations of several climate change-related exposures

Exposure	Long-term conceptualization
Tropical cyclones	- Count of tropical cyclone events (frequency) - Tropical cyclone days over a specific time period (duration)
Flooding	- Average yearly flood events (frequency) - Cumulative daily square feet flooded (duration, intensity)
Power outages	- Average annual power outage events (frequency) - Total yearly customers without power within specific geographies (duration, intensity)

Examples are non-exhaustive. There is currently no standard definition for long-term exposure to climate change-relevant events, which could include several months to several years. Researchers should select the duration of a long-term climate change-relevant exposure appropriate to their research question and outcome of interest.

An additional consideration is that individuals and communities can adapt to certain climate change-related exposures over time. Adaptation can act as an effect modifier between climate mixtures and health outcomes and be in the form of changes in individual behaviors, residential mobility, infrastructure changes, or other avenues. Individuals could purchase indoor air filters or use facemasks to protect against wildfire smoke.[57] Cities have implemented programs to provide residents access to public temperature-controlled areas during extreme heat.[58] As climate change poses threats to public health, individuals and communities will respond to reduce adverse outcomes to climate change-related exposures, but adaptation efforts may vary. However, incorporating such adaptations poses challenges as data related to adaptation are limited. Simulations and prediction models have been used to integrate adaptation in understanding its role in climate mixture exposures,[59,60] but the dearth of available data limits our ability to analyze the possible effects of adaptation on the relationship between climate mixtures and adverse health.

Future directions

As climate change exacerbates weather events and downstream exposures, the exposome framework can be used as a guide to integrate exposure mixtures to accurately capture their health impacts. Using an example climate mixture, we presented several possible research questions of interest as well as examples of the appropriate methodologies to evaluate mixtures. Methods exist to analyze simultaneous exposures, but studying climate mixtures necessitates additional considerations such as violations of the positivity assumption, the complexity of defining long-term exposure, and limited data. Future research directions should aim to address these gaps and account for the nuances of climate mixtures and more generally of climate change-related exposures.

One limitation when integrating climate change-related exposure data with other cohort data—ideally those with -omics data available—for exposome research and analyses is that if cohort participants live close to each other, there will not be enough variability in the climate exposures to allow for enough statistical power to discover relationships. To effectively incorporate climate change-related exposures in exposome research, therefore, a wide geographical distribution of study participants may be key. The UK Biobank,[61] for example, has -omics data from individuals across the United Kingdom, and given the country's wide geographic range, there is likely high variability in exposure to climate change-related exposures within the cohort (eg, temperatures, storms, snow, flooding). Researchers could then identify representative subgroups and analyze whether exposure to climate change-related events is linked to molecular or other -omics outcomes of interest. Variability in climate change-related exposures is key to connecting these external macro-level exposures to internal omics-level outcomes.

One future direction is to use new ways to gather data on climate change-related exposures to supplement limited data in some domains like flooding. Researchers should consider leveraging novel sources of data such as social media, news outlets, images (eg, from satellites), or videos. In the case of climate change-related exposures such as flooding, these data sources can provide information about the event's spatial and temporal extent, allowing researchers to validate, update, or improve their exposure measures.

Relevant to studies linking climate mixtures and health, data should be collected to account for climate adaptation and differences in the ability to adapt. Societies and individuals will likely adapt to climate change, building new infrastructure or modifying behaviors. As the threat of physically destructive disasters is growing, governments may invest in fortifying electrical infrastructure to prevent or minimize subsequent power outages. In the face of rising temperatures and increasing likelihood of extreme heat events, individuals may rely more on air conditioners, installing them if they did not have one previously. However, the ability to adapt differs by subpopulation, and will have limits. For example, low-income individuals may not be able to afford air conditioners, while those facing energy insecurity may limit air conditioning use to minimize electricity bills, resulting in cooling hardship.[62,63] Another adaptation technique is relocating from high- to lower-risk climate change-related disaster areas, which includes evacuations in response to immediate wildfire disaster or tropical cyclones and pre-emptive moves from flood-prone neighborhoods. However, health status (eg, reliance on electricity-dependent medical equipment) or socioeconomic status may limit mobility. Obtaining data about adaptation across subpopulations and then accounting for them is necessary to accurately estimate the relationship between climate change-related exposures and adverse health outcomes.

As the exposome framework emphasizes cumulative environmental exposures, future exposome research can examine the possible joint impact of climate and non-climate environmental exposures on health. Climate mixtures and related exposures are external, and studies examining the associated health impacts have predominantly relied on administrative data (eg, hospitalizations). On the other hand, exposomic studies, such as metabolomics, center on internal biological processes using biospecimens for analysis[64,65] and have been predominantly used cohort or panel data. Although there are challenges in synthesizing these different exposome aspects,[66] it is a necessary step to accurately estimate cumulative environmental exposure. Additionally, exposome research in the context of climate change may uncover unexpected combinations of factors, both related and not related to climate change, that are particularly detrimental to population health.

Climate change-related exposures will continue to pose risks to population health, which will likely increase over time. Understanding the current tools and gaps in evaluating the comprehensive impact of these exposures on health can explicate their role as part of the exposome. By more explicitly considering climate change-related exposures in the field of exposomics, exposome research can move towards the direction of discovering unexpected pathways linking climate change and health.

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Data availability

No new data were generated or analyzed in support of this research.

Conflict of interest statement

The authors have no conflicts of interest to disclose.

References

1. Vermeulen R, Schymanski EL, Barabási AL, Miller GW. The exposome and health: where chemistry meets biology. Science. 2020;367(6476):392–396. doi:10.1126/science.aay3164
2. Climate Central. Weather-related Power Outages Rising. 2024. Accessed April 25, 2024. https://www.climatecentral.org/climate-matters/weather-related-power-outages-rising
3. Farhat YA, Kim SH, Seyfferth AL, Zhang L, Neumann RB. Altered arsenic availability, uptake, and allocation in rice under elevated temperature. Sci Total Environ. 2021;763:143049. doi:10.1016/j.scitotenv.2020.143049
4. Bolan S, Padhye LP, Jasemizad T, *et al.* Impacts of climate change on the fate of contaminants through extreme weather events. Sci Total Environ. 2024;909:168388. doi:10.1016/j.scitotenv.2023.168388
5. Schaffer-Smith D, Myint SW, Muenich RL, Tong D, DeMeester JE. Repeated hurricanes reveal risks and opportunities for social-ecological resilience to flooding and water quality problems. Environ Sci Technol. 2020;54(12):7194–7204. doi:10.1021/acs.est.9b07815
6. Ebi KL, Vanos J, Baldwin JW, *et al.* Extreme weather and climate change: population health and health system implications. Annu Rev Public Health. 2021;42(1):293–315. doi:10.1146/annurev-publhealth-0–105026
7. Lavados PM, Olavarría VV, Hoffmeister L. Ambient temperature and stroke risk: evidence supporting a short-term effect at a population level from acute environmental exposures. Stroke 2018;49(1):255–261. doi:10.1161/STROKEAHA.117.017838
8. Ebi KL, Capon A, Berry P, *et al.* Hot weather and heat extremes: health risks. Lancet. 2021;398(10301):698–708. doi:10.1016/S0140-6736(21)01208-3
9. Morello-Frosch R, Obasogie OK. The climate gap and the color line–racial health inequities and climate change. N Engl J Med. 2023;388(10):943–949. doi:10.1056/NEJMsb2213250
10. Knutson T, Camargo SJ, Chan JCL, *et al.* Tropical cyclones and climate change assessment: part ii: projected response to anthropogenic warming. Bull Am Meteorol Soc. 2020;101(3):E303–E322. doi:10.1175/BAMS-D-8–0194.1
11. Xu R, Yu P, Abramson MJ, *et al.* Wildfires, global climate change, and human health. N Engl J Med. 2020;383(22):2173–2181. doi:10.1056/NEJMsr2028985

12. Andrews O, Quéré CL, Kjellstrom T, Lemke B, Haines A. Implications for workability and survivability in populations exposed to extreme heat under climate change: a modelling study. Lancet Planet Health. 2018;2(12):e540–e547. doi:10.1016/S2542-5196(18)30240-7
13. Marsooli R, Lin N, Emanuel K, Feng K. Climate change exacerbates hurricane flood hazards along US Atlantic and Gulf Coasts in spatially varying patterns. Nat Commun. 2019;10(1):3785. doi:10.1038/s41467-9–11755-z
14. Cook BI, Mankin JS, Anchukaitis KJ. Climate change and drought: from past to future. Curr Clim Change Rep. 2018;4(2):164–179. doi:10.1007/s40641-8–0093-2
15. Kenward A, Raja U. Blackout: Extreme Weather, Climate Change and Power Outages. Climate Central; 2014:23.
16. McMichael C, Barnett J, McMichael AJ. An ill wind? Climate change, migration, and health. Environ Health Perspect. 2012;120(5):646–654. doi:10.1289/ehp.1104375
17. IPCC. *Climate Change 2022: Impacts, Adaptation, and Vulnerability*. 2022. Accessed February 20, 2024. https://www.ipcc.ch/report/ar6/wg2/downloads/report/IPCC_AR6_WGII_SummaryForPolicymakers.pdf
18. Ridder NN, Ukkola AM, Pitman AJ, Perkins-Kirkpatrick SE. Increased occurrence of high impact compound events under climate change. Npj Clim Atmos Sci. 2022;5(1):1–8. doi:10.1038/s41612-1–00224-4
19. Gibson EA, Goldsmith J, Kioumourtzoglou MA. Complex mixtures, complex analyses: an emphasis on interpretable results. Curr Environ Health Rep. 2019;6(2):53–61. doi:10.1007/s40572-9–00229-5
20. Gibson EA, Nunez Y, Abuawad A, *et al.* An overview of methods to address distinct research questions on environmental mixtures: an application to persistent organic pollutants and leukocyte telomere length. Environ Health. 2019;18(1):76. doi:10.1186/s12940-9–0515-1
21. Stafoggia M, Breitner S, Hampel R, Basagaña X. Statistical approaches to address multi-pollutant mixtures and multiple exposures: the state of the science. Curr Environ Health Rep. 2017;4(4):481–490. doi:10.1007/s40572-7–0162-z
22. Joubert BR, Kioumourtzoglou MA, Chamberlain T, *et al.* Powering research through innovative methods for mixtures in epidemiology (PRIME) program: novel and expanded statistical methods. IJERPH. 2022;19(3):1378. doi:10.3390/ijerph19031378
23. Yu L, Liu W, Wang X, *et al.* A review of practical statistical methods used in epidemiological studies to estimate the health effects of multi-pollutant mixture. Environ Pollut. 2022;306:119356. doi:10.1016/j.envpol.2022.119356
24. Chiu YH, Bellavia A, James-Todd T; EARTH Study Team, *et al.* Evaluating effects of prenatal exposure to phthalate mixtures on birth weight: a comparison of three statistical approaches. Environ Int. 2018;113:231–239. doi:10.1016/j.envint.2018.02.005
25. Bai J, Ma Y, Zhao Y, Yang D, Mubarik S, Yu C. Mixed exposure to phenol, parabens, pesticides, and phthalates and insulin resistance in NHANES: a mixture approach. Sci Total Environ. 2022;851(Pt 2):158218. doi:10.1016/j.scitotenv.2022.158218
26. Samanic C, Hoppin JA, Lubin JH, Blair A, Alavanja MCR. Factor analysis of pesticide use patterns among pesticide applicators in the Agricultural Health Study. J Expo Sci Environ Epidemiol 2005;15(3):225–233. doi:10.1038/sj.jea.7500396
27. Akinyemiju T, Chen Q, Wilson LE, *et al.* Healthcare access domains mediate racial disparities in ovarian cancer treatment quality in a US patient cohort: a structural equation modelling analysis. Cancer Epidemiol Biomarkers Prev. 2023;32(1):74–81. doi:10.1158/5–9965.EPI-2–0650
28. Martinez SA, Beebe LA, Thompson DM, Wagener TL, Terrell DR, Campbell JE. A structural equation modeling approach to understanding pathways that connect socioeconomic status and smoking. Plos One. 2018;13(2):e0192451. doi:10.1371/journal.pone.0192451
29. NOAA Climate.gov. Former Hurricane Hilary brought Southern California its first-ever tropical storm watch. Accessed October 24, 2023. http://www.climate.gov/news-features/event-tracker/former-hurricane-hilary-brought-southern-california-its-first-ever
30. Kossin JP. Is the North Atlantic hurricane season getting longer? Geophys Res Lett. 2008;35(23). doi:10.1029/2008GL036012
31. Li S, Banerjee T. Spatial and temporal pattern of wildfires in California from 2000 to 2019. Sci Rep. 2021;11(1):8779. doi:10.1038/s41598-1–88131-9
32. Abatzoglou JT, Williams AP. Impact of anthropogenic climate change on wildfire across western US forests. Accessed May 22, 2022. https://www.pnas.org/doi/10.1073/pnas.1607171113
33. Do V, McBrien H, Flores NM, *et al.* Spatiotemporal distribution of power outages with climate events and social vulnerability in the USA. Nat Commun. 2023;14(1):2470. doi:10.1038/s41467-3–38084-6
34. Westreich D, Cole SR. Invited commentary: positivity in practice. Am J Epidemiol. 2010;171(6):674–677. doi:10.1093/aje/kwp436
35. Miller G, Bennett M. Integrating exposomics into the biomedical enterprise. 2023. Accessed September 22, 2024. https://www.cshl.edu/wp-content/uploads/2024/03/Banbury_EXPOS_Output_Two-Pager-Final_20240205.pdf
36. Stetler C. *Epigenomics and Epitranscriptomics Front and Center at Council*. National Institute of Environmental Health Sciences; 2024. Accessed September 22, 2024. https://factor.niehs.nih.gov/2024/3/community-impact/council
37. Casey JA, Kioumourtzoglou M-A, Padula A, *et al.* Measuring long-term exposure to wildfire PM2.5 in California: Time-varying inequities in environmental burden. Proc. Natl. Acad. Sci. 2024;121(8):e2306729121.
38. Parks RM, Anderson GB, Nethery RC, Navas-Acien A, Dominici F, Kioumourtzoglou MA. Tropical cyclone exposure is associated with increased hospitalization rates in older adults. Nat Commun. 2021;12(1):1545. doi:10.1038/s41467-1–21777-1
39. Zhang W, Sheridan SC, Birkhead GS, *et al.* Power outage: an ignored risk factor for COPD exacerbations. Chest 2020;158(6):2346–2357. doi:10.1016/j.chest.2020.05.555
40. Qu Y, Zhang W, Ye B, *et al.* Power outage mediates the associations between major storms and hospital admission of chronic obstructive pulmonary disease. BMC Public Health. 2021;21(1):1961. doi:10.1186/s12889-1–12006-x
41. Saulnier DD, Hanson C, Ir P, Mölsted Alvesson H, von Schreeb J. The effect of seasonal floods on health: analysis of six years of national health data and flood maps. Int J Environ Res Public Health 2018;15(4):665. doi:10.3390/ijerph15040665
42. Ranstam J, Cook JA. LASSO regression. Br J Surg. 2018;105(10):1348. doi:10.1002/bjs.10895
43. Ding E, Wang Y, Liu J, Tang S, Shi X. A review on the application of the exposome paradigm to unveil the environmental determinants of age-related diseases. Hum Genomics. 2022;16(1):54. doi:10.1186/s40246-2–00428-6
44. Yang X, Zhang M, Lu T, *et al.* Metabolomics study and meta-analysis on the association between maternal pesticide exposome and birth outcomes. Environ Res. 2020;182:109087. doi:10.1016/j.envres.2019.109087
45. Huang W, Pan XF, Tang S, *et al.* Target exposome for characterizing early gestational exposure to contaminants of emerging concern and association with gestational diabetes mellitus.

Environ Sci Technol. 2023;57(36):13408–13418. doi:10.1021/acs.est.3c04492
46. Bobb JF, Claus Henn B, Valeri L, Coull BA. Statistical software for analyzing the health effects of multiple concurrent exposures via Bayesian kernel machine regression. Environ Health. 2018; 17(1):67. doi:10.1186/s12940-8–0413-y
47. Bobb JF, Valeri L, Claus Henn B, *et al.* Bayesian kernel machine regression for estimating the health effects of multi-pollutant mixtures. Biostatistics. 2015;16(3):493–508. doi:10.1093/biostatistics/kxu058
48. McGee G, Wilson A, Webster TF, Coull BA. Bayesian multiple index models for environmental mixtures. Biometrics 2023;79(1): 462–474. doi:10.1111/biom.13569
49. Sánchez BN, Budtz-Jørgensen E, Ryan LM, Hu H. Structural equation models. J Am Stat Assoc. 2005;100(472):1443–1455. doi: 10.1198/016214505000001005
50. Diday E, Simon JC. Clustering analysis. In: Fu KS, ed. Digital Pattern Recognition. Communication and Cybernetics. Springer; 1976:7–94. doi:10.1007/978-3-2–96303-2_3
51. James G, Witten D, Hastie T, Tibshirani R. An Introduction to Statistical Learning with Applications in R. New York: Springer; 2013.
52. Sajjad M, Lin N, Chan JCL. Spatial heterogeneities of current and future hurricane flood risk along the U.S. Atlantic and Gulf coasts. Sci Total Environ. 2020;713:136704. doi:10.1016/j.scitotenv.2020.136704
53. PRISM Climate Group at Oregon State University. PRISM Climate Data. Accessed July 16, 2024. https://prism.oregonstate.edu/
54. Carrión D, Arfer KB, Rush J, *et al.* A 1-km hourly air-temperature model for 13 northeastern U.S. states using remotely sensed and ground-based measurements. Environ Res. 2021;200: 111477. doi:10.1016/j.envres.2021.111477
55. U.S. Department of Energy. OE-417 Electric Emergency Incident and Disturbance Report. 2021. Accessed January 11, 2022. https://www.oe.netl.doe.gov/docs/OE417_Form_Instructions_05312021.pdf
56. Brelsford C, Tennille S, Myers A, *et al.* A dataset of recorded electricity outages by United States county 2014–2022. Sci Data. 2024;11(1):271. doi:10.1038/s41597-4–03095-5
57. Hervieux-Moore Z, Dominici F. Human behaviour and wildfire smoke. Nat Hum Behav. 2022;6(10):1327–1328. doi:10.1038/s41562-2–01400-z
58. NYC Government. NYC Cooling Centers. Accessed July 13, 2023. https://finder.nyc.gov/coolingcenters
59. Stone B, Mallen E, Rajput M, *et al.* Compound climate and infrastructure events: how electrical grid failure alters heat wave risk. Environ Sci Technol. 2021;55(10):6957–6964. doi: 10.1021/acs.est.1c00024
60. Stone BJr, Gronlund CJ, Mallen E, *et al.* How Blackouts during heat waves amplify mortality and morbidity risk. Environ Sci Technol. 2023;57(22):8245–8255. doi:10.1021/acs.est.2c09588
61. UK Biobank Limited 2024. UK Biobank. Accessed June 12, 2024. https://www.ukbiobank.ac.uk
62. Cong S, Nock D, Qiu YL, Xing B. Unveiling hidden energy poverty using the energy equity gap. Nat Commun. 2022;13(1):2456. doi: 10.1038/s41467-2–30146-5
63. Hernández D. Understanding 'energy insecurity' and why it matters to health. Soc Sci Med. 2016;167:1–10. doi:10.1016/j.socscimed.2016.08.029
64. Walker DI, Valvi D, Rothman N, Lan Q, Miller GW, Jones DP. The metabolome: a key measure for exposome research in epidemiology. Curr Epidemiol Rep. 2019;6(2):93–103. doi:10.1007/s40471-9–00187-4
65. González-Domínguez R, Jáuregui O, Queipo-Ortuño MI, Andrés-Lacueva C. Characterization of the human exposome by a comprehensive and quantitative large-scale multianalyte metabolomics platform. Anal Chem. 2020;92(20):13767–13775. doi: 10.1021/acs.analchem.0c02008
66. Stingone JA, Buck Louis GM, Nakayama SF, *et al.* Toward greater implementation of the exposome research paradigm within environmental epidemiology. Ann Rev Public Health. 2017;38(1): 315–327. doi:10.1146/annurev-publhealth-082516-012750

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Commentary