Assessment of extreme heat and hospitalizations to inform early warning systems

Ambarish Vaidyanathan[a,1], Shubhayu Saha[a], Ana M. Vicedo-Cabrera[b], Antonio Gasparrini[b], Nabill Abdurehman[c], Richard Jordan[d], Michelle Hawkins[e], Jeremy Hess[f], and Anne Elixhauser[g]

[a]National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, GA 30341; [b]Department of Social and Environmental Health Research, London School of Hygiene and Tropical Medicine, London WC1E 7HT, United Kingdom; [c]Oak Ridge Institute of Science and Education, Oak Ridge, TN 37831; [d]Social & Scientific Systems, Inc., Rockville, MD 20852; [e]National Weather Service, National Oceanic and Atmospheric Administration, Silver Spring, MD 20910; [f]Center for Health and the Global Environment, University of Washington, Seattle, WA 98105; and [g]Agency for Healthcare Research and Quality, Rockville, MD 20852

Edited by Nancy M. Reid, University of Toronto, Toronto, Canada, and approved December 12, 2018 (received for review April 28, 2018)

Heat early warning systems and action plans use temperature thresholds to trigger warnings and risk communication. In this study, we conduct multistate analyses, exploring associations between heat and all-cause and cause-specific hospitalizations, to inform the design and development of heat–health early warning systems. We used a two-stage analysis to estimate heat–health risk relationships between heat index and hospitalizations in 1,617 counties in the United States for 2003–2012. The first stage involved a county-level time series quasi-Poisson regression, using a distributed lag nonlinear model, to estimate heat–health associations. The second stage involved a multivariate random-effects meta-analysis to pool county-specific exposure–response associations across larger geographic scales, such as by state or climate region. Using results from this two-stage analysis, we identified heat index ranges that correspond with significant heat-attributable burden. We then compared those with the National Oceanic and Atmospheric Administration National Weather Service (NWS) heat alert criteria used during the same time period. Associations between heat index and cause-specific hospitalizations vary widely by geography and health outcome. Heat-attributable burden starts to occur at moderately hot heat index values, which in some regions are below the alert ranges used by the NWS during the study time period. Locally specific health evidence can beneficially inform and calibrate heat alert criteria. A synchronization of health findings with traditional weather forecasting efforts could be critical in the development of effective heat–health early warning systems.

public health | extreme heat | public policy | evidence-based decision making | early warning systems

Extreme heat is an established hazard. Risk for a range of conditions is associated with extreme heat exposure (1, 2), including morbidity from heat illness (3), electrolyte and renal dysfunction (4, 5), and exacerbations of chronic respiratory (6) and cardiovascular (7) disease, as well as all-cause mortality (3). The association between the particular temperatures at which risks are manifested and the magnitude of the effects vary regionally due to acclimatization, air conditioning prevalence, demography, and other factors (8).

Successful risk management varies by setting and includes prevention strategies ranging from engineering controls such as air conditioning, management controls such as shifts in work schedules and activity restrictions, and behavioral controls encouraged through heat early warning systems and action plans (9). These systems and plans are activities that link forecasts of heat exposure with risk communication and risk reduction activities aimed at reducing exposure and limiting adverse health impacts among the exposed such as cooling centers, neighbor check-ins, and maintenance of air conditioning availability (10), which have been linked with reduced morbidity and mortality.

Given variability in temperature thresholds at which risks increase, one central consideration in heat early warning systems is the threshold at which warnings should be issued (11). Guidance recommends setting thresholds based on analysis of associations between heat exposure (measured using a variety of metrics) and adverse health effects (9). In the United States, the National Oceanic and Atmospheric Administration's National Weather Service (NWS) issues excessive heat watch, warning, and heat advisory alerts as weather conditions warrant. While NWS provides guidance to its Weather Forecast Offices (WFOs) on appropriate thresholds for issuing these alerts, WFOs are encouraged to work with local officials to define locally appropriate alert thresholds (12). There is no standard protocol for incorporating local epidemiological analyses, as relevant data and expertise may not be locally available. In addition to these constraints, risk assessment has been complicated by a lack of consensus regarding exposure assessment (e.g., which temperature metrics to use), standardization of heat-sensitive health outcomes (e.g., morbidity measures or mortality) and resulting heat attributable health impacts, and standard analytical approaches, despite emerging consensus in the field that best practices include basing thresholds on recent time-series analyses of the relationship between temperature and the best available local health data (9, 13). Recent analyses have demonstrated

Significance

Heat early warning systems and action plans have been shown to reduce risks of heat exposure, and best practice recommends that plans be built around local epidemiologic evidence and emergency management capacity. This evaluation provides useful information for heat early warning system and action plan administrators regarding the temperature ranges at which health impacts are manifest, the morbidity outcomes most sensitive to heat, and alignment between alert thresholds and temperatures at which disease burden is most pronounced. The results suggest opportunities for improvement and for refinement of prevention messaging as well as coordination between meteorological and public health authorities at multiple levels before, during, and after periods of extreme heat.

Author contributions: A.V., A.G., and A.E. designed research; A.V. performed research; A.V., S.S., A.M.V.-C., M.H., and J.H. contributed new reagents/analytic tools; A.V., N.A., and R.J. analyzed data; S.S., R.J., J.H., and A.E. provided administrative support; A.V., A.M.V.-C., and A.G. performed statistical analysis; A.G., R.J., and M.H. provided technical support; A.V., N.A., and R.J. performed acquisition, analysis, and interpretation of data; R.J. and A.E. provided material support; A.V. led this research effort; and A.V. wrote the paper with assistance from all authors.

The authors declare no conflict of interest.

This article is a PNAS Direct Submission.

[1]To whom correspondence should be addressed. Email: rishv@cdc.gov.

This article contains supporting information online at www.pnas.org/lookup/suppl/doi:10.1073/pnas.1806393116/-/DCSupplemental.

Published online March 4, 2019.

that morbidity impacts, when available, may be most appropriate, as these outcomes are more prevalent than mortality endpoints (14, 15).

In many locales in the United States, this goal remains aspirational. While risks associated with heat exposure in the United States have been well characterized for certain at-risk populations and regions (6, 16–18), there have been no comprehensive, national-scale investigations of regional-scale relationships between heat and morbidity-based health outcomes for the general population. Moreover, most assessments have estimated average health risks for combined endpoints across an entire summertime heat exposure spectrum, ignoring the known differential sensitivity of certain outcomes to specific temperature ranges (14, 19). As a result, a clear, consistent nationwide assessment of adverse health impacts associated with heat exposure in the United States has been elusive, complicating the work of setting appropriate local warning thresholds. This disconnect has the potential to compromise the efficacy of heat risk communication and to limit the public health utility of related activities such as surveillance for heat-related illness.

In this study, we performed multistate analyses to explore relationships between extreme heat and hospitalizations, covering a majority of the US population. The hospitalizations data that are used for this study are a census of all hospital admissions, regardless of age or insurance provider. Specifically, our objectives for this assessment were as follows: (*i*) to explore the relationship between heat index (20), which is a heat metric that combines the effect of humidity and temperature, and hospitalizations across heat index ranges observed during summer months; (*ii*) to develop exposure–response (E-R) associations for all-cause and cause-specific hospitalizations, including cardiovascular, respiratory, diabetic, renal, and fluid and electrolyte illnesses; (*iii*) to synthesize heat-attributable burden—adverse health impacts in terms of fractions and numbers; and (*iv*) to identify heat index ranges, stratified by US climate region (21), that correspond with significant adverse health impacts and to compare those against current NWS heat alert criteria for those same regions.

Results

Our assessment examined ∼50 million inpatient hospitalization records, covering 1,617 counties across 22 states for the summer months of 2003–2012, to model the relationship between heat index and adverse health outcomes. This multistate hospitalization database accounts for every single patient treated as an inpatient in hospitals, regardless of any age criteria or the type of insurance used to pay for services. We provide a state-specific summary of population coverage and number of counties included in this assessment in Table 1. Also in Table 1, we show the population-weighted distribution of daily maximum heat index and the range of values for which heat alerts are typically issued. We provide the crude rates of summertime hospitalizations from all causes and for specific outcomes in *SI Appendix*, Table S1. The states considered for this assessment accounted for 55.1% of the US total population and are spread out across all nine US climate regions. We excluded 390 counties for population size of less than 10,000, although this exclusion only reduced the sample size of inpatient hospitalization records by 0.6%.

For most states, the median heat alert criteria fell between the 95th and 99th percentile summertime heat index distribution. While most of the states in the same climate region share a similar temperature climatology, we found significant intraregional variability in the Southwest climate region (e.g., comparing Arizona with Colorado and Utah). However, this variation was

ENVIRONMENTAL SCIENCES

Table 1. State-specific population and heat index distribution with information on heat index values for issuing heat alerts

Climate region	State	No. of counties with population greater than 10,000 people	Average yearly state population (2003–2012)*, millions	Percent of average yearly US population (2003–2012)	Daily maximum heat index distribution, °F: 5th percentile	25th percentile	Median	75th percentile	95th percentile	Median and range of heat index values used for issuing heat alerts
Central	Illinois	87	12.6	4.2	62	74	82	91	104	109 (101, 118)
	Indiana	88	6.4	2.1	64	75	82	91	103	108 (100, 116)
	Kentucky	99	4.1	1.4	67	78	85	93	104	107 (101, 116)
	Missouri	89	5.7	1.9	67	79	88	98	109	109 (102, 116)
	West Virginia	44	1.7	0.6	64	74	80	87	96	104 (96, 113)
East North Central	Iowa	76	2.8	0.9	63	75	83	92	106	110 (98, 120)
Northeast	Maryland	24	5.7	1.9	65	75	83	90	100	104 (97, 111)
	New York	61	19.3	6.4	61	71	78	84	95	100 (95, 111)
	Rhode Island	5	1.1	0.4	59	69	75	83	93	101 (93, 113)
Northwest	Oregon	29	3.7	1.2	57	67	74	80	88	90 (82, 101)
South	Kansas	39	2.5	0.8	68	80	89	99	109	108 (98, 114)
Southeast	Florida	65	18.3	6.1	85	92	96	100	105	109 (107, 111)
	Georgia	127	9.1	3.0	76	85	91	97	104	107 (101, 111)
	North Carolina	97	9.1	3.0	71	82	88	95	102	107 (102, 112)
	Virginia	115	7.7	2.5	67	77	85	92	101	106 (100, 112)
Southwest	Arizona	14	6.1	2.0	82	90	96	101	106	104 (96, 109)
	Colorado	38	4.7	1.6	61	74	80	84	89	91 (91, 92)
	Utah	20	2.6	0.9	59	73	81	85	90	100 (100, 104)
West	California	55	36.5	12.1	69	77	82	86	91	92 (86, 97)
	Nevada	10	2.5	0.8	73	83	90	94	99	99 (93, 103)
West North Central	Nebraska	27	1.5	0.5	65	78	86	95	107	109 (104, 115)
	South Dakota	18	0.6	0.2	60	73	82	89	100	106 (100, 112)

*Only including counties in the state with population greater than 10,000.

mostly due to the high summertime heat index values prevalent in metropolitan areas of Phoenix, AZ and surrounding areas.

For this analysis, associations between heat index and hospitalization outcomes during summer months were assessed through a two-stage time-series analysis. Nonlinear and delayed associations were estimated for each county and then pooled at state and climate region level through a metaregression analysis. Risk estimates for hospitalizations are reported in terms of mean percent change (and 95% CI) in daily hospitalizations for heat index above the minimum morbidity heat index (MMHI). The MMHI corresponds to the heat index value above which heat-related morbidity risk starts to increase. County-specific maps of MMHI for each hospitalization outcome are provided in *SI Appendix*, Fig. S1. In Fig. 1, we present the mean percent change (and 95% CI) in daily hospitalizations observed for summertime heat index values for each climate region. Comparing across health outcomes, we found that the largest increases in slope of the overall E-R associations were observed for outcomes such as renal failure and fluid- and electrolyte-related disorders; cardiovascular-, respiratory-, and diabetes-related illnesses showed a steady but much lower percent increase in daily hospitalizations for a unit change in heat index values. For all-cause hospitalizations, we found statistically significant E-R associations for most states over a wide range of heat index values; however the effect sizes were much smaller compared with renal failure and fluid- and electrolyte-disorder-related hospitalizations. Also noteworthy were the findings on the varying risk sensitivity of cause-specific health outcomes to moderately high heat index values, indicating that the health burden from heat exposure is apparent below heat alert thresholds (denoted by gold bands in Fig. 1).

We present the state-specific heat-attributable adverse health impacts, that is, the heat attributable fraction (AF) and attributable number (AN) per summer, in Fig. 2 for each hospitalization outcome considered in this assessment. We summarize the mean and 95% CI for AF and AN across all heat index values above the MMHI.

For most states, AFs associated with renal failure and fluid- and electrolyte-related disorders showed a much greater sensitivity to heat index values above MMHI than other health outcomes. Within each state and for a given hospitalization outcome, the

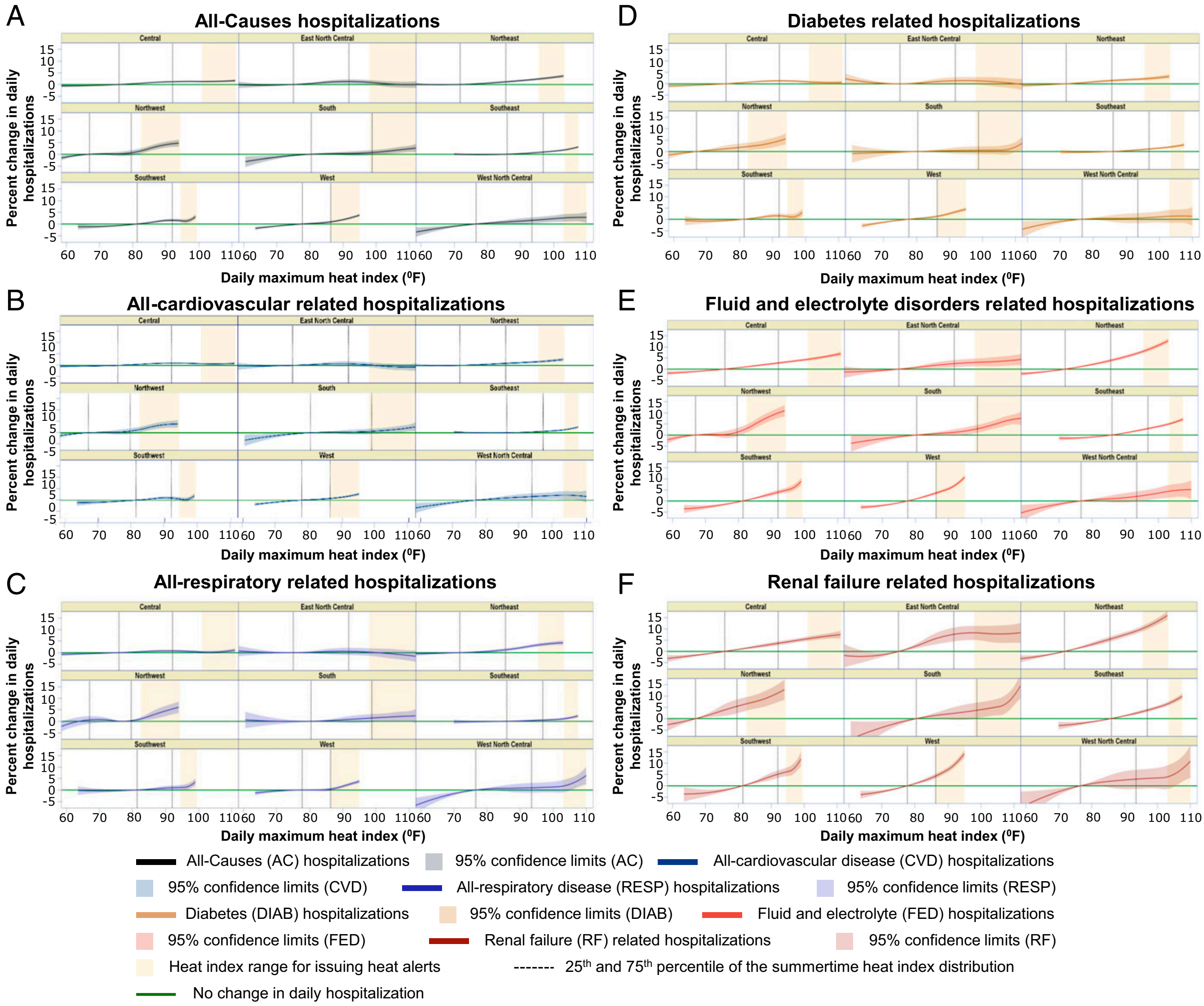

Fig. 1. (*A*–*F*) Overall E-R associations for various hospitalization outcomes, by US climate regions (percent change in risk estimated from the minimum morbidity heat index for a cumulative lag period of 2 d).

county-level variation in AF was minimal; however, significant county-level differences were observed between hospitalization outcomes (*SI Appendix*, Fig. S2). County-level maps for cardiovascular and respiratory diseases, as well as hospitalizations for all causes, showed a similar pattern, with most counties having a mean AF that is less than or equal to 1.3%. For renal failure and fluid- and electrolyte-related disorders, mean AFs were significantly higher than for other outcomes, with some counties having mean AFs greater than 3%. For diabetes-related hospitalizations, regional differences were observed with mean AFs greater for counties in the Northwest, Southwest, and West but relatively lower for counties in other regions. The spatial patterns of mean ANs (*SI Appendix*, Fig. S3) reflect location-specific baseline numbers for each hospitalization outcome, which are mostly driven by population sizes. Essentially, areas with high risk and small population sizes have burden comparable to that in areas with low risk but a fairly substantial population. Moreover, for a given location, heat-attributable adverse health impacts are distributed unevenly across summertime heat index values. Summary of AF (*SI Appendix*, Table S2) and AN (*SI Appendix*, Table S3) by heat index ranges for each hospitalization outcome and by state are provided in *SI Appendix*. In most states, AFs and ANs correspond well with person-days of exposure observed under each heat index range.

In Fig. 3, we translate information gleaned from aforementioned results on heat-attributable adverse health impacts into a 1D heat chart. In doing so, we identify "heat-sensitive zones," based on heat index ranges at which positively significant adverse health impacts (AFs/ANs) are observed for different climate regions and health outcomes considered in this assessment. The chart also offers a comparison between heat index ranges used for issuing alerts and those associated with peak adverse health impacts. Evidently, in colder regions of the United States (e.g., the central region) a large proportion of adverse health impacts tend to occur at moderate heat index ranges—well below the heat index values used by some WFOs at the time of this study for issuing alerts. In warmer regions of the United States (e.g., the southern region) heat index ranges that are sensitive to adverse health impacts overlap with those used for issuing alerts. However, in certain regions (e.g., the southwestern region) peak adverse health impacts are observed at heat index ranges that are above the median heat alert criteria.

Discussion

Our assessment is comprehensive in scope and scale, and has implications for current and future risk management related to heat exposure. Prior assessments that have tried to identify heat alert thresholds based on heat–health risk relationships are either city-specific or for communities covering a few states (11, 22). This study's novelty lies in the comprehensive assessment of heat exposure on various morbidity outcomes, including those that are less well characterized in published literature. In addition, we use a nationally consistent study design that employed a systematic modeling framework to link exposure to fine-scale, cause-specific hospitalizations to characterize adverse health impacts for the general population across climatologically diverse locations. We generated overall E-R associations and attributable health risk/burden estimates based on the census of all hospital admissions for the states included in this assessment, representing all climatic regions of the United States, providing a firm basis to demonstrate prevailing heat-attributable health impacts at various public health decision-making scales. We showed the importance of assessing multiple health outcomes, as risk sensitivity (slope) and magnitude of cause-specific E-R

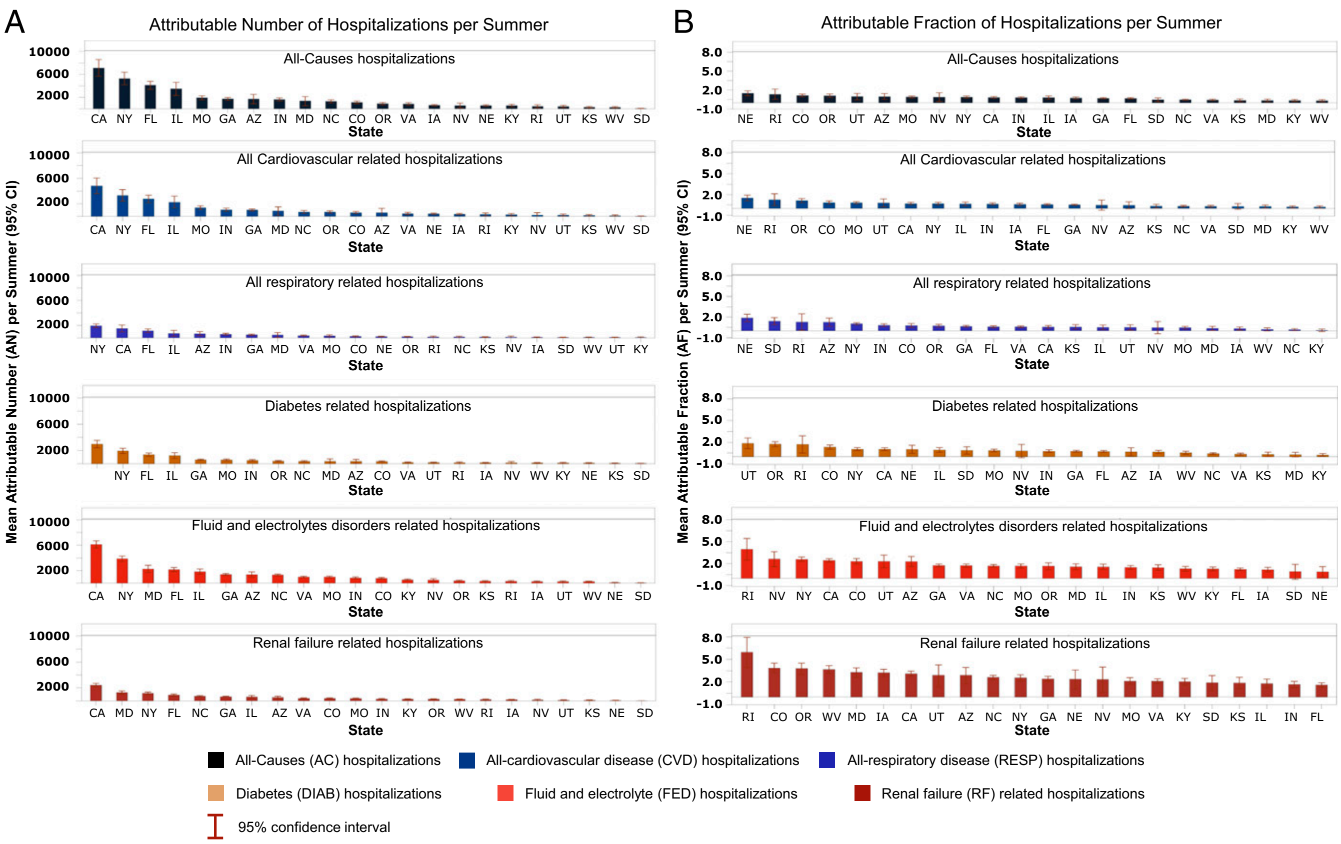

Fig. 2. State-specific (*A*) AN and (*B*) AF of hospitalizations above minimum morbidity heat index for a cumulative lag period of 2 d.

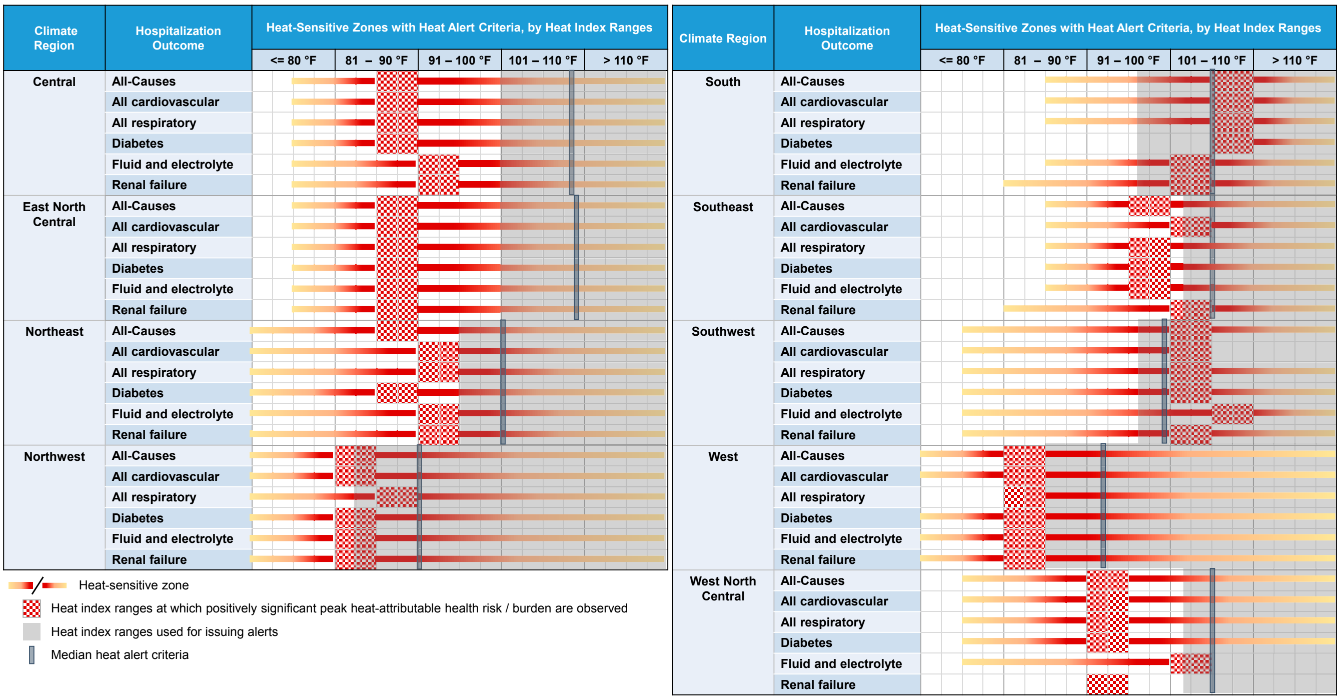

Fig. 3. Region-specific heat-sensitive zones with heat alert criteria.

associations tend to differ across outcomes. We also identified a systematic dissociation in some geographic areas between the temperatures at which heat alerts are issued and the temperatures at which peak impacts are observed.

This misalignment in some geographic areas between the temperatures at which health burdens become significant and temperatures at which alerts are issued raises critical questions. Following the methodology of issuing heat alerts based on the extremity of heat index distribution regardless of differential population sensitivity could generally fail to account for a large proportion of heat-attributable adverse health impacts observed at moderately hot conditions. This may be an important consideration, especially among those populations residing in cooler regions, with no structural adaptations such as air conditioning. While it is likely that there should be better alignment between alert thresholds and regional heat epidemiology, it is not clear exactly where warning thresholds should be set. There are a number of issues to consider, including the potential for warning fatigue (17). Conversely, in warmer locations, peak heat-attributable burden occurs past the median temperature for heat alerts, yet the burden curves generally show a monotonic rise above these threshold temperatures, raising questions about the effectiveness of current intervention strategies, heat alert messaging, and related activities. Potentially, this highlights inherent communication challenges in delivering actionable risk information and prevention guidelines to various stakeholders, including vulnerable populations. Additional research regarding specific protective measures and appropriate timing for risk reduction measures is needed to inform future risk management decisions.

Our results show promise for the use of regionally specific health evidence to inform and calibrate heat alert protocols (22). Further, graduated heat alert protocols may help warn for low, moderate, and peak adverse health impacts. Such graduated alerts, such as the air quality index (23), are currently used to identify areas impacted by poor air quality. In addition to empirical alignment of warnings with risks, such recalibrated heat alerts and more specific messaging might improve message relevance and facilitate better stakeholder engagement (24). In addition, web-enabled resources detailing individual preventative options (25), especially at low and moderately high temperatures, coupled with graduated community-level interventions, such as opening cooling shelters (26) during more extreme situations like heat waves, could potentially minimize heat-related adverse health impacts more effectively. These initiatives could strengthen heat preparedness and response capabilities but require additional coordination across various local, state, and federal agencies.

There are some limitations to our assessment. Although our analysis included hospitalizations for more than 1,200 counties covering 55% of the total US population, E-R associations may not fully characterize the underlying heat–health relationship in areas that are sparsely populated or in regions where certain key states are omitted. While adding more counties would improve population coverage and generalizability of the findings, data access limitations prevented inclusion of additional counties. Another limitation is the identification of state- and region-level heat index ranges that are used for issuing alerts. Our primary goal was to explore the discrepancy between heat index values used for issuing alerts and those that are associated with significant heat-attributable health burden for the time period used in this assessment; however, heat alert criteria, which are set by WFOs, are occasionally revised and sometimes changed based on epidemiologic evidence (11). Further, this assessment does not present any evidence on how some of the population-level health risks can be modified by individual risk factors (age, race, or occupational status) or by community-level factors (poverty, density, land use, and land cover). Despite including robust daily, county-level environmental predictors in our time-series analyses, our results may be affected by residual confounding (27), especially should there be an omitted or misspecified confounder that fluctuates over time in a manner similar to heat index. Further, exposure misclassification could result from using modeled data sources, especially in areas where modeled estimates of heat metrics do not comport well with those derived from station-based measurements. Finally, relying on ambient weather data may also misrepresent true exposures, particularly in regions where prevalence of air conditioning is higher (28).

Heat-related illnesses are preventable (29) adverse health outcomes. Heat early warning systems and action plans have been shown to reduce risks of heat exposure, and best practice recommends that plans be built around local epidemiologic evidence and emergency management capacity. Our evaluation provides useful information for heat early warning system and action plan administrators regarding the temperature ranges at which health impacts are manifest, the morbidity outcomes most sensitive to heat, and alignment between alert thresholds and temperatures at which disease burden is most pronounced. The results suggest opportunities for improvement and for refinement of prevention messaging as well as coordination between meteorological and public health authorities at multiple levels before, during, and after extreme heat events. Improving risk management related to extreme heat involves multiple stakeholders and input from a range of disciplines. Our results could be a starting point for enhanced dialogue among various stakeholders involved in heat–health activities and for enhanced collaboration among various organizations, including those that facilitated our access to high-resolution health data and expertise on weather forecasting and statistical modeling. Furthering these collaborations to develop a community of practice for systematically assessing and disseminating weather-related health impacts could strengthen preparedness and response capacity, increase public awareness, and potentially reduce the substantial burden of disease associated with extreme heat.

Materials and Methods

Meteorological Data. Hourly meteorological predictions came from the North American Land Data Assimilation System Phase 2 (NLDAS) model (30), available for temperature, humidity, and other weather parameters at 0.125° grid resolution. The hourly gridded data were made available to the Centers for Disease Control and Prevention (CDC) as part of an interagency agreement with the National Aeronautics and Space Administration. We first calculated hourly heat index using hourly temperature and humidity information at a grid level. The heat index formula was obtained from NWS's weather prediction center website (https://www.wpc.ncep.noaa.gov/html/heatindex_equation.shtml). This formula was a refinement of the regression equation presented by Rothfusz (31). Furthermore, we used a multistage geo-imputation approach to convert grid-level meteorological data to county-level estimates. We first calculated the population within each NLDAS grid cell using 2010 population estimates by US Census blocks. We then converted NLDAS grid polygons with population information to centroids and related all of the grid-cell centroids to the counties in the conterminous United States based on a containment relationship. If a county did not have a grid-cell centroid within its boundary, we assigned a grid-cell centroid closest to the county boundary. Finally, we created a population-weighted average from all of the grid-cell centroids to obtain county-level estimates of daily maximum heat index, for the summer months (May 1 through September 30) and for years 2003–2012. We used daily maximum heat index as the primary exposure metric in this health risk assessment. The data are available from CDC's Environmental Public Health Tracking Network (https://ephtracking.cdc.gov).

In addition, we obtained data on heat alerts (excessive heat warnings, watches, and heat advisories) from NWS for 2007–2012. This dataset contained information on the WFO and the warning area within that WFO jurisdiction for which alerts were issued, as well as the date of alerts. We also gathered information on the geographical boundaries for warning areas within WFO, which changed over time during 2007–2012. Since the warning areas do not spatially align with county boundaries, we used spatial analysis techniques to reconcile boundary differences. First, we related the centroid of each US Census block to the warning areas and created a census-block-level alert database with date information. Subsequently, we aggregated this block-level dataset to counties and created a daily, county-level heat alert dataset. Further, we merged this alert database with county-level daily maximum heat index information. We used the resulting county-level linked database to summarize median, 5th, and 95th percentile heat index values used for issuing alerts by state and climate region. Our intent was to capture the most common range of heat index values used for issuing alerts within each state or climate region, knowing that heat alerts are specific to area served by the WFO and are seldom issued to cover large geographic areas.

Hospitalization Data. We accessed hospitalizations data for 22 states (Arizona, California, Colorado, Florida, Georgia, Iowa, Illinois, Indiana, Kansas, Kentucky, Maryland, Missouri, North Carolina, Nebraska, Nevada, New York, Oregon, Rhode Island, South Dakota, Utah, Virginia, and West Virginia) spread out across nine US climate regions (Central, East North Central, Northeast, Northwest, South, Southeast, Southwest, West, and West North Central) from the Agency for Health Research and Quality (AHRQ) Healthcare Cost Utilization Project (HCUP) (32) for the years 2003–2012. These are inpatient records for all patients visiting a hospital in these states. Fig. 4 provides a map summary of the states with hospitalization data and their relationship to climate regions; a description of these regions is available from the National Centers for Environmental Information (https://www.ncdc.noaa.gov/monitoring-references/maps/us-climate-regions.php). Using the Clinical Classification Software (CCS) developed by AHRQ (https://www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp), we selected daily patient records for all available diagnoses combined and for the following illnesses based on the principal or secondary diagnoses: cardiovascular (CCS: 98–101, 106–110, 115) (7, 33), respiratory-related (CCS: 122, 127–128) (6, 33, 34), diabetes (CCS: 49–50), renal failure (CCS: 157), and electrolyte imbalance (CCS: 55) (5, 34). We summarized the extracted patient records for these conditions for the summer months to obtain counts by county of residence and day.

Statistical Analysis. We conducted a two-stage analysis (35) to estimate E-R relationships for all-cause and cause-specific hospitalizations across states and climatic regions. The theory and development of methods for modeling overall E-R associations, conducting meta-analysis, and estimating attributable risk from distributed lag models are articulated in several research articles published in scientific journals (35–39). A succinct summary of various aspects of our statistical analyses is provided below.

Assessment of the E-R associations: County-level time-series analyses (first stage). The first stage involved a county-level time-series quasi-Poisson regression using a distributed lag nonlinear model for the summer months (May 1 through September 30) to estimate location-specific heat index–morbidity associations. This class of models can describe complex nonlinear and lagged dependencies through the combination of two functions specified in a cross-basis term of the exposure variable, defining both E-R association and the lag-response distribution (36).

The model formula is as follows:

$$\log(E(y_t)) = \alpha + s(x_{t,i};\boldsymbol{\theta}) + PM_{t,i} + Ozone_{t,i} + DOW_i + factor(year_i) + ns(DOY_i,\ df=4) + ns(date_i,\ df=2),$$

where $y_{t,i}$ is the number of hospitalizations in day t and county i. The cross-basis term of heat index $(s(x_{t,i};\boldsymbol{\theta}))$ is a bidimensional function s and coefficients $\boldsymbol{\theta}$ which defines an exposure-lag-response risk surface accounting for 2 d of lag. It included a natural cubic B-spline function with internal knots at 50th and 90th percentile of the county-specific heat index distribution in the E-R dimension and a strata function defining two levels in lag 0 and lag 1–2. This simplified the computational demands of our modeling approach and at the same time captured the main association and the potential harvesting. However, we considered modeling overall E-R associations by fitting a natural spline with two internal knots equally spaced on the log scale for various lag periods, ranging from 0 to 7 d. State-specific lag-response relationships between heat index and various health outcomes considered in this assessment are provided in *SI Appendix*, Figs. S4–S9. While the most appropriate cumulative lag period varied by state, a 2-d period seemed the most sensitive across most states and health outcomes. Perusing previously published literature (40–44) reiterated that a 2-d cumulative lag period for exploring delayed effects of heat exposure on hospitalizations was appropriate. The main model also included a linear function of daily 24-h average fine particulate matter concentration $(PM_{t,i})$, average 8-h ozone daily maximum concentration $(Ozone_{t,i})$, indicators for day of the week $(DOWi)$, indicator for year $(factor(year_i))$, natural cubic B-spline of the day of the year with four degrees of freedom to control for seasonality $(ns(DOY_i,\ df=4))$, and natural cubic B-spline of the time with two degrees of freedom for long-term trends $(ns(date_i,\ df=2))$. Each bidimensional function was reduced to unidimensional overall cumulative E-R curves, which were then used as input for the second-stage pooled analysis. We excluded counties with an average population of fewer than 10,000 people for the analysis period to avoid model convergence issues resulting from small sample size.

Assessment of the E-R associations: Pooled analyses to generate state- and county-level summaries (second stage). Our second stage involved a multivariate

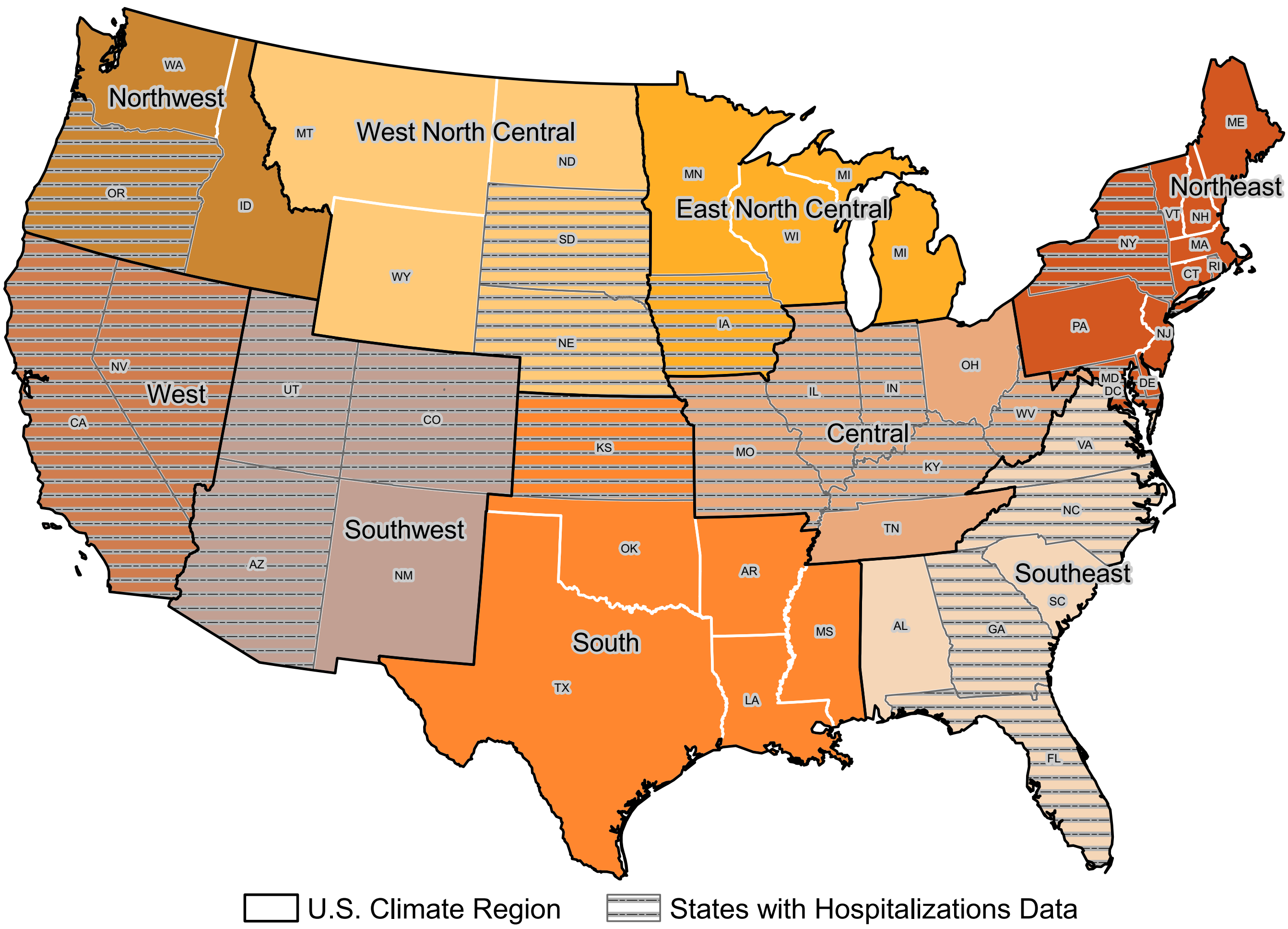

Fig. 4. States with hospitalization data and US climate regions.

random-effects meta-analysis (28, 29) to pool the county-specific unidimensional overall cumulative E-R associations generated in the first stage across larger geographic scales, such as by state or climate region. The meta-analytic model included a geographic scale factor (indicator for climate region or state) used for predicting E-R associations. We evaluated for residual heterogeneity in the meta-analytic model by examining the Cochran Q test results and I^2 statistic (37, 45). We then used the fitted meta-analytical model to derive the best linear unbiased prediction (BLUP) of the overall cumulative E-R association in each county (35). BLUP-based predictions allow sparsely populated areas, which are typically characterized by imprecise effect estimates, to borrow information from largely populated neighboring areas that share similar characteristics (36, 37). County-specific MMHI (46, 47), which corresponds to a minimum morbidity percentile between the 25th and the 75th percentiles of the summertime heat index distribution, was derived from the BLUPs of the overall cumulative E-R association in each location.

Estimation of the heat-attributable adverse health impacts. The MMHI was used as the reference point for estimating the number and fraction of hospitalizations attributable to heat (AN and AF). AN was calculated as the sum of all hospitalizations in days with heat index values higher than the estimated MMHI in a specific county. AF corresponded to the ratio of AN by the total number of hospitalizations (39). We calculated empirical confidence limits using Monte Carlo simulations (n = 2,000), assuming a multivariate normal distribution of the BLUP-based predictions. We also calculated ANs and AFs, by 5 °F increments in heat index for each hospitalization outcome considered in this assessment. Fig. 3 combines this attributable burden information with the heat index ranges used for issuing heat alerts. First, heat-sensitive zones were derived using region-specific heat-attributable burden information for all outcomes considered in this assessment and are denoted in Fig. 3 as horizontal bars shaded in a yellow (low burden) to red (high burden) color gradient. The operating range for this heat-sensitive zone is the heat index values over which the attributable burden is statistically significant. In addition, heat index ranges that are associated with peak burden were identified by red-checkered boxes. Finally, the heat index range used for issuing heat alerts (denoted by shaded gray areas) and median heat alert criteria (denoted by gray vertical bars) were juxtaposed with region-specific heat-sensitive zones.

All primary statistical analyses were performed with R software (version 3.0.3) using the packages dlnm and mvmeta. We used SAS v9.4 and ArcGIS 9.3 for descriptive analysis and for creating displays. The health datasets used in this analysis cannot be shared due to data privacy and security provisions for safeguarding medical information, which is covered by Health Insurance Portability and Accountability Act of 1996.

ACKNOWLEDGMENTS. We thank Dr. Dana Flanders, Dr. Josephine Malilay, Heather Strosnider, Dr. Fuyuen Yip, and other reviewers, both internal and external to authors' affiliated organizations, who provided insightful comments toward the improvement of this manuscript and acknowledge the support provided by the CDC's Office for Public Health Preparedness and Response and National Centers for Environmental Health for the project. This work would not have been possible without the data submitted by the following state data organizations that participate as HCUP State Inpatient Databases: Arizona Department of Health Services, California Office of Statewide Health Planning and Development, Colorado Hospital Association, Florida Agency for Health Care Administration, Georgia Hospital Association, Illinois Department of Public Health, Indiana Hospital Association, Iowa Hospital Association, Kansas Hospital Association, Kentucky Cabinet for Health and Family Services, Maryland Health Services Cost Review Commission, Missouri Hospital Industry Data Institute, Nebraska Hospital Association, Nevada Department of Health and Human Services, New York State Department of Health, North Carolina Department of Health and Human Services, Oregon Association of Hospitals and Health Systems, Oregon Office of Health Analytics, Rhode Island Department of Health, South Dakota

Association of Healthcare Organizations, Utah Department of Health, Virginia Health Information, West Virginia Department of Health and Human Resources, and West Virginia Health Care Authority. The findings and conclusions in this paper are those of the authors and do not necessarily represent the official position of the CDC and other organizations participating in this assessment.

1. Ye X, et al. (2012) Ambient temperature and morbidity: A review of epidemiological evidence. *Environ Health Perspect* 120:19–28.
2. Li M, Gu S, Bi P, Yang J, Liu Q (2015) Heat waves and morbidity: Current knowledge and further direction-a comprehensive literature review. *Int J Environ Res Public Health* 12:5256–5283.
3. Kovats RS, Hajat S (2008) Heat stress and public health: A critical review. *Annu Rev Public Health* 29:41–55.
4. Basu R, Pearson D, Malig B, Broadwin R, Green R (2012) The effect of high ambient temperature on emergency room visits. *Epidemiology* 23:813–820.
5. Knowlton K, et al. (2009) The 2006 California heat wave: Impacts on hospitalizations and emergency department visits. *Environ Health Perspect* 117:61–67.
6. Anderson GB, et al. (2013) Heat-related emergency hospitalizations for respiratory diseases in the Medicare population. *Am J Respir Crit Care Med* 187:1098–1103.
7. Schwartz J, Samet JM, Patz JA (2004) Hospital admissions for heart disease: The effects of temperature and humidity. *Epidemiology* 15:755–761.
8. Basu R, Samet JM (2002) Relation between elevated ambient temperature and mortality: A review of the epidemiologic evidence. *Epidemiol Rev* 24:190–202.
9. McGregor GR, Bessemoulin P, Ebi K, Menne B (2015) *Heatwaves and Health: Guidance on Warning-System Development* (World Meteorological Organization, Geneva).
10. Toloo GS, Fitzgerald G, Aitken P, Verrall K, Tong S (2013) Are heat warning systems effective? *Environ Health* 12:27.
11. Metzger KB, Ito K, Matte TD (2010) Summer heat and mortality in New York City: How hot is too hot? *Environ Health Perspect* 118:80–86.
12. Hawkins MD, Brown V, Ferrell J (2017) Assessment of NOAA national weather service methods to warn for extreme heat events. *Weather Clim Soc* 9:5–13.
13. Hess JJ, Ebi KL (2016) Iterative management of heat early warning systems in a changing climate. *Ann N Y Acad Sci* 1382:21–30.
14. Petitti DB, Hondula DM, Yang S, Harlan SL, Chowell G (2016) Multiple trigger points for quantifying heat-health impacts: New evidence from a hot climate. *Environ Health Perspect* 124:176–183.
15. Chen T, Sarnat SE, Grundstein AJ, Winquist A, Chang HH (2017) Time-series analysis of heat waves and emergency department visits in Atlanta, 1993 to 2012. *Environ Health Perspect* 125:057009.
16. Hess JJ, Saha S, Luber G (2014) Summertime acute heat illness in U.S. emergency departments from 2006 through 2010: Analysis of a nationally representative sample. *Environ Health Perspect* 122:1209–1215.
17. Noe RS, Jin JO, Wolkin AF (2012) Exposure to natural cold and heat: Hypothermia and hyperthermia Medicare claims, United States, 2004-2005. *Am J Public Health* 102: e11–e18.
18. Saha S, Brock JW, Vaidyanathan A, Easterling DR, Luber G (2015) Spatial variation in hyperthermia emergency department visits among those with employer-based insurance in the United States–A case-crossover analysis. *Environ Health* 14:20.
19. Ho HC, Knudby A, Walker BB, Henderson SB (2017) Delineation of spatial variability in the temperature–mortality relationship on extremely hot days in greater Vancouver, Canada. *Environ Health Perspect* 125:66–75.
20. Anderson GB, Bell ML, Peng RD (2013) Methods to calculate the heat index as an exposure metric in environmental health research. *Environ Health Perspect* 121: 1111–1119.
21. Karl T, Koss WJ (1984) Regional and national monthly, seasonal, and annual temperature weighted by area, 1895-1983 (National Climatic Data Center, Asheville, NC).
22. Wellenius GA, et al. (2017) Heat-related morbidity and mortality in New England: Evidence for local policy. *Environ Res* 156:845–853.
23. Environmental Protection Agency (2016) AirNow: Air quality index (AQI) basics. Available at https://airnow.gov/index.cfm?action=aqibasics.aqi. Accessed August 15, 2017.
24. Foster H (2013) Interactive hazard preparation strategy efficacy: Considerations for future community engagement programs. *Aust J Emerg Manage* 28:10–16.
25. Centers for Disease Control and Prevention (2017) Keep your cool in hot weather! Available at https://www.cdc.gov/features/extremeheat/index.html. Accessed August 15, 2017.
26. Toloo G, FitzGerald G, Aitken P, Verrall K, Tong S (2013) Evaluating the effectiveness of heat warning systems: Systematic review of epidemiological evidence. *Int J Public Health* 58:667–681.
27. Flanders WD, et al. (2011) A method for detection of residual confounding in time-series and other observational studies. *Epidemiology* 22:59–67.
28. Davis RE, Knappenberger PC, Michaels PJ, Novicoff WM (2003) Changing heat-related mortality in the United States. *Environ Health Perspect* 111:1712–1718.
29. Choudhary E, Vaidyanathan A (2014) Heat stress illness hospitalizations–Environmental public health tracking program, 20 States, 2001-2010. *MMWR Surveill Summ* 63:1–10.
30. Mitchell KE, et al. (2004) The multi-institution North American Land Data Assimilation System (NLDAS): Utilizing multiple GCIP products and partners in a continental distributed hydrological modeling system. *J Geophys Res* 109:D07S90.
31. Rothfusz LP (1990) The heat index "equation" (or, more than you ever wanted to know about heat index). National Weather Service Technical Attachment SR 90–23 (National Weather Service, Ft. Worth, TX).
32. Agency for Healthcare Research and Quality (2017) Healthcare Cost and Utilization Project (HCUP) (Agency for Healthcare Research and Quality, Rockville, MD).
33. Lin S, et al. (2009) Extreme high temperatures and hospital admissions for respiratory and cardiovascular diseases. *Epidemiology* 20:738–746.
34. Green RS, et al. (2010) The effect of temperature on hospital admissions in nine California counties. *Int J Public Health* 55:113–121.
35. Gasparrini A, et al. (2015) Mortality risk attributable to high and low ambient temperature: A multicountry observational study. *Lancet* 386:369–375.
36. Gasparrini A (2014) Modeling exposure-lag-response associations with distributed lag non-linear models. *Stat Med* 33:881–899.
37. Gasparrini A, Armstrong B, Kenward MG (2012) Multivariate meta-analysis for non-linear and other multi-parameter associations. *Stat Med* 31:3821–3839.
38. Gasparrini A, Armstrong B (2013) Reducing and meta-analysing estimates from distributed lag non-linear models. *BMC Med Res Methodol* 13:1.
39. Gasparrini A, Leone M (2014) Attributable risk from distributed lag models. *BMC Med Res Methodol* 14:55.
40. Hajat S, et al. (2006) Impact of high temperatures on mortality: Is there an added heat wave effect? *Epidemiology* 17:632–638.
41. Bunker A, et al. (2016) Effects of air temperature on climate-sensitive mortality and morbidity outcomes in the elderly; a systematic review and meta-analysis of epidemiological evidence. *EBioMedicine* 6:258–268.
42. Guo Y, Punnasiri K, Tong S (2012) Effects of temperature on mortality in Chiang Mai city, Thailand: A time series study. *Environ Health* 11:36.
43. Lam HC, Li AM, Chan EY, Goggins WB, 3rd (2016) The short-term association between asthma hospitalisations, ambient temperature, other meteorological factors and air pollutants in Hong Kong: A time-series study. *Thorax* 71:1097–1109.
44. Phung D, et al. (2016) High temperature and risk of hospitalizations, and effect modifying potential of socio-economic conditions: A multi-province study in the tropical Mekong Delta Region. *Environ Int* 92–93:77–86.
45. Higgins JP, Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. *Stat Med* 21:1539–1558.
46. Curriero FC, et al. (2002) Temperature and mortality in 11 cities of the eastern United States. *Am J Epidemiol* 155:80–87.
47. Armstrong B (2006) Models for the relationship between ambient temperature and daily mortality. *Epidemiology* 17:624–631.