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CLINICAL RESEARCH

Elevated Ambient Temperature Associated With Increased Cardiovascular Disease–Risk Among Patients on Hemodialysis

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Introduction: In many parts of the world, ambient temperatures have increased due to climate change. Due to loss of renal function, which impacts the regulation of thermoregulatory mechanisms, the ability to adapt and to be resilient to changing conditions is particularly concerning among individuals with kidney failure. The aim of this study was to assess the effect of heat on mortality and health care utilization among US patients on hemodialysis.

Methods: We conducted a retrospective analysis from 2011 to 2016 in the contiguous United States during warmer months among eligible patients on dialysis who were identified in the United States Renal Data System (USRDS). Daily ambient temperature was estimated on a 1 km grid and assigned to ZIP-code. Case-crossover design with conditional Poisson models were used to assess the risk of developing adverse health outcomes associated with temperature exposure.

Results: Overall, exposure to high temperature is associated with elevated risk for both mortality and health care utilization among hemodialysis patients. The risk ratios for all-cause mortality and daily temperature were 1.07 (95% confidence interval [CI]: 1.03–1.11), 1.17 (1.14–1.21) for fluid disorder-related hospital admissions, and 1.19 (1.16–1.22) for cardiovascular event-related emergency department (ED) visits, comparing 99th percentile versus 50th percentile daily temperatures. Larger effects were observed for cumulative lagged exposure 3 days prior to the outcome and for Southwest and Northwest climate regions.

Conclusion: Heat exposure is associated with elevated risk for cardiovascular disease (CVD)–related mortality and health care utilization among this vulnerable population. Furthermore, the effect appears to be potentially cumulative in the short-term and varies geographically.

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In the past decade, there have been rising average seasonal temperatures and an increased frequency of extreme heat events. Studies have demonstrated that exposure to high temperatures can increase mortality and morbidity among frail populations, including the elderly and those with chronic health conditions.[1–4] The effects may be mediated through several mechanisms, including dehydration, exacerbation of underlying health conditions, and heat-related illness.[5–7]

Patients receiving maintenance hemodialysis are a vulnerable population with a high burden of disease.[8] Although there is a growing literature on the impact of air pollution in this population,[9–15] limited data are available on the impact of heat and extreme heat events.[16,17] In a regional study of patients receiving maintenance hemodialysis at urban clinics from a single large dialysis organization, extreme heat events were associated with an increased risk of hospitalizations

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and mortality in northeastern United States.[17] A second, related study using the same cohort suggested effect modification of extreme heat events by ozone levels.[16] Nationally representative data inclusive of rural areas, and of other regions of the country with more severe temperature fluctuation, are currently lacking.[18,19]

To address this knowledge gap, we examined the effect of heat on morbidity and mortality among patients receiving maintenance hemodialysis throughout the United States. We hypothesized that exposure to extreme heat would increase the risk of adverse health outcomes in this population. Understanding the potential impact of heat may help inform public health strategies to reduce risk for these vulnerable patients.

METHODS

To study the association between heat and adverse health outcomes, an open cohort of patients with end-stage kidney disease who are receiving in-center hemodialysis between 2011 and 2016 was identified using data from the USRDS. Study inclusion criteria were as follows: subjects (i) with Medicare as the primary payer, (ii) whose time on dialysis exceeded 3 months (to assure Medicare coverage stability), and (iii) who received maintenance in-center hemodialysis treatment. To better assess the elevated temperature effect, the analysis period was restricted to the warmer months (May through October) during the study period.

Exposure Assessment

In this study, we focused on assessing the effect of the daily average temperature. Daily maximum and minimum temperatures at 1 km resolution were obtained from Daymet Version 4,[20] which has been widely used in epidemiological studies assessing health outcomes associated with temperature.[21-23] Daymet temperature product is modeled utilizing the surface observations from the Global Historical Climatology Network, and Daymet ambient temperature has been validated to be accurate estimations at weather stations.[24-26] Grid cells within the contiguous United States boundary were identified for the restriction of available calculation power to process for Hawaii, Alaska and Puerto Rico. Gridded average temperature was calculated as the mean value of minimum and maximum temperature (by National Oceanic and Atmospheric Administration definition for daily average temperature) at 1 km grid cell, and ZIP code temperature is the average of temperature measurements of grid cells that falls within the specific ZIP code for each given day during study period.

Outcome Assessment

The outcome of interests included all-cause and cause-specific morbidity (hospital admission and ED visits) and mortality. Diagnostic codes (ICD-9 and ICD-10) associated with each hospital admission and ED visit records were used to categorize each outcome into cause-specific groupings of CVD (overall), dysrhythmia or conduction disorder, fluid and electrolyte disorders, and heart failure events. For hospital admissions, the primary, secondary, and tertiary discharge codes were used to classify events into cause-specific categories. For ED visits, all codes recorded were used because the information on primary versus nonprimary codes was not available. Detailed list of outcomes and associated diagnostic codes are listed in Supplementary Table S1. Counts of daily outcomes were aggregated to ZIP-code level based on the ZIP-code of the dialysis clinic last visited before each outcome occurred, and this approach took potential location changes into account. Daily ZIP-code level temperature was linked to outcome based on the ZIP code.

Statistical Analysis

We conducted a time-stratified case-crossover study with conditional Poisson regression to estimate associations between daily health outcome counts and elevated temperature at the ZIP code level. Conditional-Poisson regression models have been widely used in environmental epidemiology, notably in investigating the short-term effect of exposure such as weather variables or air pollution on health outcomes such as mortality or health care utilization.[27,28] The primary analysis focused on the associations between same-day temperatures and health outcome counts, modeled using natural cubic spline with 5 degrees of freedom (4 equidistant interior knots). Short-term lagged effects were also assessed using distributed lag nonlinear models to estimate the cumulative effect of temperature up to 3 days earlier. To control the plausible temporal trends and the regional differences, we performed the analysis by strata defined by day of week, month, year and core-based statistical areas. In addition, we adjusted for daily relative-humidity for its potential confounding effect. A case-crossover design eliminates the need to adjust for individual level time-invariant confounders, including age, sex (self-reported sex categories), race or ethnicity, and socioeconomic status. To describe the strength of nonlinear association between adverse health event counts and temperature, we reported risk ratios based on 2 sets of contrast: 95th versus the 50th percentile, and 99th versus the 50th percentile of the study area temperature during the study period.

We tested for effect modification by climate regions. Climate regions were designated based on National Oceanic and Atmospheric Administration classification (Supplementary Table S2). Contiguous United States is divided into 9 geographic regions, which are clusters based on climate patterns (Supplementary Table S2).

Sensitivity Analysis

To assess the potential effects of different outcome classification methods on the effect estimates, we performed sensitivity analysis on cause-specific hospital admission using 3 different approaches of specifying cause-specific event as follows: (i) with primary diagnostic code only; (ii) with primary, secondary, and tertiary codes; (iii) with all recorded diagnostic codes. The 3 methods generated similar effect estimates with overlapping Cis, the primary code-only method tended to generate the highest estimates, and the all-code methods generate the lowest estimates. In addition, we performed negative control tests by randomizing exposure by ZIP code and date to assure the model is robust by obtaining null effect with randomized exposure variable.

Table 1. Study population baseline characteristics

Characteristics	*n* (%)
N	670,491
Female	287,914 (42.9)
Age at baseline (yr), mean (SD)	61.6 (14.8)
Age at baseline categories, yr	
18–44	90,666 (13.5)
45–64	177,992 (41.5)
65–74	160,365 (23.9)
75 and older	141,468 (21.1)
Race and ethnicity	
American Indian/Alaskan Native	8937 (1.3)
Asian	22,345 (3.3)
Black	221,848 (33.1)
Hispanic	93,745 (14.0)
Pacific Islander	6483 (1.0)
White	309,778 (46.2)
Other	7355 (1.1)
Primary reason for kidney failure	
Diabetes	312,437 (46.6)
Hypertension	198,161 (29.6)
Glomerulonephritis	62,566 (9.3)
Baseline comorbid conditions	
Cardiovascular disease	326,559 (48.7)
Diabetes	373,283 (55.7)
Chronic obstructive pulmonary disease	53,092 (7.9)

RESULTS

A total of 670,491 patients with kidney failure who received maintenance hemodialysis were identified from the USRDS database for the contiguous United States during 2011 to 2016. Among those, 42.9% were female (defined using self-reported sex), 57.1% were male, 46.2% were White, 33.1% were Black, and approximately 45% were 65 years or older when they initiated dialysis. Diabetes was reported to be the primary reason for kidney failure (Table 1). At baseline, about half of the patients reported to have cardiovascular conditions, and more than half reported to have diabetes as a comorbidity in addition to the cause of kidney failure.

During the warmer months of 2011 to 2016, the median average daily ZIP-code level temperature was 22.3 °C (mean = 21.5 °C, interquartile range: 17.8–25.9 °C, 95th percentile = 29.5 °C, 99th percentile = 32.3 °C) (Figure 1). During the study period, a total of 142,215 mortality events, 1,177,170 hospital admissions, and 2,236,926 ED visits were identified and incorporated into the analysis (Table 2). Among those, 306,981 hospital admissions and 298,543 ED visits were identified as cardiovascular events (Table 2).

Positive associations of same-day effects of average daily temperature on adverse health outcomes were observed (Figure 2a). The risk ratio for all-cause mortality and daily temperature associated with the exposure on the same day was 1.05 (95% CI: 1.03–1.08) comparing the 95th to the 50th percentiles, and 1.07 (1.03–1.11) comparing the 99th and 50th percentiles. The effect of temperature on ED visits was higher than on hospitalizations or mortality events. For hospital admission, the highest risk ratio was observed for electrolyte and fluid disorders with risk ratio of 1.17 (1.14–1.21) for the same-day exposure comparing 99th and 50th percentiles. For ED visits, the highest risk ratio was observed for all-cause cardiovascular events with risk ratio of 1.19 (1.16–1.22). Lagged cumulative effects of temperature up to 3 days earlier is presented in Figure 2b. Higher effect estimates were observed for lagged cumulative effect compared to the same-day effects. Additional analysis using daily maximum and minimum temperature have been performed (Supplementary Figures S1–S4). Similar effects have been observed for daily maximum temperature and minimum temperature compared to the effects for daily average temperature. Overall, consistent positive associations were observed between ambient temperature and mortality and health care service utilizations among patients on hemodialysis. In Figure 3, we present the lagged cumulative effects of temperature by climate region with region-specific contrast temperatures specified. Among the 9 climate regions, the southwest and northwest tended to experience greater effect estimates for all outcomes assessed. The southeast and south regions tended to experience relatively lower effect estimates compared to other climate regions.

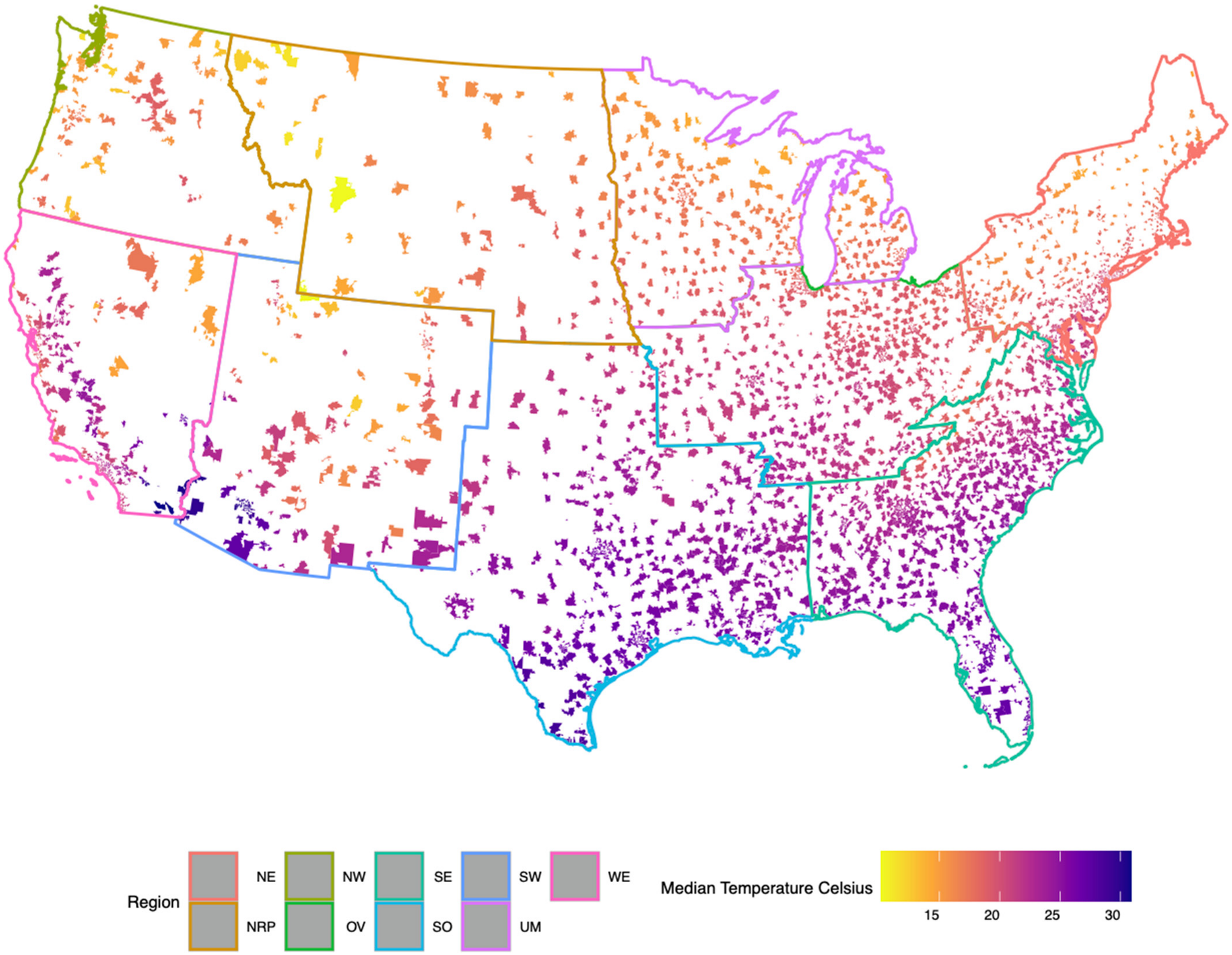

Figure 1. ZIP-code level warmer months (May–October) average daily temperature of the contiguous United States 2011–2016. NE, northeast; NRP, Northern Rockies and Plains; NW, northwest; OV, Ohio Valley; SE, southeast; SO, south; SW, southwest; UM, Upper Midwest; WE, west.

DISCUSSION

This analysis of over 670,000 adults with end-stage kidney disease undergoing maintenance hemodialysis from 2011 to 2016 throughout the US demonstrated significant associations between environmental heat exposure and CVD exacerbation and mortality. Health care utilization, including ED visits and hospitalizations, for all-cause visits and a range of cardiovascular conditions, demonstrated a significant relationship with heat exposure. The findings of the analysis consistently demonstrated an exposure-dependent response, with 95th percentile temperature demonstrating an increased risk compared to the 50th percentile, and an even higher risk with 99th percentile temperature days compared to the 50th percentile.

The greatest relative risk of ED visits was observed for all-cause conditions and all-cause cardiovascular conditions. For hospitalizations, the greatest risk observed was for fluid and electrolyte derangements. Mortality risk was also increased with heat exposure and extreme heat exposure, with a similar exposure-dependent response, among same-day and lagged accumulated heat effect.

Regional variability was observed in mortality risk and health care utilization. In the southwest, northwest, and northeast regions, statistically significant increases in mortality with heat and extreme heat exposure were demonstrated. An increased risk of ED

Table 2. Counts of mortality, hospital admission, and emergency department visits among patients on hemodialysis from May through October in the contiguous United States, 2011–2016

Causes	Mortality	Hospital admission	Emergency department visit
All-cause	142,215	1,177,170	2,236,926
Cardiovascular disease	–	306,981	298,543
Dysrhythmia/conduction diseases	–	48,226	252,560
Heart failure	–	130,121	266,066
Fluid electrolytes disorder	–	202,372	328,689

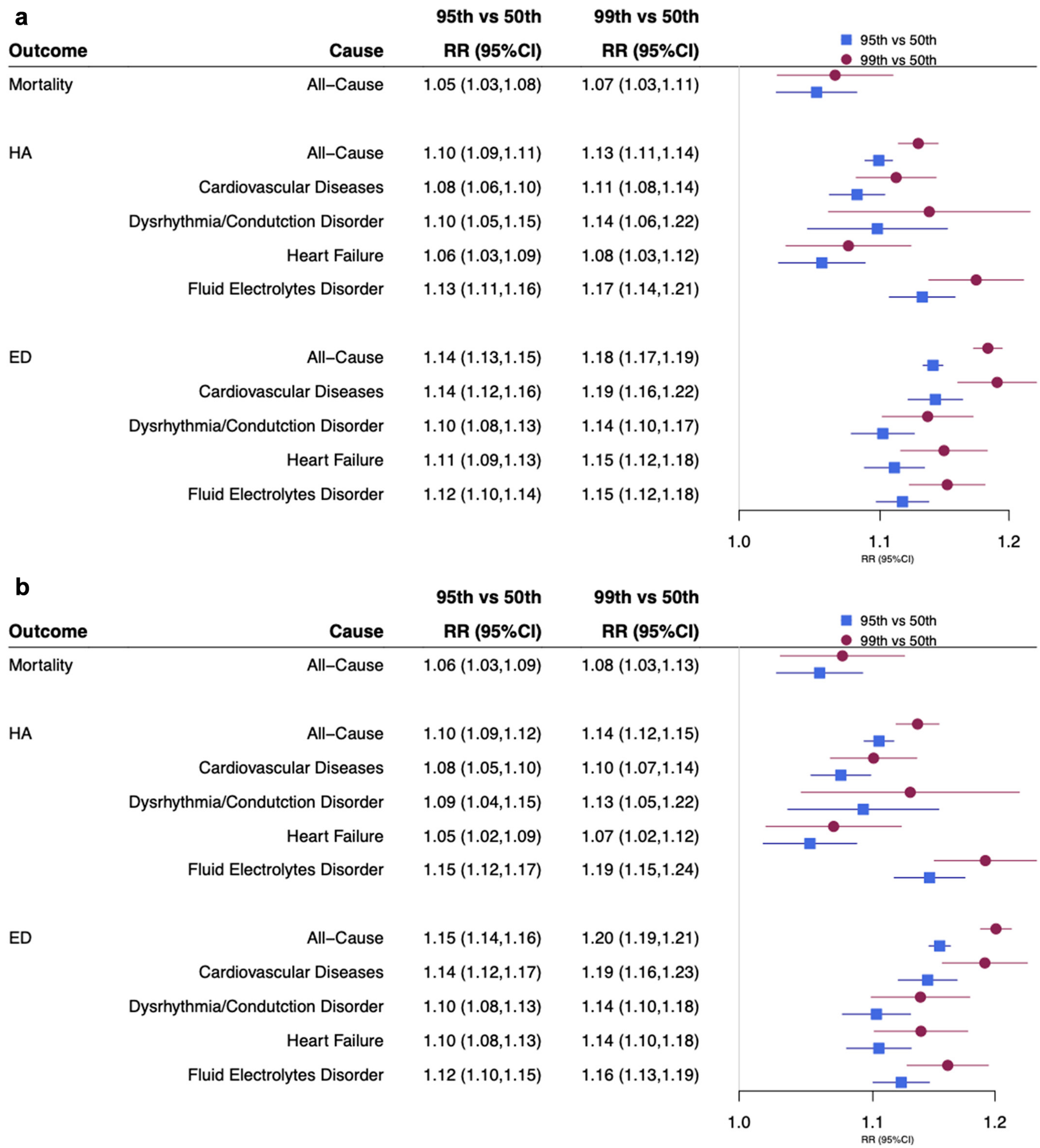

Figure 2. Effect (risk ratios [RR] and 95% confidence interval [CI]) of exposure to daily ambient temperature on mortality and health care utilization among patients on hemodialysis in the contiguous United States 2011–2016. a) Same-day effect, b) lagged cumulative effect. ED, emergency department visit; HA, hospital admission.

visits and hospitalizations related to heat exposure with an exposure-dependent response observed was demonstrated in nearly all regions. Mortality risk was significant only in 2 regions, and that could be due to the following reasons. In interpreting results, we considered 2 factors; the precision of the effect estimate (how wide the CI is) and magnitude of the effect estimate itself (how high or low the effect estimate is). The precision of effect estimates is restricted by sample size (event number). Mortality is the event type with the least counts in the analysis at the national level, and when doing region specific analysis, the total number

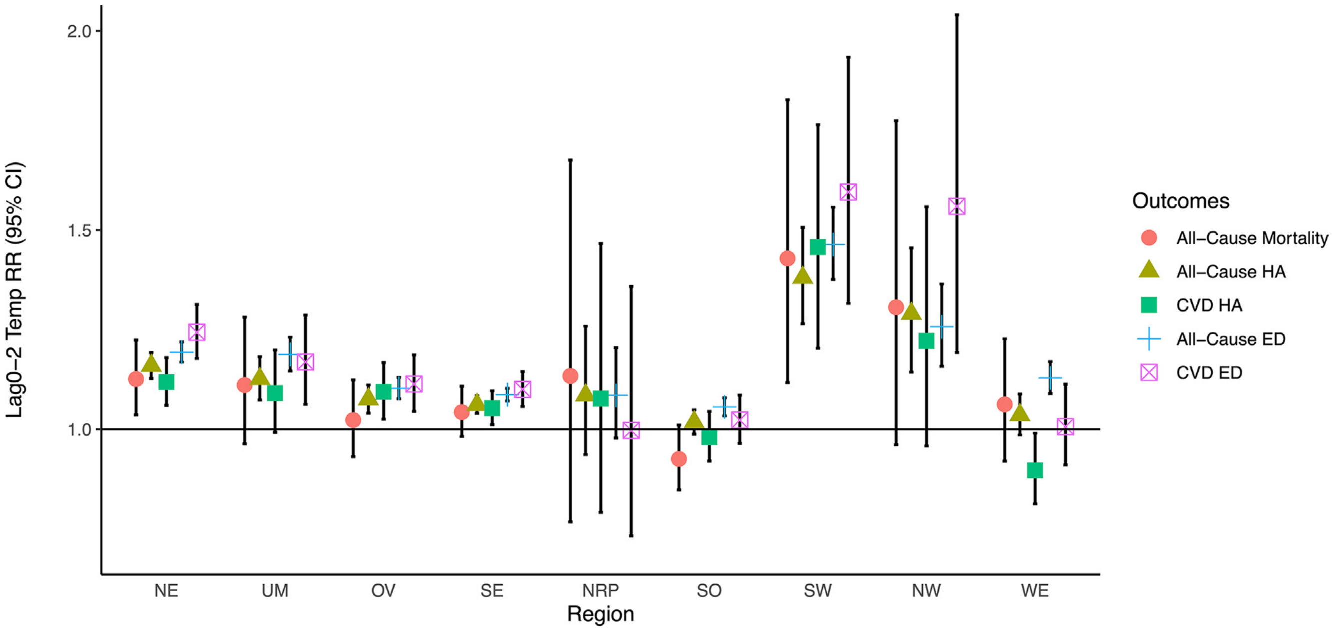

Figure 3. Lagged cumulative effect (risk ratio and 95% confidence interval for 99th vs. 50th comparison) of daily average temperature on mortality and health care utilization among patients on hemodialysis in the contiguous United States 2011–2016 by climate regions. CVD, cardiovascular disease; ED, emergency department visit; HA, hospital admission; NE, northeast; NRP, Northern Rockies and Plains; NW, northwest; OV, Ohio Valley; SE, southeast; SO, south; SW, southwest; UM, Upper Midwest; WE, west.

of mortality cases was accordingly divided into smaller values. Thus, the mortality effect estimate in a region with larger population size, such as the northeast, is of the narrower CI. In addition, temperature could have various impacts in different regions due to other factors related to vulnerability, including accessibility to care, quality of care, and air condition availability; thus, regions with higher vulnerability, such as the southwest, could experience disproportionate burden resulting from heat exposure. Furthermore, effects of environmental exposures such as temperature and air pollution tend to be relatively smaller in magnitude for mortality than the effect on health care utilization events. This is likely due to the harvesting effect that patients develop conditions that result in health care utilizations which reduce the risk of dying. Thus, in general, we would expect the mortality effect to be smaller in magnitude, which will lead to insignificant effect estimates with lower 95th CI below null.

A range of biological mechanisms have been discussed in the literature with respect to heat exposure impacts on kidney function, as well as the development of heat-related illness, and exacerbation of other chronic disease.[29] The spectrum of heat related illnesses includes mild disease such as heat cramps, edema and syncope; moderate disease such as heat exhaustion; and at the most severe end, heat stroke.[30]

The natural physiological processes to handle heat exposure include radiation, convection, and evaporative cooling, which are maintained until the most extreme end of the spectrum, in which thermoregulatory mechanisms fail to maintain homeostasis and heat illness ensues.[29] All along this spectrum, dehydration and electrolyte changes may occur, but on the extreme end, critical protein denaturation, systemic inflammatory response, changes in sympathetic tone, changes in peripheral blood flow, and oxidative stress may result.[31] These pathways can cause clinically significant disease, particularly among individuals with preexisting conditions that increase their susceptibility to changes in circulating volume, electrolytes, inflammation, and sympathetic tone, especially those with renal disease dependent upon dialysis.[32]

Clinical outcomes beyond the spectrum of heat illness can occur, considering these mechanisms. Heat-related exacerbation of CVD, respiratory disease, and renal injury have been extensively documented and observed days to weeks after heat exposure.[29] In dialysis-dependent patients, dehydration and electrolyte changes may be exacerbated with heat exposure, particularly because their experience and education with kidney failure has resulted in caution with excess fluid or electrolyte intake. Those with preexisting CVD, such as congestive heart failure, may be more susceptible to rapid volume changes and even more considerate of their volume and salt intake. Although adequate hydration is essential to avoiding volume depletion during heat exposure, overhydration or intake of salt-rich and sugar-rich beverages can be detrimental.[33] Ingestion of salt and sugar with inadequate water may result in a hyperosmolar state, with subsequent vasopressin release and hypertension, resulting in volume retention and weight gain and contributing to heart failure exacerbation. Patients receiving maintenance hemodialysis are known to have an enhanced sensitivity to aldosterone, causing increased plasma volume for the same level of aldosterone compared to healthy individuals.[34]

Multiple classes of medications, such as diuretics and psychotropic medications as well as alcohol and substance use, can further contribute to thermoregulatory system impairment.[29] Older adults, who are at increased risk of kidney failure, have impaired thermoregulatory response and compromised vasomotor tone, which in light of heat-related impacts on volume status and vasomotor tone, may be more vulnerable to clinical outcomes.[35] In addition, those with unstable housing or lower socioeconomic status may live in an environment less insulated against heat or have other protective measures such as air conditioning, which could contribute to the regional effect differences observed in this study.

The findings here of increased health care utilization for cardiovascular conditions, including arrhythmia and heart failure, as well as electrolyte derangements, could be explained by these mechanisms of impaired thermoregulation, changes in circulating volume and electrolytes, and sympathetic tone changes with heat exposure. An exposure-response relationship was observed, which from a physiological standpoint can be explained with increased heat exposure resulting in greater evaporative losses and electrolyte changes.

In this analysis, longer lags beyond 3 days demonstrated a null effect, which may indicate that dialysis, which corrects for the derangements in electrolytes and circulating volume, may be a protective factor, whether from volume and electrolyte corrections or from being in a cooled environment for hours and permitting core temperature normalization.

Acclimatization plays a critical role in protecting against heat-related illness and other consequences of heat exposure. Individuals living in regions with higher environmental heat exposure can adapt their thermoregulatory response to heat exposure whereas other regions less adapted physiologically, or environmentally, may be more prone to illness. In this analysis, the regional variability in health care utilization and mortality was notable. In regions with less typical exposure to extreme heat and less common air conditioning exposure, such as the northwest, a greater risk of health care utilization and mortality were demonstrated, as compared to regions more typically exposed to environmental heat such as the south and southeast.

Previous studies have reported on health effects related to exposure to elevated temperature. Similar to our findings, previous studies among the general population have reported positive association between heat exposure and health outcomes.[25] A recent investigation of ambient heat exposure and hospital utilization and mortality among patients on maintenance hemodialysis evaluated potential mediators for morbidity, including interdialytic weight gain and predialysis blood pressure.[16] The authors found that exposure to ambient heat was associated with reduced blood pressure and interdialytic weight gain, and with increased the risk of hospital admission and mortality. These findings are consistent with our findings in this analysis and the proposed mechanism by which heat exposure and associated dehydration and electrolyte losses contribute to additional outcomes, such as arrythmia.

This study has several strengths. The USRDS registry is broadly representative of patients receiving maintenance hemodialysis across the US, and ours is the first national study on the effect of elevated temperature on this patient population. In addition, the information on the last dialysis clinic visited before each outcome extracted from the USRDS claims enables us to map the exposure to each outcome accurately. Previous studies have shown that US patients on hemodialysis reside close to their dialysis clinics with average distances of 6.1 to 7.9 miles, which indicates that ZIP-code level exposure assigned on the basis of clinic address is a valid surrogate.[36,37] In addition, Daymet temperature product with full coverage and high temporal and spatial resolution grants the quality of exposure classification. Daymet measurements allowed us to perform the analysis at the ZIP-code level, which is the finest geographic unit information available for this specific study population. Furthermore, the case-crossover study design enables us to control for individual-level time-invariant factors such as age, sex, socioeconomic status, and race by design with the individuals in the risk set acting as their own control.

Despite the strengths, these findings should be considered in the context of the following limitations. First, exposure misclassification is always a concern in studies of environmental exposures because the individual level of exposure is not known. The assumption is made that the ambient temperature is similar across patients living in the same ZIP-code area and that the degree of exposure misclassification does not vary simultaneously with daily variation in the outcomes and heat exposure. Second, although Daymet is a well-established meteorology dataset, it is also reported to underestimate urban heat island effect on apparent temperature, which likely led to conservative effect estimates in our study.[25] Future studies should incorporate additional temperature measurements to better understand the health effect of heat, including the urban heat island effects. Finally, we did not control ambient air pollution in our analysis. However, ambient air pollutants such as ozone or matter are likely to be the potential effect modifiers of the association studied, rather than potential confounders, because air pollutant concentrations are not likely to have an impact on the ambient temperature. Furthermore, in our previous studies on the health effect of air pollution among patients on dialysis, we observed independent temperature effect and null ozone effect on health outcomes as other's studies.[25]

Climate change is increasing the risk of extreme heat events throughout the US and posing a threat to health, particularly among vulnerable populations, such as those on maintenance hemodialysis.[29] Early identification and warning systems for heat exposure are important tools at the community level to increase preparedness. Methods for preparation include education regarding the risks of heat exposure and methods for protection, such as hydration and electrolyte repletion, cooling, and behavioral changes to reduce endogenous heat production and exogenous heat exposure.[30]

Clinicians play an important role in communicating risks with patients and especially among patients with end-stage kidney disease, with whom messaging regarding fluid intake and electrolytes is essential. This may be a challenging but important moment to educate patients and families on the importance of cautious fluid monitoring during heat events. Reviewing early signs of heat illness are important, because interventions in the early stages of heat illness are reversible and less critical than later stages and severe disease.

CONCLUSION

The impact of heat exposure on health is significant, particularly among patients with kidney failure on maintenance hemodialysis. The findings of this analysis contribute to our understanding of the burden of CVD-related morbidity and mortality with increased heat exposure. Further characterization of the burden of disease is warranted, particularly with respect to dialysis treatment regimen adjustment to limit cardiovascular and electrolyte complications. Nevertheless, these findings can inform discussions with patients and families about health risks of heat exposure and methods for prevention and planning at the individual, health care, and community levels.

DISCLOSURE

All the authors declared no competing interests.

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The data reported here have been supplied by the USRDS. The interpretation and reporting of these data are the responsibility of the authors(s) and in no way should be seen as an official policy or interpretation of the United States government. The views expressed in the manuscript do not necessarily reflect the views or policies of the United States Environmental Protection Agency.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Effect (risk ratios [RR] and 95% confidence interval) of exposure to daily maximum ambient temperature on mortality and health care utilization among patients on hemodialysis in the contiguous United States from 2011 to 2016. a) Same-day effect, b) lagged cumulative effect.

Figure S2. Effect (risk ratios [RR] and 95% confidence interval) of exposure to daily minimum ambient temperature on mortality and health care utilization among patients on hemodialysis in the contiguous United States from 2011 to 2016. a) Same-day effect, b) lagged cumulative effect.

Figure S3. Lagged cumulative effect (risk ratio [RR] and 95% confidence interval) of daily maximum temperature on mortality and health care utilization among patients on hemodialysis in the contiguous United States from 2011 to 2016 by climate regions.

Figure S4. Lagged cumulative effect (risk ratio [RR] and 95% confidence interval) of daily minimum temperature on mortality and health care utilization among patients on hemodialysis in the contiguous United States from 2011 to 2016 by climate regions.

Table S1. ICD-9 and ICD-10 codes used for classifying health outcomes.

Table S2. Climate region designation.

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