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Short-term exposures to temperature and risk of sudden cardiac death in women

A case-crossover analysis in the Nurses' Health Study

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Background: Sudden cardiac death (SCD) is a major source of mortality and is the first manifestation of heart disease for most cases. Thus, there is a definite need to identify risk factors for SCD that can be modified on the population level. Short-term exposures to temperature have been implicated as a potential risk factor. Our objective was to determine if short-term temperature exposures were associated with increased risk of SCD in a US-based time-stratified case-crossover study.

Methods: A total of 465 cases of SCD were identified among participants of the prospective Nurses' Health Study (NHS). Control days were selected from all other matching days of the week within the same month as the case day. Average ambient temperature on the current day (Lag_0) and preceding 27 days ($Lags_{1–27}$) was determined at the residence level using 800-m resolution estimates. Conditional logistic distributed lag nonlinear models (DLNMs) were used to assess the relative risk (RR) of the full range of temperature exposures over the lag period.

Results: Warmer exposures in the days before event and colder temperatures 21–28 days prior were associated with increased risks of SCD. These results were driven by associations in regions other than the Northeast and among married women.

Conclusions: Both warm and cold ambient temperatures are suggestively associated with risks of SCD among middle-aged and older women living across the United States.

Keywords: Sudden cardiac death; Mortality; Heart disease; Risk factors

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The data used in our analyses are not publicly available due to privacy reasons. Researchers interested in obtaining access to the Nurses' Health Study (NHS) data and computing code should submit an external collaborator form (https://nurseshealthstudy.org/researchers).

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Introduction

Sudden cardiac death (SCD) accounts for approximately 180,000–400,000 deaths in the United States each year.[1–3] The lifetime risk of SCD has been estimated to be 10.9% among men and 2.8% among women, although lifestyle factors (e.g., blood pressure) only explain some of this risk.[4] Therefore, there is a need to identify risk factors that can be modified on a population level to broadly impact SCD risk.

Seasonal patterns in cardiovascular incidence and mortality have been observed in countries around the world,[5,6] with consistently higher disease incidence in winter months.[7,8] Although many studies have observed this pattern for SCD as well,[7–10] some studies have observed higher incidence of SCD in the summer.[9,11–16] Exposures to extreme temperatures have also been associated with increased odds of SCD or out-of-hospital cardiac arrest (OHCA) in multiple study settings.[7,8,16–44] Less is known, however, on the impact of more moderate temperatures on SCD or on associations in United States populations.[13,45] Our objective was to examine the association between short-term temperature and changes in temperature with risks of SCD in women living throughout the United States. We also wanted to examine these associations among subpopulations (defined by region, season, and marital status [as a measure of socioeconomic status]).

What this study adds

This study adds to a growing body of literature that short-term temperatures are a population-level risk factor for sudden cardiac death (SCD). It adds to the limited body of evidence on the impacts of nonextreme temperatures on SCD and suggests that both warm and cold temperatures are associated with an increasing risk of SCD.

Methods

Study population

The Nurses' Health Study (NHS) is a prospective cohort study that began in 1976 with 121,701 married female registered nurses, 30–55 years of age, who each completed a mailed questionnaire. At the study inception, the nurses resided in 11 states (CA, CT, FL, MA, MD, MI, NJ, NY, OH, PA, and TX); however, due to residential mobility, there are now at least 10 cohort members in all 50 states and the District of Columbia. Follow-up questionnaires, with response rates above 90%, are mailed every 2 years to update information on risk factors and the occurrence of major illnesses.[46,47] Information on residential address is updated for each questionnaire, enabling residential mobility over follow-up to be accounted for. The study protocol was approved by the Institutional Review Board of Brigham and Women's Hospital, and implied consent was inferred from the return of questionnaires.

Sudden cardiac death case ascertainment

Deaths in the cohort are identified by reports from next of kin, postal authorities, or by searching the National Death Index (NDI). Details on the method of classifying SCD in this cohort have been published previously.[3] Briefly, SCDs were confirmed by physician review of medical records and next-of-kin reports regarding the circumstances surrounding the death if not adequately documented in the medical record. Cardiac deaths were considered sudden if the death or cardiac arrest occurred within 1 hour of the onset of symptoms. To increase specificity for arrhythmic death, we also required there be no evidence of circulatory collapse or a neurologic event before the disappearance of the pulse.[48] Unwitnessed deaths or deaths that occurred during sleep where the participant was documented to be symptom free within the preceding 24 hours were considered probable SCDs if an autopsy or circumstances suggested that the death could have been arrhythmic.[49] SCD follow-up included all cases from the start of the cohort through the end of 2012. We excluded cases without complete information on date of death (n = 6) and those (n = 27) that occurred before temperature data were available.

Short-term exposures to temperature

Gridded (800-m resolution) daily ambient temperature data from 1981 to 2012 were obtained from the Parameter-Elevation Regressions on Independent Slopes Model (PRISM) Climate Group time series datasets[50] from the Northwest Alliance for Computational Science & Engineering (NASCE).[51] The predictions were produced from climatologically aided interpolation, have been shown to predict accurately (r^2 = 0.99 and mean absolute error = 1.49 °F) when compared with weather station values, and have determined to be highly useful for environmental epidemiology studies.[52] Briefly, temperature data from all weather stations across the conterminous United States from 1981 onward were compiled into a weighted regression model, accounting for elevation and other climatological factors, to produce grid-level daily average surface air temperature. Ambient average daily temperature data were assigned to each participants' residential addresses for the 27 days before each case and control day.

Statistical methods

We used a nested time-stratified case-crossover design to assess the associations of temperature on the current day (Lag_0), the preceding 27 days ($Lags_{1–27}$), the preceding week (average of $Lags_{0–6}$), and previous weeks (average of $Lags_{7–13}$, average of $Lags_{14–20}$, and average of $Lags_{21–27}$) with risk of SCD.[53,54] Control days were selected to include all other matching days of the week within the same calendar month. The case-crossover design has been shown to effectively control for interindividual personal characteristics (e.g., age, sex, and race/ethnicity) and confounders; the time-stratified approach additionally controls for other potential confounders that vary with time, including lifestyle

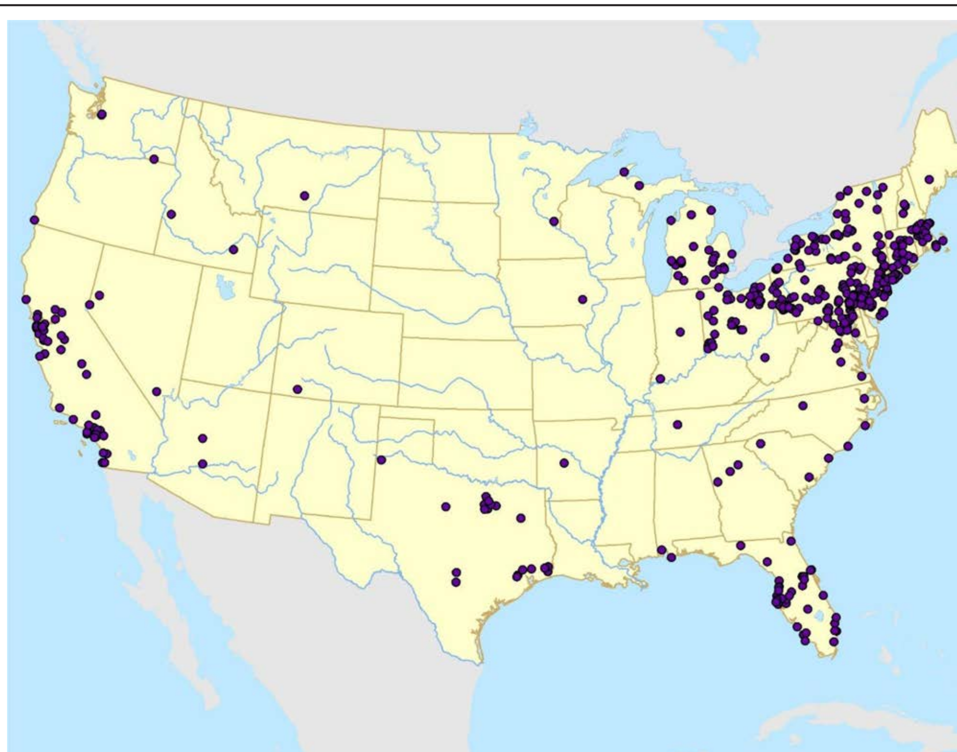

Figure 1. Residential addresses of the 465 participants who died of an SCD within the NHS.

factors, seasonality, and long-term secular trends. Therefore, our models do not adjust for personal characteristics.

We performed conditional logistic regression stratifying on the matched set to obtain relative risks (RRs) and 95% confidence intervals (CIs) for each of the week averages. For comparability across measures, we present RRs for an interquartile range (IQR) increase in temperature. Deviations from linearity in the dose-response were assessed through the use of cubic regression splines.[55] Likelihood ratio tests comparing the model with the spline to a linear model were used to determine statistically significant deviations from linearity. To assess the overall impact of exposures from the current day to 27 days prior, we used distributed lag nonlinear models (DLNMs).[56] The models included natural splines with 3 degrees of freedom each for temperature and the lag periods.

To assess potential effect modification by season (spring, summer, fall, and winter), region (Northeast: yes/no), and marital status (married: yes/no, as a proxy for socioeconomic status), we calculated the DLNM within strata. A two-sided *P* value of 0.05 was considered statistically significant. All analyses were performed in SAS, version 9.4, or R, version 4.3.1.

Results

There were a total of 465 cases of SCD between January 1981 and December 2012. A total of 1555 control days were selected. The spatial distribution of the cases is shown in Figure 1. The cases were all women, predominantly white, and mainly lived in the Northeast (Table 1). The average age at the time of SCD was 73.4 (SD = 6.5) years, and events were least likely to happen in the fall and on Wednesdays.

The distributions of the exposures are presented in Table 2. The means and SDs were similar, regardless of the exposure time window, with averages around 11.5 °C and SDs around 10 °C. The range of temperature exposures was wide, with differences between the 1st and 99th percentiles of over 40 °C.

Increasing temperature in the 3 weeks prior ($Lags_{0–20}$) was suggestively associated with increasing risks of SCD (Table 3). Each IQR increase (15.90 °C) in the days before an event (average of $Lags_{0–6}$) was associated with an RR = 1.44 (95% CI = 0.83, 2.50) of SCD in models including all 4 weeks of average exposures. Increasing average exposures on $Lags_{21–27}$ were associated with decreasing risks (RR = 0.88 [95% CI = 0.47, 1.62]), although this exposure-response displayed deviations from linearity (*P* value for test for linearity = 0.004). As shown in Figure 2, associations between temperature and SCD were more pronounced directly before and almost a month prior to the event, with cold effects being the most important after Lag_{25}. When examining the impacts of exposure on specific lag days (Figure 3), warmer temperatures were important on Lag_0, while U-shaped associations were observed for Lag_{13}, Lag_{20}, and Lag_{27}. In stratified models (Figure S1; http://links.lww.com/EE/A288), it was clear that although a little under half of the participants lived outside of the Northeast, the overall pattern in the full dataset was being driven by the pattern in these other regions. In the Northeast, there were stronger effects in the earlier lag days and stronger effects of warmer temperatures than in the other regions. Similarly, the patterns in the overall dataset were driven by those among married women, although they represented less than half of the included participants. The patterns among the four seasons were different, with the largest associations with cold temperatures in the winter at longer lags but with shorter lags in the spring and summer and elevated associations with warmer temperatures at shorter lags in all non-winter seasons.

Discussion

In this study of women from the US general population, increasing temperatures on the days before an event and decreasing temperatures almost a month prior were suggestively associated with increased risk of sudden cardiac death. These associations were driven by participants living outside the Northeast and by those who were married.

Our findings of an impact of temperature on SCD are consistent with the international literature on this topic,[8,13,16,19,20,22,37,38,44,45,57] although many studies have focused specifically on temperature extremes.[7,19,37,38,45,57] An early study in Canada found that among men under 65 years of age, cold snaps (defined as days on which the mean temperature was at least 4.4 °C lower than the day before) were associated with 16% increase in the number of SCDs.[7] Similar findings were shown in a Tunisian study, where there was an increase in SCD when temperatures dropped below 15 °C.[8] In a series of Finnish case-crossover studies conducted within The Finnish Study of Genotype and Phenotype Characteristics of Sudden Cardiac Death (FinGesture), exposures to cold spells (defined as 3 or more consecutive days with a daily minimum temperature below the fifth percentile for that address 1961–2011) in the 7 days preceding the death were consistently associated with an increased odds of SCD (odds ratio [OR] = 1.33 [95% CI = 1.00, 1.78]). These associations were strongest for longer cold spells, in autumn and winter, and in

Table 1.

Selected characteristics at the time of death of the 465 women from the NHS with a SCD between January 1981 and December 2012

Characteristic	n (%) or mean ± SD
Age (yrs)	73.4 ± 6.5
Race	
African American	6 (1.3)
White	447 (96.1)
Other race	12 (2.6)
Prior evidence of coronary heart disease	
Yes	2 (0.4)
No	463 (99.6)
Smoking status	
Current	104 (22.4)
Former	197 (42.4)
Never	164 (35.3)
Regular aspirin use	
Yes	167 (35.9)
No	216 (46.5)
Missing	82 (17.6)
Marital status	
Married	208 (44.7)
Single/widowed/divorced	257 (55.3)
Husband's educational attainment	
Less than high school	23 (5.0)
High school	79 (17.0)
More than high school	131 (28.2)
Missing or never married	232 (49.9)
Census region of residence	
Northeast	241 (51.8)
Midwest	69 (14.8)
West	62 (13.3)
South	93 (20.0)
Season of death	
Spring (March to May)	125 (26.9)
Summer (June to August)	106 (22.8)
Fall (September to November)	95 (20.4)
Winter (December to February)	139 (29.9)
Day of week of death	
Sunday	65 (14.0)
Monday	68 (14.6)
Tuesday	83 (17.9)
Wednesday	55 (11.8)
Thursday	72 (15.5)
Friday	60 (12.9)
Saturday	62 (13.3)

Table 2.

Distributions of average daily temperature (°C) for the 2020 (465 cases and 1555 controls) days included in the analyses

			Distribution percentiles					
Time window	Mean	SD	50th	IQR	25th	75th	1st	99th
All days								
Lag 0	11.52	10.07	12.21	16.08	3.81	19.89	–12.00	29.36
Lag 1	11.58	10.08	12.13	16.05	3.93	19.98	–11.17	29.40
Lag 2	11.59	10.08	11.88	16.08	3.93	20.01	–10.66	29.24
Lag 3	11.51	10.07	11.94	16.24	3.70	19.93	–11.55	29.56
Lag 4	11.47	10.07	11.82	16.14	3.54	19.68	–11.68	29.42
Lag 5	11.50	10.09	11.95	15.99	3.78	19.77	–12.29	29.26
Lag 6	11.42	10.17	11.86	16.31	3.51	19.82	–11.48	29.12
Lag 7	11.57	10.10	12.29	16.04	3.89	19.92	–11.60	29.36
Lag 8	11.56	10.10	12.02	16.07	3.89	19.95	–11.31	29.42
Lag 9	11.58	10.13	12.00	16.13	3.81	19.94	–10.66	29.33
Lag 10	11.53	10.17	11.86	16.46	3.55	20.01	–11.51	29.69
Lag 11	11.51	10.21	11.94	16.29	3.59	19.88	–12.27	29.37
Lag 12	11.45	10.21	12.04	16.34	3.49	19.83	–12.49	29.50
Lag 13	11.37	10.24	11.89	16.58	3.24	19.82	–11.36	29.24
Lag 14	11.58	10.16	12.34	16.33	3.62	19.95	–11.28	29.44
Lag 15	11.54	10.20	12.34	16.29	3.73	20.02	–11.56	29.47
Lag 16	11.58	10.21	12.04	16.27	3.71	19.98	–10.68	29.46
Lag 17	11.63	10.18	12.03	16.56	3.64	20.19	–11.77	29.75
Lag 18	11.64	10.15	12.09	16.36	3.67	20.03	–11.89	29.37
Lag 19	11.58	10.07	12.27	16.24	3.68	19.91	–11.50	29.29
Lag 20	11.46	10.18	12.01	16.44	3.49	19.93	–11.15	29.24
Lag 21	11.64	10.22	12.32	16.60	3.55	20.15	–10.77	29.36
Lag 22	11.59	10.34	12.50	16.61	3.53	20.13	–11.71	29.67
Lag 23	11.60	10.36	12.16	16.83	3.40	20.23	–11.06	29.78
Lag 24	11.64	10.33	12.17	16.62	3.64	20.26	–11.77	29.88
Lag 25	11.73	10.26	12.09	16.45	3.88	20.33	–12.19	29.47
Lag 26	11.72	10.11	12.35	16.34	3.82	20.15	–11.50	29.52
Lag 27	11.62	10.17	12.26	16.62	3.54	20.15	–10.90	29.54

Table 3.

Case-crossover–based associations per IQR increase of average daily temperature in the 28 days prior and risk of SCD from 1981 to 2012 among 465 women in the NHS

Time window	Case days	Control days	IQR	RR (95% CI)
Avg 0–6	465	1,555	15.90	1.44 (0.83, 2.50)
Avg 7–13	465	1,555	16.09	1.15 (0.64, 2.06)
Avg 14–20	465	1,555	16.23	1.35 (0.74, 2.48)
Avg 21–27[a]	465	1,555	16.53	0.88 (0.47, 1.62)

Lag_0 represents exposures on the current day, Lag_1 on the previous day, etc. All exposures are modeled simultaneously.

[a]The average of $Lags_{21-27}$ displayed statistically significant deviations from linearity but is included for completeness.

those with prior ischemic heart disease and not taking cardioprotective medications, and in those with higher levels of coronary stenosis.[37,38,57] In a study of 243 sudden cardiac deaths in Israel, a ratio of observed to expected deaths of 1.20 (listed as not statistically significant) was observed for temperatures <15 °C on the day of event, compared with 1.00 for temperatures of 15–30 and 0.75 for temperatures >30. Associations were stronger among those with known heart disease.[9] The findings of these studies are in alignment with our findings at both ends of the temperature range. In a Taiwanese study among patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy, a total of 68 SCDs were confirmed by autopsy. SCDs peaked in summer months, increasing temperature on the day of the event (OR = 1.23 [95% CI = 1.16, 1.31], per SD increase) was associated with odds of SCD, after adjustment for other meteorological factors (e.g., sunshine duration, humidity).[20] Among SCDs identified from autopsies in Budapest, Hungary (1995–2002), there was a negative correlation between daily mean temperature and number of SCDs.[14] A negative correlation between minimum daily temperature sudden cardiac deaths was observed in Tokyo between 2012 and 2013.[58] There have also been numerous studies that have observed increases in SCD with both hot and cold temperatures,[19,22] indicating that there are complex patterns between SCD and temperature that vary around the world. In one of only a few studies on this topic in the United States, the relative risk of SCDs occurring in Olmstead County, MN was elevated in all seasons relative to the summer and in colder (below 17 °C) temperatures.[13] In a study using daily mortality data from 50 US cities, exposures to both cold (daily maximum temperature less than or equal to the first percentile) and hot (daily minimum temperature ≥99th percentile) days were associated with increases in cardiac arrest deaths, and there was evidence that these associations were modified by average temperatures and temperature variability, availability of heating and cooling.[45]

An association between short-term exposures to temperature and SCD is biologically plausible through multiple mechanisms. These have previously been summarized by Ryti et al. and include changes in blood composition factors, changes in blood pressure, changes in autonomic function, changes in cardiac oxygen demand, and changes in endothelial function.[57] For example, in studies where individuals were exposed to a few hours of moving air to induce cooling, increases in platelets, red blood cells, fibrinogen, cholesterol, and blood viscosity were observed, with larger increases in elderly participants compared with young adults.[59,60] Similar effects have also been observed in studies of individuals subjected to high temperatures.[61] Blood pressure has also been shown to vary with ambient temperature, with evidence of higher blood pressure in colder, as opposed to warmer, temperatures.[60,62–64] Exposures to extreme temperatures have also been shown to alter autonomic function and that this dysregulation increases with age.[65,66] Lastly, emerging evidence suggests that extremes in short-term temperature exposures are associated with ventricular arrhythmias, which may underlie the findings observed with SCD.[67–69]

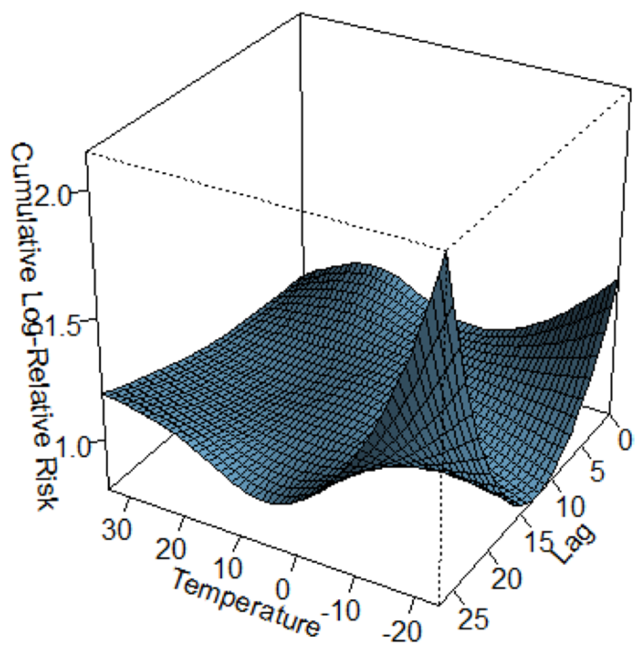

Figure 2. Cumulative RRs for associations between temperature on the day of event (Lag_0) or before 28 days ($Lags_{1–27}$) and SCD that occurred from 1981 to 2012 in 465 women in the NHS, all relative to the minimum mortality temperature.

Our study has several limitations. We do not have information on time-activity patterns for participants, and we do not know how well ambient temperature predictions predicted personal temperature exposures in this cohort. This would likely lead to nondifferential exposure misclassification, which would limit our power to detect statistically significant effects. The cohort is comprised of females who at enrollment were married and had a nursing degree. This potentially limits generalizability, especially if there are biological mechanisms that are not as relevant for men or for populations with different distributions of ambient temperature exposures. Lastly, although our study is comprised of one of the largest prospective collections of SCDs among women, due to the rarity of the event in an all female general population sample, power was limited to detect effects.

The study also has numerous strengths. This is one of only a small number of studies to examine the associations between short-term temperature exposures across a wide range of temperatures and SCD. As opposed to most of the existing literature, we examined associations at all levels of temperature, not just extremes such as cold spells or heat waves. Additionally, we examined the impact of temperature for the entire country, not just a selected city or metropolitan area. Our use of a fine-spatial scale (800 m) data allowed a more precise prediction of exposure, relative to previous work that used coarser (10–30 km) resolution estimates. Due to this study being embedded in the prospective NHS cohort, we were able to look at the impact of multiple potential effect modifiers, with information collected prospectively.

In conclusion, in this study of US women, increases in temperature in the week before an SCD were suggestively associated with increasing risk of SCD. Short-term decreases in temperature relative to the prior week were also associated with increased risk of SCD. These findings, paired with literature

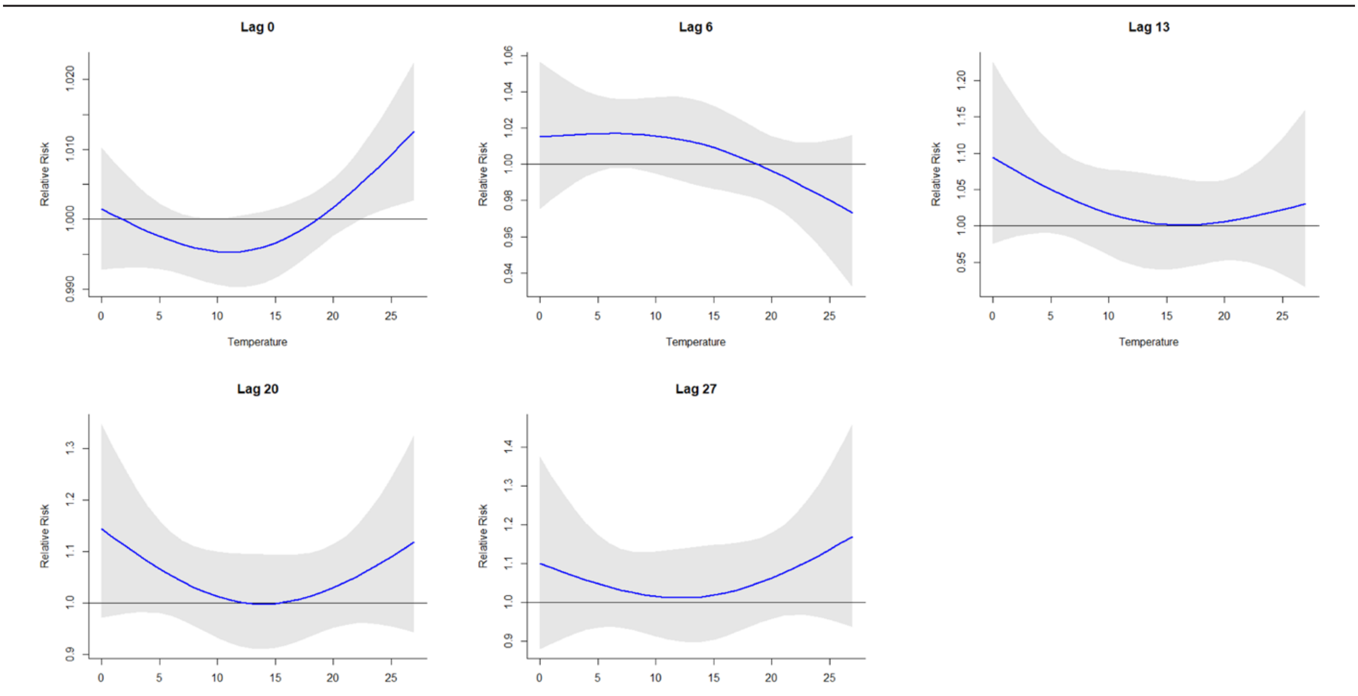

Figure 3. RRs for associations between temperature and SCD that occurred from 1981 to 2012 in 465 women in the NHS, all relative to the minimum mortality temperature. Plots show the effect across the temperature range on lag days (top left to bottom right) 0, 6, 13, 20, and 27.

from around the world, suggest that ambient temperature may be an emerging population-level risk factor for SCD.

Conflict of interest statement

The authors declare that they have no conflicts of interest with regard to the content of this report.

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