Environmental Science and Pollution Research (2019) 26:694–705
https://doi.org/10.1007/s11356-018-3653-z

RESEARCH ARTICLE

# Socio-geographic disparity in cardiorespiratory mortality burden attributable to ambient temperature in the United States

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Received: 10 August 2018 / Accepted: 31 October 2018 / Published online: 9 November 2018


## Abstract

Compared with relative risk, attributable fraction (AF) is more informative when assessing the mortality burden due to some environmental exposures (e.g., ambient temperature). Up to date, however, available AF-based evidence linking temperature with mortality has been very sparse regionally and nationally, even for the leading mortality types such as cardiorespiratory deaths. This study aimed to quantify national and regional burden of cardiorespiratory mortality (CRM) attributable to ambient temperature in the USA, and to explore potential socioeconomic and demographic sources of spatial heterogeneity between communities. Daily CRM and weather data during 1987–2000 for 106 urban communities across the mainland of USA were acquired from the publicly available National Morbidity, Mortality and Air Pollution Study (NMMAPS). We did the data analysis using a three-stage analytic approach. We first applied quasi-Poisson regression incorporated with distributed lag nonlinear model to estimate community-specific temperature-CRM associations, then pooled these associations at the regional and national level through a multivariate meta-analysis, and finally estimated the temperature-AF of CRM and performed subgroup analyses stratified by community-level characteristics. Both low and high temperatures increased short-term CRM risk, while temperature-CRM associations varied by regions. Nationally, the fraction of cardiorespiratory deaths caused by the total non-optimum, low, and high temperatures was 7.58% (95% empirical confidence interval, 6.68–8.31%), 7.15% (6.31–7.85%), and 0.43% (0.37–0.46%), respectively. Greater temperature-AF was identified in two northern regions (i.e., Industrial Midwest and North East) and communities with lower temperature and longitude, higher latitude, and moderate humidity. Additionally, higher vulnerability appeared in locations with higher urbanization level, more aging population, less White race, and lower socioeconomic status. Ambient temperature may be responsible for a large fraction of cardiorespiratory deaths. Also, temperature-AF of CRM varied considerably by geographical and climatological factors, as well as community-level disparity in socioeconomic status.

Yunquan Zhang and Qianqian Xiang contributed equally to this work.

Responsible editor: Philippe Garrigues

**Electronic supplementary material** The online version of this article (https://doi.org/10.1007/s11356-018-3653-z) contains supplementary material, which is available to authorized users.

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**Keywords** Climate change · Temperature · Cardiorespiratory mortality · Attributable fraction · United States

## Introduction

Large bodies of previous epidemiologic studies have linked ambient temperature with many mortality outcomes, and this evidence has increased rapidly over the recent decades (Amegah et al. 2016; Basu 2009; Benmarhnia et al. 2015; Moghadamnia et al. 2017; Ryti et al. 2016; Song et al. 2017). Because of acclimatization and different adaptation responses, various shapes of temperature-mortality associations have been identified by researchers across the world through time-series or case-crossover designs (Chung et al. 2009; Guo et al. 2014; Ma et al. 2015a; Medina-Ramon and Schwartz 2007; Scovronick et al. 2018). Nevertheless, there is a wide consensus in this field that both extremely low and extremely high temperatures elevate short-term mortality rates (Gasparrini et al. 2015; Guo et al. 2014). Furthermore, the total excess mortality caused by temperature exposures will not experience a sharp decline by the end of the twenty-first century, according to a recent multi-country projection under climate change scenarios (Gasparrini et al. 2017).

When estimating temperature-health associations in environmental epidemiology, most research has widely employed ratio measures, such as relative risk (RR) and odds ratio (OR), to communicate the mortality impact of exposures to cold and hot weather (Gasparrini and Leone 2014). These ratio measures provide summary characteristics of cold and heat effects simplified from the exposure-response curves, thus failing to capture the comprehensive impact of temperature exposure (Gasparrini 2011). Attributable fraction (AF), a measure of relative excess risk, which has been widely applied to evaluate the disease burden due to some specific risk factors (e.g., air pollution) (Steenland and Armstrong 2006), is an novel index for temperature-related health assessment until recently (Gasparrini et al. 2015; Lee et al. 2017; Onozuka and Hagihara 2017) because of the complex temperature effects (nonlinear and delayed). Compared with mortality risks at certain temperatures, calculating AF of mortality would have greater practical significance in guiding and planning public health policy to minimize temperature-related deaths (Gasparrini et al. 2015; Gasparrini and Leone 2014). Up to date, however, available AF-based evidence has been very sparse regionally and nationally, even for the leading mortality types such as cardiorespiratory deaths.

In 2015, the whole globe experienced totally 17.9 million (32.1%) cardiovascular deaths and 3.8 million (6.8%) chronic respiratory deaths, ranking 1st and 3rd among all causes of deaths, respectively (Wang et al. 2016). These cardiorespiratory deaths can be generally attributed to exposures to metabolic (e.g., high total cholesterol and high systolic blood pressure), behavioral (e.g., dietary, physical activity, and tobacco smoke), and environmental/occupational risks (e.g., air pollution and occupational carcinogens) (Collaborators 2016; Feigin et al. 2016; Forouzanfar et al. 2015; Lim et al. 2012). Additionally, in many epidemiologic studies, ambient temperature has been identified as an important risk factor that may trigger cardiorespiratory deaths (Anderson and Bell 2009; Gasparrini et al. 2012b; Moghadamnia et al. 2017; Ryti et al. 2016). However, little interest from the national and regional perspective has focused on the component/fraction of cardiorespiratory deaths caused by high and low temperatures (Yang et al. 2015).

There have existed many lines of epidemiologic evidence suggesting that temperature-mortality associations may be to some extent modified by individual characteristics such as biological (e.g., age) and socioeconomic (e.g., education attainment) status (Huang et al. 2015; Moghadamnia et al. 2017; Zanobetti et al. 2013). At the community level, however, socio-geographic and demographic disparities in temperature-related mortality burden have not been fully investigated and well understood around the world, even in the developed countries (Hajat and Kosatky 2010). In this study, we thus conducted a nationwide observational investigation in USA, and aimed to quantify national and regional mortality burden of cardiorespiratory diseases attributable to ambient temperatures, and to explore potential socioeconomic and demographic sources of spatial heterogeneity between communities.

## Materials and methods

### Data collection

We acquired daily cardiorespiratory mortality and weather data during 1987–2000 for 106 urban communities across the mainland of USA, from the publicly available National Morbidity, Mortality and Air Pollution Study (NMMAPS). Daily counts of cardiorespiratory mortality were originally collected from the National Center for Health Statistics, and meteorological exposures including average temperatures and relative humidity were constantly monitored by the National Climatic Data Center. More details could be found in several previous publications (Peng et al. 2005; Samet et al. 2000).

The 106 large communities included in this study were divided into seven regions: North West, Upper Midwest, Industrial Midwest, North East, Southern California, South West, and South East. The total cardiorespiratory deaths were collapsed into cardiovascular and respiratory causes, and stratified by three age groups (i.e., 0–65, 65–75, and 75+ years old). We used daily mean temperature as the main temperature exposure, because it can better represent the average exposure throughout the whole day and night and provide more easily interpreted results within a policy context (Guo et al. 2011; Guo et al. 2017).

## Statistical analysis

The 14-year time-series data from 106 US communities were analyzed by adopting a three-stage analytic approach, which has been widely applied in previous studies (Gasparrini and Armstrong 2013; Gasparrini et al. 2012a). In the first stage, we used time-series regression separately in each community to model community-specific associations of cardiorespiratory mortality with ambient temperature. In the second stage, we conducted a multivariate meta-analysis to pool temperature-mortality associations at the regional and national levels (Gasparrini et al. 2012a). In the last stage, we calculated mortality fraction attributable to non-optimum temperatures (i.e., cold and heat) (Gasparrini and Leone 2014), and assessed the potential community-level modifiers (e.g., geographical and climatological) of temperature-attributable mortality by stratified analyses. All the analyses were performed with R software (version 3.3.2) using the packages of "dlnm" and "mvmeta", and effects of $p < 0.05$ (two-sided) were considered statistically significant.

### First-stage time-series regression

We applied a standard time-series quasi-Poisson regression allowing for overdispersed death counts to assess community-specific relationships between temperature and cardiorespiratory mortality. To capture the nonlinear and lagged effects of temperature on mortality, we incorporated a distributed lag nonlinear model (DLNM) defined by the flexible "cross-basis" function (Gasparrini 2011; Gasparrini et al. 2010) into the time-series regression. Motivated by previous multi-country investigations (Gasparrini et al. 2015; Guo et al. 2014), we modeled the exposure-response association in each community using a quadratic B-spline with three internal knots (10th, 75th, and 90th), and the lag-response association using a natural cubic B-spline (NCS) with three internal knots at equally spaced log-scale values. Additionally, we chose a maximum of 21 days for the lag period so as to include the long-lasting effects of low temperatures and the potential mortality displacement of the effects of high temperatures. Some sensitivity analyses were performed to test these modeling choices.

To fully eliminate the potential confounding effects, we included the following covariates in our time-series regression models: (1) a NCS with 7 degrees of freedom (*df*) per year for calendar time to control the seasonality and long-term trends (Chen et al. 2013; Ma et al. 2014); (2) an indicator of day of the week (Guo et al. 2014; Zhang et al. 2018a); (3) 3 *df* NCS at equally spaced quantiles for the current day's mean relative humidity (Chen et al. 2013; Zhang et al. 2018b). After formulating the core models, reduction of community-specific parameters derived from the cross-basis function was then performed to obtain the overall cumulative temperature-mortality associations. This step could largely simplify the second-stage pooling analysis of community-specific associations, and meanwhile preserve the complexity of the estimated dependency (Gasparrini and Armstrong 2013).

### Second-stage multivariate meta-analysis

To obtain the regional- and national-level temperature-mortality associations, we conducted the pooling analysis of the reduced community-specific parameters in the first stage using a multivariate meta-analytical model (Gasparrini et al. 2012a). The fitted meta-analytical model was then applied in return to derive the best linear unbiased prediction (BLUP) of the overall cumulative temperature-mortality association in each community. The BLUP approach is expected to provide more accurate community-specific assessments in temperature-mortality association, especially for locations with small daily mortality counts, because it makes a trade-off between the first-stage community-specific associations and the second-stage pooled association (Gasparrini et al. 2012a).

### Third-stage calculation of attributable fraction

Based on the BLUP of the overall cumulative temperature-mortality association for each community, we located the minimum mortality percentile (MMP) of temperature distribution by comparing the mortality risks at community-specific temperature ranges. The MMP was then referred as the optimum exposure to calculate the attributable RR of mortality (Gasparrini and Leone 2014). Specifically, for each day of the series of each community, the attributable deaths in the next 21 days could be calculated according to the overall cumulative RR corresponding to each day's temperature. Regional and national attributable deaths could be thus obtained by summing up community-specific estimates, and its ratios with the corresponding total number of observed deaths give the total attributable mortality fractions (%) (Hu et al. 2018; Lin et al. 2016). By dividing the total series into days with temperatures lower or higher than the minimum mortality temperature, we could also obtain attributable mortality fraction due to cold and heat, respectively (Gasparrini et al. 2015). We reported the empirical confidence intervals (empirical CIs) of temperature-attributable mortality fraction using Monte Carlo simulations of the second-stage BLUPs of the reduced coefficients, which was based on the assumption of a multivariate normal distribution.

To illustrate the potential effect modification when assessing temperature-attributable mortality fraction, we first excluded the outliers in AF by visual inspection and then did some subgroup analyses stratified by four quartiles (Q1: [lowest, 25th percentile); Q2: [25th, 50th); Q3: [50th, 75th); Q4: [75th, highest]) of community-specific characteristics (e.g., geographical, climatological, demographic, and socioeconomic). Also, we performed the significance tests between subgroups in AF estimates using a previously described meta-regression method in temperature-mortality studies (Guo 2017; Yang et al. 2015). Specifically, the AF estimates of stratum-level analyses (e.g., Q1~Q4 of average temperature) were included as dependent variable in the meta-regression model, while the predictor (Q1~Q4 of average temperature) was included as independent variable. The likelihood ratio test was used to examine whether the AFs of Q2~Q4 were statistically different from that of Q1 (the reference stratum). Besides, we fitted nonparametric local polynomial regression (LOESS) curves to intuitively demonstrate the modifying effects of these included factors on temperature-attributable mortality fraction.

## Results

Table 1 describes the summary statistics of daily cardiorespiratory deaths and weather conditions for the seven US regions between 1987 and 2000. Average daily count of total included death cases was 1056.2 (range 808–1604) for cardiorespiratory mortality, 882.7 (678–1230) for cardiovascular mortality, and 173.5 (97–412) for respiratory mortality, respectively. Climate characteristics varied by communities and regions, especially for northern and southern areas. We observed a large range of temperatures (8.3–26.5 °C) for the 106 communities, with region-specific averages ranging from 11.8 °C in Industrial Midwest to 20.9 °C in South West. The national average exposure was 64.8% for relative humidity, with the lowest in South West (46.7%) and the highest in South East (69.1%). Details of community-specific statistics were provided in Table S1.

Figure 1 shows national and region-specific overall cumulative associations of temperature with cardiorespiratory mortality, with the corresponding minimum mortality percentiles. The exposure-response curve was generally V-shaped at the national level, while U-shaped in North West, Southern California, and South West, and inverse J-shaped in Upper Midwest and South East. Despite great heterogeneity, these associations provided clear evidence that both low and high temperatures increased the risks of cardiorespiratory mortality. Generally, the median of MMPs was at about 90th percentiles for the whole nation (106 communities) and most regions, with the exception of North West and Southern California (to be near the 60 percentile).

Figure S1 demonstrates the cardiorespiratory mortality fraction attributable to the total and separated low and high temperatures in the 106 communities, which varied substantially between communities with the highest consistently observed in Chicago. For all communities, cold weather accounted for the most majority (89–99%) of the total temperature-attributable burden. On the national average, as shown in Table 2, the fraction of cardiorespiratory deaths caused by the total non-optimum, low, and high temperatures was 7.58% (95% empirical CI, 6.68–8.31%), 7.15% (6.31–7.85%), and 0.43% (0.37–0.46%), respectively. The total

**Table 1** Region-specific summary statistics (mean and range) for daily cardiorespiratory deaths, annual average temperature, and relative humidity in 106 US communities, 1987–2000

| Region | Number of communities | Daily cardiorespiratory deaths | | | Temperature(°C) | Humidity (%) |
|---|---|---|---|---|---|---|
| | | Total | CVD | Respiratory | | |
| North West | 14 | 104.7 | 83.9 | 20.8 | 13.7 | 63.9 |
| | | (62–174) | (45–136) | (3–60) | (9.6–18.4) | (51.2–76.1) |
| Upper Midwest | 9 | 47.5 | 39.1 | 8.3 | 12.5 | 64.9 |
| | | (25–84) | (16–73) | (0–21) | (8.8–15.1) | (62.4–66.4) |
| Industrial Midwest | 20 | 234.7 | 198.6 | 36.0 | 11.8 | 67.8 |
| | | (154–557) | (133–509) | (11–79) | (9.1–15.5) | (61.3–70.3) |
| North East | 19 | 217.1 | 186.9 | 30.2 | 12.6 | 66.6 |
| | | (138–382) | (117–351) | (10–69) | (8.3–16.3) | (61.6–70.5) |
| Southern California | 7 | 166.5 | 136.4 | 30.1 | 18.6 | 62.4 |
| | | (101–372) | (86–246) | (8–129) | (17.5–20.7) | (47.7–73.8) |
| South West | 10 | 78.1 | 63.3 | 14.8 | 20.9 | 46.7 |
| | | (39–146) | (30–116) | (2–47) | (15.8–26.5) | (27.8–74.4) |
| South East | 27 | 207.6 | 174.5 | 33.1 | 19.3 | 69.1 |
| | | (143–342) | (119–273) | (10–93) | (15.7–25.1) | (58.4–77.9) |
| National | 106 | 1056.2 | 882.7 | 173.5 | 15.5 | 64.8 |
| | | (808–1604) | (678–1230) | (97–412) | (8.3–26.5) | (27.8–77.9) |

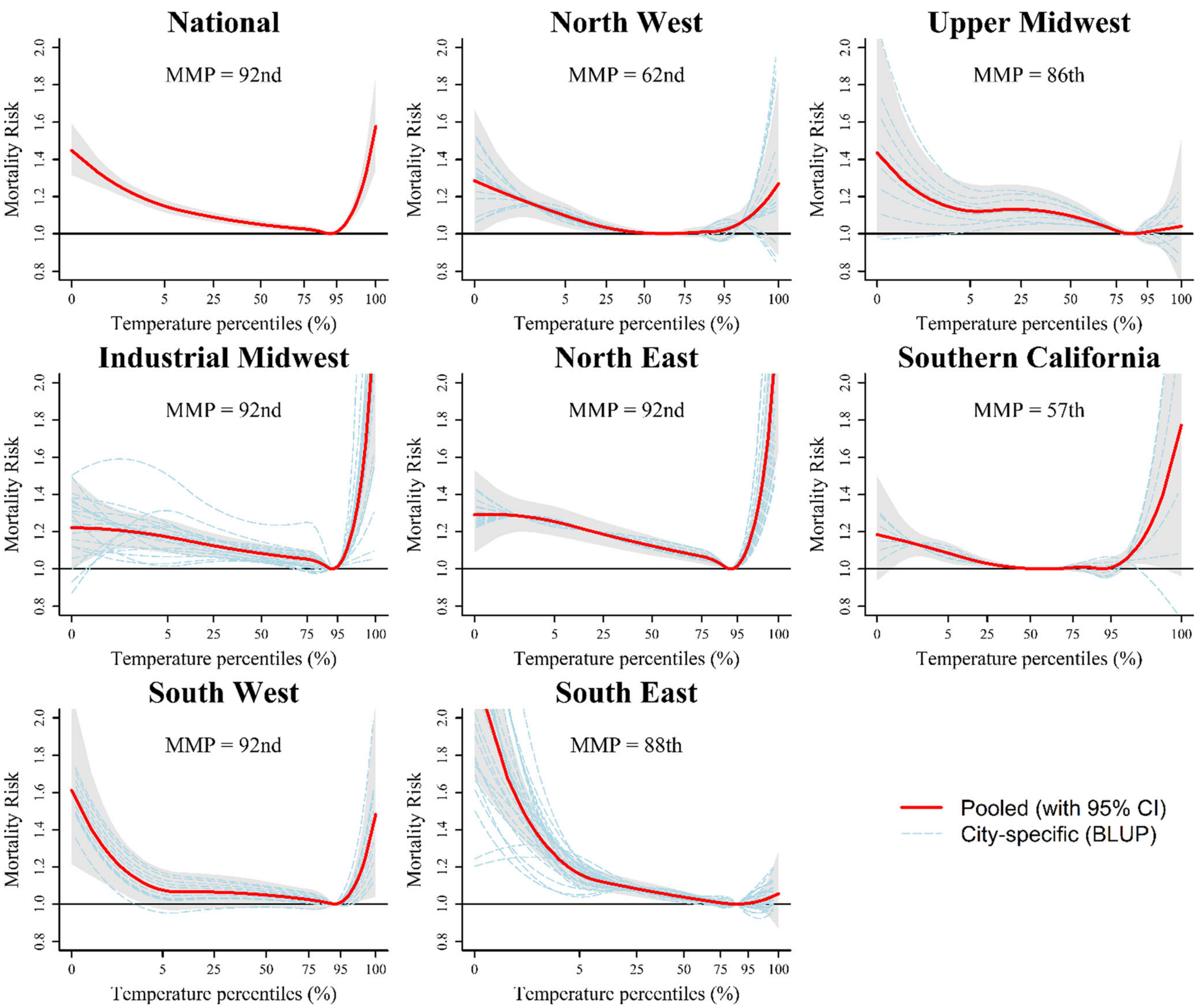


**Fig. 1** National and region-specific curves for overall cumulative associations of temperature with cardiorespiratory mortality along lag 0–21 days. The continuous bold red lines are the pooled exposure-response curves with (the 95% CIs, shaded gray), and the long-dashed light blue lines represent community-specific associations predicted by BLUP. MMP, minimum mortality percentile; BLUP, the best linear unbiased prediction

attributable fraction was relatively higher for cardiovascular mortality (8.03%, 95% empirical CI, 7.19–8.75%) than that for respiratory mortality (6.34%, 4.08–7.65%). This difference was mainly observed in cold-attributable burden, with the contrary finding in terms of heat-related mortality. Compared with younger groups, the elderly aged over 75 years suffered significantly greater burden of both cold- and heat-attributable mortality fraction.

Besides, region-specific results also showed some geographical differences in estimates of attributable fraction. Two northern regions, namely Industrial Midwest and North East, were identified as the most vulnerable areas to temperature-attributable mortality burden, with the corresponding total fractions of 11.19% (9.39–12.81%) and 9.11% (6.95–11.03%), respectively. Much lower fractions were estimated for other regions, ranging from 5.36% (3.34–6.93%) in South East to 6.13% (3.77–8.17%) in North West. Also, similar results were found for mortality burden due to both cold and heat. Figure 2 and Table S2 further illustrate temperature-attributable fractions of cardiovascular mortality by communities and regions. Comparably, about one in ten cardiovascular deaths were caused by non-optimum temperature exposures in Industrial Midwest and North East, which was approximately twice larger than the least affected region (South East).

Tables 3 and 4 calculate attributable fractions of cardiorespiratory mortality among four subgroups stratified by quartiles of community-level characteristics. The estimated burden related to temperature generally varied between strata, and some of the differences were statistically significant. For instance, total attributable fraction peaked in Q2 stratum of

**Table 2** Fraction (95% empirical CI) of cardiorespiratory mortality attributable to ambient temperature, stratified by cause, age, and region in 106 US communities, 1987–2000

| | Total | Cold | Heat |
|---|---|---|---|
| Total cardiorespiratory | 7.58 (6.68, 8.31) | 7.15 (6.31, 7.85) | 0.43 (0.37, 0.46) |
| Cause | | | |
| Cardiovascular | 8.03 (7.19, 8.75) | 7.57 (6.78, 8.30) | 0.46 (0.40, 0.49) |
| Respiratory | 6.34 (4.08, 7.65) | 5.38 (3.43, 6.51) | 0.97 (−0.02, 1.86) |
| Age (years) | | | |
| 0–65 | 5.46 (4.02, 6.41) | 5.14 (3.84, 6.25) | 0.32 (0.14, 0.46) |
| 65–75 | 5.79 (4.29, 6.93) | 5.37 (3.90, 6.37) | 0.43 (0.28, 0.52) |
| 75+ | 9.14 (8.02, 10.03) | 8.65 (7.51, 9.51) | 0.48 (0.42, 0.52) |
| Region | | | |
| North West | 6.13 (3.77, 8.17) | 5.83 (3.55, 7.90) | 0.30 (0.17, 0.41) |
| Upper Midwest | 5.77 (3.22, 8.37) | 5.46 (2.92, 7.59) | 0.30 (0.08, 0.48) |
| Industrial Midwest | 11.19 (9.39, 12.81) | 10.53 (8.67, 11.93) | 0.66 (0.54, 0.74) |
| North East | 9.11 (6.95, 11.03) | 8.46 (6.39, 10.38) | 0.65 (0.53, 0.75) |
| Southern California | 5.59 (3.41, 7.55) | 5.27 (3.25, 7.34) | 0.32 (0.23, 0.39) |
| South West | 5.61 (2.92, 7.72) | 5.32 (2.94, 7.41) | 0.29 (0.13, 0.41) |
| South East | 5.36 (3.34, 6.93) | 5.20 (3.40, 6.89) | 0.16 (0.07, 0.24) |

average temperature, namely communities with average temperature between 25th and 50th percentile of overall temperature distribution. Further pairwise comparison indicated that the estimate of stratum Q1 was significantly higher than that of Q4 ($p = 0.039$), while the differences with other strata were not significant, with the $p$ value of 0.774 for Q2 vs. Q1, and 0.085 for Q3 vs. Q1, respectively. Additionally, higher mortality fractions appeared in locations with higher latitude (Q3 and Q4), lower longitude (Q1 and Q2), and moderate humidity (Q2 or Q3). In terms of demographic and socioeconomic factors (Table 4), our stratified analysis found greater temperature-related burden in regions with high urbanization level (e.g., more urban proportion, higher population density, and larger population size), more aging population, less White race, and lower socioeconomic status (e.g., high proportion of poverty, low-educated and unemployed people). Most of the significant differences were observed in stratum Q3 or Q4 compared with Q1. Furthermore, the above evidence was enhanced by the fitted nonparametric LOESS curves shown in Figs. S2, S3, and S4, which intuitively described the relation between these included community-level characteristics and mortality fraction.

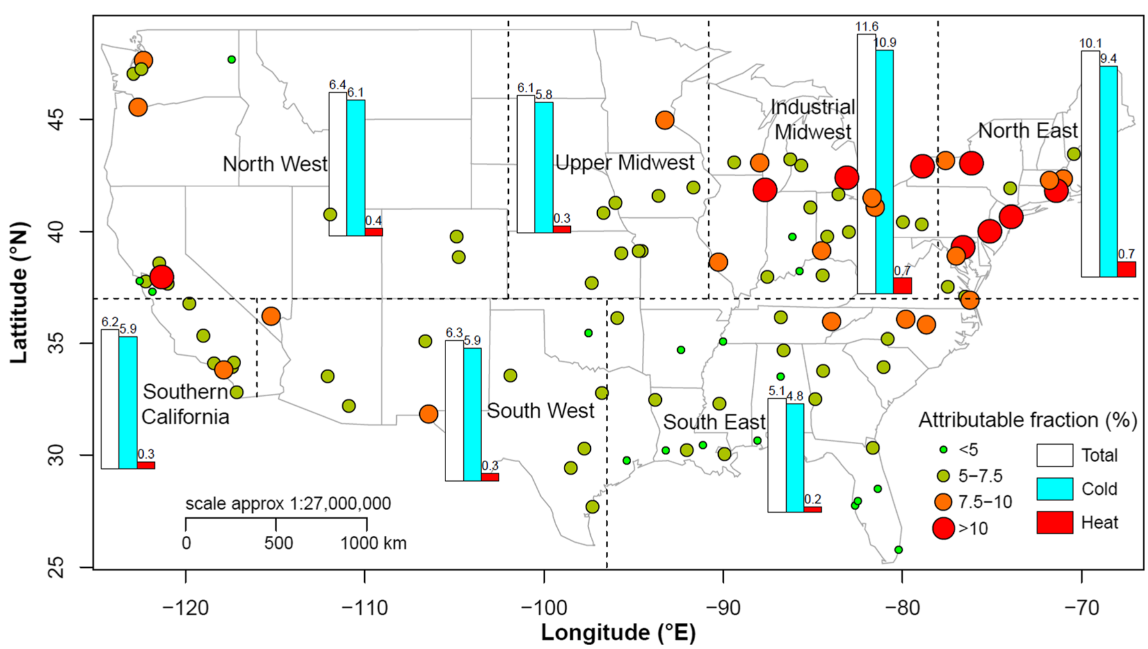


**Fig. 2** Fractions of cardiovascular mortality attributable to ambient temperatures by communities and regions during 1987–2000

**Table 3** Temperature-attributable fractions (95% empirical CI) of cardiorespiratory mortality and related pairwise comparison between subgroups stratified by geographical and climatological factors

| Characteristics | Total | | Cold | | Heat | |
|---|---|---|---|---|---|---|
| | AF (empirical CI) | *p* value[a] | AF (empirical CI) | *p* value[a] | AF (empirical CI) | *p* value[a] |
| Average temperature (°C) | | | | | | |
| Q1 [8.3, 12.1] | 7.68 (6.10, 9.08) | Ref | 7.23 (5.66, 8.61) | Ref | 0.45 (0.34, 0.55) | Ref |
| Q2 [12.1, 15.0] | 7.99 (6.41, 9.42) | 0.774 | 7.45 (5.77, 8.77) | 0.838 | 0.55 (0.45, 0.62) | 0.147 |
| Q3 [15.0, 18.4] | 5.77 (4.04, 7.20) | 0.085 | 5.49 (3.81, 6.88) | 0.109 | 0.28 (0.20, 0.34) | *0.008* |
| Q4 [18.4, 26.5] | 5.35 (3.60, 6.87) | *0.039* | 5.14 (3.41, 6.80) | 0.068 | 0.21 (0.12, 0.28) | *< 0.001* |
| Average humidity (%) | | | | | | |
| Q1 [27.8, 62.4] | 5.60 (3.82, 7.10) | Ref | 5.33 (3.65, 6.86) | Ref | 0.27 (0.18, 0.34) | Ref |
| Q2 [62.4, 66.7] | 8.13 (6.38, 9.75) | *0.035* | 7.56 (5.77, 8.99) | *0.029* | 0.57 (0.47, 0.65) | *< 0.001* |
| Q3 [66.7, 70.1] | 7.67 (5.95, 9.17) | 0.077 | 7.26 (5.55, 8.72) | 0.094 | 0.41 (0.30, 0.49) | *0.027* |
| Q4 [70.1, 77.9] | 5.61 (4.09, 6.95) | 0.993 | 5.36 (3.76, 6.71) | 0.978 | 0.26 (0.18, 0.31) | 0.849 |
| Latitude (°N) | | | | | | |
| Q1 [25.8, 33.9] | 5.61 (4.03, 7.06) | Ref | 5.40 (3.83, 6.97) | Ref | 0.21 (0.13, 0.27) | Ref |
| Q2 [33.9, 38.0] | 5.24 (3.49, 6.66) | 0.741 | 4.97 (3.31, 6.39) | 0.838 | 0.27 (0.18, 0.34) | 0.147 |
| Q3 [38.0, 41.1] | 8.00 (6.26, 9.54) | *0.036* | 7.45 (5.80, 8.92) | 0.109 | 0.55 (0.45, 0.63) | *0.008* |
| Q4 [41.1, 47.7] | 8.16 (6.50, 9.58) | *0.021* | 7.68 (6.03, 9.02) | 0.068 | 0.48 (0.36, 0.57) | *< 0.001* |
| Longitude (°W) | | | | | | |
| Q1 [70.4, 81.4] | 8.50 (6.62, 10.06) | Ref | 7.96 (6.18, 9.46) | Ref | 0.55 (0.45, 0.62) | |
| Q2 [81.4, 88.7] | 6.74 (5.13, 8.13) | 0.131 | 6.40 (4.81, 7.88) | 0.173 | 0.35 (0.24, 0.43) | *0.002* |
| Q3 [88.7, 101.0] | 5.66 (3.92, 7.14) | *0.018* | 5.40 (3.69, 6.88) | *0.028* | 0.26 (0.14, 0.34) | *< 0.001* |
| Q4 [101.0, 122.9] | 5.73 (4.35, 7.04) | *0.013* | 5.41 (4.04, 6.55) | *0.016* | 0.31 (0.24, 0.37) | *< 0.001* |

*AF* attributable fraction, *CI* confidence interval

[a] The lowest quartile (Q1) of community-specific characteristics was set as the reference. Stratum-specific estimates were compared through a likelihood ratio test based on the meta-regression model. Italic emphasis indicated that the comparison between subgroup AF was statistically significant

Our sensitivity analysis suggested that the main results were not largely dependent on the modeling specifications of *df*/year for seasonal control (Table S3) and knots for exposure-response association (Table S4). The estimated attributable fraction showed some differences when varying the lag period from 14 to 28 days, but results kept consistent that mortality burden caused by both cold and heat peaked in Industrial Midwest and North East (Table S5).

## Discussion

Using data from 106 large communities, we conducted a nationwide investigation on temperature-related burden on cardiorespiratory mortality in the USA. Our analyses largely relied on recent advances in time-series modeling, which enabled us to account for the nonlinear and heterogeneous temperature-mortality dependencies across locations. Furthermore, we adopted a uniform analytic strategy for each location based on a relative temperature scale, thus making our community- and region-specific estimates more comparable in a wide range of climates.

The evidence is generally clear in epidemiological studies that both cold and heat are associated with increased mortality risk (Basu 2009; Hajat and Kosatky 2010; Moghadamnia et al. 2017; Ryti et al. 2016). In large countries such as China that covers a broad span of latitudes and longitudes, population vulnerability to temperature extremes may also vary substantially in different geographical regions, with various minimum mortality temperatures (Ma et al. 2015a; Yang et al. 2015). Through our national and regional analysis, as expected, consistent findings were also observed in USA using cardiorespiratory mortality data. Such great heterogeneity in temperature-related mortality impacts could be usually explained by the long-term acclimatization (Gasparrini et al. 2015; Guo et al. 2014).

Compared with all-cause mortality estimated in a previous international investigation (Gasparrini et al. 2015), we found an intuitively larger temperature-attributable fraction for cardiorespiratory mortality (7.58%, 6.68 to 8.31), particularly for cardiovascular disease (CVD) mortality (8.03%, 7.19 to 8.75). Similar findings were also observed in several recent large-scale studies. For instance, Lee et al. reported an average of 15.63% (15.04 to 16.11) of CVD mortality in five East-Asian countries/regions (i.e., Japan, South Korea, Chinese Taiwan,

**Table 4** Temperature-attributable fractions (95% empirical CI) of cardiorespiratory mortality and related pairwise comparison between subgroups stratified by community-level demographic and socioeconomic factors

| Characteristics | Total | | Cold | | Heat | |
|---|---|---|---|---|---|---|
| | AF (empirical CI) | *p* value[a] | AF (empirical CI) | *p* value[a] | AF (empirical CI) | *p* value[a] |
| Urban proportion (%) | | | | | | |
| Q1 [46.5, 88.6] | 5.85 (4.39, 7.31) | Ref | 5.56 (3.95, 7.17) | Ref | 0.29 (0.16, 0.38) | Ref |
| Q2 [88.6, 95.0] | 6.10 (4.26, 7.71) | 0.828 | 5.85 (3.90, 7.57) | 0.816 | 0.25 (0.15, 0.33) | 0.581 |
| Q3 [95.0, 98.6] | 6.08 (4.58, 7.41) | 0.825 | 5.77 (4.20, 7.12) | 0.850 | 0.32 (0.23, 0.38) | 0.659 |
| Q4 [98.6, 100.0] | 7.88 (6.89, 8.87) | *0.024* | 7.39 (6.74, 8.04) | *0.039* | 0.49 (0.41, 0.55) | *0.003* |
| Population density (/km$^2$) | | | | | | |
| Q1 [31, 148] | 5.22 (3.17, 6.97) | Ref | 5.01 (3.03, 6.72) | Ref | 0.21 (0.11, 0.29) | Ref |
| Q2 [148, 352] | 6.77 (4.98, 8.32) | 0.230 | 6.39 (4.56, 7.80) | 0.271 | 0.38 (0.26, 0.45) | *0.011* |
| Q3 [352, 746] | 5.80 (4.15, 7.24) | 0.642 | 5.56 (4.01, 7.05) | 0.652 | 0.24 (0.15, 0.31) | 0.625 |
| Q4 [746, 6423] | 7.68 (6.26, 8.94) | *0.038* | 7.18 (5.72, 8.41) | 0.062 | 0.50 (0.43, 0.57) | *< 0.001* |
| Population size (10$^4$) | | | | | | |
| Q1 [15.3, 35.3] | 5.46 (3.96, 6.85) | Ref | 5.20 (3.77, 6.47) | Ref | 0.27 (0.12, 0.37) | Ref |
| Q2 [35.3, 63.2] | 6.53 (4.63, 8.14) | 0.356 | 6.19 (4.25, 7.80) | 0.384 | 0.35 (0.24, 0.43) | 0.318 |
| Q3 [63.2, 98.7] | 6.46 (4.66, 7.83) | 0.361 | 6.14 (4.48, 7.49) | 0.362 | 0.32 (0.22, 0.40) | 0.525 |
| Q4 [98.7, 951.9] | 7.03 (5.71, 8.17) | 0.105 | 6.61 (5.36, 7.68) | 0.121 | 0.42 (0.36, 0.47) | *0.031* |
| White proportion (%)[b] | | | | | | |
| Q1 [28.1, 58.3] | 7.85 (6.76, 8.94) | Ref | 7.32 (6.27, 8.37) | Ref | 0.53 (0.45, 0.61) | Ref |
| Q2 [58.3, 71.2] | 6.15 (4.34, 7.56) | 0.087 | 5.92 (4.26, 7.24) | 0.132 | 0.22 (0.14, 0.28) | *< 0.001* |
| Q3 [71.2, 80.9] | 6.42 (4.92, 7.74) | 0.116 | 6.09 (4.57, 7.44) | 0.175 | 0.33 (0.23, 0.40) | *< 0.001* |
| Q4 [80.9, 97.7] | 5.94 (4.77, 7.11) | *0.019* | 5.60 (4.43, 6.77) | *0.032* | 0.34 (0.22, 0.43) | *0.005* |
| Elderly proportion (%)[c] | | | | | | |
| Q1 [6.7, 10.2] | 5.50 (3.87, 6.87) | Ref | 5.21 (3.64, 6.62) | Ref | 0.29 (0.20, 0.35) | Ref |
| Q2 [10.2, 11.4] | 6.47 (4.73, 7.94) | 0.387 | 6.13 (4.40, 7.52) | 0.403 | 0.33 (0.23, 0.41) | 0.503 |
| Q3 [11.4, 13.0] | 7.78 (5.98, 9.39) | *0.049* | 7.27 (5.45, 8.84) | 0.074 | 0.51 (0.42, 0.59) | *< 0.001* |
| Q4 [13.0, 22.6] | 7.68 (6.18, 9.18) | *0.044* | 7.29 (5.91, 8.67) | *0.045* | 0.39 (0.30, 0.48) | 0.094 |
| Poverty proportion (%) | | | | | | |
| Q1 [6.5, 10.4] | 6.13 (4.32, 7.94) | Ref | 5.86 (4.12, 7.60) | Ref | 0.27 (0.15, 0.37) | Ref |
| Q2 [10.4, 12.5] | 6.36 (4.93, 7.61) | 0.841 | 6.02 (4.60, 7.30) | 0.887 | 0.34 (0.25, 0.41) | 0.313 |
| Q3 [12.5, 15.8] | 6.75 (4.92, 8.58) | 0.637 | 6.50 (4.51, 8.49) | 0.635 | 0.25 (0.15, 0.33) | 0.783 |
| Q4 [15.8, 27.9] | 8.12 (7.41, 8.83) | *0.045* | 7.60 (6.71, 8.49) | 0.081 | 0.52 (0.43, 0.59) | *< 0.001* |
| Unemployment proportion (%) | | | | | | |
| Q1 [2.7, 4.8] | 5.76 (4.40, 7.12) | Ref | 5.48 (4.14, 6.82) | Ref | 0.28 (0.18, 0.36) | Ref |
| Q2 [4.8, 5.7] | 6.03 (4.44, 7.24) | 0.786 | 5.73 (4.14, 7.05) | 0.804 | 0.30 (0.20, 0.36) | 0.745 |
| Q3 [5.7, 7.5] | 6.79 (5.06, 8.29) | 0.339 | 6.45 (4.65, 8.00) | 0.375 | 0.33 (0.23, 0.42) | 0.454 |
| Q4 [7.5, 11.8] | 7.67 (6.51, 8.83) | *0.036* | 7.17 (6.04, 8.30) | 0.059 | 0.50 (0.42, 0.56) | *< 0.001* |
| High education proportion (%)[d] | | | | | | |
| Q1 [65.8, 77.9] | 7.56 (6.36, 8.76) | Ref | 7.08 (5.82, 8.34) | Ref | 0.48 (0.40, 0.55) | Ref |
| Q2 [77.9, 82.6] | 6.01 (4.38, 7.40) | 0.115 | 5.72 (4.12, 7.04) | 0.167 | 0.30 (0.21, 0.37) | *< 0.001* |
| Q3 [82.6, 85.1] | 5.64 (4.26, 7.02) | *0.040* | 5.37 (3.96, 6.78) | 0.076 | 0.27 (0.16, 0.35) | *< 0.001* |
| Q4 [85.1, 92.2] | 5.95 (4.42, 7.48) | 0.105 | 5.58 (4.27, 6.89) | 0.106 | 0.37 (0.25, 0.46) | 0.095 |

*AF* attributable fraction, *CI* confidence interval

[a] The lowest quartile (Q1) of community-specific characteristics was set as the reference. Stratum-specific estimates were compared through a likelihood ratio test based on the meta-regression model. Italic emphasis indicated that the comparison between subgroup AF was statistically significant

[b] Percentage of people with White race

[c] Percentage of people ≥ 65 years old

[d] Percentage of people with 9+ education years

Vietnam, and Philippines) (Lee et al. 2017). By including 16 large cities across mainland China, Yang et al. attributed respectively a combined fraction of 17.1% (14.4 to 19.1) of CVD mortality and 14.5% (11.5 to 17.0) of stroke mortality to ambient temperature (Yang et al. 2015; Yang et al. 2016). In spite of substantial differences among study cities, these multi-city studies provided strong evidence of the great burden of CVD mortality attributable to non-optimum temperature exposures. This would have some important implications in providing alterative targets for public health intervention, especially in countries/locations with high CVD prevalence or temperature-related burden.

In the context of global warming, heat-mortality assessment has arouse extensive attention all around the world during the past decades (Basu 2009; Hajat and Kosatky 2010). Our study indicated that most of the attributable cardiorespiratory deaths were caused by cold days, with a proportion of more than 90% in temperature-associated mortality burden. This result was broadly congruent with prior AF-based temperature-mortality studies at the regional (Carson et al. 2006), national (Yang et al. 2015; Yang et al. 2016), and international scales (Gasparrini et al. 2015). The substantial difference between cold- and heat-attributable mortality was mainly due to the high minimum mortality percentiles (Fig. 1), resulting in most days with temperatures lower than the optimum temperature (Gasparrini et al. 2015). According to the projection of temperature-attributable deaths under different climate change scenarios, cold-related mortality will decrease gradually while heat-related mortality will increase rapidly (Ballester et al. 2011; Gasparrini et al. 2017; Guo et al. 2016; Vardoulakis et al. 2014; Weinberger et al. 2017). Even the balance of these differences may vary across locations, a net increase of temperature-attributable deaths is foreseeable in 209 US cities under future climate change, assuming constant temperature-mortality relationships without any future adaptation (Schwartz et al. 2015). Also, there is emerging evidence showing similar trends for temperature-related years of life lost projection (Li et al. 2018a, b). However, cold weather will still remain to be an important public health threat in most regions across the world (Gasparrini et al. 2017). Therefore, effective climate policies in response to future global warming should also take into comprehensive consideration cold-related health impacts.

In mainland USA, our results showed some regional differences in the estimated temperature-related burden on cardiorespiratory mortality, with the highest attributable fraction observed in Industrial Midwest and North East (Table 2 and Fig. 2). This could be partly related to the low longitudes and high latitudes of included locations in these two regions, which were associated with increased estimates of AF caused by both cold and heat (Table 3). Also, there was existing epidemiological evidence indicating that latitude and longitude may modify temperature-mortality associations (Guo et al. 2017; Huang et al. 2015; Moghadamnia et al. 2017; Xiao et al. 2015). However, these investigations focused on mortality risk rather than attributable fraction, making its results less comparable with the present study. Since geographical coordinates like latitudes are usually highly correlated with local climate characteristics (especially for temperature distribution), geographical effect modification could be regarded as the indirect contribution of climate and acclimatization, as previously discussed (Curriero et al. 2002; Huang et al. 2015; Medina-Ramon and Schwartz 2007). This assumption was also observed in our subgroup results stratified by latitude and average temperature. Additionally, we found unforeseen evidence that moderate humid regions suffered greatly from temperature-related burden, which was somewhat inconsistent with a recent multi-city study in Zhejiang Province, China, linking elevated AF with high humidity (Zeng et al. 2017). Such discrepancy in effect modification by humidity is generally difficult to unravel, since relevant AF-based evidence was rather sparse worldwide. Further epidemiological investigations are thus needed to clarify whether and how humidity mediates or modifies the temperature-attributable mortality.

Due to the degradation of physiological function and adaptive ability, together with the prevalence of pre-existing chronic conditions, the elderly were generally vulnerable to mortality risk associated with both cold and heat (Benmarhnia et al. 2015; Yu et al. 2012). Our results showed elevated temperature-attributable burden of cardiorespiratory mortality as age increased (Table 2). Similar findings were also elucidated in two multi-city studies in Europe (Baccini et al. 2011) and mainland China (Yang et al. 2015). At the community level, epidemiologic evidence has suggested that high proportion of people aged 65+ years tended to enhance heat-related mortality risk (Chen et al. 2016; Hajat and Kosatky 2010; Huang et al. 2015), as also highlighted in the present study. In the context of population aging and global warming, the health burden caused by heat may dramatically increase in the coming decades (Lee and Kim 2016; Li et al. 2016). For cold-related mortality effects, however, this amplified evidence was not consistently observed (Curriero et al. 2002; Huang et al. 2015).

According to previous findings (Benmarhnia et al. 2015; Phung et al. 2016; Romero-Lankao et al. 2012), persons with low individual-level socioeconomic status (SES) generally exhibited high vulnerability to health risks associated with extreme temperatures, because of poor living conditions, low cognitive ability, and limited access to health care, etc. For the well-documented heat effects, a meta-analysis including 15 studies showed a RR ratio of 1.03 (1.01, 1.05) in low-SES persons relative to those with high SES (Benmarhnia et al. 2015). In this study, we assessed the potential effect modification of community-level ecologic SES on temperature-attributable mortality. The results congruously indicated that poverty, unemployment, and low average education years could worsen cold- and heat-related burden (Table 4), which greatly agreed with several previous investigations in USA (Anderson and Bell 2009; Zanobetti et al. 2013). In comparison with heat effects, these socioeconomic factors were less significant in explaining cold-attributable mortality. Such phenomenon could be also ascertained in a prior RR-based analysis using similar dataset (Anderson and Bell 2009). Racial and ethnic disparities in temperature-associated morbidity and mortality have been observed in previous evidence (Gronlund 2014; Taylor et al. 2018). In American cities, being a racial or ethnic minority (e.g., black or Non-Hispanic) is generally associated with poorer physical health and lower individual SES. Hence, an extremely low proportion of White race may reflect a low ecologic SES, thus leading to raised temperature-related vulnerability.

Due to potential differences in many aspects such as population structure and density, lifestyles, and public infrastructure, rural and urban regions may show some disparity in susceptibility to mortality in temperature extremes (Bennett et al. 2014; Ma et al. 2015b; Madrigano et al. 2015; Zhang et al. 2017). Until now, however, research has not yielded a consensus on this topic (Chen et al. 2016; Gabriel and Endlicher 2011; Sheridan and Dolney 2003). In this national investigation spanning across 106 US urban communities, we found significantly greater burden in highly urbanized areas than those with low-moderate urbanization level. Our subgroup analyses by population density and population size provided additional positive evidence for this finding. Several prior heat-mortality studies also found greater vulnerability in communities characterized by more urbanized areas and higher population densities (Goggins et al. 2012; Ma et al. 2015b), which was generally linked with the presence of an urban heat island effect in densely-populated metropolises. However, the underlying reasons for increased cold-attributable mortality burden might be considerably complex but might have some practical significance in public health early warming and policy making.

This study has several limitations that should be acknowledged. First, in line with several previous large-scale studies, we used a single temperature point (i.e., MMP) to calculate the attributable fraction. Nevertheless, emerging evidence showed that the 95% confidence intervals for MMP can be quite large, suggesting the caution and uncertainty of using a single temperature point in temperature-AF estimation (Tobias et al. 2017). Second, some ecological biases including exposure misclassification may exist when using a time-series study design to assess temperature-mortality associations (Gasparrini and Armstrong 2010). Third, the included 106 communities could be only regarded as a national representative of US urban areas, thus limiting the generalization of our results to the rural populations. Fourth, in our main analysis, we did not take into consideration the effects of air pollution due to data unavailability in many communities. However, previous evidence has suggested that temperature-related mortality effects changed little with and without adjusting for air pollutants (Gasparrini et al. 2015; Guo et al. 2014; Lim et al. 2015). Additionally, as shown in our sensitive analyses (Table S5) and a previous investigation (Gasparrini et al. 2015), estimates of temperature-AF may be influenced by model specifications such as lag periods. Motivated by previous multi-country investigations using similar database in US communities, we chose a lag period of 21 days to assess temperature-AF. This may also pose some uncertainty on our results, because there is still no consensus on model choices under the DLNM framework (Gasparrini et al. 2010).

## Conclusions

In summary, our results strengthened the evidence that both low and high temperatures increased short-term risks of cardiorespiratory mortality. Despite some regional differences in estimates of attributable fraction, cold weather was consistently found to be responsible for the most majority of temperature-related mortality burden. Moreover, the estimated burden varied considerably by geographical and climatological factors, as well as community-level disparity in socioeconomic status. These findings may contribute to the promotion of climate-related public health decision-making aiming to protect vulnerable populations and communities from ambient extreme temperatures.

**Acknowledgments** We greatly thank the developers of the National Mortality Morbidity Air Pollution Studies (NMMAPS), and thank Dr. Roger D. Peng and his colleagues for making the NMMAPS database publicly available. Additionally, we thank the anonymous reviewers very much, whose insightful comments and suggestions contributed a lot to improving the quality of our manuscript.

**Author contributions** Yunquan Zhang conceived and designed the experiments; Zan Ding and Zhiying Zhan collected the data; Yunquan Zhang performed the data analysis; Yunquan Zhang, Qianqian Xiang, and Yong Yu drafted the manuscript. Zan Ding and Kejia Hu helped revise the manuscript. All authors read and approved the final manuscript.

## Compliance with ethical standards

**Conflict of interest** The authors declare they have no competing financial interests.

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