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Temperature change between neighboring days and mortality in United States: A nationwide study

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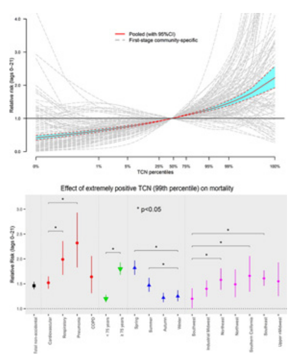
HIGHLIGHTS

- The impact of TCN on mortality and effect modification are insufficiently studied.
- A large multi-city analysis at national level was conducted in United States.
- A significant non-linear TCN–mortality association at national level was observed.
- Positive TCN was associated with an elevated risk, varied with region and season.
- Older people and those with respiratory disease were particularly susceptible to TCN.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Temperature change between neighboring days (TCN), an indicator to reflect sudden temperature variation, has been identified as an independent risk factor for human health by small-scale studies. However, the adverse impact of TCN on mortality and effect modification are insufficiently studied, and a larger multi-cities analysis at national level is needed to provide an insightful knowledge.
Methods: Using daily mortality and meteorological data from 106 communities of United States during 1987 to 2000, we employed a quasi-Poisson regression with distributed lag non-linear model to quantitatively estimate the effect of TCN on mortality for each community and a multivariate meta-analysis to pool the community-specific estimates.
Results: At national level, a monotonic increasing curve of TCN–mortality association was observed, which indicated that negative TCN (temperature decrease from the previous day) was associated with reduced mortality and positive TCN (temperature increase) elevated the risk of mortality. The relative risk for lag 0–21 days was 0.63 (95% confidence interval: 0.59–0.68) for extremely negative TCN (1st percentile) and 1.46 (1.39–1.54) for extremely positive TCN (99th percentile) on non-accidental mortality. We also found prominent effects of extreme TCNs on mortality for cardiovascular, respiratory, pneumonia, and COPD diseases. People ≥75 years and those with respiratory disease, especially pneumonia-deaths, were identified as a particularly vulnerable population to TCN. The TCN–mortality association was modified by season and region.

Abbreviations: AT, apparent temperature; CI, confidence interval; *df*, degrees of freedom; DLNM, distributed lag non-linear model; TCN, temperature change between neighboring days; DTR, diurnal temperature range; RR, relative risk; RRR, relative risk ratio.

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Conclusions: A positive TCN was associated with an elevated risk of mortality in United States, with different effect patterns by region and season. Identification of the effect modifiers presented a significantly stronger influence on older adults and those with respiratory disease.

1. Introduction

Human health is sensitive to weather and climate (Hosking and Campbell-Lendrum, 2012; McMichael, 2013). Numerous studies have focused on the effects of absolute ambient temperatures such as daily minimum, mean, maximum, and apparent temperature on mortality, proposing a W-, J-, V-, or U-shaped temperature–mortality association (Carmona et al., 2016; Chung et al., 2015; Curriero et al., 2002; Gasparrini et al., 2015; Guo et al., 2014; Ma et al., 2015; Wu et al., 2013). Meanwhile, an increasing number of epidemiological studies have discovered significant effects of short-term temperature variations such as diurnal temperature change (DTR) (Lim et al., 2012, 2015; Zhou et al., 2014) and temperature change between neighboring days (TCN) (Cheng et al., 2016; Ikram et al., 2015; Liu et al., 2015; Xu et al., 2014) on human health. DTR (calculated as maximum temperature minus minimum temperature within 1 day) was usually adopted as an intra-day indicator of temperature variation while TCN (calculated as the current day's temperature minus the previous day's temperature) as an inter-day indicator (Guo et al., 2016; Vicedo-Cabrera et al., 2016).

Although many investigations have focused on the DTR–mortality association and vulnerable populations for large DTR (Ding et al., 2015, 2016a; Kim et al., 2016; Lim et al., 2012, 2015; Yang et al., 2013; Zhou et al., 2014), less evidence is available on the adverse effect of TCN on mortality (Cheng et al., 2016; Liu et al., 2015; Vicedo-Cabrera et al., 2016). TCN may be an important meteorological indicator to reflect short-term temperature stability and has been recently identified as an independent risk factor for human health (Cheng et al., 2014, 2016; Ikram et al., 2015; Liu et al., 2015; Xu et al., 2014). A relevant research indicated that sudden temperature change was associated with risk factors of human health (e.g., increased levels of blood cholesterol, plasma fibrinogen concentration, platelet viscosity, peripheral vasoconstriction, heart rate, and blood pressure) (Schneider et al., 2008). Several previous reports on the TCN–mortality association were conducted only in a single city or a small number of cities (Guo et al., 2011; Lin et al., 2013; Vicedo-Cabrera et al., 2016), and a larger multi-city analysis at national level, covering a wide range of climate patterns and latitudes, is needed to provide a better understanding of the association.

Previous studies have shown that the TCN–mortality association was non-linear, and excess deaths were not only caused by the current day's TCN, but also by the exposure during the several previous days, even weeks (so-called lag effects) (Cheng et al., 2014; Guo et al., 2011; Lin et al., 2013). A distributed lag non-linear model (DLNM) has been commonly used to assess the exposure–response association, with an absolute advantage to simultaneously present the non-linear and lag effects between a predictor and an outcome in time-series data (Gasparrini et al., 2010). On the other hand, little information is available on effect modification of the TCN–mortality association to identify vulnerable subpopulations, which might be essential for improving awareness of high risk groups to protect themselves. A few previous small-scale investigations suggested that age, gender, mortality cause, and season might modify the effect of TCN on mortality, without testing the significance of effect modification (Cheng et al., 2014; Guo et al., 2011; Ikram et al., 2015; Lin et al., 2013).

Therefore, the aim of this study was to examine the TCN–mortality association at the national level of United States, using a regression model combined with DLNM to estimate the impact of TCN across a wide range of communities and employing a multivariate meta-analysis to combine the community-specific results. We also aimed to evaluate the effect modification of the effect of TCN on mortality by mortality causes, age, season, and region. The geography and climate of United States are extremely diverse. Based on the national data from United States with over 320 million people and 9.9 million km^2 areas, our study could provide a better understanding for the association between TCN and mortality and the effect modification.

2. Materials and methods

2.1. Data collection

We downloaded the National Morbidity, Mortality, and Air Pollution Study (NMMAPS) data, a publicly available database covering 108 urbanized communities across United States, from the Internet-based Health and Air Pollution Surveillance System (IHAPSS). A detailed description of NMMAPS can be found elsewhere (Dominici et al., 2002; Samet et al., 2000). It consists of daily time-series data of mortality, weather conditions, and air pollution concentrations from January 1, 1987 to December 31, 2000 (totally 5114 days) for each community. The daily numbers of deaths from non-accidental, cardiovascular, respiratory, pneumonia, and chronic obstructive pulmonary disease (COPD) causes were extracted, and we collapsed the non-accidental mortality into 2 categories (<75 and ≥ 75 years old). Daily meteorological data including temperatures (mean, minimum, and maximum), mean relative humidity, and mean dew point temperature were also extracted.

Our study included a total of 106 large communities in the mainland of United States with adequate data. As shown in Fig. 1, we divided the communities into 7 geographical regions: Northeast, Industrial Midwest, Upper Midwest, Northwest, Southeast, Southwest, and South California. Daily temperatures measured in degrees Fahrenheit were transformed into degrees Centigrade. Daily mean apparent temperature (AT), an aggregative indicator of temperature and humidity, was calculated through the formula: $AT = -2.653 + 0.994 \times$ mean temperature $+ 0.0153 \times$ (dew point temperature)^2 (Davis et al., 2016; Lim et al., 2015). According to previous studies (Cheng et al., 2016; Guo et al., 2011; Lin et al., 2013; Xu et al., 2014; Vicedo-Cabrera et al., 2016), TCN that calculated by subtracting the previous day's mean temperature from the current day's mean temperature was chosen as the exposure index, as mean temperature represents the exposure throughout the whole day and night. Negative TCN represents temperature decrease and positive TCN represents temperature increase between neighboring days.

2.2. Statistical analysis

Although the community-specific TCN–mortality association was usually considered with an absolute scale of TCN, this might make it difficult to combine the cumulative exposure-response curves across communities with non-overlapping TCN ranges; thus, the effect of TCN on mortality in each community was elevated in terms of percentiles of TCN distribution. In the current study, we used a three-stage approach to analyze data.

In the first stage, we used a quasi-Poisson regression model combined with a DLNM to quantitatively estimate the magnitude of the effect of TCN on mortality for each community, assuming a quasi-Poisson distribution allowing for overdispersed daily death counts. As a flexible “cross-basis” function, TCN was defined by a combination of a B-spline with 5 degrees of freedom (*df*) for TCN space to cover the tails of the community-specific TCN distribution (knots at 10th, 50th, and 90th percentiles) and a natural cubic spline with 4 *df* for lag space (knots at

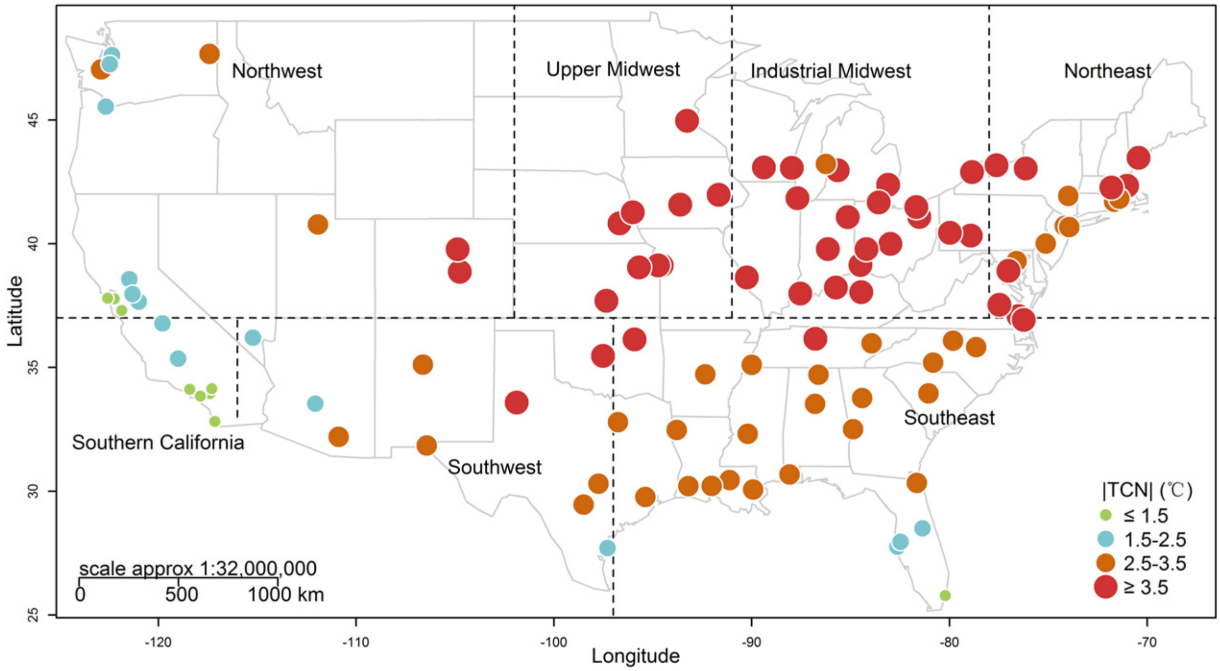

Fig. 1. Average of absolute value of daily temperature change between neighboring days (TCN) for 106 communities from 1987 to 2000 shown on American geographic map.

equally spaced log-values). According to previous studies (Cheng et al., 2014; Xu et al., 2014), we used a maximum lag of 21 days for lag effects of TCN. A natural cubic spline with 7 *df* per year for time was used to control for the seasonal patterns and long-term trends, and the moving average of lag 0–3 days for mean temperature ($MeanT_{0-3}$) was controlled by the use of a natural cubic spline with 3 *df* at equally spaced quantiles. The effect of day of week (*DOW*) was also controlled as a categorical variable. Thus, the core model is given as following:

$$Y_t \sim Poisson(\mu_t)$$
$$Log(\mu_t) = \alpha + \beta TC_{t,l} + NS(Time_t, 14 \times 7) + NS(MeanT_{0-3t}, 3) + \gamma DOW_t \quad (1)$$

where t is the day of observation ($t = 1, 2, 3\ldots5114$), and Y_t is the observed daily death counts; α is the intercept; $TC_{t,l}$ is a matrix of variables obtained through the DLNM to model non-linear and distributed lag effects of TCN, β is the vector of coefficients for $TC_{t,l}$, and l is the lag days; $NS(.)$ is the natural cubic spline. γ is the coefficient vector of *DOW*.

A TCN of 0 °C was used as a reference for calculating relative risks (RRs) and 95% confidence intervals (CIs) across the study period. We defined the 1st and 99th percentiles of daily TCN distribution as extremely negative and positive TCNs, respectively, and we examined the effects of extreme TCNs for the whole sample and specified subgroups of mortality causes, age, and region. In addition, the effects of extreme TCNs were examined for the whole period, as well as stratifying by the spring (March to May), summer (June to August), autumn (September to November), and winter (December to February of the next year), as season might modify the TCN–mortality association. In the stratification analyses by season, we used a natural cubic spline with 3 *df* per season (3 months) for time (i.e., the sequence of days of calendar time for a specific season of 14 years) in the core model to control for the long-term trends and seasonality. For example, in the summer season analysis, time = 1, 2, 3… 1288 (each summer season has 92 days, 1288 = 92 × 14).

In the second stage, a multivariate meta-analysis with a random effects model by maximum likelihood was used to pool reduced estimates at the regional or national level, as methods previously described (Gasparrini et al., 2012). For the reduced estimates, the community-specific bi-dimensional parameters of the cross-basis function of TCN obtained from the first-stage model were reduced to one-dimensional summary, expressing the overall cumulative exposure–response relationship (Gasparrini and Armstrong, 2013). The reduction was performed for the summary by transforming the original parameter beta of the cross-basis above to compute parameters gamma for the one-dimensional natural cubic splines, which reduced the number of parameters to be pooled and preserved the complexity of the estimated dependency (Gasparrini and Armstrong, 2013). We assessed the heterogeneity across communities through a Cochran Q test and a multivariate extension of I^2 index (Gasparrini et al., 2012).

In the third stage, to identify which subgroup was particularly vulnerable to TCN, relative risk ratio (RRR) with 95% CI was employed to test the statistically significant difference between subgroups of each potential effect modifier (i.e., mortality causes, age, season, or region). We created separate models stratified by the modifiers of the TCN–mortality association, and then calculated the RRR, the ratio of 2 *RRs* of the strata of each modifier (e.g., the difference between cardiovascular-deaths and respiratory-deaths), and its 95% CI using the following equation:

$$Exp\left[(\ln(RR_1) - \ln(RR_2)) \pm 1.96\sqrt{Se_1^{\,2} + Se_2^{\,2}}\right] \quad (2)$$

where RR_1 and RR_2 are the estimates for the 2 subgroups; Se_1 and Se_2 are the standard errors of $\ln(RR_1)$ and $\ln(RR_2)$ (Ding et al., 2016b; Zeka et al., 2006). The natural logarithm transformation is necessary to make RRs asymptotically normal due to RRs are not generally normal distributed. A hypothesized modifier significantly modified the TCN–mortality association if the new 95% CI of RRR did not include 1. R software version 3.1.2 (R Foundation for Statistical Computing, http://www.R-project.org) was used for data analysis, with "dlnm" package to create the community-specific DLNMs in the first-stage and "mvmeta" package to fit the multivariate meta-analyses.

3. Results

3.1. Descriptive statistics

Fig. 1 illustrates the distinct patterns of TCN and Table 1 summarizes the descriptive statistics for weather conditions of United States from

1987 to 2000. Most communities from Upper Midwest, Industrial Midwest, and Northeast regions had a large temperature variability (|TCN| ≥ 3.5 °C) while some from Northwest and Southern California with small variability (|TCN| ≤ 1.5 °C) (Fig. 1). As shown in Table 1, at national level, the average TCN was 0.0 °C (range, −29.9 °C to 24.7 °C) for the whole period, and season-specific average TCN was 0.2 °C (−25.3 °C to 22.4 °C), 0.0 °C (−18.2 °C to 13.9 °C), −0.2 °C (−23.1 °C to 18.0 °C), and 0.0 °C (−29.9 °C to 24.7 °C) for spring, summer, autumn, and winter, respectively; compared to the warm season (summer and autumn), temperature fluctuated more markedly in the cold season (spring and winter), with larger ranges and standard deviations of TCN. Similar seasonal patterns of TCN were found in all 7 geographical regions. At regional level, southern regions (Southern California, Southwest, and Southeast; 1.8–3.5 °C) were more stable than northern regions (Northwest, Upper Midwest, Industrial Midwest, and Northeast; 2.8–4.5 °C), with smaller standard deviations of TCN; eastern regions (Northeast and Southeast; 4.1 °C and 3.5 °C) changed more markedly than western regions (Northwest, Southern California, and Southwest;

Table 1
Summary statistics of daily weather conditions (TCN by season[a] and region) for 106 communities of United States, 1987–2000.

	Mean	SD	Min	Percentiles					Max
				1st	25th	50th	75th	99th	
TCN (°C)									
National level									
Full year	0.0	3.7	−29.9	−11.3	−1.7	0.2	2.0	8.9	24.7
Spring	0.2	4.0	−25.3	−11.8	−1.7	0.5	2.4	9.3	22.4
Summer	0.0	2.6	−18.2	−7.6	−1.3	0.2	1.6	6.2	13.9
Autumn	−0.2	3.6	−23.1	−11.1	−1.8	0.1	1.8	8.2	18.0
Winter	0.0	4.4	−29.9	−12.8	−2.2	0.2	2.5	10.4	24.7
Southwest region									
Full year	0.0	3.4	−25.3	−10.8	−1.4	0.3	1.8	7.6	18.7
Spring	0.2	3.7	−25.3	−11.5	−1.5	0.6	2.2	8.5	15.8
Summer	0.0	2.4	−15.7	−7.6	−1.0	0.1	1.1	6.1	11.7
Autumn	−0.2	3.3	−21.3	−11.2	−1.5	0.2	1.7	6.8	14.4
Winter	0.0	3.9	−24.8	−12.1	−1.7	0.5	2.3	8.3	18.7
Industrial Midwest region									
Full year	0.0	4.3	−28.5	−12.4	−2.2	0.3	2.6	10.0	22.4
Spring	0.2	4.7	−25.1	−13.7	−2.2	0.6	3.2	10.4	22.4
Summer	0.0	3.0	−17.8	−8.3	−1.7	0.3	1.8	6.5	13.9
Autumn	−0.2	4.2	−21.7	−12.2	−2.5	0.1	2.4	9.4	16.4
Winter	0.0	5.0	−28.5	−13.8	−2.8	0.1	3.2	11.3	20.5
Northeast region									
Full year	0.0	4.1	−22.5	−11.7	−2.2	0.2	2.4	9.8	23.2
Spring	0.2	4.3	−22.5	−12.1	−2.2	0.5	2.8	10.3	20.4
Summer	0.0	3.0	−16.9	−8.1	−1.7	0.2	1.8	7.2	13.3
Autumn	−0.2	3.9	−18.3	−11.0	−2.4	0.1	2.2	8.7	16.7
Winter	0.0	4.9	−22.3	−13.3	−2.7	0.2	3.0	11.2	23.2
Northwest region									
Full year	0.0	2.8	−23.7	−8.4	−1.4	0.1	1.7	7.0	24.7
Spring	0.1	3.0	−23.7	−8.9	−1.4	0.2	1.8	7.2	16.2
Summer	0.0	2.7	−18.2	−7.8	−1.4	0.2	1.7	6.1	12.1
Autumn	−0.1	2.8	−20.8	−8.6	−1.5	0.0	1.4	6.6	18.0
Winter	0.0	2.8	−21.5	−8.4	−1.3	0.0	1.4	7.8	24.7
Southern California region									
Full year	0.0	1.8	−16.1	−5.1	−0.8	0.0	0.9	4.6	12.9
Spring	0.1	2.0	−16.1	−5.8	−0.8	0.1	1.1	4.9	12.7
Summer	0.0	1.5	−12.2	−4.6	−0.6	0.0	0.8	4.0	12.9
Autumn	−0.1	1.7	−13.8	−5.1	−0.9	−0.1	0.7	4.4	10.3
Winter	0.0	1.8	−8.2	−4.7	−1.1	0.0	1.1	5.0	8.8
Southeast region									
Full year	0.0	3.5	−27.9	−11.1	−1.5	0.3	1.9	7.9	18.1
Spring	0.1	3.6	−22.6	−11.1	−1.5	0.5	2.2	7.8	16.7
Summer	0.0	2.2	−14.0	−6.2	−1.1	0.1	1.2	5.1	9.7
Autumn	−0.2	3.3	−19.4	−10.8	−1.6	0.2	1.7	7.1	14.2
Winter	0.0	4.6	−27.9	−13.1	−2.3	0.6	2.8	9.5	18.1
Upper Midwest region									
Full year	0.0	4.5	−29.9	−12.7	−2.4	0.3	2.8	10.6	19.4
Spring	0.2	4.8	−22.9	−13.3	−2.5	0.6	3.3	11.0	19.0
Summer	0.0	3.1	−14.9	−8.7	−1.6	0.4	2.0	6.5	13.1
Autumn	−0.2	4.5	−23.1	−13.2	−2.8	0.2	2.7	9.4	16.8
Winter	0.0	5.3	−29.9	−14.2	−3.0	0.2	3.3	12.6	19.4
|TCN| (°C)	2.7	2.6	0.0	0.0	0.8	1.9	3.7	11.9	29.9
Mean temperature (°C)									
Full year	15.4	9.9	−30.0	−9.6	8.5	16.5	23.3	32.8	46.2
Spring	15.0	7.6	−18.1	−4.0	10.0	15.5	20.6	29.3	39.0
Summer	24.9	4.8	5.0	13.7	21.7	25.2	28.3	36.1	46.2
Autumn	15.9	7.7	−19.0	−2.6	10.7	16.5	21.7	30.6	39.9
Winter	5.6	8.2	−30.0	−15.0	0.2	5.7	11.6	22.8	30.3
Min temperature (°C)	9.1	9.6	−36.1	−15.6	2.2	9.4	16.7	25.6	34.4
Max temperature (°C)	20.4	10.6	−27.2	−5.6	13.3	21.7	28.9	39.4	59.4
Relative humidity (%)	65.7	18.0	4.4	17.3	54.4	67.6	78.9	97.4	100.0

TCN, temperature change between neighboring days; SD, standard deviation; |TCN|, absolute value of TCN.

[a] Spring, March to May; summer, June to August; autumn, September to November; winter, December to February of the next year.

1.8–3.4 °C). TCN also obviously varied across 106 communities of United States (Table S1). The national average of daily minimum, mean, and maximum temperature and relative humidity was 9.1 °C, 15.4 °C, 20.4 °C, and 65.7%, respectively. TCN is positively correlated with mean temperature in all communities and seasons, with low-to-moderate correlations ranging from 0.05 to 0.49 (Table S2).

Table 2 displays the statistics for the number of daily deaths by mortality causes, age, season, and region. A total of 10,302,030 non-accidental deaths (5,252,586 people ≥75 years of age) in United States were covered during 1987–2000, with over half of them died from cardio-respiratory disease. At national level, the daily average number of non-accidental deaths was 2014.5, with a crude diurnal death rate of 1.87 per 100,000. The diurnal death rate of older people (≥75 years) was 18.03/100,000. More people died during the cold (2.06/100,000 for winter and 1.87/100,000 for spring) than warm season (1.75/100,000 for summer and 1.81/100,000 for autumn). The diurnal death rates per 100,000 in Industrial Midwest, Northeast, and Upper Midwest regions (2.20–2.31) were much higher than those in the other regions (1.49–1.78).

3.2. TCN–mortality association

A statistically significant association between TCN and mortality on average for 106 large communities of United States was found. Fig. 2 shows the pooled cumulative effect of TCN on non-accidental mortality at national level, together with 106 community-specific curves. The TCN–mortality association varied across communities; most communities presented a protective effect for negative TCN and a risky effect for positive TCN. With an RR of 1 for 0 °C TCN, the pooled association was a monotonic increasing curve from left to right, which indicated that a negative TCN reduced the risk of mortality and a positive TCN elevated the risk at national level. The non-linear line rapidly increased when TCN was over 95th percentile of distribution, meaning that a large temperature increase between neighboring days had a profound adverse impact on mortality. The multivariate Cochran Q test for heterogeneity was significant ($P < 0.001$), and the I^2 statistics indicated that 27.8% of the total variability was attributable to between-study heterogeneity.

3.3. Effects of extreme TCNs on mortality

Fig. 3 shows the cumulative effects of extremely negative and positive TCNs on non-accidental mortality for 106 communities of United States. Consistent with the directions of estimated effects at regional and national levels, a significant protective effect of extremely negative TCN (RR < 1) was discovered among 38 communities and a significant risky effect of extremely positive TCN (RR > 1) among 43 communities. In general, the magnitude of estimated effects varied with community, with a median (inter-quartile range) value of 0.61 (0.48–0.78) for extremely negative TCN and 1.48 (1.19–1.91) for extremely positive TCN. The effects of extreme TCNs on mortality could persist for 3 weeks, with the strongest effect at lag 2–4 days (Fig. S1).

Table 3 presents the effects of extreme TCNs on mortality for the whole sample and specified subgroups for lag 0–21 days. The RRs of extremely negative and positive TCNs on non-accidental mortality were 0.63 (95% CI, 0.59–0.68) and 1.46 (1.39–1.54). For specific causes of death, the RR of extremely positive TCN on cardiovascular, respiratory, pneumonia, and COPD mortality for lags 0–21 was 1.52 (1.40–1.65), 1.99 (1.68–2.36), 2.32 (1.83–2.93), and 1.64 (1.31–2.06), respectively.

3.4. Effect modification of TCN–mortality association

Table 3 also presents the effect modification of the effects of extreme TCNs on mortality by mortality causes, age, season, and region. Compared to people dying from cardiovascular cause, decedents from respiratory disease showed an increased risk of dying on extremely positive TCN days, with a RRR of 1.31 (95% CI, 1.08–1.58). Especially, people with pneumonia, a subset of respiratory, were the most vulnerable to extreme TCNs, with RRRs of 0.57 (0.42–0.77) for extremely negative TCN and 1.53 (1.19–1.95) for extremely positive TCN. However, the risks of dying from COPD did not differ from those of dying from cardiovascular cause (Table 3). Compared with younger group, people ≥75 years showed a greater risk of the association of extremely positive TCN and non-accidental mortality, with a RRR of 1.50 (1.36–1.64).

Extremely positive TCN affected individuals more heavily during spring (1.82 [1.68–1.97]) and summer (1.47 [1.34–1.62]) than winter (1.25 [1.15–1.37]), but no significant difference between autumn and winter was detected. For the effect of extremely positive TCN on non-

Table 2
Summary statistics for daily non-accidental mortality by mortality causes, age, season[a], and region for 106 communities of United States, 1987–2000.

	Total deaths	Diurnal death rate[b]	Mean	SD	Min	25%	50%	75%	Max
Total non-accidental	10,302,030	1.87	2014.5	164.3	1661	1892	1979	2107	2813
Cause-specific									
Cardiovascular	4,514,122	0.82	882.7	87.3	678	817	867	937	1230
Respiratory	887,166	0.16	173.5	41.5	97	145	163	193	412
Pneumonia	423,395	0.08	82.8	23.5	32	67	78	93	227
COPD	459,695	0.08	89.9	21.0	40	75	87	100	210
Age (years)									
<75	5,049,444	0.97	987.4	71.3	793	939	985	1033	1300
≥75	5,252,586	18.03	1027.1	130.1	769	933	1007	1098	1671
Season									
Spring	2,589,526	1.87	2010.5	108.3	1716	1936	2000	2074	2453
Summer	2,421,577	1.75	1880.1	67.3	1661	1837	1880	1920	2382
Autumn	2,484,706	1.81	1950.3	85.8	1708	1885	1948	2011	2242
Winter	2,806,621	2.06	2220.1	142.6	1932	2123	2198	2295	2813
Region (number of communities)									
Southwest (10)	781,243	1.54	152.8	26.0	85	134	151	168	267
Industrial Midwest (20)	2,282,676	2.31	446.4	39.7	342	418	442	470	828
Northeast (19)	2,101,570	2.31	410.9	43.3	289	380	407	439	614
Northwest (14)	1,050,168	1.58	205.4	23.3	145	189	203	220	308
Southern California (7)	1,518,114	1.49	296.9	37.0	218	272	291	314	541
Southeast (27)	2,099,169	1.78	410.5	39.7	310	383	406	432	588
Upper Midwest (9)	469,090	2.20	101.0	12.1	64	93	100	108	157

COPD, chronic obstructive pulmonary disease.
[a] Spring, March to May; summer, June to August; autumn, September to November; winter, December to February of the next year.
[b] The daily average death counts per 100,000 population, based on the 2000 United States population census.

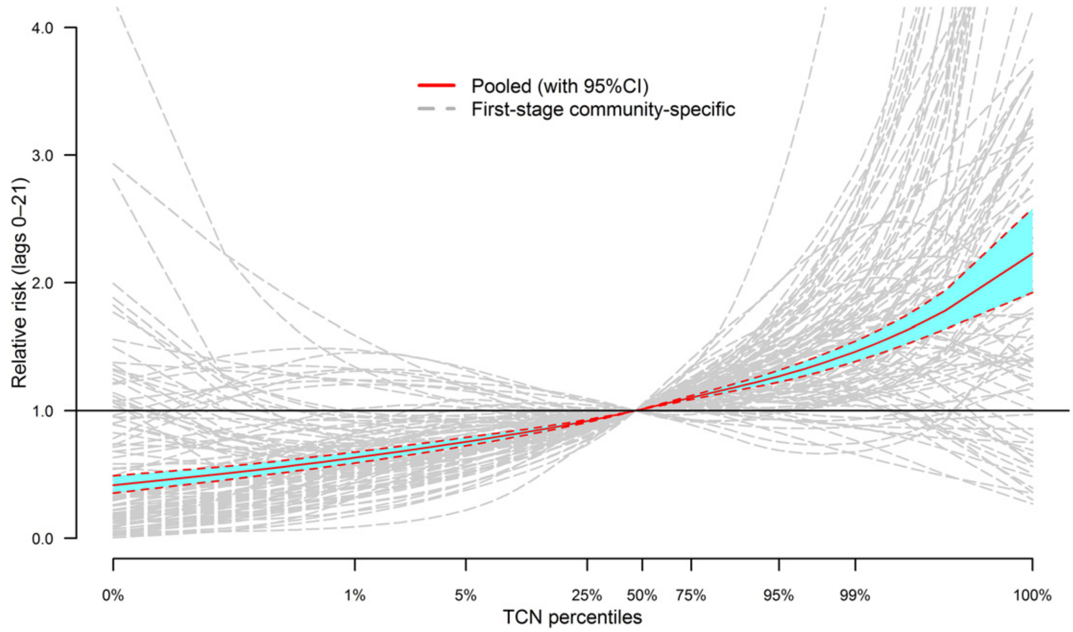

Fig. 2. Pooled cumulative association curve of TCN and non-accidental mortality at the national level of United States from the multivariate meta-analysis (red curve), together with 106 community-specific curves (grey dotted lines). The percentiles on the x-axis correspond to the average distribution of TCN across all communities; reference to 0 °C.

accidental mortality, we found some evidence of regional differences, with the highest effect of 1.66 (1.34–2.06) in Southern California and the smallest RR of 1.20 (1.01–1.41) in Southwest region. Southern California, Southeast, and Northeast had higher mortality risks on extremely positive TCN days than Southwest, with RRRs from 1.32 (1.07–1.64) to 1.38 (1.06–1.83) (Table 3). Table 4 shows the region-specific effects of extreme TCNs on non-accidental mortality by season. In all regions, temperature decrease from the previous day was associated with reduced mortality risk, with weaker protective effects in autumn and winter; temperature increase elevated the risk, especially in spring and summer seasons.

3.5. Sensitivity analysis

Several sensitivity analyses were performed to test the robustness of our main results. First, the nationwide TCN–mortality association by using an alternative indicator of TCN (derived from daily maximum or minimum temperature) showed a similar shape of the pooled curve (Fig. S2). Second, compared with the core model analysis, we found no difference in estimated effects by altering the *df* for time (6 or 8 *df* per year) or for $MeanT_{0-3}$ (2 or 4 *df*) (Fig. S3) or adding the moving average of lag 0–3 days for relative humidity (RH_{0-3}) (Table S3). As well, the effects of extreme TCNs on morality changed little when we used the moving average of lags 0–3 for AT (AT_{0-3}) instead of $MeanT_{0-3}$, with the largest change of 0.12 (RR 2.32 vs 2.20) for pneumonia mortality (Table S4). Overall, the sensitivity analyses indicated that the estimates were not sensitive to the main modeling assumption. Third, as the RR of extremely positive TCN in Arlington City was very high (6.61 [1.43–30.62]), we excluded the extreme RR and found almost identical results (Table S5). Forth, the effects of alternative extreme TCNs (5th and 95th percentiles) on non-accidental mortality were also shown, with similar but weaker effect patterns (Fig. S4 and Table 5).

4. Discussion

Covering > 10 million non-accidental deaths during 1987–2000 from 106 communities of United States, the informative dataset guaranteed our nationwide analysis as the largest study to investigate the association of TCN and daily mortality and evaluate the effect modification by mortality causes, age, season, and region. At national level, a significant TCN–mortality association as a monotonic increasing curve from left to right was observed, indicating that a temperature increase between neighboring days elevated the risk of mortality. People ≥75 years and those with respiratory disease, especially pneumonia-deaths, showed higher risks of dying on positive TCN days. We also found some evidence that season and region modified the effect of TCN on mortality.

We observed a non-linear TCN–mortality association, which revealed that negative TCN was a protective factor and positive TCN was a risk factor for mortality. In accordance with previous studies (Cheng et al., 2014; Goldberg et al., 2011; Guo et al., 2011; Lin et al., 2013), we found that positive TCN markedly elevated mortality risk, reminding us of the necessity to focus on sudden temperature change apart from absolute temperature. Exposed to temperature increase, human body regulates heat exchange between body and ambient temperature, but it is possible that the degree of temperature increase is too large for regulation system to adapt, particularly for individuals with some chronic conditions (Guo et al., 2012; Zanobetti et al., 2012). A rapid temperature change was related to the dehydration, salt depletion, and increased surface blood circulation, which might induce the occurrence of death (Bouchama and Knochel, 2002).

The effect of TCN depended on both the degree and direction of temperature change, and we observed that negative TCN was significantly linked with reduced mortality risk in United States, supported by some small-scale studies (Cheng et al., 2014; Lin et al., 2013; Plavcova and Kysely, 2010). For example, contrary to the adverse effect of positive TCN, a protective effect of negative TCN last for 21 days has been revealed on both non-accidental and cardiovascular mortality in Maanshan, a subtropical inland Chinese city (Cheng et al., 2014); in 2 other subtropical coastland Chinese cities, large temperature decrease was found to be associated with reduced risk of mortality, with the strongest protective effect on the current day (Lin et al., 2013). However, using daily summer data during 1996–2004, a previous study found that both a drop and an increase of > 3 °C in temperature between adjacent days markedly elevated the risk of non-accidental mortality in

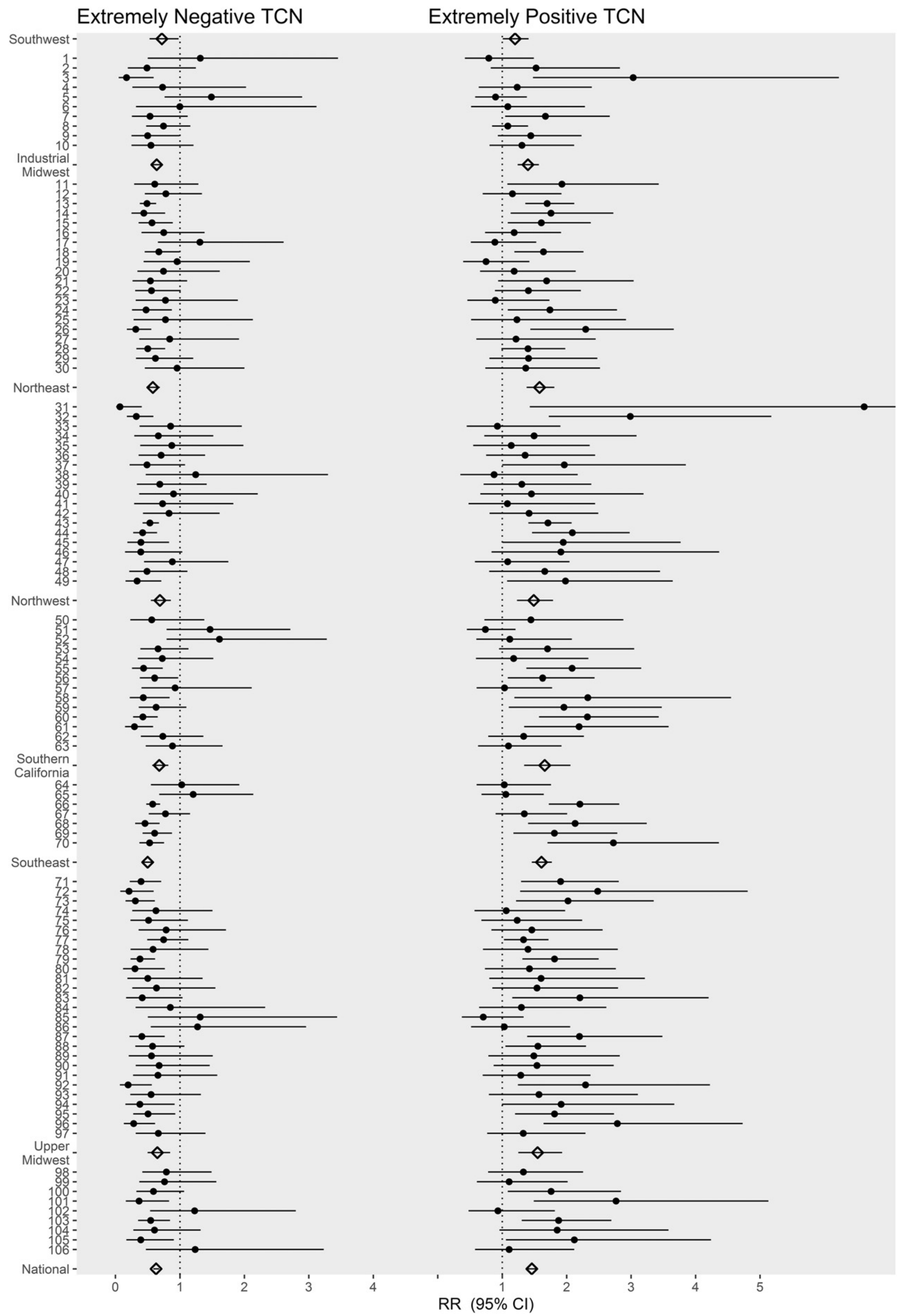
Extremely Negative TCN
Extremely Positive TCN
Southwest
Industrial Midwest
Northeast
Northwest
Southern California
Southeast
Upper Midwest
National
RR (95% CI)

Table 3
Lags 0–21 cumulative effects of extreme TCNs (1st and 99th percentiles) on non-accidental mortality by mortality causes, age, season[a], and region.

	Extremely negative TCN[b]		Extremely positive TCN[c]	
	RR (95% CI)	RRR (95% CI)	RR (95% CI)	RRR (95% CI)
Total non-accidental	**0.63 (0.59–0.68)**	–	**1.46 (1.39–1.54)**	–
Cause-specific				
Cardiovascular	**0.63 (0.56–0.70)**	1.00	**1.52 (1.40–1.65)**	1.00
Respiratory	**0.41 (0.33–0.51)**	**0.65 (0.51–0.84)**	**1.99 (1.68–2.36)**	**1.31 (1.08–1.58)**
Pneumonia	**0.36 (0.27–0.47)**	**0.57 (0.42–0.77)**	**2.32 (1.83–2.93)**	**1.53 (1.19–1.95)**
COPD	**0.50 (0.39–0.65)**	0.79 (0.61–1.06)	**1.64 (1.31–2.06)**	1.08 (0.85–1.38)
Age (years)				
<75	**0.79 (0.73–0.85)**	1.00	**1.20 (1.13–1.28)**	1.00
≥75	**0.50 (0.46–0.54)**	**0.63 (0.57–0.71)**	**1.80 (1.68–1.93)**	**1.50 (1.36–1.64)**
Season				
Spring	**0.45 (0.41–0.49)**	**0.56 (0.49–0.64)**	**1.82 (1.68–1.97)**	**1.46 (1.29–1.63)**
Summer	**0.61 (0.54–0.68)**	**0.76 (0.65–0.88)**	**1.47 (1.34–1.62)**	**1.18 (1.03–1.34)**
Autumn	**0.78 (0.71–0.86)**	0.98 (0.85–1.11)	**1.22 (1.13–1.32)**	0.98 (0.87–1.09)
Winter	**0.80 (0.73–0.88)**	1.00	**1.25 (1.15–1.37)**	1.00
Region				
Southwest	**0.72 (0.53–0.98)**	1.00	**1.20 (1.01–1.41)**	1.00
Industrial Midwest	**0.64 (0.55–0.73)**	0.89 (0.63–1.23)	**1.40 (1.24–1.57)**	1.17 (0.95–1.43)
Northeast	**0.58 (0.48–0.69)**	0.81 (0.56–1.14)	**1.58 (1.38–1.81)**	**1.32 (1.07–1.64)**
Northwest	**0.69 (0.55–0.86)**	0.96 (0.65–1.40)	**1.49 (1.23–1.79)**	1.24 (0.97–1.60)
Southern California	**0.68 (0.57–0.82)**	0.94 (0.66–1.36)	**1.66 (1.34–2.06)**	**1.38 (1.06–1.83)**
Southeast	**0.50 (0.43–0.59)**	**0.69 (0.49–0.99)**	**1.61 (1.46–1.77)**	**1.34 (1.11–1.63)**
Upper Midwest	**0.65 (0.50–0.85)**	0.90 (0.60–1.36)	**1.55 (1.25–1.93)**	1.29 (0.99–1.71)

RR, relative risk; RRR, relative risk ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; the bold indicates a statistically significant association.
[a] Spring, March to May; summer, June to August; autumn, September to November; winter, December to February of the next year.
[b] 1st percentile of TCN.
[c] 99th percentile of TCN.

Brisbane, Australia, with a RR of 1.157 (1.024–1.307) for TCN < −3 °C and 1.198 (0.997–1.438) for TCN > 3 °C at lag 0 (Guo et al., 2011). The discrepancy might be caused by differences of climate weather, geographic features, and population characteristics (e.g., socioeconomic status, age structure, and racial composition) (McMichael et al., 2008; Stafoggia et al., 2006). Currently, the underlying physiological mechanism why temperature decrease from the previous day was associated with reduced mortality remains unknown, and further evidence for the exact mechanism of TCN on human health is needed.

We found prominent effects of extreme TCNs on mortality for cardiovascular, respiratory, pneumonia, and COPD diseases. Some previous investigations have documented that sudden temperature changes such as TCN (Guo et al., 2011) and DTR (Ding et al., 2015; Lim et al., 2015; Zhou et al., 2014) were proposed to be closely associated with cardiovascular- and respiratory-related mortality. Temperature change could reduce the resistance of immune system to respiratory infections and affect the physiological changes in the circulatory system (Carder et al., 2005; Schneider et al., 2008). The characteristics of individuals that put them at a higher mortality risk may result from weaker intrinsic susceptibility factors or a greater likelihood of large inter-day temperature variation exposure. Inconsistent with previous studies in China (Cheng et al., 2014; Guo et al., 2011; Lin et al., 2013), we found that respiratory-deaths, especially pneumonia-deaths, showed a higher risk of dying on extremely positive TCN days than cardiovascular-deaths. This difference might be caused by adaptive capacity, lifestyles, family income, or access of health care. On the other hand, age was usually considered as a significant modifier of the TCN–mortality association (Cheng et al., 2014; Guo et al., 2011), and our study confirmed a higher risk of dying on extremely positive TCN days among people ≥75 years as compared to the younger group. The reduced ability to thermo-regulate and control body temperature efficiently in older adults might be a major reason for their increased susceptibility to extreme TCNs (Cheng et al., 2014; Ding et al., 2016a; Plavcova and Kysely, 2010). In addition, older people generally have poor health with a higher prevalence of co-morbidities, which likely enhance their susceptibility.

In stratified analyses by season, our study found some evidence that individuals were more susceptible to extreme TCNs during spring and summer than autumn and winter. A rapid increase in temperature from the previous day in a heating season (spring, acted as a transitional season from winter to summer), as well as a hot season (summer), caused more deaths; a protective effect of a sudden drop in temperature in spring and summer was more obvious. In previous studies, season as an effect modifier of the TCN–mortality relationship was rarely examined. With season-specific analysis, a study in Maanshan, China reported that the effect of TCN on all types of considered mortality in the cool season (November to the next April) was slightly high (Cheng et al., 2014). Moreover, there were more likely to have an interaction of TCN and mean temperature on mortality. For example, plotting the estimated joint effects based on a generalized additive model, Guo and his colleagues (2011) found that a large inter-day temperature variation increased the adverse effect of mean temperature on mortality when mean temperature was lower than 26 °C in Brisbane, Australia. On the other hand, DTR is another meteorological indicator to reflect sudden temperature variation, and the effect of DTR on mortality differed by season (Ding et al., 2015; Kim et al., 2016; Lim et al., 2012). For instance, higher DTR effects on non-accidental, cardiovascular, and respiratory mortality were reported in the cool season in 9 Chinese cities (Ding et al., 2015; Zhou et al., 2014), but in 6 metropolitan areas in Korea, the pooled effect of DTR on non-accidental mortality at lags 0–4 was greatest in fall, at 0.8% (95% CI, 0.5–1.2%) with an increment of 1 °C, and followed by summer, at 0.6% (0.2–1.1%) (Lim et al., 2012). A future examination with a deeper consideration of season-specific effects of sudden temperature changes might be warranted to provide detailed evidence.

Our region-specific analyses revealed that significant effect of extremely positive TCN on non-accidental mortality was observed in all regions, with stronger adverse effects in Southern California, Southeast,

Fig. 3. Lags 0–21 cumulative effects of extremely negative (1st percentile) and positive (99th percentile) TCNs on non-accidental mortality for 106 communities, 7 geographical regions, and the national level of United States.

Table 4
Region-specific lags 0–21 cumulative effects of extreme TCNs (1st and 99th percentiles) on non-accidental mortality by season[a].

	Southwest	Industrial Midwest	Northeast	Northwest	Southern California	Southeast	Upper Midwest
Extremely negative TCN[b]							
Spring	**0.45 (0.33–0.60)**	**0.41 (0.34–0.50)**	**0.48 (0.38–0.61)**	**0.45 (0.33–0.61)**	**0.41 (0.30–0.56)**	**0.47 (0.38–0.59)**	**0.40 (0.28–0.56)**
Summer	0.70 (0.45–1.09)	**0.64 (0.46–0.89)**	0.76 (0.52–1.11)	**0.52 (0.38–0.71)**	**0.50 (0.39–0.64)**	**0.56 (0.44–0.71)**	0.64 (0.40–1.01)
Autumn	0.90 (0.62–1.29)	**0.76 (0.59–0.98)**	**0.68 (0.54–0.87)**	**0.63 (0.48–0.82)**	**0.76 (0.60–0.96)**	0.96 (0.77–1.20)	0.74 (0.52–1.07)
Winter	0.81 (0.55–1.20)	**0.71 (0.56–0.89)**	**0.68 (0.52–0.91)**	0.83 (0.65–1.07)	0.79 (0.61–1.03)	**0.77 (0.59–0.99)**	1.15 (0.80–1.65)
Extremely positive TCN[c]							
Spring	**1.54 (1.24–1.93)**	**1.77 (1.53–2.06)**	**1.65 (1.39–1.95)**	**1.89 (1.48–2.40)**	**2.55 (1.71–3.81)**	**1.71 (1.46–1.99)**	**2.31 (1.57–3.41)**
Summer	1.06 (0.77–1.47)	**1.46 (1.15–1.86)**	**1.56 (1.16–2.11)**	**1.62 (1.23–2.14)**	**1.93 (1.45–2.56)**	**1.50 (1.22–1.84)**	1.32 (0.95–1.82)
Autumn	0.93 (0.70–1.23)	**1.21 (1.02–1.43)**	**1.35 (1.16–1.57)**	**1.73 (1.35–2.21)**	**1.61 (1.23–2.11)**	1.03 (0.87–1.21)	1.24 (0.92–1.67)
Winter	1.24 (0.98–1.56)	**1.30 (1.03–1.63)**	**1.45 (1.19–1.76)**	1.09 (0.84–1.42)	**1.67 (1.11–2.49)**	**1.24 (1.03–1.50)**	1.21 (0.86–1.71)

Results are expressed as relative risks (95% confidence intervals); the bold indicates a statistically significant association.
[a] Spring, March to May; summer, June to August; autumn, September to November; winter, December to February of the next year.
[b] 1st percentile of TCN.
[c] 99th percentile of TCN.

and Northeast regions. In general, the magnitude of estimated effects of TCN in United States varied with region. For the effect of extremely positive TCN, a study in China has also shown that the overall estimated RR at lags 0–4 for non-accidental mortality was 1.31 (95% CI, 1.04–1.66) in Guangzhou and 1.46 (1.15–1.84) in Taishan (Lin et al., 2013). For TCN > 3 °C, there was a significant effect on cardiovascular mortality (1.35 [1.03–1.77]) in Brisbane, but no significant (1.03 [0.93–1.14]) was observed in Los Angeles (Guo et al., 2011). The effect of TCN on mortality differed in different regions, depending on factors such as climates (e.g., tropical, subtropical, temperate, or monsoon climate), geographic features, and socio-economic level (e.g., use of air conditioning or health care systems).

Several limitations in our study should be presented. First, we did not control for the impact of air pollutants in the core model, because these data in a considerable amount of communities were not available; however, the relationship between TCN and mortality might not substantially differ with or without the effects of air pollutants. Second, individual characteristics such as race/ethnicity, marital status, occupation, level of education, socioeconomic status, location of death, and people with some preexisting medical conditions have been reported to modify the DTR–mortality relationship (Ding et al., 2016a; Kim et al., 2016; Lim et al., 2012; Yang et al., 2013), but whether these factors significantly modify the effect of TCN is still unknown. Gender also has previously been demonstrated to be a strong effect modifier of TCN on mortality (Cheng et al., 2014; Guo et al., 2011). The current study did not consider these potential modifiers due to the unavailability of data, and we proposed more epidemiological studies exploring the effect modification of the effect of TCN on human health. Third, as an ecological study, temperature data from surface weather observation stations in communities replacing accurate temperature for individuals to investigate the TCN effect introduced some inevitable exposure measurement errors; however, the errors are likely to be random and may result in an underestimation of RRs (Guo et al., 2013). On the other hand, the use of heating and cooling systems, which caused different temperature conditions between indoor and outdoor, and individuals spend more time indoor may also moderate the impact of outdoor temperature variability on human health.

5. Conclusions

In conclusion, a significant impact of TCN on mortality was discovered in United States at the national level, and the effect patterns of

Table 5
Lags 0–21 cumulative effects of alternative extreme TCNs (5th and 95th percentiles) on non-accidental mortality by mortality causes, age, season[a], and region.

	Extremely negative TCN[b]		Extremely positive TCN[c]	
	RR (95% CI)	RRR (95% CI)	RR (95% CI)	RRR (95% CI)
Total non-accidental	**0.76 (0.72–0.79)**	–	**1.27 (1.22–1.32)**	–
Cause-specific				
Cardiovascular	**0.76 (0.71–0.81)**	1.00	**1.28 (1.21–1.36)**	1.00
Respiratory	**0.59 (0.52–0.67)**	**0.78 (0.67–0.90)**	**1.58 (1.41–1.78)**	**1.23 (1.08–1.41)**
Pneumonia	**0.56 (0.47–0.67)**	**0.74 (0.61–0.89)**	**1.74 (1.48–2.04)**	**1.36 (1.14–1.61)**
COPD	**0.65 (0.55–0.76)**	0.86 (0.72–1.02)	**1.41 (1.21–1.63)**	1.10 (0.93–1.28)
Age (years)				
<75	**0.87 (0.83–0.91)**	1.00	**1.12 (1.07–1.16)**	1.00
≥75	**0.65 (0.62–0.69)**	**0.75 (0.70–0.81)**	**1.46 (1.39–1.53)**	**1.30 (1.23–1.39)**
Season				
Spring	**0.60 (0.57–0.64)**	**0.72 (0.66–0.79)**	**1.48 (1.40–1.57)**	**1.29 (1.19–1.40)**
Summer	**0.74 (0.69–0.80)**	**0.89 (0.81–0.98)**	**1.32 (1.23–1.41)**	**1.15 (1.05–1.26)**
Autumn	**0.87 (0.81–0.92)**	1.05 (0.95–1.14)	**1.17 (1.11–1.23)**	1.02 (0.94–1.10)
Winter	**0.83 (0.78–0.89)**	1.00	**1.15 (1.08–1.22)**	1.00
Region				
Southwest	0.84 (0.70–1.00)	1.00	1.09 (0.97–1.23)	1.00
Industrial Midwest	**0.75 (0.69–0.82)**	0.89 (0.74–1.10)	**1.24 (1.15–1.35)**	1.14 (0.99–1.32)
Northeast	**0.72 (0.64–0.80)**	0.86 (0.69–1.06)	**1.31 (1.21–1.42)**	**1.20 (1.04–1.38)**
Northwest	**0.77 (0.67–0.89)**	0.92 (0.73–1.16)	**1.37 (1.21–1.54)**	**1.26 (1.06–1.48)**
Southern California	**0.80 (0.72–0.90)**	0.95 (0.78–1.19)	**1.34 (1.19–1.52)**	**1.23 (1.04–1.46)**
Southeast	**0.66 (0.60–0.72)**	**0.79 (0.64–0.96)**	**1.32 (1.24–1.42)**	**1.21 (1.06–1.39)**
Upper Midwest	**0.81 (0.70–0.95)**	0.96 (0.77–1.23)	**1.34 (1.17–1.54)**	**1.23 (1.02–1.47)**

RR, relative risk; RRR, relative risk ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; the bold indicates a statistically significant association.
[a] Spring, March to May; summer, June to August; autumn, September to November; winter, December to February of the next year.
[b] 5th percentile of TCN.
[c] 95th percentile of TCN.

TCN differed across communities and regions. A positive TCN was associated with an elevated risk of mortality. Older adults and people with respiratory and pneumonia disease were particularly susceptible to TCN. The TCN–mortality association was modified by season and region. Identification of the effect modifiers may help develop targeted intervention strategies to reduce the TCN-related mortality.

Competing financial interests

The authors declare no competing financial interests.

Author's contributions

Z.D. designed the study and directed its implementation. Z.Y.Z., Y.Z., S.J.P., X.Z., and C.W. collected and cleaned the data. Z.Y.Z. performed all statistical analysis and plotted the figures. Z.Y.Z. and Z.D. drafted the manuscript. Y.Z., Z.Y.Z., and Z.D. revised the manuscript and interpreted the results. All authors read and approved the final manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.scitotenv.2017.01.177.

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