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Individual- and community-level effect modifiers of the temperature-mortality relationship in 66 Chinese communities

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Abstract

Objectives: To examine the modification of temperature-mortality association by factors at the individual and community levels.

Design and methods: This study investigated this issue using a national database comprising daily data of 66 Chinese communities for the period of 2006-2011. A time series model was utilized to estimate the mortality effects of high and low temperatures, and then examined the modification of the relationship by individual factors (age, sex, place of death, and cause of death) and community-specific factors (annual average temperature, population density, sex ratio, percentage of older population, health access, household income, and latitude).

Results: We found significant effects of both cold and hot weathers on mortality in China. At the individual level, age and place of death were found to be significant modifiers of cold effect, while age, sex, place of death, and cause of death were effect modifiers of heat effect. At the community level, communities with lower socio-economic status were generally more vulnerable to the mortality effects of high and low temperatures.

Conclusions: This study identifies susceptibility based on both individual- and community-level effect modifiers; more attention should be given to these vulnerable individuals and communities to reduce adverse health effects of extreme temperatures.

Keywords: Temperature, mortality, effect modification, time series analysis

Strengths and limitations of this study

Strengths:

- We used a large database to examine the temperature-mortality relationship in China;
- This is a national effort to assess the temperature-mortality relationship using data from a wide geographical coverage of China;
- We examined the effect modifers at the individual and community levels

simultaneously.

Limitations:

- We were not able to control for air pollution and influenza epidemics in the analysis due to data unavailability;
- We used ambient temperature as a surrogate for personal exposure, which might cause exposure misclassification;
- The small number of daily mortality count in some communities might lead to imprecise risk estimation.

Introduction

Epidemiological studies have demonstrated significant association between ambient temperature and mortality [1, 2]. This relationship was generally found to be V-, U-, or J-shaped, with increased mortality at high and low temperatures and minimum mortality occurring at various temperature points [3-8].

The health impacts of temperature variation are likely to be heterogeneous across regions with different geographic conditions, climate, and population characteristics [9, 10]. Identification of factors affecting the health susceptibility to temperature variation has been recognized as an important step to protect the vulnerable population [11]. And some studies have also reported that some individual-level factors were associated with the health effects of temperature variation, such as age, sex, and socio-economic status [3, 11-17].

Being the largest developing country, China has experienced noticeable climate change over the past decades [18]. The annual average temperature has risen by 0.5-0.8 °C during the past century [19]. Meanwhile, some weather extreme events, such as heat wave, cold spell, have also been witnessed in China, resulting in substantially excessive mortalities [20-22]. However, few studies have examined how temperature-mortality relationships differ among different subpopulations and regions in China [23].

One of our recent analyses examined the health effects of heat wave and associated effect modifiers based on a national database comprising data from 66 Chinese communities [24], the present study aimed to examine the effect modifiers of temperature-mortality relationship in China. We evaluated whether individual characteristics (age, sex, place of death, cause of death) and community-level factors (average temperature, population density, sex ratio, percentage of older population, health access, average annual income, and latitude) could modify the temperature-mortality relationship. This study is one of the largest studies of temperature-mortality relationship to date in China.

Materials and methods

Data collection

The Climate and Health Impact National Assessment Study (CHINAs) project is a national effort to assess short-term temperature-mortality relationship in 66 Chinese communities with more than 44 million residents. These communities provided a wide geographical coverage of China (Figure 1), details of the data have been described elsewhere [23, 24].

Community-specific daily mortality data covering the period from January 1 2006 to December 31 2011 were obtained from Chinese Center for Disease Control and Prevention (China CDC). China CDC is the government agency in charge of health data collection in China. A death, whether occurred in a hospital or at home, must be reported to local CDC. In both situations, the hospital or community/village doctors completed a standard death certificate card regarding the death information including some individual-level information, such as age, sex, cause of death and date of death, and place of death. In this study, we classified location of death into "in-hospital deaths" and "out-of-hospital deaths", the former included deaths occurred in hospitals, clinics, or medical centers, as well as outpatients admitted to the emergency room; while "out-of-hospital deaths" was defined as all other deaths, such as deaths in homes.

During the study period, the causes of death were coded according to the 10th revision of the International Classification of Diseases (ICD-10). The mortality data were classified into deaths due to all non-accidental causes (ICD-10: A00-R99), cardiovascular diseases (ICD-10: I00-I99), and respiratory diseases (ICD-10: J00-J99). Stratified data sets were also created with daily death counts by sex, age group, and place of death (outside or in a hospital).

Community-specific daily meteorological data for the same period were retrieved from the China National Weather Data Sharing System (http://cdc.cma.gov.cn/home.do), which is publicly accessible. For each community, there was one basic-reference land surface automatic weather observation station, which provided the weather information for each community. Meteorological data consisted of daily mean, minimum, maximum and apparent temperatures (°C), relative humidity (%), and atmospheric pressure (hpa).

The proportion of missing mortality and meteorological data was very low. The highest proportion was found for maximum temperature with missing rate less than 0.2%.

Community-level variables (annual average temperature, population density, sex ratio, percentage of population older than 65 years old, hospital beds for per thousand population, annual household income, and latitude) were obtained from the sixth national census values [25].

Analysis of temperature–mortality relationship

Daily mean temperature was chosen as the temperature indicator for this analysis as it provided more easily interpreted results in a policy context [3]. Within each community, the relationship between daily mortality and temperature was estimated using a distributed lag non-linear model (dlnm) with daily death counts as the dependent variable. The "dlnm" model has been widely applied to investigate the health effects of air pollution and temperature. This approach has the ability to simultaneously investigate the non-linear and delayed effects of exposure on daily mortality [26, 27]. This model used a ''cross-basis'' function, which allowed a two-dimensional relationship of the non-linear effect of daily temperature variation at each lag and the nonlinear effects across lag days to be estimated [26]. The method accounted for the over-dispersed Poisson data using the assumption that the total variance was proportional to the total number, with the over-dispersion constant estimated through quasi-likelihood. In ''cross-basis'' function, we used the spline function for temperature and the polynomial function for the lag structure. The model can be specified as:

$$\text{Log } E(Yt) = \alpha + cb(temp, df=5; lag, df=3) + s(t, df=6/year) + \beta_1 * DOW + \beta_2 * PH + COVs$$

where E(Yt) denotes the expected daily mortality count on day t, cb means the ''cross-basis'' function, s() indicates a smooth function based on natural splines for nonlinear variables. In this study, the number of knots was set as 3, and it was placed at equally-spaced percentiles of the temperature distribution for each community. t is the day of study (an integer value for day 1 to n of the time series, to control for long-term and seasonal trends), β is the regression coefficient, DOW is a categorical variable for day of week, PH is the binary variable indicating public holidays, and COVs are the potential confounding factors, including smooth function of relative humidity (df=3) and atmospheric pressure (df=3). Atmospheric pressure has been associated with changes in oxygen saturation and pulse rate in elderly subjects [28] as well as with daily mortality [29] and hence was chosen as a control variable in this study.

We plotted the relative risks against temperature and lag days to show the overall relationship between mean temperature and mortality.

Our initial results showed that the temperature–mortality relationships were approximately V- or U-shaped, with a minimum mortality temperature (MMT), a pattern that rendered it necessary to divide the series into two segments with reference to the MMT (Figure s1 showed examples of a few communities). Thus, we estimated the linear relationships below and above the city-specific MMT in accordance with previous studies [30, 31], assuming that the mortality effects of temperatures below and above the MMT were linear. The community-specific MMT was determined in accordance with previous studies [30, 31]. In brief, in the model multiple temperatures were tested based on minimum residual deviance of the model. For example, by visual inspection of the dose–response curve, we may identify that the potential MMT might be within 25 to 28 °C, and we then examined the potential MMT from 25 to 28 °C (by 0.1 °C) to identify the model with minimum residual deviance. The MMT estimates have been reported in one of our previous studies [23], on average, the MMT was found at about 76th percentile of the temperature distribution.

Previous studies have suggested that the low temperature effect persisted for longer days, even weeks, while high temperature effects were shorter term (usually 0-2 days) [20, 32]. In light of these findings, we modeled the effects of heat and cold effects with two different regression models: daily temperature at lag 0-2 days was used to model the heat effect and lag 0-21 days was used to represent the cold effect.

We examined community-specific temperature–mortality relationship and summarized measures of the heat and cold effects. Specifically, for each community we calculated the change in mortality risk for 1 °C decrease in temperature below the minimum mortality temperature (cold effect) and for 1 °C temperature increase above the minimum mortality temperature (hot effect).

Heterogeneity of the effect estimates was observed among the communities, so we used a random-effect meta analysis model was used to combine the heat and cold effect estimates of the 66 communities to generate overall effects at the regional and national levels [33].

Effect modifiers of temperature-mortality relationship

For the potential effect modifiers at the individual level, the effect estimates were obtained for each stratum of potential modifying factor, including cause of death (non-accidental, cardiovascular and respiratory mortalities), age (0-64, 65-74, 75-84, 85-), sex (males and females), and place of death (within or outside of a hospital). A random-effect meta-analysis approach was used to generate overall effects for each category.

For the community-level effect modification, random-effect meta-regression models were used by including potential effect modifiers in the random-effect mea-analysis to examine their contribution to the observed variation in the effect estimates among the communities [34].

Sensitivity analysis

Sensitivity analyses were performed by changing the df of long-term and seasonal trends (7-10 df/year). All statistical tests were two-sided, and values of $p < 0.05$ were considered as statistically significant.

Results of the analysis were expressed as excess relative risk (ERR) of mortality increase for 1 °C increase above the MMT (heat effect) or 1 °C decrease below the MMT (cold effect). ERR was calculated using the formula: ERR=(RR−1) × 100%, where RR (relative risk) was obtained through the time series models. All statistical analyses were performed using the R software (version 2.15.1) (R Development Core Team, Austria). The distributed lag nonlinear models were fitted using the R package “dlnm”, and meta-analysis was conducted using the “metafor” package.

Results

Table s1 summarized the daily mortality and weather statistics by community. During the study period, a total of 1,260,913 deaths were reported in the 66 communities, including 552,866 and 198,777 deaths from cardiovascular and respiratory systems. The communities differed in population size and daily mortality count. The community-specific mean number of daily deaths ranged from 2 to 23. Most of the deceased were above 65 years of age (71.5%), and male (58.2%). A substantial fraction of deaths (72.8%) occurred out of a hospital.

Table s1 and Figure s2 illustrated the distribution of daily temperature in the 66 communities. The 66 communities in this study had a wide range of climates, with annual mean temperatures ranging from 4.6 °C in Yi’an County in Northeast China (community ID, 230223) to 22.9 °C in Hepu County in Southeast Region (community ID, 450521). Among the seven regions, Southern region had the highest mean temperature, and northeastern region had the lowest temperature.

Supplementary Figure s3 showed the diagnostic graphs illustrating the residuals against time for a few communities. There were no discernible seasonal pattern and no autocorrelation in the residuals, indicating acceptable goodness of fit of the models.

We found significant mortality effects from both low and high temperatures. The overall effect estimates for all the 66 communities and each of the seven regions were illustrated in Table 1. The strongest cold effect was observed for the North and Central regions, and Northeast Region had the lowest mortality effect from cold weather. For the mortality effect of high temperature, the highest effect was observed in South China, and the lowest effect in Northwest Region.

Table 1 Percentage increase in daily mortality for 1 °C decrease below the threshold and 1 °C increase above the threshold by geographic region, China, 2006-2011

Regions	No. of communities	Regional estimates (95% CI)	
		Cold effect	Heat effect
East	16	2.53 (2.12-2.94）	1.19 (0.94-1.44)
Central	9	4.47 (2.88-6.09)	1.28 (0.92-1.65)
North	8	4.69 (1.99-7.45)	1.26 (0.90-1.63)
Northeast	7	1.58 (0.99-2.17)	0.67 (0.32-1.02)
Northwest	8	2.25 (0.86-3.65)	0.43 (-0.03-0.90)
South	7	3.78 (3.24-4.32)	1.32 (0.90-1.73)
Southwest	11	3.42 (2.49-4.35)	1.25 (0.91-1.59)
All communities	66	3.17 (2.73-3.61)	1.11 (0.97-1.25)

Individual-level effect modifiers

In the stratified analyses by various individual-level factors, the cold and heat effects were found to vary by age, sex, and place of death (Table 2).

Cold-related mortality risk had a general increasing pattern with age, the highest risk was observed among those aged 85 years and above (the ERR being 3.91%, 95% CI: 3.35%-4.48%). Location of death was a strong modifier of the cold effect with an ERR of 2.18% (95% CI: 1.63%-2.74%) for dying in a hospital, and 3.66% (95% CI: 3.09%-4.24%) for the deaths occurring out a hospital. Other personal characteristics had similar association.

The individual factors that increased susceptibility to heat effect included old age, female, dying out of a hospital, dying of respiratory diseases. Sex was a strong effect modifier, the ERR being 1.45% (95% CI: 1.22%-1.69%) for females and 0.90% (95% CI: 0.72%-1.08%) for males. The hot weather had stronger health effects for those with respiratory conditions compared with those dying of cardiovascular illness and non-accidental diseases.

Table 2 Comparison of heat- and cold-related mortality risks by individual-specific effect modifiers

Variables	Effect estimates (%)	
	Cold effect	Heat effect
Sex		
Male	3.12 (2.68, 3.56)	0.90 (0.72, 1.08)
Female	3.17 (2.67, 3.67)	1.45 (1.22, 1.69)
Age group		
<64y	2.31 (1.789, 2.83)	0.83 (0.61, 1.05)
65-74y	3.12, 2.46, 3.78)	0.92 (0.62, 1.22)
75-84y	3.38 (2.83, 3.94)	1.32 (1.09, 1.56)
>85y	3.91 (3.35, 4.48)	1.65 (1.30, 2.00)
Death cause		
Non-accidental	3.16 (2.73, 3.61)	1.11 (0.97, 1.25)
Cardiovascular	3.75 (3.23, 4.28)	1.14 (0.96, 1.33)
Respiratory	3.85 (3.11, 4.59)	1.58 (1.25, 1.92)
Location of death		
Out of hospital	3.66 (3.09, 4.24)	1.23 (1.04, 1.42)
In a hospital	2.18 (1.63, 2.74)	0.90 (0.68, 1.13)

Community-level effect modifiers

We evaluated whether the observed temperature-mortality relationship could be explained by some community-specific factors, such as average temperature, relative humidity, population density, sex ratio, percentage of people with low education level, population aged 75 years and above, living in urban setting, hospital beds per thousand population, average income, and latitude (Table 3). Cold effects were slightly higher in warmer communities. A 7.2 °C increase in annual average temperature was associated with a 0.59% decrease in cold-related relative risk. Communities with higher education level, more residents living in urban area, better health care facility, higher household income and higher latitude were less susceptible to the cold impacts. While higher vulnerability to heat-associated mortality risk was identified for communities with a higher temperature and lower latitude.

Table 3 Increase in heat- and cold-related mortality per IQR increase in community-specific effect modifiers

Community-specific variable	IQR*	Change in relative effect (%)		Change in relative effect (%)	
		Cold effect	P value	Heat effect	P value
Annual temperature	7.2°C	0.59 (-0.06, 1.23)	0.07	0.26 (0.05, 0.46)	0.01
Male-female sex ratio	6.1	0.23 (-0.31, 0.78)	0.40	0.07 (-0.10, 0.25)	0.42
Population density	2257	-0.02 (-0.13, 0.09)	0.73	0.001 (-0.003, 0.04)	0.94
Older population fraction	3%	-0.38 (-0.99, 0.22)	0.22	0.10 (-0.08, 0.28)	0.27
Years of education	2.5	-0.63 (-1.30, 0.03)	0.06	-0.05 (-0.27, 0.16)	0.64
Living in urban setting	58%	-0.85 (-1.68, -0.02)	0.04	-0.10 (-0.36, 0.16)	0.46
Hospital beds per thousand population	1.6	-0.34 (-0.64, -0.04)	0.03	0.03 (-0.07, 0.13)	0.51
Average income	$30k	-0.39 (-0.71, -0.07)	0.02	0.005 (-0.09, 0.10)	0.92
Latitude	7.9	-0.58 (-1.10, -0.05)	0.03	-0.17 (-0.34, 0.003)	0.054

* IQR: Interquartile range

Sensitivity analysis

We found generally similar effect estimates using different degree of freedom (7-10 df/year) for temporal adjustment compared with those of the main analyses, suggesting a robust result of this analysis.

Discussion

In this large multi-community study, we provided unique evidence on individual- and community-specific indicators that were related to the vulnerability to temperature-related mortality risk in China. Our analysis found that most of the effect modifiers were generally similar for individual- and community-level factors, which enhanced the possibility that these factors were valid potential markers of vulnerability, which contributed to the advantage of this study. The underlying mechanisms for the observed excess mortality during days with high temperature may be related to the stress placed on the respiratory and circulatory systems to increase heat loss through skin surface blood circulation [35]. This coupled with an increase in blood viscosity and cholesterol levels may lead to elevated mortality risk. The possible mechanisms for the cold-related mortality risk have also been suggested. One underlying reason might be the higher prevalence of respiratory infection during winter season, particularly influenza epidemics, and an increase in plasma cholesterol and plasma fibrinogen with low temperatures, coupled with a higher blood pressure in cold weather, could lead to thrombosis through haemoconcentration and trigger an acute mortality event [36]. Moreover, the extremely cold weather might have also contributed to the excess mortality by reducing access to a hospital.

Socio-economic inequalities at community and individual levels have been linked with a higher burden of environmental risks, including those from weather variation [3, 11, 37, 38]. For example, higher mortality effect of high temperature were observed for those at older age, dying out of a hospital and with existing cardiopulmonary conditions [11]. Regional differences in the association between ambient temperature and mortality may be partly due to dissimilar population structure in terms of age, sex, education attainment and other socio-economic status [3].

Our study found that low socio-economic conditions were generally associated with higher mortality risk from both high and low temperatures, which was generally consistent with several previous studies. For example, study about the heat-related mortality risk in Chicago in 1995 found that people with existing medical conditions, and low socio-economic status were the vulnerable population [39]. In Texas, heat-related excess mortality was higher among the elderly, men, and persons involved in heavy labor [40]. An analysis examining effect indicators of the temperature-mortality association in 107 US cities found that age, cause of death, place of death, median household income, unemployment rate, usage of air conditioning, education level were potential markers of vulnerability to temperature extremes [3]. Similar findings have also been observed in other studies [12, 15, 41, 42].

Our study suggested that the temperature-mortality association increased with age, with those aged over 85 years being the most susceptible population, which was consistent with several previous studies [43, 44]. The older persons were generally at poor health status, had preexisting medical conditions and diminished ability to detect changes in their body temperature, and thus had reduced thermoregulatory capacity, which might be the major reason for their increased susceptibility to temperature extremes [12, 20, 45].

Educational level was a good indicator of socio-economic status that conveyed susceptibility [41]. For both cold and heat effects, our study found a generally higher mortality risk for areas with lower education level, which was consistent with a study of seven US cities [12, 46] and Curriero et al.'s study of eleven US cities [44]. Persons with more education attainment were more likely to have greater wealth and better health access, dietary intake, better domestic heating system in winter and air conditioning usage in summer [47]. Higher mortality rates among the low-educated population have also been observed in several other studies, such as a cohort study in US [48].

Location of death was found to be an important effect modifier of the mortality effect of cold and hot weathers in the present study, which has also been reported in a few studies [11, 12], however, these two studies [11, 12] found the effect modification was mainly for heat effects, while our study found that it was more obvious for cold effects, the underlying reason for this discrepancy remained unknown. Finding of higher vulnerability for those dying out of hospitals was biologically plausible. It was possible that people dying out of a hospital had higher intensity of exposure to ambient environment, and it was also partly due to the better health care received by the residents living in a hospital, as it was likely that those dying out of a hospital usually had lower socio-economic status [12].

The factors leading to the community vulnerability to mortality effects of temperature were found to be community-specific temperature, urbanization, education level, health care facility, household income and latitude, and the effect modification was particularly noteworthy for cold effect. Previous studies also found that group-level factors could explain some heterogeneity in community-specific effects [3, 44, 49, 50]. This phenomenon may be due to the general health and nutrition status, health care access, and overall knowledge, attitude and adaptation capacity to the health effects of temperature. A study examining the temperature-related mortality in Chicago also showed that areas with lower socio-economic status had higher mortality risk [49]. Anderson, et al's study including 107 US communities also examined the community-specific effect modifiers, and found that communities with higher unemployment rate, more population with lower education attainment, more population living in urban environment were more vulnerable to the temperature extremes [3].

Of particular, we found that southern communities with lower latitude and higher annual average temperature had temperature-related mortality risk, particularly from cold effect, which has also been reported elsewhere [4, 14, 44]. The higher cold effect in southern areas may suggest the evidence for acclimatization. Though the winter temperature was higher in south China than in north areas, the lacking of centralized heating system in south China made people in south areas suffer more from the cold weather, causing excess mortality risk [20]. While the higher heat effect in south region observed in this study might be due to the more exposure opportunity and higher intensity of heat exposure by the population in south China. However, some other studies have reported that low latitude areas had lower risk from heat effects, which was inconsistent with findings from our study [43, 51].

Though previous studies suggested that the global temperature rising might be a net harmful health effect [52], our study suggested that cold weather was also an important health hazard, which should not be neglected. This finding also indicated that the health impact of cold weather, particularly its long delayed effects, should be considered when projecting health impact of future climate change.

A few limitations should be noted when interpreting the findings from this study. One limitation was that we were not able to control for air pollution and influenza epidemics in the analysis due to data unavailability. Our previous work suggested that the health effects of temperature extremes remained similar after controlling for various air pollutants and influenza epidemics [20]. However, O'Neill et al examined the mortality impact of temperature controlling for both ozone and particulate matter and found that the effect of high temperature on mortality reduced by about 30% but the associations persisted [53]. And Goldberg's study in Canada also suggested that air pollution could not distort the temperature-mortality relationship to a great extent [54]. Another limitation was the use of ambient temperature as a surrogate for personal exposure. The misclassification derived from this assumption will be largely determined by the extent to which ambient and micro-environmental temperatures are correlated [14], which was likely be affected by adaptive mechanisms such as use of air conditioning. Furthermore, another important limitation was that for both individual- or community- level analyses of effect modifiers, we cannot control the potential confounding effect of one modifier by another, due to the high correlation between some variables, we cannot simply put them in the same model, making the observed effect modification difficult to attribute to one specific factor. It should also be noted that the small number of daily mortality count in some communities might lead to imprecise risk estimation. Another limitation was that this study used weather data from only one weather observation station for each community, however, a community in this study covered relative small geographic area, and the weather data from one station could generally represent the local weather pattern.

The findings from this study have some implications for policymakers and scientific community by providing the evidence of temperature-mortality relationship in China and related effect modifiers at individual- and community-levels. The identified susceptible subpopulations provided evidence for the targeted temperature-mortality prevention measures. The community-level effect modifiers indicate the necessity of multi-city study and indicate that community specific prevention strategies are warranted.

Conclusions

In summary, this study identifies susceptibility of mortality effects of temperatures based on both individual- and community-level effect modifiers, more attention should be given to these vulnerable individuals and vulnerable communities to reduce adverse health effects of extreme temperatures.

Competing interests

The authors declare no competing interests.

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Authors' contributions

HLL and WJM provided the mortality data. HLL and JPX conceived of the study, participated in the study design, statistical analysis, and drafted the manuscript. TL, JPX collected the meteorological data and result interpretation. TL and HLL participated in the study design and coordination. All authors read and approved the final manuscript.

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Figure legends:

Figure 1. The map of China showing the location the 66 communities.

Figure s1. The cumulative effects of daily mean temperature on mortality over past 21 days for some communities in each region.

Figure s2. The distribution of daily mean temperature among the 66 Chinese communities.

Figure s3. The time series of mortality residuals against time trend for a few community examples.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

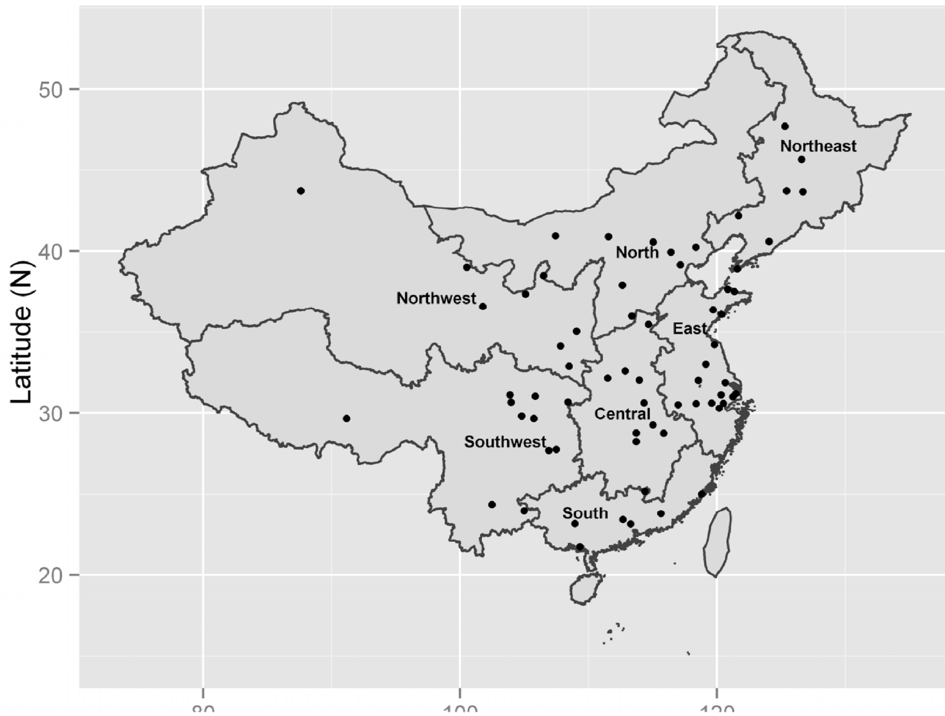
	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 & 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4 & 5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4 & 5
Bias	9	Describe any efforts to address potential sources of bias	5 & 6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5 & 6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A

		(*e*) Describe any sensitivity analyses	6
Results			
Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	N/A
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15	Report numbers of outcome events or summary measures over time	6
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8
		(*b*) Report category boundaries when continuous variables were categorized	8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10 & 11
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is	13

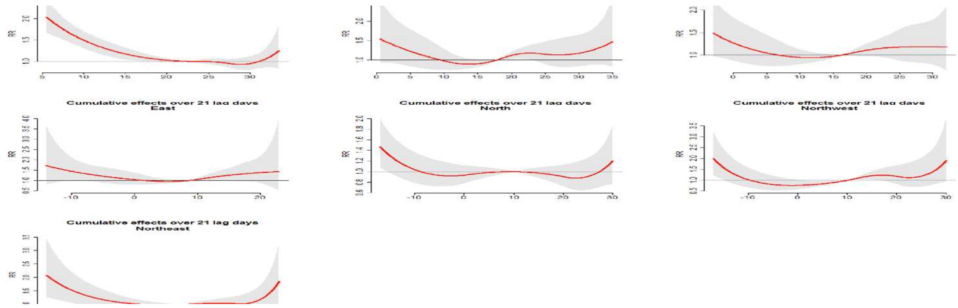
	based

*Give information separately for exposed and unexposed groups.

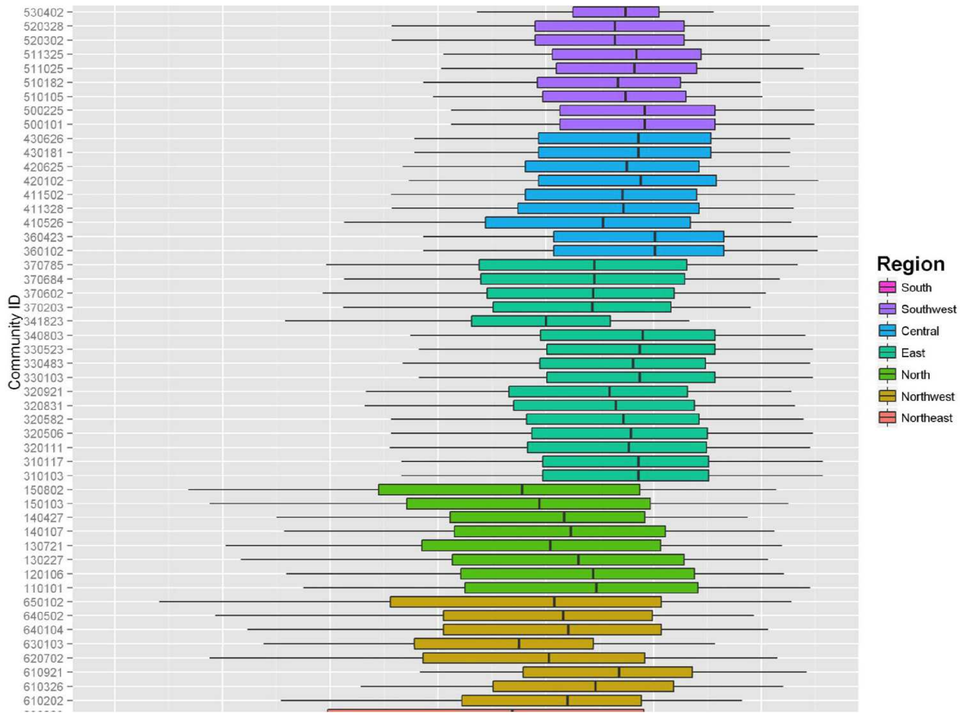
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.



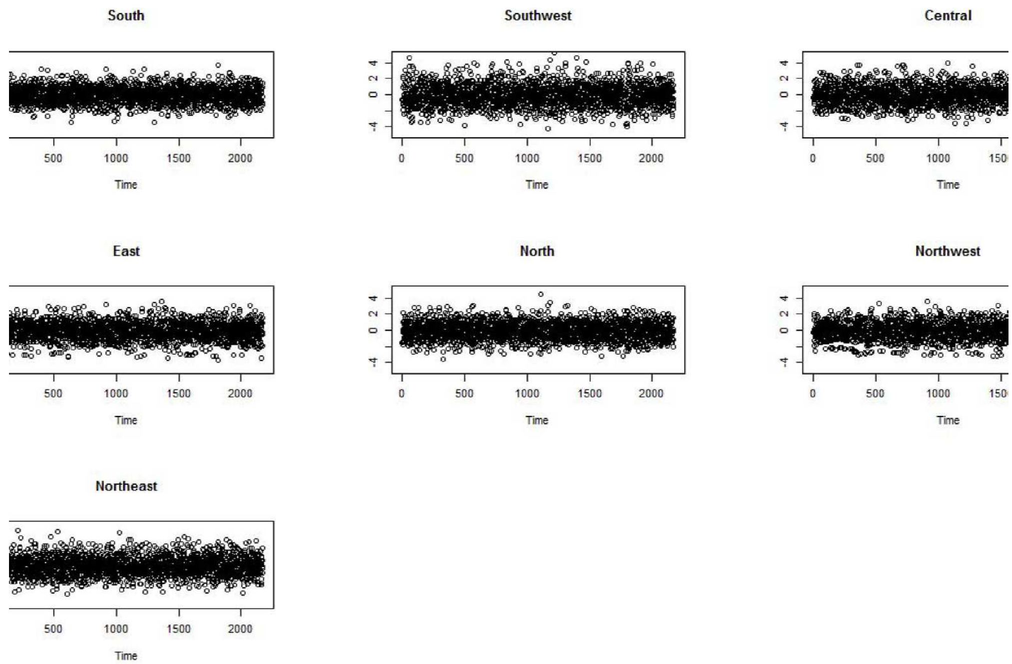
The map of China showing the location the 66 communities.
297x210mm (200 x 200 DPI)



The cumulative effects of daily mean temperature on mortality over past 21 days for some communities in each region
297x209mm (203 x 86 DPI)



The distribution of daily mean temperature among the 66 Chinese communities
297x210mm (200 x 200 DPI)



The time series of mortality residuals against time trend for a few community examples
297x210mm (200 x 200 DPI)

Table s1. Summary statistics for daily mortality and temperature across the 66 Chinese communities.

Community code	Region	Daily deaths	Daily mean temperature (°C)				
			Mean	P25	P50	P75	Max
110101	North	8	13.4	2.5	14.7	24.1	34.5
120106	North	11	13.1	2.1	14.4	23.8	32.1
130227	North	3	11.9	1.3	13.0	22.8	30.6
130721	North	3	9.5	-1.5	10.4	20.7	31.9
140107	North	6	11.3	1.5	12.3	21.1	31.2
140427	North	4	10.0	1.1	11.7	19.2	28.7
150103	North	3	8.1	-2.9	9.4	19.7	32.5
150802	North	6	6.5	-5.5	7.8	18.7	31.4
210204	Northeast	10	11.3	2.7	12.8	20.8	29.4
210682	Northeast	8	9.5	-0.1	10.9	19.8	28.0

210921	Northeast	10	8.3	-3.9	9.8	20.9	29.3
220102	Northeast	6	6.5	-6.3	8.5	19.7	30.4
220211	Northeast	3	5.8	-6.2	7.6	18.7	28.5
230103	Northeast	16	5.6	-8.2	7.6	19.7	30.6
230223	Northeast	6	4.6	-10.3	6.9	19.1	31.5
310103	East	6	17.5	9.7	18.6	25.1	35.7
310117	East	9	17.5	9.7	18.6	25.1	35.7
320111	East	8	16.6	8.3	17.7	24.9	34.5
320506	East	9	16.8	8.7	17.9	25.0	34.8
320582	East	14	16.3	8.2	17.2	24.2	33.9
320831	East	6	15.3	7.0	16.5	23.8	33.1
320921	East	8	14.9	6.6	15.9	23.2	32.8
330103	East	5	17.8	10.1	18.7	25.7	34.8

330483	East	11	17.2	9.5	18.1	24.8	34.5
330523	East	7	17.8	10.1	18.7	25.7	34.8
340803	East	2	17.7	9.5	19.0	25.7	34.1
341823	East	5	8.9	3.1	10.0	16.0	23.3
350521	South	11	21.2	16.1	21.8	26.7	31.9
360102	Central	4	18.7	10.8	20.1	26.5	35.2
360423	Central	4	18.7	10.8	20.1	26.5	35.2
370203	East	9	13.2	5.1	14.3	21.6	29.0
370602	East	8	13.1	4.6	14.4	21.9	30.4
370684	East	8	13.3	4.0	14.5	22.9	31.7
370785	East	13	13.3	3.8	14.5	23.1	33.4
410526	Central	18	13.9	4.4	15.3	23.4	32.8
411328	Central	18	15.8	7.4	17.2	24.2	33.0

411502	Central	7	16.0	8.1	17.1	24.0	33.1
420102	Central	11	17.6	9.3	18.8	25.8	35.3
420625	Central	7	16.2	8.1	17.5	24.2	32.6
430181	Central	19	17.4	9.3	18.6	25.3	32.7
430626	Central	14	17.4	9.3	18.6	25.3	32.7
440104	South	18	22.7	18.3	24.1	27.7	33.5
440282	South	6	20.3	14.2	21.8	26.7	32.2
441284	South	6	22.7	18.2	24.2	27.7	33.1
441424	South	15	21.6	16.8	23.3	27.0	31.8
450126	South	13	21.6	16.6	23.3	27.1	31.3
450521	South	8	22.9	19.0	24.5	27.9	31.9
500101	Southwest	23	18.8	11.3	19.2	25.7	34.9
500225	Southwest	13	18.8	11.3	19.2	25.7	34.9

510105	Southwest	7	16.5	9.7	17.4	23.0	30.1
510182	Southwest	13	16.0	9.2	16.7	22.5	29.9
511025	Southwest	17	17.7	11.0	18.2	24.0	33.9
511325	Southwest	7	17.9	10.6	18.4	24.4	35.4
520302	Southwest	6	15.7	9.0	16.4	22.8	30.8
520328	Southwest	5	15.7	9.0	16.4	22.8	30.8
530402	Southwest	5	16.5	12.5	17.4	20.5	25.6
532627	Southwest	10	17.4	13.1	19.0	22.4	28.5
540102	Southwest	2	9.7	3.9	10.3	15.3	22.6
610202	Northwest	3	10.4	2.2	12.0	18.9	28.2
610326	Northwest	4	13.6	5.1	14.6	21.9	32.0
610921	Northwest	3	16.1	7.9	16.8	23.6	34.2
620702	Northwest	6	8.7	-1.4	10.3	19.2	31.5

630103	Northwest	2	6.1	-2.2	7.5	14.4	25.7
640104	Northwest	4	10.3	0.5	12.1	20.7	30.6
640502	Northwest	4	9.9	0.5	11.6	19.9	29.3
650102	Northwest	4	8.1	-4.5	10.8	20.7	32.8

BMJ Open

Individual- and community-level effect modifiers of the temperature-mortality relationship in 66 Chinese communities

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Individual- and community-level effect modifiers of the temperature-mortality relationship in 66 Chinese communities

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Abstract

Objectives: To examine the modification of temperature-mortality association by factors at the individual and community levels.

Design and methods: This study investigated this issue using a national database comprising daily data of 66 Chinese communities for 2006-2011. A "threshold-natural cubic spline" distributed lag non-linear model was utilized to estimate the mortality effects of daily mean temperature, and then examined the modification of the relationship by individual factors (age, sex, education level, place of death, and cause of death) using a meta-analysis approach and community-level factors (annual temperature, population density, sex ratio, percentage of older population, health access, household income, and latitude) using a meta-regression method.

Results: We found significant effects of both high and low temperatures on mortality in China. The pooled excess mortality risk was 1.04% (95% CI: 0.90%, 1.18%) for 1 °C temperature decrease under the minimum mortality temperature (MMT), and 3.44% (95% CI: 3.00%, 3.88%) for 1 °C temperature increase above MMT. At the individual level, age and place of death were found to be significant modifiers of cold effect, while age, sex, place of death, cause of death and education level were effect modifiers of heat effect. At the community level, communities with lower socio-economic status and higher annual temperature were generally more vulnerable to the mortality effects of high and low temperatures.

Conclusions: This study identifies susceptibility based on both individual- and community-level effect modifiers; more attention should be given to these vulnerable individuals and communities to reduce adverse health effects of extreme temperatures.

Keywords: Temperature, mortality, effect modification, time series analysis

Strengths and limitations of this study

Strengths:

➢ We used a large database to examine daily mean temperature-mortality relationship in China;

- This is a national effort to assess the temperature-mortality relationship using data from a wide geographical coverage of China;
- We examined the effect modifiers at the individual and community levels simultaneously.

Limitations:

- We were not able to control for air pollution and influenza epidemics due to data unavailability;
- We used ambient temperature as a surrogate for personal exposure, which might cause exposure misclassification;
- The small number of daily mortality count in some communities might lead to imprecise risk estimation.

Introduction

Epidemiological studies have demonstrated significant association between ambient temperature and mortality [1, 2]. This relationship was generally found to be V-, U-, or J-shaped, with increased mortality at high and low temperatures and minimum mortality occurring at various temperature points [3-8]. Exposure to high temperature may cause dehydration and increase blood viscosity and cause some adverse health outcomes, for some vulnerable sub-populations, it is likely to lead to excess cardiovascular and respiratory deaths [9]; while during the cold period, the ability to regulate body temperatures is reduced, the cardiorespiratory system can not adjust well to the outside temperature change, especially for those persons with preexisting cardiovascular and respiratory diseases [10].

The health impacts of temperature variation are likely to be heterogeneous across regions with different geographic conditions, climate, and population characteristics [11, 12]. Identification of factors affecting the health susceptibility to temperature variation has been recognized as an important step to protect the vulnerable population [13]. And some studies have also reported that some individual-level factors were associated with the health effects of temperature variation, such as age, sex, and socio-economic status [3, 13-19].

Being the largest developing country, China has experienced noticeable climate change over the past decades [20]. The annual average temperature has risen by 0.5-0.8 °C during the past century [21]. Meanwhile, some weather extreme events, such as heat wave, cold spell, have also been witnessed in China, resulting in substantially excessive mortalities [10, 22, 23]. However, few studies have examined how temperature-mortality relationships differ among different subpopulations and regions in China [24].

One of our recent analyses examined the health effects of heat wave and associated effect modifiers based on a national database comprising data from 66 Chinese communities [25], the present study aimed to examine the effect modifiers of temperature-mortality relationship in China. We evaluated whether individual characteristics (age, sex, place of death, education level, and cause of death) and community-level factors (average temperature, population density, sex ratio, percentage of older population, health access, average annual income, and latitude) could modify the temperature-mortality relationship. This study is one of the largest studies of temperature-mortality relationship to date in China.

Materials and methods

Data collection

The Climate and Health Impact National Assessment Study (CHINAs) project is a national effort to assess short-term temperature-mortality relationship in 66 Chinese communities with more than 44 million residents. The 66 communities are distributed across seven geographical regions of China in terms of characteristics of geography, climate, natural ecology: northeast China (Heilongjiang, Liaoning, Jilin), north China (Beijing, Tianjin, Hebei, Shanxi, Neimenggu), northwest China (Shanxi, Gansu, Ningxia, Xinjiang, Qinghai), east China (Jiangsu, Zhejiang, Anhui, Shandong and Shanghai), central China (Henan, Hubei, Hunan and Jiangxi), southwest China (Sichuan, Xizang, Guizhou, Yunnan and Chongqing), and south China (Fujian, Guangdong and Guangxi). These communities provided a wide geographical coverage of China (Figure 1), details of the data have been described elsewhere [24, 25].

Community-specific daily mortality data covering the period from January 1 2006 to December 31 2011 were obtained from Chinese Center for Disease Control and Prevention (China CDC). China CDC is the government agency in charge of health data collection in China. A death, whether occurred in a hospital or at home, must be reported to local CDC. In both situations, the hospital or community/village doctors completed a standard death certificate card regarding the death information including some individual-level information, such as age, sex, education level, cause of death and date of death, and place of death. In this study, we classified location of death into "in-hospital deaths" and "out-of-hospital deaths", the former included deaths occurred in hospitals, clinics, or medical centers, as well as outpatients admitted to the emergency room; while "out-of-hospital deaths" was defined as all other deaths, such as deaths in homes.

During the study period, the causes of death were coded according to the 10th revision of the International Classification of Diseases (ICD-10). The mortality data were classified into deaths due to all non-accidental causes (ICD-10: A00-R99), cardiovascular diseases (ICD-10: I00-I99), and respiratory diseases (ICD-10: J00-J99). Stratified data sets were also created with daily death counts by sex, age group, and place of death (outside or in a hospital).

Community-specific daily meteorological data for the same period were retrieved from the China National Weather Data Sharing System (http://cdc.cma.gov.cn/home.do), which is publicly accessible. For each community, there was one basic-reference land surface automatic weather observation station, which provided the weather information for each community. Meteorological data consisted of daily mean, minimum, maximum and apparent temperatures (°C), relative humidity (%), and atmospheric pressure (hpa).

The proportion of missing mortality and meteorological data was very low. The highest proportion was found for maximum temperature with missing rate less than 0.2%.

Community-level variables (annual average temperature, population density, sex ratio, percentage of population older than 65 years old, hospital beds for per thousand population, annual household income, and latitude) were obtained from the sixth national census values [26].

Analysis of temperature–mortality relationship

Daily mean temperature was chosen as the temperature indicator for this analysis as it provided more easily interpreted results in a policy context [3]. Within each community, the relationship between daily mean temperature and mortality was estimated using a distributed lag non-linear model (dlnm) with daily death counts as the dependent variable. The "dlnm" model has been widely applied to investigate the health effects of air pollution and temperature. This approach has the ability to simultaneously investigate the non-linear and delayed effects of exposure on daily mortality, termed as exposure-lag-response associations [27, 28]. This model used a "cross-basis" function, which allowed a two-dimensional relationship of the non-linear effect of daily temperature variation at each lag and the nonlinear effects across lag days to be estimated [27]. The method accounted for the over-dispersed Poisson data using the assumption that the total variance was proportional to the total number, with the over-dispersion constant estimated through quasi-likelihood. In "cross-basis" function, we used the spline function for temperature and the polynomial function for the lag structure. The model can be specified as:

$$\text{Log E(Yt)} = \alpha + \text{cb(temp, df=5; lag, df=3)} + \text{s(t, df=6/year)} + \beta_1\text{*DOW} + \beta_2\text{*PH} + \text{COVs}$$

where E(Yt) denotes the expected daily mortality count on day t, cb means the "cross-basis" function, s() indicates a smooth function based on natural splines for nonlinear variables. In this study, the number of knots was set as 3, and it was placed at equally-spaced percentiles of the temperature distribution for each community. t is the day of study (an integer value for day 1 to n of the time series, to control for long-term and seasonal trends), β is the regression coefficient, DOW is a categorical variable for day of week, PH is the binary variable indicating public holidays, and COVs are the potential confounding factors, including smooth function of relative humidity (df=3), precipitation (df=3), duration of sunshine (df=3) and atmospheric pressure (df=3) [29, 30]. We examined the residuals (the difference between fitted and observed values) of the model to check whether there were discernable patterns and autocorrelation by means of residual plot and partial autocorrelation function (PACF) plot. The PACF of residuals of the model was less than 0.1, indicating no serial autocorrelations in the residuals and sufficient confounder control [19].

We plotted the relative risks against temperature and lag days to show the overall relationship between mean temperature and mortality. Our initial results showed that the temperature–mortality relationships were approximately V- or U-shaped, with a minimum mortality temperature (MMT), a pattern that rendered it necessary to divide the series into two segments with reference to the MMT. Thus, we estimated the linear relationships below and above the city-specific MMT in accordance with previous studies [31, 32], assuming that the mortality effects of temperatures below and above the MMT were linear. The community-specific MMT was determined in accordance with previous studies and used as the reference temperature for the analysis [31, 32]. In brief, in the model multiple temperatures were tested based on minimum residual deviance of the model. For example, by visual inspection of the dose–response curve, we may identify that the potential MMT might be within 25 to 28 °C, and we then examined the potential MMT from 25 to 28 °C (by 0.1 °C) to identify the model with minimum residual deviance [24].

Previous studies have suggested that the low temperature effect persisted for longer days, even weeks, while high temperature effects were shorter term (usually 0-2 days) [22, 33]. In light of these findings, we modeled the effects of heat and cold effects with two different regression models: daily temperature at lag 0-2 days was used to model the heat effect and lag 0-21 days was used to represent the cold effect.

We examined community-specific temperature–mortality relationship and summarized measures of the heat and cold effects. Specifically, for each community we calculated the change in mortality risk for 1 °C decrease in temperature below the minimum mortality temperature (cold effect) and for 1 °C temperature increase above the minimum mortality temperature (heat effect).

Heterogeneity of the effect estimates was observed among the communities, so we used a random-effect meta analysis model was used to combine the heat and cold effect estimates of the 66 communities to generate overall effects at the regional and national levels [34].

Effect modifiers of temperature-mortality relationship

For the potential effect modifiers at the individual level, the effect estimates were obtained for each stratum of potential modifying factor, including cause of death (non-accidental, cardiovascular and respiratory mortalities), age (0-64, 65-74, 75-84, 85-), sex (males and females), education level (low: less than 6 years of schooling, medium: 6–9 years, and high: 9 years and above), and place of death (within or outside of a hospital). A random-effect meta-analysis approach was used to generate overall effects for each category.

For the community-level effect modification, random-effect meta-regression models were used by including potential effect modifiers in the random-effect meta-analysis to examine their contribution to the observed variation in the effect estimates among the communities [35].

Sensitivity analysis

Sensitivity analyses were performed by changing the df of long-term and seasonal trends (7-10 df/year). All statistical tests were two-sided, and values of $p < 0.05$ were considered as statistically significant.

Results of the analysis were expressed as excess relative risk (ERR) of mortality increase for 1 °C increase above the MMT (heat effect) or 1 °C decrease below the MMT (cold effect). ERR was calculated using the formula: ERR=(RR−1) × 100%, where RR (relative risk) was obtained through the time series models. All statistical analyses were performed using the R software (version 2.15.1) (R Development Core Team, Austria). The distributed lag nonlinear models were fitted using the R package "dlnm", and meta-analysis was conducted using the "metafor" package.

Results

Supplementary Table s1 summarized the daily mortality and weather statistics by community. During the study period, a total of 1,260,913 deaths were reported in the 66 communities, including 552,866 and 198,777 deaths from cardiovascular and respiratory systems. The communities differed in population size and daily mortality count. The community-specific mean number of daily deaths ranged from 2 to 23. Most of the deceased were above 65 years of age (71.5%), and male (58.2%). A substantial fraction of deaths (72.8%) occurred out of a hospital.

Supplementary Table s1 and Figure s1 illustrated the distribution of daily temperature in the 66 communities. The 66 communities in this study had a wide range of climates, with annual mean temperatures ranging from 4.6 °C in Yi'an County in Northeast China (community ID, 230223) to 22.9 °C in Hepu County in

Southeast Region (community ID, 450521). Among the seven regions, Southern region had the highest mean temperature, and northeastern region had the lowest temperature.

Supplementary Figures s2 and s3 showed the diagnostic graphs of the model, including the plot of the residuals and the plot of PACF for a few communities. There were no discernible seasonal patterns and no autocorrelation in the residuals, indicating acceptable goodness of fit of the models.

Figure s4 showed the temperature-mortality association and the identified MMT in a few communities. Figure s5-s8 showed the association for males, females, cardiovascular and respiratory mortalities, respectively. The results showed that the curves varied across communities, but generally was U- or V-shaped. We found significant mortality effects from both low and high temperatures, with a most comfortable temperature value; in general, the MMT was found to be higher in southern regions. The overall effect estimates for all the 66 communities and each of the seven regions were illustrated in Table 1. The strongest cold effect was observed for the North and Central regions, and Northeast Region had the lowest mortality effect from cold weather. For the mortality effect of high temperature, the highest effect was observed in South China, and the lowest effect in Northwest Region.

Table 1 Percentage increase in daily mortality for 1 °C decrease below the threshold and 1 °C increase above the threshold by geographic region, China, 2006-2011

Regions	No. of communities	Regional estimates (95% CI)	
		Cold effect	Heat effect
East	16	2.92 (2.46-3.38）	1.19 (0.79-1.58)
Central	9	4.55 (2.99-6.14)	1.25 (0.71-1.79)
North	8	5.46 (3.40-7.56)	1.09 (0.72-1.46)

Northeast	7	1.88 (1.31-2.46)	1.74 (-0.40 -3.93)
Northwest	8	2.38 (0.85-3.94)	0.55 (-0.04-1.15)
South	7	4.44 (3.59-5.29)	1.38 (0.54-2.23)
Southwest	11	3.49 (2.63-4.36)	1.24 (0.85-1.62)
All communities	66	3.44 (3.00, 3.88)	1.04 (0.90, 1.18)

Individual-level effect modifiers

In the stratified analyses by various individual-level factors, the cold and heat effects were found to vary by age, sex, and place of death (Table 2).

Cold-related mortality risk had a general increasing pattern with age, the highest risk was observed among those aged 85 years and above (the ERR being 4.11%, 95% CI: 3.53%-4.69%). Location of death was a strong modifier of the cold effect with an ERR of 2.34% (95% CI: 1.76%-2.93%) for dying in a hospital, and 3.93% (95% CI: 3.40%-4.46%) for the deaths occurring out a hospital. Other personal characteristics had similar association.

The individual factors that increased susceptibility to heat effect included old age, female, dying out of a hospital, dying of respiratory diseases and education level. For example, sex was a strong effect modifier, the ERR being 1.36% (95% CI: 1.06%-1.66%) for females and 0.89% (95% CI: 0.70%-1.08%) for males. The hot weather had stronger health effects for those with respiratory conditions (ERR: 1.37%, 95% CI: 0.99%-1.75%) compared with those dying of cardiovascular illness (ERR: 1.20%, 95% CI: 0.99%-1.41%) and non-accidental diseases (ERR: 1.04%, 95% CI: 0.90%-1.18%). And people with lower education level had higher heat effect (ERR: 1.38%, 95% CI: 1.16%-1.60%) than those with moderate education level (ERR: 0.58%, 95% CI: 0.34%-0.83%) and higher level (ERR: 0.84%, 95% CI: 0.47%-1.21%).

Table 2 Comparison of heat- and cold-related mortality risks by individual-specific effect modifiers

Variables	Effect estimates (%)	
	Cold effect	Heat effect
Sex		
Male	3.39 (2.92, 3.87)	0.89 (0.70, 1.08)
Female	3.48 (2.99, 3.98)	1.36 (1.06, 1.66)
Age group		
<64y	2.55 (2.03, 3.06)	0.71 (0.47, 0.95)
65-74y	3.49, 2.81, 4.18)	0.84 (0.58, 1.11)
75-84y	3.72 (3.12, 4.33)	1.25 (1.02, 1.48)
>85y	4.11 (3.53, 4.69)	1.72 (1.32, 2.13)
Death cause		
Non-accidental	3.44 (3.00, 3.88)	1.04 (0.90, 1.18)
Cardiovascular	3.95 (3.42, 4.49)	1.20 (0.99, 1.41)
Respiratory	4.14 (3.36, 4.92)	1.37 (0.99, 1.75)
Location of death		
Out of hospital	3.93 (3.40, 4.46)	1.22 (1.01, 1.44)
In a hospital	2.34 (1.76, 2.93)	0.79 (0.57, 1.01)
Education level		
Low	3.17 (2.73, 3.61)	1.38 (1.16, 1.60)
Medium	3.33 (2.73, 3.92)	0.58 (0.34, 0.83)
High	3.31 (2.27, 4.36)	0.84 (0.47, 1.21)

Community-level effect modifiers

We evaluated whether the observed temperature-mortality relationship could be explained by some community-level factors, such as average temperature, population density, sex ratio, percentage of people with low education level, population aged 75 years and above, living in urban setting, hospital beds per thousand population, average income, and latitude (Table 3). The analysis found that the cold effects were slightly higher in warmer communities. A 7.2 °C increase in annual average temperature was associated with a 0.59% (95% CI: -0.04%, 1.21%) increase in cold-related relative risk. While ommunities with higher education level, more residents living in urban area, better health care facility, and higher latitude were less susceptible to the cold impacts. For the heat effects, we found that annual temperature, living in urban setting, income and latitude were significant effect modifiers, for example, a 7.2 °C increase in annual average temperature was associated with a 0.31% (95% CI: 0.11%, 0.51%) increase in heat-related mortality risk.

Table 3 Increase in heat- and cold-related mortality per IQR increase in community-specific effect modifiers

Community-specific variable	IQR*	Change in relative effect (%)		Change in relative effect (%)	
		Cold effect	P value	Heat effect	P value
Annual temperature	7.2°C	0.59 (-0.04, 1.21)	0.06	0.31 (0.11, 0.51)	0.01
Male-female sex ratio	6.1	0.38 (-0.15, 0.92)	0.16	0.09 (-0.10, 0.28)	0.35
Population density	2257	-0.05 (-0.16, 0.07)	0.44	-0.02 (-0.05, 0.01)	0.16
Older population fraction	3%	-0.47 (-1.07, 0.12)	0.12	0.14 (-0.06, 0.34)	0.16
Years of education	2.5	-0.57 (-1.24, 0.10)	0.10	-0.13 (-0.33, 0.07)	0.21
Living in urban setting	58%	-0.89 (-1.72, -0.05)	0.04	-0.23 (-0.49, 0.04)	0.09
Hospital beds per thousand population	1.6	-0.31 (-0.60, -0.02)	0.04	0.04 (-0.06, 0.14)	0.46
Average income	$30k	-0.23 (-0.55, 0.09)	0.16	0.01 (-0.08, 0.10)	0.10
Latitude	7.9	-0.52 (-1.03, -0.01)	0.04	-0.20 (-0.37, -0.04)	0.02

* IQR: Interquartile range, which is the difference of the 3rd quartile and the 1st quartile of each factor.

Sensitivity analysis

We found generally similar effect estimates using different degree of freedom (7-10 df/year) for temporal adjustment compared with those of the main analyses, suggesting a robust result of this analysis.

Discussion

In this large multi-community study, we provided unique evidence on individual- and community-specific indicators that were related to the vulnerability to temperature-related mortality risk in China. Our analysis found that most of the effect modifiers were generally similar for individual- and community-level factors, which enhanced the possibility that these factors were valid potential markers of vulnerability, which contributed to the advantage of this study. The underlying mechanisms for the observed excess mortality during days with high temperature may be related to the stress placed on the respiratory and circulatory systems to increase heat loss through skin surface blood circulation [36]. This coupled with an increase in blood viscosity and cholesterol levels may lead to elevated mortality risk. The possible mechanisms for the cold-related mortality risk have also been suggested. One underlying reason might be the higher prevalence of respiratory infection during winter season, particularly influenza epidemics, and an increase in plasma cholesterol and plasma fibrinogen with low temperatures, coupled with a higher blood pressure in cold weather, could lead to thrombosis through haemoconcentration and trigger an acute mortality event [37]. Moreover, the extremely cold weather might have also contributed to the excess mortality by reducing access to a hospital.

Socio-economic inequalities at community and individual levels have been linked with a higher burden of environmental risks, including those from weather variation [3, 13, 38, 39]. For example, higher mortality effect of high temperature were observed for those at older age, dying out of a hospital and with existing cardiopulmonary conditions [13]. Regional differences in the association between ambient temperature and mortality may be partly due to dissimilar population structure in terms of age, sex, education attainment and other socio-economic status [3].

Our study found that low socio-economic conditions were generally associated with higher mortality risk from both high and low temperatures, which was generally consistent with several previous studies. For example, study about the heat-related mortality risk in Chicago in 1995 found that people with existing medical conditions, and low socio-economic status were the vulnerable population [40]. In Texas, heat-related excess mortality was higher among the elderly, men, and persons involved in heavy labor [41]. An analysis examining effect indicators of the temperature-mortality association in 107 US cities found that age, cause of death, place of death, median household income, unemployment rate, usage of air conditioning, education level were potential markers of vulnerability to temperature extremes [3]. Similar findings have also been observed in other studies [14, 17, 42, 43].

Our study suggested that the temperature-mortality association increased with age, with those aged over 85 years being the most susceptible population, which was consistent with several previous studies [44, 45]. The older persons were generally at poor health status, had preexisting medical conditions and diminished ability to detect changes in their body temperature, and thus had reduced thermoregulatory capacity, which might be the major reason for their increased susceptibility to temperature extremes [14, 22, 46].

Education level was a good indicator of socio-economic status that conveyed susceptibility [42]. For both cold and heat effects, our study found a generally higher mortality risk for areas with lower education level, which was consistent with a study of seven US cities [14, 47] and Curriero et al.'s study of eleven US cities [45]. Persons with more education attainment were more likely to have greater wealth and better health access, dietary intake, better domestic heating system in winter and air conditioning usage in summer [48]. Higher mortality rates among the low-educated population have also been observed in several other studies, such as a cohort study in US [49].

Location of death was found to be an important effect modifier of the mortality effect of cold and hot weathers in the present study, which has also been reported in a few studies [13, 14], however, these two studies [13, 14] found the effect modification was mainly for heat effects, while our study found that it was more obvious for cold effects, the underlying reason for this discrepancy remained unknown. Finding of higher vulnerability for those dying out of hospitals was biologically plausible. It was possible that people dying out of a hospital had higher intensity of exposure to ambient environment, and it was also partly due to the better health care received by the residents living in a hospital, as it was likely that those dying out of a hospital usually had lower socio-economic status [14].

The factors leading to the community vulnerability to mortality effects of temperature were found to be community-specific temperature, urbanization, education level, health care facility, household income and latitude, and the effect modification was particularly noteworthy for cold effect. Previous studies also found that group-level factors could explain some heterogeneity in community-specific effects [3, 45, 50, 51]. This phenomenon may be due to the general health and nutrition status, health care access, and overall knowledge, attitude and adaptation capacity to the health effects of temperature. A study examining the temperature-related mortality in Chicago also showed that areas with lower socio-economic status had higher mortality risk [50]. Anderson, et al's study including 107 US communities also examined the community-specific effect modifiers, and found that communities with higher unemployment rate, more population with lower education attainment, more population living in urban environment were more vulnerable to the temperature extremes [3].

Of particular, we found that southern communities with lower latitude and higher annual average temperature had temperature-related mortality risk, which has also been reported elsewhere [4, 16, 45]. The higher cold effect in southern areas may suggest the evidence for acclimatization. Though the winter temperature was higher in south China than in north areas, the lacking of centralized heating system in south China made people in south areas suffer more from the cold weather, causing excess mortality risk [22]. While the higher heat effect in south region observed in this study might be due to the more exposure opportunity and higher intensity of heat exposure by the population in south China. However, some other studies have reported that low latitude areas had lower risk from heat effects, which was inconsistent with findings from our study [44, 52].

Though previous studies suggested that the global temperature rising might be a net harmful health effect [53], our study suggested that cold weather was also an important health hazard, which should not be neglected. This finding also indicated that the health impact of cold weather, particularly its long delayed effects, should be considered in the health effect analysis and projecting health impact of future climate change.

A few limitations should be noted when interpreting the findings from this study. One limitation was that we were not able to control for air pollution and influenza epidemics in the analysis due to data unavailability. Our previous work suggested that the health effects of temperature extremes remained similar after controlling for various air pollutants and influenza epidemics [22]. However, O'Neill et al examined the mortality impact of temperature controlling for both ozone and particulate matter and found that the effect of high temperature on mortality reduced by about 30% but the associations persisted [54]. And Goldberg's study in Canada also suggested that air pollution could not distort the temperature-mortality relationship to a great extent [55]. Another limitation was the use of ambient temperature as a surrogate for personal exposure. The misclassification derived from this assumption will be largely determined by the extent to which ambient and micro-environmental temperatures are correlated [16], which was likely be affected by adaptive mechanisms such as use of air conditioning. Furthermore, for both individual- or community- level analyses of effect modifiers, we cannot control the potential confounding effect of one modifier by another, due to the high correlation between some variables, we cannot simply put them in the same model, making the observed effect modification difficult to attribute to one specific factor. It should also be noted that the small number of daily mortality count in some communities might lead to imprecise risk estimation, and for this reason, we only examined the effects on mortality from respiratory and cardiovascular systems, further studies on more specific diseases are warranted in future studies.

Another limitation was that this study used weather data from only one weather observation station for each community, however, a community in this study covered relative small geographic area, and the weather data from one station could generally represent the local weather pattern.

The findings from this study have some public health implications for policymakers and scientific community by providing the evidence of temperature-mortality relationship in China and related effect modifiers at individual- and community-levels. Climate adaptation planning should be taken as one local issue, which means adaptation strategy development should take into consideration local weather conditions, population characteristics and socioeconomic status. The identified susceptible subpopulations from this study provided evidence for the targeted temperature-mortality prevention and adaptation measures. The community-level effect modifiers indicate the necessity of multi-city study and indicate that community specific prevention strategies are warranted.

Conclusions

In summary, this study identifies susceptibility of mortality effects of temperatures based on both individual- and community-level effect modifiers, more attention should be given to these vulnerable individuals and vulnerable communities to reduce adverse health effects of extreme temperatures.

Competing interests

The authors declare no competing interests.

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Authors' contributions

ZJH, YNL, LJW and MGZ provided the mortality data. HLL, WJM, TL and JPX conceived of the study, participated in the study design, statistical analysis, and drafted the manuscript. TL, JPX, WLZ, XL and YHZ collected the meteorological data and result interpretation. TL, SLT, KLE and HLL participated in the study design and coordination. All authors read and approved the final manuscript.

Data sharing statement

All data have been included in the manuscript, no additional data are available.

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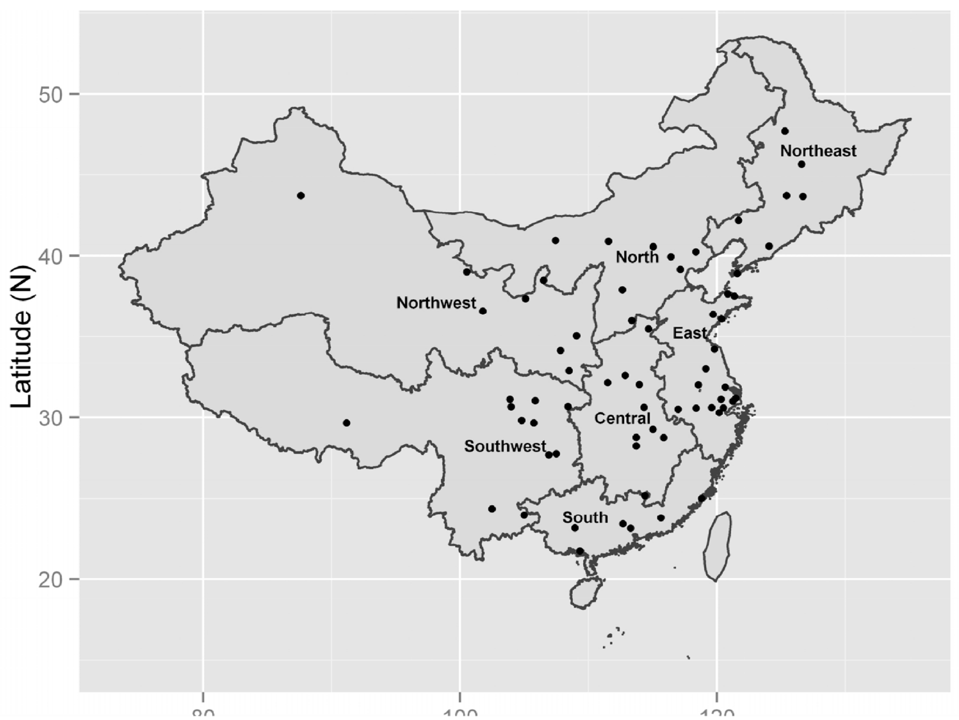
Figure legends:

Figure 1. The map of China showing the location the 66 communities.



The map of China showing the location the 66 communities.
297x210mm (200 x 200 DPI)

Individual- and community-level effect modifiers of the temperature-mortality relationship in 66 Chinese communities

Table s1. Summary statistics for daily mortality and temperature across the 66 Chinese communities.

Community code	Region	Daily deaths	Daily mean temperature (°C)				
			Mean	P25	P50	P75	Max
110101	North	8	13.4	2.5	14.7	24.1	34.5
120106	North	11	13.1	2.1	14.4	23.8	32.1
130227	North	3	11.9	1.3	13.0	22.8	30.6
130721	North	3	9.5	-1.5	10.4	20.7	31.9
140107	North	6	11.3	1.5	12.3	21.1	31.2

140427	North	4	10.0	1.1	11.7	19.2	28.7
150103	North	3	8.1	-2.9	9.4	19.7	32.5
150802	North	6	6.5	-5.5	7.8	18.7	31.4
210204	Northeast	10	11.3	2.7	12.8	20.8	29.4
210682	Northeast	8	9.5	-0.1	10.9	19.8	28.0
210921	Northeast	10	8.3	-3.9	9.8	20.9	29.3
220102	Northeast	6	6.5	-6.3	8.5	19.7	30.4
220211	Northeast	3	5.8	-6.2	7.6	18.7	28.5
230103	Northeast	16	5.6	-8.2	7.6	19.7	30.6
230223	Northeast	6	4.6	-10.3	6.9	19.1	31.5
310103	East	6	17.5	9.7	18.6	25.1	35.7
310117	East	9	17.5	9.7	18.6	25.1	35.7
320111	East	8	16.6	8.3	17.7	24.9	34.5

320506	East	9	16.8	8.7	17.9	25.0	34.8
320582	East	14	16.3	8.2	17.2	24.2	33.9
320831	East	6	15.3	7.0	16.5	23.8	33.1
320921	East	8	14.9	6.6	15.9	23.2	32.8
330103	East	5	17.8	10.1	18.7	25.7	34.8
330483	East	11	17.2	9.5	18.1	24.8	34.5
330523	East	7	17.8	10.1	18.7	25.7	34.8
340803	East	2	17.7	9.5	19.0	25.7	34.1
341823	East	5	8.9	3.1	10.0	16.0	23.3
350521	South	11	21.2	16.1	21.8	26.7	31.9
360102	Central	4	18.7	10.8	20.1	26.5	35.2
360423	Central	4	18.7	10.8	20.1	26.5	35.2
370203	East	9	13.2	5.1	14.3	21.6	29.0

370602	East	8	13.1	4.6	14.4	21.9	30.4
370684	East	8	13.3	4.0	14.5	22.9	31.7
370785	East	13	13.3	3.8	14.5	23.1	33.4
410526	Central	18	13.9	4.4	15.3	23.4	32.8
411328	Central	18	15.8	7.4	17.2	24.2	33.0
411502	Central	7	16.0	8.1	17.1	24.0	33.1
420102	Central	11	17.6	9.3	18.8	25.8	35.3
420625	Central	7	16.2	8.1	17.5	24.2	32.6
430181	Central	19	17.4	9.3	18.6	25.3	32.7
430626	Central	14	17.4	9.3	18.6	25.3	32.7
440104	South	18	22.7	18.3	24.1	27.7	33.5
440282	South	6	20.3	14.2	21.8	26.7	32.2
441284	South	6	22.7	18.2	24.2	27.7	33.1

441424	South	15	21.6	16.8	23.3	27.0	31.8
450126	South	13	21.6	16.6	23.3	27.1	31.3
450521	South	8	22.9	19.0	24.5	27.9	31.9
500101	Southwest	23	18.8	11.3	19.2	25.7	34.9
500225	Southwest	13	18.8	11.3	19.2	25.7	34.9
510105	Southwest	7	16.5	9.7	17.4	23.0	30.1
510182	Southwest	13	16.0	9.2	16.7	22.5	29.9
511025	Southwest	17	17.7	11.0	18.2	24.0	33.9
511325	Southwest	7	17.9	10.6	18.4	24.4	35.4
520302	Southwest	6	15.7	9.0	16.4	22.8	30.8
520328	Southwest	5	15.7	9.0	16.4	22.8	30.8
530402	Southwest	5	16.5	12.5	17.4	20.5	25.6
532627	Southwest	10	17.4	13.1	19.0	22.4	28.5

540102	Southwest	2	9.7	3.9	10.3	15.3	22.6
610202	Northwest	3	10.4	2.2	12.0	18.9	28.2
610326	Northwest	4	13.6	5.1	14.6	21.9	32.0
610921	Northwest	3	16.1	7.9	16.8	23.6	34.2
620702	Northwest	6	8.7	-1.4	10.3	19.2	31.5
630103	Northwest	2	6.1	-2.2	7.5	14.4	25.7
640104	Northwest	4	10.3	0.5	12.1	20.7	30.6
640502	Northwest	4	9.9	0.5	11.6	19.9	29.3
650102	Northwest	4	8.1	-4.5	10.8	20.7	32.8

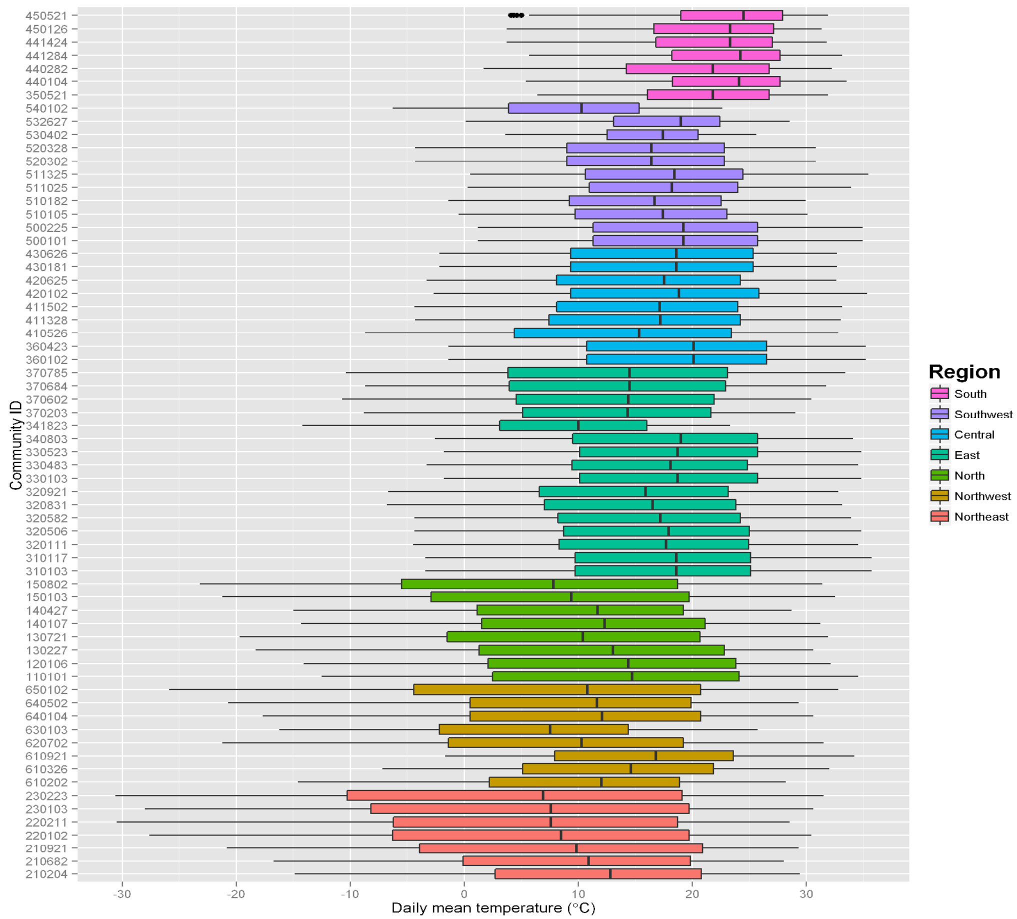


Figure s1. The distribution of daily mean temperature among the 66 Chinese communities.

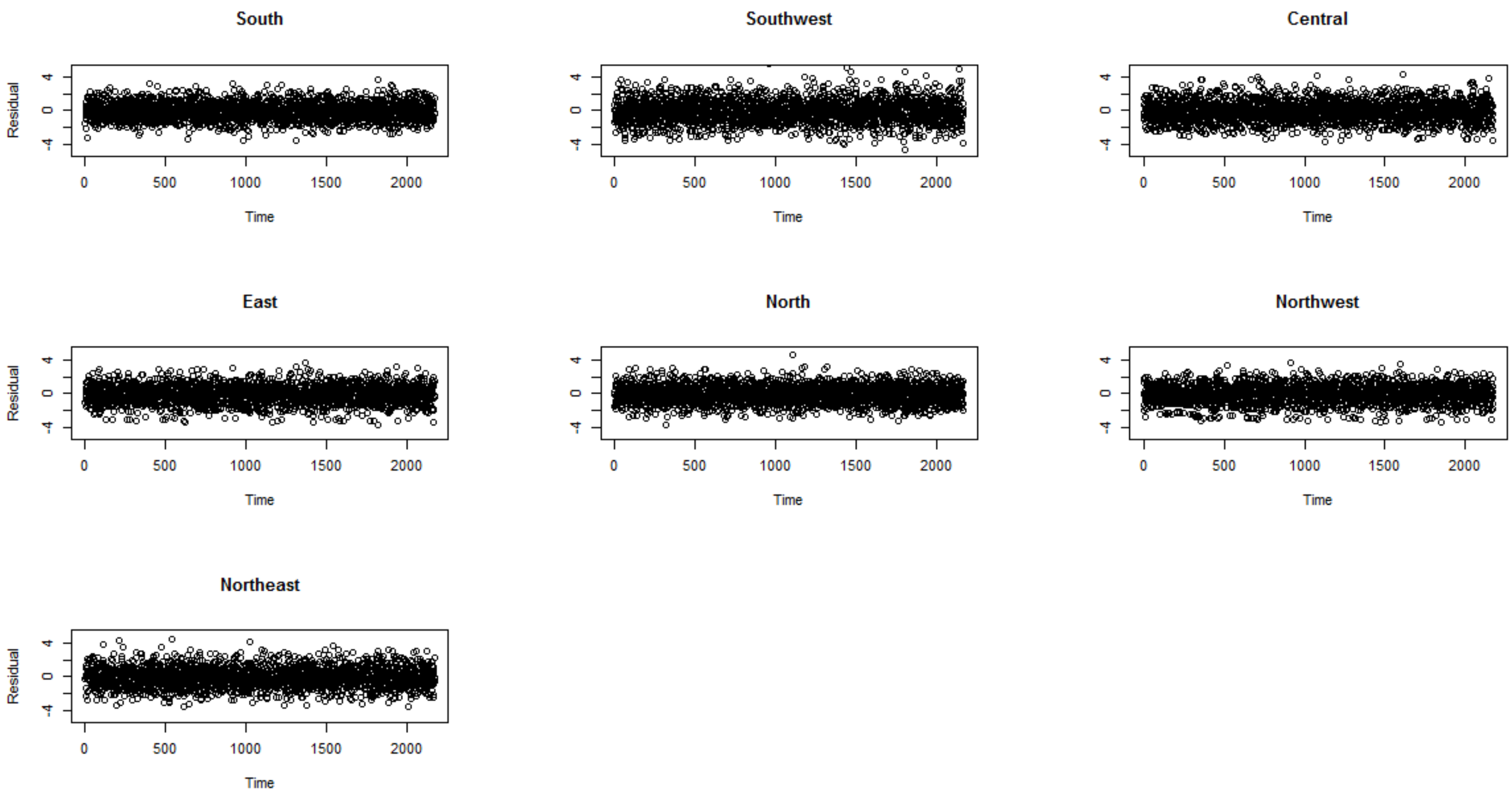


Figure s2. The time series of mortality residuals against time trend for a few community.

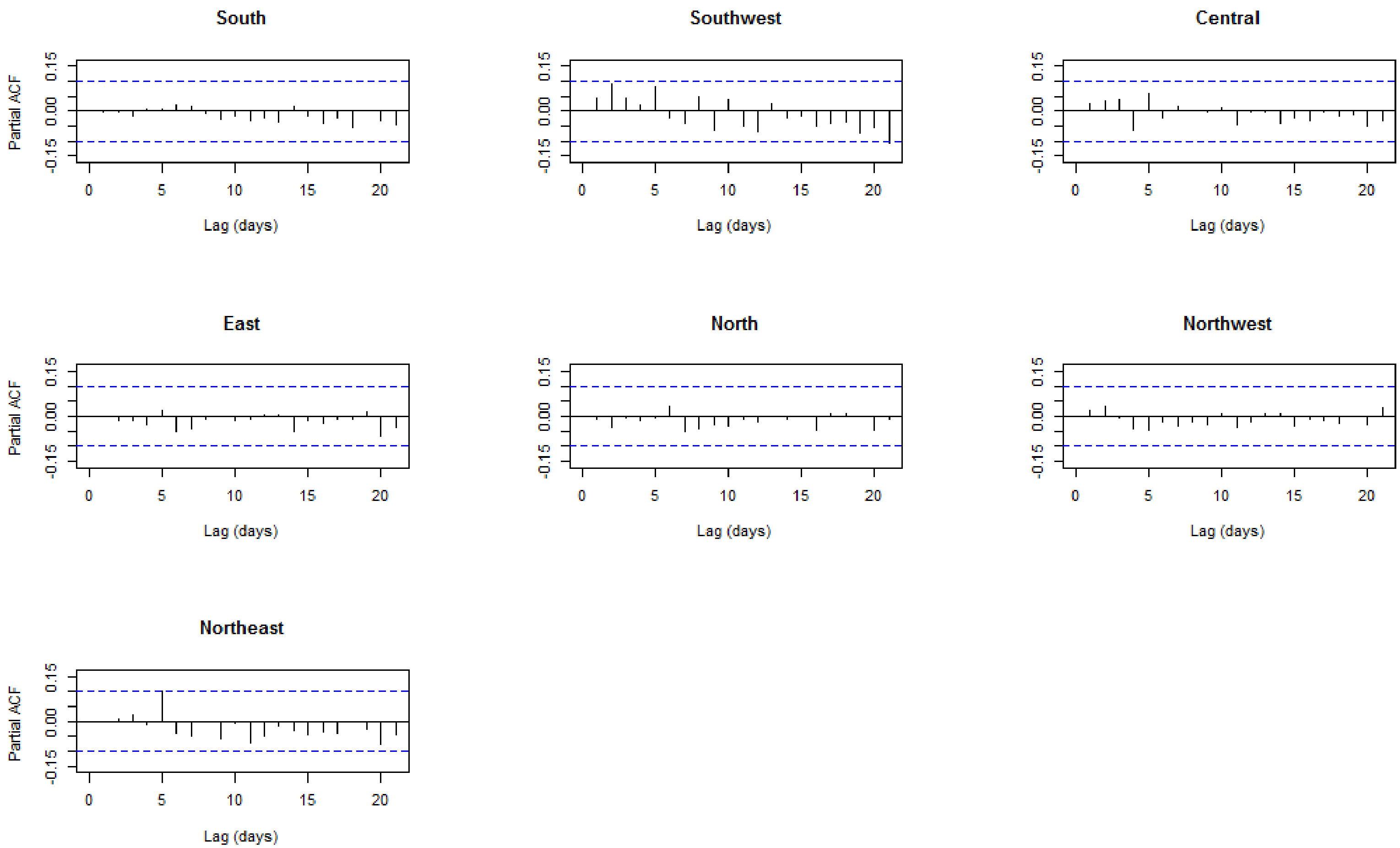


Figure s3. Diagnostic graphs of the model (PACF of the residuals of the model).

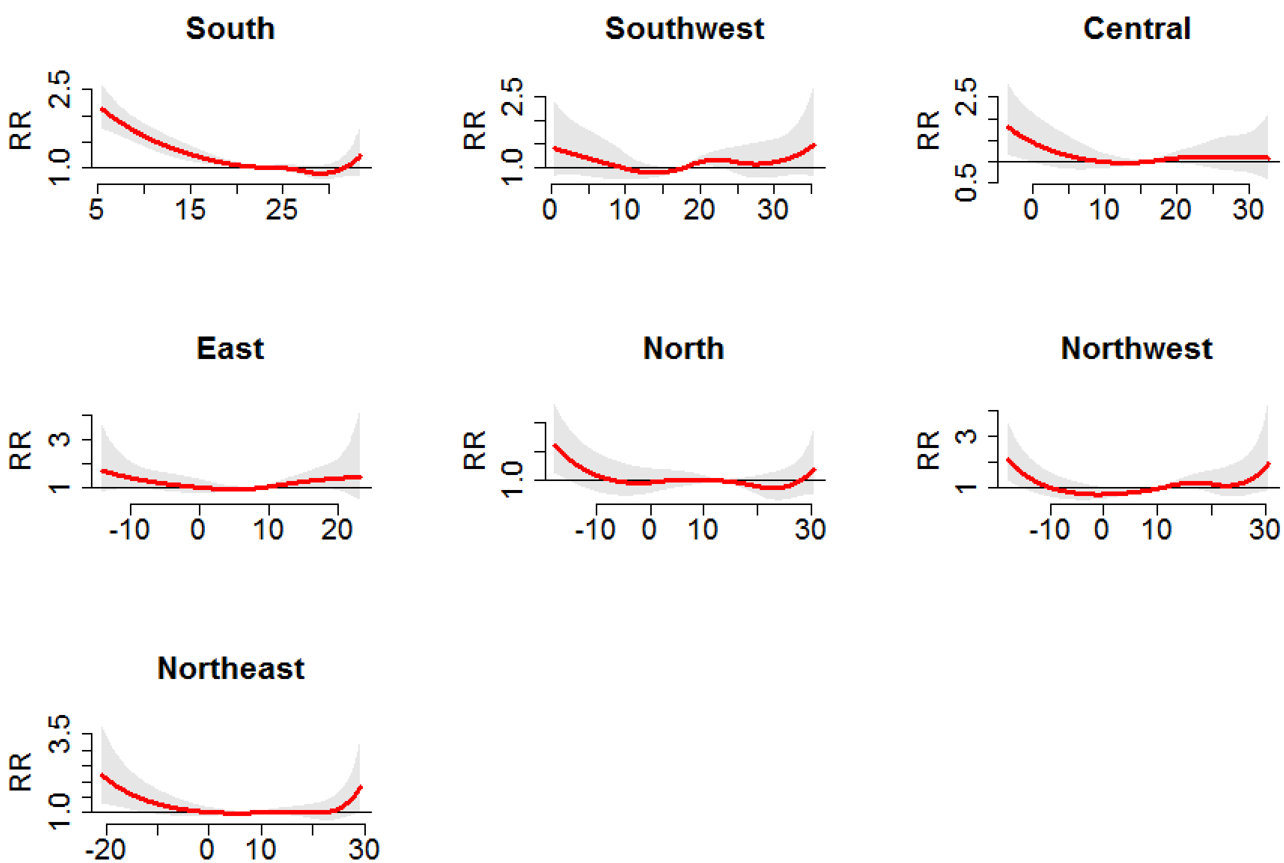


Figure s4. The cumulative effects of daily mean temperature on all-cause mortality over past 21 days for some communities in each region.

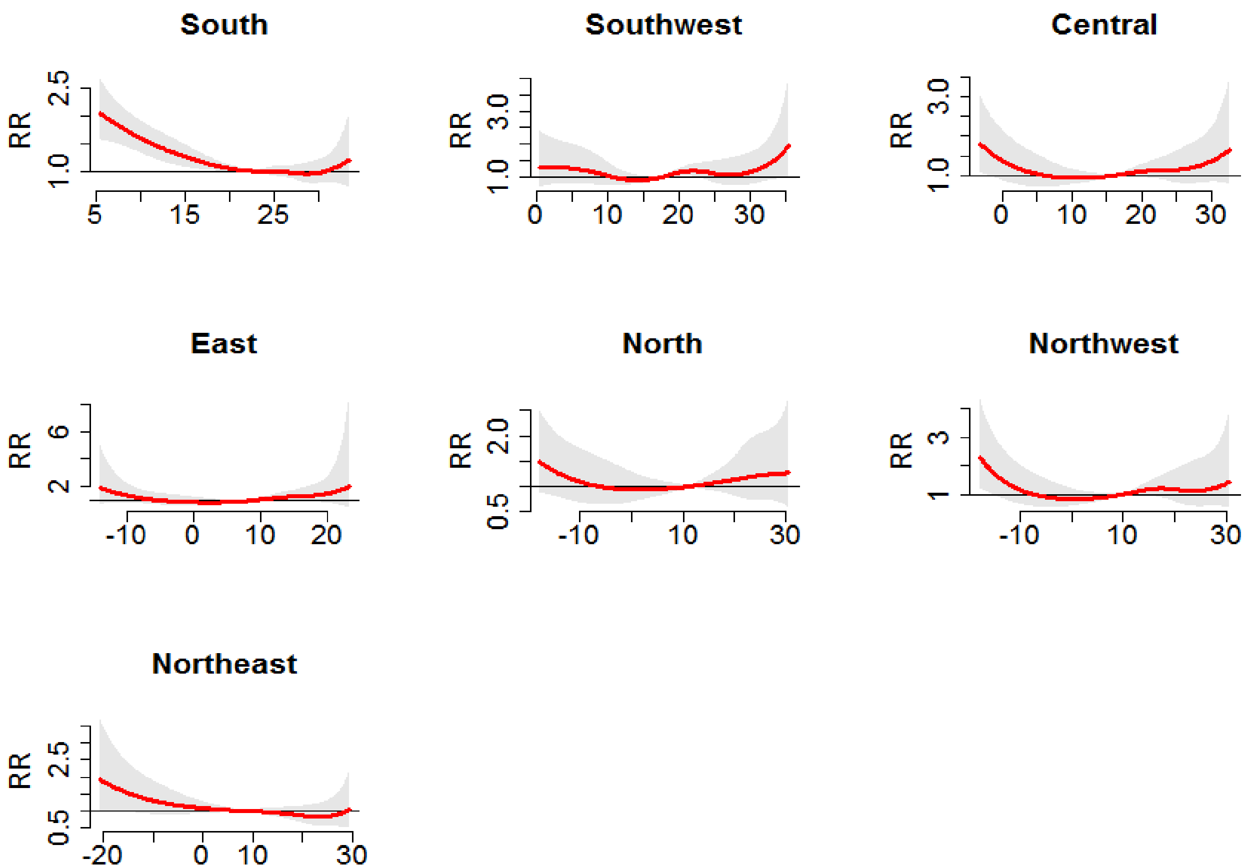


Figure s5. The cumulative effects of daily mean temperature on mortality among males over past 21 days for some communities in each region.

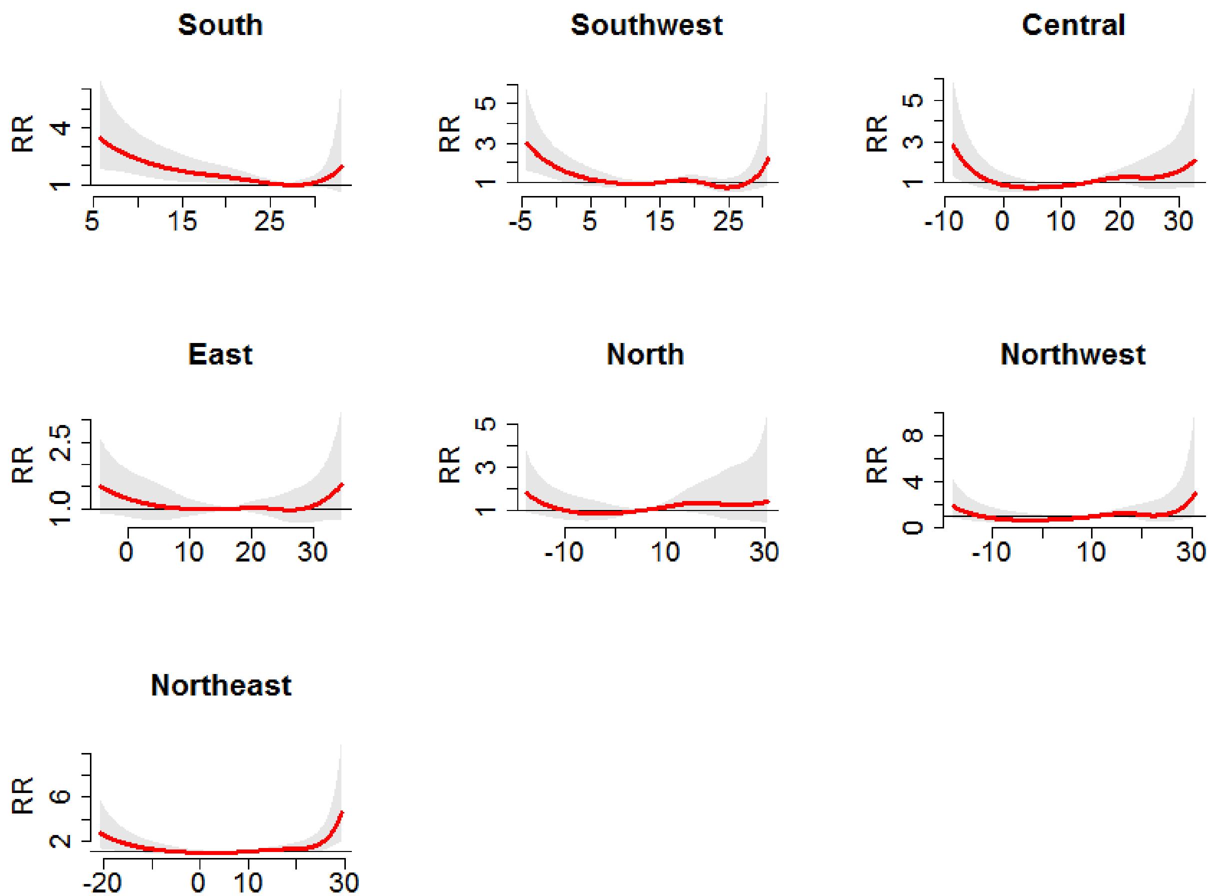


Figure s6. The cumulative effects of daily temperature on mortality among females over past 21 days for some communities in each region.

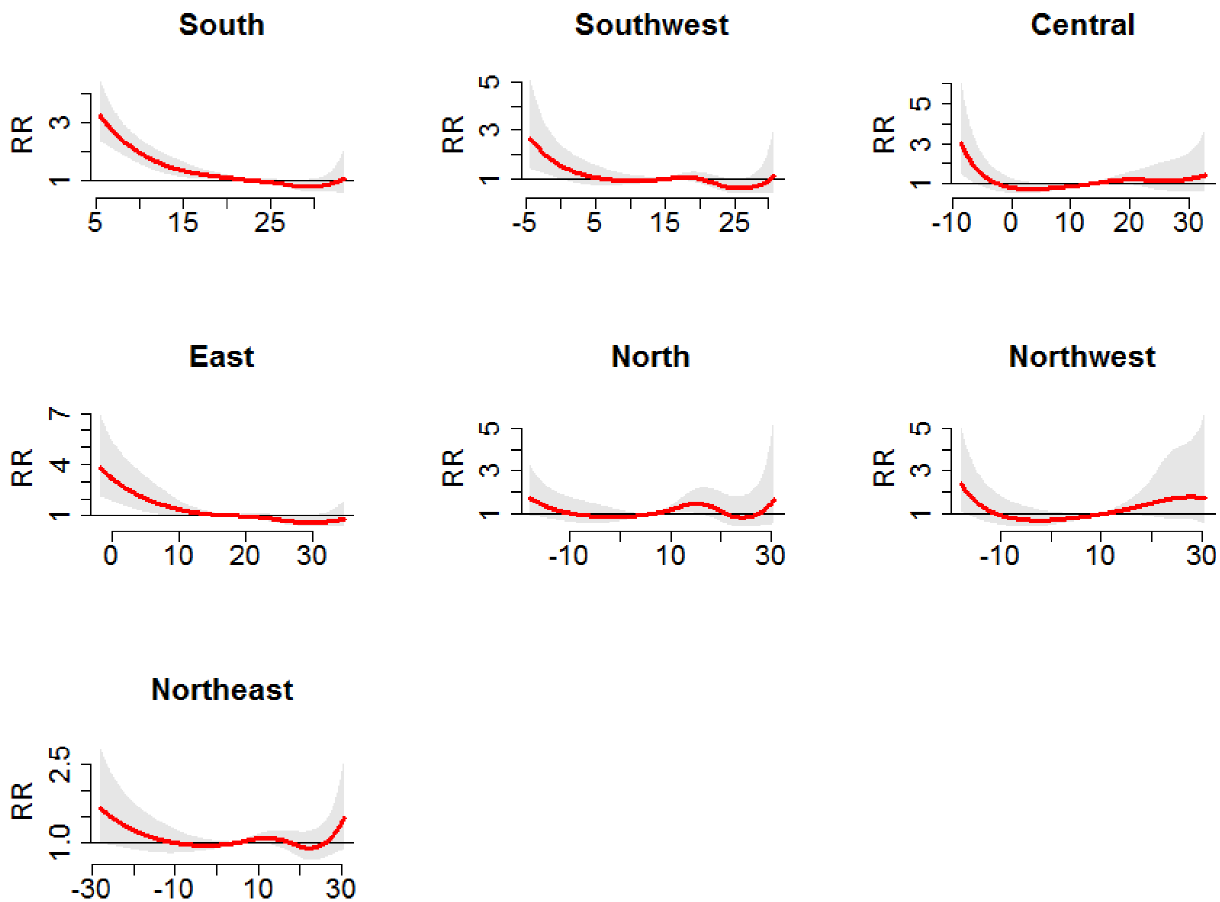


Figure s7. The cumulative effects of daily temperature on cardiovascular mortality over past 21 days for some communities in each region.

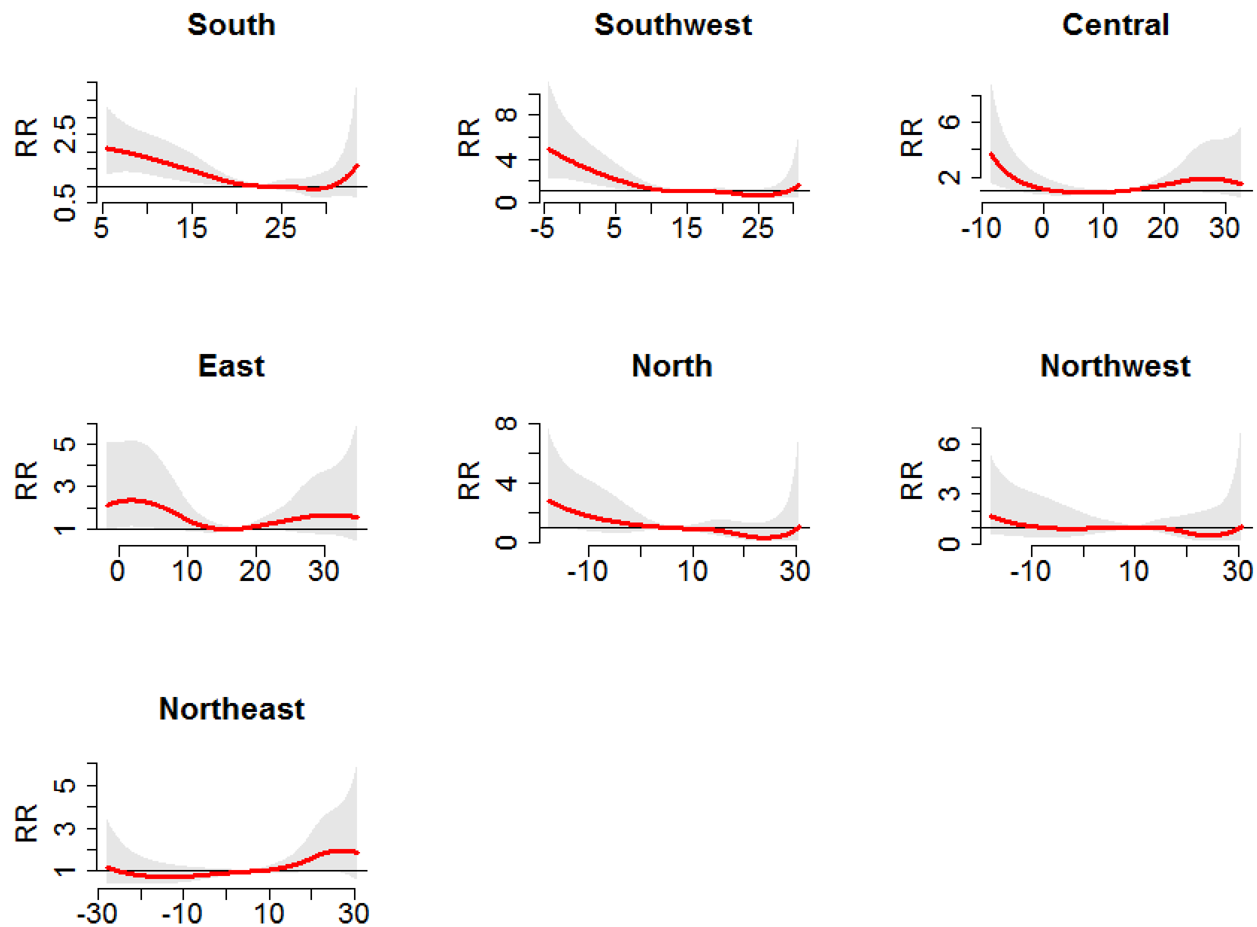


Figure s8. The cumulative effects of daily temperature on respiratory mortality over past 21 days for some communities in each region.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 & 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4 & 5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4 & 5
Bias	9	Describe any efforts to address potential sources of bias	5 & 6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5 & 6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A

		(*e*) Describe any sensitivity analyses	6
Results			
Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	N/A
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15	Report numbers of outcome events or summary measures over time	6
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8
		(*b*) Report category boundaries when continuous variables were categorized	8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10 & 11
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is	13

based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.