Cardiovascular mortality risk attributable to ambient temperature in China

Jun Yang [1,*], Peng Yin [2, *], Maigeng Zhou [2], Chun-Quan Ou [3], Yuming Guo [4], Antonio Gasparrini [5], Yunning Liu [2], Yujuan Yue [1], Shaohua Gu [1], Shaowei Sang [1], Guijie Luan [2], Qinghua Sun [6], Qiyong Liu [1]

[1] State Key Laboratory for Infectious Disease Prevention and Control, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, National Institute for Communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing 102206, China

[2] The National Center for Chronic and Noncommunicable Disease Control and Prevention, Beijing 100050, China

[3] State Key Laboratory of Organ Failure Research, Department of Biostatistics, Guangdong Provincial Key Laboratory of Tropical Disease Research, School of Public Health and Tropical Medicine, Southern Medical University, Guangzhou 510515, China

[4] Division of Epidemiology and Biostatistics, School of Public Health, University of Queensland, Queensland 4006, Australia

[5] Department of Social and Environmental Health Research, London School of Hygiene & Tropical Medicine, Keppel Street WC1E 7HT, London, United Kingdom

[6] College of Public Health, Division of Environmental Health Sciences, The Ohio State University, Ohio 43210, USA

[*]: Co-first authors

E-mail addresses:
JY: smart_yjun@163.com; PY: yinpengcdc@163.com;
MZ:maigengzhou@126.com; CQ:ouchunquan@hotmail.com;
YG: y.guo1@uq.edu.au; AG: antonio.gasparrini@lshtm.ac.uk;
YL: liuyunning0723@163.com; YY: yujuanlamei@126.com;
SG:gushaohua1989@sina.com; SS:sangshaowei1@163.com;
GL: luanguijie@sina.com; SQ: Qinghua.Sun@osumc.edu;
QY: liuqiyong@icdc.cn.

Correspondence to Prof. Qi-Yong Liu. Address: 155 Changbai Road, Changping, Beijing 102206, China; Tel: +86-010-589000741. Email: liuqiyong@icdc.cn.

ABSTRACT

Objective To examine cardiovascular disease (CVD) mortality burden attributable to ambient temperature; to estimate effect modification of this burden by gender, age and education level.

Methods We obtained daily data on temperature and CVD mortality from 15 Chinese mega-cities during 2007-2013, including 1,936,116 CVD deaths. A quasi-Poisson regression combined with distributed lag non-linear model was used to estimate the temperature-mortality association for each city. Then, a multivariate meta-analysis was used to derive the overall effect estimates of temperature at national level. Attributable fraction of deaths were calculated for cold and heat (i.e. temperature below and above minimum-mortality temperatures, MMT), respectively. The MMT was defined as the specific temperature associated to the lowest mortality risk.

Results The MMT varied from 70th to 99th percentile of temperature in 15 cities, centering at 78th at the national level. In total, 17.1% (95% empirical CI: 14.4-19.1%) of CVD mortality (330,352 deaths) was attributable to ambient temperature, with substantial differences among cities, from 10.1% in Shanghai to 23.7% in Guangzhou. Most of the attributable deaths were due to cold, with a fraction of 15.8% (13.1-17.9%) corresponding to 305,902 deaths, compared to 1.3% (1.0-1.6%) and 24,450 deaths for heat.

Conclusions This study emphasizes how cold weather is responsible for most part of the temperature-related CVD death burden. Our results may have important implications for the development of policies to reduce CVD mortality from extreme temperatures.

Key Words: Cardiovascular disease, death, ambient temperature, attributable fraction, China

Word count: 2996

What is already known on this subject?

Cardiovascular disease is the leading cause of mortality and particularly sensitive to climate change. Extreme ambient temperatures are associated with an increased relative risk of CVD mortality.

What might this study add?

Temperature was responsible for advancing 17.1% of CVD mortality. The majority of CVD mortality burden of ambient temperature was caused by cold. The daily attributable fraction due to temperature had a significant peak in the cold months (November to February). CVD mortality burden of both cold and hot temperatures were higher among the elderly and those with lower education level.

How might this impact on clinical practice?

Cold temperature palys an important role in the winter excess mortality of CVD. Public health policies and adapative measures should be extended to reduce the temperature-related particularly cold-related CVD mortality, especially in the developing countries. More attention should be paid to the vulnerable subpopulations.

INTRODUCTION

In recent decades, reports have pointed out that extreme weathers (e.g., heatwaves and cold spells) due to climate change is one of most serious challenge worldwide, with direct (e.g., excess morbidity and mortality) impacts on human health.[1] The definition and implementation of adaptation and mitigation strategies to extreme weathers require a comprehensive and in-depth understanding and quantification of the effects of weather factors on human health.

Cardiovascular diseases (CVD) are highly sensitive to weather variations.[2 3] CVD includes coronary heart disease, strokes and other heart diseases, and represents the top cause of death globally. In the last decades, the prevalent rate have changed differently between developed and developing countries, with a decline in many high-income countries but a rapid increase in low- and middle-income countries.[4] Based on economic development, population aging and changes in diet and physical activity, annual CVD events are predicted to increase by an additional 23% and 7.7 million CVD deaths over 2010 to 2030 alone in China.[5]

Estimating how much temperatures affect CVD mortality is a very important for development of health care system to reduce temperature-induced CVD events, for example, clinics, hospitals, and nursing centers should add more staff and increase their rotation during extreme cold and hot days. However, most of previous studies examined the relation in terms of ratio measures, such as relative risk (RR) and odds ratio (OR), providing estimates of the exposure-response relationship.[6-10] These indicators provided limited information on the excess burden due to the exposure, comparing to relative attributable measures, such as attributable fraction and attributable number, which are more suitable for estimating potential benefits of preventive interventions.

To date, only few studies have reported estimates of the temperature-related mortality using attributable risk, such as absolute excess (numbers) or relative excess (fraction) of deaths.[11-13] These studies limited the analysis to one single city and applied relatively simple statistical models unable to capture the non-linear and delayed effects of temperatures. Moreover, less evidence was available on this topic from developing countries. In this contribution, we aimed to provide figures of attributable burden of CVD mortality due to temperatures, separating the contributions of cold and heat effects from a national-scale analysis in China, and to assess the effect modification of temperatures on CVD mortality by individual characteristics (e.g., gender, age group and education level).

METHODS

Data collection

We collected daily number of death data and meteorological data from 15 large cities in China (Harbin, Changchun, Beijing, Shenyang, Tianjin, Shijiazhuang, Jinan, Zhengzhou, Shanghai, Nanjing, Chengdu, Chongqing, Changsha, Kunming and

Guangzhou) during 2007-2013 (Figure 1). The latitudes varied from 23.2N of Guangzhou to 45.4N of Harbin. Our study was restricted to the urban areas because the Death Registry has not been well established in suburban and rural regions in China.

The daily counts of death data were obtained from the China Information System of Death Register and Report of Chinese Center for Disease Control and Prevention (China CDC) from 1 January 2007 to 31 December 2013. The causes of death were coded by China CDC according to the International Classification of Diseases, Tenth Revision (ICD-10): cardiovascular disease (ICD-10: I00-I99). In addition, we stratified the data by different groups, including gender and age group (0-64, 65-74 and 75+ years), and education level (illiterate, primary education, and high school and above).

The daily weather data were collected from China Meteorological Data Sharing Service System (http://cdc.nmic.cn/home.do) from one weather monitoring station for each city during the study period. Weather data include daily mean temperature, maximum and minimum temperatures, relative humidity, and atmospheric pressure. We used mean daily temperature to estimate the effects of temperature on CVD mortality, as it represents the exposure throughout the entire day and night and provides more easily interpretable results in a policy context.

Statistical analysis

We conducted a two-stage analysis to estimate the CVD mortality risk attributable to cold and hot temperatures. At the first stage, individual-city data were analyzed and city-specific effect estimates were extracted and subsequently used in a second-stage meta-analysis to produce pooled estimates.

At the first stage, we adopted the distributed lag non-linear model (DLNM) combined with a quasi-Poisson regression to examine city-specific non-linear and lag effects of temperature on CVD mortality. The city-specific Poisson regression model is given as following:

$$Log[E(Y_t)]=\alpha+\beta Temp_{t,l}+NS(Time,8*7)+NS(Hum_t,3)+NS(Press_{\mathrm{t}},3)+\gamma Dow_t+vHoliday_t$$

where Y_{t} is the observed daily deaths at calendar day t (t=1,2,3…2557); α is the intercept; $\mathrm{Temp}_{t,l}$ was the cross-basis matrix produced by DLNM.[14] This matrix is obtained by the combination of the exposure-response function with a natural cubic spline with 3 internal knots placed at the 10th, 75th and 90th percentiles of city-specific temperature distributions, and the lag-response function modelled with a natural cubic spline with 3 internal knots placed at equally spaced values in the log scale. The maximum lag was set up to 21 days, for effects of cold temperature appeared only after some delay and lasted for several days, whereas effects of hot temperature were immediate and possibly affected by mortality displacement.[15] [16] NS(.) means a natural cubic spline; 8 df per year for time was used to control for the long-term and seasonality;[17] 3 df was used for relative humidity (Hum) and atmospheric pressure (Press);[9] Day of the week (Dow) and public holidays (Holiday) were also included in the model as indicator variables.[9 16]

At the second stage, a multivariate meta-analysis was applied to obtain the nationally-pooled effect estimates, and then to produce the best linear unbiased prediction (BLUP) for city-specific relationships, using a method recently developed.[15] Compared with previous meta-analysis method, this methodology offers greater flexibility to capture the complex non-linear and delayed associations between exposure and outcome from multiple locations. To pool the associations between temperature and CVD mortality, we reduced the 16 estimated parameters of the cross-basis, representing the bi-dimensional exposure-lag-response surface, to the 4 parameters of the one-dimensional overall cumulative exposure-response curve. Heterogeneity was assessed through a multivariate extension of the I^2 statistics,[18] which quantifies the percentage of variability due to the true differences across cities.

The minimum-mortality temperature (MMT) is derived by the lowest point of the overall cumulative exposure-response curve, and it is interpreted as the optimal temperature characterized by the lowest risk of CVD mortality. The MMT, corresponding to a minimum mortality percentile (MMP) of temperature between the 1st and 99th, was selected from the city-specific cumulative overall temperature-mortality association, which were re-centered on these values. The total attributable number of deaths due to non-optimal temperatures is calculated by summing the contributions from all the days of the series, using the MMT/MMP as the reference. The ratio with the total number of deaths produces the total attributable fraction. The components attributable to cold and hot temperature were computed by summing the subsets corresponding to days with temperature below or above the MMT, respectively. Empirical confidence intervals (eCI) were obtained by Monte Carlo simulations assuming a multivariate normal distribution of the BLUPs of the reduced coefficients.[19]

Significance tests on the effect modification of gender, age and education level were performed in the second-stage meta-regression. The coefficients of all stratum-level analyses were included in the same multivariate-meta regression estimated by maximum likelihood, and the models with and without indicators for each characteristic were compared through a likelihood ratio test to determine whether the coefficients describing the temperature-mortality association change between the groups.

Sensitivity analyses were performed to test the robustness of our results by changing location of knots for exposure-response and using 14-28 lag days, 6-10 df for time trend and 3-6 df for relative humidity and atmospheric pressure in the analyses, respectively.

All data analyses were performed using the R software (version 3.0.3, R Development

Core Team 2010). The “dlnm” package was used to fit the distributed lag non-linear model and the “mvmeta” package to conduct the multivariate mate-analysis. For all statistical tests, two-tailed $P<0.05$ were considered statistically significant.

RESULTS

Table 1 shows the descriptive data on population size, daily CVD mortality and mean temperature in the 15 Chinese cities included in the analysis. This study included more than 183.72 million permanent residents with daily mean CVD mortality counts ranging from 30 to 100 in various cities. The annual mean temperature ranged from 5.3 ^{o}C in Harbin to 21.6 ^{o}C in Guangzhou. Temperature ranges between cities were more varied during cold season (Table S1).

Figure 2 shows the overall cumulative exposure-response curves (best linear unbiased predictions) in those cities, with the corresponding MMT and temperature distribution. Generally, the temperature-mortality relationships were U-shaped at lag 0-21 days. The histogram plots show that most daily mean temperatures are below the MMT.

Table 2 reveals that the median MMP was 78th, ranging between 70th and 99th percentile of temperature. The I^2 statistics indicates a large and significant between-city heterogeneity (86.6%, $P<0.001$). In total, 17.1% (95% empirical CI: 14.4-19.1%) of CVD mortality, corresponding to 330,352 deaths, was attributed to temperature, although it varies substantially across cities, with the highest estimate in

Guangzhou (23.7%) and the lowest estimate in Shanghai (10.1%). Cold temperature accounted for most of the burden, with a fraction of 15.8% (13.1-17.9%), corresponding to 305,902 deaths, while the burden due to hot temperature was comparatively smaller, with a fraction of 1.3% (1.0-1.5%) , corresponding to 24,450 deaths (Figure 1 and Table S2).

The burden and heat /cold pattern was similar among males and females, while both hot and cold attributable risks were higher among the elderly and those with low education level, but the differences within these subgroups were not statistically significant (P>0.05). The attributable fraction due to temperature were 16.4% (13.6-18.8%), 16.9% (14.1-19.1%) and 17.3% (14.6-19.4%) for people with age less than 65, 65-74 years and older than 75, respectively; figures of 18.1%(15.1-20.2%), 17.1%(14.1-19.1%) and 16.5%(13.9-18.7%) were estimated for the illiterate, people with primary school and those with higher education level, respectively (Table 3).

The daily attributable fraction due to temperature generally had a significant seasonal trend, with much higher in the cold months (November to February) than the hot months (May to September). There was also a small peak in June or July (Figure S1).

Analyses were performed to test the sensitivity of our results to modelling choices. The effect estimates were similar when we changed location of knots for the exposure-response relationship and 4-6 df for relative humidity and air pressure in the analyses; slightly smaller estimates were produced when using shorter maximum lag days or changing df for the time trends (e.g. 6 or 10), respectively (Table S3).

DISCUSSION

To the best of our knowledge, this is the first study to examine CVD mortality attributable to ambient temperature in developing countries and the first study to explore effect modification of such risk by individual characteristics. The minimum-mortality temperatures were generally distributed around 78th percentile of temperature. The cold temperature was responsible for most of temperature-related CVD mortality. The attributable burdens of both hot and cold temperatures were higher among the elderly and those with lower education level.

The association between ambient temperature and CVD mortality has been well documented in numerous epidemiological studies.[3 6 7 9 10] However, most of these studies measured the association using some ratio indicators, such as RR and OR. There were very few studies examining the attributable burden, either as absolute excess (attributable numbers) or relative excess (attributable fractions) of CVD deaths.[11-13] Recently, an international study using similar design by Gasparrini and colleagues estimated a 11.3% of all-cause deaths were attributable to ambient temperatures in China,[17] which was much smaller than our estimate of 17.1% of CVD deaths. Carson and colleagues[12] also reported a much smaller attributable fraction (4.6%) of CVD deaths due to cold but none to hot temperature in London. These evindences confirmed that temperature-mortality association varied by regions, populations and climates.

The mechanistic effects of ambient temperature on cardiovascular pathophysiology are profound, which may be involved in the changes in vascular tone, autonomic nervous system response, arrhythmia, and oxidative stress. The vascular tone change was observed from repeated measurements on two consecutive days during colder months (October-April) among 868 elderly individuals in Japan, a 1°C lower indoor temperature was significantly associated with 0.22 mmHg higher daytime systolic blood pressure and 0.34 mmHg higher sleep-trough morning blood pressure surge.[20] Another study of rats exposed in a cold room at 4 degree ºC demonstrated attenuated sympathetic nerve stimulation (NS)-induced overflow of noradrenaline in the perfused mesenteric arterial bed.[21] Cold exposure was also found to increase the frequency of heart rate variability and ventricular ectopic beats.[22] In addition, exposure to cold caused significant increase of inflammatory cytokines and methane dicarboxylic aldehyde (MDA) and decline of superoxide dismutase(SOD) and glutathione peroxidase (GSH-Px) activity,[23] and the genes involved in the hypoxia-inducible factor signaling pathway were activated in which oxidative stress-associated genes were significantly upregulated, including superoxide dismutase 2 (SOD2) and epoxide hydrolase 2 (EPHX2).[24] On the other hand, exposure to hot weather may induce profound physiologic changes, such as increase in blood viscosity and cardiac output leading to dehydration, hypotension, surface blood circulation increase and even endothelial cell damage.[25] These responses may overload the heart function and cause haemoconcentration, and induce a failure of thermoregulation. Further mechanistic studies are warranted to disentangle these complex relationships between CVD and ambient temperature.

Our results showed that cold effects accounted for over 90% percent of temperature-related CVD mortality. These findings indicate that cold temperature plays an important role in the winter excess mortality of CVD. The policymaker, local community and the public should strengthen the awareness of preventing harmful health effect of cold temperature, especially for people in southern areas, where central heating was not available in winter. Moreover, attributable fraction of CVD mortality due to temperature varies by cities, ranging from 10.1% to 23.7%. Generally, the hot-related mortality fraction was higher in the north than in the south while there was higher cold-related fraction in the south; the hot/cold-related mortality fraction was moderately correlated with annual mean temperature [Spearman Correlation Coefficient r_s=-0.626 for hot effect (P=0.013); r_s=0.502 for cold effect (P=0.051)]. Consistently, the MMT increased from the north to the south, which was strongly correlated with annual mean temperature (Spearman Correlation Coefficient r_s=0.772; P=0.001). This phenomenon indicates that people could acclimatize to their local environmental conditions through physiological adaptation and individual behaviors. Populations in northern regions are more vulnerable to heat, while people in southern regions are more sensitive to cold weather. The popularity of air conditioning and household heating appliances can be helpful to mitigate the health effects of hot and cold temperatures, respectively.

Many epidemiological studies have provided evidence that susceptibility to cold and hot temperatures is modified by age, gender and education level. For both hot and cold temperatures, the effects were clearly larger in the elderly than in the youth. Aging induces physiological changes in thermoregulation and homeostasis, together with the prevalence of preexisting chronic conditions, limiting capacity to prevent CV events, and use of medication, offering susceptibility to hot and cold stress.[26] Given the increasing disease burden of CVD in China, it has been a significant challenge to the government and the societal infrastructure that affects not only the economic growth, but also the healthcare system. Age-appropriate primary care exacerbated by user fees and social protection, and community-based measures should be targeted particularly for the elderly, especially at time of hot and cold weathers.

Effect modification by gender varied among different regions and population. For example, the impact of hot temperature was higher for women in Mexico, but higher for men in Sao Paulo.[27] The differences in occupational exposure, physiology and thermoregulatory may contribute to the temperature-related susceptibility between genders.[9] [28] [29] Education level is viewed as one of the most important indicators relating to one’s overall socioeconomic status. Previous investigations have reported that those with low socioeconomic status have a greater vulnerability to temperature-related mortality,[9 27] which may be associated with poorer health status, limited access to health care, poor housing conditions, lack of knowledge and unhealthy behavior patterns such as smoking. These disadvantage factors may reduce their capacity to take proper precautions in the heat or cold to prevent CV events.

This study has some limitations. Firstly, this study applies specifically to urban populations and isn't necessarily able to be generalized to the rural areas in China where cold and heat effects may be greater because of even less consistent access to central heating or air conditioning. Similar with previous time-series investigations, this study only assessed short-term effects of temperature on CVD mortality after controlling for long-term trend and other covariates. While a large element of CVD may be due to long-term pathology. Thirdly, the attributable fraction was calculated assuming the causality between cold/hot temperatures and mortality, although the evidence is still limited on this association. However, extensive epidemiological studies have shown that the cold and hot temperatures have impacts on human mortality[2 3 8-11] and morbidity[24 30]. Fourthly, the use of data on temperatures were from fixed monitoring sites rather than measuring individual exposure, which may create to some extent measurement errors in the exposure. However, these errors are likely to be random. Meanwhile, we cannot ignore the misclassification bias since CV cause of death was assigned according to ICD 10 code on death certificate. Fifthly, air pollutants data were not controlled for in this study, because these data were not available. However, previous studies have found that the effect of temperature on mortality did not change when controlling for air pollution.[9 16]

CONCLUSIONS

The cold temperature was responsible for most of temperature-related CVD mortality in China. Our results may contribute significantly to the understanding of the adverse health effects of cold and hot temperatures on CVD mortality. It may also have important public health implications for policymakers and local communities with the aim to protect vulnerable subpopulations from ambient extreme temperatures.

Contributiors

J.Y. and Q.L. initiated the study. M.Z., Y.P. and Q.L. collected the data. J.Y., Y.L. and G.L. cleaned the data. J.Y. performed statistical analysis. A.G. developed the statistical methods and software implementation. J.Y. and C.Q.O. drafted the manuscript. Y.G., A.G., Y.Y., S.G., S.S., Q.S. and Q.L. revised the manuscript. All authors read and approved the final manuscript.

Funding

This study was supported by the National Basic Research Program of China (973 Program) (Grant No. 2012CB955504).

Competing interests

None.

Ethics approval

This study was approved by the Ethics Committee of Chinese Center for Disease Control and Prevention (No.201214).

Provenance and peer review

Not commissioned; externally peer reviewed.

REFERENCES

1 IPCC. Managing the Risks of Extreme Events and Disasters to Advance Climate Change Adaptation. A Special Report of Working Groups I and II of the Intergovernmental Panel on Climate Change. 2012.

2 Guo Y, Li S, Zhang Y, et al. Extremely cold and hot temperatures increase the risk of ischaemic heart disease mortality: epidemiological evidence from China. *Heart* 2013;99:195-203.

3 Zhang Y, Li S, Pan X, et al. The effects of ambient temperature on cerebrovascular mortality: an epidemiologic study in four climatic zones in China. *Environ Health* 2014;13:24.

4 WHO Disease and injury country estimates: World Health Organization, 2009. Retrieved Nov 11, 2009.

5 Moran A, Gu D, Zhao D, et al. Future cardiovascular disease in china: markov model and risk factor scenario projections from the coronary heart disease policy model-china. *Circ Cardiovasc Qual Outcomes* 2010;3:243-52.

6 Analitis A, Katsouyanni K, Biggeri A, et al. Effects of Cold Weather on Mortality: Results From 15 European Cities Within the PHEWE Project. *Am J Epidemiol* 2008;168:1397-408.

7 Braga AL, Zanobetti A, Schwartz J. The effect of weather on respiratory and cardiovascular deaths in 12 U.S. cities. *Environ Health Perspect* 2002;110:859-63.

8 Ma W, Chen R, Kan H. Temperature-related mortality in 17 large Chinese cities: How heat and cold affect mortality in China. *Environ Res* 2014;134:127-33.

9 Yang J, Ou CQ, Ding Y, et al. Daily temperature and mortality: a study of distributed lag non-linear effect and effect modification in Guangzhou. *Environ Health* 2012;11:63.

10 Yu W, Hu W, Mengersen K, Guo Y, Pan X, Connell D, et al. Time course of temperature effects on cardiovascular mortality in Brisbane, Australia. *Heart* 2011;97:1089-93.

11 Baccini M, Kosatsky T, Analitis A, et al. Impact of heat on mortality in 15 European cities: attributable deaths under different weather scenarios. *J Epidemiol Community Health* 2011;65:64-70.

12 Carson C, Hajat S, Armstrong B, et al. Declining vulnerability to temperature-related mortality in London over the 20th century. *Am J Epidemiol* 2006;164:77-84.

13 Hajat S, Armstrong B, Baccini M, et al. Impact of high temperatures on mortality: is there an added heat wave effect? *Epidemiology* 2006;17:632-8.

14 Gasparrini A, Armstrong B, Kenward MG. Distributed lag non-linear models. *Stat Med* 2010;29:2224-34.

15\. Gasparrini A, Armstrong B. Reducing and meta-analysing estimates from distributed lag non-linear models. *BMC Med Res Methodol* 2013;13:1.

16\. Guo Y, Gasparrini A, Armstrong B, Li S, et al. Global variation in the effects of ambient temperature on mortality: a systematic evaluation. *Epidemiology* 2014;25:781-9.

17\. Gasparrini A, Guo Y, Hashizume M, et al. Mortality risk attributable to high and low ambient temperature: a multicountry observational study. *Lancet* 2015.

18\. Gasparrini A, Armstrong B, Kenward MG. Multivariate meta-analysis for non-linear and other multi-parameter associations. *Stat Med* 2012;31:3821-39.

19\. Gasparrini A, Leone M. Attributable risk from distributed lag models. *BMC Med Res Methodol* 2014;14:55.

20\. Saeki K, Obayashi K, Iwamoto J, et al. Stronger association of indoor temperature than outdoor temperature with blood pressure in colder months. *J Hypertens* 2014;32:1582-9.

21. Westfall TC, Yang CL, Chen X, et al. A novel mechanism prevents the development of hypertension during chronic cold stress. *Auton Autacoid Pharmacol* 2005;25:171-7.
22. Hintsala H, Kentta TV, Tulppo M, et al. Cardiac repolarization and autonomic regulation during short-term cold exposure in hypertensive men: an experimental study. *PLoS One* 2014;9:e99973.
23. Luo B, Shi H, Wang L, Shi Y, Wang C, Yang J, et al. Rat lung response to PM2.5 exposure under different cold stresses. *Int J Environ Res Public Health* 2014;11:12915-26.
24. Tuo B, Li C, Peng L, et al. Analysis of differentially expressed genes in cold-exposed mice to investigate the potential causes of cold-induced hypertension. *Exp Ther Med* 2014;8:110-14.
25. Keatinge WR, Coleshaw SR, Easton JC, et al. ncreased platelet and red cell counts, blood viscosity, and plasma cholesterol levels during heat stress, and mortality from coronary and cerebral thrombosis. *Am J Med* 1986;81:795-800.
26. Kenney WL, Munce TA. Invited review: aging and human temperature regulation. *J Appl Physiol (1985)* 2003;95:2598-603.
27. Bell ML, O'Neill MS, Ranjit N, et al. Vulnerability to heat-related mortality in Latin America: a case-crossover study in Sao Paulo, Brazil, Santiago, Chile and Mexico City, Mexico. *Int J Epidemiol* 2008; 37:796-804.
28. Medina-Ramón M, Zanobetti A, Cavanagh DP, et al. Extreme Temperatures and Mortality: Assessing Effect Modification by Personal Characteristics and Specific Cause of Death in a Multi-City Case-Only Analysis. *Environ Health Perspect* 2006;114:1331-36.
29. Stafoggia M, Forastiere F, Michelozzi P, et al. Summer temperature-related mortality: effect modification by previous winter mortality. *Epidemiology* 2009;20:575-83.
30. Ye X, Wolff R, Yu W, et al. Ambient temperature and morbidity: a review of epidemiological evidence. *Environ Health Perspect* 2012;120:19-28.

Table 1 Descriptive data on cardiovascular mortality (CVD) and daily mean temperature (°C) in 15 Chinese cities during 2007-2013

City	Population (million)	Daily CVD deaths	Study period	Daily mean temperature percentiles							
				Min	1st	25th	50th	75th	99th	Max	Mean
Harbin	10.6	82	2007-2013	-28.0	-24.0	-8.7	7.6	19.7	27.4	30.6	5.3
Changchun	7.7	30	2007-2013	-27.6	-22.0	-6.9	8.4	19.7	26.6	30.4	6.2
Shenyang	8.1	56	2007-2013	-24.0	-19.4	-3.3	9.9	20.7	27.0	29.0	8.0
Beijing	19.6	100	2007-2013	-12.5	-7.6	2.5	14.9	24.0	30.4	34.5	13.2
Tianjin	12.9	95	2007-2013	-14.1	-7.9	2.1	14.4	23.7	30.0	32.4	12.9
Shijiazhuang	10.2	36	2007-2013	-8.4	-5.7	4.1	15.7	24.3	31.5	34.3	14.3
Jinan	6.8	59	2011-2013	-9.4	-6.4	4.2	16.3	24.0	31.3	33.0	14.4
Zhengzhou	8.6	37	2011-2013	-4.4	-3.0	5.9	17.4	25.1	32.5	34.2	15.6
Shanghai	23.0	53	2007-2013	-3.4	0.2	9.4	18.3	25.0	33.3	35.7	17.4
Nanjing	8.0	42	2007-2013	-4.5	-1.7	8.1	17.8	24.8	32.5	34.6	16.5
Chengdu	14.0	55	2007-2013	-0.5	1.9	9.7	17.3	23.0	28.2	29.3	16.4
Chongqing	28.8	180	2011-2013	3.0	4.7	11.7	19.1	25.6	34.6	36.7	19.0
Changsha	6.1	48	2007-2013	-3.0	-0.2	10.2	19.1	26.5	33.8	35.8	18.4
Kunming	6.4	32	2007-2013	-0.9	4.5	12.2	16.9	20.0	23.3	24.6	16.0
Guangzhou	12.7	45	2011-2013	5.1	6.9	16.6	23.0	27.0	30.2	30.8	21.6

Table 2 Attributable cardiovascular mortality fraction by cities computed as total and as separated components for cold and hot temperatures in 15 Chinese cities

City	MMP (MMT)*	Attributable mortality fraction (%,95%empiricalCI)		
		Total	Cold	Hot
Harbin	78(20.6)	15.2(4.3-24.1)	13.6(2.1-22.1)	1.7(0.3-2.8)
Changchun	78(20.6)	12.9(0.9-22.1)	11.1(-1.5-20.7)	1.8(0.4-3.0)
Shenyang	78(21.5)	16.2(6.8-23.8)	14.8(6.7-21.9)	1.4(0.1-2.6)
Beijing	79(24.9)	20.1(13.4-26)	18.3(11.0-24.3)	1.8(1.1-2.5)
Tianjin	78(24.5)	16.0(9.5-21.8)	14.8(7.5-21.1)	1.3(0.4-2.1)
Shijiazhuang	73(23.8)	16.1(10.3-21.3)	15.0 (7.9-20.7)	1.2(0.0-2.2)
Jinan	78(24.9)	16.7(8.5-23.1)	14.0 (5.4-21.0)	2.7(1.7-3.6)
Zhengzhou	79(25.9)	16.7(8.3-23.8)	15.2(5.0-22.6)	1.5(0.3-2.6)
Shanghai	73(24.5)	10.1(4.1-15.8)	8.8(2.2-14.7)	1.3(0.0-2.5)
Nanjing	88(27.9)	22.2(14.6-28.4)	21.5(14.2-28.6)	0.7(0.2-1.3)
Chengdu	81(24.1)	14.7(5.6-22.8)	14.5(4.9-22.5)	0.2(-1.4-1.5)
Chongqing	87(29.2)	18.1(8.0-26.7)	17.1(6.7-25.6)	1.0 (0.2-1.9)
Changsha	70(25.1)	18.1(12.3-22.5)	16.8(10.6-22.0)	1.3(-0.2-2.7)
Kunming	99(23.3)	23.0 (0.9-38.7)	23.0 (1.9-39.7)	0.0(-0.2-0.1)
Guangzhou	93(29.0)	23.7(10.6-33.8)	23.3(10.2-33.2)	0.5(-0.2-1.0)
Overall	78(-)	17.1(14.4-19.1)	15.8(13.1-17.9)	1.3(1.0-1.5)

* MMP: minimum mortality percentile of temperature (%); MMT: minimum mortality temperature (°C).

Table 3 The pooled attributable cardiovascular mortality fraction computed as total and as separated components for cold and hot temperatures, stratified by individual characteristics

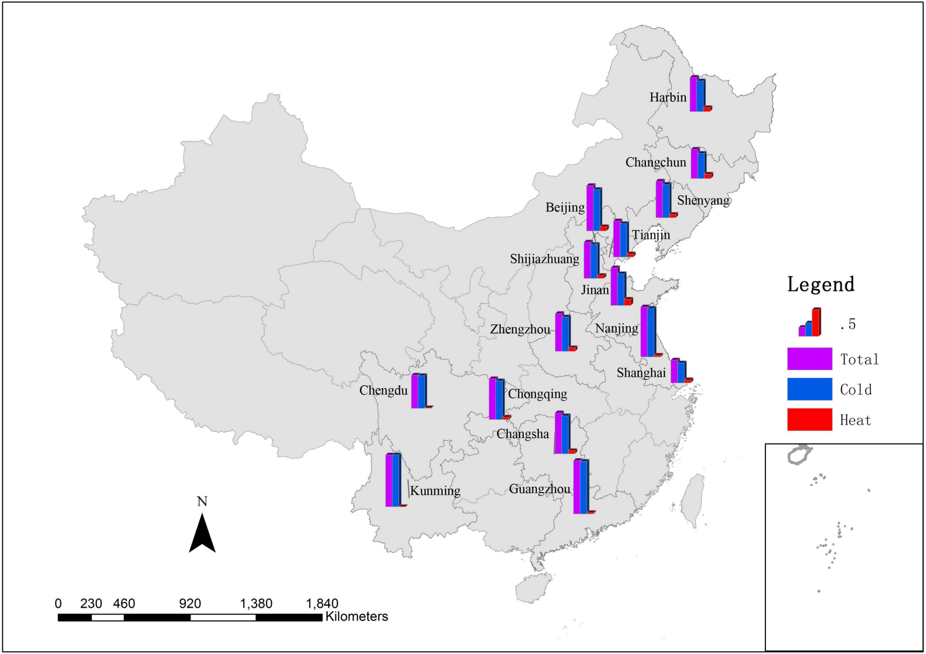
Variables	Attributable mortality fraction (%, 95%empiricalCI)		
	Total	Cold	Hot
Gender*			
Male	17.0(14.4-19.1)	15.7(12.8-17.9)	1.3(1.0-1.5)
Female	17.2(14.5-19.2)	15.9(13.3-18.1)	1.3(0.9-1.5)
Age- years*			
0-64	16.4(13.6-18.8)	15.1(12.1-17.4)	1.3(1.0-1.6)
65-74	16.9(14.1-19.1)	15.7(12.8-17.8)	1.3(0.9-1.6)
75+	17.3(14.6-19.4)	16.1(13.5-18.4)	1.2(0.9-1.5)
Education attainment*			
Illiterate	18.1(15.1-20.2)	16.9(14.2-19.2)	1.2(0.9-1.4)
Primary school	17.1(14.1-19.1)	15.8(13.0-18.1)	1.3(0.9-1.6)
High school and above	16.5(13.9-18.7)	15.2(12.6-17.6)	1.3(1.0-1.6)

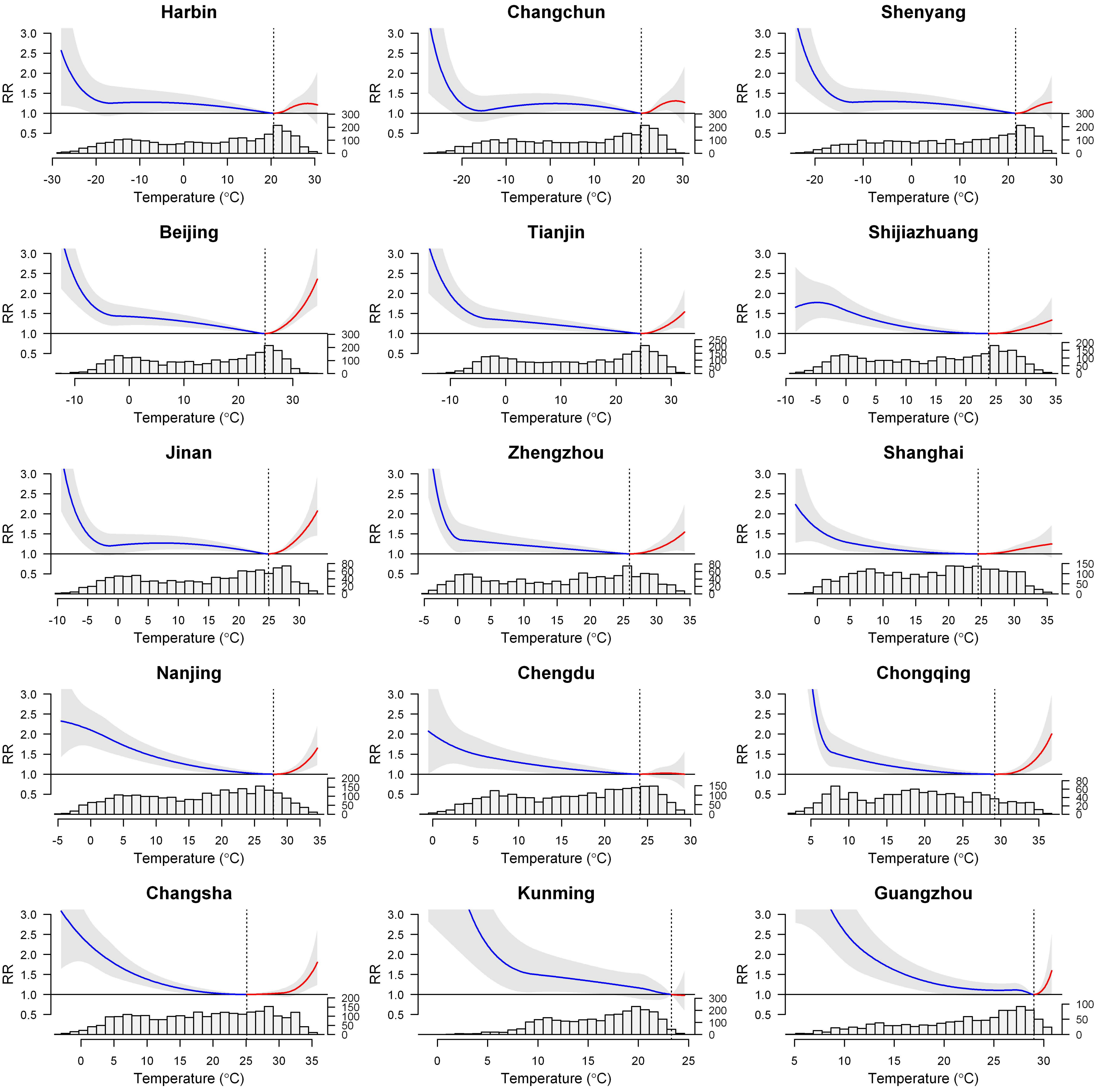
* Differences within gender, age group and education attainment were not statistically significant (P>0.05).

Figure legends

Figure 1 The locations of 15 Chinese cities in this study, with attributable cardiovascular mortality fraction computed as total and as separated components for cold and hot temperatures.

Figure 2 Overall cumulative relative risk (RR) across lag 0-21 days (with 95% empirical CI, shaded grey) in 15 Chinese cities, with histogram of daily temperature distribution. The dashed grey lines are minimum-mortality temperatures. The blue and red lines represent the exposure-response below (cold) and above (hot) the minimum-mortality temperatures.


Harbin
Changchun
Shenyang
Beijing
Tianjin
Shijiazhuang
Jinan
Zhengzhou
Nanjing
Shanghai
Chengdu
Chongqing
Changsha
Kunming
Guangzhou
Legend
.5
Total
Cold
Heat
N
0
230
460
920
1,380
1,840
Kilometers


Harbin
Changchun
Shenyang
Beijing
Tianjin
Shijiazhuang
Jinan
Zhengzhou
Shanghai
Nanjing
Chengdu
Chongqing
Changsha
Kunming
Guangzhou
RR
3.0
2.5
2.0
1.5
1.0
0.5
Temperature (°C)
-30
-20
-10
0
10
20
30
35
-5
5
15
25
300
250
200
150
100
80
60
50
40
20
0

Supplemental Materials

Cardiovascular mortality risk attributable to ambient temperature in China

Jun Yang [1,*], Peng Yin [2, *], Maigeng Zhou [2], Chun-Quan Ou [3], Yuming Guo [4], Antonio Gasparrini [5], Yunning Liu [2], Yujuan Yue [1], Shaohua Gu [1], Shaowei Sang [1], Guijie Luan [2], Qinghua Sun [6], Qiyong Liu [1]

[1] State Key Laboratory for Infectious Disease Prevention and Control, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, National Institute for Communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing 102206, China

[2] The National Center for Chronic and Noncommunicable Disease Control and Prevention, Beijing 100050, China

[3] State Key Laboratory of Organ Failure Research, Department of Biostatistics, Guangdong Provincial Key Laboratory of Tropical Disease Research, School of Public Health and Tropical Medicine, Southern Medical University, Guangzhou 510515, China

[4] Division of Epidemiology and Biostatistics, School of Public Health, University of Queensland, Queensland 4006, Australia

[5] Department of Social and Environmental Health Research, London School of Hygiene & Tropical Medicine, Keppel Street WC1E 7HT, London, United Kingdom

[6] College of Public Health, Division of Environmental Health Sciences, The Ohio State University, Ohio 43210, USA

[*]: Co-first authors

Correspondence to Prof. Qi-Yong Liu. Address: 155 Changbai Road, Changping, Beijing 102206, China; Tel: +86-010-589000741. Email: liuqiyong@icdc.cn.

Table of contents

Table S1 The monthly median temperature (^{o}C) in 15 Chinese cities.

City	Jan.	Feb.	Mar.	Apr.	May.	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.
Harbin	-17.7	-12.6	-3.8	7.0	15.6	22.0	23.8	22.4	16.5	7.5	-4.8	-14.7
Changchun	-15.5	-10.4	-2.3	7.3	16.3	21.9	23.7	22.4	16.9	8.4	-3.0	-12.7
Shenyang	-13.7	-7.2	0.6	9.1	17.8	22.3	24.6	23.6	18.0	10.1	-0.4	-9.6
Beijing	-3.6	-0.1	7.1	14.8	22.1	25.4	27.4	26.4	21.4	14.5	5.0	-1.1
Tianjin	-4.1	-0.7	6.5	14.0	21.9	25.2	27.3	26.4	21.6	14.4	5.0	-1.5
Shijiazhuang	-2.3	1.4	8.6	16.1	22.8	26.6	28.2	26.6	21.6	15.6	6.5	0.2
Jinan	-1.9	1.8	8.2	16.2	22.7	27.1	27.8	25.9	21.1	16.5	8.0	0.1
Zhengzhou	-0.3	3.1	10.0	18.4	23.3	28.0	28.9	27.3	21.3	16.8	9.2	1.9
Shanghai	4.2	6.5	10.0	15.5	21.7	24.2	30.2	29.3	25.2	20.2	13.7	7.3
Nanjing	2.5	5.2	10.0	16.1	22.2	24.9	29.0	28.4	23.6	18.5	11.5	5.4
Chengdu	5.1	8.2	11.8	17.1	21.3	23.8	25.4	25.4	21.6	17.3	12.8	7.2
Chongqing	6.8	9.6	15.0	19.9	22.5	25.9	30.1	30.5	22.5	18.5	15.1	8.8
Changsha	4.3	7.7	12.7	18.2	23.5	27.1	31.4	29.5	24.6	19.7	13.7	7.8
Kunming	9.7	12.9	15.4	17.9	20.1	21.0	20.9	20.3	19.0	16.5	12.2	9.9
Guangzhou	11.5	15	17.9	22.6	26.2	27.9	28.1	28.3	26.9	22.7	20.0	13.3

Table S2 Attributable cardiovascular deaths by cities computed as total and as separated components for cold and hot temperatures in 15 Chinese cities

City	MMP (MMT)*	Attributable mortality number (n, 95%eCI)		
		Total	Cold	Hot
Harbin	78(20.6)	31804(8912-50288)	28349(4493-46251)	3455(545-5899)
Changchun	78(20.6)	9806(711-16719)	8414(-1141-15690)	1391(330-2310)
Shenyang	78(21.5)	22934(9543-33694)	20907(9435-31022)	2027(174-3634)
Beijing	79(24.9)	50936(33982-66060)	46374(28055-61753)	4563(2789-6362)
Tianjin	78(24.5)	38758(22882-52645)	35711(18163-51018)	3047(1040-5021)
Shijiazhuang	73(23.8)	14234(9049-18804)	13189(6963-18302)	1045(24-1977)
Jinan	78(24.9)	10621(5398-14733)	8930(3423-13369)	1692(1114-2275)
Zhengzhou	79(25.9)	6608(3280-9425)	6029(1995-8965)	579(101-1020)
Shanghai	73(24.5)	13613(5448-21140)	11874(2886-19729)	1739(67-3345)
Nanjing	88(27.9)	23443(15384-30011)	22664(14966-30197)	780(168-1339)
Chengdu	81(24.1)	20329(7679-31488)	20048(6761-31181)	280(-1868-2014)
Chongqing	87(29.2)	35015(15450-51727)	33001(13044-49498)	2014(380-3606)
Changsha	70(25.1)	21895(14863-27258)	20280(12852-26631)	1615(-288-3294)
Kunming	99(23.3)	18865(778-31678)	18872(1518-32569)	-7(-156-93)
Guangzhou	93(29.0)	11490(5111-16354)	11259(4930-16047)	231(-74-496)
Overall	78(-)	330352(278504-369304)	305902(253081-347504)	24450(18528-29629)

* MMP: minimum mortality percentile of temperature (%); MMT: minimum mortality temperature (°C).

Table S3 Sensitivity analyses of calculating the fraction (%, 95%empiricalCI) attributable to temperature by changing location of knots of exposure-response-maximum lag for mean temperature and degrees of freedom (df) for covariates

Model choices	Total	Cold	Hot
Knots for exposure-response: 10th, 50th and 75th	17.5(14.8-19.5)	16.3(13.7-18.3)	1.2(0.9-1.5)
Knots for exposure-response: 25th, 75th and 90th	17.2(14.1-19.5)	15.9(12.8-18.4)	1.3(0.9-1.6)
Lag period: 14 days	14.1(12.2-15.8)	12.5(10.6-14.2)	1.5(1.2-1.8)
Lag period: 28 days	17.1(12.9-20.2)	15.6(11.6-18.4)	1.6(0.4-2.4)
Df for year:6	14.1(11.7-16.0)	12.4(9.9-14.4)	1.7(0.9-2.5)
Df for year: 10	13.9(10.9-16.2)	12.6(9.5-14.7)	1.4(0.9-1.7)
Df for relative humidity: 4	17.0 (14.3-18.9)	15.7(13.2-17.9)	1.3(0.9-1.5)
Df for relative humidity: 6	17.0 (14.4-19.2)	15.7(13.1-17.9)	1.3(0.9-1.5)
Df for air pressure: 4	17.1(14.4-19.3)	15.9(13.1-18)	1.3(0.9-1.5)
Df for air pressure: 6	17.1(14.5-19.2)	15.9(13.3-18)	1.3(0.9-1.5)

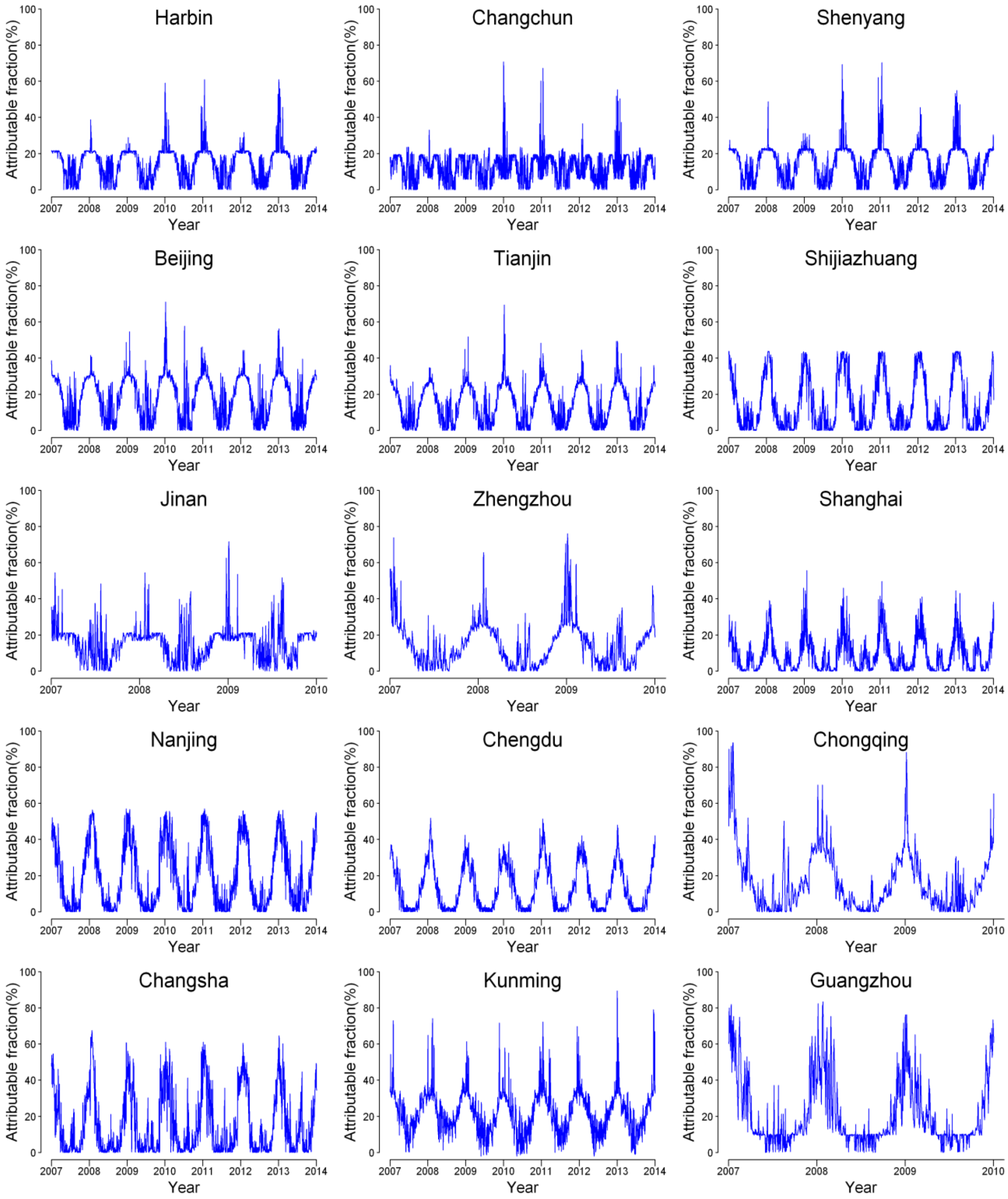

Harbin
Changchun
Shenyang
Beijing
Tianjin
Shijiazhuang
Jinan
Zhengzhou
Shanghai
Nanjing
Chengdu
Chongqing
Changsha
Kunming
Guangzhou

Figure S1 Daily attributable cardiovascular mortality fraction (%) due to temperature in 15 Chinese cities during 2007-2013.