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Keywords:	ambient temperatures, attributable fraction, attributable number, mortality, effect modification

Burden of non-accidental mortality and subgroups by specific causes and individual characteristics attributable to ambient temperatures in Yuxi, China

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Abstract

Objective: To examine the total non-accidental mortality burden attributable to ambient temperatures and assess the effect modification of the burden by specific causes and individual characteristics in Yuxi, China.

Methods: Using daily mortality and meteorological data from 2009–2016, we applied a quasi-Poisson model combined with a distributed lag non-linear model to estimate the temperature–mortality association with the assessment of attributable fraction and number. We calculated attributable fractions and deaths with 95% empirical confidence intervals (eCIs), that were due to cold and heat, defined as temperatures below and above the median temperature, and for mild and extreme temperatures, defined by cutoffs at the 2.5th and 97.5th temperature percentiles.

Results: We analyzed 89,467 non-accidental deaths; 4,131 were attributable to overall temperatures, with an attributable fraction of 4.75% (95% eCI 2.33, 6.79). Most of the mortality burden was caused by cold (4.08%; 0.86, 7.12), while the burden due to heat was low and non-significant (0.67%; -2.44, 3.64). Extreme cold (1.17%; 0.58, 1.69) was responsible for 24.6% (i.e., 1.17% divided by 4.75%) of the total death burden. In the stratification analyses, attributable risk due to cold was higher for cardiovascular than respiratory disease (6.18% vs 3.50%). We found a trend of risk of increased death due to ambient temperatures with increasing age, with attributable fractions of 1.83%, 2.27%, and 6.87% for age ≤64, 65 – 74, and ≥75 years old. The cold-related burden was slightly greater for females, farmers, ethnic minorities, and non-married individuals than their corresponding categories.

Conclusions: Most of the burden of death in Yuxi, China was attributable to cold, and specific causes and individual characteristics might modify the mortality burden attributable to ambient temperatures.

Key words: ambient temperatures; attributable fraction; attributable number; mortality; effect modification

Strengths and limitations of this study

- Mortality burden attributable to ambient temperature was assessed in a high plateau city in China.

- This study will for the first time evaluate the relationship between mortality burden and ambient temperature modified by national minority and occupation.
- The data only come from one city, so it should be cautious to generalize the findings to other geographic areas or climates.
- We used the data on temperature from fixed sites rather than measuring individual exposure, which may bring about measurement errors since indoor temperature is not closely correlated with outdoor temperature due to the use of air conditioning.

1. Introduction

With the global climate change, ambient temperatures has been extensively demonstrated to directly affect human health (e.g., daily morbidity and mortality) and has become one of the most severe public health problems in the world.[1-5] Exposure to extreme weather such as cold spells and heat waves represents high risk for mortality, and the extreme temperature-related mortality is expected to increase with the increasing frequency, intensity, and duration of extreme weather events.[4,6-8] Low and high temperatures are also well known to be associated with a substantial increase in a wide range of all-cause and cause-specific mortality (e.g., cardiovascular and respiratory diseases).[6,9-12]

Numerous epidemiological studies have widely used ratio measures (e.g., odds ratio, relative ratio, or rate ratio) to quantify the relationships between ambient temperatures and human health, but these offer limited information on the excess burden and actual impact of ambient temperatures.[13-15] Relative excess measures (e.g., attributable fraction) and absolute excess measures (e.g., attributable number), calculated on the basis of the estimated relative risk, have been pointed out to provide better scientific evidence for estimating the potential benefits of preventative measures, public health interventions, and resource allocation.[11,16,17] The attributable fraction and number represent the fraction and number of cases or deaths from a cause-specific disease that would be prevented without exposure to a specific risk factor, which has important implications for policy making and the potential impact of interventions.[18-20]

Use of risk assessment of the attributable fraction revealed the burden of mortality associated with ambient temperatures; however, most previous literatures estimated the mortality burden in high-income or low-altitude regions or coastlands,[11,16,19,21-23] and few were conducted in high plateau areas of developing countries.[12,24] The attributable fraction and number for the temperature–mortality association may vary by geographic features, climate, and structure of the population.[24,25] In addition, age, gender, educational attainment, and specific causes were previously identified as modifiers for estimating the effect modification of the mortality risk attributable to ambient temperatures.[26-30] However, few researchers have focused on the potential effect modification of the mortality burden by occupation, race/ethnicity, or marital status.[31]

Yuxi city is located in a high-altitude area in southwest China and experiences a unique, subtropical, plateau monsoon climate. More than 70% of indigenous people in this multi-ethnic region engage in agricultural production. The aim of this current ecological dissertation in Yuxi was to quantify the burden of non-accidental mortality attributable to ambient temperatures. We aimed to separate the contribution of temperature to mortality by heat and cold and mild and extreme temperatures by using attributable fraction and number, based on a proposed framework of attributable risk assessment within a distributed lag non-linear model (DLNM). A more in-depth purpose was to comprehensively assess the effect modification of the non-accidental mortality burden attributable to ambient temperatures by specific mortality causes (i.e., cardiovascular, heart, stroke, and respiratory diseases) and individual characteristics (i.e., age, gender, occupation, ethnicity, and marital status).

2. Methods

2.1 Study site

Located on the western edge of the Yunnan-Guizhou Plateau of southwest China, the Yuxi city area has complicated geographic features of mountains, valleys, plateaus, and basins. With an average altitude of about 2000m and 4 spring-like seasons, this area has a unique, subtropical, plateau monsoon climate, showing diversified climates with low atmospheric pressure, thin and dry air, and low seasonal variation in temperature. From the national population census in 2010, the permanent population is about 2.3 billion, and residents of ethnic minorities (e.g., Dai, Hui, Yi, Hani, and Mongolian minorities) account for 32.27% of the total population.

2.2 Data collection

Individual records such as age of death, gender, ethnicity, occupation, marital status, cause of death, and date of death for all registered deaths for the period January 1, 2009 to May 31, 2016, were obtained from the Yuxi Center for Disease Control and Prevention. The underlying causes of death were classified by medical personnel, and examination procedures were routinely performed to ensure accurate data, based on the *International Classification of Diseases*, 10th revision (ICD-10). Individual data were collapsed into a series of daily counts for the total non-accidental mortality (ICD-10 A00–R99) as well as subcategories by specific cause of death (cardiovascular [I00–I99], heart [I00–I51], stroke [I60–I69], and respiratory disease [J00–J99]), age (0–64, 65–74, and 75+ years old), gender (male and female), occupation (farmer and non-farmer), ethnicity (Han nationality and ethnic minorities), and marital status (married and non-married). Daily meteorological data for the same period were obtained from the China Meteorological Data Sharing System, including mean temperature and 4 other meteorological variables (atmospheric pressure, wind speed, sunshine duration, and relative humidity).

2.3 Patient and public involvement

This study is based on daily death number data, which could be obtained from Yuxi Center for Disease Control and Prevention without referral and free of charge. There was no patient and decedent involvement in the presented study.

2.4 Statistical analysis

As daily death number under a Poisson distribution and risk of mortality depend on exposure to temperatures of the current and previous days,[24] we applied a standard time-series quasi-Poisson regression model combined with DLNM to estimate the non-linear and lag effects of mean temperature on mortality, with day of the week, long-term trends, and the 4 other meteorological variables as potential covariates. This model can capture the complex non-linear relation and lagged effect by combining 2 functions that define the conventional exposure–response association and the additional lag–response association. The maximum lag period was set to 28 days to explore the lag structure of temperature effect, and median temperature

(17.0□) was the reference to calculate attributable risk.[31] We used natural cubic splines with 7 degrees of freedom (*df*) per year for time to describe the long-term trends and seasonality and 3 *df* for the 4 other meteorological indicators. These model specifications were consistent with previous studies.[23,32]

The total mortality burden attributable to non-reference temperatures can be assessed in terms of fraction and number of deaths, and the attributable number can be obtained from the sum of the contributions from all days in the series; its ratio with total number of deaths produces the total attributable fraction.[18] The overall cumulative relative risk corresponding to each day's temperature was used to compute the attributable fraction and number:

$$AF_{x,t} = 1 - \exp\left(-\sum_{l=l_0}^{L} \beta_{x_{t-l}}, l\right)$$

$$AN_{x,t} = AF_{x,t} \times n_t$$

where $AF_{x,t}$ and $AD_{x,t}$ are the attributable fraction and the number of cases at day *t* (1,2,3…2907), respectively; β_x is the risk associated with the exposure to ambient temperatures at level x (i.e., $\beta_x = (x - Ref) \times \beta$; *Ref* is the referenced temperature; β is the coefficient for DLNM of mean temperature; *L* is the maximum lag for the effect of mean temperature; and n_t is the observed number of deaths at day *t*.

To estimate the mortality burden from non-accidental deaths, we calculated the total attributable fraction due to the overall temperatures and divided the total effect into exposure to low and high temperatures by summing the subsets corresponding to days with temperatures below and above the median temperature. Also, we explored the mortality burden attributable to mild and extreme temperatures. Extreme cold and heat were defined as temperatures below the 2.5th percentile and above the 97.5th percentile of mean temperature, and mild cold and heat were defined as the range between the median temperature and these cutoffs. Monte-Carlo simulations were used to calculate the empirical confidence intervals (eCIs) of the attributable fraction and number, assuming a multivariate normal distribution of the best linear unbiased predictions of the deduced coefficients. All statistical analyses involved use of R v3.0.3, with the "dlnm" package to create the DLNM for mean temperature.

3. Results

3.1 Descriptive statistics

We analyzed 89,467 non-accidental deaths from Yuxi from 2009–2016, with an average of 33 deaths per day (range 12 to 72). The number of deaths due to cardiovascular disease was 41,794 (46.7%), more than half due to stroke; the proportion due to respiratory disease was 18.5% (Table 1). In individual characteristics subgroup, a higher proportion of deaths were for males, older people (≥75 years), people with Han nationality, farmers and married people than their corresponding categories. During the study period, the mean daily temperature was 16.1□ (ranging from -3.3 to 25.6□) (Table S1). The daily number of non-accidental deaths and mean temperature showed an inverse relation (Figure 1).

3.2 Exposure–response association

The overall effect of mean temperature on mortality (i.e., the total non-accidental deaths and by specified causes and individual characteristics) for lag 0–28 days and mean daily temperature distribution are in Figure 2. In general, the temperature–mortality associations were nonlinear and followed slide-shaped curves: the risks due to heat (both mild and extreme) were low and changed slightly (approximately 1), whereas the risks due to mild cold and especially extreme cold were increased. The relative risks rapidly increased with decreasing mean temperature. The distribution of mean daily temperature was skewed to the left.

3.3 Attributable fraction and number

Table 2 shows the estimated attributable fraction with 95% eCIs of daily non-accidental mortality calculated for total and separate components by heat and cold temperatures. For total non-accidental deaths, the attributable fraction was 4.75% (95% eCI 2.33, 6.79) with the whole temperature range, including heat and cold. Cold temperature was responsible for most of the mortality burden, corresponding to an attributable risk of 4.08% (0.86, 7.12), whereas the burden due to heat was low and non-significant (0.67%; -2.44, 3.64). The attributable risks of cardiovascular and stroke deaths caused by overall temperatures were 5.97% (2.74, 8.74) and 6.50% (2.22, 10.16); the point-estimated risk due to cold was higher for cardiovascular than respiratory deaths (6.18% *vs* 3.50%).

On stratification by age, the attributable risk due to ambient temperatures increased with age, with attributable fractions of 1.83%, 2.27%, and 6.87% for age ≤64, 65–74, and ≥75 years, respectively. Those engaged in agriculture had higher attributable fraction, 3.23 times (5.66% vs 1.75%) due to the overall temperatures and 3.98 times (4.93% vs 1.24%) due to cold, than non-farmers. The estimated burden due

to cold was 2.35-fold higher for ethnic minorities than Han nationality (6.55% *vs* 2.79%), whereas the point-estimated attributable fraction caused by the whole temperature range was approximately equal by gender and marital status.

Table 3 displays the estimated mortality fraction attributable to overall temperatures, separated by mild and extreme temperatures. In general, the risk of non-accidental deaths attributable to extreme cold was 1.17% (0.58, 1.69), accounting for a clearly high proportion of 24.6% of the total mortality burden (4.75%) due to the whole temperature range, whereas attributable risks due to mild cold or heat or extreme heat were non-significant. In the cause-specific analyses, the attributable fractions due to extreme cold were 1.57%, 1.63%, and 1.49% for cardiovascular disease, stroke, and heart disease, with no significant association with respiratory disease. The extreme cold-related burden for older people, females, farmers, and non-married individuals was slightly higher than their corresponding categories.

Table S2 presents the attributable number of deaths due to mean temperature, overall and by cold and heat. An estimated 4,131 non-accidental deaths were due to overall temperatures and 3,482 to cold. Table S3 shows the excess mortality due to extreme and mild cold and mild and extreme heat. Figures 3 and S1 illustrate the daily deaths attributable to cold and heat. The attributable deaths were much larger with cold than heat.

3.4 Sensitivity analysis

Sensitivity analysis to check the stability of our main findings involved changing the maximum lag days (7, 14, and 21) and the *df* of the natural cubic splines for the calendar time (5, 6, 8, and 9 per year) and for the 4 other meteorological variables one by one (2, 4, and 5). The attributable fractions for non-accidental mortality due to overall temperatures were relatively robust with sensitivity analyses (Table S2) and the results by causes of deaths and individual characteristics were robust (results not shown).

4. Discussion

We quantitatively estimated the attributable risks of non-accidental death and subgroups by specific causes and individual characteristics due to the whole temperature range and to extreme and mild cold and mild and extreme heat for 89,467 deaths between 2009 and 2016 in Yuxi, China, a high-altitude region with a unique,

subtropical, plateau monsoon climate. The temperature–mortality associations were nonlinear and followed slide-shaped curves, and the risks rapidly increased with decreasing mean temperature. Excess deaths were attributable to overall temperatures, and cold was responsible for most of the mortality burden. The estimated mortality burden attributable to cold was greater for cardiovascular deaths, older people, farmers, ethnic minorities, and non-married individuals than their corresponding categories.

In the present study, all of the cause-specific deaths we examined were closely related to ambient temperatures. The relations were non-linear, with increased relative risk with low temperature, especially extreme cold; however, the risk of high temperature changed minimally. A number of researchers have found that the temperature–response association presents a "U" or "V" shape, with increased mortality risks at extremely low and high temperatures.[25,33-35] We also examined additional non-accidental deaths attributable to ambient temperatures, with larger burden due to cold than heat. A multi-country observational study estimated a total mortality burden of death attributable to non-optimal ambient temperatures; the attributable fraction ranged from 3.37% in Thailand to 11% in China, which provides strong evidence for substantial differences between regions or climates.[16]

The cold-related mortality burden is an important public health problem in Yuxi. Findings from our study showed most of the death burden attributable to low temperature, and a much lower and non-significant burden due to heat. Previous studies have found that most of the mortality burden is caused by exposure to cold days, with comparatively lower attributable risk, or even none, due to heat exposure. For example, Hajat et al. (2006) showed that all-cause mortality attributable to heat ranged from 0.37% in London (1976–2003) to 1.45% in Milan (1985–2002), and another study conducted in London from 1986 to 1996 found that attributable fraction of mortality for each 1°C decrease below a threshold of 15°C was 5.42% (4.13, 6.69), with no burden due to heat.[36] Although extremely low or high temperature corresponded to increased relative risk of mortality, Gasparrini et al. (2015) found a relatively small part of the death burden attributable to extreme cold temperature, ranging from 0.25% to 1.06%. Similar results from 5 East Asian regions showed a 9.36% mortality burden attributable to overall temperatures, with only 0.80% due to extreme cold [19]. However, our current study estimated a larger proportion of attributable mortality fraction due to extreme cold, accounting for about one-quarter of the total mortality burden (1.17% *vs* 4.75%), even though extreme cold days represented only 2.5% of the whole study period. We found no evidence of additional deaths due to extreme heat in all categories.

Exposure to low temperature has been widely demonstrated to be strongly associated with excess cardiovascular and respiratory deaths,[19,30,37,38] and the biological processes that underlie cold-related mortality are associated with cardio-respiratory disease.[11,16,30,39] We found a higher point-estimated attributable risk caused by cold for cardiovascular than respiratory disease deaths. A multi-city study including 15 Chinese megacities also identified 15.8% of the cardiovascular mortality burden due to cold days.[25] The increased cold-related cardiovascular deaths mainly involved changes in vascular tone, autonomic nervous system response, arrhythmia, and oxidative stress.[40-42] Although we found no evidence for excess burden of respiratory deaths due to cold or heat, other reports have described increased respiratory deaths attributable to ambient temperatures.[10,43] For heart and stroke, the burden of mortality was attributable to only extreme cold, with approximately equivalent values, and other studies found excess heart and stroke deaths attributable to low and/or high temperatures.[23,26,37,44]

Age has been frequently identified as an important modifier of the association between ambient temperatures and human health.[15,25,29,45] We found that exposure to cold, particularly extreme cold, was closely related to increased death burden for older than younger people. Several previous surveys found increased age associated with point-estimated attributable risk of cardiovascular mortality and both intra-cerebral hemorrhage and ischemic stroke morbidity due to cold, with the highest values in older people.[25,31] Another nationwide study in Japan found most of the proportion of morbidity burden attributable to days with low temperature in all age groups, with an trend of increasing attributable risk with age: the attributable fraction due to cold was 15.96%, 24.84%, and 28.10% with age 18–64, 65–74, and 75–110 years, respectively.[33] Older people were more vulnerable to the temperature effects, mainly because they often have multiple pre-existing chronic conditions and physiological changes in thermoregulation and homoeostasis.[46,47] However, the effect modification of temperature-related mortality by gender has been identified.[23,29,33,48] We observed a higher mortality burden caused by exposure to the cold period among females than males in Yuxi, and the cold-related attributable risk was found higher for females than males in Hanoi, Vietnam,[49] and in 47 cities in Japan.[33] The reason for the discrepancy in temperature-related burden by gender might be owing to differences in occupational exposure, physiology and thermoregulation.

A survey in Adelaide, South Australia, provided epidemiological evidence for the impact of heat waves on worker health and safety, which implied that personal occupation might modify the temperature–mortality association.[50] Our previous studies (Ding et al., 2016a, 2016b) revealed that farmers were more likely than non-farmers to die on high DTR or cold days, and the present study also showed a higher mortality burden attributable to cold and extreme cold days for farmers than non-farmers. In southwestern China, farmers universally have a poor educational level, disadvantaged socioeconomic status, and low annual income, which may be linked to poor living conditions, malnutrition, and non-access to basic health care. In addition, farmers working in the fields may have more exposure to ambient temperatures, because farming is basically highly related to weather.[51]

A study of 9 cities in California found that with each 10°F (4.7°C) increase in mean temperature, the mortality was increased 4.9%, 2.5%, and 1.8% for Blacks, Whites, and Hispanics, respectively.[29] Also, our previous research demonstrated less risk of high DTR associated with non-accidental mortality for the current day for people of Dai ethnic minority than Han nationality.[13] To our knowledge, no study has estimated the potential effect modification of mortality burden attributable to ambient temperatures by ethnicity. We observed a greater cold- and mild cold-related death for ethnic minorities than Han nationality in Yuxi, which indicated that race/ethnicity may modify the cold-associated mortality burden. We also found lower death burden caused by cold and extreme cold for married people versus those never married, divorced, or widowed, possibly because married people can be cared for by their partners during the cold period.

5. Conclusions

Our present study revealed the non-accidental mortality burden clearly associated with ambient temperatures in Yuxi, China. A substantial burden of the deaths was due to cold, with the burden due to heat much lower. Mortality was increased with exposure to extreme cold, which was responsible for about one-quarter of the total mortality burden. In addition, the cold-related mortality burden was greater with cardiovascular than respiratory disease deaths and for people over 75 years old, females, farmers, ethnic minorities, and non-married individuals than their corresponding categories. The cold-related mortality burden in Yuxi may have important implications for public-health interventions to minimize the health effects due to adverse temperatures and for predicting the climate-change impact.

Declarations

Contributors: Q.Y.Z., Z.D., and C.Y.D. conceived and designed the experiments. L.J.L. and Y.F.W. provide primary data. P.G., S.Y.Y., J.L., Y.W., and C.Y.D. collected and cleaned the data. C.Y.D. analyzed the data and drafted the manuscript. Q.Y.Z., Z.D., and C.Y.D. revised the manuscript and interpreted the results. All authors read and approved the final manuscript.

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Table 1. Daily total non-accidental mortality and by specific causes and individual characteristics in Yuxi, China, 2009–2016.

	Total deaths	Min	Median (25th, 75th)	Max	Mean (SD)
Total non-accidental	89,467	12	32 (28, 38)	72	33.0 (7.8)
Cause-specific					
Cardiovascular	41,794	2	15 (12, 18)	37	15.4 (4.9)
Heart	17,793	0	6 (4, 8)	22	6.6 (3.0)
Stroke	22,589	0	8 (6, 10)	22	8.3 (3.3)
Respiratory	16,565	0	6 (4, 8)	21	6.1 (3.1)
Age, years					
≤64	21,678	1	8 (6, 10)	19	8.0 (2.9)
65–74	20,072	0	7 (5, 9)	19	7.4 (2.9)
≥75	47,717	4	17 (14, 21)	43	17.6 (5.6)
Gender					
Male	48,939	5	18 (14, 21)	43	18.1 (5.2)
Female	40,528	2	15 (12, 18)	36	15.0 (4.5)
Occupation					
Farmer	68,278	0	7 (5, 10)	33	7.8 (3.4)
Non-farmer	21,189	7	25 (20, 30)	57	25.2 (7.0)
Ethnic					
Han nationality	63,275	6	23 (19, 27)	54	23.4 (6.4)
Ethnic minorities	26,192	0	9 (7, 12)	24	9.7 (3.6)
Marital status					
Married	54,971	1	12 (10, 15)	32	12.7 (4.3)
Non-married	34,496	4	20 (16, 24)	49	20.3 (5.5)

Min, minimum; Max maximum; 25th, 25th percentile of the distributions; 75th, 75th percentile of the distributions.

Table 2. Attributable fraction (%) of total non-accidental mortality and by specific causes and individual characteristics due to mean daily temperature and cold and heat over lag 0–28 days in Yuxi, China.

	Total (%)	Cold (%)	Heat (%)
Total non-accidental	**4.75 (2.33, 6.79)**	**4.08 (0.86, 7.12)**	0.67 (-2.44, 3.64)
Cause-specific			
Cardiovascular	**5.97 (2.74, 8.74)**	**6.18 (1.89, 10.31)**	-0.21 (-5.04, 4.33)
Heart	5.25 (-0.40, 9.57)	6.48 (-0.70, 12.47)	-1.23 (-8.59, 5.46)
Stroke	**6.50 (2.22, 10.16)**	6.01 (-0.11, 11.41)	0.49 (-6.18, 6.15)
Respiratory	5.42 (-0.73, 9.71)	3.50 (-5.05, 10.95)	1.93 (-5.08, 7.90)
Age, years			
≤64	1.83 (-3.15, 5.95)	1.75 (-4.64, 7.10)	0.08 (-6.64, 5.64)
65–74	2.27 (-2.45, 6.30)	3.52 (-3.45, 9.37)	-1.25 (-7.4, 5.01)
≥75	**6.87 (3.68, 9.46)**	**5.34 (0.44, 9.38)**	1.53 (-2.96, 5.09)
Gender			
Male	**4.16 (0.82, 7.04)**	3.67 (-0.50, 7.72)	0.49 (-3.82, 4.31)
Female	**5.54 (2.18, 8.31)**	**4.66 (0.03, 9.07)**	0.89 (-3.21, 5.03)
Occupation			
Farmer	**5.66 (3.09, 7.92)**	**4.93 (1.28, 8.37)**	0.73 (-2.7, 3.87)
Non-farmer	1.75 (-3.58, 6.11)	1.24 (-5.77, 7.61)	0.52 (-6.82, 6.55)
Ethnic			
Han nationality	**5.38 (2.44, 7.96)**	2.79 (-1.30, 6.49)	2.59 (-0.92, 5.80)
Ethnic minorities	2.31 (-1.57, 6.76)	**6.55 (1.15, 11.75)**	-4.24 (-10.8, 1.27)
Marital status			
Married	**4.24 (1.17, 6.99)**	2.74 (-1.87, 6.53)	1.50 (-2.67, 4.83)
Non-married	**5.48 (1.69, 8.56)**	**6.10 (1.23, 10.21)**	-0.61 (-5.55, 3.95)

Results are expressed as attributable fractions (95% empirical confidence intervals), and the bold indicates a statistically significant.

Table 3. Mortality fraction (%) attributable to extreme and mild cold and mild and extreme heat by specific causes and individual characteristics.

	Extreme cold (%)	Mild cold (%)	Mild heat (%)	Extreme heat (%)
Total non-accidental	**1.17 (0.58, 1.69)**	3.06 (-0.08, 5.94)	0.57 (-2.36, 3.28)	0.12 (-0.26, 0.45)
Cause-specific				
Cardiovascular	**1.57 (0.81, 2.36)**	**4.88 (0.55, 8.60)**	-0.24 (-4.55, 3.40)	0.03 (-0.50, 0.51)
Heart	**1.49 (0.23, 2.58)**	5.25 (-1.37, 10.84)	-1.17 (-7.78, 4.53)	-0.08 (-0.87, 0.64)
Stroke	**1.63 (0.60, 2.65)**	4.65 (-1.05, 9.49)	0.38 (-5.22, 5.28)	0.13 (-0.59, 0.78)
Respiratory	1.35 (-0.15, 2.72)	2.28 (-5.64, 9.11)	1.70 (-4.01, 6.68)	0.26 (-0.48, 0.91)
Age, years				
≤64	0.44 (-0.63, 1.43)	1.34 (-4.52, 6.30)	0.06 (-5.58, 5.56)	0.02 (-0.70, 0.72)
65–74	0.68 (-0.37, 1.72)	2.91 (-3.72, 8.51)	-1.14 (-7.03, 4.22)	-0.12 (-0.83, 0.61)
≥75	**1.71 (0.91, 2.48)**	3.89 (-0.36, 7.66)	1.32 (-2.38, 4.64)	0.24 (-0.22, 0.68)
Gender				
Male	**1.02 (0.28, 1.74)**	2.76 (-1.08, 6.27)	0.41 (-3.25, 3.87)	0.09 (-0.40, 0.53)
Female	**1.36 (0.55, 2.15)**	3.48 (-0.77, 7.36)	0.76 (-3.26, 4.20)	0.15 (-0.37, 0.62)
Occupation				
Farmer	**1.42 (0.82, 2.04)**	**3.71 (0.38, 6.70)**	0.61 (-2.47, 3.39)	0.13 (-0.27, 0.52)
Non-farmer	0.39 (-0.73, 1.41)	0.84 (-5.98, 6.43)	0.45 (-6.15, 5.95)	0.07 (-0.65, 0.74)
Ethnic				
Han nationality	**1.22 (0.54, 1.91)**	1.69 (-2.20, 5.31)	2.30 (-0.73, 5.42)	0.34 (-0.06, 0.76)
Ethnic minorities	**1.03 (0.07, 1.93)**	**5.71 (0.91, 9.74)**	-3.84 (-9.8, 1.12)	-0.43 (-1.12, 0.25)
Marital status				
Married	**0.98 (0.26, 1.66)**	1.86 (-2.06, 5.17)	1.32 (-2.17, 4.62)	0.21 (-0.24, 0.61)
Non-married	**1.47 (0.59, 2.25)**	**4.88 (0.19, 9.18)**	-0.60 (-5.16, 3.37)	-0.02 (-0.58, 0.50)

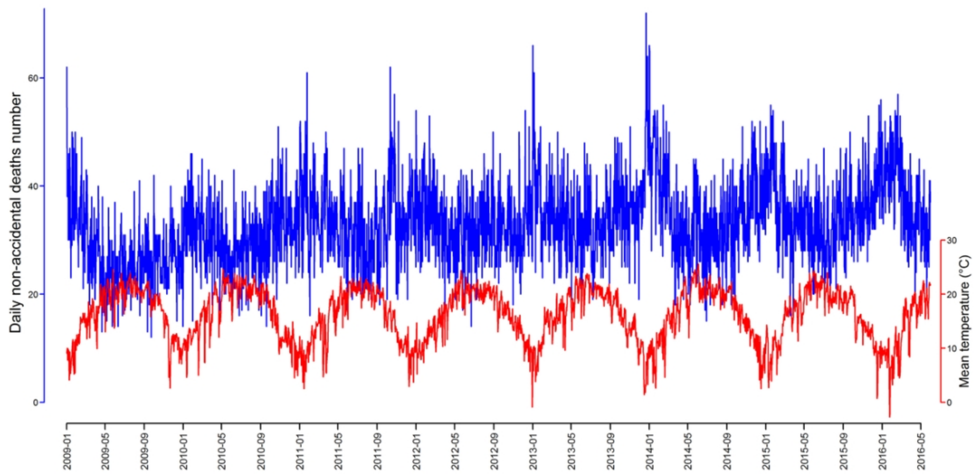
Results are expressed as attributable fractions (95% empirical confidence intervals), and the bold indicates a statistically significant.

Figure Legends

Figure 1. Time series of daily number of non-accidental deaths of Yuxi and mean temperature, 2009–2016.

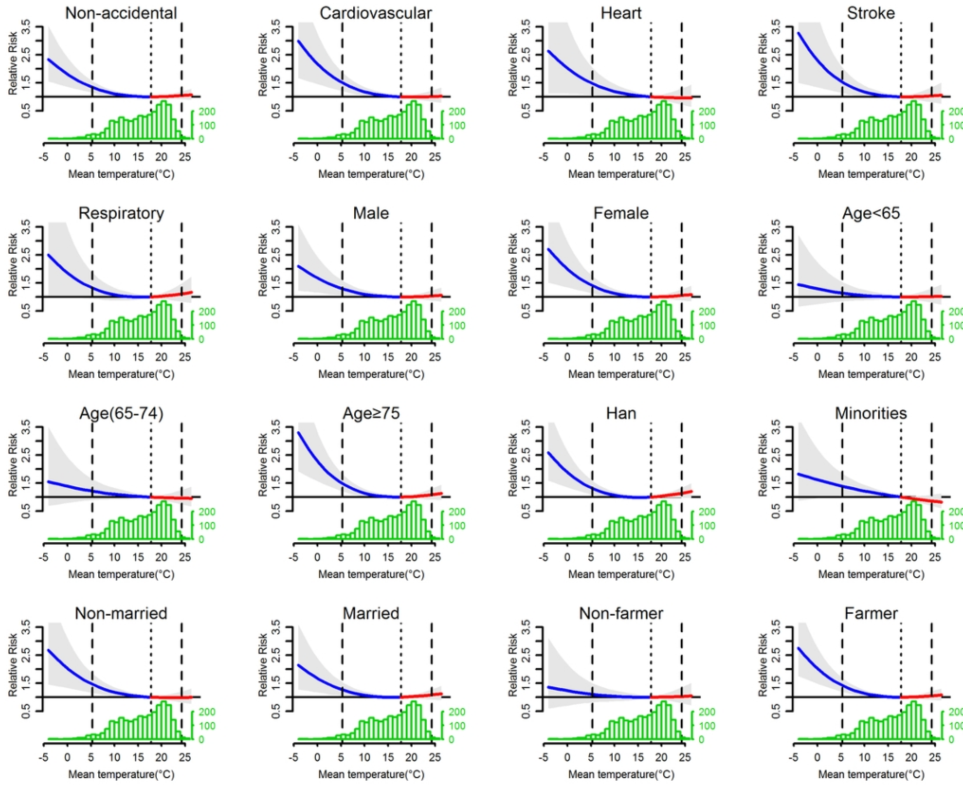
Figure 2. Overall cumulative relative risk (with 95% empirical confidence intervals, shaded grey) at a lag of 0–28 days in Yuxi, China, with histogram of daily temperature distribution. The dotted lines are the median of the mean temperature, and the dashed lines are the 2.5th and 97.5th percentiles of the distribution of mean temperature. The lines before and after the dotted lines represent the exposure response below (blue lines) and above (red lines) the median of mean temperature.

Figure 3. Daily number of total non-accidental deaths attributable to cold (blue points) and heat (red points).



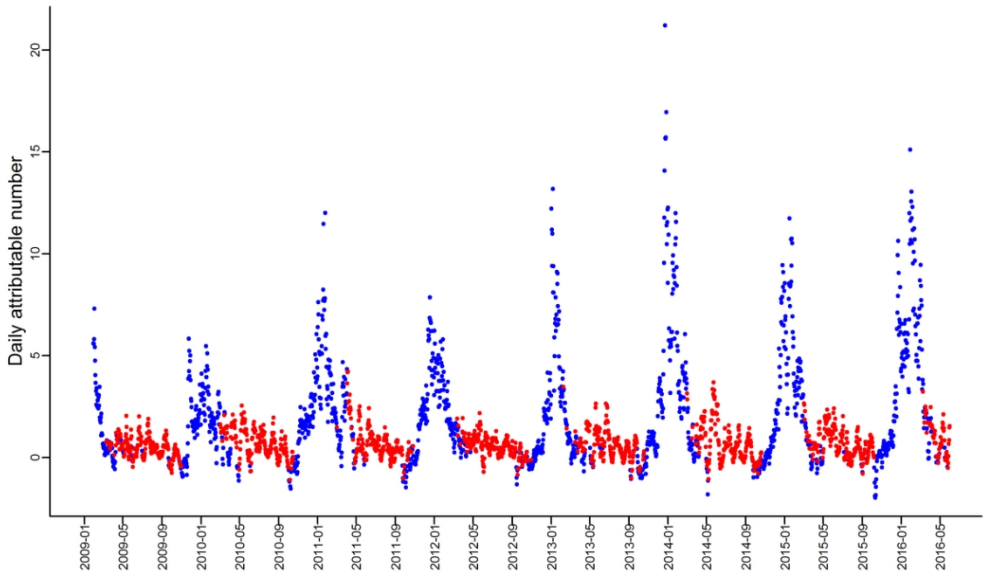
Time series of daily number of non-accidental deaths of Yuxi and mean temperature, 2009–2016

105x52mm (300 x 300 DPI)



Overall cumulative relative risk (with 95% empirical confidence intervals, shaded grey) at a lag of 0–28 days in Yuxi, China, with histogram of daily temperature distribution. The dotted lines are the median of the mean temperature, and the dashed lines are the 2.5th and 97.5th percentiles of the distribution of mean temperature. The lines before and after the dotted lines represent the exposure response below (blue lines) and above (red lines) the median of mean temperature

101x81mm (300 x 300 DPI)



Daily number of total non-accidental deaths attributable to cold (blue points) and heat (red points)

101x60mm (300 x 300 DPI)

Supplemental materials

Table S1. Descriptive statistics for weather conditions, 2009–2016.

	Min	25th	Median	75th	Max	Mean (SD)
Mean temperature (℃)	-3.3	12.3	17.0	20.2	25.6	16.1±4.9
Relative humidity (%)	25.0	58.0	71.0	78.0	95.0	67.3±14.7
Atmospheric pressure (hPa)	802.7	807.9	810.1	812.5	822.2	810.3±3.2
Wind speed (m/s)	0.5	1.9	2.5	3.2	8.6	2.7±1.1
Sunshine duration (h)	0	3.1	7.6	9.9	12.9	6.5±3.9

Table S2. Attributable number of non-accidental deaths and specific categories due to daily mean temperature, computed as total and as separated components for cold and heat temperatures over lag 0–28 days in Yuxi, China.

	Total	Cold	Heat
Total non-accidental	**4131 (2306, 5937)**	**3482 (552, 5980)**	652 (-2049, 3185)
Cause-specific			
Cardiovascular	**2419 (2622, 7476)**	**2489 (629, 4141)**	-68 (-2019, 1701)
Heart	**912 (446, 8413)**	1112 (-98, 2200)	-199 (-1456, 918)
Stroke	**1417 (2055, 8814)**	**1306 (104, 2634)**	113 (-1178, 1283)
Respiratory	854 (-428, 8228)	540 (-846, 1689)	314 (-822, 1190)
Age, years			
≤64	414 (-2421, 5413)	359 (-976, 1580)	55 (-1384, 1237)
65-74	470 (-2366, 5715)	679 (-764, 1853)	-209 (-1543, 953)
≥75	**3137 (3094, 7816)**	**2431 (102, 4392)**	710 (-1135, 2532)
Gender			
Male	**1977 (818, 5961)**	1706 (-395, 3697)	273 (-1668, 2048)
Female	**2181 (1691, 7074)**	1802 (-59, 3390)	380 (-1355, 1919)
Occupation			
Farmer	**3752 (2730, 6784)**	**3225 (801, 5403)**	530 (-1799, 2580)
Non-farmer	364 (-2842, 5120)	242 (-1320, 1486)	124 (-1293, 1350)
Ethnic			
Han nationality	**3243 (2237, 6688)**	1624 (-972, 4023)	1618 (-622, 3621)
Ethnic minorities	649 (-1165, 5773)	**1685 (332, 2934)**	-1037 (-2677, 488)
Marital status			
Married	**2262 (1118, 5804)**	1402 (-833, 3564)	860 (-1201, 2875)
Non-married	**1843 (1892, 7386)**	**2042 (334, 3527)**	-197 (-1963, 1218)

Results are expressed as attributable number (95% empirical confidence interval), and the bold indicates a statistically significant.

Table S3. Mortality number attributable to extreme and mild cold and mild and extreme heat by specific causes and individual characteristics

	Extreme cold	Mild cold	Mild heat	Extreme heat
Total non-accidental	**1054 (604, 1530)**	2556 (-117, 5016)	554 (-1930, 2984)	108 (-199, 395)
Cause-specific				
Cardiovascular	**657 (331, 946)**	**1942 (183, 3532)**	-84 (-1803, 1505)	15 (-191, 217)
Heart	**264 (72, 445)**	892 (-146, 1896)	-190 (-1385, 830)	-13 (-154, 109)
Stroke	**368 (136, 600)**	997 (-345, 2170)	87 (-1095, 1183)	28 (-129, 169)
Respiratory	223 (-30, 434)	337 (-1005, 1413)	277 (-643, 1006)	42 (-89, 161)
Age, years				
≤64	101 (-135, 308)	265 (-1039, 1292)	46 (-1121, 1094)	10 (-135, 149)
65-74	140 (-75, 331)	554 (-685, 1578)	-192 (-1434, 971)	-20 (-181, 116)
≥75	**814 (431, 1152)**	1732 (-123, 3465)	612 (-1103, 2097)	110 (-99, 313)
Gender				
Male	**503 (118, 851)**	1257 (-681, 3097)	229 (-1651, 1917)	47 (-153, 264)
Female	**556 (238, 882)**	1321 (-483, 2860)	325 (-1203, 1755)	61 (-134, 248)
Occupation				
Farmer	**977 (564, 1376)**	**2382 (27, 4440)**	446 (-1638, 2333)	92 (-173, 349)
Non-farmer	83 (-125, 295)	158 (-1263, 1389)	109 (-1137, 1255)	16 (-128, 158)
Ethnic				
Han nationality	**772 (364, 1191)**	918 (-1565, 3045)	1440 (-488, 3387)	209 (-57, 433)
Ethnic minorities	274 (-1, 500)	**1462 (162, 2576)**	-941 (-2416, 330)	-104 (-277, 62)
Marital status				
Married	**544 (165, 908)**	908 (-1292, 2815)	759 (-995, 2607)	117 (-125, 344)
Non-married	**509 (219, 781)**	**1615 (4, 3017)**	-192 (-1730, 1143)	-7 (-198, 158)

Results are expressed as attributable number (95% empirical confidence interval), and the bold indicates a statistically significant.

Table S4 Sensitivity analyses to calculate the fraction (%) with 95% empirical confidence interval attributable to temperature by changing maximum lag for mean temperature and degrees of freedom (*df*) for covariates

Model choices	Total	Cold	Heat
Lag period, days			
7	2.85 (1.62, 3.99)	0.97 (-1.16, 2.98)	1.88 (0.32, 3.31)
14	4.15 (2.78, 5.52)	2.90 (0.59, 5.15)	1.25 (-0.48, 2.93)
21	3.57 (1.51, 5.31)	3.10 (0.25, 5.76)	0.47 (-1.99, 2.89)
Df for time per year			
5	4.69 (3.10, 6.15)	4.19 (1.18, 6.73)	0.51 (-1.66, 2.81)
6	5.94 (4.07, 7.53)	4.96 (2.18, 7.72)	0.98 (-1.68, 3.49)
8	3.82 (0.92, 6.42)	4.72 (1.23, 8.07)	-0.90 (-4.31, 2.26)
9	5.07 (2.15, 7.75)	4.59 (0.57, 8.16)	0.48 (-2.98, 3.75)
Df for relative humidity			
2	4.64 (2.21, 6.83)	4.07 (0.84, 7.28)	0.57 (-2.70, 3.56)
4	4.74 (2.31, 6.88)	4.05 (0.56, 7.26)	0.69 (-2.15, 3.83)
5	4.79 (2.55, 6.92)	4.20 (1.06, 7.20)	0.60 (-2.76, 3.36)
Df for sunshine duration			
2	4.71 (2.27, 6.84)	4.18 (0.88, 7.35)	0.54 (-2.89, 3.51)
4	4.75 (2.39, 6.95)	4.08 (0.92, 7.03)	0.67 (-2.51, 3.65)
5	4.78 (2.44, 6.90)	4.13 (0.69, 7.45)	0.65 (-2.40, 3.63)
Df for atmospheric pressure			
2	4.76 (2.24, 6.87)	4.15 (0.76, 7.00)	0.62 (-2.69, 3.49)
4	4.75 (2.21, 6.97)	4.09 (0.39, 6.95)	0.67 (-2.49, 3.76)
5	4.79 (2.38, 6.95)	4.02 (1.01, 7.08)	0.77 (-2.30, 3.98)
Df for wind speed			
2	4.79 (2.26, 6.90)	4.02 (0.47, 6.88)	0.78 (-2.34, 3.52)
4	4.68 (2.34, 6.78)	4.02 (0.60, 7.07)	0.67 (-2.48, 3.68)
5	4.66 (2.31, 6.85)	4.04 (0.90, 6.94)	0.62 (-2.56, 3.75)

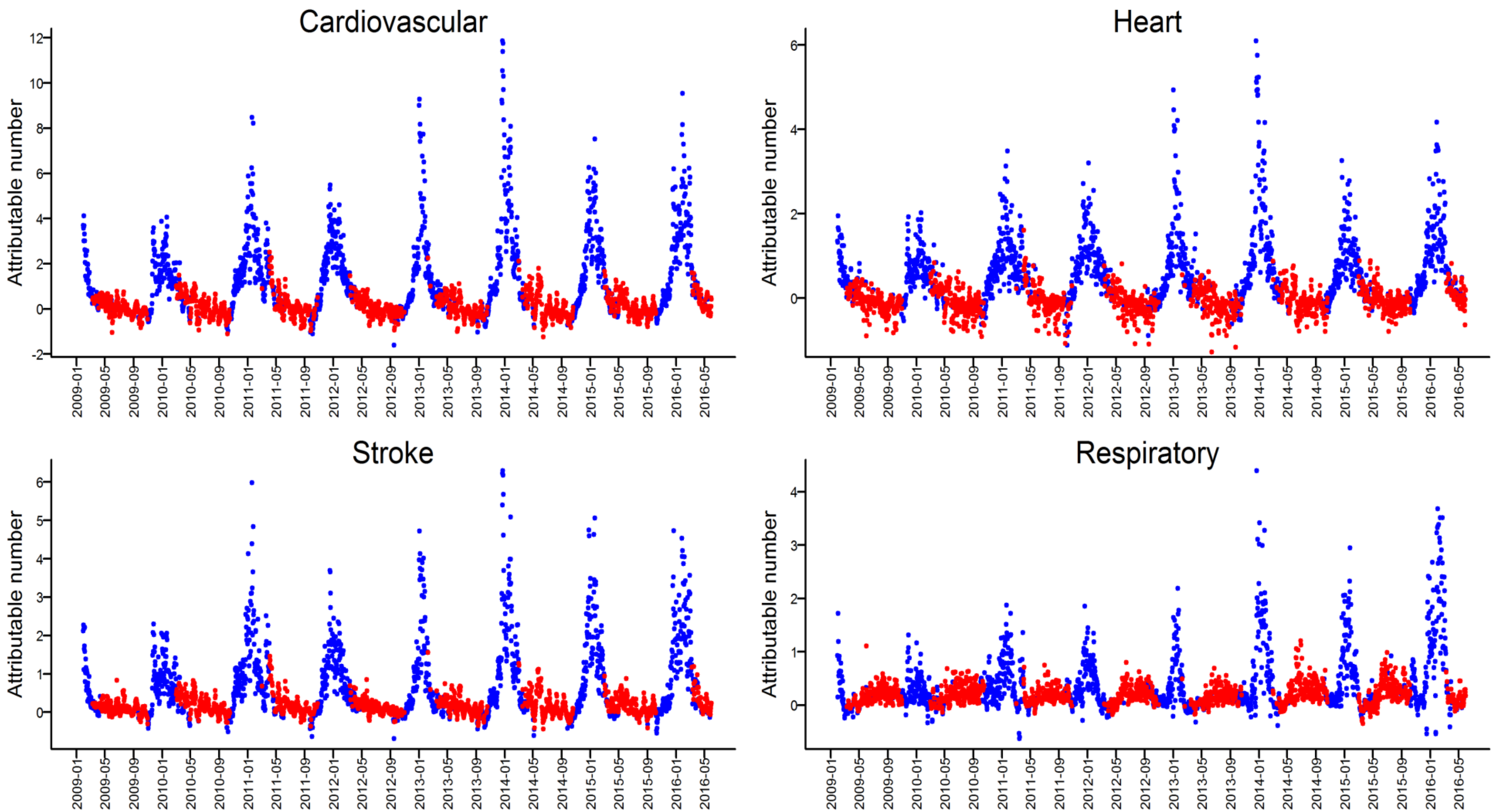


Figure S1. Daily number of cardiovascular, heart, stroke and respiratory deaths attributable to cold (blue points) and heat (red points) temperatures.

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Burden of non-accidental mortality attributable to ambient temperatures in a high plateau area of southwest China

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Burden of non-accidental mortality attributable to ambient temperatures in a high plateau area of southwest China

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Abstract

Objective: To examine the total non-accidental mortality burden attributable to ambient temperatures and assess the effect modification of the burden by specific causes of death and individual characteristics in a high plateau area in southwest China.

Methods: Using daily mortality and meteorological data from 2009 to 2016, we applied a quasi-Poisson model combined with a distributed lag non-linear model to estimate the temperature–mortality association with the assessment of attributable fraction and number. We calculated attributable fractions and deaths with 95% empirical confidence intervals (eCIs), that were due to cold and heat, defined as temperatures below and above the median temperature, and for mild and extreme temperatures, defined by cutoffs at the 2.5th and 97.5th temperature percentiles.

Results: We analyzed 89,467 non-accidental deaths; 4,131 were attributable to overall temperatures, with an attributable fraction of 4.75% (95% eCI 2.33, 6.79). Most of the mortality burden was caused by cold (4.08%; 0.86, 7.12), while the burden due to heat was low and non-significant (0.67%; -2.44, 3.64). Extreme cold (1.17%; 0.58, 1.69) was responsible for 24.6% (i.e., 1.17% divided by 4.75%) of the total death burden. In the stratification analyses, attributable risk due to cold was higher for cardiovascular than respiratory disease (6.18% vs 3.50%). We found a trend of risk of increased death due to ambient temperatures with increasing age, with attributable fractions of 1.83%, 2.27%, and 6.87% for age ≤64, 65 – 74, and ≥75 years old. The cold-related burden was slightly greater for females, farmers, ethnic minorities, and non-married individuals than their corresponding categories.

Conclusions: Most of the burden of death was attributable to cold, and specific causes and individual characteristics might modify the mortality burden attributable to ambient temperatures. The results may help make prevention measures to confront climate change for susceptible population in this region.

Key words: ambient temperatures; attributable fraction; attributable number; mortality; effect modification

Strengths and limitations of this study

- Mortality burden attributable to ambient temperature was assessed in a high plateau city in southwest China.

- To our knowledge, this study evaluated the mortality burden attributable to ambient temperature, and quantified its effect modification by national minority and occupation for the first time.
- The data only come from one city, so it should be cautious to generalize the findings to other geographic areas or climates.
- We used the data on temperature from monitoring sites rather than measuring individual exposure, which may bring about measurement errors.

1. Introduction

With the global climate change, ambient temperatures has been extensively demonstrated to directly affect human health (e.g., daily morbidity and mortality) and has become one of the most severe public health problems in the world.[1-5] Exposure to extreme weather such as cold spells and heat waves represents high risk for mortality, and the extreme temperature-related mortality is expected to increase with the increasing frequency, intensity, and duration of extreme weather events.[4,6-8] Low and high temperatures are also well known to be associated with a substantial increase in a wide range of all-cause and cause-specific mortality (e.g., cardiovascular and respiratory diseases).[6,9-12]

Numerous epidemiological studies have widely used ratio measures (e.g., odds ratio, relative ratio, or rate ratio) to quantify the relationships between ambient temperatures and human health, but these offer limited information on the excess burden and actual impact of ambient temperatures.[13-16] Relative excess measures (e.g., attributable fraction) and absolute excess measures (e.g., attributable number), calculated on the basis of the estimated relative risk, have been pointed out to provide better scientific evidence for estimating the potential benefits of preventative measures, public health interventions, and resource allocation.[11,17,18] The attributable fraction and number represent the fraction and number of cases or deaths from a cause-specific disease that would be prevented without exposure to a specific risk factor, which has important implications for policy making and the potential impact of interventions.[19-21]

Use of risk assessment of the attributable fraction revealed the burden of mortality associated with ambient temperatures; however, most previous literatures estimated the mortality burden in high-income or low-altitude regions or coastlands,[11,17,20,22-24] and few were conducted in high plateau areas of developing countries.[12,25] The attributable fraction and number for the temperature–mortality association may vary by geographic features, climate, and structure of the population.[25,26] In addition, age, gender, educational attainment, and specific causes were previously identified as modifiers for estimating the effect modification of the mortality risk attributable to ambient temperatures.[27-31] However, few researchers have focused on the potential effect modification of the mortality burden by occupation, race/ethnicity, or marital status.[32]

Yuxi city is located in a high-altitude area in southwest China and experiences a unique, subtropical, plateau monsoon climate. More than 70% of indigenous people in this multi-ethnic region engage in agricultural production. The aim of this current ecological dissertation in Yuxi was to quantify the burden of non-accidental mortality attributable to ambient temperatures. We aimed to separate the contribution of temperature to mortality by heat and cold and mild and extreme temperatures by using attributable fraction and number, based on a proposed framework of attributable risk assessment within a distributed lag non-linear model (DLNM). A more in-depth purpose was to comprehensively assess the effect modification of the non-accidental mortality burden attributable to ambient temperatures by specific mortality causes (i.e., cardiovascular, heart, stroke, and respiratory diseases) and individual characteristics (i.e., age, gender, occupation, ethnicity, and marital status).

2. Methods

2.1 Study site

Located on the western edge of the Yunnan-Guizhou Plateau of southwest China, the Yuxi city area has complicated geographic features of mountains, valleys, plateaus, and basins. With an average altitude of about 2000m and 4 spring-like seasons, this area has a unique, subtropical, plateau monsoon climate, showing diversified climates with low atmospheric pressure, thin and dry air, and a stable daily mean temperature but large temperature difference between day and night, morning or evening and daytime, indoor and outdoor. From the national population census in 2010, the permanent population is about 2.3 billion, and residents of ethnic minorities (e.g., Dai, Hui, Yi, Hani, and Mongolian minorities) account for 32.27% of the total population.

2.2 Data collection

Individual records such as age of death, gender, ethnicity, occupation, marital status, cause of death, and date of death for all registered deaths for the period January 1, 2009 to May 31, 2016, were obtained from the Yuxi Center for Disease Control and Prevention, which maintains detailed quality assurance and control measures[33,34]. The underlying causes of death were classified by medical personnel, and examination procedures were routinely performed to ensure accurate data, based on the *International Classification of Diseases*, 10th revision (ICD-10). Individual data were collapsed into a series of daily counts for the total non-accidental mortality (ICD-10 A00–R99) as well as subcategories by specific cause of death (cardiovascular [I00–I99], heart [I00–I51], stroke [I60–I69], and respiratory disease [J00–J99]), age (0–64, 65–74, and 75+ years old), gender (male and female), occupation (farmer and non-farmer), ethnicity (Han nationality and ethnic minorities), and marital status (married and non-married). Daily meteorological data for the same period were obtained from the China Meteorological Data Sharing System, including mean temperature and 4 other meteorological variables (atmospheric pressure, wind speed, sunshine duration, and relative humidity).

2.3 Patient and public involvement

This study is based on daily death number data, which could be obtained from Yuxi Center for Disease Control and Prevention without referral and free of charge. There was no patient and decedent involvement in the presented study.

2.4 Statistical analysis

As daily death number under a Poisson distribution and risk of mortality depend on exposure to temperatures of the current and previous days,[25] we applied a standard time-series quasi-Poisson regression model combined with DLNM to estimate the non-linear and lag effects of mean temperature on mortality, with day of the week, long-term trends, and the 4 other meteorological variables as potential covariates. This model can capture the complex non-linear relation and lagged effect by combining 2 functions that define the conventional exposure–response association and the additional lag–response association. The maximum lag period was set to 28 days to explore the lag structure of temperature effect, and median temperature (17.0℃) was the reference to calculate attributable risk.[32] We used natural cubic splines with 7 degrees of freedom (*df*) per year for time to describe the long-term trends and seasonality and 3 *df* for the 4 other meteorological indicators. These model specifications were consistent with previous studies.[24,35]

The total mortality burden attributable to non-reference temperatures can be assessed in terms of fraction and number of deaths, and the attributable number can be obtained from the sum of the contributions from all days in the series; its ratio with total number of deaths produces the total attributable fraction.[19] The overall cumulative relative risk corresponding to each day's temperature was used to compute the attributable fraction and number:

$$AF_{x,t} = 1 - \exp\left(-\sum_{l=l_0}^{L} \beta_{x_{t-l},l}\right)$$

$$AN_{x,t} = AF_{x,t} \times n_t$$

where $AF_{x,t}$ and $AD_{x,t}$ are the attributable fraction and the number of cases at day *t* (1,2,3…2907), respectively; β_x is the risk associated with the exposure to ambient temperatures at level x (i.e., $\beta_x = (x - Ref) \times \beta$; *Ref* is the referenced temperature; β is the coefficient for DLNM of mean temperature; *L* is the maximum lag for the effect of mean temperature; and n_t is the observed number of deaths at day *t*.

To estimate the mortality burden from non-accidental deaths, we calculated the total attributable fraction due to the overall temperatures and divided the total effect into exposure to low and high temperatures by summing the subsets corresponding to days with temperatures below and above the median temperature. Also, we explored the mortality burden attributable to mild and extreme temperatures. Extreme cold and heat were defined as temperatures below the 2.5th percentile (5.4°C) and above the 97.5th percentile (23.1°C) of mean temperature, and mild cold and heat were defined as the range between the median temperature and these cutoffs. Monte-Carlo simulations were used to calculate the empirical confidence intervals (eCIs) of the attributable fraction and number, assuming a multivariate normal distribution of the best linear unbiased predictions of the deduced coefficients[19,36]. All statistical analyses involved use of R v3.0.3, with the "dlnm" package to create the DLNM for mean temperature.

3. Results

3.1 Descriptive statistics

We analyzed 89,467 non-accidental deaths from Yuxi between 2009 and 2016, with an average of 33 deaths per day (range 12 to 72). The number of deaths due to cardiovascular disease was 41,794 (46.7%), more than half due to stroke; the proportion due to respiratory disease was 18.5% (Table 1). In individual characteristics subgroup, a higher proportion of deaths were for males, older people (≥75 years), people with Han nationality, farmers and married people than their corresponding categories. During the study period, the mean daily temperature was 16.1 °C (ranging from -3.3 to 25.6 °C) (Table S1). The daily number of non-accidental deaths and mean temperature showed an inverse relation (Figure 1).

3.2 Exposure–response association

The overall effect of mean temperature on mortality (i.e., the total non-accidental deaths and by specified causes and individual characteristics) for lag 0–28 days and mean daily temperature distribution are presented in Figure 2. In general, the temperature–mortality associations were nonlinear and followed slide-shaped curves: the risks due to heat (both mild and extreme) were low and changed slightly (approximately 1), whereas the risks due to mild cold and especially extreme cold were increased. The relative risks rapidly increased with decreasing mean temperature. The distribution of mean daily temperature was skewed to the left.

3.3 Attributable fraction and number

Table 2 shows the estimated attributable fraction with 95% eCIs of daily non-accidental mortality calculated for total and separate components by heat and cold temperatures. For total non-accidental deaths, the attributable fraction was 4.75% (95% eCI 2.33, 6.79) with the whole temperature range, including heat and cold. Cold temperature was responsible for most of the mortality burden, corresponding to an attributable risk of 4.08% (0.86, 7.12), whereas the burden due to heat was low and non-significant (0.67%; -2.44, 3.64). The attributable risks of cardiovascular and stroke deaths caused by overall temperatures were 5.97% (2.74, 8.74) and 6.50% (2.22, 10.16); the point-estimated risk due to cold was higher for cardiovascular than respiratory deaths (6.18% *vs* 3.50%).

On stratification by age, the attributable risk due to ambient temperatures increased with age, with attributable fractions of 1.83%, 2.27%, and 6.87% for age ≤64, 65–74, and ≥75 years, respectively. Those engaged in agriculture had higher attributable fraction, 3.23 times (5.66% vs 1.75%) due to the overall temperatures and 3.98 times (4.93% vs 1.24%) due to cold, than non-farmers. The estimated burden due

to cold was 2.35-fold higher for ethnic minorities than Han nationality (6.55% *vs* 2.79%), whereas the point-estimated attributable fraction caused by the whole temperature range was approximately equal by gender and marital status.

Table 3 displays the estimated mortality fraction attributable to overall temperatures, separated by mild and extreme temperatures. In general, the risk of non-accidental deaths attributable to extreme cold was 1.17% (0.58, 1.69), accounting for a clearly high proportion of 24.6% of the total mortality burden (4.75%) due to the whole temperature range, whereas attributable risks due to mild cold or heat or extreme heat were non-significant. In the cause-specific analyses, the attributable fractions due to extreme cold were 1.57%, 1.63%, and 1.49% for cardiovascular disease, stroke, and heart disease, with no significant association with respiratory disease. The extreme cold-related burden for older people, females, farmers, and non-married individuals was slightly higher than their corresponding categories.

Table S2 presents the attributable number of deaths due to mean temperature, overall and by cold and heat. An estimated 4,131 non-accidental deaths were due to overall temperatures and 3,482 to cold. Table S3 shows the excess mortality due to extreme and mild cold and mild and extreme heat. Figures 3 and S1 illustrate the daily deaths attributable to cold and heat. The attributable deaths were much larger with cold than heat.

3.4 Sensitivity analysis

Sensitivity analysis to check the stability of our main findings involved changing the maximum lag days (7, 14, and 21) and the *df* of the natural cubic splines for the calendar time (5, 6, 8, and 9 per year) and for the 4 other meteorological variables one by one (2, 4, and 5). The attributable fractions for non-accidental mortality due to overall temperatures were relatively robust with sensitivity analyses (Table S4) and the results by causes of deaths and individual characteristics were robust (results not shown).

4. Discussion

We quantitatively estimated the attributable risks of non-accidental death and subgroups by specific causes and individual characteristics due to the whole temperature range and to extreme and mild cold and mild and extreme heat for 89,467 deaths between 2009 and 2016 in Yuxi, China, a high-altitude region with a unique,

subtropical, plateau monsoon climate. The temperature–mortality associations were nonlinear and followed slide-shaped curves, and the risks rapidly increased with decreasing mean temperature. Excess deaths were attributable to overall temperatures, and cold was responsible for most of the mortality burden. The estimated mortality burden attributable to cold was greater for cardiovascular deaths, older people, farmers, ethnic minorities, and non-married individuals than their corresponding categories.

In the present study, all of the cause-specific deaths we examined were closely related to ambient temperatures. The relations were non-linear, with increased relative risk with low temperature, especially extreme cold; however, the risk of high temperature changed minimally. A number of researchers have found that the temperature–response association presents a "U" or "V" shape, with increased mortality risks at extremely low and high temperatures.[26,37-39] We also examined additional non-accidental deaths attributable to ambient temperatures, with larger burden due to cold than heat. A multi-country observational study estimated a total mortality burden of death attributable to non-optimal ambient temperatures; the attributable fraction ranged from 3.37% in Thailand to 11% in China, which provides strong evidence for substantial differences between regions or climates.[17]

The cold-related mortality burden is an important public health problem in Yuxi. Findings from our study showed most of the death burden attributable to low temperature, and a much lower and non-significant burden due to heat, which might be owing to unique climatic condition that the differences between minimum and referent temperature was 20.3°C (-3.3°C vs 17.0°C), while those between referent and maximum temperature was 8.6°C (17.0°C vs 25.6°C). Previous studies have found that most of the mortality burden is caused by exposure to cold days, with comparatively lower attributable risk, or even none, due to heat exposure. For example, Hajat et al. (2006) showed that all-cause mortality attributable to heat ranged from 0.37% in London (1976–2003) to 1.45% in Milan (1985–2002), and another study conducted in London from 1986 to 1996 found that attributable fraction of mortality for each 1°C decrease below a threshold of 15°C was 5.42% (4.13, 6.69), with no burden due to heat.[40] Although extremely low or high temperature corresponded to increased relative risk of mortality, Gasparrini et al. (2015) found a relatively small part of the death burden attributable to extreme cold temperature, ranging from 0.25% to 1.06%. Similar results from 5 East Asian regions showed a

9.36% mortality burden attributable to overall temperatures, with only 0.80% due to extreme cold [20]. However, our current study estimated a larger proportion of attributable mortality fraction due to extreme cold, accounting for about one-quarter of the total mortality burden (1.17% *vs* 4.75%), even though extreme cold days represented only 2.5% of the whole study period. We found no evidence of additional deaths due to extreme heat in all categories.

Exposure to low temperature has been widely demonstrated to be strongly associated with excess cardiovascular and respiratory deaths,[20,31,41,42] and the biological processes that underlie cold-related mortality are associated with cardio-respiratory disease.[11,17,31,43] We found a higher point-estimated attributable risk caused by cold for cardiovascular than respiratory disease deaths. A multi-city study including 15 Chinese megacities also identified 15.8% of the cardiovascular mortality burden due to cold days.[26] The increased cold-related cardiovascular deaths mainly involved changes in vascular tone, autonomic nervous system response, arrhythmia, and oxidative stress.[44-46] Although we found no evidence for excess burden of respiratory deaths due to cold or heat, other reports have described increased respiratory deaths attributable to ambient temperatures.[10,47] For heart and stroke, the burden of mortality was attributable to only extreme cold, with approximately equivalent values, and other studies found excess heart and stroke deaths attributable to low and/or high temperatures.[24,27,41,48]

Age has been frequently identified as an important modifier of the association between ambient temperatures and human health.[15,26,30,49] We found that exposure to cold, particularly extreme cold, was closely related to increased death burden for older than younger people. Several previous surveys found increased age associated with point-estimated attributable risk of cardiovascular mortality and both intra-cerebral hemorrhage and ischemic stroke morbidity due to cold, with the highest values in older people.[26,32] Another nationwide study in Japan found most of the proportion of morbidity burden attributable to days with low temperature in all age groups, with an trend of increasing attributable risk with age: the attributable fraction due to cold was 15.96%, 24.84%, and 28.10% with age 18–64, 65–74, and 75–110 years, respectively.[37] Older people were more vulnerable to the temperature effects, mainly because they often have multiple pre-existing chronic conditions and physiological changes in thermoregulation and homoeostasis.[50,51] However, the effect modification of temperature-related mortality by gender has been identified.[24,30,37,52] We observed a higher mortality burden caused by exposure to the cold period among females than males in Yuxi, and the cold-related attributable risk was found higher for females than males in Hanoi, Vietnam,[53] and in 47 cities in Japan.[37] The reason for the discrepancy in temperature-related burden by gender might be owing to differences in occupational exposure, physiology and thermoregulation.

A survey in Adelaide, South Australia, provided epidemiological evidence for the impact of heat waves on worker health and safety, which implied that personal occupation might modify the temperature–mortality association.[54] Our previous studies (Ding et al., 2016a, 2016b) revealed that farmers were more likely than non-farmers to die on high DTR or cold days, and the present study also showed a higher mortality burden attributable to cold and extreme cold days for farmers than non-farmers. In southwestern China, farmers universally have a poor educational level, disadvantaged socioeconomic status, and low annual income, which may be linked to poor living conditions, malnutrition, and non-access to basic health care. In addition, farmers working in the fields may have more exposure to ambient temperatures, because farming is basically highly related to weather.[55]

A study of 9 cities in California found that with each 10°F (4.7°C) increase in mean temperature, the mortality was increased 4.9%, 2.5%, and 1.8% for Blacks, Whites, and Hispanics, respectively.[30] Also, our previous research demonstrated less risk of high DTR associated with non-accidental mortality for the current day for people of Dai ethnic minority than Han nationality.[13] To our knowledge, no study has estimated the potential effect modification of mortality burden attributable to ambient temperatures by ethnicity. We observed a greater cold- and mild cold-related death for ethnic minorities than Han nationality in Yuxi, which indicated that race/ethnicity may modify the cold-associated mortality burden. We also found lower death burden caused by cold and extreme cold for married people versus those never married, divorced, or widowed, possibly because married people can be cared for by their partners during the cold period.

Our study has some limitations. First, the data were from a single city, so generalizing the findings to other geographic areas or climates should be cautioned. Second, the data of temperature were from monitoring sites rather than exposure measuring of individual. Third, although the concentration of daily mean PM_{10}, NO_2 and SO_2 in Yuxi are much lower than those in other 17 Chinese cities [56], we did not control for the potential confounding effects by air pollution due to the unavailability of the complete pollution data in the study area.

5. Conclusions

Our study conducted in a high plateau city in southwest China found that most of the death burden attributable to cold temperature. Our study may have implications for both the research domain and public health policy arena, which may help policymakers develop intervention strategies to minimize the health effects due to adverse temperatures and predict the climate-change impact in this region. Local residents, especially the vulnerable populations such as older people and farmers, need to strengthen their awareness of cold exposure, such as the adaptation of houses (e.g., using the air conditioning systems), spending less time outdoors or wearing more clothing when the temperature drops.

Declarations

Contributors: Q.Y.Z., Z.D., and C.Y.D. conceived and designed the experiments. L.J.L. and Y.F.W. provide primary data. P.G., S.Y.Y., J.L., Y.W., and C.Y.D. collected and cleaned the data. C.Y.D. analyzed the data and drafted the manuscript. Q.Y.Z., Z.D., and C.Y.D. revised the manuscript and interpreted the results. All authors read and approved the final manuscript.

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Table 1. Daily total non-accidental mortality and by specific causes and individual characteristics in Yuxi, China, 2009–2016.

	Total deaths	Min	Median (25th, 75th)	Max	Mean (SD)
Total non-accidental	89,467	12	32 (28, 38)	72	33.0 (7.8)
Cause-specific					
Cardiovascular	41,794	2	15 (12, 18)	37	15.4 (4.9)
Heart	17,793	0	6 (4, 8)	22	6.6 (3.0)
Stroke	22,589	0	8 (6, 10)	22	8.3 (3.3)
Respiratory	16,565	0	6 (4, 8)	21	6.1 (3.1)
Age, years					
≤64	21,678	1	8 (6, 10)	19	8.0 (2.9)
65–74	20,072	0	7 (5, 9)	19	7.4 (2.9)
≥75	47,717	4	17 (14, 21)	43	17.6 (5.6)
Gender					
Male	48,939	5	18 (14, 21)	43	18.1 (5.2)
Female	40,528	2	15 (12, 18)	36	15.0 (4.5)
Occupation					
Farmer	68,278	0	7 (5, 10)	33	7.8 (3.4)
Non-farmer	21,189	7	25 (20, 30)	57	25.2 (7.0)
Ethnic					
Han nationality	63,275	6	23 (19, 27)	54	23.4 (6.4)
Ethnic minorities	26,192	0	9 (7, 12)	24	9.7 (3.6)
Marital status					
Married	54,971	1	12 (10, 15)	32	12.7 (4.3)
Non-married	34,496	4	20 (16, 24)	49	20.3 (5.5)

Min, minimum; Max maximum; 25th, 25th percentile of the distributions; 75th, 75th percentile of the distributions.

Table 2. Attributable fraction (%) of total non-accidental mortality and by specific causes and individual characteristics due to mean daily temperature and cold and heat over lag 0–28 days in Yuxi, China.

	Total (%)	Cold (%)	Heat (%)
Total non-accidental	**4.75 (2.33, 6.79)**	**4.08 (0.86, 7.12)**	0.67 (-2.44, 3.64)
Cause-specific			
Cardiovascular	**5.97 (2.74, 8.74)**	**6.18 (1.89, 10.31)**	-0.21 (-5.04, 4.33)
Heart	5.25 (-0.40, 9.57)	6.48 (-0.70, 12.47)	-1.23 (-8.59, 5.46)
Stroke	**6.50 (2.22, 10.16)**	6.01 (-0.11, 11.41)	0.49 (-6.18, 6.15)
Respiratory	5.42 (-0.73, 9.71)	3.50 (-5.05, 10.95)	1.93 (-5.08, 7.90)
Age, years			
≤64	1.83 (-3.15, 5.95)	1.75 (-4.64, 7.10)	0.08 (-6.64, 5.64)
65–74	2.27 (-2.45, 6.30)	3.52 (-3.45, 9.37)	-1.25 (-7.4, 5.01)
≥75	**6.87 (3.68, 9.46)**	**5.34 (0.44, 9.38)**	1.53 (-2.96, 5.09)
Gender			
Male	**4.16 (0.82, 7.04)**	3.67 (-0.50, 7.72)	0.49 (-3.82, 4.31)
Female	**5.54 (2.18, 8.31)**	**4.66 (0.03, 9.07)**	0.89 (-3.21, 5.03)
Occupation			
Farmer	**5.66 (3.09, 7.92)**	**4.93 (1.28, 8.37)**	0.73 (-2.7, 3.87)
Non-farmer	1.75 (-3.58, 6.11)	1.24 (-5.77, 7.61)	0.52 (-6.82, 6.55)
Ethnic			
Han nationality	**5.38 (2.44, 7.96)**	2.79 (-1.30, 6.49)	2.59 (-0.92, 5.80)
Ethnic minorities	2.31 (-1.57, 6.76)	**6.55 (1.15, 11.75)**	-4.24 (-10.8, 1.27)
Marital status			
Married	**4.24 (1.17, 6.99)**	2.74 (-1.87, 6.53)	1.50 (-2.67, 4.83)
Non-married	**5.48 (1.69, 8.56)**	**6.10 (1.23, 10.21)**	-0.61 (-5.55, 3.95)

Results are expressed as attributable fractions (95% empirical confidence intervals), and the bold indicates a statistically significant.

Table 3. Mortality fraction (%) attributable to extreme and mild cold and mild and extreme heat by specific causes and individual characteristics.

	Extreme cold (%)	Mild cold (%)	Mild heat (%)	Extreme heat (%)
Total non-accidental	**1.17 (0.58, 1.69)**	3.06 (-0.08, 5.94)	0.57 (-2.36, 3.28)	0.12 (-0.26, 0.45)
Cause-specific				
Cardiovascular	**1.57 (0.81, 2.36)**	**4.88 (0.55, 8.60)**	-0.24 (-4.55, 3.40)	0.03 (-0.50, 0.51)
Heart	**1.49 (0.23, 2.58)**	5.25 (-1.37, 10.84)	-1.17 (-7.78, 4.53)	-0.08 (-0.87, 0.64)
Stroke	**1.63 (0.60, 2.65)**	4.65 (-1.05, 9.49)	0.38 (-5.22, 5.28)	0.13 (-0.59, 0.78)
Respiratory	1.35 (-0.15, 2.72)	2.28 (-5.64, 9.11)	1.70 (-4.01, 6.68)	0.26 (-0.48, 0.91)
Age, years				
≤64	0.44 (-0.63, 1.43)	1.34 (-4.52, 6.30)	0.06 (-5.58, 5.56)	0.02 (-0.70, 0.72)
65–74	0.68 (-0.37, 1.72)	2.91 (-3.72, 8.51)	-1.14 (-7.03, 4.22)	-0.12 (-0.83, 0.61)
≥75	**1.71 (0.91, 2.48)**	3.89 (-0.36, 7.66)	1.32 (-2.38, 4.64)	0.24 (-0.22, 0.68)
Gender				
Male	**1.02 (0.28, 1.74)**	2.76 (-1.08, 6.27)	0.41 (-3.25, 3.87)	0.09 (-0.40, 0.53)
Female	**1.36 (0.55, 2.15)**	3.48 (-0.77, 7.36)	0.76 (-3.26, 4.20)	0.15 (-0.37, 0.62)
Occupation				
Farmer	**1.42 (0.82, 2.04)**	**3.71 (0.38, 6.70)**	0.61 (-2.47, 3.39)	0.13 (-0.27, 0.52)
Non-farmer	0.39 (-0.73, 1.41)	0.84 (-5.98, 6.43)	0.45 (-6.15, 5.95)	0.07 (-0.65, 0.74)
Ethnic				
Han nationality	**1.22 (0.54, 1.91)**	1.69 (-2.20, 5.31)	2.30 (-0.73, 5.42)	0.34 (-0.06, 0.76)
Ethnic minorities	**1.03 (0.07, 1.93)**	**5.71 (0.91, 9.74)**	-3.84 (-9.8, 1.12)	-0.43 (-1.12, 0.25)
Marital status				
Married	**0.98 (0.26, 1.66)**	1.86 (-2.06, 5.17)	1.32 (-2.17, 4.62)	0.21 (-0.24, 0.61)
Non-married	**1.47 (0.59, 2.25)**	**4.88 (0.19, 9.18)**	-0.60 (-5.16, 3.37)	-0.02 (-0.58, 0.50)

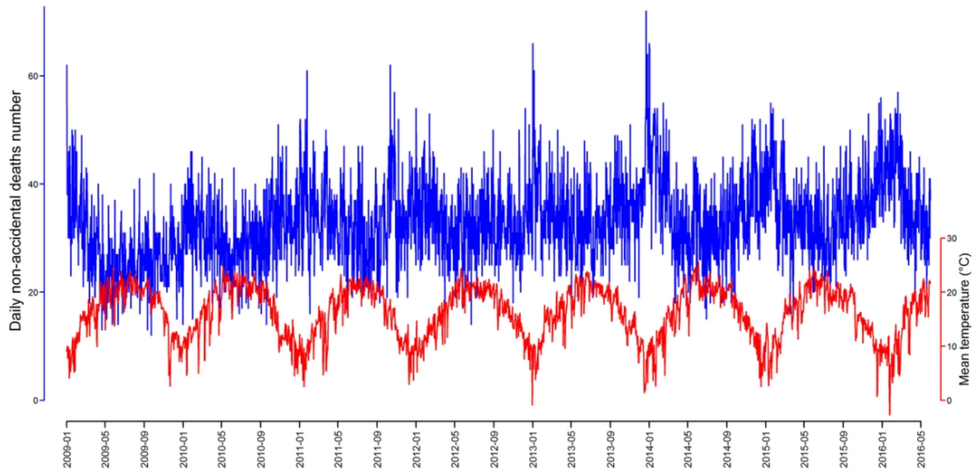
Results are expressed as attributable fractions (95% empirical confidence intervals), and the bold indicates a statistically significant.

Figure Legends

Figure 1. Time series of daily number of non-accidental deaths of Yuxi and mean temperature, 2009–2016.

Figure 2. Overall cumulative relative risk (with 95% empirical confidence intervals, shaded grey) at a lag of 0–28 days in Yuxi, China, with histogram of daily temperature distribution. The dotted lines are the median of the mean temperature, and the dashed lines are the 2.5th and 97.5th percentiles of the distribution of mean temperature. The lines before and after the dotted lines represent the exposure response below (blue lines) and above (red lines) the median of mean temperature.

Figure 3. Daily number of total non-accidental deaths attributable to cold (blue points) and heat (red points).



Time series of daily number of non-accidental deaths of Yuxi and mean temperature, 2009–2016

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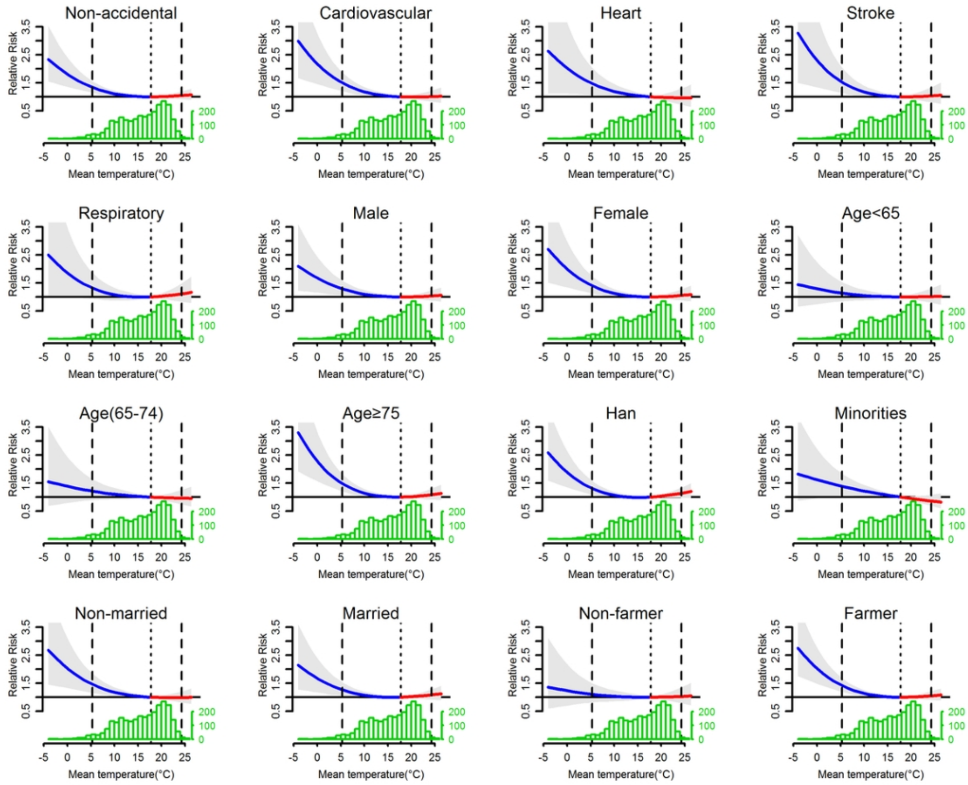
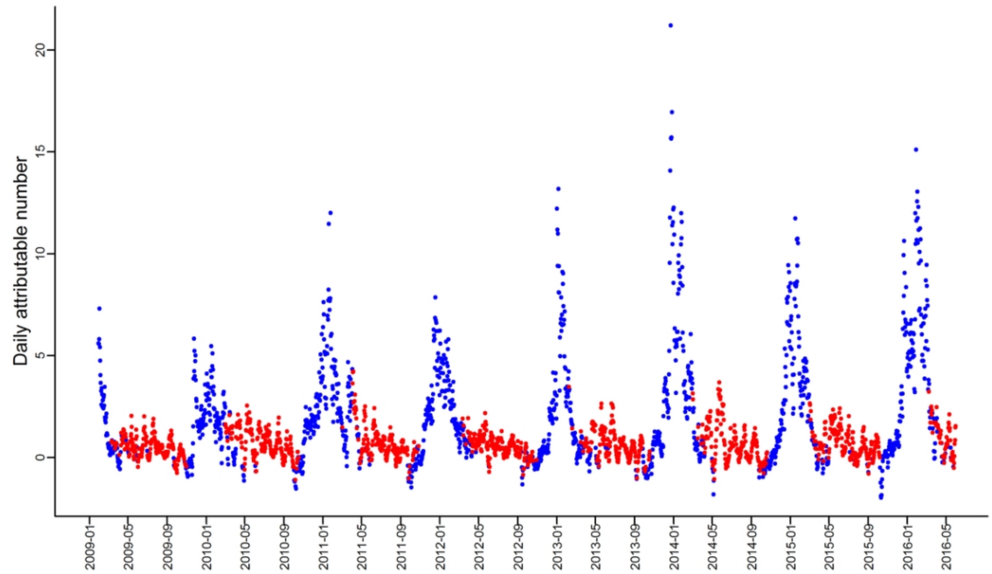


Overall cumulative relative risk (with 95% empirical confidence intervals, shaded grey) at a lag of 0–28 days in Yuxi, China, with histogram of daily temperature distribution. The dotted lines are the median of the mean temperature, and the dashed lines are the 2.5th and 97.5th percentiles of the distribution of mean temperature. The lines before and after the dotted lines represent the exposure response below (blue lines) and above (red lines) the median of mean temperature

101x81mm (300 x 300 DPI)



Daily number of total non-accidental deaths attributable to cold (blue points) and heat (red points)

101x60mm (300 x 300 DPI)

Supplemental materials

Table S1. Descriptive statistics for weather conditions, 2009–2016.

	Min	25th	Median	75th	Max	Mean (SD)
Mean temperature (℃)	-3.3	12.3	17.0	20.2	25.6	16.1±4.9
Relative humidity (%)	25.0	58.0	71.0	78.0	95.0	67.3±14.7
Atmospheric pressure (hPa)	802.7	807.9	810.1	812.5	822.2	810.3±3.2
Wind speed (m/s)	0.5	1.9	2.5	3.2	8.6	2.7±1.1
Sunshine duration (h)	0	3.1	7.6	9.9	12.9	6.5±3.9

Table S2. Attributable number of non-accidental deaths and specific categories due to daily mean temperature, computed as total and as separated components for cold and heat temperatures over lag 0–28 days in Yuxi, China.

	Total	Cold	Heat
Total non-accidental	**4131 (2306, 5937)**	**3482 (552, 5980)**	652 (-2049, 3185)
Cause-specific			
Cardiovascular	**2419 (2622, 7476)**	**2489 (629, 4141)**	-68 (-2019, 1701)
Heart	**912 (446, 8413)**	1112 (-98, 2200)	-199 (-1456, 918)
Stroke	**1417 (2055, 8814)**	**1306 (104, 2634)**	113 (-1178, 1283)
Respiratory	854 (-428, 8228)	540 (-846, 1689)	314 (-822, 1190)
Age, years			
≤64	414 (-2421, 5413)	359 (-976, 1580)	55 (-1384, 1237)
65-74	470 (-2366, 5715)	679 (-764, 1853)	-209 (-1543, 953)
≥75	**3137 (3094, 7816)**	**2431 (102, 4392)**	710 (-1135, 2532)
Gender			
Male	**1977 (818, 5961)**	1706 (-395, 3697)	273 (-1668, 2048)
Female	**2181 (1691, 7074)**	1802 (-59, 3390)	380 (-1355, 1919)
Occupation			
Farmer	**3752 (2730, 6784)**	**3225 (801, 5403)**	530 (-1799, 2580)
Non-farmer	364 (-2842, 5120)	242 (-1320, 1486)	124 (-1293, 1350)
Ethnic			
Han nationality	**3243 (2237, 6688)**	1624 (-972, 4023)	1618 (-622, 3621)
Ethnic minorities	649 (-1165, 5773)	**1685 (332, 2934)**	-1037 (-2677, 488)
Marital status			
Married	**2262 (1118, 5804)**	1402 (-833, 3564)	860 (-1201, 2875)
Non-married	**1843 (1892, 7386)**	**2042 (334, 3527)**	-197 (-1963, 1218)

Results are expressed as attributable number (95% empirical confidence interval), and the bold indicates a statistically significant.

Table S3. Mortality number attributable to extreme and mild cold and mild and extreme heat by specific causes and individual characteristics

	Extreme cold	Mild cold	Mild heat	Extreme heat
Total non-accidental	**1054 (604, 1530)**	2556 (-117, 5016)	554 (-1930, 2984)	108 (-199, 395)
Cause-specific				
Cardiovascular	**657 (331, 946)**	**1942 (183, 3532)**	-84 (-1803, 1505)	15 (-191, 217)
Heart	**264 (72, 445)**	892 (-146, 1896)	-190 (-1385, 830)	-13 (-154, 109)
Stroke	**368 (136, 600)**	997 (-345, 2170)	87 (-1095, 1183)	28 (-129, 169)
Respiratory	223 (-30, 434)	337 (-1005, 1413)	277 (-643, 1006)	42 (-89, 161)
Age, years				
≤64	101 (-135, 308)	265 (-1039, 1292)	46 (-1121, 1094)	10 (-135, 149)
65-74	140 (-75, 331)	554 (-685, 1578)	-192 (-1434, 971)	-20 (-181, 116)
≥75	**814 (431, 1152)**	1732 (-123, 3465)	612 (-1103, 2097)	110 (-99, 313)
Gender				
Male	**503 (118, 851)**	1257 (-681, 3097)	229 (-1651, 1917)	47 (-153, 264)
Female	**556 (238, 882)**	1321 (-483, 2860)	325 (-1203, 1755)	61 (-134, 248)
Occupation				
Farmer	**977 (564, 1376)**	**2382 (27, 4440)**	446 (-1638, 2333)	92 (-173, 349)
Non-farmer	83 (-125, 295)	158 (-1263, 1389)	109 (-1137, 1255)	16 (-128, 158)
Ethnic				
Han nationality	**772 (364, 1191)**	918 (-1565, 3045)	1440 (-488, 3387)	209 (-57, 433)
Ethnic minorities	274 (-1, 500)	**1462 (162, 2576)**	-941 (-2416, 330)	-104 (-277, 62)
Marital status				
Married	**544 (165, 908)**	908 (-1292, 2815)	759 (-995, 2607)	117 (-125, 344)
Non-married	**509 (219, 781)**	**1615 (4, 3017)**	-192 (-1730, 1143)	-7 (-198, 158)

Results are expressed as attributable number (95% empirical confidence interval), and the bold indicates a statistically significant.

Table S4 Sensitivity analyses to calculate the fraction (%) with 95% empirical confidence interval attributable to temperature by changing maximum lag for mean temperature and degrees of freedom (*df*) for covariates

Model choices	Total	Cold	Heat
Lag period, days			
7	2.85 (1.62, 3.99)	0.97 (-1.16, 2.98)	1.88 (0.32, 3.31)
14	4.15 (2.78, 5.52)	2.90 (0.59, 5.15)	1.25 (-0.48, 2.93)
21	3.57 (1.51, 5.31)	3.10 (0.25, 5.76)	0.47 (-1.99, 2.89)
Df for time per year			
5	4.69 (3.10, 6.15)	4.19 (1.18, 6.73)	0.51 (-1.66, 2.81)
6	5.94 (4.07, 7.53)	4.96 (2.18, 7.72)	0.98 (-1.68, 3.49)
8	3.82 (0.92, 6.42)	4.72 (1.23, 8.07)	-0.90 (-4.31, 2.26)
9	5.07 (2.15, 7.75)	4.59 (0.57, 8.16)	0.48 (-2.98, 3.75)
Df for relative humidity			
2	4.64 (2.21, 6.83)	4.07 (0.84, 7.28)	0.57 (-2.70, 3.56)
4	4.74 (2.31, 6.88)	4.05 (0.56, 7.26)	0.69 (-2.15, 3.83)
5	4.79 (2.55, 6.92)	4.20 (1.06, 7.20)	0.60 (-2.76, 3.36)
Df for sunshine duration			
2	4.71 (2.27, 6.84)	4.18 (0.88, 7.35)	0.54 (-2.89, 3.51)
4	4.75 (2.39, 6.95)	4.08 (0.92, 7.03)	0.67 (-2.51, 3.65)
5	4.78 (2.44, 6.90)	4.13 (0.69, 7.45)	0.65 (-2.40, 3.63)
Df for atmospheric pressure			
2	4.76 (2.24, 6.87)	4.15 (0.76, 7.00)	0.62 (-2.69, 3.49)
4	4.75 (2.21, 6.97)	4.09 (0.39, 6.95)	0.67 (-2.49, 3.76)
5	4.79 (2.38, 6.95)	4.02 (1.01, 7.08)	0.77 (-2.30, 3.98)
Df for wind speed			
2	4.79 (2.26, 6.90)	4.02 (0.47, 6.88)	0.78 (-2.34, 3.52)
4	4.68 (2.34, 6.78)	4.02 (0.60, 7.07)	0.67 (-2.48, 3.68)
5	4.66 (2.31, 6.85)	4.04 (0.90, 6.94)	0.62 (-2.56, 3.75)

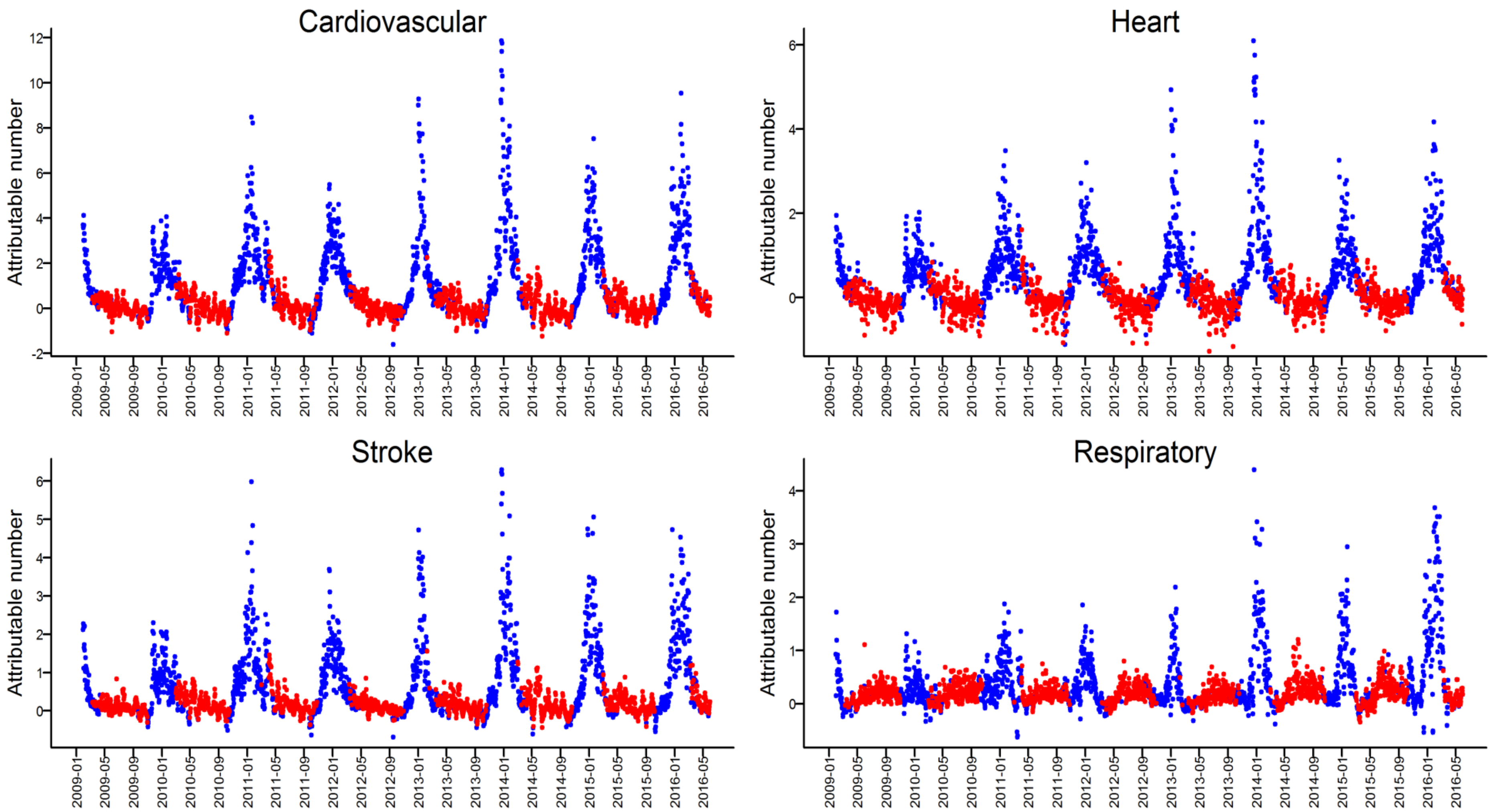


Figure S1. Daily number of cardiovascular, heart, stroke and respiratory deaths attributable to cold (blue points) and heat (red points) temperatures.

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Burden of non-accidental mortality attributable to ambient temperatures: a time-series study in a high plateau area of southwest China

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Burden of non-accidental mortality attributable to ambient temperatures: a time-series study in a high plateau area of southwest China

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Abstract

Objective: To examine the total non-accidental mortality burden attributable to ambient temperatures and assess the effect modification of the burden by specific causes of death and individual characteristics in a high plateau area in southwest China.

Methods: Using daily mortality and meteorological data from 2009 to 2016, we applied a quasi-Poisson model combined with a distributed lag non-linear model to estimate the temperature–mortality association with the assessment of attributable fraction and number. We calculated attributable fractions and deaths with 95% empirical confidence intervals (eCIs), that were due to cold and heat, defined as temperatures below and above the median temperature, and for mild and extreme temperatures, defined by cutoffs at the 2.5th and 97.5th temperature percentiles.

Results: We analyzed 89,467 non-accidental deaths; 4,131 were attributable to overall temperatures, with an attributable fraction of 4.75% (95% eCI 2.33, 6.79). Most of the mortality burden was caused by cold (4.08%; 0.86, 7.12), while the burden due to heat was low and non-significant (0.67%; -2.44, 3.64). Extreme cold (1.17%; 0.58, 1.69) was responsible for 24.6% (i.e., 1.17% divided by 4.75%) of the total death burden. In the stratification analyses, attributable risk due to cold was higher for cardiovascular than respiratory disease (6.18% vs 3.50%). We found a trend of risk of increased death due to ambient temperatures with increasing age, with attributable fractions of 1.83%, 2.27%, and 6.87% for age ≤64, 65 - 74, and ≥75 years old. The cold-related burden was slightly greater for females, farmers, ethnic minorities, and non-married individuals than their corresponding categories.

Conclusions: Most of the burden of death was attributable to cold, and specific causes and individual characteristics might modify the mortality burden attributable to ambient temperatures. The results may help make prevention measures to confront climate change for susceptible population in this region.

Key words: ambient temperatures; attributable fraction; attributable number; mortality; effect modification

Strengths and limitations of this study

- Mortality burden attributable to ambient temperature was assessed in a high plateau city in southwest China.

- To our knowledge, this study evaluated the mortality burden attributable to ambient temperature, and quantified its effect modification by national minority and occupation for the first time.
- The data only come from one city, so it should be cautious to generalize the findings to other geographic areas or climates.
- We used the data on temperature from monitoring sites rather than measuring individual exposure, which may bring about measurement errors.

1. Introduction

With the global climate change, ambient temperatures has been extensively demonstrated to directly affect human health (e.g., daily morbidity and mortality) and has become one of the most severe public health problems in the world.[1-5] Exposure to extreme weather such as cold spells and heat waves represents high risk for mortality, and the extreme temperature-related mortality is expected to increase with the increasing frequency, intensity, and duration of extreme weather events.[4,6-8] Low and high temperatures are also well known to be associated with a substantial increase in a wide range of all-cause and cause-specific mortality (e.g., cardiovascular and respiratory diseases).[6,9-12]

Numerous epidemiological studies have widely used ratio measures (e.g., odds ratio, relative ratio, or rate ratio) to quantify the relationships between ambient temperatures and human health, but these offer limited information on the excess burden and actual impact of ambient temperatures.[13-16] Relative excess measures (e.g., attributable fraction) and absolute excess measures (e.g., attributable number), calculated on the basis of the estimated relative risk, have been pointed out to provide better scientific evidence for estimating the potential benefits of preventative measures, public health interventions, and resource allocation.[11,17,18] The attributable fraction and number represent the fraction and number of cases or deaths from a cause-specific disease that would be prevented without exposure to a specific risk factor, which has important implications for policy making and the potential impact of interventions.[19-21]

Use of risk assessment of the attributable fraction revealed the burden of mortality associated with ambient temperatures; however, most previous literatures estimated the mortality burden in high-income or low-altitude regions or coastlands,[11,17,20,22-24] and few were conducted in high plateau areas of developing countries.[12,25] The attributable fraction and number for the temperature–mortality association may vary by geographic features, climate, and structure of the population.[25,26] In addition, age, gender, educational attainment, and specific causes were previously identified as modifiers for estimating the effect modification of the mortality risk attributable to ambient temperatures.[27-31] However, few researchers have focused on the potential effect modification of the mortality burden by occupation, race/ethnicity, or marital status.[32]

Yuxi city is located in a high-altitude area in southwest China and experiences a unique, subtropical, plateau monsoon climate. More than 70% of indigenous people in this multi-ethnic region engage in agricultural production. The aim of this current ecological dissertation in Yuxi was to quantify the burden of non-accidental mortality attributable to ambient temperatures. We aimed to separate the contribution of temperature to mortality by heat and cold and mild and extreme temperatures by using attributable fraction and number, based on a proposed framework of attributable risk assessment within a distributed lag non-linear model (DLNM). A more in-depth purpose was to comprehensively assess the effect modification of the non-accidental mortality burden attributable to ambient temperatures by specific mortality causes (i.e., cardiovascular, heart, stroke, and respiratory diseases) and individual characteristics (i.e., age, gender, occupation, ethnicity, and marital status).

2. Methods

2.1 Study site

Located on the western edge of the Yunnan-Guizhou Plateau of southwest China, the Yuxi city area has complicated geographic features of mountains, valleys, plateaus, and basins. With an average altitude of about 2000m and 4 spring-like seasons, this area has a unique, subtropical, plateau monsoon climate, showing diversified climates with low atmospheric pressure, thin and dry air, and a stable daily mean temperature but large temperature difference between day and night, morning or evening and daytime, indoor and outdoor. From the national population census in 2010, the permanent population is about 2.3 billion, and residents of ethnic minorities (e.g., Dai, Hui, Yi, Hani, and Mongolian minorities) account for 32.27% of the total population.

2.2 Data collection

Individual records such as age of death, gender, ethnicity, occupation, marital status, cause of death, and date of death for all registered deaths for the period January 1, 2009 to May 31, 2016, were obtained from the Yuxi Center for Disease Control and Prevention, which maintains detailed quality assurance and control measures[33,34]. The underlying causes of death were classified by medical personnel, and examination procedures were routinely performed to ensure accurate data, based on the *International Classification of Diseases*, 10th revision (ICD-10). Individual data were collapsed into a series of daily counts for the total non-accidental mortality (ICD-10 A00–R99) as well as subcategories by specific cause of death (cardiovascular [I00–I99], heart [I00–I51], stroke [I60–I69], and respiratory disease [J00–J99]), age (0–64, 65–74, and 75+ years old), gender (male and female), occupation (farmer and non-farmer), ethnicity (Han nationality and ethnic minorities), and marital status (married and non-married). Daily meteorological data for the same period were obtained from the China Meteorological Data Sharing System, including mean temperature and 4 other meteorological variables (atmospheric pressure, wind speed, sunshine duration, and relative humidity).

2.3 Patient and public involvement

This study is based on daily death number data, which could be obtained from Yuxi Center for Disease Control and Prevention without referral and free of charge. There was no patient and decedent involvement in the presented study.

2.4 Statistical analysis

As daily death number under a Poisson distribution and risk of mortality depend on exposure to temperatures of the current and previous days,[25] we applied a standard time-series quasi-Poisson regression model combined with DLNM to estimate the non-linear and lag effects of mean temperature on mortality, with day of the week, long-term trends, and the 4 other meteorological variables as potential covariates. This model can capture the complex non-linear relation and lagged effect by combining 2 functions that define the conventional exposure–response association and the additional lag–response association. The maximum lag period was set to 28 days to explore the lag structure of temperature effect, and median temperature (17.0℃) was the reference to calculate attributable risk.[32] We used natural cubic splines with 7 degrees of freedom (*df*) per year for time to describe the long-term trends and seasonality and 3 *df* for the 4 other meteorological indicators. These model specifications were consistent with previous studies.[24,35]

The total mortality burden attributable to non-reference temperatures can be assessed in terms of fraction and number of deaths, and the attributable number can be obtained from the sum of the contributions from all days in the series; its ratio with total number of deaths produces the total attributable fraction.[19] The overall cumulative relative risk corresponding to each day's temperature was used to compute the attributable fraction and number:

$$AF_{x,t} = 1 - \exp\left(-\sum_{l=l_0}^{L} \beta_{x_{t-l},l}\right)$$

$$AN_{x,t} = AF_{x,t} \times n_t$$

where $AF_{x,t}$ and $AD_{x,t}$ are the attributable fraction and the number of cases at day *t* (1,2,3…2907), respectively; β_x is the risk associated with the exposure to ambient temperatures at level x (i.e., $\beta_x = (x - Ref) \times \beta$; *Ref* is the referenced temperature; β is the coefficient for DLNM of mean temperature; *L* is the maximum lag for the effect of mean temperature; and n_t is the observed number of deaths at day *t*.

To estimate the mortality burden from non-accidental deaths, we calculated the total attributable fraction due to the overall temperatures and divided the total effect into exposure to low and high temperatures by summing the subsets corresponding to days with temperatures below and above the median temperature. Also, we explored the mortality burden attributable to mild and extreme temperatures. Extreme cold and heat were defined as temperatures below the 2.5th percentile (5.4°C) and above the 97.5th percentile (23.1°C) of mean temperature, and mild cold and heat were defined as the range between the median temperature and these cutoffs. Monte-Carlo simulations were used to calculate the empirical confidence intervals (eCIs) of the attributable fraction and number, assuming a multivariate normal distribution of the best linear unbiased predictions of the deduced coefficients[19,36]. All statistical analyses involved use of R v3.0.3, with the "dlnm" package to create the DLNM for mean temperature.

3. Results

3.1 Descriptive statistics

We analyzed 89,467 non-accidental deaths from Yuxi between 2009 and 2016, with an average of 33 deaths per day (range 12 to 72). The number of deaths due to cardiovascular disease was 41,794 (46.7%), more than half due to stroke; the proportion due to respiratory disease was 18.5% (Table 1). In individual characteristics subgroup, a higher proportion of deaths were for males, older people (≥75 years), people with Han nationality, farmers and married people than their corresponding categories. During the study period, the mean daily temperature was 16.1 °C (ranging from -3.3 to 25.6 °C) (Table S1). The daily number of non-accidental deaths and mean temperature showed an inverse relation (Figure 1).

3.2 Exposure–response association

The overall effect of mean temperature on mortality (i.e., the total non-accidental deaths and by specified causes and individual characteristics) for lag 0–28 days and mean daily temperature distribution are presented in Figure 2. In general, the temperature–mortality associations were nonlinear and followed slide-shaped curves: the risks due to heat (both mild and extreme) were low and changed slightly (approximately 1), whereas the risks due to mild cold and especially extreme cold were increased. The relative risks rapidly increased with decreasing mean temperature. The distribution of mean daily temperature was skewed to the left.

3.3 Attributable fraction and number

Table 2 shows the estimated attributable fraction with 95% eCIs of daily non-accidental mortality calculated for total and separate components by heat and cold temperatures. For total non-accidental deaths, the attributable fraction was 4.75% (95% eCI 2.33, 6.79) with the whole temperature range, including heat and cold. Cold temperature was responsible for most of the mortality burden, corresponding to an attributable risk of 4.08% (0.86, 7.12), whereas the burden due to heat was low and non-significant (0.67%; -2.44, 3.64). The attributable risks of cardiovascular and stroke deaths caused by overall temperatures were 5.97% (2.74, 8.74) and 6.50% (2.22, 10.16); the point-estimated risk due to cold was higher for cardiovascular than respiratory deaths (6.18% *vs* 3.50%).

On stratification by age, the attributable risk due to ambient temperatures increased with age, with attributable fractions of 1.83%, 2.27%, and 6.87% for age ≤64, 65–74, and ≥75 years, respectively. Those engaged in agriculture had higher attributable fraction, 3.23 times (5.66% vs 1.75%) due to the overall temperatures and 3.98 times (4.93% vs 1.24%) due to cold, than non-farmers. The estimated burden due

to cold was 2.35-fold higher for ethnic minorities than Han nationality (6.55% *vs* 2.79%), whereas the point-estimated attributable fraction caused by the whole temperature range was approximately equal by gender and marital status.

Table 3 displays the estimated mortality fraction attributable to overall temperatures, separated by mild and extreme temperatures. In general, the risk of non-accidental deaths attributable to extreme cold was 1.17% (0.58, 1.69), accounting for a clearly high proportion of 24.6% of the total mortality burden (4.75%) due to the whole temperature range, whereas attributable risks due to mild cold or heat or extreme heat were non-significant. In the cause-specific analyses, the attributable fractions due to extreme cold were 1.57%, 1.63%, and 1.49% for cardiovascular disease, stroke, and heart disease, with no significant association with respiratory disease. The extreme cold-related burden for older people, females, farmers, and non-married individuals was slightly higher than their corresponding categories.

Table S2 presents the attributable number of deaths due to mean temperature, overall and by cold and heat. An estimated 4,131 non-accidental deaths were due to overall temperatures and 3,482 to cold. Table S3 shows the excess mortality due to extreme and mild cold and mild and extreme heat. Figures 3 and S1 illustrate the daily deaths attributable to cold and heat. The attributable deaths were much larger with cold than heat.

3.4 Sensitivity analysis

Sensitivity analysis to check the stability of our main findings involved changing the maximum lag days (7, 14, and 21) and the *df* of the natural cubic splines for the calendar time (5, 6, 8, and 9 per year) and for the 4 other meteorological variables one by one (2, 4, and 5). The attributable fractions for non-accidental mortality due to overall temperatures were relatively robust with sensitivity analyses (Table S4) and the results by causes of deaths and individual characteristics were robust (results not shown).

4. Discussion

We quantitatively estimated the attributable risks of non-accidental death and subgroups by specific causes and individual characteristics due to the whole temperature range and to extreme and mild cold and mild and extreme heat for 89,467 deaths between 2009 and 2016 in Yuxi, China, a high-altitude region with a unique,

subtropical, plateau monsoon climate. The temperature–mortality associations were nonlinear and followed slide-shaped curves, and the risks rapidly increased with decreasing mean temperature. Excess deaths were attributable to overall temperatures, and cold was responsible for most of the mortality burden. The estimated mortality burden attributable to cold was greater for cardiovascular deaths, older people, farmers, ethnic minorities, and non-married individuals than their corresponding categories.

Inconsistent with previous ecological evidences that the temperature–mortality associations were "U" or "V" shaped curve, with increased mortality risks at extremely low and high temperatures [26,37-39], a slide-shaped curve was captured in our study, which shows increased relative risk with low temperature, especially extreme cold but the risk of high temperature changed minimally. The different pattern of temperature–mortality associations might attribute to the unique climate in this high-altitude region. Yuxi city has a distinct subtropical plateau monsoon climate, with four spring-like seasons year round, giving the city a stable daily mean temperature but large temperature difference between day and night, morning or evening and daytime, indoor and outdoor. Although the city has a stable daily mean temperature of 16.1 ± 4.9°C full year, the daily diurnal temperature range was averaging 10.4°C (ranging from 1.1°C to 21.7°C). Furthermore, We also examined additional non-accidental deaths attributable to ambient temperatures, with larger burden due to cold than heat. A multi-country observational study estimated a total mortality burden of death attributable to non-optimal ambient temperatures; the attributable fraction ranged from 3.37% in Thailand to 11% in China, which provides strong evidence for substantial differences between regions or climates.[17]

The cold-related mortality burden is an important public health problem in Yuxi. Findings from our study showed most of the death burden attributable to low temperature, and a much lower and non-significant burden due to heat, which might be owing to unique climatic condition that the differences between minimum and referent temperature was 20.3°C (-3.3°C vs 17.0°C), while those between referent and maximum temperature was 8.6°C (17.0°C vs 25.6°C). Previous studies have found that most of the mortality burden is caused by exposure to cold days, with comparatively lower attributable risk, or even none, due to heat exposure. For example, Hajat et al. (2006) showed that all-cause mortality attributable to heat ranged from 0.37% in London (1976–2003) to 1.45% in Milan (1985–2002), and another study conducted in London from 1986 to 1996 found that attributable fraction of mortality for each 1°C decrease below a threshold of 15°C was 5.42% (4.13, 6.69), with no burden due to heat.[40] Although extremely low or high temperature corresponded to increased relative risk of mortality, Gasparrini et al. (2015) found a relatively small part of the death burden attributable to extreme cold temperature, ranging from 0.25% to 1.06%. Similar results from 5 East Asian regions showed a 9.36% mortality burden attributable to overall temperatures, with only 0.80% due to extreme cold [20]. However, our current study estimated a larger proportion of attributable mortality fraction due to extreme cold, accounting for about one-quarter of the total mortality burden (1.17% *vs* 4.75%), even though extreme cold days represented only 2.5% of the whole study period. We found no evidence of additional deaths due to extreme heat in all categories.

Exposure to low temperature has been widely demonstrated to be strongly associated with excess cardiovascular and respiratory deaths,[20,31,41,42] and the biological processes that underlie cold-related mortality are associated with cardio-respiratory disease.[11,17,31,43] We found a higher point-estimated attributable risk caused by cold for cardiovascular than respiratory disease deaths. A multi-city study including 15 Chinese megacities also identified 15.8% of the cardiovascular mortality burden due to cold days.[26] The increased cold-related cardiovascular deaths mainly involved changes in vascular tone, autonomic nervous system response, arrhythmia, and oxidative stress.[44-46] Although we found no evidence for excess burden of respiratory deaths due to cold or heat, other reports have described increased respiratory deaths attributable to ambient temperatures.[10,47] For heart and stroke, the burden of mortality was attributable to only extreme cold, with approximately equivalent values, and other studies found excess heart and stroke deaths attributable to low and/or high temperatures.[24,27,41,48]

Age has been frequently identified as an important modifier of the association between ambient temperatures and human health.[15,26,30,49] We found that exposure to cold, particularly extreme cold, was closely related to increased death burden for older than younger people. Several previous surveys found increased age associated with point-estimated attributable risk of cardiovascular mortality and both intra-cerebral hemorrhage and ischemic stroke morbidity due to cold, with the highest values in older people.[26,32] Another nationwide study in Japan found most of the proportion of morbidity burden attributable to days with low temperature in all age groups, with an trend of increasing attributable risk with age: the attributable fraction due to cold was 15.96%, 24.84%, and 28.10% with age 18–64, 65–74, and 75–110 years, respectively.[37] Older people were more vulnerable to the temperature effects, mainly because they often have multiple pre-existing chronic conditions and physiological changes in thermoregulation and homoeostasis.[50,51] However, the effect modification of temperature-related mortality by gender has been identified.[24,30,37,52] We observed a higher mortality burden caused by exposure to the cold period among females than males in Yuxi, and the cold-related attributable risk was found higher for females than males in Hanoi, Vietnam,[53] and in 47 cities in Japan.[37] The reason for the discrepancy in temperature-related burden by gender might be owing to differences in occupational exposure, physiology and thermoregulation.

A survey in Adelaide, South Australia, provided epidemiological evidence for the impact of heat waves on worker health and safety, which implied that personal occupation might modify the temperature–mortality association.[54] Our previous studies (Ding et al., 2016a, 2016b) revealed that farmers were more likely than non-farmers to die on high DTR or cold days, and the present study also showed a higher mortality burden attributable to cold and extreme cold days for farmers than non-farmers. In southwestern China, farmers universally have a poor educational level, disadvantaged socioeconomic status, and low annual income, which may be linked to poor living conditions, malnutrition, and non-access to basic health care. In addition, farmers working in the fields may have more exposure to ambient temperatures, because farming is basically highly related to weather.[55]

A study of 9 cities in California found that with each 10°F (4.7°C) increase in mean temperature, the mortality was increased 4.9%, 2.5%, and 1.8% for Blacks, Whites, and Hispanics, respectively.[30] Also, our previous research demonstrated less risk of high DTR associated with non-accidental mortality for the current day for people of Dai ethnic minority than Han nationality.[13] To our knowledge, no study has estimated the potential effect modification of mortality burden attributable to ambient temperatures by ethnicity. We observed a greater cold- and mild cold-related death for ethnic minorities than Han nationality in Yuxi, which indicated that race/ethnicity may modify the cold-associated mortality burden. We also found lower death burden caused by cold and extreme cold for married people versus those never married, divorced, or widowed, possibly because married people can be cared for by their partners during the cold period.

Our study has some limitations. First, the data were from a single city, so generalizing the findings to other geographic areas or climates should be cautioned. Second, the data of temperature were from monitoring sites rather than exposure measuring of individual. Third, although the concentration of daily mean PM_{10}, NO_2 and SO_2 in Yuxi are much lower than those in other 17 Chinese cities [56], we did not control for the potential confounding effects by air pollution due to the unavailability of the complete pollution data in the study area. Last, in the previous multi-country or multicenter studies [5,26], MMT was reasonably used to assess the temperature–mortality associations due to each site corresponding to a MMT. However, inconsistent with those previous studies, our study only involved one city with median temperature as common referent value, which might lead the results incomparable with previous studies. Sensitive analysis with the MMT as referent temperature showed that all of the results were stable substantially when compared to the results estimated by median temperature. But the MMT differed among the sub-groups, which leaded the incomparable results in one city (Table S5).

5. Conclusions

Our study conducted in a high plateau city in southwest China found that most of the death burden attributable to cold temperature. Our study may have implications for both the research domain and public health policy arena, which may help policymakers develop intervention strategies to minimize the health effects due to adverse temperatures and predict the climate-change impact in this region. Local residents, especially the vulnerable populations such as older people and farmers, need to strengthen their awareness of cold exposure, such as the adaptation of houses (e.g., using the air conditioning systems), spending less time outdoors or wearing more clothing when the temperature drops.

Declarations

Contributors: Q.Y.Z., Z.D., and C.Y.D. conceived and designed the experiments. L.J.L. and Y.F.W. provide primary data. P.G., S.Y.Y., J.L., Y.W., and C.Y.D. collected and cleaned the data. C.Y.D. analyzed the data and drafted the manuscript.

Q.Y.Z., Z.D., and C.Y.D. revised the manuscript and interpreted the results. All authors read and approved the final manuscript.

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Table 1. Daily total non-accidental mortality and by specific causes and individual characteristics in Yuxi, China, 2009–2016.

	Total deaths	Min	Median (25^{th}, 75^{th})	Max	Mean (SD)
Total non-accidental	89,467	12	32 (28, 38)	72	33.0 (7.8)
Cause-specific					
Cardiovascular	41,794	2	15 (12, 18)	37	15.4 (4.9)
Heart	17,793	0	6 (4, 8)	22	6.6 (3.0)
Stroke	22,589	0	8 (6, 10)	22	8.3 (3.3)
Respiratory	16,565	0	6 (4, 8)	21	6.1 (3.1)
Age, years					
≤64	21,678	1	8 (6, 10)	19	8.0 (2.9)
65–74	20,072	0	7 (5, 9)	19	7.4 (2.9)
≥75	47,717	4	17 (14, 21)	43	17.6 (5.6)
Gender					
Male	48,939	5	18 (14, 21)	43	18.1 (5.2)
Female	40,528	2	15 (12, 18)	36	15.0 (4.5)
Occupation					
Farmer	68,278	0	7 (5, 10)	33	7.8 (3.4)
Non-farmer	21,189	7	25 (20, 30)	57	25.2 (7.0)
Ethnic					
Han nationality	63,275	6	23 (19, 27)	54	23.4 (6.4)
Ethnic minorities	26,192	0	9 (7, 12)	24	9.7 (3.6)
Marital status					
Married	54,971	1	12 (10, 15)	32	12.7 (4.3)
Non-married	34,496	4	20 (16, 24)	49	20.3 (5.5)

Min, minimum; Max maximum; 25^{th}, 25^{th} percentile of the distributions; 75^{th}, 75^{th} percentile of the distributions.

Table 2. Attributable fraction (%) of total non-accidental mortality and by specific causes and individual characteristics due to mean daily temperature and cold and heat over lag 0–28 days in Yuxi, China.

	Total (%)	Cold (%)	Heat (%)
Total non-accidental	**4.75 (2.33, 6.79)**	**4.08 (0.86, 7.12)**	0.67 (-2.44, 3.64)
Cause-specific			
Cardiovascular	**5.97 (2.74, 8.74)**	**6.18 (1.89, 10.31)**	-0.21 (-5.04, 4.33)
Heart	5.25 (-0.40, 9.57)	6.48 (-0.70, 12.47)	-1.23 (-8.59, 5.46)
Stroke	**6.50 (2.22, 10.16)**	6.01 (-0.11, 11.41)	0.49 (-6.18, 6.15)
Respiratory	5.42 (-0.73, 9.71)	3.50 (-5.05, 10.95)	1.93 (-5.08, 7.90)
Age, years			
≤64	1.83 (-3.15, 5.95)	1.75 (-4.64, 7.10)	0.08 (-6.64, 5.64)
65–74	2.27 (-2.45, 6.30)	3.52 (-3.45, 9.37)	-1.25 (-7.4, 5.01)
≥75	**6.87 (3.68, 9.46)**	**5.34 (0.44, 9.38)**	1.53 (-2.96, 5.09)
Gender			
Male	**4.16 (0.82, 7.04)**	3.67 (-0.50, 7.72)	0.49 (-3.82, 4.31)
Female	**5.54 (2.18, 8.31)**	**4.66 (0.03, 9.07)**	0.89 (-3.21, 5.03)
Occupation			
Farmer	**5.66 (3.09, 7.92)**	**4.93 (1.28, 8.37)**	0.73 (-2.7, 3.87)
Non-farmer	1.75 (-3.58, 6.11)	1.24 (-5.77, 7.61)	0.52 (-6.82, 6.55)
Ethnic			
Han nationality	**5.38 (2.44, 7.96)**	2.79 (-1.30, 6.49)	2.59 (-0.92, 5.80)
Ethnic minorities	2.31 (-1.57, 6.76)	**6.55 (1.15, 11.75)**	-4.24 (-10.8, 1.27)
Marital status			
Married	**4.24 (1.17, 6.99)**	2.74 (-1.87, 6.53)	1.50 (-2.67, 4.83)
Non-married	**5.48 (1.69, 8.56)**	**6.10 (1.23, 10.21)**	-0.61 (-5.55, 3.95)

Results are expressed as attributable fractions (95% empirical confidence intervals), and the bold indicates a statistically significant.

Table 3. Mortality fraction (%) attributable to extreme and mild cold and mild and extreme heat by specific causes and individual characteristics.

	Extreme cold (%)	Mild cold (%)	Mild heat (%)	Extreme heat (%)
Total non-accidental	**1.17 (0.58, 1.69)**	3.06 (-0.08, 5.94)	0.57 (-2.36, 3.28)	0.12 (-0.26, 0.45)
Cause-specific				
Cardiovascular	**1.57 (0.81, 2.36)**	**4.88 (0.55, 8.60)**	-0.24 (-4.55, 3.40)	0.03 (-0.50, 0.51)
Heart	**1.49 (0.23, 2.58)**	5.25 (-1.37, 10.84)	-1.17 (-7.78, 4.53)	-0.08 (-0.87, 0.64)
Stroke	**1.63 (0.60, 2.65)**	4.65 (-1.05, 9.49)	0.38 (-5.22, 5.28)	0.13 (-0.59, 0.78)
Respiratory	1.35 (-0.15, 2.72)	2.28 (-5.64, 9.11)	1.70 (-4.01, 6.68)	0.26 (-0.48, 0.91)
Age, years				
≤64	0.44 (-0.63, 1.43)	1.34 (-4.52, 6.30)	0.06 (-5.58, 5.56)	0.02 (-0.70, 0.72)
65–74	0.68 (-0.37, 1.72)	2.91 (-3.72, 8.51)	-1.14 (-7.03, 4.22)	-0.12 (-0.83, 0.61)
≥75	**1.71 (0.91, 2.48)**	3.89 (-0.36, 7.66)	1.32 (-2.38, 4.64)	0.24 (-0.22, 0.68)
Gender				
Male	**1.02 (0.28, 1.74)**	2.76 (-1.08, 6.27)	0.41 (-3.25, 3.87)	0.09 (-0.40, 0.53)
Female	**1.36 (0.55, 2.15)**	3.48 (-0.77, 7.36)	0.76 (-3.26, 4.20)	0.15 (-0.37, 0.62)
Occupation				
Farmer	**1.42 (0.82, 2.04)**	**3.71 (0.38, 6.70)**	0.61 (-2.47, 3.39)	0.13 (-0.27, 0.52)
Non-farmer	0.39 (-0.73, 1.41)	0.84 (-5.98, 6.43)	0.45 (-6.15, 5.95)	0.07 (-0.65, 0.74)
Ethnic				
Han nationality	**1.22 (0.54, 1.91)**	1.69 (-2.20, 5.31)	2.30 (-0.73, 5.42)	0.34 (-0.06, 0.76)
Ethnic minorities	**1.03 (0.07, 1.93)**	**5.71 (0.91, 9.74)**	-3.84 (-9.8, 1.12)	-0.43 (-1.12, 0.25)
Marital status				
Married	**0.98 (0.26, 1.66)**	1.86 (-2.06, 5.17)	1.32 (-2.17, 4.62)	0.21 (-0.24, 0.61)
Non-married	**1.47 (0.59, 2.25)**	**4.88 (0.19, 9.18)**	-0.60 (-5.16, 3.37)	-0.02 (-0.58, 0.50)

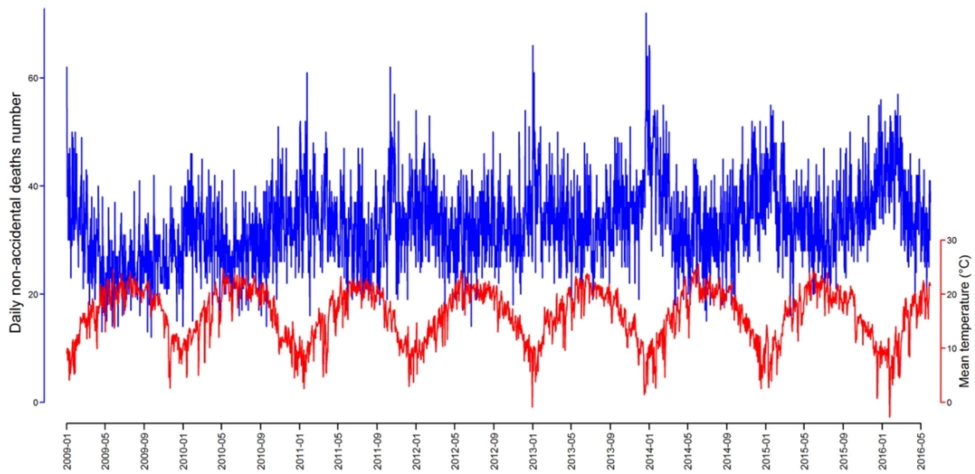
Results are expressed as attributable fractions (95% empirical confidence intervals), and the bold indicates a statistically significant.

Figure Legends

Figure 1. Time series of daily number of non-accidental deaths of Yuxi and mean temperature, 2009–2016.

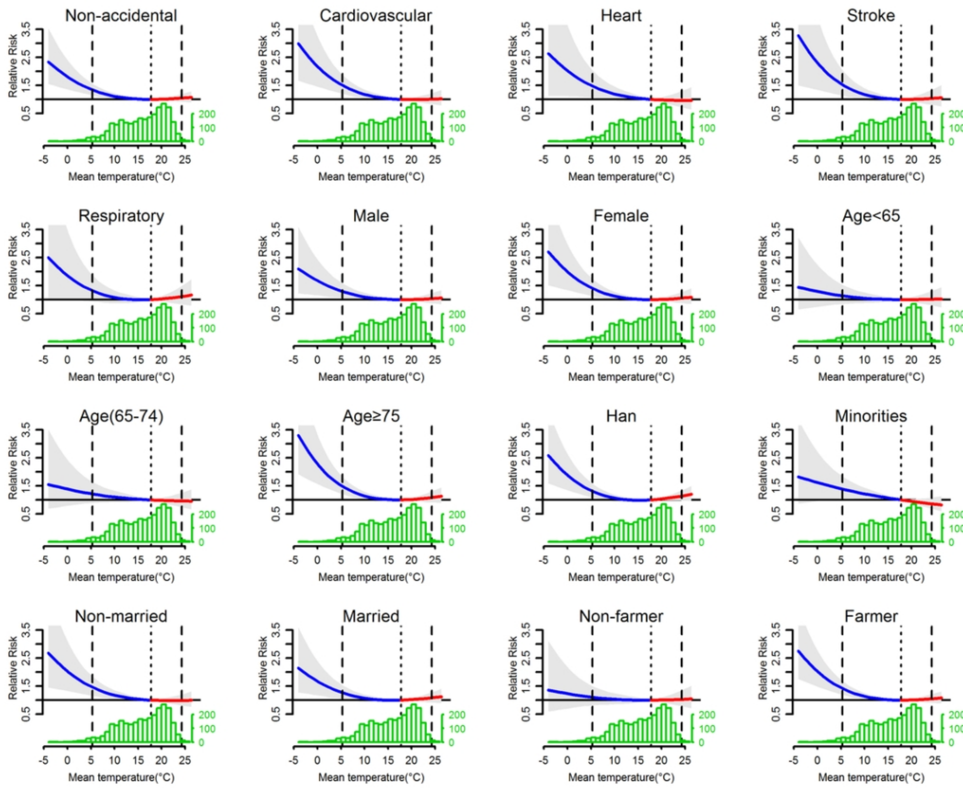
Figure 2. Overall cumulative relative risk (with 95% empirical confidence intervals, shaded grey) at a lag of 0–28 days in Yuxi, China, with histogram of daily temperature distribution. The dotted lines are the median of the mean temperature, and the dashed lines are the 2.5th and 97.5th percentiles of the distribution of mean temperature. The lines before and after the dotted lines represent the exposure response below (blue lines) and above (red lines) the median of mean temperature.

Figure 3. Daily number of total non-accidental deaths attributable to cold (blue points) and heat (red points).



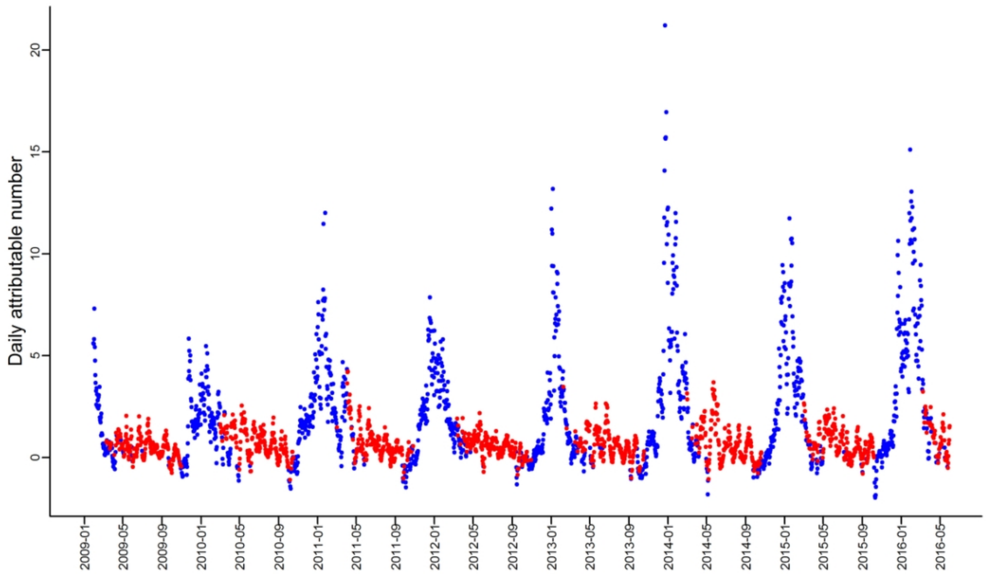
Time series of daily number of non-accidental deaths of Yuxi and mean temperature, 2009–2016

105x52mm (300 x 300 DPI)



Overall cumulative relative risk (with 95% empirical confidence intervals, shaded grey) at a lag of 0–28 days in Yuxi, China, with histogram of daily temperature distribution. The dotted lines are the median of the mean temperature, and the dashed lines are the 2.5th and 97.5th percentiles of the distribution of mean temperature. The lines before and after the dotted lines represent the exposure response below (blue lines) and above (red lines) the median of mean temperature

101x81mm (300 x 300 DPI)



Daily number of total non-accidental deaths attributable to cold (blue points) and heat (red points)

101x60mm (300 x 300 DPI)

Supplemental materials

Table S1. Descriptive statistics for weather conditions, 2009–2016.

	Min	25^{th}	Median	75^{th}	Max	Mean (SD)
Mean temperature (°C)	-3.3	12.3	17.0	20.2	25.6	16.1±4.9
Relative humidity (%)	25.0	58.0	71.0	78.0	95.0	67.3±14.7
Atmospheric pressure (hPa)	802.7	807.9	810.1	812.5	822.2	810.3±3.2
Wind speed (m/s)	0.5	1.9	2.5	3.2	8.6	2.7±1.1
Sunshine duration (h)	0	3.1	7.6	9.9	12.9	6.5±3.9

Table S2. Attributable number of non-accidental deaths and specific categories due to daily mean temperature, computed as total and as separated components for cold and heat temperatures over lag 0–28 days in Yuxi, China.

	Total	Cold	Heat
Total non-accidental	**4131 (2306, 5937)**	**3482 (552, 5980)**	652 (-2049, 3185)
Cause-specific			
Cardiovascular	**2419 (2622, 7476)**	**2489 (629, 4141)**	-68 (-2019, 1701)
Heart	**912 (446, 8413)**	1112 (-98, 2200)	-199 (-1456, 918)
Stroke	**1417 (2055, 8814)**	**1306 (104, 2634)**	113 (-1178, 1283)
Respiratory	854 (-428, 8228)	540 (-846, 1689)	314 (-822, 1190)
Age, years			
≤64	414 (-2421, 5413)	359 (-976, 1580)	55 (-1384, 1237)
65-74	470 (-2366, 5715)	679 (-764, 1853)	-209 (-1543, 953)
≥75	**3137 (3094, 7816)**	**2431 (102, 4392)**	710 (-1135, 2532)
Gender			
Male	**1977 (818, 5961)**	1706 (-395, 3697)	273 (-1668, 2048)
Female	**2181 (1691, 7074)**	1802 (-59, 3390)	380 (-1355, 1919)
Occupation			
Farmer	**3752 (2730, 6784)**	**3225 (801, 5403)**	530 (-1799, 2580)
Non-farmer	364 (-2842, 5120)	242 (-1320, 1486)	124 (-1293, 1350)
Ethnic			
Han nationality	**3243 (2237, 6688)**	1624 (-972, 4023)	1618 (-622, 3621)
Ethnic minorities	649 (-1165, 5773)	**1685 (332, 2934)**	-1037 (-2677, 488)
Marital status			
Married	**2262 (1118, 5804)**	1402 (-833, 3564)	860 (-1201, 2875)
Non-married	**1843 (1892, 7386)**	**2042 (334, 3527)**	-197 (-1963, 1218)

Results are expressed as attributable number (95% empirical confidence interval), and the bold indicates a statistically significant.

Table S3. Mortality number attributable to extreme and mild cold and mild and extreme heat by specific causes and individual characteristics

	Extreme cold	Mild cold	Mild heat	Extreme heat
Total non-accidental	**1054 (604, 1530)**	2556 (-117, 5016)	554 (-1930, 2984)	108 (-199, 395)
Cause-specific				
Cardiovascular	**657 (331, 946)**	**1942 (183, 3532)**	-84 (-1803, 1505)	15 (-191, 217)
Heart	**264 (72, 445)**	892 (-146, 1896)	-190 (-1385, 830)	-13 (-154, 109)
Stroke	**368 (136, 600)**	997 (-345, 2170)	87 (-1095, 1183)	28 (-129, 169)
Respiratory	223 (-30, 434)	337 (-1005, 1413)	277 (-643, 1006)	42 (-89, 161)
Age, years				
≤64	101 (-135, 308)	265 (-1039, 1292)	46 (-1121, 1094)	10 (-135, 149)
65-74	140 (-75, 331)	554 (-685, 1578)	-192 (-1434, 971)	-20 (-181, 116)
≥75	**814 (431, 1152)**	1732 (-123, 3465)	612 (-1103, 2097)	110 (-99, 313)
Gender				
Male	**503 (118, 851)**	1257 (-681, 3097)	229 (-1651, 1917)	47 (-153, 264)
Female	**556 (238, 882)**	1321 (-483, 2860)	325 (-1203, 1755)	61 (-134, 248)
Occupation				
Farmer	**977 (564, 1376)**	**2382 (27, 4440)**	446 (-1638, 2333)	92 (-173, 349)
Non-farmer	83 (-125, 295)	158 (-1263, 1389)	109 (-1137, 1255)	16 (-128, 158)
Ethnic				
Han nationality	**772 (364, 1191)**	918 (-1565, 3045)	1440 (-488, 3387)	209 (-57, 433)
Ethnic minorities	274 (-1, 500)	**1462 (162, 2576)**	-941 (-2416, 330)	-104 (-277, 62)
Marital status				
Married	**544 (165, 908)**	908 (-1292, 2815)	759 (-995, 2607)	117 (-125, 344)
Non-married	**509 (219, 781)**	**1615 (4, 3017)**	-192 (-1730, 1143)	-7 (-198, 158)

Results are expressed as attributable number (95% empirical confidence interval), and the bold indicates a statistically significant.

Table S4 Sensitivity analyses to calculate the fraction (%) with 95% empirical confidence interval attributable to temperature by changing maximum lag for mean temperature and degrees of freedom (*df*) for covariates

Model choices	Total	Cold	Heat
Lag period, days			
7	2.85 (1.62, 3.99)	0.97 (-1.16, 2.98)	1.88 (0.32, 3.31)
14	4.15 (2.78, 5.52)	2.90 (0.59, 5.15)	1.25 (-0.48, 2.93)
21	3.57 (1.51, 5.31)	3.10 (0.25, 5.76)	0.47 (-1.99, 2.89)
Df for time per year			
5	4.69 (3.10, 6.15)	4.19 (1.18, 6.73)	0.51 (-1.66, 2.81)
6	5.94 (4.07, 7.53)	4.96 (2.18, 7.72)	0.98 (-1.68, 3.49)
8	3.82 (0.92, 6.42)	4.72 (1.23, 8.07)	-0.90 (-4.31, 2.26)
9	5.07 (2.15, 7.75)	4.59 (0.57, 8.16)	0.48 (-2.98, 3.75)
Df for relative humidity			
2	4.64 (2.21, 6.83)	4.07 (0.84, 7.28)	0.57 (-2.70, 3.56)
4	4.74 (2.31, 6.88)	4.05 (0.56, 7.26)	0.69 (-2.15, 3.83)
5	4.79 (2.55, 6.92)	4.20 (1.06, 7.20)	0.60 (-2.76, 3.36)
Df for sunshine duration			
2	4.71 (2.27, 6.84)	4.18 (0.88, 7.35)	0.54 (-2.89, 3.51)
4	4.75 (2.39, 6.95)	4.08 (0.92, 7.03)	0.67 (-2.51, 3.65)
5	4.78 (2.44, 6.90)	4.13 (0.69, 7.45)	0.65 (-2.40, 3.63)
Df for atmospheric pressure			
2	4.76 (2.24, 6.87)	4.15 (0.76, 7.00)	0.62 (-2.69, 3.49)
4	4.75 (2.21, 6.97)	4.09 (0.39, 6.95)	0.67 (-2.49, 3.76)
5	4.79 (2.38, 6.95)	4.02 (1.01, 7.08)	0.77 (-2.30, 3.98)
Df for wind speed			
2	4.79 (2.26, 6.90)	4.02 (0.47, 6.88)	0.78 (-2.34, 3.52)
4	4.68 (2.34, 6.78)	4.02 (0.60, 7.07)	0.67 (-2.48, 3.68)
5	4.66 (2.31, 6.85)	4.04 (0.90, 6.94)	0.62 (-2.56, 3.75)

Results are expressed as attributable fractions (95% empirical confidence intervals), and the bold indicates a statistically significant.

Table S5. Attributable fraction (%) of total non-accidental mortality and by specific causes and individual characteristics due to daily mean temperature and cold and heat over lag 0-28 days with minimum mortality temperature (MMT) as the referent temperature.

	Total death	MMT	Total(%)	Cold(%)	Heat(%)
Total non-accident	89,467	16.7	4.66 (2.26, 6.85)	3.93 (0.60, 7.01)	0.73 (-2.69, 3.88)
Cause-specific					
Cardiovascular	41,794	19.7	6.57 (-1.01, 12.97)	6.42 (1.82, 9.37)	0.15 (-1.40, 1.62)
Heart	17,793	24.7	8.76 (-33.20, 36.26)	8.76 (0.35, 9.26)	0 (0, 0)
Stroke	22,589	17.7	6.48 (1.76, 10.02)	5.92 (-0.45, 11.17)	0.57 (-4.22, 4.94)
Respiratory	16,565	14.7	5.89 (-3.58, 13.34)	3.67 (-4.89, 10.02)	2.23 (-8.88, 11.19)
Age, years					
≤64	21,678	17.7	1.94 (-2.77, 5.73)	1.68 (-4.87, 7.06)	0.26 (-4.83, 4.96)
65-74	20,072	24.7	6.84 (-30.05, 32.26)	6.84 (-2.53, 6.33)	0 (0, 0)
≥75	47,717	16.7	6.72 (3.60, 9.47)	5.19 (0.65, 9.20)	1.54 (-2.87, 5.51)
Gender					
Male	48,939	17.7	4.08 (0.77, 6.75)	3.52 (-0.97, 7.46)	0.56 (-2.85, 3.73)
Female	40,528	16.7	5.44 (2.04, 8.43)	4.5 (-0.18, 8.73)	0.95 (-3.72, 5.23)
Occupation					
Farmer	68,278	16.7	5.52 (2.95, 7.90)	4.75 (1.10, 8.10)	0.77 (-2.93, 4.18)
Nonfarmer	21,189	15.7	1.87 (-5.49, 7.85)	1.22 (-5.80, 7.16)	0.66 (-8.75, 8.56)
Ethnic					
Han nationality	63,275	14.7	6.49 (1.48, 10.89)	3.24 (-1.29, 6.30)	3.25 (-2.54, 8.50)
Ethnic minorities	26,192	24.7	19.55 (-7.14, 38.61)	19.55 (-1.87, 6.2)	0 (0, 0)
Married status					
Married	54,971	15.7	4.60 (0.53, 8.18)	2.80 (-1.59, 6.48)	1.80 (-3.55, 6.54)
Unmarried	34,496	20.7	6.89 (-4.51, 16.26)	6.86 (1.89, 8.74)	0.03 (-0.77, 0.81)

Results are expressed as attributable fractions (95% empirical confidence intervals), and the bold indicates a statistically significant.

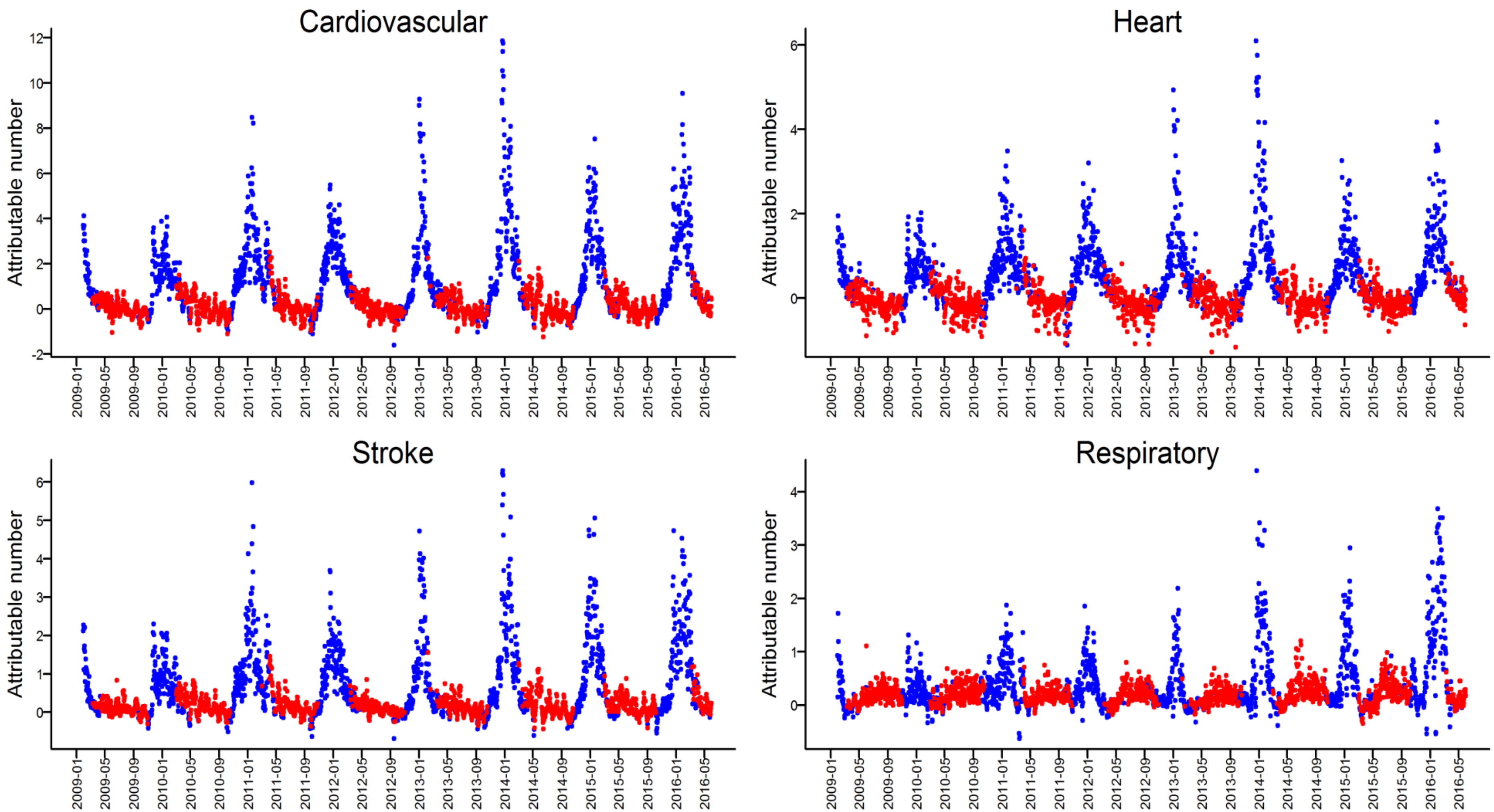


Figure S1. Daily number of cardiovascular, heart, stroke and respiratory deaths attributable to cold (blue points) and heat (red points) temperatures.

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			**3-4**
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			**4-6**
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	4-5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	not applicable
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
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	*5-6*
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
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	5-6
		(*b*) Describe any methods used to examine subgroups and interactions	5-6
		(*c*) Explain how missing data were addressed	not applicable
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	not applicable

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	6
Results			6-8
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	6-7
		(b) Give reasons for non-participation at each stage	not applicable
		(c) Consider use of a flow diagram	not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6-7
		(b) Indicate number of participants with missing data for each variable of interest	not applicable
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	not applicable
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	not applicable
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	not applicable
		Cross-sectional study—Report numbers of outcome events or summary measures	6-7
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	6-8
		(*b*) Report category boundaries when continuous variables were categorized	not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			8-12
Key results	18	Summarise key results with reference to study objectives	8-9
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	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			12-13
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 based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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 www.strobe-statement.org.