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

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3 **Burden of non-accidental mortality and subgroups by**
4 **specific causes and individual characteristics attributable to**
5 **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]

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

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

33 34 35 36 37 38 39 40 41 42 **2. Methods**

43 44 **2.1 Study site**

45 Located on the western edge of the Yunnan-Guizhou Plateau of southwest China,
46 the Yuxi city area has complicated geographic features of mountains, valleys, plateaus,
47 and basins. With an average altitude of about 2000m and 4 spring-like seasons, this
48 area has a unique, subtropical, plateau monsoon climate, showing diversified climates
49 with low atmospheric pressure, thin and dry air, and low seasonal variation in
50 temperature. From the national population census in 2010, the permanent population
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3 is about 2.3 billion, and residents of ethnic minorities (e.g., Dai, Hui, Yi, Hani, and
4 Mongolian minorities) account for 32.27% of the total population.
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6 **2.2 Data collection**

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8 Individual records such as age of death, gender, ethnicity, occupation, marital
9 status, cause of death, and date of death for all registered deaths for the period January
10 1, 2009 to May 31, 2016, were obtained from the Yuxi Center for Disease Control and
11 Prevention. The underlying causes of death were classified by medical personnel, and
12 examination procedures were routinely performed to ensure accurate data, based on
13 the *International Classification of Diseases*, 10th revision (ICD-10). Individual data
14 were collapsed into a series of daily counts for the total non-accidental mortality
15 (ICD-10 A00–R99) as well as subcategories by specific cause of death
16 (cardiovascular [I00–I99], heart [I00–I51], stroke [I60–I69], and respiratory disease
17 [J00–J99]), age (0–64, 65–74, and 75+ years old), gender (male and female),
18 occupation (farmer and non-farmer), ethnicity (Han nationality and ethnic minorities),
19 and marital status (married and non-married). Daily meteorological data for the same
20 period were obtained from the China Meteorological Data Sharing System, including
21 mean temperature and 4 other meteorological variables (atmospheric pressure, wind
22 speed, sunshine duration, and relative humidity).
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33 **2.3 Patient and public involvement**

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35 This study is based on daily death number data, which could be obtained from
36 Yuxi Center for Disease Control and Prevention without referral and free of charge.
37 There was no patient and decedent involvement in the presented study.
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41 **2.4 Statistical analysis**

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43 As daily death number under a Poisson distribution and risk of mortality depend
44 on exposure to temperatures of the current and previous days,^[24] we applied a
45 standard time-series quasi-Poisson regression model combined with DLNM to
46 estimate the non-linear and lag effects of mean temperature on mortality, with day of
47 the week, long-term trends, and the 4 other meteorological variables as potential
48 covariates. This model can capture the complex non-linear relation and lagged effect
49 by combining 2 functions that define the conventional exposure–response association
50 and the additional lag–response association. The maximum lag period was set to 28
51 days to explore the lag structure of temperature effect, and median temperature
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(17.0°C) 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:

$$AF_{x,t} = 1 - \exp\left(-\sum_{l=0}^L \beta_{x_{t-l}}, l\right)$$

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

where $AF_{x,t}$ and $AN_{x,t}$ 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°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 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

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3 to cold was 2.35-fold higher for ethnic minorities than Han nationality (6.55% vs
4 2.79%), whereas the point-estimated attributable fraction caused by the whole
5 temperature range was approximately equal by gender and marital status.
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8 Table 3 displays the estimated mortality fraction attributable to overall
9 temperatures, separated by mild and extreme temperatures. In general, the risk of non-
10 accidental deaths attributable to extreme cold was 1.17% (0.58, 1.69), accounting for
11 a clearly high proportion of 24.6% of the total mortality burden (4.75%) due to the
12 whole temperature range, whereas attributable risks due to mild cold or heat or
13 extreme heat were non-significant. In the cause-specific analyses, the attributable
14 fractions due to extreme cold were 1.57%, 1.63%, and 1.49% for cardiovascular
15 disease, stroke, and heart disease, with no significant association with respiratory
16 disease. The extreme cold-related burden for older people, females, farmers, and non-
17 married individuals was slightly higher than their corresponding categories.
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21 Table S2 presents the attributable number of deaths due to mean temperature,
22 overall and by cold and heat. An estimated 4,131 non-accidental deaths were due to
23 overall temperatures and 3,482 to cold. Table S3 shows the excess mortality due to
24 extreme and mild cold and mild and extreme heat. Figures 3 and S1 illustrate the daily
25 deaths attributable to cold and heat. The attributable deaths were much larger with
26 cold than heat.
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30 31 32 33 **3.4 Sensitivity analysis**

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35 Sensitivity analysis to check the stability of our main findings involved changing
36 the maximum lag days (7, 14, and 21) and the *df* of the natural cubic splines for the
37 calendar time (5, 6, 8, and 9 per year) and for the 4 other meteorological variables one
38 by one (2, 4, and 5). The attributable fractions for non-accidental mortality due to
39 overall temperatures were relatively robust with sensitivity analyses (Table S2) and
40 the results by causes of deaths and individual characteristics were robust (results not
41 shown).
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48 49 **4. Discussion**

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51 We quantitatively estimated the attributable risks of non-accidental death and
52 subgroups by specific causes and individual characteristics due to the whole
53 temperature range and to extreme and mild cold and mild and extreme heat for 89,467
54 deaths between 2009 and 2016 in Yuxi, China, a high-altitude region with a unique,
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3 subtropical, plateau monsoon climate. The temperature–mortality associations were
4 nonlinear and followed slide-shaped curves, and the risks rapidly increased with
5 decreasing mean temperature. Excess deaths were attributable to overall temperatures,
6 and cold was responsible for most of the mortality burden. The estimated mortality
7 burden attributable to cold was greater for cardiovascular deaths, older people,
8 farmers, ethnic minorities, and non-married individuals than their corresponding
9 categories.
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14 In the present study, all of the cause-specific deaths we examined were closely
15 related to ambient temperatures. The relations were non-linear, with increased relative
16 risk with low temperature, especially extreme cold; however, the risk of high
17 temperature changed minimally. A number of researchers have found that the
18 temperature–response association presents a “U” or “V” shape, with increased
19 mortality risks at extremely low and high temperatures.[25,33-35] We also examined
20 additional non-accidental deaths attributable to ambient temperatures, with larger
21 burden due to cold than heat. A multi-country observational study estimated a total
22 mortality burden of death attributable to non-optimal ambient temperatures; the
23 attributable fraction ranged from 3.37% in Thailand to 11% in China, which provides
24 strong evidence for substantial differences between regions or climates.[16]
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32 The cold-related mortality burden is an important public health problem in Yuxi.
33 Findings from our study showed most of the death burden attributable to low
34 temperature, and a much lower and non-significant burden due to heat. Previous
35 studies have found that most of the mortality burden is caused by exposure to cold
36 days, with comparatively lower attributable risk, or even none, due to heat exposure.
37 For example, [Hajat et al. \(2006\)](#) showed that all-cause mortality attributable to heat
38 ranged from 0.37% in London (1976–2003) to 1.45% in Milan (1985–2002), and
39 another study conducted in London from 1986 to 1996 found that attributable fraction
40 of mortality for each 1°C decrease below a threshold of 15°C was 5.42% (4.13, 6.69),
41 with no burden due to heat.[36] Although extremely low or high temperature
42 corresponded to increased relative risk of mortality, [Gasparrini et al. \(2015\)](#) found a
43 relatively small part of the death burden attributable to extreme cold temperature,
44 ranging from 0.25% to 1.06%. Similar results from 5 East Asian regions showed a
45 9.36% mortality burden attributable to overall temperatures, with only 0.80% due to
46 extreme cold [19]. However, our current study estimated a larger proportion of
47 attributable mortality fraction due to extreme cold, accounting for about one-quarter
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3 of the total mortality burden (1.17% vs 4.75%), even though extreme cold days
4 represented only 2.5% of the whole study period. We found no evidence of additional
5 deaths due to extreme heat in all categories.
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8 Exposure to low temperature has been widely demonstrated to be strongly
9 associated with excess cardiovascular and respiratory deaths,[19,30,37,38] and the
10 biological processes that underlie cold-related mortality are associated with cardio-
11 respiratory disease.[11,16,30,39] We found a higher point-estimated attributable risk
12 caused by cold for cardiovascular than respiratory disease deaths. A multi-city study
13 including 15 Chinese megacities also identified 15.8% of the cardiovascular mortality
14 burden due to cold days.[25] The increased cold-related cardiovascular deaths mainly
15 involved changes in vascular tone, autonomic nervous system response, arrhythmia,
16 and oxidative stress.[40-42] Although we found no evidence for excess burden of
17 respiratory deaths due to cold or heat, other reports have described increased
18 respiratory deaths attributable to ambient temperatures.[10,43] For heart and stroke,
19 the burden of mortality was attributable to only extreme cold, with approximately
20 equivalent values, and other studies found excess heart and stroke deaths attributable
21 to low and/or high temperatures.[23,26,37,44]
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30 Age has been frequently identified as an important modifier of the association
31 between ambient temperatures and human health.[15,25,29,45] We found that
32 exposure to cold, particularly extreme cold, was closely related to increased death
33 burden for older than younger people. Several previous surveys found increased age
34 associated with point-estimated attributable risk of cardiovascular mortality and both
35 intra-cerebral hemorrhage and ischemic stroke morbidity due to cold, with the highest
36 values in older people.[25,31] Another nationwide study in Japan found most of the
37 proportion of morbidity burden attributable to days with low temperature in all age
38 groups, with an trend of increasing attributable risk with age: the attributable fraction
39 due to cold was 15.96%, 24.84%, and 28.10% with age 18–64, 65–74, and 75–110
40 years, respectively.[33] Older people were more vulnerable to the temperature effects,
41 mainly because they often have multiple pre-existing chronic conditions and
42 physiological changes in thermoregulation and homeostasis.[46,47] However, the
43 effect modification of temperature-related mortality by gender has been
44 identified.[23,29,33,48] We observed a higher mortality burden caused by exposure to
45 the cold period among females than males in Yuxi, and the cold-related attributable
46 risk was found higher for females than males in Hanoi, Vietnam,[49] and in 47 cities
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3 in Japan.[33] The reason for the discrepancy in temperature-related burden by gender
4 might be owing to differences in occupational exposure, physiology and
5 thermoregulation.
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8 A survey in Adelaide, South Australia, provided epidemiological evidence for
9 the impact of heat waves on worker health and safety, which implied that personal
10 occupation might modify the temperature–mortality association.[50] Our previous
11 studies (Ding et al., 2016a, 2016b) revealed that farmers were more likely than non-
12 farmers to die on high DTR or cold days, and the present study also showed a higher
13 mortality burden attributable to cold and extreme cold days for farmers than non-
14 farmers. In southwestern China, farmers universally have a poor educational level,
15 disadvantaged socioeconomic status, and low annual income, which may be linked to
16 poor living conditions, malnutrition, and non-access to basic health care. In addition,
17 farmers working in the fields may have more exposure to ambient temperatures,
18 because farming is basically highly related to weather.[51]
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21 A study of 9 cities in California found that with each 10°F (4.7°C) increase in
22 mean temperature, the mortality was increased 4.9%, 2.5%, and 1.8% for Blacks,
23 Whites, and Hispanics, respectively.[29] Also, our previous research demonstrated
24 less risk of high DTR associated with non-accidental mortality for the current day for
25 people of Dai ethnic minority than Han nationality.[13] To our knowledge, no study
26 has estimated the potential effect modification of mortality burden attributable to
27 ambient temperatures by ethnicity. We observed a greater cold- and mild cold-related
28 death for ethnic minorities than Han nationality in Yuxi, which indicated that
29 race/ethnicity may modify the cold-associated mortality burden. We also found lower
30 death burden caused by cold and extreme cold for married people versus those never
31 married, divorced, or widowed, possibly because married people can be cared for by
32 their partners during the cold period.
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47 **5. Conclusions**

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49 Our present study revealed the non-accidental mortality burden clearly associated
50 with ambient temperatures in Yuxi, China. A substantial burden of the deaths was due
51 to cold, with the burden due to heat much lower. Mortality was increased with
52 exposure to extreme cold, which was responsible for about one-quarter of the total
53 mortality burden. In addition, the cold-related mortality burden was greater with
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3 cardiovascular than respiratory disease deaths and for people over 75 years old,
4 females, farmers, ethnic minorities, and non-married individuals than their
5 corresponding categories. The cold-related mortality burden in Yuxi may have
6 important implications for public-health interventions to minimize the health effects
7 due to adverse temperatures and for predicting the climate-change impact.
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11 12 **Declarations**

13
14 **Contributors:** Q.Y.Z., Z.D., and C.Y.D. conceived and designed the experiments.
15 L.J.L. and Y.F.W. provide primary data. P.G., S.Y.Y., J.L., Y.W., and C.Y.D.
16 collected and cleaned the data. C.Y.D. analyzed the data and drafted the manuscript.
17 Q.Y.Z., Z.D., and C.Y.D. revised the manuscript and interpreted the results. All
18 authors read and approved the final manuscript.
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34 **Competing interests:** The authors declare no competing financial interests.
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38 **Data sharing statement:** Please contact the corresponding author for data requests.
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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; 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.

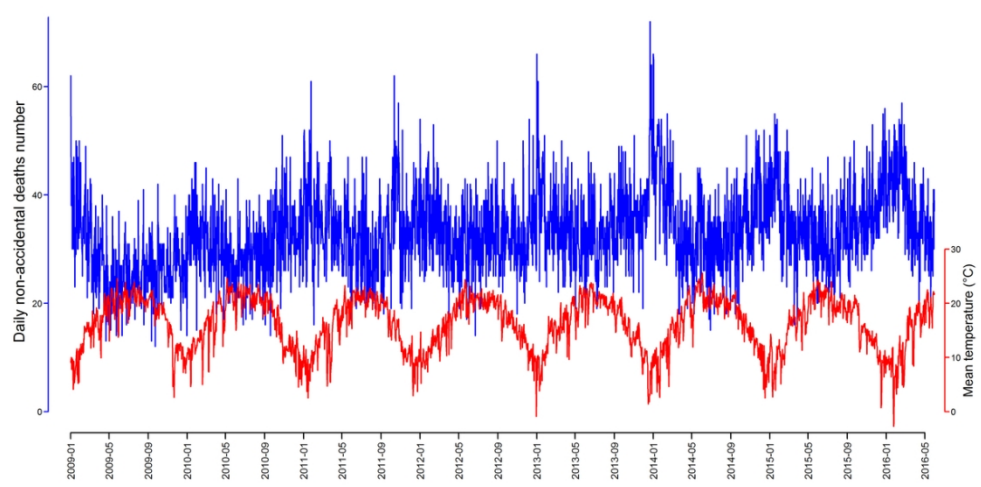
Figure Legends

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.

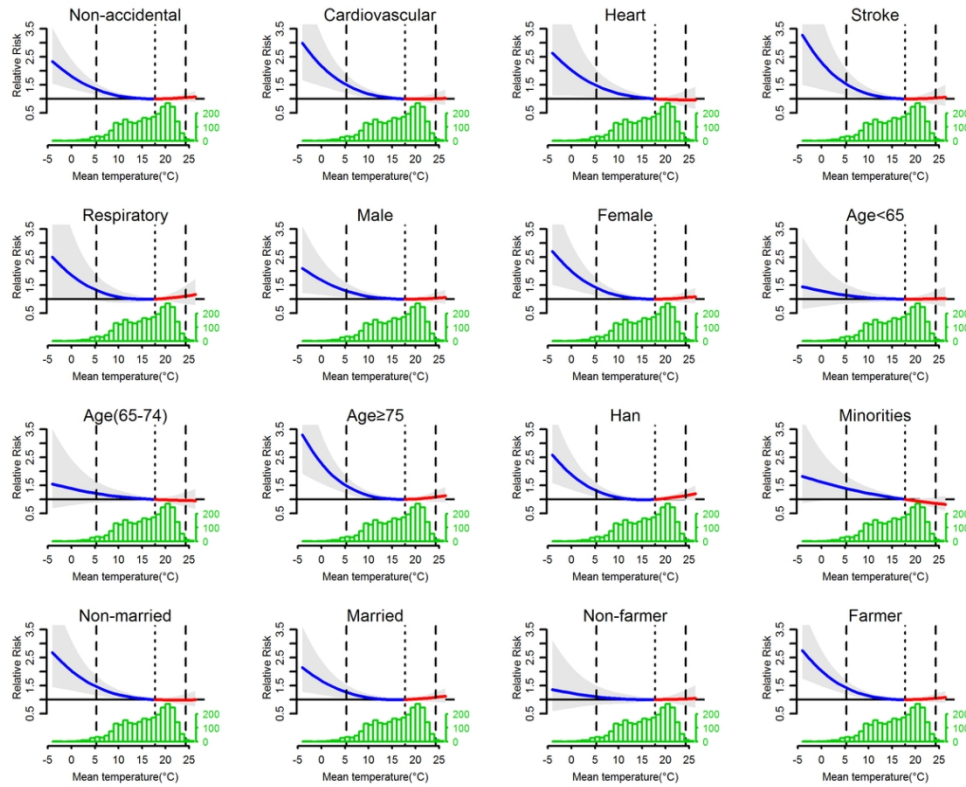
Figure 3. Daily number of total non-accidental deaths attributable to cold (blue points) and heat (red points).

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

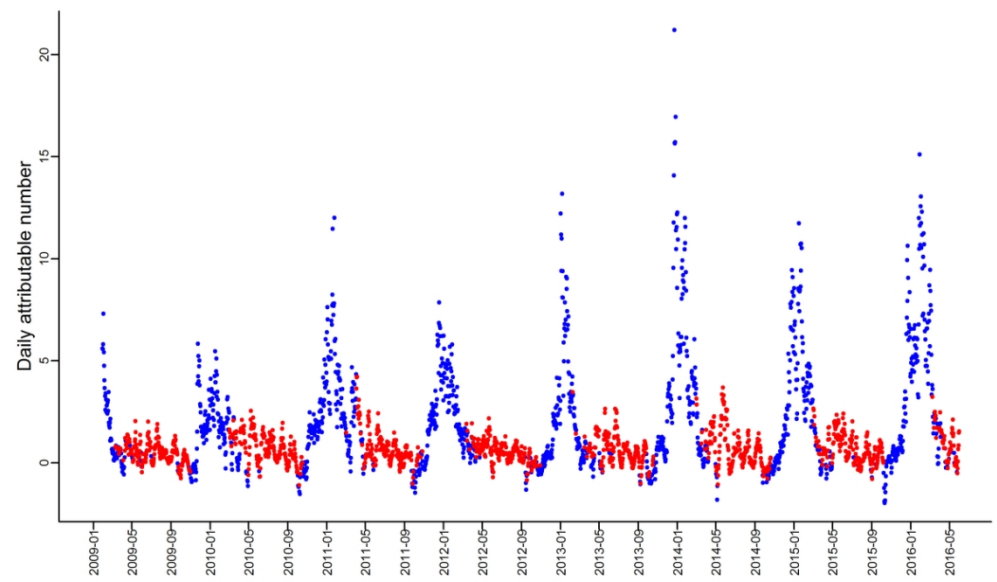
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Overall cumulative relative risk (with 95% empirical confidence intervals, shaded grey) at a lag of 0–28 days in Yuxi, China, with histogram of daily temperature distribution. The dotted lines are the median of the mean temperature, and the dashed 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

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

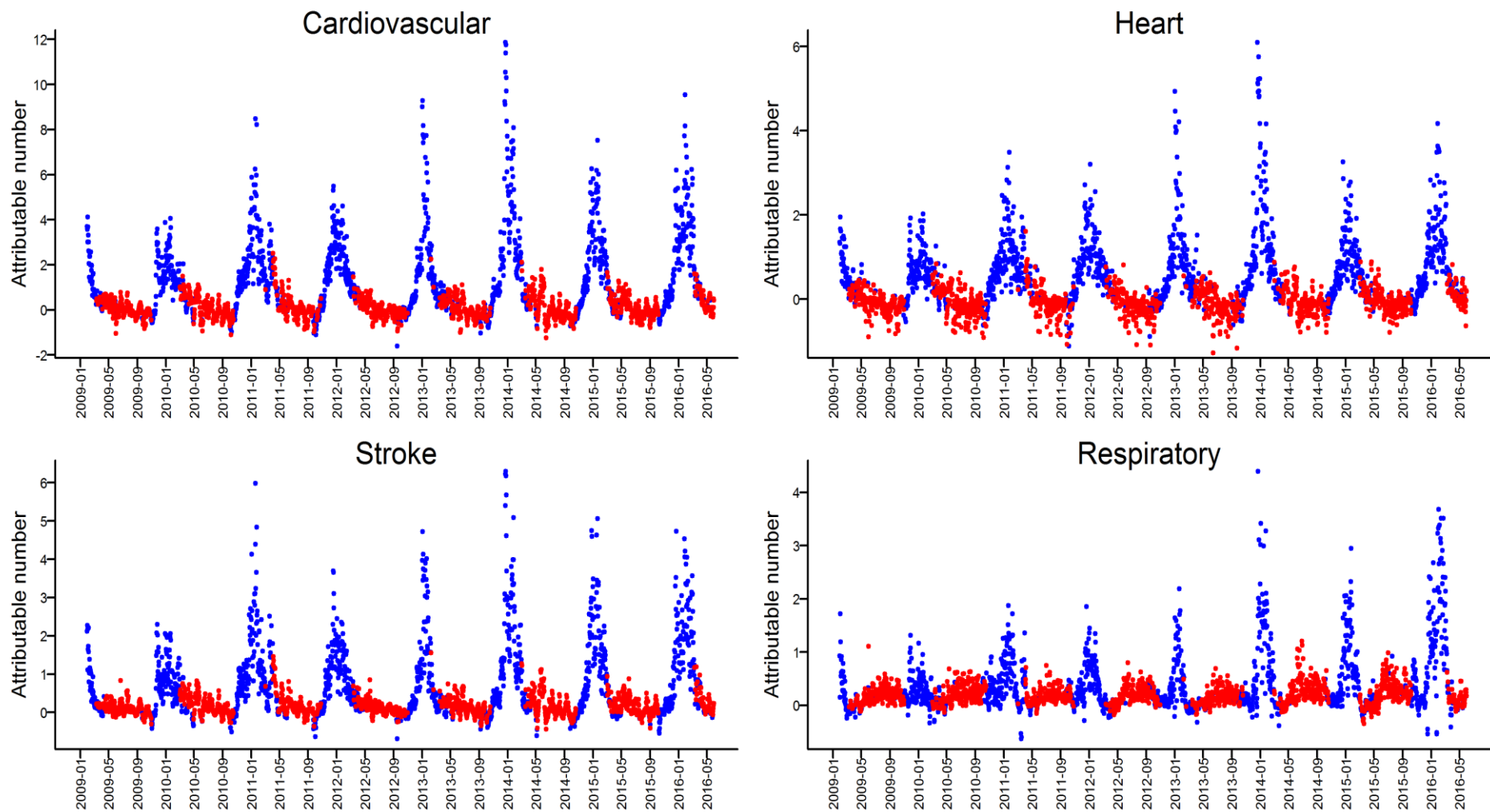


Figure S1. Daily number of cardiovascular, heart, stroke and respiratory deaths attributable to cold (blue points) and heat (red points) temperatures.

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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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4 **1 Burden of non-accidental mortality attributable to ambient**
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6 **2 temperatures in a high plateau area of southwest China**
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1 **Abstract**

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

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

13 *Results:* We analyzed 89,467 non-accidental deaths; 4,131 were attributable to overall
14 temperatures, with an attributable fraction of 4.75% (95% eCI 2.33, 6.79). Most of the
15 mortality burden was caused by cold (4.08%; 0.86, 7.12), while the burden due to heat
16 was low and non-significant (0.67%; -2.44, 3.64). Extreme cold (1.17%; 0.58, 1.69)
17 was responsible for 24.6% (i.e., 1.17% divided by 4.75%) of the total death burden. In
18 the stratification analyses, attributable risk due to cold was higher for cardiovascular
19 than respiratory disease (6.18% vs 3.50%). We found a trend of risk of increased
20 death due to ambient temperatures with increasing age, with attributable fractions of
21 1.83%, 2.27%, and 6.87% for age ≤ 64 , 65 – 74, and ≥ 75 years old. The cold-related
22 burden was slightly greater for females, farmers, ethnic minorities, and non-married
23 individuals than their corresponding categories.

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

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

30 **Strengths and limitations of this study**

- 31 • Mortality burden attributable to ambient temperature was assessed in a high
32 plateau city in southwest China.
33

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

9 1. Introduction

10 With the global climate change, ambient temperatures has been extensively
11 demonstrated to directly affect human health (e.g., daily morbidity and mortality) and
12 has become one of the most severe public health problems in the world.[1-5]
13 Exposure to extreme weather such as cold spells and heat waves represents high risk
14 for mortality, and the extreme temperature-related mortality is expected to increase
15 with the increasing frequency, intensity, and duration of extreme weather events.[4,6-
16 8] Low and high temperatures are also well known to be associated with a substantial
17 increase in a wide range of all-cause and cause-specific mortality (e.g., cardiovascular
18 and respiratory diseases).[6,9-12]

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

31 Use of risk assessment of the attributable fraction revealed the burden of
32 mortality associated with ambient temperatures; however, most previous literatures
33 estimated the mortality burden in high-income or low-altitude regions or

1 coastlands,[11,17,20,22-24] and few were conducted in high plateau areas of
2 developing countries.[12,25] The attributable fraction and number for the
3 temperature–mortality association may vary by geographic features, climate, and
4 structure of the population.[25,26] In addition, age, gender, educational attainment,
5 and specific causes were previously identified as modifiers for estimating the effect
6 modification of the mortality risk attributable to ambient temperatures.[27-31]
7 However, few researchers have focused on the potential effect modification of the
8 mortality burden by occupation, race/ethnicity, or marital status.[32]

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

22 **2. Methods**

23 **2.1 Study site**

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

33 **2.2 Data collection**

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1 Individual records such as age of death, gender, ethnicity, occupation, marital
2 status, cause of death, and date of death for all registered deaths for the period January
3 1, 2009 to May 31, 2016, were obtained from the Yuxi Center for Disease Control and
4 Prevention, which maintains detailed quality assurance and control measures[33,34].
5 The underlying causes of death were classified by medical personnel, and
6 examination procedures were routinely performed to ensure accurate data, based on
7 the *International Classification of Diseases*, 10th revision (ICD-10). Individual data
8 were collapsed into a series of daily counts for the total non-accidental mortality
9 (ICD-10 A00–R99) as well as subcategories by specific cause of death
10 (cardiovascular [I00–I99], heart [I00–I51], stroke [I60–I69], and respiratory disease
11 [J00–J99]), age (0–64, 65–74, and 75+ years old), gender (male and female),
12 occupation (farmer and non-farmer), ethnicity (Han nationality and ethnic minorities),
13 and marital status (married and non-married). Daily meteorological data for the same
14 period were obtained from the China Meteorological Data Sharing System, including
15 mean temperature and 4 other meteorological variables (atmospheric pressure, wind
16 speed, sunshine duration, and relative humidity).

17 18 **2.3 Patient and public involvement**

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

22 23 **2.4 Statistical analysis**

24 As daily death number under a Poisson distribution and risk of mortality depend
25 on exposure to temperatures of the current and previous days,[25] we applied a
26 standard time-series quasi-Poisson regression model combined with DLNM to
27 estimate the non-linear and lag effects of mean temperature on mortality, with day of
28 the week, long-term trends, and the 4 other meteorological variables as potential
29 covariates. This model can capture the complex non-linear relation and lagged effect
30 by combining 2 functions that define the conventional exposure–response association
31 and the additional lag–response association. The maximum lag period was set to 28
32 days to explore the lag structure of temperature effect, and median temperature
33 (17.0°C) was the reference to calculate attributable risk.[32] We used natural cubic
34 splines with 7 degrees of freedom (*df*) per year for time to describe the long-term

1 trends and seasonality and 3 *df* for the 4 other meteorological indicators. These model
 2 specifications were consistent with previous studies.[24,35]

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

$$AF_{x,t} = 1 - \exp \left[- \sum_{l=0}^L \beta_{x_{t-l}} \right]$$

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

9 where $AF_{x,t}$ and $AD_{x,t}$ are the attributable fraction and the number of cases at day t
 10 (1,2,3...2907), respectively; β_x is the risk associated with the exposure to ambient
 11 temperatures at level x (i.e., $\beta_x = (x - Ref) \times \beta$; *Ref* is the referenced temperature;
 12 β is the coefficient for DLNM of mean temperature; L is the maximum lag for the
 13 effect of mean temperature; and n_t is the observed number of deaths at day t .

14 To estimate the mortality burden from non-accidental deaths, we calculated the
 15 total attributable fraction due to the overall temperatures and divided the total effect
 16 into exposure to low and high temperatures by summing the subsets corresponding to
 17 days with temperatures below and above the median temperature. Also, we explored
 18 the mortality burden attributable to mild and extreme temperatures. Extreme cold and
 19 heat were defined as temperatures below the 2.5th percentile (5.4°C) and above the
 20 97.5th percentile (23.1°C) of mean temperature, and mild cold and heat were defined
 21 as the range between the median temperature and these cutoffs. Monte-Carlo
 22 simulations were used to calculate the empirical confidence intervals (eCIs) of the
 23 attributable fraction and number, assuming a multivariate normal distribution of the
 24 best linear unbiased predictions of the deduced coefficients[19,36]. All statistical
 25 analyses involved use of R v3.0.3, with the “dlnm” package to create the DLNM for
 26 mean temperature.

27 3. Results

28 3.1 Descriptive statistics

1 We analyzed 89,467 non-accidental deaths from Yuxi between 2009 and 2016,
2 with an average of 33 deaths per day (range 12 to 72). The number of deaths due to
3 cardiovascular disease was 41,794 (46.7%), more than half due to stroke; the
4 proportion due to respiratory disease was 18.5% (Table 1). In individual
5 characteristics subgroup, a higher proportion of deaths were for males, older people
6 (≥ 75 years), people with Han nationality, farmers and married people than their
7 corresponding categories. During the study period, the mean daily temperature was
8 16.1 °C (ranging from -3.3 to 25.6 °C) (Table S1). The daily number of non-
9 accidental deaths and mean temperature showed an inverse relation (Figure 1).

10 **3.2 Exposure–response association**

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

19 **3.3 Attributable fraction and number**

20 Table 2 shows the estimated attributable fraction with 95% eCIs of daily non-
21 accidental mortality calculated for total and separate components by heat and cold
22 temperatures. For total non-accidental deaths, the attributable fraction was 4.75%
23 (95% eCI 2.33, 6.79) with the whole temperature range, including heat and cold. Cold
24 temperature was responsible for most of the mortality burden, corresponding to an
25 attributable risk of 4.08% (0.86, 7.12), whereas the burden due to heat was low and
26 non-significant (0.67%; -2.44, 3.64). The attributable risks of cardiovascular and
27 stroke deaths caused by overall temperatures were 5.97% (2.74, 8.74) and 6.50%
28 (2.22, 10.16); the point-estimated risk due to cold was higher for cardiovascular than
29 respiratory deaths (6.18% vs 3.50%).

30 On stratification by age, the attributable risk due to ambient temperatures
31 increased with age, with attributable fractions of 1.83%, 2.27%, and 6.87% for age
32 ≤ 64 , 65–74, and ≥ 75 years, respectively. Those engaged in agriculture had higher
33 attributable fraction, 3.23 times (5.66% vs 1.75%) due to the overall temperatures and
34 3.98 times (4.93% vs 1.24%) due to cold, than non-farmers. The estimated burden due

1 to cold was 2.35-fold higher for ethnic minorities than Han nationality (6.55% vs
2 2.79%), whereas the point-estimated attributable fraction caused by the whole
3 temperature range was approximately equal by gender and marital status.

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

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

20 3.4 Sensitivity analysis

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

29 4. Discussion

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

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

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

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

1 9.36% mortality burden attributable to overall temperatures, with only 0.80% due to
2 extreme cold [20]. However, our current study estimated a larger proportion of
3 attributable mortality fraction due to extreme cold, accounting for about one-quarter
4 of the total mortality burden (1.17% vs 4.75%), even though extreme cold days
5 represented only 2.5% of the whole study period. We found no evidence of additional
6 deaths due to extreme heat in all categories.

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

21 Age has been frequently identified as an important modifier of the association
22 between ambient temperatures and human health.[15,26,30,49] We found that
23 exposure to cold, particularly extreme cold, was closely related to increased death
24 burden for older than younger people. Several previous surveys found increased age
25 associated with point-estimated attributable risk of cardiovascular mortality and both
26 intra-cerebral hemorrhage and ischemic stroke morbidity due to cold, with the highest
27 values in older people.[26,32] Another nationwide study in Japan found most of the
28 proportion of morbidity burden attributable to days with low temperature in all age
29 groups, with an trend of increasing attributable risk with age: the attributable fraction
30 due to cold was 15.96%, 24.84%, and 28.10% with age 18–64, 65–74, and 75–110
31 years, respectively.[37] Older people were more vulnerable to the temperature effects,
32 mainly because they often have multiple pre-existing chronic conditions and
33 physiological changes in thermoregulation and homeostasis.[50,51] However, the
34 effect modification of temperature-related mortality by gender has been

1 identified.[24,30,37,52] We observed a higher mortality burden caused by exposure to
2 the cold period among females than males in Yuxi, and the cold-related attributable
3 risk was found higher for females than males in Hanoi, Vietnam,[53] and in 47 cities
4 in Japan.[37] The reason for the discrepancy in temperature-related burden by gender
5 might be owing to differences in occupational exposure, physiology and
6 thermoregulation.

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

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

30 Our study has some limitations. First, the data were from a single city, so
31 generalizing the findings to other geographic areas or climates should be cautioned.
32 Second, the data of temperature were from monitoring sites rather than exposure
33 measuring of individual. Third, although the concentration of daily mean PM₁₀, NO₂
34 and SO₂ in Yuxi are much lower than those in other 17 Chinese cities [56], we did not

1 control for the potential confounding effects by air pollution due to the unavailability
2 of the complete pollution data in the study area.

3 4 **5. Conclusions**

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

14 15 **Declarations**

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

21
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29
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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; 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.

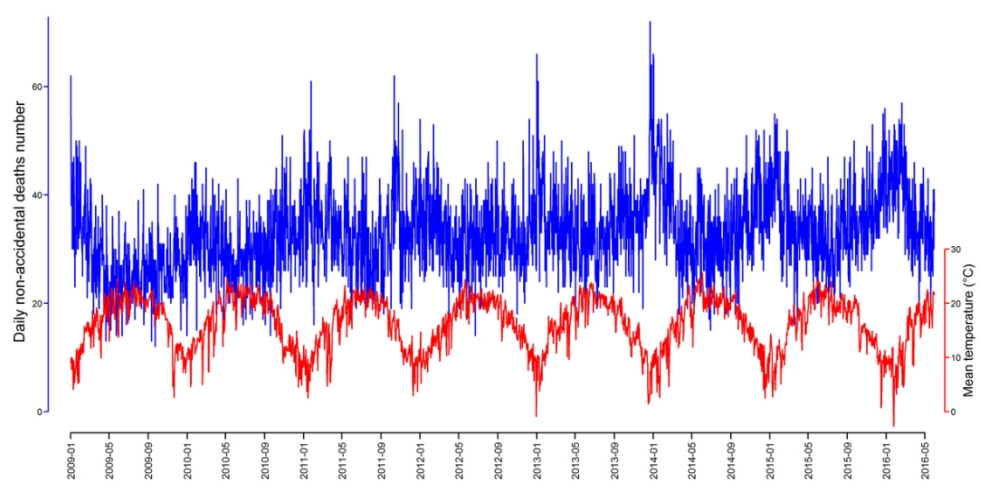
Figure Legends

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.

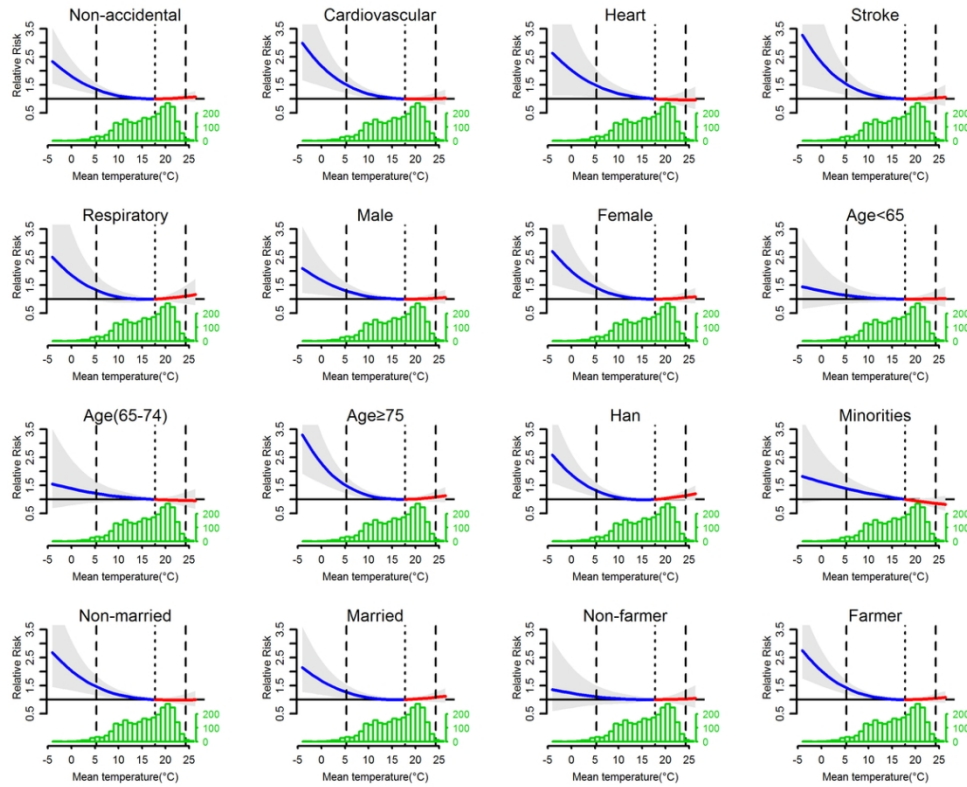
Figure 3. Daily number of total non-accidental deaths attributable to cold (blue points) and heat (red points).

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

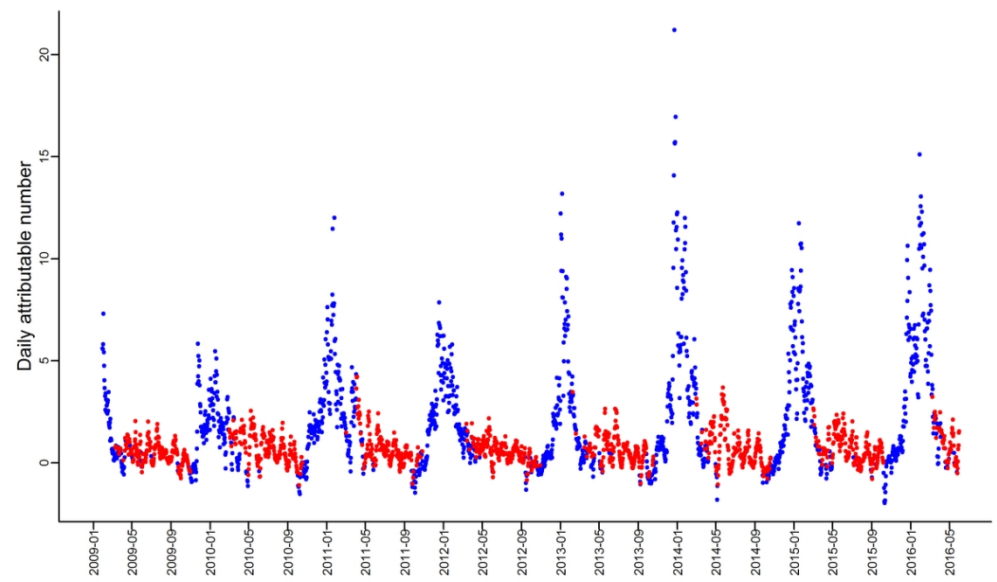
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Overall cumulative relative risk (with 95% empirical confidence intervals, shaded grey) at a lag of 0–28 days in Yuxi, China, with histogram of daily temperature distribution. The dotted lines are the median of the mean temperature, and the dashed 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

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

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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)

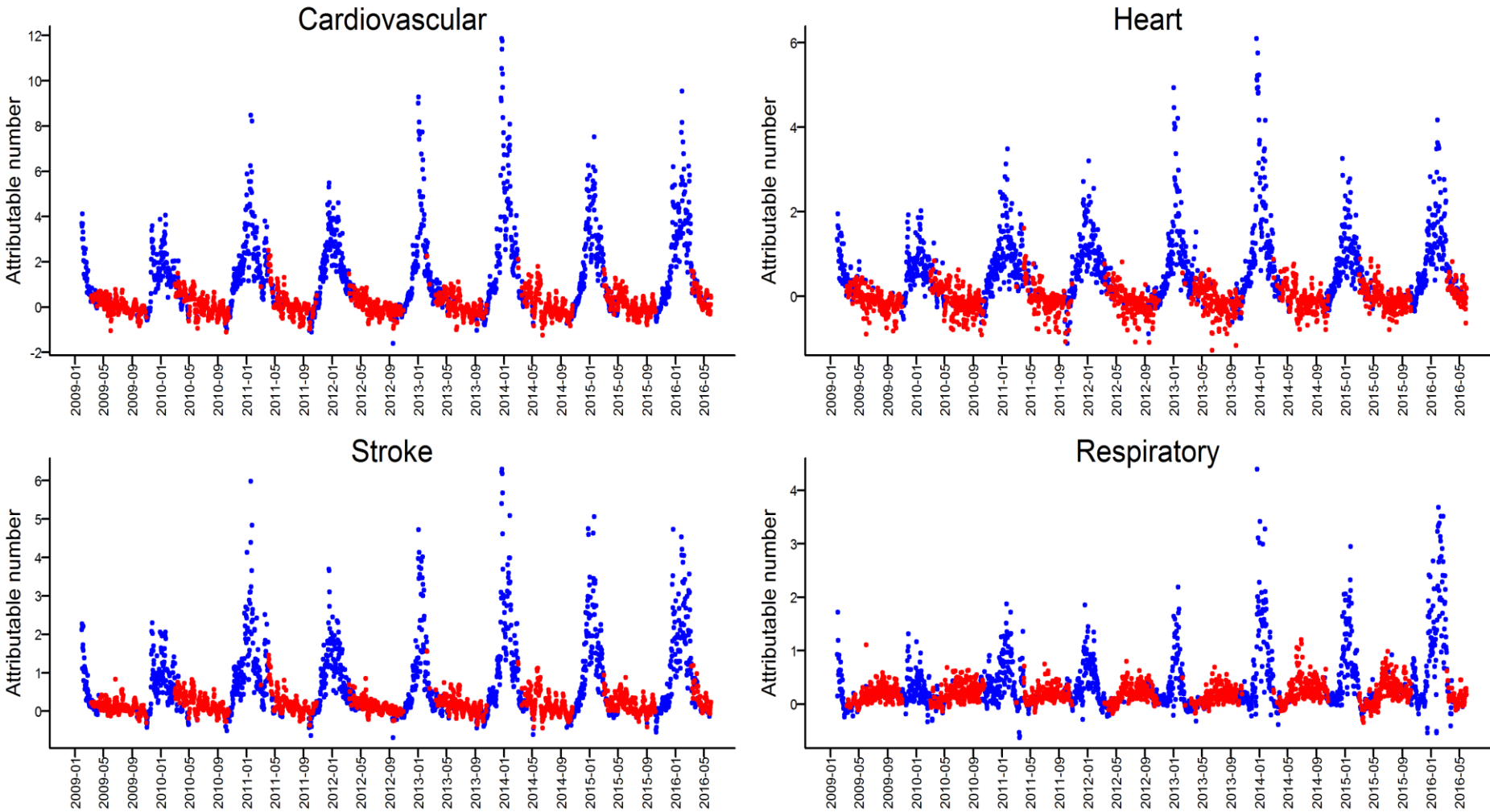


Figure S1. Daily number of cardiovascular, heart, stroke and respiratory deaths attributable to cold (blue points) and heat (red points) temperatures.

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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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4 **1 Burden of non-accidental mortality attributable to ambient**
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6 **2 temperatures: a time-series study in a high plateau area of**
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8 **3 southwest China**
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1 **Abstract**

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

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

13 *Results:* We analyzed 89,467 non-accidental deaths; 4,131 were attributable to overall
14 temperatures, with an attributable fraction of 4.75% (95% eCI 2.33, 6.79). Most of the
15 mortality burden was caused by cold (4.08%; 0.86, 7.12), while the burden due to heat
16 was low and non-significant (0.67%; -2.44, 3.64). Extreme cold (1.17%; 0.58, 1.69)
17 was responsible for 24.6% (i.e., 1.17% divided by 4.75%) of the total death burden. In
18 the stratification analyses, attributable risk due to cold was higher for cardiovascular
19 than respiratory disease (6.18% vs 3.50%). We found a trend of risk of increased
20 death due to ambient temperatures with increasing age, with attributable fractions of
21 1.83%, 2.27%, and 6.87% for age ≤ 64 , 65 – 74, and ≥ 75 years old. The cold-related
22 burden was slightly greater for females, farmers, ethnic minorities, and non-married
23 individuals than their corresponding categories.

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

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

30 **Strengths and limitations of this study**

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

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

9 1. Introduction

10 With the global climate change, ambient temperatures has been extensively
11 demonstrated to directly affect human health (e.g., daily morbidity and mortality) and
12 has become one of the most severe public health problems in the world.[1-5]
13 Exposure to extreme weather such as cold spells and heat waves represents high risk
14 for mortality, and the extreme temperature-related mortality is expected to increase
15 with the increasing frequency, intensity, and duration of extreme weather events.[4,6-
16 8] Low and high temperatures are also well known to be associated with a substantial
17 increase in a wide range of all-cause and cause-specific mortality (e.g., cardiovascular
18 and respiratory diseases).[6,9-12]

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

31 Use of risk assessment of the attributable fraction revealed the burden of
32 mortality associated with ambient temperatures; however, most previous literatures
33 estimated the mortality burden in high-income or low-altitude regions or

1 coastlands,[11,17,20,22-24] and few were conducted in high plateau areas of
2 developing countries.[12,25] The attributable fraction and number for the
3 temperature–mortality association may vary by geographic features, climate, and
4 structure of the population.[25,26] In addition, age, gender, educational attainment,
5 and specific causes were previously identified as modifiers for estimating the effect
6 modification of the mortality risk attributable to ambient temperatures.[27-31]
7 However, few researchers have focused on the potential effect modification of the
8 mortality burden by occupation, race/ethnicity, or marital status.[32]

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

22 **2. Methods**

23 **2.1 Study site**

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

33 **2.2 Data collection**

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3 1 Individual records such as age of death, gender, ethnicity, occupation, marital
4 2 status, cause of death, and date of death for all registered deaths for the period January
5 3 1, 2009 to May 31, 2016, were obtained from the Yuxi Center for Disease Control and
6 4 Prevention, which maintains detailed quality assurance and control measures[33,34].
7 5 The underlying causes of death were classified by medical personnel, and
8 6 examination procedures were routinely performed to ensure accurate data, based on
9 7 the *International Classification of Diseases*, 10th revision (ICD-10). Individual data
10 8 were collapsed into a series of daily counts for the total non-accidental mortality
11 9 (ICD-10 A00–R99) as well as subcategories by specific cause of death
12 10 (cardiovascular [I00–I99], heart [I00–I51], stroke [I60–I69], and respiratory disease
13 11 [J00–J99]), age (0–64, 65–74, and 75+ years old), gender (male and female),
14 12 occupation (farmer and non-farmer), ethnicity (Han nationality and ethnic minorities),
15 13 and marital status (married and non-married). Daily meteorological data for the same
16 14 period were obtained from the China Meteorological Data Sharing System, including
17 15 mean temperature and 4 other meteorological variables (atmospheric pressure, wind
18 16 speed, sunshine duration, and relative humidity).

17 18 **2.3 Patient and public involvement**

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

22 23 **2.4 Statistical analysis**

24 As daily death number under a Poisson distribution and risk of mortality depend
25 on exposure to temperatures of the current and previous days,[25] we applied a
26 standard time-series quasi-Poisson regression model combined with DLNM to
27 estimate the non-linear and lag effects of mean temperature on mortality, with day of
28 the week, long-term trends, and the 4 other meteorological variables as potential
29 covariates. This model can capture the complex non-linear relation and lagged effect
30 by combining 2 functions that define the conventional exposure–response association
31 and the additional lag–response association. The maximum lag period was set to 28
32 days to explore the lag structure of temperature effect, and median temperature
33 (17.0°C) was the reference to calculate attributable risk.[32] We used natural cubic
34 splines with 7 degrees of freedom (*df*) per year for time to describe the long-term

1 trends and seasonality and 3 *df* for the 4 other meteorological indicators. These model
 2 specifications were consistent with previous studies.[24,35]

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

$$AF_{x,t} = 1 - \exp \left[- \sum_{l=0}^L \beta_{x_{t-l}} \right]$$

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

9 where $AF_{x,t}$ and $AD_{x,t}$ are the attributable fraction and the number of cases at day t
 10 (1,2,3...2907), respectively; β_x is the risk associated with the exposure to ambient
 11 temperatures at level x (i.e., $\beta_x = (x - Ref) \times \beta$; *Ref* is the referenced temperature;
 12 β is the coefficient for DLNM of mean temperature; L is the maximum lag for the
 13 effect of mean temperature; and n_t is the observed number of deaths at day t .

14 To estimate the mortality burden from non-accidental deaths, we calculated the
 15 total attributable fraction due to the overall temperatures and divided the total effect
 16 into exposure to low and high temperatures by summing the subsets corresponding to
 17 days with temperatures below and above the median temperature. Also, we explored
 18 the mortality burden attributable to mild and extreme temperatures. Extreme cold and
 19 heat were defined as temperatures below the 2.5th percentile (5.4°C) and above the
 20 97.5th percentile (23.1°C) of mean temperature, and mild cold and heat were defined
 21 as the range between the median temperature and these cutoffs. Monte-Carlo
 22 simulations were used to calculate the empirical confidence intervals (eCIs) of the
 23 attributable fraction and number, assuming a multivariate normal distribution of the
 24 best linear unbiased predictions of the deduced coefficients[19,36]. All statistical
 25 analyses involved use of R v3.0.3, with the “dlnm” package to create the DLNM for
 26 mean temperature.

27 3. Results

28 3.1 Descriptive statistics

1 We analyzed 89,467 non-accidental deaths from Yuxi between 2009 and 2016,
2 with an average of 33 deaths per day (range 12 to 72). The number of deaths due to
3 cardiovascular disease was 41,794 (46.7%), more than half due to stroke; the
4 proportion due to respiratory disease was 18.5% (Table 1). In individual
5 characteristics subgroup, a higher proportion of deaths were for males, older people
6 (≥ 75 years), people with Han nationality, farmers and married people than their
7 corresponding categories. During the study period, the mean daily temperature was
8 16.1 °C (ranging from -3.3 to 25.6 °C) (Table S1). The daily number of non-
9 accidental deaths and mean temperature showed an inverse relation (Figure 1).

10 **3.2 Exposure–response association**

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

19 **3.3 Attributable fraction and number**

20 Table 2 shows the estimated attributable fraction with 95% eCIs of daily non-
21 accidental mortality calculated for total and separate components by heat and cold
22 temperatures. For total non-accidental deaths, the attributable fraction was 4.75%
23 (95% eCI 2.33, 6.79) with the whole temperature range, including heat and cold. Cold
24 temperature was responsible for most of the mortality burden, corresponding to an
25 attributable risk of 4.08% (0.86, 7.12), whereas the burden due to heat was low and
26 non-significant (0.67%; -2.44, 3.64). The attributable risks of cardiovascular and
27 stroke deaths caused by overall temperatures were 5.97% (2.74, 8.74) and 6.50%
28 (2.22, 10.16); the point-estimated risk due to cold was higher for cardiovascular than
29 respiratory deaths (6.18% vs 3.50%).

30 On stratification by age, the attributable risk due to ambient temperatures
31 increased with age, with attributable fractions of 1.83%, 2.27%, and 6.87% for age
32 ≤ 64 , 65–74, and ≥ 75 years, respectively. Those engaged in agriculture had higher
33 attributable fraction, 3.23 times (5.66% vs 1.75%) due to the overall temperatures and
34 3.98 times (4.93% vs 1.24%) due to cold, than non-farmers. The estimated burden due

1 to cold was 2.35-fold higher for ethnic minorities than Han nationality (6.55% vs
2 2.79%), whereas the point-estimated attributable fraction caused by the whole
3 temperature range was approximately equal by gender and marital status.

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

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

20 3.4 Sensitivity analysis

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

29 4. Discussion

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

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3 1 subtropical, plateau monsoon climate. The temperature–mortality associations were
4 2 nonlinear and followed slide-shaped curves, and the risks rapidly increased with
5 3 decreasing mean temperature. Excess deaths were attributable to overall temperatures,
6 4 and cold was responsible for most of the mortality burden. The estimated mortality
7 5 burden attributable to cold was greater for cardiovascular deaths, older people,
8 6 farmers, ethnic minorities, and non-married individuals than their corresponding
9 7 categories.

10 8 Inconsistent with previous ecological evidences that the temperature–mortality
11 9 associations were “U” or “V” shaped curve, with increased mortality risks at
12 10 extremely low and high temperatures [26,37-39], a slide-shaped curve was captured in
13 11 our study, which shows increased relative risk with low temperature, especially
14 12 extreme cold but the risk of high temperature changed minimally. The different
15 13 pattern of temperature–mortality associations might attribute to the unique climate in
16 14 this high-altitude region. Yuxi city has a distinct subtropical plateau monsoon climate,
17 15 with four spring-like seasons year round, giving the city a stable daily mean
18 16 temperature but large temperature difference between day and night, morning or
19 17 evening and daytime, indoor and outdoor. Although the city has a stable daily mean
20 18 temperature of $16.1 \pm 4.9^{\circ}\text{C}$ full year, the daily diurnal temperature range was
21 19 averaging 10.4°C (ranging from 1.1°C to 21.7°C). Furthermore, We also examined
22 20 additional non-accidental deaths attributable to ambient temperatures, with larger
23 21 burden due to cold than heat. A multi-country observational study estimated a total
24 22 mortality burden of death attributable to non-optimal ambient temperatures; the
25 23 attributable fraction ranged from 3.37% in Thailand to 11% in China, which provides
26 24 strong evidence for substantial differences between regions or climates.[17]

27 25 The cold-related mortality burden is an important public health problem in Yuxi.
28 26 Findings from our study showed most of the death burden attributable to low
29 27 temperature, and a much lower and non-significant burden due to heat, which might
30 28 be owing to unique climatic condition that the differences between minimum and
31 29 referent temperature was 20.3°C (-3.3°C vs 17.0°C), while those between referent and
32 30 maximum temperature was 8.6°C (17.0°C vs 25.6°C). Previous studies have found
33 31 that most of the mortality burden is caused by exposure to cold days, with
34 32 comparatively lower attributable risk, or even none, due to heat exposure. For
35 33 example, Hajat et al. (2006) showed that all-cause mortality attributable to heat
36 34 ranged from 0.37% in London (1976–2003) to 1.45% in Milan (1985–2002), and

1 another study conducted in London from 1986 to 1996 found that attributable fraction
2 of mortality for each 1°C decrease below a threshold of 15°C was 5.42% (4.13, 6.69),
3 with no burden due to heat.[40] Although extremely low or high temperature
4 corresponded to increased relative risk of mortality, Gasparrini et al. (2015) found a
5 relatively small part of the death burden attributable to extreme cold temperature,
6 ranging from 0.25% to 1.06%. Similar results from 5 East Asian regions showed a
7 9.36% mortality burden attributable to overall temperatures, with only 0.80% due to
8 extreme cold [20]. However, our current study estimated a larger proportion of
9 attributable mortality fraction due to extreme cold, accounting for about one-quarter
10 of the total mortality burden (1.17% vs 4.75%), even though extreme cold days
11 represented only 2.5% of the whole study period. We found no evidence of additional
12 deaths due to extreme heat in all categories.

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

27 Age has been frequently identified as an important modifier of the association
28 between ambient temperatures and human health.[15,26,30,49] We found that
29 exposure to cold, particularly extreme cold, was closely related to increased death
30 burden for older than younger people. Several previous surveys found increased age
31 associated with point-estimated attributable risk of cardiovascular mortality and both
32 intra-cerebral hemorrhage and ischemic stroke morbidity due to cold, with the highest
33 values in older people.[26,32] Another nationwide study in Japan found most of the
34 proportion of morbidity burden attributable to days with low temperature in all age

1 groups, with an trend of increasing attributable risk with age: the attributable fraction
2 due to cold was 15.96%, 24.84%, and 28.10% with age 18–64, 65–74, and 75–110
3 years, respectively.[37] Older people were more vulnerable to the temperature effects,
4 mainly because they often have multiple pre-existing chronic conditions and
5 physiological changes in thermoregulation and homoeostasis.[50,51] However, the
6 effect modification of temperature-related mortality by gender has been
7 identified.[24,30,37,52] We observed a higher mortality burden caused by exposure to
8 the cold period among females than males in Yuxi, and the cold-related attributable
9 risk was found higher for females than males in Hanoi, Vietnam,[53] and in 47 cities
10 in Japan.[37] The reason for the discrepancy in temperature-related burden by gender
11 might be owing to differences in occupational exposure, physiology and
12 thermoregulation.

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

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

1 married, divorced, or widowed, possibly because married people can be cared for by
2 their partners during the cold period.

3 Our study has some limitations. First, the data were from a single city, so
4 generalizing the findings to other geographic areas or climates should be cautioned.
5 Second, the data of temperature were from monitoring sites rather than exposure
6 measuring of individual. Third, although the concentration of daily mean PM₁₀, NO₂
7 and SO₂ in Yuxi are much lower than those in other 17 Chinese cities [56], we did not
8 control for the potential confounding effects by air pollution due to the unavailability
9 of the complete pollution data in the study area. Last, in the previous multi-country or
10 multicenter studies [5,26], MMT was reasonably used to assess the temperature–
11 mortality associations due to each site corresponding to a MMT. However,
12 inconsistent with those previous studies, our study only involved one city with median
13 temperature as common referent value, which might lead the results incomparable
14 with previous studies. Sensitive analysis with the MMT as referent temperature
15 showed that all of the results were stable substantially when compared to the results
16 estimated by median temperature. But the MMT differed among the sub-groups,
17 which leded the incomparable results in one city (Table S5).

18 **5. Conclusions**

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

28 **Declarations**

29 **Contributors:** Q.Y.Z., Z.D., and C.Y.D. conceived and designed the experiments.
30 L.J.L. and Y.F.W. provide primary data. P.G., S.Y.Y., J.L., Y.W., and C.Y.D.
31 collected and cleaned the data. C.Y.D. analyzed the data and drafted the manuscript.
32

1 Q.Y.Z., Z.D., and C.Y.D. revised the manuscript and interpreted the results. All
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3
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9
10 **Competing interests:** The authors declare no competing financial interests.

11
12 **Data sharing statement:** Please contact the corresponding author for data requests.

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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; 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)

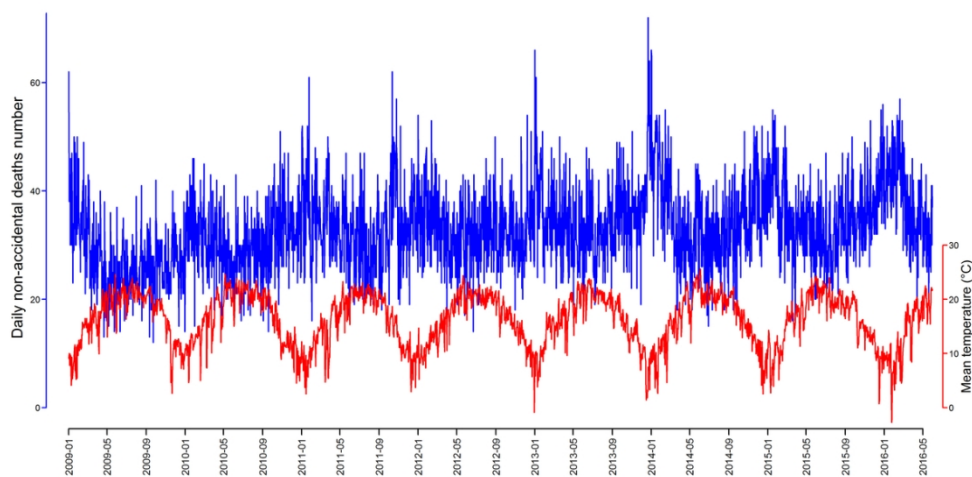
Results are expressed as attributable fractions (95% empirical confidence intervals), and the bold indicates a statistically significant.

Figure Legends

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

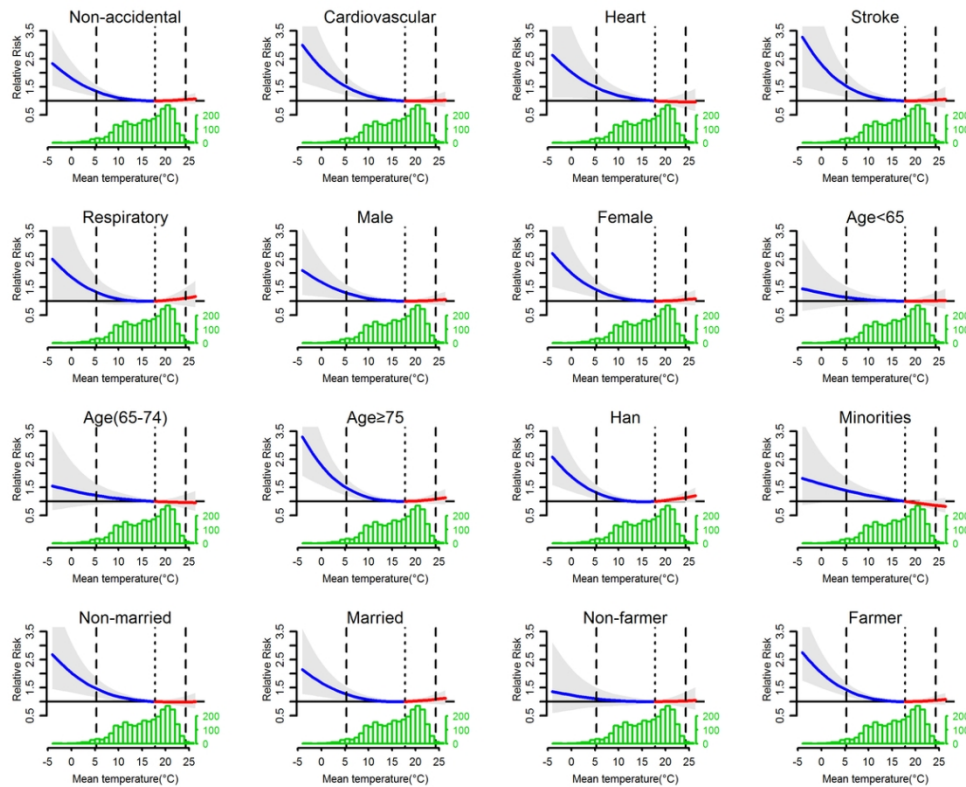
Figure 2. Overall cumulative relative risk (with 95% empirical confidence intervals, shaded grey) at a lag of 0–28 days in Yuxi, China, with histogram of daily temperature distribution. The dotted lines are the median of the mean temperature, and the dashed lines are the 2.5th and 97.5th percentiles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



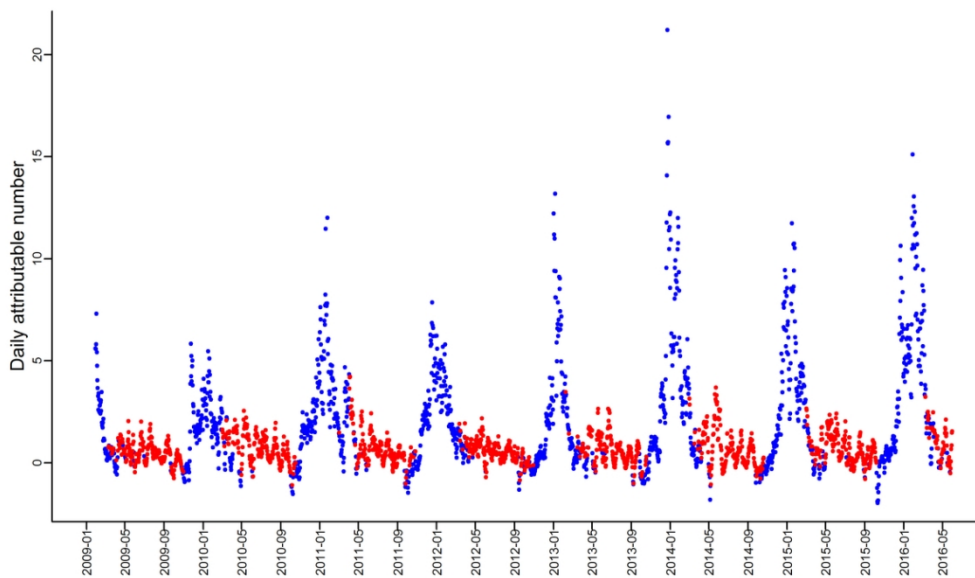
Time series of daily number of non-accidental deaths of Yuxi and mean temperature, 2009–2016

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	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.

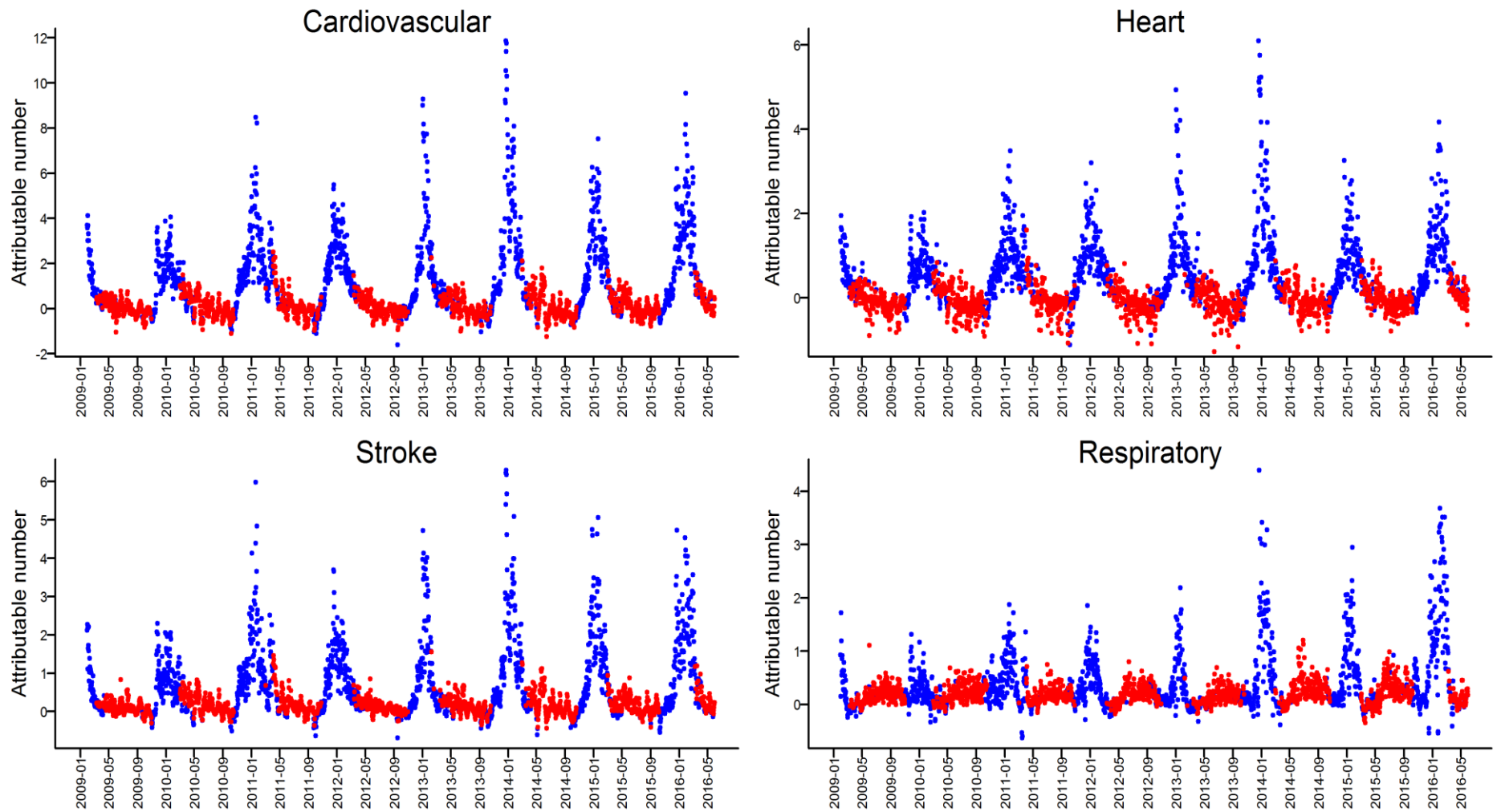


Figure S1. Daily number of cardiovascular, heart, stroke and respiratory deaths attributable to cold (blue points) and heat (red points) temperatures.

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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	not applicable
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	not applicable

		<i>Cross-sectional study</i> —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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	not applicable
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	not applicable
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	not applicable
		<i>Cross-sectional study</i> —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.