Association between ambient temperature and mortality risk and burden: time series study in 272 main Chinese cities

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ABSTRACT

OBJECTIVE

To examine the association between temperature and cause specific mortality, and to quantify the corresponding disease burden attributable to non-optimum ambient temperatures.

DESIGN

Time series analysis.

SETTING

272 main cities in China.

POPULATION

Non-accidental deaths in 272 cities covered by the Disease Surveillance Point System of China, from January 2013 to December 2015.

MAIN OUTCOME MEASURES

Daily numbers of deaths from all non-accidental causes and main cardiorespiratory diseases. Potential effect modifiers included demographic, climatic, geographical, and socioeconomic characteristics. The analysis used distributed lag non-linear models to estimate city specific associations, and multivariate meta-regression analysis to obtain the effect estimates at national and regional levels.

RESULTS

1 826 186 non-accidental deaths from total causes were recorded in the study period. Temperature and mortality consistently showed inversely J shaped associations. At the national average level, relative to the minimum mortality temperature (22.8°C, 79.1st centile), the mortality risk of extreme cold temperature (at −1.4°C, the 2.5th centile) lasted for more than 14 days, whereas the risk of extreme hot temperature (at 29.0°C, the 97.5th centile) appeared immediately and lasted for two to three days. 14.33% of non-accidental total mortality was attributable to non-optimum temperatures, of which moderate cold (ranging from −1.4 to 22.8°C), moderate heat (22.8 to 29.0°C), extreme cold (−6.4 to −1.4°C), and extreme heat (29.0 to 31.6°C) temperatures corresponded to attributable fractions of 10.49%, 2.08%, 1.14%, and 0.63%, respectively. The attributable fractions were 17.48% for overall cardiovascular disease, 18.76% for coronary heart disease, 16.11% for overall stroke, 14.09% for ischaemic stroke, 18.10% for haemorrhagic stroke, 10.57% for overall respiratory disease, and 12.57% for chronic obstructive pulmonary diseases. The mortality risk and burden were more prominent in the temperate monsoon and subtropical monsoon climatic zones, in specific subgroups (female sex, age ≥75 years, and ≤9 years spent in education), and in cities characterised by higher urbanisations rates and shorter durations of central heating.

CONCLUSION

This nationwide study provides a comprehensive picture of the non-linear associations between ambient temperature and mortality from all natural causes and main cardiorespiratory diseases, as well as the corresponding disease burden that is mainly attributable to moderate cold temperatures in China. The findings on vulnerability characteristics can help improve clinical and public health practices to reduce disease burden associated with current and future abnormal weather.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Epidemiological studies have commonly focused on the effects of extreme temperature events or aimed to characterise associations between temperature and mortality

Previous studies have evaluated the mortality burden from all causes and very few specific diseases attributable to non-optimum temperatures

A comprehensive evaluation is lacking on the burden of cause specific mortality associated with non-optimum temperatures

WHAT THIS STUDY ADDS

This nationwide study in China provides a comprehensive picture of the non-linear associations between ambient temperature and mortality from all natural causes and main cardiorespiratory diseases, showing a consistent inversely J shaped association

This study also provides attributable fractions of cause specific mortality to moderate cold, moderate heat, extreme cold, and extreme heat temperatures

The mortality risk and burden are more prominent in the temperate monsoon and subtropical monsoon zones, in specific subgroups (female sex, age ≥75 years, and ≤9 years spent in education), and in cities characterised by higher urbanisations rates and shorter durations of central heating

Introduction

In the context of global climate change, accumulating epidemiological evidence indicates that abnormal ambient temperatures could increase the risk of death from a wide range of cardiorespiratory diseases.[1-3] Knowledge of the optimum temperatures that correspond to minimum mortality (termed as the minimum mortality temperature), as well as the relative risks of mortality from various cardiorespiratory diseases due to non-optimum temperatures, are important to investigate the underlying pathophysiological pathways and to project disease burden associated with climate change.[4]

Previous studies have focused on either estimating the relative risks for extreme weather events or characterising the associations between exposure and response.[5] Consequently, less is known about the relative contribution of moderate and extreme non-optimum temperatures to the whole disease burden using measures such as attributable fractions and attributable numbers.[6-8] Such evidence is important for planning suitable risk communication to the public, tailoring the programmes for public health interventions and evaluating the overall disease burden due to non-optimum ambient temperature.[6] Furthermore, previous single city or regional studies have adopted various analytical approaches and different model specifications (particularly lag periods), reducing the comparability of results across climates and populations.[1,2,3] In a multicentre study, researchers evaluated the exposure-response associations between temperature and total mortality and estimated the total mortality risk attributable to moderate and extreme non-optimum temperatures.[6,9] However, little knowledge was available about the optimum temperatures and the relative risks of mortality from cardiorespiratory diseases associated with non-optimum temperatures, as well as the relative contributions of moderate and extreme non-optimum temperatures on cause specific mortality. Also, researchers used various study periods in the multicentre study,[6,9] which added to the study heterogeneity and limited the comparisons of mortality risk and burden in diverse climatic zones.

Therefore, with an established nationwide dataset including 272 main Chinese cities, the present study aimed to examine the associations between temperature as a whole and cause specific mortality, and to quantify the corresponding disease burden attributable to moderate and extreme non-optimum temperatures. We then examined various potential effect modifiers, including demographic, climatic, geographical, and socioeconomic characteristics.

Methods

Data collection

The present study was based on a national database on weather conditions and cause specific mortality counts in 272 main Chinese cities, from 1 January 2013 to 31 December 2015, which have been described in previous publications.[10-12] These cities were previously selected because they had an average of more than three non-accidental deaths per day according to the death registry of China's Disease Surveillance Points System. To ensure adequate representation at the national and provincial levels, surveillance points were randomly selected by an iterative method involving multistage stratification that took into account the sociodemographic characteristics of the Chinese population.[13] The Disease Surveillance Points System included 605 districts and counties (equal to the number of districts at the administrative level in China) from almost all cities at or above the prefecture level. In each city, the Disease Surveillance Points System covered up to eight districts or counties, depending on the total population size of this city. The data from this death registry have been widely used in policy formulation and disease burden assessment in China and worldwide.[14] In the present study, the population covered by the Disease Surveillance Points System accounted for 26% of the total population in these cities (312m/1 215m people).

The 272 cities were located in five climatic zones, which were proposed by the China Meteorological Administration (fig SM1).[15] The temperate monsoon zone (116 cities) is mainly characterised by high temperatures and rainy summers, and cold and dry winters; the subtropical monsoon zone (140 cities) mainly presents high temperatures and more rain in the summer with mild temperatures and less rain in the winter; the temperate continental zone (six cities) typically has a dry climate and scarce rainfall; the alpine zone (five cities) covers the Qinghai-Tibet plateau region, represented by plenty of snow in the winter half year and a mild cool climate in the summer half year; and the tropical monsoon zone (five cities) is characterised by high temperature and rain throughout the year. The proportions of subpopulations covered by the Disease Surveillance Points System in the total population of each climatic zone were 26% (130m/497m people), 26% (167m/650m), 22% (8m/37m), 33% (6m/18m), 15% (2m/13m), respectively.

We extracted daily death records in each city from the Disease Surveillance Points System, which is administrated by the Chinese Center for Disease Control and Prevention. Daily time series data of deaths for each city were constructed by aggregation of all deaths covered by the Disease Surveillance Points System. We assessed a range of causes of deaths based on the sole primary diagnosis coded by ICD-10 (international classification of diseases, 10th revision), including non-accidental causes (referred as "total" in the present study; codes A00-R99), cardiovascular disease (codes I00-I99), coronary heart disease (codes I20-I25), stroke (codes I60-I69), haemorrhagic stroke (codes: I60-I61), ischaemic stroke (codes I63), respiratory diseases (codes J00-J98), and chronic obstructive pulmonary disease (codes J41-J44). "Cardiovascular disease" included coronary heart disease and stroke, "stroke" included ischaemic stroke and haemorrhagic stroke, and "respiratory disease" included chronic obstructive pulmonary disease. We then divided daily total deaths by sex, age groups (5-64, 65-74, and ≥75 years), and educational attainment (low, ≤9 years of education; high, >9 years of education).

We derived daily mean temperature and mean relative humidity in each city from the China Meteorological Data Sharing Service System (http://data.cma.cn/). To allow for a sensitivity analysis, we obtained air pollution data from China's National Urban Air Quality Realtime Publishing Platform. To allow for a meta-regression analysis, we collected the gross domestic product (GDP) per capita and urbanisation rates for each city from statistic yearbooks at national or provincial levels. We collected data on duration of central heating in each city from the websites of local governments.

Statistical analysis

First stage analysis

We first examined the associations between temperature and mortality in each city by using standard time series regression models in this area.[16] To account for the non-linear and delayed effects of temperature on each cause of mortality, this stage analysis applied an overdispersed generalised linear model in combination with a distributed lag non-linear model (DLNM).[6] Consistent with previous studies, our main model included a natural cubic B spline of calendar day with 12 degrees of freedom per year to control for seasonality and long term trends in mortality, a natural cubic B spline of the present day relative humidity with three degrees of freedom, and a categorical variable of day of the week.[7 17] We then introduced the cross basis function of daily temperature built by the DLNM, which included a quadratic B spline with three internal knots placed at the 10th, 75th, and 90th centiles of city specific temperature distributions; and a lag response curve with a natural cubic B spline with an intercept and three internal knots placed at equally spaced values in the log scale, with the maximum lag up to 21 days.[6 9 18]

Second stage analysis

In the second stage, we obtained the best linear unbiased prediction (BLUP) of the city specific cumulative (≤21 lag days) associations between temperature and mortality at both regional (climatic zones) and national levels using a recently developed multivariate meta-regression approach.[19 20] The BLUP approach made use of a trade-off between the city specific association and the second stage pooled estimation, which could thus provide more precise estimations, especially in cities with small numbers of deaths. We included city specific average temperature, temperature range, indicators for climatic zones, GDP per capita, and urbanisation rates as meta-predictors in BLUP estimations.[6]

We then derived the minimum mortality temperature in each city from the BLUP of the overall cumulative association between temperature and mortality. We referred to the minimum mortality temperature as the optimum temperature, and used it as the reference for calculating the attributable risk. The quadratic B spline of temperature in the first stage analysis was then re-centred according to each city's minimum mortality temperature to obtain accurate risk estimates at a given temperature. We specified the exposure-response curves with two boundary knots that corresponded to the averages of minimum and maximum temperature in each city. This choice generates pooled exposure-response curves with the uniform distribution of temperatures at national or regional levels. We also illustrated the lag patterns in mortality risks associated with the average extreme cold temperature (2.5th centile) and the average extreme hot temperature (97.5th centile).

Estimation of attributable fractions

For each day of the mortality time series mortality in each city, we calculated the overall cumulative relative risk by comparing each day's temperature to the minimum mortality temperature. The attributable deaths and the fraction of attributable deaths during the present day and 21 lagged days were then calculated according to a previously described method.[21] We obtained the total counts of deaths attributable to non-optimum temperatures by summing the contributions from all the days in the series and gained the total attributable fraction by dividing the total number of deaths by the total number of attributable deaths.

We empirically calculated the attributable fractions associated with extreme cold, moderate cold, moderate heat, and extreme heat by summing the subsets of days with relevant temperature ranges according to each city's specific centiles of temperature distribution (that is, <2.5th centile, 2.5th centile up to the minimum mortality temperature, minimum mortality temperature up to the 97.5th centile, and >97.5th centile, respectively).[6] Finally, we derived empirical confidence intervals through Monte Carlo simulations with the assumption of a multivariate normal distribution for the BLUPs of the estimation coefficients.[21]

Effect modification analysis

Firstly, we separately evaluated the attributable mortality burden in subgroups classified by age, sex, and educational attainment using the above two stage models to identify the potential vulnerable subpopulations to the effects of non-optimum ambient temperatures. Secondly, in addition to the analyses in different climatic zones, we did heterogeneity tests on city level characteristics of climate, geography and socioeconomic conditions. In brief, we fit univariable meta-regression models based on the above BLUP analyses. Each model included a single meta-predictor (that is, annual mean temperature, temperature variation (standard deviation), temperature range, mean humidity, latitude, longitude, GDP per capita, and urbanisation rate). The associations between temperature and mortality were predicted for the values of the approximate 25th and 75th centiles of these characteristics.[20] Furthermore, we fit multivariable meta-regression models with all city characteristics included. We tested the statistical significance for the meta-predictor(s) through a multivariate Wald test.

Thirdly, we fit separate multivariable meta-regression models to evaluate the effect modifications by duration of central heating and city characteristics listed above in the mortality risk and burden due to non-optimum temperatures. Finally, we plotted the associations between minimum mortality temperatures and city characteristics to see how local acclimatisation varied by city.

Sensitivity analysis

As it was not easy to determine an appropriate lag for temperature's effects, we used alternative maximum lag periods of seven, 14, and 28 days in the total mortality analysis. We also controlled for the two day average concentrations of fine particulate matter and ozone (as indicators of air pollution) in another analysis. We used R software (version 3.4.2, R Foundation for Statistical Computing) to perform all analyses, with the dlnm package to fit DLNM and the mvmeta package to conduct the multivariate meta-analysis. For all statistical tests, two tailed P values less than 0.05 were considered statistically significant.

Patient and public involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for recruitment, design, or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Results

Descriptive statistics

Table 1 provides the descriptive statistics on average number of daily deaths during the study period and weather conditions in 272 Chinese cities from 2013 to 2015. We recorded a daily average of 16 total non-accidental deaths, which differed among 272 cities according to the size of permanent populations. During the study period, we found 1 826 186 non-accidental deaths from total causes, 856 522 from overall cardiovascular disease, 306 601 from coronary heart disease, 415 227 from overall stroke, 124 539 from ischaemic stroke, 186 879 from haemorrhagic stroke, 217 321 from overall respiratory diseases, and 159 206 from chronic obstructive pulmonary disease. We saw large variations in climatic conditions among these cities with an annual mean temperature of 15°C and an annual mean relative humidity of 68%. The data on duration of central heating were available in 121 northern cities, and daily air pollutant concentrations were available in 69 cities with three year data, 74 cities with two year data, and 129 cities with one year data. No data on daily mortality and weather conditions were missing for any of the cities during the study.

Regression results

Associations between temperature and mortality

Figure 1 illustrates the BLUP on the pooled cumulative exposure-response curves for the associations between daily temperature and cause specific mortality in 272 main Chinese cities. The curves were consistently inversely J shaped with increased mortality risks for non-optimum temperatures. The minimum mortality temperatures were similar for all mortality causes, and lower temperatures had larger mortality risks than higher temperatures.

As shown in figure 2, the mortality risks of extreme cold temperature (−1.4°C, on average) generally occurred on lag day 1, increased up to lag day 5, and decreased to lag day 15 with mild effects on subsequent days. By contrast, the mortality risks of extreme hot temperature (29.0°C on average) were the strongest on the present day, attenuated drastically to lag day 2 or 3, and followed by a significant mortality displacement (that is, relative risks below 1.0) on the subsequent days for almost all death causes (fig 3).

Table 2 summarises the BLUP characteristics of the cumulative associations between temperature and cause specific mortality over lag days 0 to 21. At the national level, the minimum mortality temperature was 22.8°C, corresponding to the 79.1st centile (mean) of temperature distribution. The minimum mortality centile varied slightly by causes of death between the 70.5th and 85.1th centiles, corresponding to the temperature range of 21.6°C to 23.7°C. Compared with the minimum mortality temperatures, extreme cold temperature had larger relative risks than extreme hot temperature on mortality. The relative risks of mortality from cardiovascular disease associated with extreme cold temperature were larger than those of mortality from respiratory disease. The minimum mortality temperature and cold related relative risks for mortality from haemorrhagic stroke was higher than those for mortality from ischaemic stroke. The distributions of

Table 1 | Summary descriptive statistics on average number of daily non-accidental deaths and weather conditions in 272 Chinese cities, 2013-15

Variables	Mean (standard deviation)	Minimum value	25th centile	50th centile	75th centile	Maximum value
No of non-accidental deaths*						
Total	16 (16)	3	7	12	20	165
Cardiovascular disease	8 (7)	1	3	6	10	65
Coronary heart disease	3 (3)	0	1	2	3	28
Stroke	4 (4)	0	2	3	5	33
Ischaemic stroke	1 (1)	0	0	1	2	8
Haemorrhagic stroke	2 (2)	0	1	1	2	17
Respiratory disease	2 (3)	0	1	1	3	34
Chronic obstructive pulmonary disease	2 (2)	0	0	1	2	29
Weather						
Temperature (°C)	15 (5)	−0.5	12	16	18	25
Humidity (%)	68 (10)	35	61	71	77	91

*Total=non-accidental deaths from all causes; cardiovascular disease includes coronary heart disease and stroke, stroke includes ischaemic stroke and haemorrhagic stroke, and respiratory disease includes chronic obstructive pulmonary disease.

Fig 1 | Pooled cumulative exposure-response curves for associations between daily temperature and cause specific mortality over lag days 0-21 in 272 main Chinese cities, 2013-15, by cause of death. Solid lines=mean relative risks of mortality (temperatures v the minimum mortality temperature); shaded areas=95% confidence intervals; total=non-accidental deaths from all causes

minimum mortality centiles and temperatures for each cause of death are provided in table SM1.

Attributable fractions

Figure 4 illustrates the attributable fractions of various causes of mortality associated with different components of non-optimum temperatures at the national level. The overall attributable fractions of non-optimum temperatures on total mortality were 14.33% (95% empirical confidence interval 13.06% to 15.14%). However, attributable fractions were higher for cardiovascular diseases and lower for respiratory diseases. Attributable fractions were 17.48% (15.97% to 18.65%) for overall cardiovascular disease, 18.76% (17.14% to 19.83%) for coronary heart disease, 16.11% (14.03% to 17.87%) for overall stroke, 14.09% (10.90% to 17.04%) for ischaemic stroke, 18.10% (15.30% to 20.45%) for haemorrhagic stroke,

Fig 2 | Overall lag structure in effects of extreme cold temperature on daily cause specific mortality in 272 main Chinese cities, 2013-15, by cause of death. Effects were defined as the risks at −1.4°C (that is, the mean of the 2.5th centile of temperature distributions) compared with the estimated minimum mortality temperature. Solid lines=mean estimates; shaded areas=95% confidence intervals; total=non-accidental deaths from all causes

10.57% (8.83% to 12.04%) for overall respiratory disease, and 12.57% (10.31% to 12.57%) for chronic obstructive pulmonary disease.

Compared with hot temperatures, cold temperatures were responsible for most of the attributable fractions (proportions ranging from 73.20% to 88.52% by different causes of mortality). We further separated the overall attributable fraction of total mortality due to non-optimum temperatures into four components, including moderate cold (ranging from −1.4 to 22.8°C), moderate heat (22.8 to 29.0°C), extreme cold (−6.4 to −1.4°C), and extreme heat (29.0 to 31.6°C) temperatures. Moderate cold contributed to the largest attributable fraction (ranging from 64.55% to 80.57%), whereas only a small fraction of mortality was attributable to extreme cold (5.80% to 10.16%) or extreme heat (2.73% to 4.90%) for various death causes. As an example, moderate cold, moderate

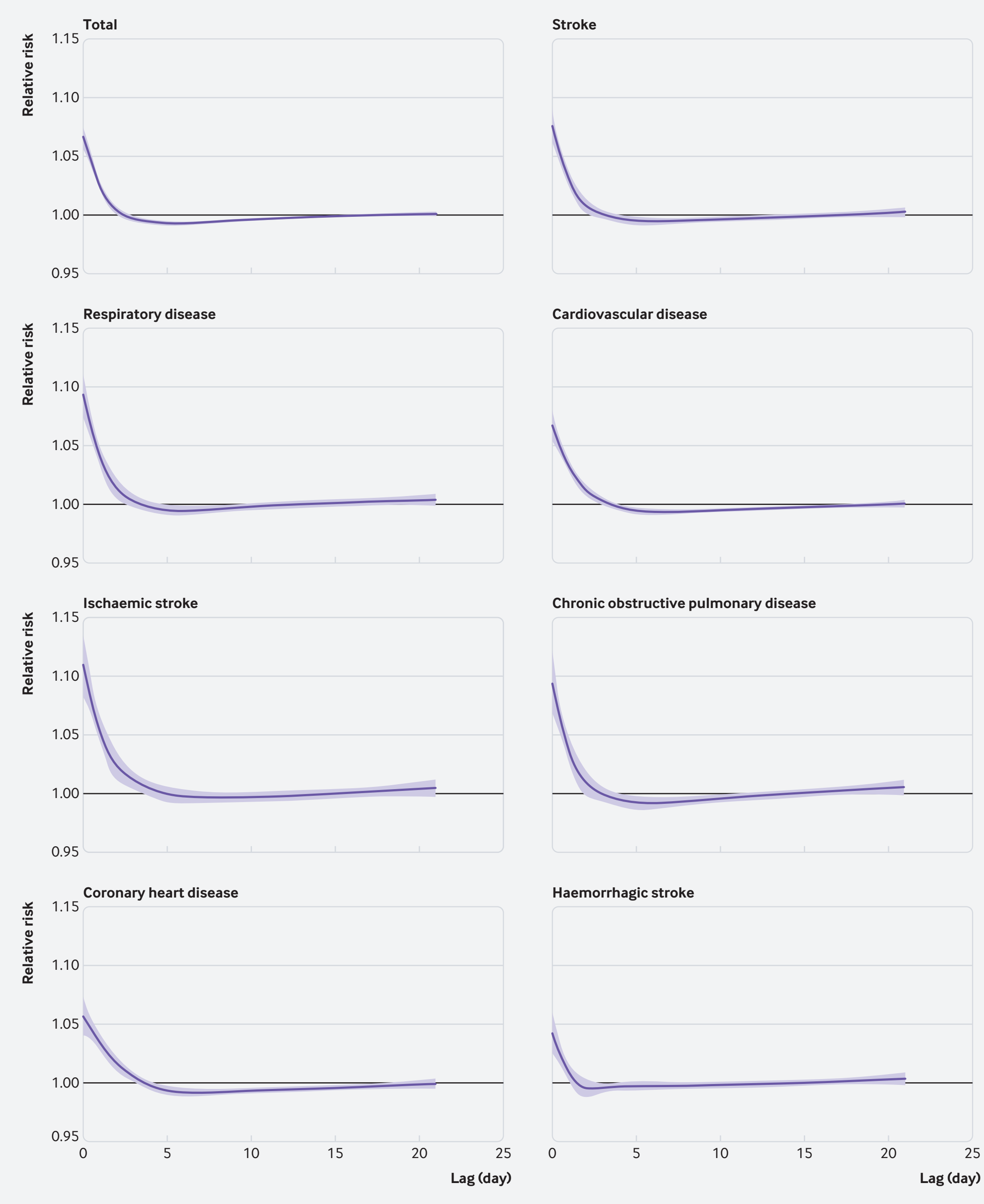

Fig 3 | Overall lag structure in effects of extreme hot temperature on daily cause specific mortality in 272 main Chinese cities, 2013-15, by cause of death. Effects were defined as the risks at 29°C (that is, the mean of the 97.5th centile of temperature distributions) compared with the estimated minimum mortality temperature. Solid lines=mean estimates; shaded areas=95% confidence intervals; total=non-accidental deaths from all causes

heat, extreme cold, and extreme heat temperatures were responsible for attributable fractions of 10.49%, 2.08%, 1.14%, and 0.63% for total mortality, respectively. We provide numerators and denominators for all these attributable fractions in table SM2.

Estimations in climatic zones

When dividing all the 272 cities into five climatic zones, we found different exposure-response curves and lag structure for the BLUP estimations on the associations between temperature and total mortality. According to the exposure-response curves (fig SM2), we saw significant mortality increments associated with non-optimum temperatures in the temperate monsoon zone and subtropical monsoon zone. The minimum mortality centile in the subtropical monsoon zone was higher than that in the temperate monsoon zone (table 3). The relative risks for cold temperatures

Table 2 | Relative risks of daily cause specific mortality associated with non-optimum ambient temperatures in 272 main Chinese cities, 2013-15

Death causes*	Minimum mortality centile†	Minimum mortality temperature (°C)	Relative risk (95% CI) Extreme low‡	Extreme high‡
Total	79.1	22.8	1.68 (1.57 to 1.81)	1.16 (1.12 to 1.21)
Cardiovascular disease	80.3	22.8	1.92 (1.75 to 2.10)	1.22 (1.16 to 1.28)
Coronary heart disease	78.1	23.1	1.96 (1.74 to 2.22)	1.19 (1.11 to 1.28)
Stroke	80.0	22.6	1.85 (1.63 to 2.09)	1.24 (1.16 to 1.32)
Ischaemic stroke	70.5	21.8	1.78 (1.46 to 2.16)	1.41 (1.26 to 1.59)
Haemorrhagic stroke	85.1	23.7	1.59 (1.34 to 1.89)	1.10 (1.02 to 1.19)
Respiratory disease	71.2	21.6	1.53 (1.36 to 1.74)	1.36 (1.24 to 1.48)
Chronic obstructive pulmonary disease	79.6	21.7	1.54 (1.35 to 1.77)	1.26 (1.14 to 1.39)

*Total=non-accidental deaths from all causes; cardiovascular disease includes coronary heart disease and stroke; stroke includes ischaemic stroke and haemorrhagic stroke; and respiratory disease includes chronic obstructive pulmonary disease.
†Minimum mortality centile of temperature distributions.
‡Low=2.5th centile of temperature distribution (−1.4°C on average); high=97.5th centile of temperature distribution (29.0°C on average). Data presented as means and 95% confidence intervals.

were larger in the temperate monsoon zone than in the subtropical monsoon zone, while those for hot temperatures were in the opposite direction. Similar to the nationwide estimates, cold temperatures accounted for the largest proportions of mortality burden. The mortality burden (especially the heat related burden) in the temperate monsoon zone was higher than in the subtropical monsoon zone. Estimations of mortality relative risks and burdens were statistically insignificant in the other three climatic zones, with much wider confidence intervals (figs SM2-4; table 3).

Results of effect modification

Figure 5 presents the attributable fractions of non-optimum temperatures for total mortality in subgroups by age, sex, and educational attainment at the national level. The overall attributable fraction was higher in specific subgroups (female sex, age ≥75 years, and ≤9 years spent in education). The attributable fractions for different components of non-optimum temperatures were similar for various subgroups (numerators and denominators are listed in table SM3).

We saw significant heterogeneity between cities in the estimations of associations between temperature and mortality (I^2=40.6% for total mortality). According to the top panels of figures SM5-SM12 and results of the Wald test, we saw a significant difference (P=0.03) between the two predicted exposure-response curves divided by the 25th and 75th centiles of GDP per capita. These figures also showed significant differences in the lag patterns for the effects of extreme hot temperature (P<0.001) and extreme cold temperature (P=0.009) divided by the 25th and 75th centiles of urbanisation rates. The above differences remained statistically significant in meta-regression models including all city characteristics. In a meta-regression model with all continuous variables of characteristics, we found a mild increment in mortality risk associated with extreme hot temperature (relative risk 1.02, P=0.02) per 10% increase in urbanisation rates. Furthermore, we found a modest decrease in mortality risk associated with extreme cold temperature (relative risk 0.98, P<0.001) for every additional 10 days of central heating.

We also found a modest decrease (β=−0.43%, P=0.04) in cold related attributable fractions of total mortality associated with an additional 10 days of central heating when considering all city characteristics together. There were no significant differences in estimations of temperature-mortality association curves, relative risks, and disease burdens in relation to other city characteristics. Minimum mortality temperatures decreased with a colder climate, larger temperature variation or range, higher latitude, and longer duration of central heating (fig SM13).

Results of sensitivity analysis

In the first sensitivity analysis (table SM4), the minimum mortality centiles and temperatures, relative risks of mortality, and attributable fractions increased from a maximum lag of seven days to 21 days, and remained almost unchanged when the maximum lag was extended to 28 days. The estimations on the temperature-mortality associations and disease burden did not change after controlling for the simultaneous exposure to air pollutants (table SM5).

Discussion

Principal findings

Using uniform and the most up-to-date methodology, we characterised the exposure-response associations between ambient temperature and mortality from all natural causes, overall cardiovascular disease, coronary heart disease, overall stroke, haemorrhagic stroke, ischaemic stroke, overall respiratory diseases, and chronic obstructive pulmonary disease in 272 main Chinese cities. We further estimated the consequent disease burden of non-optimum cold and hot temperatures in five different climatic zones and for different subgroups. In addition, we examined a variety of socioeconomic, geographical, and climatic characteristics as potential effect modifiers. Our results showed that both cold and hot temperatures were associated with increased mortality risks from various cardiopulmonary diseases, and non-optimum temperatures (especially moderate cold) were responsible for a considerable fraction of premature deaths in China. Finally, we identified some effect modifications by climatic zones, demographic characteristics, and socioeconomic characteristics.

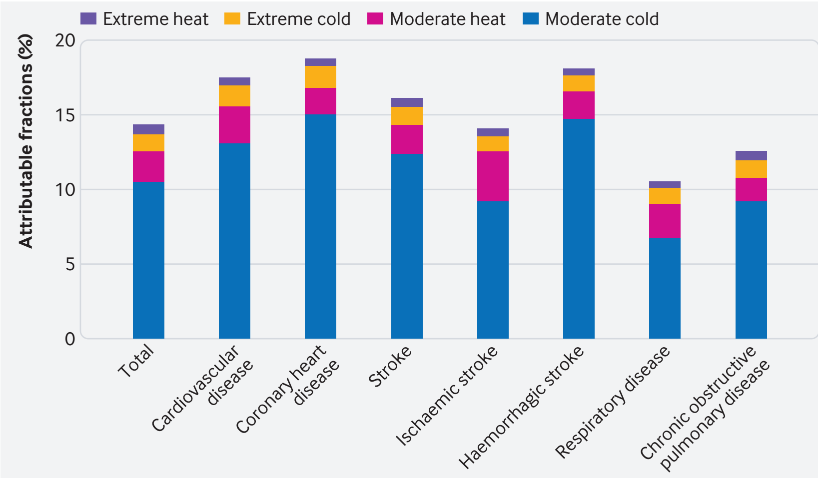

Fig 4 | National average fractions of mortality attributable to moderate and extreme non-optimum temperatures, classified by different causes of death. At the national average level, moderate cold temperatures range from −1.4 to 22.8°C, moderate heat temperatures range from 22.8 to 29.0°C, extreme cold temperatures range from −6.4 to −1.4°C, and extreme heat temperatures range from 29.0 to 31.6°C. Total=non-accidental deaths from all causes

Principal findings and interpretations

We found associations between temperature and mortality to be consistently inversely J shaped, which have been shown in the majority of previous multicity studies.[1-3 9 17] Also consistent with previous studies, the effects of cold temperature could last longer than two weeks, whereas the effects of hot temperature appeared immediately, persisted only two or three days, and were followed by a mortality displacement.[9 22 23] Accordingly, we estimated much higher relative risks for cold temperatures than for hot temperatures. The findings on the lag patterns implied that prompt and transient preventive measures could help address heat related health risks, while prolonged protection would be need to address cold related risks. In the present study, the minimum mortality centile for the association between temperature and total mortality was centred at 84th centile (median) of temperature, which was similar to China's estimate (15 cities) reported in a previous global analysis.[6]

We also evaluated the mortality burden attributable to non-optimum temperatures and separated the attributable fractions due to different components of non-optimum temperatures. Our findings showed that non-optimum temperature could account for an overall attributable fraction of 14.33% in total mortality in China, which was comparable to China's estimate of 11.00% reported in the global analysis.[6] Consistent with this study, the present analysis showed that cold temperature was mainly responsible for the mortality burden, which was caused by the right shifted minimum mortality temperature (leading to more cold days) in the temperature distribution as well as the higher and more delayed effects of cold temperature than of hot temperature (fig 1, fig 2, and fig 3). The prolonged mortality effects of cold temperature might be explained by the indirect pathway through influenza infection.[24] Moderate cold and moderate heat resulted in much larger attributable fractions than extreme cold and extreme heat, merely because they accounted for more days.

The present study provides ample evidence about the mortality risk and burden of various non-optimum temperatures on major cardiorespiratory diseases, which have rarely been investigated. The overall attributable fractions of cardiovascular and stroke mortality in our study were similar to those reported previously in 15 or 16 large Chinese cities.[7 8] We found higher minimum mortality temperatures and cold related relative risks for cardiovascular diseases than for respiratory diseases. Accordingly, the overall attributable fractions of cardiovascular mortality attributable to cold temperature were larger than of respiratory mortality. The stronger and more prominent effects of cold temperature found on the cardiovascular system than on the respiratory system were consistent with previous studies,[17 25 26] and were also biologically plausible. For example, the effects from cold temperatures on the cardiovascular system are often due to potential complications associated with increased cardiovascular risks in relation to changes in autonomic nervous system, blood pressure, thermogenesis, inflammatory response, and oxidative stress.[27 28] The effects from cold temperatures on the respiratory system might be due to increased respiratory infections in cold days.[29] Compared with ischaemic stroke mortality, haemorrhagic stroke mortality was more affected by cold temperature and less affected by hot temperatures, which might be explained by the elevated blood pressure in cold weather and reduced blood pressure in hot weather.[30]

In this nationwide analysis, we also identified potential effect modification in terms of demographic, climatic, and socioeconomic characteristics, which were important to develop evidence based health protection plans against abnormal weather or climate changes.[31] We found that the mortality burden attributable to non-optimum temperatures were larger in people who were aged 75 years and older, who were female, and who spent relatively less time in education (up to nine years), which may be explained by potential vulnerabilities in these subgroups.[32] Compared with the subtropical monsoon zone, the temperate monsoon zone had a larger mortality burden due to non-optimum temperatures, especially in hot temperatures. This finding could be due to the weak capability of heat adaptation in the temperate monsoon zone, reflected by the much lower minimum mortality centile in this zone than in the subtropical monsoon zone (72.1st centile *v* 82.5th centile). The increased effects from hot temperatures in colder regions was also consistent with previous studies.[17 23]

The associations between temperature and mortality and the resulting disease burden were weak and statistically non-significant in the temperate continental zone, alpine zone, and tropical monsoon zone, which could be due to high statistical uncertainty in relation to the small populations and the few cities

Table 3 | Relative risk and attributable fractions of daily total mortality associated with non-optimum ambient temperatures in 272 main Chinese cities, 2013-15, by climatic zone

Climatic zone	Minimum mortality centile*	Minimum mortality temperature (°C)	Relative risk (95% CI)†		Attributable fraction (%; 95% eCI)‡		
			Extreme low	Extreme high	Overall	Cold	Heat
Nationwide	79.1	22.8	1.68 (1.57 to 1.81)	1.16 (1.12 to 1.21)	14.33 (13.06 to 15.14)	11.62 (10.64 to 12.38)	2.71 (1.98 to 2.98)
Temperate monsoon	72.1	22.7	1.52 (1.37 to 1.68)	1.06 (1.03 to 1.09)	17.41 (15.62 to 18.97)	12.13 (10.89 to 13.26)	5.28 (4.11 to 6.41)
Subtropical monsoon	82.5	22.5	1.33 (1.25 to 1.41)	1.27 (1.17 to 1.38)	13.04 (11.56 to 14.34)	11.93 (10.68 to 13.11)	1.11 (0.74 to 1.46)
Temperate continental	25.3	−7.6	1.06 (0.83 to 1.36)	1.77 (0.93 to 3.38)	8.27 (−48.10 to 48.63)	1.70 (−9.63 to 6.23)	6.57 (−55.68 to 48.62)
Alpine	33.7	−2.9	1.09 (0.89 to 1.34)	1.21 (0.69 to 2.13)	5.92 (−59.45 to 39.61)	3.68 (−18.80 to 20.15)	2.24 (−50.21 to 28.37)
Tropical monsoon	92.1	29.1	1.25 (0.86 to 1.81)	1.04 (0.92 to 1.18)	3.88 (−6.05 to 29.80)	3.51 (−4.22 to 23.23)	0.37 (−7.05 to 10.42)

*Minimum mortality centile of temperature distributions.
†Data presented as means and 95% confidence intervals. Extreme low=2.5th centile of temperature distribution (−1.4°C on average); extreme high=97.5th centile of temperature distribution (29.0°C on average).
‡Data presented as the means and 95% empirical confidence intervals.

included. We also found some significant modifications in terms of socioeconomic characteristics. In multivariate meta-regression models, GDP per capita and urbanisation rates could modify the temperature-mortality association and its lag structure. Increased urbanisation rates corresponded to stronger effects from hot temperatures, which might be due to so-called heat island effects[33]; and a longer duration of central heating decreased mortality risk and burden attributable to cold temperature, increasing the adaptive capability against cold exposure.[33]

Strengths and limitations

This study had several major strengths. Firstly, we used the largest database of good internal consistency in data collection in developing countries, which had reliable external representativeness for our findings. Secondly, our results provided novel and robust evidence on the mortality risk and burden from both all natural causes and main cardiorespiratory diseases attributable to various non-optimum temperatures. Thirdly, this investigation also provided ample evidence regarding the associations between temperature and mortality in various climatic zones, vulnerable subgroups, as well as the determinants of acclimatisation in terms of climatic, geographical, and socioeconomic characteristics at the city level.

Limitations must also be acknowledged. Firstly, as done in most previous epidemiological studies, we used temperature data from fixed site outdoor monitors rather than individual direct measurements, which could have resulted in exposure measurement errors. However, these errors are considered likely to be random and to underestimate the effects.[34] Secondly, also similar to most previous studies, this investigation was inherently an ecological study in which individual level confounders were not controlled. Therefore, the estimated mortality risks and attributable fractions due to non-optimum temperatures should be interpreted cautiously. Thirdly, although the death registry used in the present study was under strict quality control, we cannot exclude the possibility of diagnosis or coding errors for death causes in such a large scale nationwide study.

Additionally, the number of cities differed by climatic zones according to the climatic divisions and the inclusion criteria, probably attenuating the comparability of our findings in different climatic zones. Furthermore, previous studies have reported that abnormal temperatures could induce suicide,[35 36] but we failed to evaluate the burden of suicide mortality attributable to non-optimum temperatures because of the very few cases (fewer than one per day on average in most cities). Finally, although the seasonality had been adjusted by modelling the time trends, the effects of non-optimum temperatures (especially cold temperatures) need to be cautiously interpreted because of the possible residual confounding by the cold season and influenza.[24] However, previous studies have shown that influenza accounted for a very small proportion of winter mortality and that controlling for

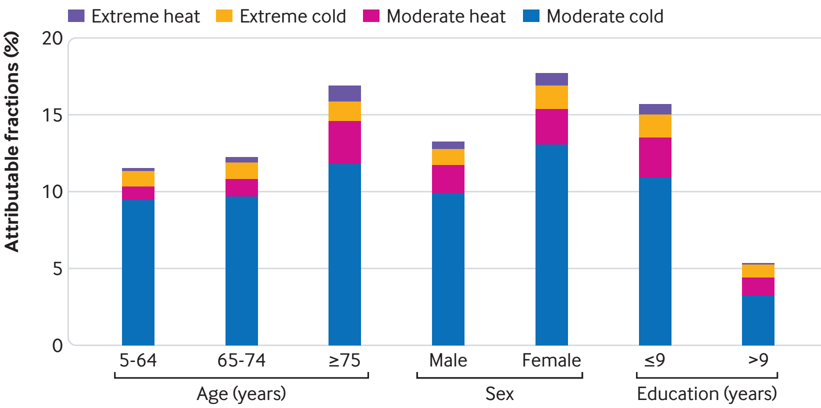

Fig 5 | National average fractions of total mortality attributable to moderate and extreme non-optimum temperature, classified by age, sex, and education. At the national average level, moderate cold temperatures range from −1.4 to 22.8°C, moderate heat temperatures range from 22.8 to 29.0°C, extreme cold temperatures range from −6.4 to −1.4°C, and extreme heat temperatures range from 29.0 to 31.6°C. Total=non-accidental deaths from all causes

it would not substantially change the effect estimates of cold temperature.[37 38]

Conclusions and implications

This nationwide study provided a comprehensive picture of the non-linear associations between ambient temperature and mortality from all natural causes and main cardiorespiratory diseases in China. Our study further evaluated corresponding mortality burden attributable to non-optimum temperatures, in which moderate cold temperatures were mainly responsible. Our results have important implications for the possible inclusion of non-optimum temperatures in the future assessment of the disease burden overall. The findings on individual level and city level characteristics of vulnerability can help improve clinical and public health practices to reduce the disease burden associated with current and future abnormal weather.

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Ethical approval: The institutional review board at the School of Public Health, Fudan University, approved the study protocol (No 2014-07-0523) with a waiver of informed consent. Data were analysed at aggregate level and no participants were contacted.

Data sharing: The mortality data can only be applied for through a government data sharing portal (www.phsciencedata.cn/Share/edtShare.jsp). Data on the environment and city characteristics are available on the government's statistic yearbooks or websites listed in the methods section.

The lead authors (HK and MZ) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Web appendix: Supplementary materials