The impact of non-optimum temperatures, heatwaves and cold spells on out-of-hospital cardiac arrest onset in a changing climate in China: a multi-center, time-stratified, case-crossover study

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Summary

Background Out-of-hospital cardiac arrest (OHCA) is a time-critical and fatal medical emergency that has been linked to non-optimal temperatures. However, the future burden of OHCA due to non-optimal temperatures, heatwaves, and cold spells under climate change has not been well evaluated.

Methods We conducted a time-stratified case-crossover study in 15 Northern Chinese cities throughout 2020 to estimate the exposure-response relationships of non-optimal temperatures, heatwaves, and cold spells with hourly OHCA onset in hot and cold seasons. We obtained future daily average temperatures by using 20 general circulation models under two greenhouse gas emission scenarios: one with certain emission control and the other with relaxed control. Lastly, we projected the change of OHCA burden under these two climate scenarios.

Findings We analyzed a total of 29,671 OHCA patients and found that high temperatures and heatwaves as well as low temperatures and cold spells were all significantly associated with an increased risk of OHCA onset. Under the scenario of uncontrolled emissions, the attributable fraction (AF) of OHCA due to high temperatures and heatwaves would increase by 4.94% and 6.99% from the 2010s to 2090s, respectively. The AF due to low temperatures would decrease by 1.27% by the 2090s and the effects of cold spells were projected to be marginal after the 2050s. Under a medium emission control scenario, the upward trend of heat-related OHCA burden would become flat, and the decline in cold-related OHCA burden would also slow down.

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Interpretation Our study provides evidence of significant morbidity risk and burden of OHCA associated with global warming across Northern China. Our findings indicate that the increase in OHCA burden attributable to heat could not be offset by the decrements attributable to cold, emphasizing the importance of mitigation policies for limiting global warming and reducing the associated risks of OHCA onset.

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Keywords: Climate change; Ambient temperature; Heat wave; Cold spell; Out-of-hospital cardiac arrest

Research in context

Evidence before this study

We searched PubMed, Web of Science, Embase, and Google Scholar up to January 28, 2023, using search terms “ambient temperature”, “heatwave”, “heat”, “cold spell”, “cold”, “out-of-hospital cardiac arrest”, “OHCA”, “climate change”, “projection”, “estimation”, and “prediction” without language restrictions, to identify papers exploring the relationships between non-optimal temperatures, heatwaves, and cold spells with out-of-hospital cardiac arrest (OHCA) onset, and projecting future OHCA morbidity burden associated with these factors in a changing climate. There has been no study quantifying the future burdens of OHCA associated with heatwaves and cold spells under climate change scenarios. Only one previous time-series study has projected a net reduction in future OHCA onset burden related to non-optimal temperatures across various climate scenarios in Japan. Additionally, most researches linked OHCA onset, a time-critical and fatal emergency, with temperature metrics (non-optimal temperatures, heatwaves, and cold spells) during calendar days, which could be challenged by unclear chronological order of exposure and events. Therefore, particularly in the context of global warming, it is crucial to estimate future OHCA morbidity burden using the relationship between temperature metrics and the hourly onset of OHCA.

Added value of this study

This study comprehensively assessed the future OHCA morbidity burden related to non-optimal temperatures, heatwaves, and cold spells in Northern China under different climate change scenarios. Using an individual-level, case-crossover study design and more accurate exposure windows, we found that non-optimal temperatures, heatwaves, and cold spells were all significantly associated with OHCA onset. Our results also suggest that the increase in OHCA burden due to heat cannot be counterbalanced by the decrease due to cold, particularly under uncontrolled emission scenarios.

Implications of all the available evidence

As global warming accelerates, the health impacts of OHCA due to high temperatures and heatwaves in China are expected to increase continuously, even under a medium emission scenario. Targeted public health interventions (such as early warning systems) and mitigation policies (such as strict greenhouse-gas emission policies) are necessary to mitigate the OHCA risks associated with non-optimal temperatures, heatwaves, and cold spells in the context of global climate change.

Introduction

Out-of-hospital cardiac arrest (OHCA) is the most time-critical and fatal medical emergency, contributing to a large proportion of premature deaths and loss of disability-adjusted life years worldwide.[1] The OHCA constitutes a heavy burden with the incidence varying from 23.2 to 170 per 100,000 persons,[2,3] which has a low survival to hospital discharge ranging from 3.1% to 20.4%.[4] Therefore, there is an urgent need for identifying and reducing the risk factors for the onset of OHCA.[5]

Previous studies have shown that non-optimal temperatures, heatwaves, and cold spells are associated with OHCA, but the results are not consistent.[6–9] For example, a time-series analysis conducted in Australia found that heatwaves increased the risk of OHCA onset, but daily high temperatures were not significantly associated with OHCA onset.[6] In contrast, another time-series study in Japan indicated that both high and low temperatures were significantly associated with the increased risk of OHCA.[8] These inconsistencies may not solely be attributed to regional heterogeneity, but also to differences in statistical methods and study designs. Specifically, most of these studies employed a time-series design that is subject to ecological fallacy, which refers to the possibility that associations observed at the population or group level may not necessarily reflect the true exposure-response association at the individual level.[10] Moreover, most prior studies have examined the association between OHCA and temperature metrics using hospitalization data aggregated on the calendar day level,[6–8,11] while the utilization of hourly onset information of OHCA in assessing individual-level exposures could be crucial for this time-critical and fatal emergency.[12,13]

Climate change is emerging as the most pressing public health challenge of the 21st century. In the context of a warming climate, only one prior study has projected a net reduction in future OHCAs in various climate scenarios in Japan,[14] after accounting for the disease burden associated with high and low temperatures, which was projected from the baseline daily temperature-OHCA relationship estimated through a time-series study design. It is thus imperative to confirm this finding using the relationship between temperature and the hourly onset of OHCA estimated using an individual-level, case-crossover study design, which can adjust for individual-level confounders that remain stable over time through self-matching and has more reasonable chronological order.[12,13] Additionally, a growing number of studies have reported intensified health effects of both heatwaves and cold spells, compared to heat and cold.[15,16] Because of climate change, both the frequency and duration of heatwaves will increase significantly in the future,[17,18] while cold spells will become fewer.[19] However, the impacts of heatwaves and cold spells on OHCA have been less investigated, especially using a time-stratified case-crossover design at the individual level. Furthermore, the future burdens of OHCA associated with heatwaves and cold spells under climate change scenarios have not been quantified.

In the present study, based on the hourly onset information of OHCA from a multicenter registry with a large population in China, we utilized the individual-level case-crossover design to estimate the association between non-optimum temperatures, heatwaves, and cold spells with OHCA onset, respectively. We then thereby quantified and compared the future excess morbidity burden of OHCA related to high temperatures, low temperatures, heatwaves, and cold spells under climate change scenarios.

Methods

OHCA data

The baseline associations were analyzed based on the BASeline Investigation of Out-of-hospital Cardiac Arrest (BASIC-OHCA) study, which was the first prospective, multicenter, and population-based registry in China that covers more than 120 million population in 30 cities (See Supplementary Table S1 in the appendix for details). The registry was established by the Qilu Hospital of Shandong University and funded by the Ministry of Science and Technology of the People's Republic of China, which has been previously described.[20] Since August 1, 2019, OHCA patients assessed by the emergency medical service (EMS) staff were consecutively enrolled by participating EMS agencies. Data collection and reporting were based on the Utstein templates, which were developed by international experts in resuscitation science specifically for reporting on the epidemiology, treatment, and outcomes of OHCA in a standardized manner.[21] The study was approved by the ethics committee of the coordinating center, Qilu Hospital of Shandong University (authorization number 2019012) with the waiver of patient consent. All EMS agencies that contributed data to BASIC-OHCA agreed on this ethics approval. This study was presented according to the guidelines of Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).

Till the end of 2019, all participating EMS agencies have regularly registered OHCA patients. We retrieved the data of OHCA cases of presumed cardiac etiology with clear onset time (at an hourly level or less) and address from January 1 to December 31, 2020. As the majority of OHCA patients enrolled by the participating EMS agencies were concentrated in North China, we restricted our analysis to 15 northern cities to reduce the between-city heterogeneity in climate conditions (Supplementary Figure S1). Detailed data collection and quality control procedures were described in the appendix (Supplementary Method S1). In order to enable separate analyses of high temperatures and heatwaves, as well as low temperatures and cold spells,[22] we restricted the current analyses to the summer (June 1st to August 31st, defined as hot season) and winter (December 1st to February 29th, defined as cold season).

Environment data

Hourly temperature and relative humidity data were obtained from weather stations in the China Meteorological Data Service Center (http://data.cma.cn/). The address of each OHCA onset was geocoded into longitude and latitude, and then matched to the nearest weather stations with a distance of less than 100 km.[13] The average distances from all patients to their nearest station is 13.8 km. Hourly concentrations of fine particulate matter ($PM_{2.5}$) were also collected from the nearest fixed-site station in the National Urban Air Quality Real-time Publishing Platform (http://106.37.208.233:20035/) to allow for the adjustment of air pollution.

Projected daily temperature series under climate change scenarios

We retrieved future daily average temperature series from General Circulation Models (GCMs) developed by the Coupled Model Intercomparison Project Phase 6 (CMIP6), which has established climate model test standards and developed mechanisms to share climate simulation data with the global scientific community.[23] Each run of GCM can produce a series of daily mean temperatures for each site from 2011 to 2100. Additionally, we selected two Shared Socioeconomic Path (SSP) scenarios from CMIP6, which are used in conjunction with the GCMs to provide climate projections for different possible futures based on future socioeconomic conditions and associated greenhouse gas emissions. Although China has been increasingly prioritizing low-carbon development, it may be challenging to peak greenhouse gas emissions by 2050 due to the geographical environment and socioeconomic development factors for northern cities with established heavy industry. Therefore, in accordance with previous research,[24–26] we chose SSP2-4.5 and SSP5-8.5, which represent the future scenarios with assumptions of certain carbon emission control and no greenhouse-gas emission control, respectively. Briefly, similar to previous projection studies,[24–28] we selected 20 GCMs under two climate change scenarios, and these GCMs are representative of the range of future climate projections across the CMIP6 models (Supplementary Table S2). By virtue of a set of widely used dimensionality reduction (at a 1.0° × 1.0° spatial resolution) and recalibration procedures (see Supplementary Method S2 for details),[28] we calculated the daily average temperatures among 20 GCMs from 2011 to 2100 by season.

The definition of heatwaves, cold spells, and lags of exposures

There is no uniform standard for defining heatwaves and cold spells, but definitions incorporating a duration and a percentile cutoff in the temperature distribution are widely used in recent multicenter studies to account for the climate adaptations for various regions.[25] To avoid selection bias, we adopted 12 common definitions of heatwaves and cold spells by combining four relative thresholds (90th, 92.5th, 95th, and 97.5th, for heatwaves, and 10th, 7.5th, 5th, and 2.5th, for cold spells, percentiles of daily average temperatures) with three durations (≥2, ≥3, and ≥4 days), respectively (Supplementary Tables S3 and S4 for details). We determined the primary definition in the main analyses by identifying the statistical minimums based on various criteria, including the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), deviance and Pearson's chi-squared test statistic.[25] As almost all analyses evaluated the health impacts of heatwaves and cold spells at the daily level, we considered the moving 24 h averages prior the onset hour of OHCA as 1 day to avoid exposure misclassification in relation to chronological order within 1 day, and accordingly calculated multiple 24-h averages as lag days. We did not apply hourly-level exposures to reduce computational burden while maintaining comparability with most previous findings based on daily lags.[6–9]

Data analysis

Analyses of the baseline exposure-response associations

We utilized an individual-level, time-stratified, case-crossover approach to analyze the associations between heat (high temperatures and heatwaves) and cold (low temperatures and cold spells) with OHCA onset, respectively. For each individual patient, the levels of temperature exposures before the hour of OHCA onset were compared with those of control periods of the same individual when the event had not occurred. The control days were selected based on three criteria: same day of the week as the case day to account for any potential confounding effects, before and/or after the case day (time-stratified) to control for time trends, and only in the same month as the case day to adjust for seasonal patterns (see Supplementary Method S3 in the appendix for details). This study design enables us to effectively account for individual-level and city-level covariates that exhibit stability over a short period.[12,13,29] Examples of such factors include sex, race, lifestyles such as smoking behaviors, socioeconomic status, and healthcare infrastructure that are unlikely to change within a month. Conditional logistic regression models with distributed lag models were employed to explore the relationships of heat and cold with OHCA, respectively. Consistent with previous studies,[13,25,28] we set a maximum lag of 1 week (lag 0–6 days) for hot and 2 weeks (lag over 0–13 days) for cold. We determined the cumulative lag of heat and cold in main analyses by analyzing their respective lag patterns. Daily mean temperature was constructed by cross-basis function with three degrees of freedom (*df*) for both exposure and lag dimensions. Heatwave and cold spell were separately set as 0–1 variables developed by a natural cubic spline function with three *df* for lag dimension. Then, we included a natural cubic spline with three *df* for relative humidity and a binary indicator of public holidays in the models. The choice of these parameters was empirically determined according to previous researches,[6,7,13,25,28] and detailed information on models can be found in the appendix (Supplementary Method S4).

Projection of future OHCA morbidity burden under climate scenarios

According to a widely used framework for calculating the future burden of disease,[17,25,28] we quantified the OHCA morbidity burden due to high temperatures and heatwaves (only for hot seasons), and low temperatures and cold spells (only for cold seasons) in each city based on projected temperature series under climate change scenarios. Specifically, we first calculated expected excess OHCA cases related to heat and cold per year (2011–2100) for each set of climate scenarios (SSP2-4.5 and SSP5-8.5) and GCMs by city, respectively. Then, we computed the attributable fraction (AF) by dividing the number of attributable OHCA cases by the total number of OHCA cases.

To quantify the overall impact of future climate change on OHCA morbidity, we computed the decadal AF of OHCA related to high temperatures, heatwaves, low temperatures, and cold spells for each city/county and combinations of SSPs and GCMs, respectively. Subsequently, the AF as GCM-ensemble averages aggregated by region, decade, and SSP were further calculated using the corresponding total number of OHCA cases as the denominator. More detailed information about this calculation is provided in the appendix (Supplementary Method S5). To account for the uncertainty in the estimation of the exposure-response relationships and the variability of the modeled temperature outputs, we generated 1000 samples of the coefficients of exposure-response relationships through Monte Carlo simulations,[28] for each of GCMs. Therefore, empirical confidence intervals (eCIs) corresponding to the 2.5th and 97.5th percentiles of the distribution of the results across coefficients and all GCMs were obtained.

Sensitivity analyses

Multiple sensitivity analyses were conducted to test the robustness of our results. First, we included 0–24 h average concentrations of $PM_{2.5}$ before the onset hour in the main model to examine the potential confounding of air pollution. Second, we used different parameters in our models according to previous studies,[6,7,13,25,28] including the maximum lag (i.e., 21 days for cold effects and 10 days for heat effects), the *df* for fitting nonlinear relationships (i.e., $df = 2–4$), the natural cubic B spline function in defining the cross-basis function, and the *df* for relative humidity (i.e., $df = 2–4$). To account for the potential impact of future adaptation,[17,30] we employed an approach suggested by a previous study,[17] wherein the heatwave and cold spell thresholds were defined based on the 90th and 10th percentile, respectively, of the future temperature distributions, instead of relying on unchanged thresholds identified from baseline temperature distributions.

All statistical analyses were conducted in R (Version 4.0.0, R Project for Statistical Computing) with the “dlnm” and “survival” packages for fitting main models. A two-tailed P value < 0.05 was considered as statistical significance.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Descriptive statistics

We finally included a total of 29,671 EMS-assessed cardiac OHCA cases from 15 OHCA cities in north China, of which 12,852 cases occurred in the hot season and 16,819 cases occurred in the cold season.

The average mean temperatures in the hot and cold season of these cities in 2020 were 23.8 °C and −3.0 °C, respectively. The average mean temperatures in the hot season ranged from 17.0 °C in Xining to 26.5 °C in Jining, while in the cold season, it ranged from −14.7 °C in Harbin to 3.68 °C in Xuzhou (Supplementary Table S5).

The baseline exposure-response relationships

During hot seasons, the lowest risk of OHCA onset is estimated at 19 °C, which is considered as the minimum morbidity temperature (referent temperature) in subsequent analyses of high temperatures (Fig. 1A). With the rise of temperatures, the risks become statistically significant beyond 23 °C. The lag pattern for the effect of high temperatures on OHCA is similar to that of heatwaves, which is most pronounced on the day of onset and tends to disappear after lag 2 d (Fig. 2A and Supplementary Figure S2). During cold seasons, the lowest risk of OHCA is estimated at the highest temperature (17.6 °C), and the risk shows a monotonically increasing trend with decreasing temperatures (Fig. 1B). The lag pattern for the effect of low temperatures is also similar to that of cold spells, which appear at lag 3 d and then disappeared after lag 10 d (Fig. 2B and Supplementary Figure S3). Therefore, cumulative lags of 3 days and 10 days were used to calculate odds ratios (ORs) of heat and cold, respectively. The risk estimates of heat and cold on OHCA onset are summarized in Supplementary Figures S4–S6. After evaluating the AIC, BIC, deviance and Pearson’s chi-squared test statistic values (Supplementary Table S6), $HW\_D_2\_T_{90}$ and $CS\_D_2\_T_{90}$ were determined to be the primary definitions of heatwave and cold spell in projecting future disease burden.

The OHCA morbidity burdens under climate change scenarios

Using multiple climate change scenarios, our results show that, even under the medium emission-control pathway (SSP2-4.5), future high temperatures in north China will experience an approximately linear upward trend (Fig. 3), with a total increase of nearly 2.4 °C from the 2010s to 2090s, resulting in a rise of AF of OHCA related to high temperatures from 4.24% to 6.54% in 2090s, and this trend is more evident under the unrestricted emission-control pathway (SSP5-8.5). The duration of heatwaves is also expected to increase nearly 10-fold till the 2090s (Fig. 4A and Supplementary Table S7), thus contributing to an increase in the AF related to heatwaves from 0.47% in the 2010s to 5.39%

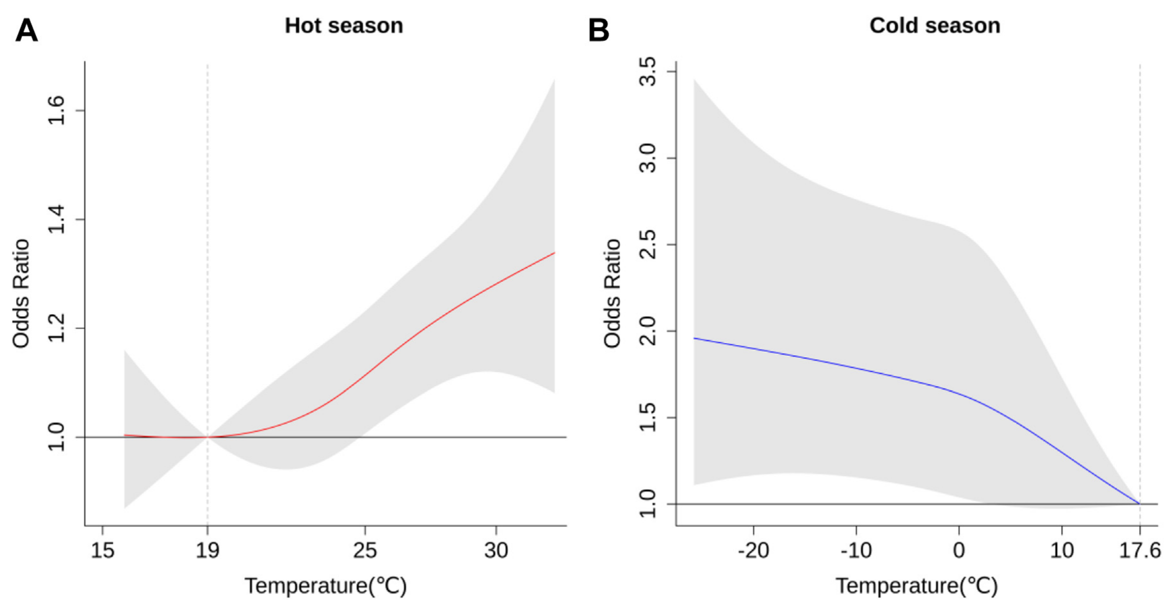

***Fig. 1:* Cumulative exposure-response curves for temperature with OHCA onset by season.** (A) Hot season (June 1st–August 31st). The cumulative lag effect was capture over 0–2 days for high temperatures, and the lowest risk of OHCA onset was estimated at 19 °C. (B) Cold season (December 1st–February 29th). The cumulative lag effect was capture over 0–10 days for low temperatures, and the lowest risk of OHCA onset was estimated at 17.6 °C. The solid red and blue lines are the odds ratios of OHCA onset, and the gray areas are the 95% confidence intervals. Abbreviation: OHCA, out-of-hospital cardiac arrest.

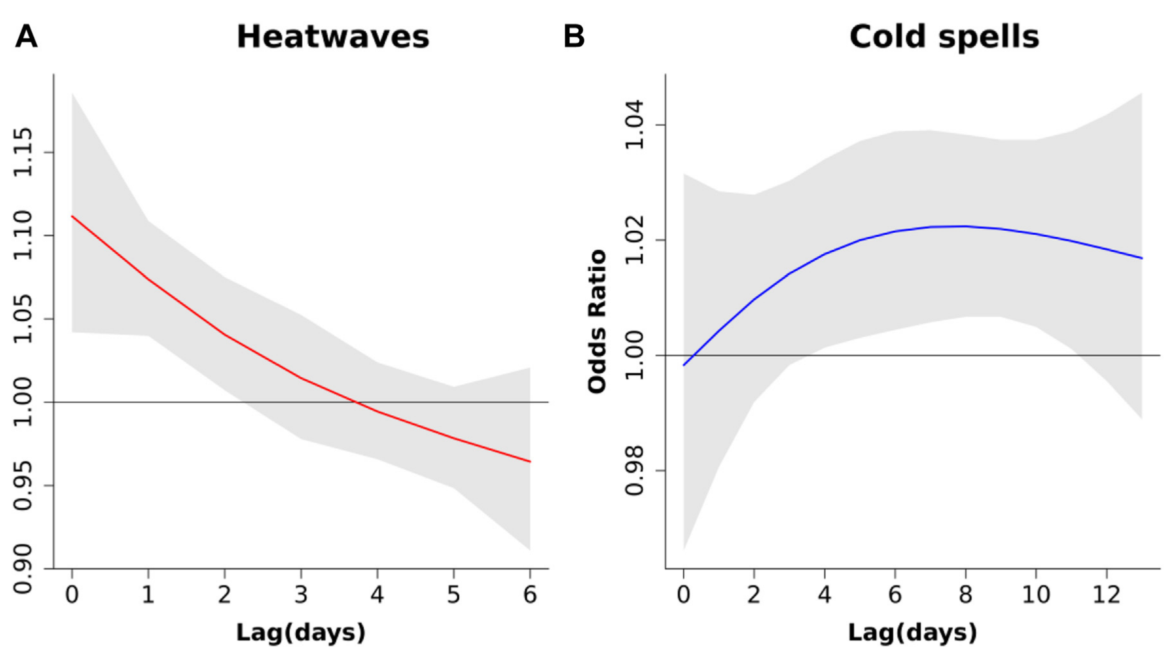

***Fig. 2:* The pooled lag structure for the odds ratios of OHCA onset associated with cold spells and heatwaves.** (A) Heatwaves: the temperature was above the 90% quantile of the historical temperature distribution during hot season (June 1st–August 31st) for 2 days or more. (B) Cold spells: the temperature was below the 10% quantile of the historical temperature distribution during cold season (December 1st–February 29th) for 2 days or more. The solid red and blue lines are the odds ratios of OHCA onset, and the gray areas are the 95% confidence intervals. Abbreviation: OHCA, out-of-hospital cardiac arrest.

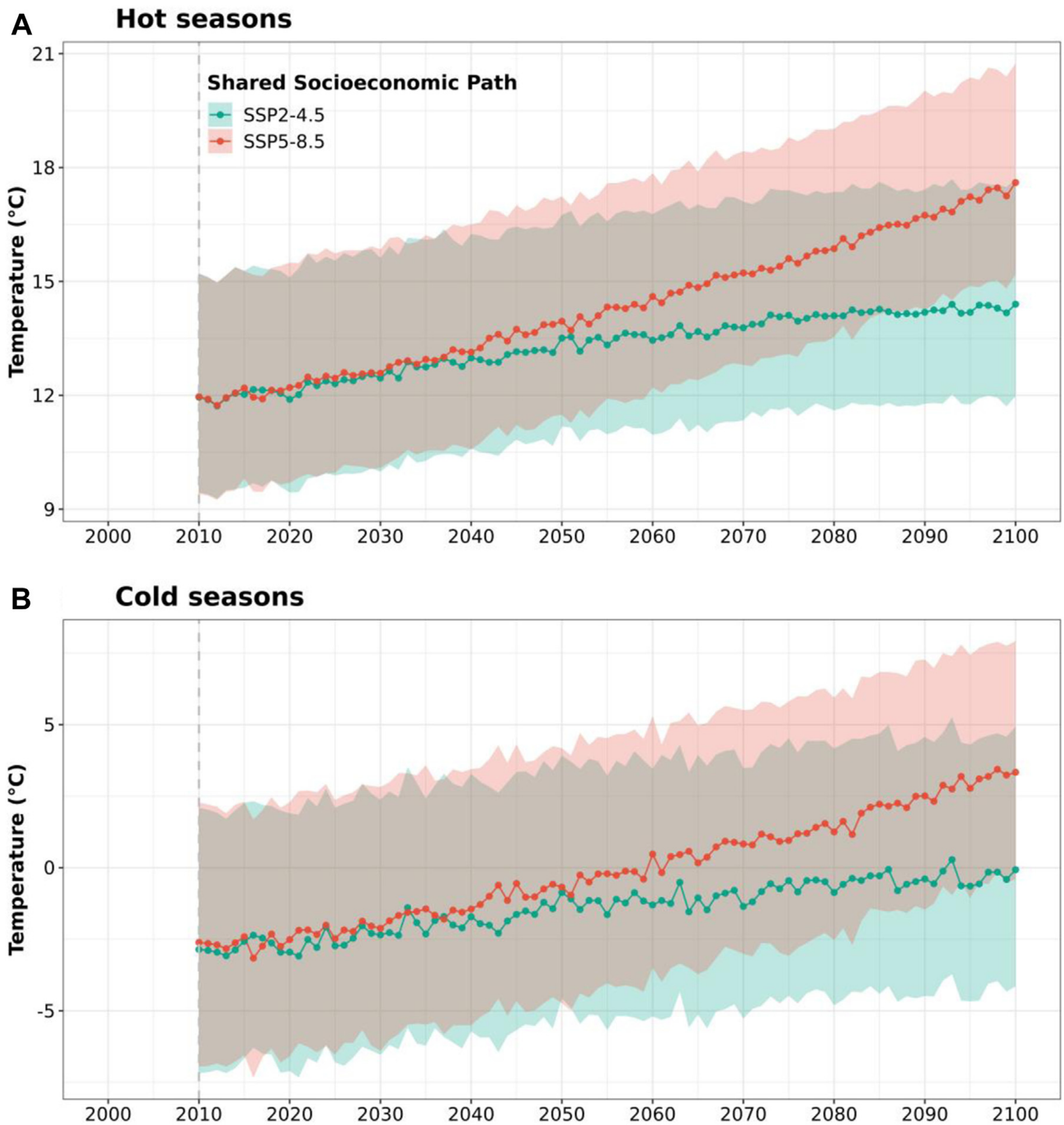

Fig. 3: **The annual trends for daily mean temperature since 2011–2100 under SSP2-4.5 and SSP5-8.5 scenarios in North China. (A) Hot seasons (June–August). (B) Cold seasons (December–February).** These trends were calculated based on the modeling results from all included cities. All values correspond to the average value calculated from the 20 general circulation models. The colored areas represent the Inter Quartile Range for the results of the ensemble of all models (N = 20).

in the 2090s. The upward trend would be also more prominent under the SSP5-8.5 scenario (Fig. 5A).

In contrast, the AF of OHCA related to low temperatures and cold spells show opposite trends, especially under the SSP5-8.5 scenario. Specifically, cold spells are projected to almost disappear after the 2050s (Fig. 4B and Supplementary Table S8), and the AF of OHCA due to low temperatures decreased from 6.06% in the 2010s to 5.55% in the 2090s (Fig. 5B). The estimates of future OHCA morbidity burden for heat and cold under different scenarios are provided in Supplementary Table S9.

Sensitivity analysis

After controlling for the concomitant exposure to $PM_{2.5}$, the ORs of OHCA onset with high temperatures,

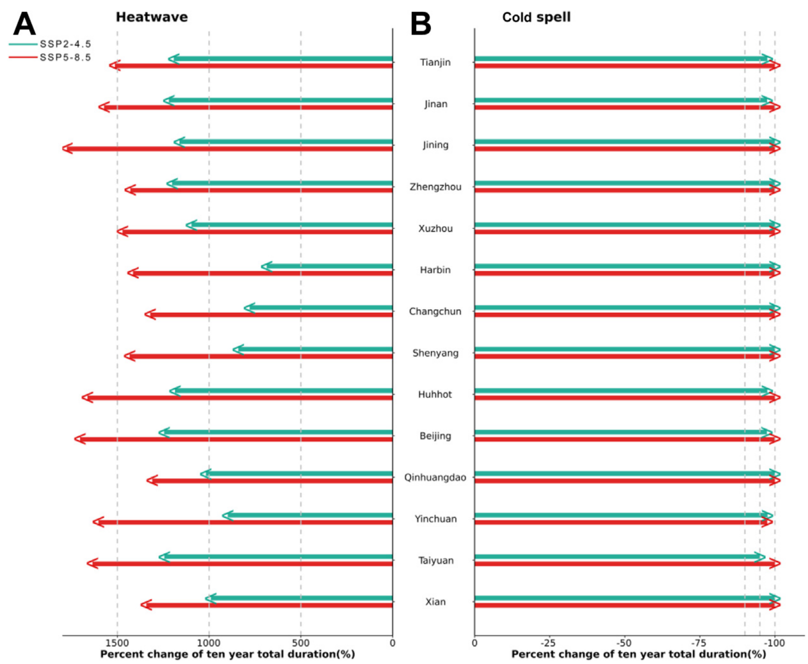

Fig. 4: **Mean percent change in total decade duration in 2091–2100 for heatwaves (A) and 2051–2060 for cold spells (B) in comparison to 2011–2020, in North China under SSP2-4.5 and SSP5-8.5 scenarios.** All values correspond to the average value calculated from the 20 general circulation models.

heatwaves, low temperatures, and cold spells are not appreciably changed (Supplementary Figures S7–S9). These OR estimates are also robust to the use of varying model parameters (Supplementary Figures S10–S17). The projected increases in AF of OHCA morbidity due to heatwaves are significantly lower after accounting for future adaptation compared to projections that did not consider adaptation. However, the projected increases in AF of morbidity due to cold spells did not decline as rapidly as those without consideration of future adaptation (Supplementary Figure S18).

Discussion

Based on a multicenter OHCA registry in China, the present study utilized an individual-level, time-stratified case-crossover design to separately establish exposure-response relationships of high temperatures, heatwaves, low temperatures and cold spells with OHCA onset, and further projected the changes in relevant OHCA burden under future climate change scenarios. To the best of our knowledge, this is the first study quantifying the excess OHCA morbidity burden due to heatwaves and cold spells under various climate change scenarios. One additional strength of our study is the utilization of hourly onset information of OHCA to define exposure time windows, which can effectively reduce exposure misalignment and ensure a more reasonable chronological order. Under the context of global warming, we found a sharp rise in OHCA morbidity burden attributable to increasing heat, especially under the SSP5-8.5 scenario. In contrast, there would be an apparent decrease in OHCA morbidity burden attributable to cold. At the end of this century, the morbidity burden of OHCA caused by heatwaves was almost equal to that caused by high temperatures. There will be a large decrease in burden due to cold spells, but only a slight decrease in burden due to low temperatures. Overall, the decrease in the burden of OHCA attributed to cold could not offset the increase in the burden attributed to heat.

In this study, we found that high temperatures, heatwaves, low temperatures, and cold spells were all significantly associated with OHCA onset, and the effect of low temperatures was significantly greater than that of high temperatures, which was not exactly consistent with previous studies.[6–9,11,31,32] For example, a case-crossover study conducted in Israel indicated that cumulative exposure to high temperatures had a considerably higher impact on OHCA onset than low temperatures (OR = 3.34 for heat and OR = 1.75 for cold).[32] Additionally, another time-series study revealed that high temperatures did not exhibit any impact on OHCA onset, whereas low temperatures and heatwaves were associated with increased incidence.[6] These inconsistencies may be due to the differences in study design, statistical methods, population characteristics, and so on. The present study added to the growing

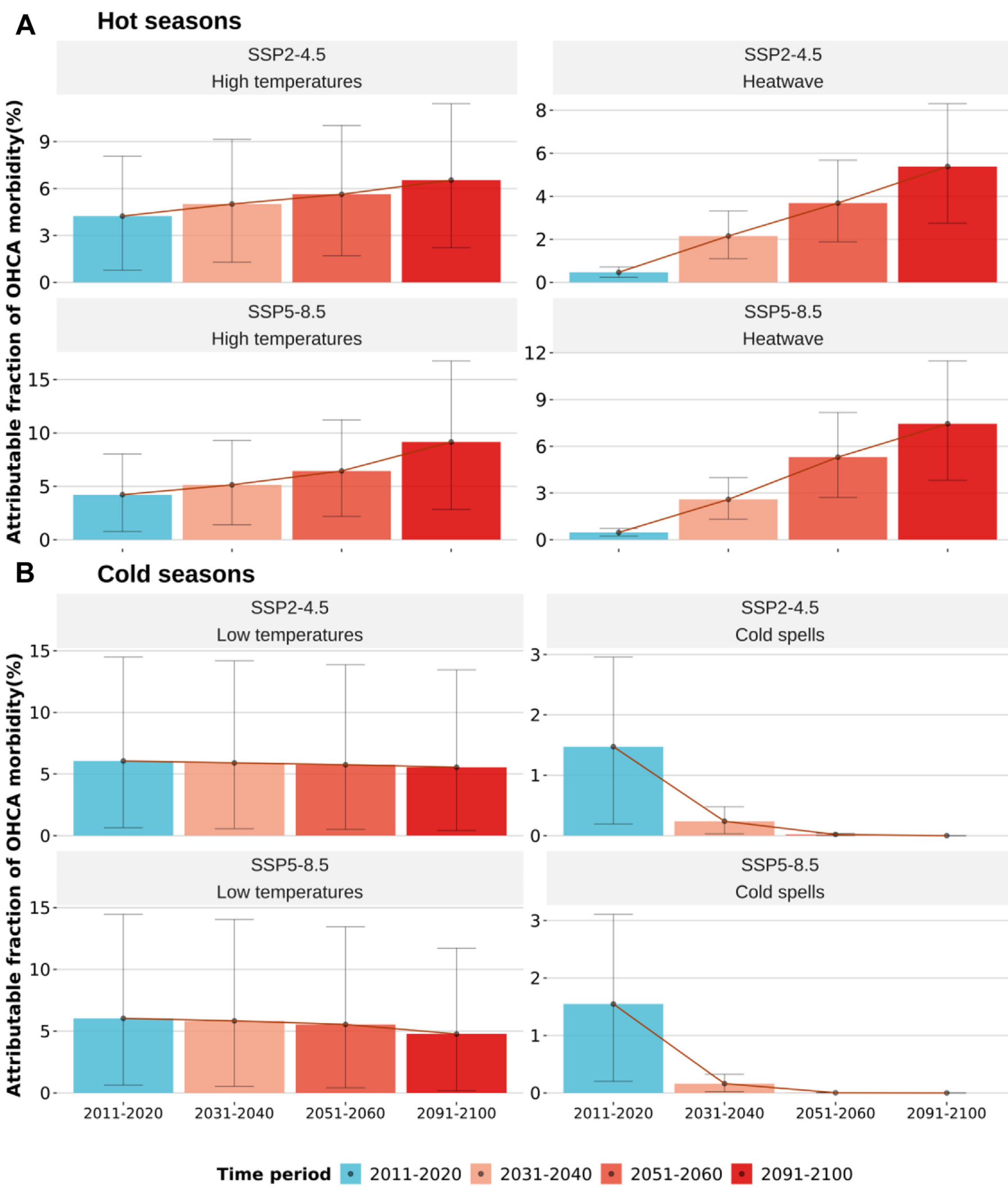

Fig. 5: **Projections of attributable fraction of OHCA morbidity due to high temperatures and heatwaves during hot seasons (June–August) (A), and low temperatures and cold spells during cold seasons (December–February) (B), in four periods and two shared socioeconomic paths.** These data were calculated from the pooled results for all included cities. The vertical lines represent 95% empirical confidence intervals for attributable fraction of OHCA morbidity. Please refer to Supplementary Table S9 in appendix for specific effect estimates. Abbreviation: SSP, shared socioeconomic paths.

evidence utilizing hourly onset information of OHCA and case-crossover design at the individual level. Similar to previous research,[6,31] we found that the minimum morbidity centile for the association between temperatures and OHCA onset was centered at the 19th centile during the summer and the 100th centile during the winter.

The associations between ambient temperatures and the increased risk of cardiac OHCA onset are biologically plausible in terms of the following possible physiological mechanisms. The effects of heat on OHCA may be driven by dehydration, which can lead to electrolyte disturbance and a potential hyperexcitability state of the myocardiocytes, and dehydration may also cause a toxic level of some medications, such as digitalis in old patients, which is potentially pro-arrhythmic.[6,33] Besides, sweating and blood vessels in the skin dilation in hot weather can increase skin blood flow and volume depletion, leading to the blood supply to other major organs diminished, such as the heart, and cardiac preload and afterload decreased.[7,34] As for the mechanisms of cold effects on the risk of OHCA onset, low temperatures will activate the sympathetic nervous system by stimulating thermoreceptors in the skin, consequently raising the levels of systemic catecholamine, which is associated with heart rate increasing and blood pressure raising, further leading to increased risk of arrhythmia.[6,35] Moreover, cold-induced hypothermia can alter many biological indicators (e.g., vascular resistance and blood viscosity) that may pile up the risk of thrombosis and plaque rupture.[36] Additionally, the lagged effect of temperatures can potentially be attributed to the delayed physiological response to temperature exposure, wherein the impact on the human body may not be immediate but may instead manifest after a certain time lag.[8,32] The observed lag patterns of temperature indicators were consistent with previous researches exploring the impact of temperatures on acute cardiovascular events.[13,32]

Our study suggested that climate change may result in an increase in the burden of temperature-related OHCA, which is particularly pronounced under the scenario of uncontrolled emissions. These findings are consistent with previous studies indicating temperature-related all-cause mortality and cardiovascular mortality will increase under different global warming scenarios.[25,37] However, a study in Japan pointed out that climate change would contribute to a marked reduction in temperature-related OHCA.[14] In addition to differences in research design and population, the reasons for this inconsistency may also be that the locations of this study are cities in north China, which all belong to a temperate climate with cold winters. Therefore, even in the context of global warming, the temperature of these cities in winter will still be low in the future.

One of the critical advantages and novelty of our study lies in the projection of the burden of OHCA morbidity related to heatwaves and cold spells in the context of global warming. Our results indicated the growth rate of AF related to heatwaves might greatly exceed that of AF associated with high temperatures, which is probably because heatwaves, being a form of cumulative temperature exposure, increase faster than the average temperatures when the average temperatures exceed a certain threshold.[27] This also explains why the rate of decrease in AF associated with cold spells, as a type of accumulated temperature, would be faster than that of AF related to low temperatures. Furthermore, our findings also revealed that from the 2010s to the 2090s, the AF caused by heatwaves may increase at a much faster rate under SSP5-8.5 than under SSP2-4.5. Although there are currently no studies predicting the burden of OHCA attributable to heatwaves and cold spells, these conclusions are similar to previous researches exploring the future burden of all-cause or cardiovascular disease,[17,18,27] such as one large-scale study showing that the percentage change in heatwaves-related excess deaths in China from 1971–2020 to 2030–2080 was 308% in Representative Concentration Pathway (RCP) 8.5 and only 199% in RCP4.5.[17] The large differences in OHCA morbidity burden related to heatwaves under different emission scenarios emphasize that strict greenhouse-gas emission policies. Additionally, similar to previous literatures,[17,27] the morbidity burden caused by heatwaves under adaptive scenarios was found to be smaller than that under non-adaptive scenarios, highlighting the significance of developing climate change adaptation strategies.

The present study has several limitations. First, consistent with previous epidemiological studies,[13,25] our analysis derived exposure data from nearby fixed-site monitors instead of individual-level measurements, which might result in inevitable exposure misclassification. Such error, however, is likely to be randomly distributed and could only bias our estimates towards the null.[38] Second, due to the nature of the case-crossover design and limited sample size, we could not estimate OR for each city; alternatively, we used the uniform OR for all northern cities of China, so that we could not explore the between-city heterogeneity of changes in future OHCA burden under climate warming. Third, limited by the data availability, we only employed the data during 2020 to represent the baseline incidence of OHCA in northern China. Moreover, in the projection analysis, we used baseline exposure-response relationships without considering any changes over time, and only considered two SSPs to represent future climate change scenarios. Therefore, our projections results should be interpreted as potential impacts that are based on well-defined yet hypothetical scenarios, rather than precise predictions of future excess OHCA morbidity. Lastly, we only evaluated two extreme scenarios of complete adaptation and no adaptation, and did not account for adaptation scenarios related to non-optimal temperatures. Thus, in future research, more comprehensive and refined adaptation scenarios should be considered to better understand the potential impacts of climate change on acute cardiovascular events.

In conclusion, based on an individual-level case-crossover design, this multicenter study provides novel and comprehensive evidence for the morbidity risks and burden of OHCA in association with non-optimal temperatures, heatwaves, and cold spells across north China under various climate change scenarios. Under the global warming scenario, the burden of OHCA due to high temperatures is expected to rise dramatically and eventually exceed that attributed to low temperatures. Furthermore, under the scenario of uncontrolled emissions, although there is a significant decrease in the burden of OHCA related to cold spells, it still cannot compensate for the increase in the burden related to heatwaves. Our findings could provide abundant evidence for the control and prevention of OHCA in the context of global warming.

Contributors
YC, RC, and FX conceived the study. JL, CL, and JZ wrote the first and successive drafts of the manuscript. JL, CL, and JZ analyzed the data. CP, GZ, HT, YM, YZ, XH, CL, SY, JM, JZ, CW, YB, KC, RL, YH, QC, XZ, YC, RC, and FX carried out the programming to extract the data and curate the dataset. CP, YC, RC, and FX edited and revised manuscript. YC, RC, and FX verified the underlying data. All authors read, discussed, and approved the final manuscript. The corresponding authors (YC, RC, and FX) had full access to all the data in the study and had final responsibility for the decision to submit for publication after obtaining approval from all co-authors.

Data sharing statement
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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Declaration of interests
The authors declare that they have no competing interests.

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Appendix A. Supplementary data
Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2023.100778.

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