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Cold Spells and the Onset of Acute Myocardial Infarction: A Nationwide Case-Crossover Study in 323 Chinese Cities

Yixuan Jiang,[1] Shaodong Yi,[2*] Chuanyu Gao,[3] Yuguo Chen,[4] Jiyan Chen,[5] Xianghua Fu,[6] Lixia Yang,[7] Xiangqing Kong,[8] Mao Chen,[9] Haidong Kan,[1,10] Dingcheng Xiang,[2] Xi Su,[11] and Renjie Chen[1,10]*

[1]School of Public Health, Key Lab of Public Health Safety of the Ministry of Education and National Health Commission Key Lab of Health Technology Assessment, Fudan University, Shanghai, China
[2]Department of Cardiology, General Hospital of Southern Theater Command of People's Liberation Army (PLA), Guangzhou, China
[3]Department of Cardiology, People's Hospital of Zhengzhou University, Henan Provincial People's Hospital, Fuwai Central China Cardiovascular Hospital, Zhengzhou, China
[4]Department of Emergency and Chest Pain Center, Qilu Hospital, Cheeloo College of Medicine, Shandong University, Jinan, China
[5]Department of Cardiology, Guangdong Cardiovascular Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China
[6]Department of Cardiology, Second Hospital of Hebei Medical University, Shijiazhuang, China
[7]Department of Cardiology, 920th Hospital of Joint Logistics Support Force of the Chinese PLA, Yunnan, China
[8]Department of Cardiology, First Affiliated Hospital with Nanjing Medical University, Nanjing, China
[9]Department of Cardiology, West China Hospital, Sichuan University, Chengdu, China
[10]Integrated Research on Disaster Risk International Center of Excellence on Risk Interconnectivity and Governance on Weather/Climate Extremes Impact and Public Health, Fudan University, Shanghai, China
[11]Department of Cardiology, Wuhan Asia General Hospital, Wuhan, China

Background: Few studies have explored the relationships between cold spells and acute myocardial infarction (AMI) using the information of symptom onset.

Objectives: We assessed the impact of cold spells on AMI onset and the potential effect modifiers.

Methods: We conducted a time-stratified case-crossover study among 456,051 eligible patients with AMI from 2,054 hospitals in 323 Chinese cities between January 2015 and June 2021 during cold seasons (November to March). Nine definitions of cold spells were used by combining three relative temperature thresholds (i.e., lower than the 7.5th, 5th, and 2.5th percentiles) and three durations of at least 2–4 consecutive d. Conditional logistic regressions with distributed lag models were applied to evaluate the cumulated effects of cold spells on AMI onset over lags 0–6 d, after adjusting for daily mean temperature.

Results: The associations generally appeared on lag 1 d, peaked on lag 3 d, and became nonsignificant approximately on lag 5 d. Cold spells defined by more stringent thresholds of temperature were associated with higher risks of AMI onset. For cold spell days defined by a daily mean temperature of ≤7.5th percentile and durations of ≥2 d, ≥3 d, and ≥4 d, the percentage changes in AMI risk were 4.24% [95% confidence interval (CI): 2.31%, 6.20%], 3.48% (95% CI: 1.62%, 5.38%), and 2.82% (95% CI: 0.98%, 4.70%), respectively. Significant AMI risks associated with cold spells were observed among cases from regions without centralized heating, whereas null or much weaker risks were found among those from regions with centralized heating. Patients ≥65 years of age were more susceptible to cold spells.

Discussion: This national case-crossover study presents compelling evidence that cold spells could significantly increase the risk of AMI onset. https://doi.org/10.1289/EHP11841

Introduction

Ischemic heart disease (IHD) remains one of the leading causes of death and constitutes a considerate burden both in terms of health and economic loss.[1,2] Approximately 182 million disability-adjusted life-years (DALYs) and 9 million deaths were estimated to result from IHD globally in 2019.[1,3] Therefore, it is of great public health relevance to identify modifiable risk factors of IHD onset. Acute myocardial infarction (AMI) is a common subtype of IHD, and its higher incidence during cold seasons has been widely observed.[4,5] Notably, the Global Burden of Disease Study 2019 has listed nonoptimum temperature as one of the environmental risk factors. That project reported that nonoptimum ambient temperature was responsible for 11 million DALYs and 597,000 deaths due to IHD worldwide and attributed 6.08% of IHD deaths to low temperature.[6,7]

A cold spell often manifests as a duration of several consecutive days of anomalously low temperatures. During the last few decades, extreme cold weather events, such as cold spells, have increased in frequency, intensity, and severity in many regions.[8,9] A cold spell could be more harmful and lethal to human health than daily low temperatures, and its added effects or independent effects from daily low temperature have been documented.[10,11] As a main outcome affected by low temperatures, IHD or AMI events were associated with cold spells in a limited number of epidemiological studies, and the existing study results have been inconsistent and inconclusive.[11–14] Owing to the lack of standardized definitions, previous studies often defined cold spells using various temperature thresholds (such as percentiles of temperature distribution or absolute temperatures) and durations of cold days,[15,16] contributing to the incomparability of results. Given the long-term local acclimatization of residents in different regions, it is of great necessity to use relative thresholds when defining cold spells. In

*These authors contributed equally to this work.

Address correspondence to Dingcheng Xiang, Department of Cardiology, General Hospital of Southern Theater Command of PLA, 111 Liuhua Rd., Guangzhou 510010, China. Telephone: 86 (20) 8868 6556. Email: dcxiang@foxmail.com. And, Xi Su, Department of Cardiology, Wuhan Asia General Hospital, 300 Taizihu North Rd., Wuhan 430056, China. Telephone: 86 (27) 8478 8999. Email: yaxin_suxi@163.com. And, Renjie Chen, Department of Environmental Health, School of Public Health, Fudan University, P.O. Box 249, 130 Dong-An Rd., Shanghai 200032, China. Telephone: 86 (21) 5423 7908. Email: chenrenjie@fudan.edu.cn.

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addition, given that this kind of evidence was obtained mainly from some single-city studies, its generalizability to other regions has been limited.[16,17] Furthermore, previous studies often used IHD/AMI deaths or hospitalizations, which are not as sensitive and immediate as disease onset.[10,11,14,18] To our knowledge, studies exploring the associations between cold spells and AMI events based on the time of disease onset have been rarely conducted, especially at the national level.

To protect people against the cold weather, China implemented an urban centralized heating policy beginning in the 1950s.[19] Most cities to the north of the line of the Qin Mountains and the Huai River (i.e., the heating region) have a centrally controlled public heating system (i.e., a centralized heating system) during cold season (i.e., from November to March). Generally, heat is generated by government-owned heating companies and is supplied via pipelines to each household in the city. In contrast, there is no centralized heating in cities south of the line (i.e., the nonheating region). Up to now, little evidence has been reported on the potential difference in the cold spell–AMI associations between regions with and without centralized heating.

Therefore, based on a large-scale national database in China, we designed this case-crossover study based on individual cases. The aim of the present study was to clarify the associations of cold spells with AMI onset and explore the possible effect modifiers.

Methods

Study Population and Health Data

We extracted data on AMI onset from the Chinese Cardiovascular Association (CCA) Database–Chest Pain Center. As a nationwide registry, this database was established by the CCA in 2015. Up to now, chest pain centers have been widely established in $\sim 96\%$ of county-level municipalities across China.[20] Hospitals with chest pain centers in China are required to register information of all patients presenting with acute chest pain in this database, including demographic characteristics (e.g., age, sex), date and hour of symptom onset, clinical diagnosis, examinations results, and treatment. The Expert Committee and the Executive Committee of the China Chest Pain Center monitors the operation of all chest pain centers. Strict internal and external data quality control are performed routinely to ensure the validity of the data recorded in the CCA Database. More details have been described in previous studies.[21,22]

For the present analysis, we collected AMI data only from hospitals with certified chest pain centers that were reported between 1 January 2015 and 30 June 2021 during the cold season (from November to March). The diagnoses of AMI were ascertained by cardiologists or clinicians based on clinical symptoms, electrocardiographic measurement, and biochemical tests, according to the guidelines issued by the Chinese Society of Cardiology.[23,24] Time of AMI onset was self-reported with an hourly precision. We excluded patients that were transferred from other hospitals or who did not provide the time of symptom onset. This study has been approved by the institutional review board of the School of Public Health, Fudan University (IRB#2021-04-0889). All data were deidentified before the formal analysis with a waiver of informed consent.

Study Design

We investigated the associations of cold spells with AMI onset using a time-stratified case-crossover design, which has been widely applied in exploring the short-term associations between environmental exposure and acute cardiovascular events.[25,26] For each patient, the case day was defined as the day of self-reported onset of AMI symptom; the control days were defined as other days in the same year, month, and day of the week to control for long- and mid-term variations and seasonality. Accordingly, each case day was matched with 3 or 4 control d. For instance, if the AMI symptom occurred on Friday, 10 February 2017, we would define 10 February 2017 as the case day, and all other Fridays in February 2017 (i.e., 3, 17, and 24 February) would be defined as control days.

Exposure Assessment

We extracted daily temperature and relative humidity data from the China Meteorological Data Service Center (http://data.cma.cn/). Considering the long-term local acclimatization of residents among different climatic regions in China, this study used station-specific relative thresholds [7.5th, 5th, and 2.5th percentiles (P7.5, P5, and P2.5) of daily temperature distributions] during the study period. Meanwhile, we considered various durations of cold spell days: ≥ 2 d (≥ 2 consecutive d), ≥ 3 d (≥ 3 consecutive d), and ≥ 4 d (≥ 4 consecutive d). In total, we used nine cold spell definitions by combining the abovementioned three thresholds and three durations. Then, we divided the number of days during the study period into cold spell or non–cold spell days for each weather station. Daily concentrations of criteria air pollutants [i.e., fine particulate matter (PM ≤ 2.5 μm in aerodynamic diameter, $PM_{2.5}$); nitrogen dioxide (NO_2); sulfur dioxide (SO_2); ozone (O_3); and carbon monoxide (CO)] were collected from the National Urban Air Quality Real-time Publishing Platform (https://air.cnemc.cn:18014/) to allow for possible adjustment.

Given that more than half of the participants did not report complete addresses for where the patient's symptoms occurred (i.e., onset address), we matched the data of cold spell, temperature, and relative humidity from the nearest meteorological station, and the air pollutants data from the nearest air quality monitoring station with each participant according to the address of the reporting hospital. For cold spell data, we assigned a binary variable (1 for cold spell days, and 0 for non–cold spell days) for up to 6 d before each case and control day. For instance, lag 0 d refers to the concurrent day of AMI onset. For other environmental data (i.e., temperature, relative humidity, and air pollutants), we also matched exposure during 0–6 d before each case and control day. Furthermore, to minimize exposure misclassifications, only hospitals within 100 km of the nearest meteorological stations were included.[27] Meanwhile, air pollution data were assigned only to patients from hospitals that were within 50 km of the nearest fixed-site air quality monitoring stations.[28] The missing rate was 0.3% for data of cold spell, temperature, and relative humidity, and it was 5.1% for air pollutant data. We omitted the missing data of environmental variables before statistical descriptions and analyses.

Statistical Analyses

The distributions of sex and age ($<$ or ≥ 65 y) were compared between the total AMI population that were recorded in the CCA Database–Chest Pain Center during our study period and the studied population before formal analyses. Patients with missing age and sex information were omitted when comparing the statistical distributions. Conditional logistic regression models, combined with distributed lag models (DLMs), were used to examine the associations between cold spells and AMI onset over multiple lag periods. A maximum of 6 lag days (i.e., 1 wk including the present day) were empirically determined in DLMs because our preliminary analysis did not indicate any effects at lags >1 wk, which was also supported by previous studies of similar design.[12,16] Specifically, DLMs were applied to build a cross-basis function for cold spell days (as a binary variable) using a natural cubic spline function with 4 degrees of freedom (df) for lag space.[17,18] Then, the cross-basis function was included in a conditional logistic regression model. To investigate the effects of cold spells independent of daily temperature, we further included daily mean temperature in the main models using a cross-basis function constructed by a distributed lag nonlinear model. The cross-basis function for temperature was constructed using natural cubic spline functions with 4 df for both the exposure space and lag space, using the same lag period with cold spells (i.e., 0–6 d). Other covariates in main model were a natural cubic spline with 3 df for relative humidity (0–6 d average prior to the case or control day), and public holidays (a binary indicator). We further calculated Akaike information criterion (AIC) values to evaluate the goodness-of-model fits for different cold spell definitions. The model with the minimum AIC value represented the best fit, and the corresponding cold spell definition was deemed as the optimum.

To explore the possible heterogeneity in the cold spell–AMI associations by the presence of centralized heating policy, we ran separate models for patients from regions with or without centralized heating. Information on the centralized heating in each city were collected from the websites of local governments. The specific implementation periods of the centralized heating policy varied slightly in different heating cities of China, but they were all presented within the same cold duration from November to March.

We further stratified analyses by sex (male vs. female), age (<65 vs. ≥ 65 y), and regions (divided according to economic development levels in China). Patients with missing age and sex information were omitted in the analyses stratified by age and sex, respectively. The Chinese mainland is divided by the Chinese government into four economic regions (i.e., the Eastern, Northeast, Central, and Western regions) according to economic development and geographical characteristics.[29] The socioeconomic and medical care levels in the Eastern region were deemed to be appreciably higher than in the rest of China. Given that the Central region and the Western region were both less developed and geographically adjacent, we pooled them into a combined Central and Western region in the present analysis. Stratum-specific estimates of overall cumulative risks were compared by using a z-test based on the following formula:

$$z = \frac{\beta_1 - \beta_2}{\sqrt{SE_1^2 + SE_2^2}}, \quad (1)$$

where β_1 and β_2 are the stratum-specific regression coefficients (ln relative risk), and SE_1 and SE_2 are the corresponding standard errors.[30] We then calculated p-values for the between-subgroup differences using the method proposed by Altman et al.[31]

Several sensitivity analyses were conducted to test the robustness of the results. First, we additionally adjusted for air pollutants in the models both nationally and by region (i.e., nonheating and heating regions). The concentrations of criteria air pollutants on lag 0 d were included in the main model one by one and all simultaneously. Second, we redefined the case day as the date of hospitalization (i.e., the date that the patient was admitted into a hospital), and the control days as the other days in the same year, month, and day of the week. Third, we applied different dfs for lag dimensions of cold spell in DLMs ($df = 4–7$). Last, we restricted the analysis to patients with both a hospital address and an onset address, and fitted separate models using cold spell data that were matched based on the hospital address (i.e., hospital-address analysis) and the patient's onset address (i.e., onset-address analysis) among those with both addresses ($n = 223{,}143$).

All statistical analyses were conducted in R (version 4.0.0; R Development Core Team), using two-sided tests with an α of 0.05. Estimates derived from the conditional logistic regression models were converted into percentage changes and 95% confidence intervals (95% CIs) in the risk of AMI onset by comparing the cold spell days to non–cold spell days, using the following equations:

$$\text{Percentage change} = (e^{\beta} - 1) \times 100\%, \quad (2)$$

$$\text{Lower } 95\% \text{ CI} = (e^{\beta - 1.96 \times SE} - 1) \times 100\%, \quad (3)$$

$$\text{Upper } 95\% \text{ CI} = (e^{\beta + 1.96 \times SE} - 1) \times 100\%, \quad (4)$$

where β is the regression coefficient (ln relative risk), and SE is the standard error. The geographic distribution of the included hospitals was mapped in ArcGIS (version 10.7; ESRI). The map outline was obtained from the China Resource and Environment Science and Data Center.

Results

Descriptive Results

In total, 611,288 patients with AMI were initially reported in the CCA Database–Chest Pain Center during cold seasons between 1 January 2015 and 30 June 2021. According to the inclusion and exclusion criteria, 456,051 eligible patients from 2,054 certified hospitals in 323 cities were finally analyzed (Figure 1; Figure S1). The distributions of sex and age ($<$ or ≥ 65 y) were similar between total patients with AMI and those finally included in the formal analysis (Table S1). Among the included patients, 49.7% were ≥ 65 years of age and 73.1% were male (Table S2). In addition, 87 and 20 of the included patients were missing age and sex information, respectively. Baseline demographic characteristics (i.e., sex and age) of the included patients, and indicators of economic development and medical care levels were generally comparable between the heating and nonheating regions (Table S3). The mean concentrations of $PM_{2.5}$, NO_2, SO_2, and CO were slightly higher in the heating region. The average difference $\pm$ standard deviation (SD) between the hour of being admitted into a hospital and the hour of symptom onset was 14 ± 21 h, and the P25, median (P50), and P75 of the difference were 2, 4, and 14 h, respectively. Among patients from the heating region who had provided complete onset addresses, $\sim 75\%$ lived in urban areas.

As shown in Table 1, the annual numbers of cold spell days averaged among all weather stations decreased from 24 to 5 with more stringent cold spell definitions. Daily average temperature and humidity during the study period were 6.6°C and 64.5%, respectively. The temperature thresholds for defining cold spell days were much lower in the heating region (Table S3). The frequency of cold spells occurring in at least 1 d during the case periods was consistently higher than that during the control periods (Table S4).

Regression Results

Figure 2 presents the lag structure of the associations between cold spells and AMI onset over a 0- to 6-d period (see Excel Table S1 for numeric data). Similar patterns were observed for various cold spell definitions. Generally, the risk of AMI onset appeared on lag 1 d and peaked on lag 3 d. Thereafter, the associations were attenuated and became nonsignificant after ~ 5 d.

The risk estimates varied by different cold spell definitions (Table 2). Generally, the more stringent thresholds of temperature resulted in higher risk estimates, whereas prolonging the duration did not necessarily yield larger estimates of cold spells. For example, for cold spells defined by $\leq$P7.5 with $\geq$2-, 3-, and 4-d durations, the percentage changes in the risk of AMI onset were 4.24% (95% CI: 2.31%, 6.20%), 3.48% (95% CI: 1.62%, 5.38%), and 2.82% (95%

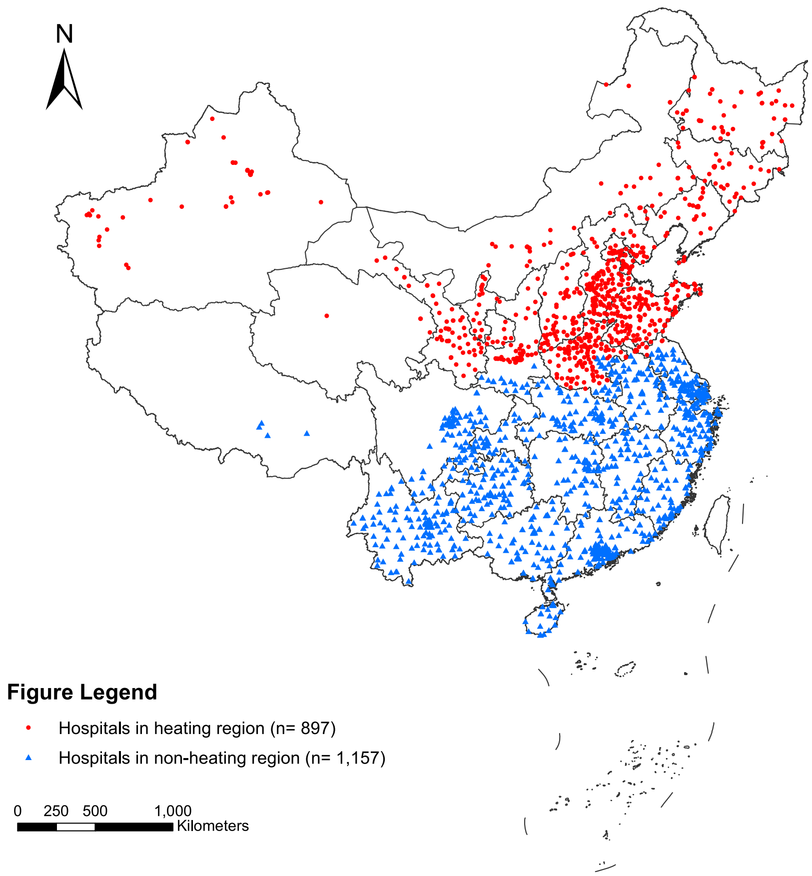

Figure 1. Geographic distribution of the 2,054 hospitals across China from 2015 to 2021. The red circles represent the sites of hospitals in the heating region, whereas the blue triangles represent the sites of hospitals in the nonheating region. The map outline in this figure was obtained from the China Resource and Environment Science and Data Center (http://www.resdc.cn). This figure was produced by using ArcGIS (version 10.7; ESRI).

CI: 0.98%, 4.70%), respectively. The cold spell definition using a combination of ≤P7.5 and ≥3 d resulted in the smallest AIC value.

The associations of cold spells with AMI onset varied greatly across the heating and nonheating regions (Table 2; Figures S2 and S3, Excel Tables S2 and S3). In general, significant AMI risks were observed among patients in the nonheating region for cold spells of all definitions, and they became positive on lag 1 d, increased modestly before lag 3 d, and turned nonsignificant on approximately lag 5 d. In contrast, null or much weaker associations were found among those in the heating region. Between-group differences were statistically significant for cold spell definitions based on daily mean temperatures of ≤P2.5 and durations of at least 2 or 3 d.

Table 1. Summary statistics of annual cold spell days with different definitions averaged from all weather stations in the Chinese mainland from January 2015 to June 2021.

	Cold spell days per year (*n*)				
Cold spell definitions	Mean	SD	Minimum	Median	Maximum
≤P7.5 with ≥2-d duration	24	9	2	22	56
≤P7.5 with ≥3-d duration	20	10	0	19	56
≤P7.5 with ≥4-d duration	17	10	0	16	56
≤P5 with ≥2-d duration	15	9	0	13	48
≤P5 with ≥3-d duration	13	9	0	11	46
≤P5 with ≥4-d duration	10	9	0	8	44
≤P2.5 with ≥2-d duration	7	7	0	5	33
≤P2.5 with ≥3-d duration	6	6	0	4	33
≤P2.5 with ≥4-d duration	5	6	0	2	32

Note: P2.5, 2.5th percentile of the daily mean temperature distribution; P5, 5th percentile of the daily mean temperature distribution; P7.5, 7.5th percentile of the daily mean temperature distribution; SD, standard deviation.

Table 3 summarizes the percentage changes in the risk of AMI onset associated with cold spells in different subgroups. The risk estimates were positive and statistically significant for cold spells of all definitions among male patients. For females, the associations were significant only for cold spells defined by ≤P7.5 and durations of ≥2 or 3 d, as well as ≤P5 and a duration of ≥2 d. For males, the associations appeared to be slightly stronger, but no significant effect modification by sex was observed for any cold spell definition. The risk estimates were much higher among patients ≥65 years of age than among their younger counterparts, with statistically significant between-subgroup differences for most cold spells definitions (Table 3). Moreover, null associations were found in the Northeast region, where the climate was the coldest and the centralized heating operated for the longest period, whereas the risk estimates were both statistically significant and similar in the Eastern and the combined Central and Western regions (Table S5).

In sensitivity analyses, the risk estimates did not vary greatly after adjusting for air pollutants at both the national and heating region levels (Tables S6–S8). The associations remained statistically significant but were attenuated in the analysis based on the hospitalization dates (Table S9). Changing dfs for lag dimensions of cold spell in DLMs generally yielded similar results (Table S10). Estimates were also not considerably changed when using cold spell data that were matched based on patient's onset address compared with those based on the hospital address (Table S11).

Discussion

In this nationwide case-crossover study in 323 Chinese cities, we found that cold spells were significantly associated with AMI onset. The associations were independent of the effects of low

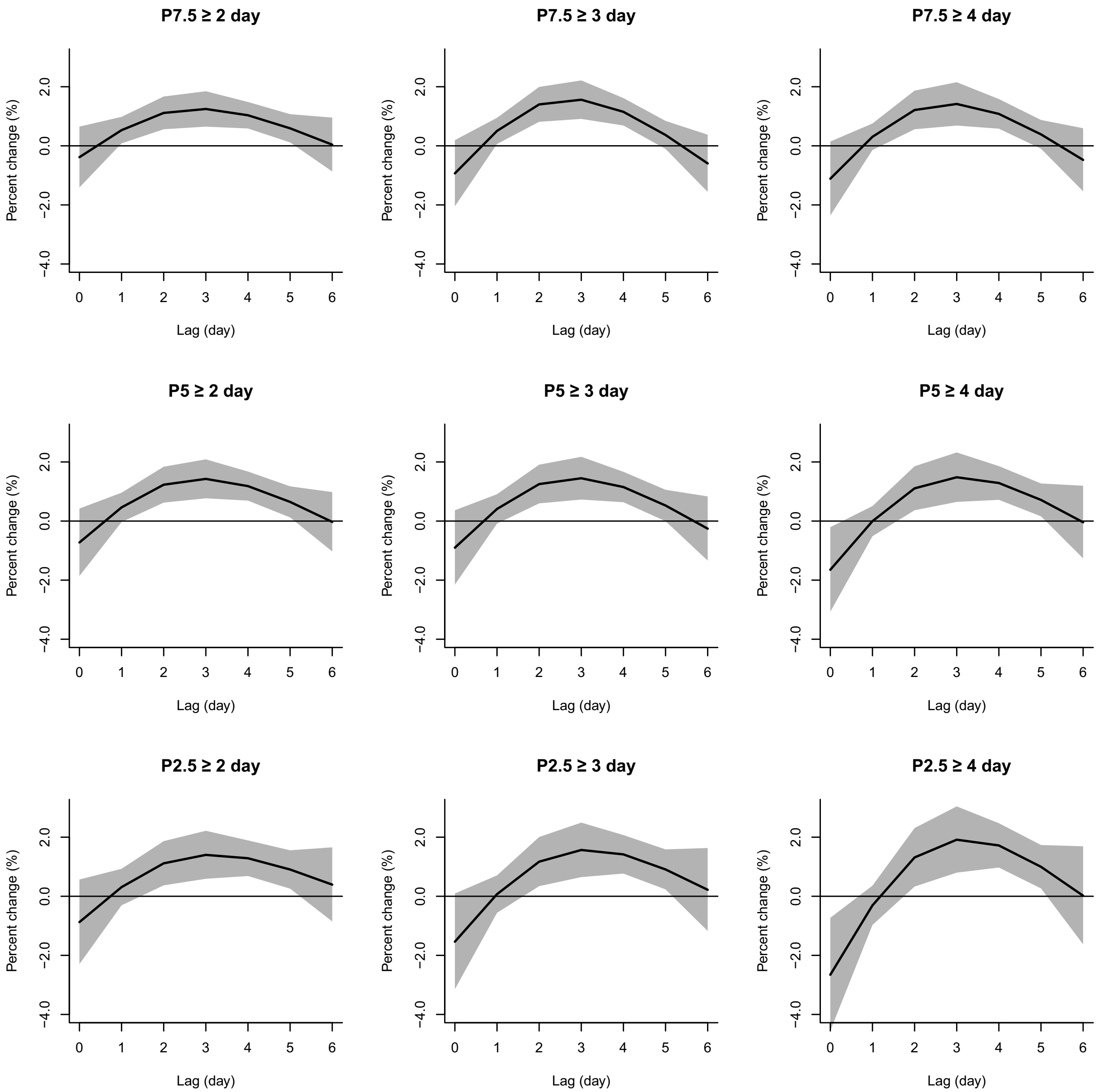

Figure 2. Lag structures for the associations of AMI onset with cold spells using different definitions ($n = 456{,}051$ eligible patients). The solid black lines are the lag-specific percentage changes in the risk of AMI onset associated with cold spells, and the gray areas are their 95% confidence intervals. The cold spell definitions include a range of combinations with temperatures lower than different percentiles (P7.5, P5, and P2.5) of daily temperature distributions and durations of no less than 2, 3, and 4 d. The corresponding numeric data can be found in Excel Table S1. Note: AMI, acute myocardial infarction; P2.5, 2.5th percentile of the daily mean temperature distribution; P5, 5th percentile of the daily mean temperature distribution; P7.5, 7.5th percentile of the daily mean temperature distribution.

temperatures, lasting up to 5 d, with a peak on lag 3 d. Significant associations were observed in the nonheating region but not in the heating region. Patients ≥65 years of age were more susceptible to the impacts of cold spells. To our knowledge, this is the largest case-crossover study to assess the relationships of cold spells with AMI onset based on individual cases.

Although low temperature has been widely considered as a risk factor for cardiovascular diseases,[32–34] the effects of cold spells have been less studied and the results remain controversial. Some studies reported significantly increased IHD/AMI mortality or morbidity associated with cold spells,[12,14,18] whereas others found no associations.[13,35] This heterogeneity might be interpreted by differences in study design, health outcomes (i.e., symptom onset, hospitalization, or mortality), sample size, and cold spell definitions. Studies based on hospitalizations or mortality could be subject to temporal mismatch of exposure and disease onset.[11,14,18] Accordingly, studies that use individual information on disease onset may avoid this kind of misclassification. Up to now, only a few small-scale case-crossover studies explored the impact of cold spells on AMI onset, and these were in Lithuania and the UK.[12,15] However, those studies defined cold spells using single-temperature thresholds, and only one of them investigated the independent effects of cold spell after adjusting for daily mean temperature (in the UK).[15] In contrast, by virtue of this large-scale, nationwide registry, the present case-crossover study examined the associations of cold spells with AMI onset using various cold spell definitions, with adjustment for the cumulative effects

Table 2. Percentage change (%) and 95% CIs in the risk of AMI onset associated with cold spells cumulated over lags 0–6 d nationally and in the heating and nonheating regions from January 2015 to June 2021.

Cold spell definitions	Nationwide	Heating	Nonheating	AIC[a]	p-Value[b]
≤P7.5 with ≥2-d duration	4.24 (2.31, 6.20)	3.33 (0.59, 6.14)	4.92 (2.01, 7.90)	1,238,179	0.45
≤P7.5 with ≥3-d duration	3.48 (1.62, 5.38)	2.30 (−0.32, 5.00)	4.44 (1.61, 7.34)	1,238,176	0.29
≤P7.5 with ≥4-d duration	2.82 (0.98, 4.70)	2.12 (−0.45, 4.76)	3.21 (0.40, 6.09)	1,238,185	0.59
≤P5 with ≥2-d duration	4.25 (2.11, 6.44)	2.52 (−0.50, 5.63)	5.48 (2.21, 8.85)	1,238,181	0.20
≤P5 with ≥3-d duration	3.66 (1.55, 5.81)	1.74 (−1.18, 4.75)	5.04 (1.79, 8.40)	1,238,183	0.15
≤P5 with ≥4-d duration	2.90 (0.78, 5.06)	1.58 (−1.35, 4.60)	3.43 (0.18, 6.78)	1,238,185	0.42
≤P2.5 with ≥2-d duration	4.61 (1.89, 7.40)	0.80 (−2.89, 4.63)	7.37 (3.10, 11.82)	1,238,188	0.02
≤P2.5 with ≥3-d duration	3.84 (1.09, 6.67)	−0.66 (−4.36, 3.20)	7.38 (3.06, 11.89)	1,238,188	0.01
≤P2.5 with ≥4-d duration	2.96 (0.12, 5.89)	−0.70 (−4.56, 3.32)	4.68 (0.37, 9.17)	1,238,186	0.07

Note: The sample sizes in the heating and nonheating regions were 234,627, and 221,424, respectively. AIC, Akaike information criterion; AMI, acute myocardial infarction; CI, confidence interval; P2.5, 2.5th percentile of the daily mean temperature distribution; P5, 5th percentile of the daily mean temperature distribution; P7.5, 7.5th percentile of the daily mean temperature distribution.
[a]AIC values for the nationwide models.
[b]p-Values for the differences between the heating and nonheating regions.

of daily temperature over multiple lag days. The impact was significant within 1 wk, and more transient than that on AMI mortality (e.g., 2 wk to 1 month), as reported in the literature.[36,37] This difference is reasonable because there is always a duration (typically between several days and a few weeks) from disease symptom onset to death, except for sudden death. We further found that more stringent thresholds of temperature generally lead to larger risk estimates, which might be partly explained by the reduced likelihood of overlapped cold spell days during the case and control periods.

The impacts of cold spells on AMI onset were of biological plausibility. Previous evidence has indicated that temperature decline could result in peripheral vasoconstriction, increased arterial pressure, elevated plasma fibrinogen concentrations, increased platelet viscosity, and aggravated the cardiac workload,[38–40] all of which may eventually lead to AMI onset. Furthermore, coronary artery spasm resulting from low temperature exposure could also exacerbate unstable angina, and consequently accelerate progression to AMI.[41] Due to the brittle cardiovascular system and weakened thermoregulation function, these pathophysiological changes would be more pronounced among elderly people during cold days. The underlying comorbidities and disturbed internal environment might also contribute to their vulnerability to cold.[42] All these factors help explain the higher risk of AMI onset associated with cold spells among individuals ≥65 years of age.

All the temperature thresholds for defining cold spell days were well below the thermoneutral temperature ($\sim 22°C$) for humans,[43,44] and even lower in the heating region, which was reasonable because of the higher latitudes. When ambient temperature drops below the thermoneutral temperature, humans may develop behavioral responses, such as wearing more or thicker clothes and using indoor heating.[43] Notably, we observed significantly increased risk of AMI onset only in the nonheating region. A multi-city time-series study in China also reported lower years of life lost per death of all causes attributable to nonoptimum ambient temperatures in regions with centralized heating than in other regions.[45] This heterogeneity may be due to a series of differential factors, including socioeconomic status, medical care levels, and the presence of centralized heating. Our results revealed that heating and nonheating regions were generally comparable in the baseline characteristics of study population, economic development, and medical care levels. Moreover, similar risk estimates were observed between the Eastern region and the combined Central and Western region, although the socioeconomic levels differed. However, there might still exist other unmeasured heterogeneous factors that could affect the comparison of the heating and nonheating regions. Therefore, we cannot simply attribute the between-region differences in cold spell–AMI associations to the effectiveness of the centralized heating policy. Future experimental or quasi-experimental studies with individualized indoor heating information are warranted to better clarify this issue.

The findings of this study may have important implications for AMI prevention. First, our results illustrate the time course for the associations of cold spells with AMI onset, which is very useful for developing an early warning system and setting an appropriate duration for the preventive measures when encountering a cold spell. Second, given the potential benefits of indoor heating, it is of great necessity to design more resilient public infrastructures (e.g., centralized heating) and promote the use of effective personal protective measures in regions vulnerable to cold spells. Considering the potential air pollution caused by traditional coal-powered heating, more advanced technology based on cleaner energy is thus urgently demanded. Last, special attention should be paid to susceptible individuals, such as the elderly, and tailored preventive strategies are also required.

Table 3. Percentage change (%) and 95% CIs in the risk of AMI onset associated with cold spells cumulated over lags 0–6 d, stratified by sex, and age in the Chinese mainland from January 2015 to June 2021.

	Sex			Age (y)		
Cold spell definitions	Male ($n = 333,456$)	Female ($n = 122,575$)	p-Value[a]	<65 ($n = 229,257$)	≥65 ($n = 226,707$)	p-Value[a]
≤P7.5 with ≥2-d duration	4.06 (1.80, 6.36)	4.82 (1.16, 8.62)	0.74	−0.25 (−2.84, 2.41)	8.77 (5.93, 11.68)	<0.01
≤P7.5 with ≥3-d duration	3.15 (0.97, 5.37)	4.46 (0.90, 8.14)	0.55	−0.54 (−3.06, 2.04)	7.48 (4.75, 10.28)	<0.01
≤P7.5 with ≥4-d duration	2.68 (0.52, 4.88)	3.30 (−0.21, 6.92)	0.78	−1.02 (−3.52, 1.55)	6.63 (3.93, 9.39)	<0.01
≤P5 with ≥2-d duration	4.08 (1.57, 6.65)	4.85 (0.77, 9.09)	0.77	0.40 (−2.51, 3.39)	8.08 (4.94, 11.30)	<0.01
≤P5 with ≥3-d duration	3.75 (1.27, 6.28)	3.58 (−0.40, 7.73)	0.95	0.40 (−2.47, 3.37)	6.83 (3.77, 9.99)	<0.01
≤P5 with ≥4-d duration	3.31 (0.82, 5.87)	1.96 (−2.02, 6.10)	0.59	0.15 (−2.77, 3.14)	5.61 (2.54, 8.76)	0.01
≤P2.5 with ≥2-d duration	5.03 (1.83, 8.32)	3.77 (−1.35, 9.14)	0.70	3.17 (−0.60, 7.09)	5.82 (1.95, 9.84)	0.35
≤P2.5 with ≥3-d duration	4.47 (1.23, 7.81)	2.42 (−2.72, 7.84)	0.53	2.91 (−0.94, 6.91)	4.51 (0.63, 8.55)	0.59
≤P2.5 with ≥4-d duration	3.58 (0.24, 7.03)	0.67 (−4.61, 6.23)	0.38	1.70 (−2.27, 5.82)	3.98 (0.02, 8.11)	0.44

Note: AMI, acute myocardial infarction; CI, confidence interval; P2.5, 2.5th percentile of the daily mean temperature distribution; P5, 5th percentile of the daily mean temperature distribution; P7.5, 7.5th percentile of the daily mean temperature distribution.
[a]p-Values for between-subgroup differences.

The main strengths of this study are listed as follows. First, we used a standardized and nationally representative registry database of patients with AMI that covered almost all main cities and hospitals across the Chinese mainland. The considerable sample size (456,000) ensured adequate statistical power of analysis, and the wide geographic coverage guaranteed representativeness of the whole country or other countries with similar climatic features. Second, the detailed information on time of disease onset assisted in reducing temporal mismatch of exposure and AMI incidence, thereby facilitating more accurate estimations of their associations.

There were also some limitations. First, as done in prior epidemiological analyses, cold spells were defined according to temperatures derived from nearby fixed-site meteorological stations, inevitably leading to exposure measurement errors. Nevertheless, such misclassification has been reported to be random and nondifferential and, thus, could only bias our estimates toward the null.[46] Second, we matched environmental data based on hospital addresses rather than the locations of AMI onset, which may amplify the exposure misclassification issue. However, we could assume that patients with AMI were usually sent to the nearest hospital in China and that there would be very limited spatial variation of cold spells within the same city. Furthermore, our subgroup sensitivity analyses showed similar results when matching exposure according to the location of AMI onset. Third, although time-invariant risk factors could be controlled by design in the present study, there are still some confounders that vary transiently within a short period, such as short-term stress, smoking, and physical activity. Fourth, there were some inevitable misclassifications of the heating and nonheating regions in such a large-scale nationwide study. For example, there was usually no centralized heating in rural households of the heating region, whereas there might be individualized indoor heating in the nonheating region. Some cases of AMI may have occurred before the heating policy was implemented, which could have had some influence on the results of the analyses stratified by heating and nonheating regions. Nevertheless, this would not have substantially impacted our results because *a*) most patients from the heating region in the present study were speculated to be urban residents, who were very likely to experience centralized heating during cold periods; *b*) in the heating region, rural residents and urban residents (before the implementation of centralized heating) could also adopt multiple individualized measures to keep rooms warm (e.g., electric space heaters, heated brick bed, firewood cookstoves, and coal stoves); and *c*) individualized indoor heating in the nonheating region was usually transient and present only in limited locations. Fifth, we included only patients with AMI admitted to chest pain centers—those who died before arriving at the hospital were not evaluated. If cold spells could affect AMI survival, there would be bias in our estimations.

Conclusion

This national case-crossover study based on individual patients from 323 Chinese cities presents compelling evidence that cold spells were significantly associated with the onset of AMI, and this risk was independent of low ambient temperatures. For the first time we found significant heterogeneity in the excess risks associated with cold spells between the heating and nonheating regions. Our findings are helpful to improve the cold spell alert system and tailor the personalized preventive measures under the context of climate change globally.

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