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Cause-specific cardiovascular disease mortality attributable to ambient temperature: A time-stratified case-crossover study in Jiangsu province, China

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ABSTRACT

Background: Exposure to non-optimum ambient temperature has been linked to increased risk of total cardiovascular disease (CVD) mortality; however, the adverse effects on mortality from specific types of CVD remain less understood.
Objectives: To comprehensively investigate the association of ambient temperature with cause-specific CVD mortality, and to estimate and compare the corresponding mortality burden.
Methods: We conducted a time-stratified case-crossover study of 1000,014 CVD deaths in Jiangsu province, China during 2015–2019 using data from the China National Mortality Surveillance System. Residential daily 24-hour average temperature for each subject was extracted from a validated grid data at a spatial resolution of 0.0625° × 0.0625°. We fitted distributed lag non-linear models (DLNM) based on conditional logistic regression to quantitatively investigate the association of ambient temperature with total and cause-specific CVD mortality, which was used to further estimate mortality burden attributable to non-optimum ambient temperatures.
Results: With adjustment for relative humidity, we observed reverse J-shaped exposure-response associations of ambient temperature with total and cause-specific CVD mortality, with minimum mortality temperatures ranging from 19.5 °C to 23.0 °C. An estimated 20.3% of the total CVD deaths were attributable to non-optimum temperatures, while the attributable fraction (AF) of mortality from chronic rheumatic heart diseases, hypertensive diseases, ischemic heart diseases (IHD), pulmonary heart disease, stroke, and sequelae of stroke was 22.4%, 23.2%, 23.3%, 20.9%, 17.6% and 21.3%, respectively. For total and cause-specific CVDs, most deaths were attributable to moderate cold temperature. We observed significantly higher mortality burden from total and certain cause-specific CVDs in adults 80 years or older and those who were widowed.

Abbreviations: AF, attributable fraction; CI, confidence interval; CO, carbon monoxide; CRHD, chronic rheumatic heart disease; CVD, cardiovascular disease; DLNM, distributed lag non-linear model; HD, hypertensive disease; IHD, ischemic heart disease; MMP, minimum mortality percentile; MMT, minimum mortality temperature; NO_2, nitrogen dioxide; O_3, ozone; OR, odds ratio; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter ≤10 μm; PHD, pulmonary heart disease; SO_2, sulfur dioxide.

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Conclusion: Exposure to ambient temperature was significantly associated with increased risk of cause-specific CVD mortality. The burden of CVD mortality attributable to non-optimum temperature was substantial especially in older and widowed adults, and significantly varied across specific types of CVD.

1. Introduction

Cardiovascular disease (CVD) remains the leading cause of death and has posed a great public health challenge worldwide (Virani et al., 2021). According to estimates from the Global Burden of Disease (GBD) study, the global burden of CVDs has increased steadily in the past 20 years and reached 18.6 million deaths and 393 million disability-adjusted life-years (DALYs) in 2019 (Roth et al., 2020). Accumulating epidemiological evidence suggests that exposure to non-optimum ambient temperatures contributes to an increased risk of mortality from total CVDs (R. Chen et al., 2018; Silveira et al., 2019). To understand the adverse effects of ambient temperature on CVD mortality in the context of global climate change, it is important to comprehensively investigate the effects of ambient temperature on mortality from specific types of CVD.

Previous studies have reported adverse effects of ambient temperature exposure on mortality from only a limited range of specific CVDs, including hypertensive diseases (HD) (Ma et al., 2020), hypertensive heart disease (HHD) (Ma et al., 2020), ischemic heart diseases (IHD) (Ban et al., 2017; R. Chen et al., 2018; Fu et al., 2018; Ma et al., 2020; Yang et al., 2017), and stroke (Ban et al., 2017; R. Chen et al., 2018; Fu et al., 2018; Ma et al., 2020), while mortality from other common CVDs including chronic ischemic heart disease (CIHD), pulmonary heart disease (PHD), sequelae of stroke, chronic rheumatic heart diseases (CRHD), and hypertensive renal disease (HRD) is yet to be investigated, making it difficult to develop targeted clinical and public health strategies in preventing deaths from these specific CVDs against non-optimum temperature exposures. In addition, the heterogeneity of results caused by between-study differences including study design, outcome definition, exposure assessment, and temperature distribution hindered researchers from directly comparing the adverse effects of ambient temperature on mortality from different types of CVD, which is crucial in implementing effective interventions for specific types of CVD.

Therefore, we conducted a case-crossover study to comprehensively investigate the association of ambient temperature with mortality from total and 14 specific CVDs, and to quantify and compare the corresponding mortality burden attributable to ambient temperatures in Jiangsu province, China during 2015–2019. We hypothesized that non-optimum ambient temperature was associated with an increased risk of mortality from certain CVDs and the mortality burden may vary across types of CVD.

2. Methods

2.1. Study setting

Jiangsu province is situated in the eastern-central coastal China region (longitude: 116°18’−121°57’ E, latitude: 30°45’−35°20’ N) and covers an area of 107,200 km^2. In 2020, its population was 84.7 million, accounting for 5.9% of the total population in China. With a humid subtropical climate in most areas and a humid continental climate in the far north, Jiangsu province has clear-cut seasonal changes, with temperatures at an average of 3.2 °C and 27.8 °C in January and July 2019, respectively.

2.2. Study population

Using the China National Mortality Surveillance System, we identified 1000,014 CVD deaths as the underlying cause in Jiangsu province from January 1, 2015 to December 31, 2019, and collected their personal information on sex, date of birth, race, marital status, residential address, and date of death. This surveillance system was established and administrated by the Chinese Center for Disease Control and Prevention (CCDC), which covered the entire population in Jiangsu province during the study period (Liu et al., 2016). During 2015–2019, over 2.8 million deaths from any cause were identified with an estimated annual proportion of cause misclassification ranging from 2.63% to 2.82%. This study was approved by the Ethical Committee of School of Public Health, Sun Yat-sen University with a waiver of informed consent. Because the CVD mortality information used in this study was historically collected from routine surveillance data, and the identity information on the study subjects were confidential to all research investigators, the informed consent was waived.

2.3. Outcome

The CVD deaths were coded using the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10). The outcomes of interest included mortality from total CVDs (ICD-10 codes: I00-I99), and 6 main types of CVDs: CRHD (I05-I09), HD (I10-I15; including 2 subtypes: HHD [I11, I13] and HRD [I12-I13]), IHD (I20-I25; including 2 subtypes: myocardial infarction [MI; I21-I22] and CIHD [I25]), PHD (I26-I28), stroke (I60-I64; including 2 subtypes: hemorrhagic stroke [HS; I60-I62] and ischemic stroke [IS; I63]), and sequelae of stroke (I69.0-I69.4; including 2 subtypes: sequelae of HS [I69.0-I69.2] and sequelae of IS [I69.3]).

2.4. Study design

We investigated the burden of mortality from total and cause-specific CVDs attributable to ambient temperature using a time-stratified case-crossover design, in which exposure on the day of a given CVD death (case day) was compared with the exposure on days within the same stratum where the CVD death did not occur (control days) (Chen et al., 2019; Fu et al., 2018). We defined the stratum as the same month of the case day, and chose the control days as days with the same day of week before or after the case day in the stratum. This approach allowed us to control potential confounding effects of day of week, long-term trend, and seasonality (Carracedo-Martínez et al., 2010).

2.5. Exposure assessment

Daily grid data on 24-hour average 2 m air temperature (°C) in Jiangsu province during 2015–2019 were obtained using the China Meteorological Administration Land Data Assimilation System (CLDAS version 2.0) from the National Meteorological Information Center in China (spatial resolution: 0.0625° × 0.0625°; temporal resolution: 1 h) (Liu et al., 2020). For each subject, we assessed daily exposure to ambient temperature by extracting 24-hour average temperature values at his or her geocoded residential address on each of the case and control days. To account for delayed effects of ambient temperature exposure, we assessed exposures on up to 21 days before each of the case and control days (Fu et al., 2018).

2.6. Covariates

We calculated daily grid 24-hour average 2 m relative humidity (%) in Jiangsu province during 2015–2019 using daily data on 24-hour average 2 m air temperature (°C), 2 m specific humidity (kg/kg) and surface pressure (mb) from the CLDAS (Zhou et al., 2020). For each

Table 1
Characteristics of study subjects in Jiangsu province, China, 2015–2019.

Characteristic	n (%)
No. of CVD deaths (ICD-10 codes: I00-I99)	1000,014
No. of control days	3393,789
Sex, n (%)	
Male	495,039 (49.5)
Female	504,975 (50.5)
Age, years, n (%)	
Mean (SD)	79.2 (11.9)
Median (IQR)	81.8 (13.5)
< 80	428,198 (42.8)
≥ 80	571,816 (57.2)
Race, n (%)	
Han	997,599 (99.8)
Other	2415 (0.2)
Marital status, n (%)	
Married	582,749 (58.3)
Widowed	381,603 (38.2)
Unmarried	24,039 (2.4)
Divorced	8386 (0.8)
Unknown	3237 (0.3)

Abbreviations: CVD = cardiovascular disease; ICD-10 = International Statistical Classification of Diseases and Related Health Problems 10th Revision; IQR = interquartile range; SD = standardized deviation.

subject, we assessed daily exposure to relative humidity by extracting 24-hour average relative humidity values at his or her residential address on each of the case and control days. To take into consideration potential confounding by exposure to ambient air pollution, we extracted daily exposure to particulate matter with an aerodynamic diameter ≤ 2.5 μm ($PM_{2.5}$), particulate matter with an aerodynamic diameter ≤ 10 μm (PM_{10}), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), carbon monoxide (CO) and ozone (O_3) from the ChinaHighAirPollutants (CHAP) datasets (spatial resolution: 10 km × 10 km) at each subject's residential address. The CHAP datasets were generated using our proposed prediction model, which took advantage of satellite remote sensing and artificial intelligence to combine ground-based air pollutant measurements, remote sensing products, atmospheric reanalysis, model simulations, and has been validated with good performance in solving the spatiotemporal heterogeneity of air pollution in China (Wei et al., 2020, 2021a,b, 2022). Because individual-level covariates (e.g., age, sex, race, genetics, lifestyles, marital status) were unlikely to vary materially during the case and control days, we did not consider them as potential confounders in this analysis (Janes et al., 2005).

2.7. Statistical analysis

To account for nonlinear and delayed effects of ambient temperature on total and cause-specific CVD mortality, we applied a conditional logistic regression model integrated with a distributed lag non-linear model (DLNM) to derive overall exposure-response associations by cumulating the risks during a lag period of up to 21 days as proposed in previous studies (Fu et al., 2018; Gasparrini and Armstrong, 2013; Gasparrini, 2014). Odds ratio (OR) and its 95% confidence interval (CI) were estimated to quantify the associations. The main model included a natural cubic spline of mean relative humidity in the past 3 days (degree of freedom [*df*] = 3) and a cross-basis function of daily temperature built by the DLNM (Tian et al., 2019). The cross-basis function included a natural cubic spline with 3 internal knots placed equally at the temperature percentiles (i.e., 25th, 50th, 75th) and a lag response curve with a natural cubic spline with 3 internal knots placed at equally spaced values in the log scale, with the maximum lag up to 21 days (R. Chen et al., 2018; Tian et al., 2019).

For each of the total and cause-specific CVD mortality, we estimated the minimum mortality temperature (MMT) based on its overall cumulative exposure-response association and considered it as the optimum temperature. The minimum mortality percentile (MMP) was calculated as the percentile of MMT based on the distribution of ambient temperatures. A given temperature lower and higher than the MMT was defined as cold temperature and hot temperature, respectively. We further divided the cold temperature into extreme cold (<2.5th centile) and moderate cold (2.5th centile to MMT), and divided the hot temperature into moderate hot (MMT to 97.5th centile) and extreme hot (>97.5th centile) (Gasparrini et al., 2015; Pascal et al., 2018). We illustrated the overall lag structure in mortality risk associated with extreme cold temperature and extreme hot temperature exposures and estimated the corresponding cumulative odds ratios. To quantify total mortality burden attributable to non-optimum temperatures, we calculated total and cause-specific attributable fractions (AFs) using the estimated overall cumulative temperature-mortality associations of exposure to cold temperature (including extreme cold, moderate cold) and hot temperature (including moderate hot and extreme hot) as proposed in previous studies (Fu et al., 2018; Gasparrini et al., 2015). The empirical confidence interval (eCI) for an estimated AF was calculated using Monte Carlo simulations (Gasparrini and Leone, 2014). The difference of AF between mortality from given two CVDs was examined using a 2-sample z test (Altman and Bland, 2003). We further estimated number of deaths attributable to non-optimum ambient temperatures through multiplying the corresponding total number of deaths by the estimated AF.

We conducted stratified analyses by age (<80, ≥80 years), sex (male, female), and marital status (married, widowed) to identify potential vulnerable populations to non-optimum temperature exposures, and used the 2-sample z test to examine potential effect modifications

Table 2
Number of CVD deaths and distribution of ambient temperature exposures on the date of death.

	n (%)	Mean	SD	Min	P_{25}	P_{50}	P_{75}	Max
Cardiovascular diseases (ICD-10 codes: I00-I99)	1000,014 (100)	14.9	9.6	-10.6	6.4	14.8	23.2	36.3
Chronic rheumatic heart diseases (I05-I09)	8171 (0.8)	15.1	9.6	-10.1	6.3	14.8	23.5	35.0
Hypertensive diseases (I10-I15)	75,557 (7.6)	15.1	9.6	-10.5	6.6	14.8	23.3	36.0
Hypertensive heart disease (I11, I13)	66,685 (6.7)	15.1	9.6	-10.5	6.5	14.7	23.3	35.9
Hypertensive renal disease (I12-I13)	7381 (0.7)	15.3	9.4	-10.2	6.9	15.3	23.3	36.0
Ischemic heart diseases (I20-I25)	295,829 (29.6)	14.6	9.6	-10.6	6.1	14.3	23.1	36.2
Myocardial infarction (I21-I22)	169,886 (17.0)	14.5	9.7	-10.6	5.8	14.1	23.0	36.2
Chronic ischemic heart disease (I25)	121,506 (12.2)	14.9	9.6	-10.5	6.4	14.6	23.2	35.9
Pulmonary heart disease (I26-I28)	7400 (0.7)	13.7	9.6	-10.2	5.3	12.6	22.2	35.2
Stroke (I60-I64)	412,567 (41.3)	14.9	9.6	-10.6	6.3	14.8	23.2	36.3
Hemorrhagic stroke (I60-I62)	157,056 (15.7)	15.2	9.4	-10.4	6.7	15.4	23.3	36.3
Ischemic stroke (I63)	212,088 (21.2)	14.6	9.7	-10.6	6.0	14.4	23.1	36.3
Sequelae of stroke (I69.0-I69.4)	154,000 (15.4)	15.5	9.4	-10.3	7.0	15.4	23.5	35.9
Sequelae of hemorrhagic stroke (I69.0-I69.2)	13,658 (1.4)	15.5	9.3	-9.0	7.2	15.5	23.5	35.3
Sequelae of ischemic stroke (I69.3)	110,698 (11.1)	15.4	9.4	-10.3	7.0	15.4	23.5	35.6

Abbreviations: CVD = cardiovascular disease; ICD-10 = International Statistical Classification of Diseases and Related Health Problems 10th Revision; SD = standardized deviation.

Table 3
Estimated odds ratios of total and cause-specific CVD mortality associated with extreme cold and extreme hot temperatures.

	MMT, °C (MMP, %)	Odds ratio (95% CI)			
		$P_{2.5}$	Extreme cold	$P_{97.5}$	Extreme hot
Cardiovascular diseases	22.0 (70.5)	-0.6	1.79 (1.73, 1.85)	31.2	1.47 (1.43, 1.51)
Chronic rheumatic heart diseases	19.5 (62.3)	-0.7	1.77 (1.22, 2.56)	31.1	1.82 (1.31, 2.51)
Hypertensive diseases	21.8 (69.3)	-0.3	1.86 (1.63, 2.11)	31.5	1.85 (1.68, 2.04)
Hypertensive heart disease	22.0 (70.1)	-0.4	1.92 (1.67, 2.21)	31.5	1.83 (1.65, 2.03)
Hypertensive renal disease	22.1 (70.0)	-0.2	1.64 (1.08, 2.50)	31.5	1.61 (1.17, 2.20)
Ischemic heart diseases	22.2 (71.9)	-0.9	1.94 (1.82, 2.08)	31.1	1.52 (1.45, 1.60)
Myocardial infarction	22.1 (71.9)	-1.1	1.83 (1.68, 2.00)	30.9	1.52 (1.42, 1.62)
Chronic ischemic heart disease	22.4 (72.1)	-0.5	2.09 (1.89, 2.32)	31.3	1.53 (1.42, 1.65)
Pulmonary heart disease	22.3 (75.1)	-0.9	1.95 (1.27, 3.00)	30.8	1.16 (0.83, 1.62)
Stroke	22.1 (70.9)	-0.7	1.67 (1.58, 1.77)	31.1	1.37 (1.32, 1.43)
Hemorrhagic stroke	22.5 (71.7)	-0.5	1.46 (1.33, 1.60)	31.0	1.22 (1.15, 1.30)
Ischemic stroke	22.2 (71.8)	-1.0	1.82 (1.69, 1.97)	31.0	1.39 (1.31, 1.47)
Sequelae of stroke	21.9 (69.0)	0	1.83 (1.68, 2.01)	31.5	1.52 (1.42, 1.63)
Sequelae of hemorrhagic stroke	23.0 (73.2)	0.1	1.88 (1.38, 2.56)	31.5	1.48 (1.19, 1.84)
Sequelae of ischemic stroke	21.4 (67.5)	-0.2	1.81 (1.63, 2.01)	31.5	1.51 (1.39, 1.64)

Abbreviations: CI = confidence interval; CVD = cardiovascular disease; MMP = minimum mortality percentile; MMT = minimum mortality temperature.

(Altman and Bland, 2003). Several sensitivity analyses were performed to assess the robustness of our results, including: (1) adjusting for exposure to ambient $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO and O_3 on the same day of death and 1 day prior (lag 01 day) (K. Chen et al., 2018; R. Chen et al., 2018; Ren et al., 2008); (2) using alternative maximum lag periods of 14 and 28 days (Armstrong, 2006). All data analyses were performed with R (version 4.0.2). All statistical tests were 2-sided and a p value less than 0.05 was considered statistically significant.

3. Results

During the study period, we identified 1000,014 deaths from total CVDs in Jiangsu province, China, including 8171 deaths from CRHD, 75,557 deaths from HD, 295,829 deaths from IHD, 7400 deaths from PHD, 412,567 deaths from stroke, and 154,000 deaths from sequelae of stroke (Tables 1 and 2, Fig. S1). Of the CVD deaths, 49.5% were male, 57.2% died at or over 80 years, and 58.3% were married. The distribution of ambient daily temperature on the date of death from total and specific CVDs is given in Table 2, with the mean temperature ranging from 13.7 ℃ to 15.5 ℃.

Fig. 2 illustrates cumulative exposure-response curves for the association of ambient temperature with CVD mortality in Jiangsu province, China during 2015–2019. We observed a reverse J-shaped exposure-response association between ambient temperature and odds of total CVD mortality. With a MMT of 22.0 °C, exposure to both extreme cold and hot temperatures was significantly associated with increased odds of mortality (Table 3, Fig. 1). The odds increased by 79% at extreme cold temperature (−0.6 °C) and by 47% at extreme hot temperature (31.2 °C). For cause-specific CVD mortality, the MMTs ranged from 19.5 °C for CRHD and 23.0 °C for sequelae of HS. We observed similar reverse J-shaped exposure-response associations for mortality from all cause-specific CVDs, except that hot temperature was not significantly associated with increased odds of PHD mortality. The increased odds of cause-specific CVD mortality ranged from 46% for HS to 109% for CIHD

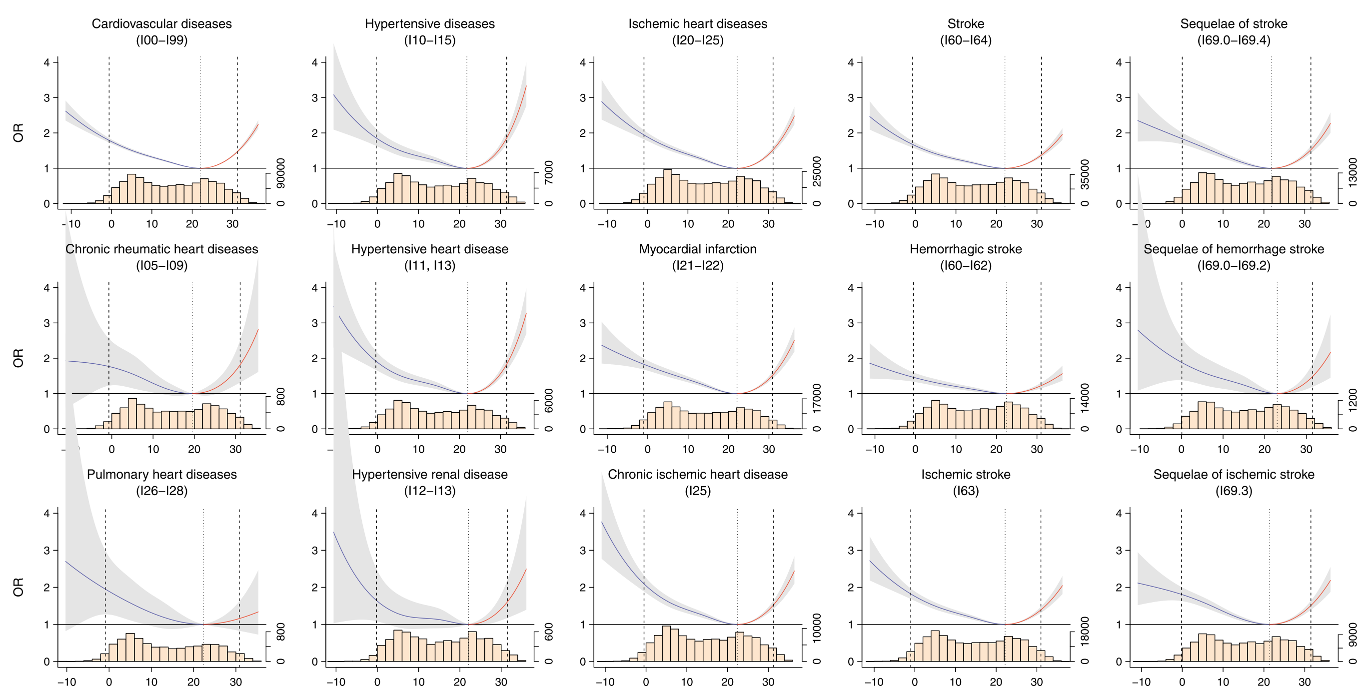

Fig. 1. Cumulative exposure-response curves for associations of ambient temperature with total and cause-specific CVD mortality over lag 0–21 days in Jiangsu province, China, 2015–2019. The solid smooth lines and shaded areas represent the odds ratio of total and cause-specific CVD mortality and its 95% CI, respectively. The solid horizontal black line in each panel indicates the odds ratio of 1. The vertical black dashed lines demonstrate the 2.5th (left) percentile of ambient temperature, minimum mortality temperature (center) and the 97.5th (right) percentile of ambient temperature, respectively. Abbreviations: CVD = cardiovascular disease; CI = confidence interval.

Table 4
Attributable fraction of total and cause-specific CVD mortality associated with non-optimum temperatures.

	MMT, °C (MMP, %)	Attributable fraction, % (95% eCI)		
		Overall	Cold	Hot
Cardiovascular diseases	22.0 (70.5)	20.3 (19.3, 21.3)	16.6 (15.6, 17.6)	3.70 (3.44, 3.97)
Chronic rheumatic heart diseases	19.5 (62.3)	22.4 (12.4, 30.3)	15.6 (5.23, 23.2)	6.81 (2.33, 10.9)
Hypertensive diseases	21.8 (69.3)	23.2 (19.4, 26.4)	17.4 (13.3, 20.9)	5.76 (4.79, 6.63)
Hypertensive heart disease	22.0 (70.1)	23.6 (19.6, 27.2)	18.0 (13.8, 21.8)	5.58 (4.63, 6.44)
Hypertensive renal disease	22.1 (70.0)	16.2 (0.94, 27.5)	11.9 (−4.04, 23.4)	4.33 (1.07, 7.28)
Ischemic heart diseases	22.2 (71.9)	23.3 (21.5, 25.1)	19.4 (17.6, 21.2)	3.91 (3.47, 4.37)
Myocardial infarction	22.1 (71.9)	23.1 (20.6, 25.5)	19.2 (16.7, 21.5)	3.93 (3.29, 4.49)
Chronic ischemic heart disease	22.4 (72.1)	23.8 (20.9, 26.5)	19.9 (16.8, 22.6)	3.95 (3.28, 4.67)
Pulmonary heart disease	22.3 (75.1)	20.9 (5.67, 32.2)	19.5 (3.46, 30.9)	1.38 (−2.22, 4.35)
Stroke	22.1 (70.9)	17.6 (15.9, 19.3)	14.5 (12.9, 16.2)	3.07 (2.67, 3.48)
Hemorrhagic stroke	22.5 (71.7)	13.3 (10.5, 16.0)	11.3 (8.42, 14.0)	1.97 (1.33, 2.60)
Ischemic stroke	22.2 (71.8)	20.3 (17.9, 22.5)	17.1 (14.8, 19.3)	3.20 (2.60, 3.70)
Sequelae of stroke	21.9 (69.0)	21.3 (19.0, 23.7)	17.2 (14.6, 19.5)	4.21 (3.47, 4.89)
Sequelae of hemorrhagic stroke	23.0 (73.2)	22.3 (11.9, 30.0)	18.8 (8.76, 26.6)	3.53 (1.26, 5.56)
Sequelae of ischemic stroke	21.4 (67.5)	20.9 (18.3, 23.4)	16.7 (14.0, 19.3)	4.21 (3.29, 5.11)

Abbreviations: CVD = cardiovascular disease; eCI = empirical confidence interval; MMP = minimum mortality percentile; MMT = minimum mortality temperature.

at extreme cold temperature and ranged from 22% for HS to 85% for HD at extreme hot temperature.

For the overall lag structure in effects of ambient temperature on total and specific CVD mortality except PHD (Fig. S2), the mortality odds of extreme cold temperature generally occurred on the first day, peaked within 1–2 days, and decreased to day 14 with mild effects on subsequent days. In comparison, the mortality odds of extreme hot temperature peaked within 0–1 days, monotonically attenuated in 5–7 days, and remained stable afterwards or followed by a mortality displacement instead. For PHD mortality, the mortality odds associated with extreme cold temperature was strongest on the present day, monotonically attenuated in 1–2 days, slightly increased from 3–5 days, and remained stable afterwards, while the mortality odds of extreme hot temperature occurred on the first day, peaked within 1–2 days and decreased on subsequent days.

Table 4 and Table S1 show the AF and attributable number of deaths from total and cause-specific CVDs attributable to different components of ambient temperature. The AF of total CVD mortality was 20.3% (95% eCI: 19.3%, 21.3%), which was translated to 203,250 deaths in Jiangsu province during 2015–2019. The AF varied across main types of CVDs, with the lowest for stroke mortality (17.6%) and highest for IHD mortality (23.3%). We observed higher AF of mortality from HHD than that from HRD (23.6% vs. 16.2%) and higher AF of mortality from IS than that from HS (20.3% vs. 13.3%; all p for difference <0.05); in contrast, we did not observe significant difference of AF between two subtypes of mortality from IHD or sequalae of stroke (both p for difference >0.05). Compared with hot temperature, cold temperature was responsible for most of the AF (proportions ranging from 69.6% for mortality from CRHD to 93.4% for mortality from PHD). By separating the overall AF of total and cause-specific CVD mortality into moderate and extreme temperatures (including extreme cold, moderate cold, moderate hot and extreme hot), we observed that moderate cold temperature contributed to the largest AF for total and cause-specific CVD mortality (proportions ranging from 63.5% for CRHD to 86.1% for PHD; Fig. 2).

Fig. 3 presents the AF of total and cause-specific CVD mortality attributable to moderate and extreme temperatures by age, sex, and marital status. The AF of mortality from total CVDs, IHD, MI, stroke, HS and sequelae of stroke was significantly higher in older adults than those who died before 80 years, while the AF of mortality from total CVDs, CRHD, IHD, stroke, and sequelae of stroke was significantly higher in widowed adults (all p for difference <0.05). The AF did not vary significantly across sex (all p for difference >0.05). In the sensitivity analyses, adjustment for exposure to ambient air pollutants and using the ambient temperature with different maximum lag periods (14 and 28 days) yielded similar results (Tables S2-S9; Figs. S3-S10).

4. Discussion

In this large case-crossover study of over 1 million CVD deaths, we quantitatively investigated the adverse effects of ambient temperature on mortality from total and cause-specific CVDs in Jiangsu province, China during 2015–2019. We found that exposure to non-optimum ambient temperatures was significantly associated with increased risk of all studied cause-specific CVD mortality. The corresponding mortality burden was substantial and varied across types of CVD, ranging from 17.6% for stroke mortality to 23.3% for IHD mortality; in addition, the mortality burden varied significantly across subtypes of mortality from HD (HHD higher than HRD) and stroke (IS higher than HS). For both total and cause-specific CVD mortality, moderate cold temperature was responsible for most of the attributable deaths. We observed significantly more attributable mortality from total and certain cause-specific CVDs in older and widowed adults.

To our knowledge, this is the first study to comprehensively quantify and compare the burden of ambient temperature on a wide range of cause-specific CVD mortality. Consistent with previous findings, our results suggest that exposure to non-optimum ambient temperatures contributes to considerable disease burden on mortality from HD, IHD (including MI), stroke, and cold temperature was responsible for most of the mortality burden (R. Chen et al., 2018; Ma et al., 2020). Compared with results from a previous time-series study in the same province, we observed higher AF of mortality from IHD (23.3% vs. 16.51%) and stroke (17.6% vs. 12.41%), and slightly lower AF of mortality from HD (23.2% vs. 26.20%). Note that the study was conducted in 11 of the 13 cities in Jiangsu province during 2014–2017, and the nature of time-series analysis did not allow for individual-level exposure assessment. In our study, we investigated all CVD deaths during 2015–2019 and employed the case-crossover design to assess individual-level exposure to ambient temperature using a high-resolution grid data, which can help achieve more precise estimates (Jaakkola, 2003; Zeger et al., 2000). Another time-series study in 272 cities in China found that non-optimum ambient temperature was responsible for a mortality burden of 18.76% for IHD and 16.10% for stroke, which was slightly lower than our estimates (AF for IHD: 23.3%; stroke: 17.6%); however, this multi-city study acknowledged that the time-series study design with the mean daily temperature at all sites outdoor monitors in a city

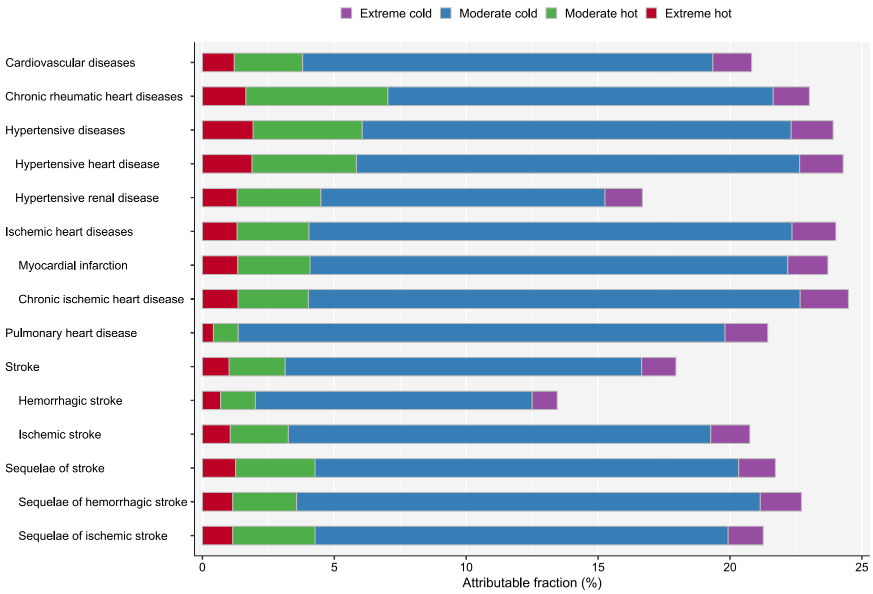

Fig. 2. Attributable fraction of total and cause-specific CVD mortality attributable to non-optimum temperature in Jiangsu province, China, 2015–2019. Extreme cold temperatures range from the lowest temperature to the 2.5th percentile of temperature distributions; moderate cold temperatures range from the 2.5th percentile of temperature distributions to the minimum mortality temperature; moderate hot temperatures range from the minimum mortality temperature to the 97.5th percentile of temperature distributions; extreme hot temperatures range from the 97.5th percentile of temperature distributions to the highest temperature. Abbreviations: CVD = cardiovascular disease.

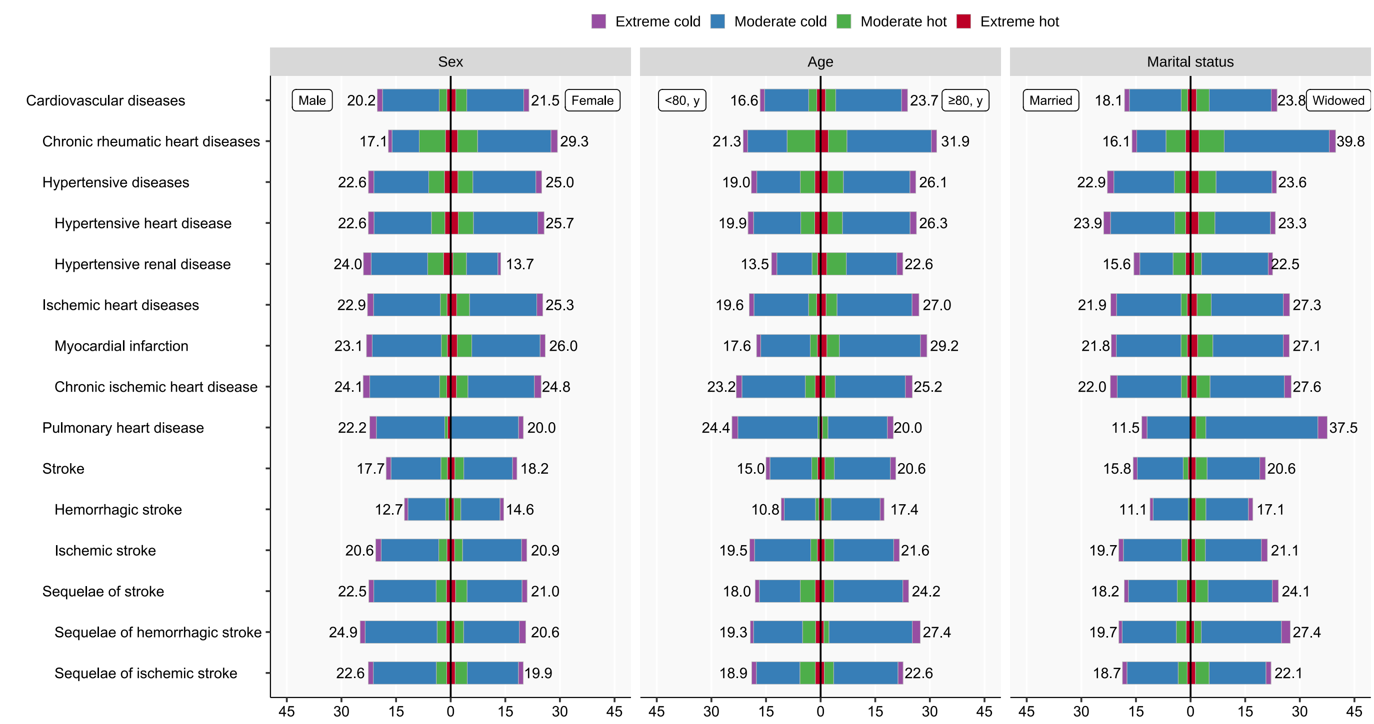

Fig. 3. Attributable fraction of total and cause-specific CVD mortality attributable to non-optimum temperatures, stratified by sex, age and marital status in Jiangsu province, China, 2015–2019. Extreme cold temperatures range from the lowest temperature to the 2.5th percentile of temperature distributions; moderate cold temperatures range from the 2.5th percentile of temperature distributions to the minimum mortality temperature; moderate hot temperatures range from the minimum mortality temperature to the 97.5th percentile of temperature distributions; extreme hot temperatures range from the 97.5th percentile of temperature distributions to the highest temperature. Abbreviations: CVD = cardiovascular disease.

could introduce exposure misclassifications and might underestimate the effects. In addition, we found that non-optimum ambient temperature was also responsible for substantial burden of mortality from CIHD, CRHD, HRD, PHD and sequelae of stroke, which has not been investigated previously. These results indicate that non-optimum ambient temperature is a risk factor for mortality from a wide range of specific CVDs. Our findings provide useful clues that reducing exposure to non-optimum temperatures may be helpful in preventing premature deaths from various types of CVD.

In this study, we found that the mortality burden attributable to non-optimum temperatures varied across specific types of CVD. Compared with mortality from stroke, the burden of mortality from both HD and IHD were significantly higher. Although the underlying mechanisms remain less clear, it has been reported that low ambient temperature could enhance sympathetic reactivity, induce physiological changes (including elevated blood pressure, higher heart rate variability, increased fibrinogen concentration, vasoconstriction, platelet aggregation and thrombotic occlusion) and further lead to HD and ischemic cardiovascular event (Keatinge et al., 1986; Liu et al., 2015). The lower burden of mortality from stroke (especially HS) than other CVDs may be due to its different biological mechanisms which warrant further investigations. Note that the case fatality rate of HS was much higher than other ischemic cardiovascular events, which might obscure the acute adverse effects of non-optimum ambient temperatures and could possibly be one of the reasons for the observed weaker effects. Furthermore, our findings suggest that non-optimum cold temperature can lead to more severe adverse effects on patients with PHD than other cause-specific CVD mortality. One possible reason is that PHD patients typically experience both cardiovascular disorders and respiratory system damages, which have been linked to non-optimum cold temperatures and may act synergically to promote the acute adverse effects (R. Chen et al., 2018). Overall, our results provide novel evidence that the adverse effects of non-optimum ambient temperature on mortality vary across types of CVD. In addition to offering useful clues for clinical practitioners and patients during CVD treatments, our findings can help policy makers develop more targeted action guidelines to prevent premature deaths from specific CVDs, especially those with higher mortality burden.

The unique strength of this study was the large sample size (over 1 million CVD deaths from a base population of 85 million for 5 years), which enabled us to systematically investigate the burden of cause-specific CVD mortality attributable to ambient temperature with sufficient statistical power. Second, the humid subtropical climate with seasons clearly cut in Jiangsu province provided us with an ideal setting to investigate the burden of mortality due to a wide range of ambient temperature (−10.6 ℃ to 36.3 ℃), making our results more generalizable to other populations. Third, we used the time-stratified case-crossover design to take advantage of individual-level exposure assessment based on the residential address and validated gridded dataset on ambient temperature with a reasonably high spatial resolution ($0.0625^\circ \times 0.0625^\circ$). To date, most studies investigating temperature and mortality employed a time-series or case-crossover design, in which city-level exposure assessment was typically applied. Only one study in India employed a case-crossover design and assessed individual-level exposure to ambient temperature; however, the spatial resolution of their daily gridded temperature data was much lower ($1^\circ \times 1^\circ$) (Fu et al., 2018).

This study also has several limitations. First, because we assessed individual-level exposure by extracting temperature data from an established grid database based on each subject's residential address and did not have data to account for personal adaptive behaviors (e.g., the use of air conditioning in summer, heating system in winter) as well as indoor air pollution exposure, exposure misclassifications might have been introduced. However, these exposure misclassifications were likely to be nondifferential, which were unlikely to significantly bias the estimates (Whitcomb and Naimi, 2020). Second, although the case-crossover study design helps us take advantage of controlling time-invariant individual-level confounders and slow time-variant variables in the model, residual or unmeasured confounding was still possible. Finally, this study was conducted in a single province in China. Although the base population was up to 84.7 million, the estimated mortality risks and disease burden due to non-optimum temperatures should be interpreted cautiously to other regions or countries.

5. Conclusion

We found that exposure to non-optimum ambient temperature was significantly associated with increased risk of cause-specific CVD mortality. The burden of CVD mortality attributable to ambient temperature was substantial especially for older and widowed adults, and significantly varied across types of CVD. These findings have important implications for the future development of targeted interventions for cause-specific CVD mortality under non-optimum ambient temperatures. Further studies are needed to confirm our findings in other populations and to elucidate the potential biological mechanisms.

CRediT authorship contribution statement

Ruijun Xu: Formal analysis, Investigation, Writing – original draft. **Chunxiang Shi**: Data curation, Writing – original draft. **Jing Wei**: Data curation, Methodology. **Wenfeng Lu**: Writing – review & editing. **Yingxin Li**: Writing – review & editing. **Tingting Liu**: Writing – review & editing. **Yaqi Wang**: Writing – review & editing. **Yun Zhou**: Validation, Methodology, Writing – review & editing. **Gongbo Chen**: Validation, Methodology, Writing – review & editing. **Hong Sun**: Conceptualization, Data curation, Funding acquisition, Supervision, Project administration, Writing – review & editing. **Yuewei Liu**: Conceptualization, Data curation, Funding acquisition, Supervision, Project administration, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2022.113498.

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