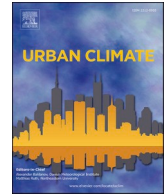




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# Exposure to hourly ambient temperature and temperature change between neighboring days and risk of emergency department visits for cause-specific cardiovascular disease

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## ABSTRACT

Little is known regarding the association between hourly exposure to ambient temperature and temperature change between neighboring days (TCN) with the risk of emergency department (ED) visits for cardiovascular disease (CVD). We conducted a time-stratified case-crossover study among 1.03 million ED visits for CVD between 2016 and 2021 in Zhejiang Province, China. Our analysis reported a reversed J-shaped relationship between hourly ambient temperature and risk of total and cause-specific CVD, with cold having the most significant effects. The risk associated with extreme cold (2.5<sup>th</sup> percentile of temperature distribution) peaked approximately 40 h after exposure, while the effects of extreme heat (97.5<sup>th</sup> percentile) were most pronounced during the concurrent hour of exposure (lag 0 h). Additionally, a decline in TCN (negative TCN) was associated with a higher risk of CVD, hypertensive disease, and stroke. In contrast, an increase in TCN (positive TCN) was associated with a lower risk of cause-specific CVD. The risks of negative and positive TCN peaked on the day of exposure and two days after exposure, respectively. These findings suggest that exposure to non-optimal temperature and TCN may increase the risk of ED visits for total and cause-specific CVD shortly after exposure, primarily driven by cold and negative TCN.

## 1. Introduction

Cardiovascular disease (CVD) is the leading cause of mortality and disability-adjusted life-years lost globally, accounting for an

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estimated 18.6 million deaths in 2019, including 4.6 million in China (WHO, 2019; Zhou et al., 2019). Investigating modifiable risk factors for CVD and identifying vulnerable populations is of paramount importance for both public health and clinical practice.

Previous studies have identified non-optimal temperatures as a potential risk factor for CVD (Ye et al., 2012; Chen et al., 2018; Silveira et al., 2019; Zhang et al., 2022b). For example, exposure to non-optimal ambient temperature was associated with increased risk of CVD morbidity (Ye et al., 2012; Zhang et al., 2022b) and mortality (Chen et al., 2018; Silveira et al., 2019). In the context of climate change, temperature fluctuations are becoming more frequent. Research suggests that sudden changes in temperature may exacerbate CVD by triggering systemic inflammation, weakening immunity, or disrupting thermoregulatory processes (Liu et al., 2015; Zhang et al., 2024). However, evidence on the association between temperature fluctuations and CVD remains limited.

Although a few time-series studies have investigated the association between exposure to ambient temperature and the risk of CVD (Liu et al., 2019; Alahmad et al., 2023; Kim et al., 2023; Lane et al., 2024), most of these studies have quantified the association on a daily scale (Liu et al., 2019; Alahmad et al., 2023; Kim et al., 2023; Lane et al., 2024), which has inherent limitations. These include difficulties in controlling for individual confounders and challenges in establishing a clear temporal sequence between non-optimal temperature and CVD. Additionally, most studies are limited to single-center settings with small sample sizes and rely on cardiovascular hospitalizations and deaths (Aghababaeian et al., 2023; Alahmad et al., 2023), which may be less sensitive than emergency department (ED) visits. To address these gaps, we estimated the association between hourly non-optimal ambient temperature and TCN and ED visits for total and cause-specific CVD using a time-stratified case-crossover design. This approach allows for the adjustment of individual confounders through self-matching and establishes a more plausible temporal relationship between temperature exposure and CVD risks (Bateson and Schwartz, 1999; Carracedo-Martínez et al., 2010; Wu et al., 2021).

Accordingly, we conducted a large-scale multicenter case-crossover study in Zhejiang province, China, from 2016 to 2021 to quantify the relationship between exposure to hourly non-optimal ambient temperature and TCN and ED visits for total CVD, and hypertensive disease (HD), ischemic heart disease (IHD), stroke, and arrhythmias.

## 2. Methods

### 2.1. Study population

This study was conducted in three cities in Zhejiang Province, China: Hangzhou, Jinhua, and Zhoushan. Located in the southeastern China, these cities experience a subtropical monsoon climate, characterized by distinct seasons, abundant sunshine, and rainfall. The annual average ambient temperature ranges from 0 to 36 °C, with periods of extreme cold from November to February and extreme heat from June to August.

From 1 January 2016 to 31 December 2021, we collected ED visit for each patient from 9 hospitals across 3 cities in Zhejiang Province: Hangzhou, Jinhua, and Zhoushan (Lv et al., 2023; Yuan et al., 2024). The primary diagnosis of ED visits was coded according to the International Classification of Diseases, 10th Revision (ICD-10) codes, which include total CVD (I00-I99), HD (I10-I15), IHD (I20-I25), arrhythmia (I47-I49), and stroke (I60-I69). For each ED visit, we extracted information on age, sex, date and time of the visit, and the corresponding ICD-10 code. This study was approved by the Ethics Committee of the Zhejiang Provincial Center for Disease Control and Prevention (Reference # AF/SC-06/01.0).

### 2.2. Exposure assessment

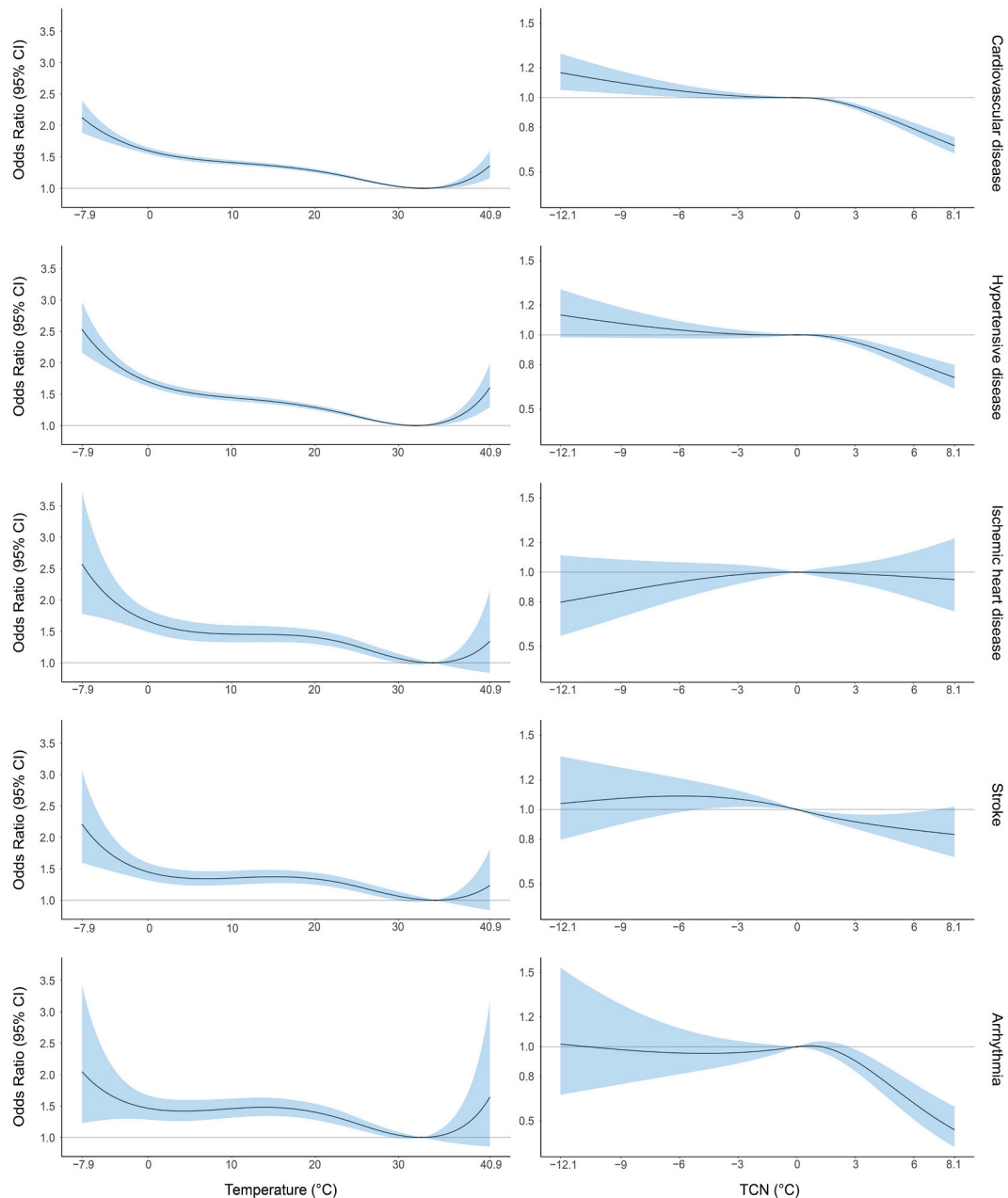
Hourly ambient temperature and relative humidity (RH) data were obtained from the China Meteorological Data Service Center (<http://data.cma.cn/>). TCN was defined as the difference in mean ambient temperature between the current and previous 24-h periods. Therefore, a negative TCN indicates a temperature decrease from the previous day to the current day, while a positive TCN indicates an increase in temperature during the same time frame. Additionally, we collected hourly concentrations of criteria air pollutants, including fine particulate matter (PM<sub>2.5</sub>), respirable particulate matter (PM<sub>10</sub>), nitrogen dioxide (NO<sub>2</sub>), sulfur dioxide (SO<sub>2</sub>), ozone (O<sub>3</sub>), and carbon monoxide (CO), from the closest fixed station of the China National Environmental Monitoring Center to allow for potential confounder adjustment. For each ED visit, we matched ambient temperature and other environmental exposures to the nearest environmental monitoring station within a 100 km radius of the hospital address using its latitude and longitude.

### 2.3. Statistical analysis

We investigated the associations between hourly ambient temperature, TCN, and the risk of total and cause-specific CVD using an individual-level, time-stratified case-crossover study design (Sun et al., 2021; Wu et al., 2021). The case period for each patient was defined as the specific hour of the ED visit for CVD. Control periods were selected using a bidirectional referent selection approach, matching the case period with the same hour of the day, day of the week, month, and year (Wu et al., 2021). For example, if a patient visited the ED for CVD at 8:00 a.m. on Monday, January 8, 15, 22, and 29, 2024 (the case period), the corresponding control periods would be at 8:00 a.m. on Monday, January 8, 15, 22, and 29, 2024 (the control periods). The study compared temperature exposure during each patient's ED visit with temperature during the matched control periods when the same person did not experience a CVD event (Maclure, 1991). This self-matching approach effectively controlled for individual-level confounders, such as age and sex, long-term trends, and seasonal variations (Bateson and Schwartz, 1999; Carracedo-Martínez et al., 2010; Wu et al., 2021).

The association between short-term exposure to ambient temperature and TCN and the risk of total and cause-specific CVD were estimated using a conditional logistic regression combined with a distributed lag non-linear model (DLNM). We used conditional

logistic regression to estimate odds ratios (ORs) with 95 % confidence intervals (CIs). For the DLNM, a flexible cross-basis term was created to model both the exposure-response function and lag-response function for ambient temperature (*cb.DMT*) and TCN (*cb.TCN*). For the exposure-response function, we used a natural cubic B-spline with 5 degrees of freedom (*df*) for hourly ambient temperature and used a natural cubic spline with 3 *df* for TCN (Chen et al., 2022a). For the lag-response function, we used a natural cubic spline with 3 *df* for lags up to 72 h for temperature, and two internal knots spaced equally at the log-scale of lags up to 3 d for TCN (Zhang et al., 2022a). Both cross-basis functions for temperature and TCN were included in the conditional logistic regression model with additionally adjusted for the 72-h moving average of RH using a natural cubic spline with 3 *df*, and a dummy variable of public holiday (Xue



**Fig. 1.** Cumulative exposure-response curves for the association between hourly ambient temperature, temperature change in neighboring days, and total and cause-specific cardiovascular disease, 2016–2021.

Notes: The mean risk estimations are represented by the solid blue lines, while the 95 % confidence intervals shown as shaded blue areas. Odds ratios and 95 % confidence intervals were calculated relative to the optimal temperature of 33.0 °C for cardiovascular disease, 32.1 °C for hypertensive disease, 34.1 °C for ischemic heart disease, 34.4 °C for stroke, and 32.7 °C for arrhythmia. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

et al., 2023). The main model formula used in this study was as follows:

$$\text{Logit}[P(Y)] = cb.DMT + cb.TCN + \text{Strata}(\text{strata}) + ns(\text{RHmean}, df = 3) + as.factor(\text{Holiday})$$

Where *strata* represents the risk set, *ns(.)* denotes natural cubic splines, *RHmean* refers to the cross-basis term for the 72-h moving average of RH, and *Holiday* is a binary variable indicating public holidays.

Based on the overall cumulative exposure-response relationship between ambient temperature, TCN and CVD, we identified the optimal temperature as the temperature percentile (bounded between the 1<sup>st</sup> and 99<sup>th</sup> percentile of temperature distribution) associated with the lowest ORs for ED visits (Sun et al., 2021; Chen et al., 2022b). To illustrate the lag-response patterns of risks for CVD, HD, IHD, stroke, and arrhythmia, we plotted the lag-response curves for extreme cold (2.5<sup>th</sup> percentile) and extreme heat (97.5<sup>th</sup> percentile), relative to the corresponding optimal temperature. For TCN, we used a reference value of 0 °C, indicating no temperature change between the current day and the previous day. We also reported the lag patterns of total and cause-specific CVD risks associated with extremely negative TCN (2.5<sup>th</sup> percentile) and extremely positive TCN (97.5<sup>th</sup> percentile) compared to the reference TCN.

To identify potentially vulnerable groups, we performed stratified analyses by age, sex, hospital grade, season, and city. Hospital grades were determined based on the China National Hospital Hierarchical Management Standard, which assesses hospitals on functions, facilities, technical capabilities, and other qualifications. We classified Tertiary A hospitals as high-ranked, with all others categorized as low-ranked hospitals (Zhang et al., 2022a). The two-sample Z-test was used to assess statistical differences between stratum-specific estimates.

## 2.4. Sensitivity analysis

To confirm the robustness of our results, we performed two sensitivity analyses. First, to address potential residual confounding, we included individual pollutants one at a time and simultaneously incorporating all five air pollutants (PM<sub>2.5</sub>, NO<sub>2</sub>, SO<sub>2</sub>, O<sub>3</sub>, and CO) into the models. Second, to assess the independent effects of ambient temperature, we excluded TCN from the main model.

All statistical analyses were conducted using R software (version 4.3.1), and a two-sided *p*-value of <0.05 was considered statistically significant.

## 3. Results

### 3.1. Descriptive statistics

A total of 1,036,496 ED visits for CVD were included, of which 545,783 were for HD (52.7 %), 105,196 for IHD (10.2 %), 171,769 for stroke (16.6 %), and 79,900 for arrhythmia (7.7 %) (Table S1). The majority of patients were under 65 years old (52.4 %), male (53.1 %), visited during the warm season (50.6 %), were admitted to the high-ranked hospitals (82.2 %), and resided in Hangzhou (54.3 %) (Table S1).

The median distance between the hospital and the meteorological and air pollution monitoring stations was 17.5 km and 4.3 km, respectively. The hourly average ambient temperature was 18.8 °C and RH was 72.9 % (Table S2). The mean TCN was −0.03 °C, with a standard deviation of 2.4 °C (Table S2). Ambient temperature was positively correlated with TCN (Spearman *r* = 0.13; Table S3) and negatively correlated with RH (Spearman *r* = −0.15; Table S3).

**Table 1**

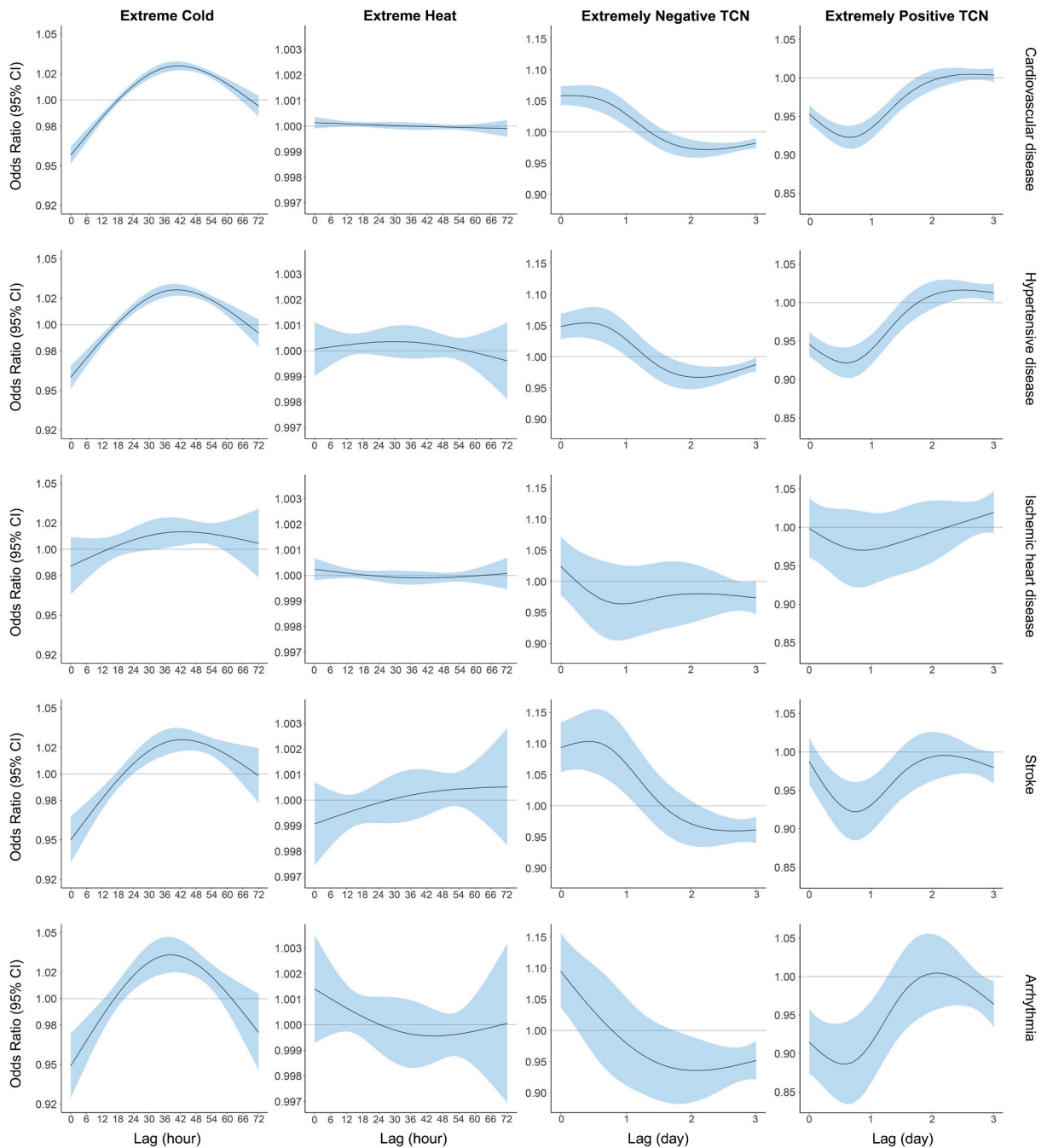
Odds ratio (95 % CI) of total and cause-specific emergency department visits for cardiovascular disease associated with non-optimal ambient temperature and temperature variations over lag 0 to 72 h after exposure.

Disease	Optimal temperature centile†	Optimal temperature (°C)	Extreme cold OR (95 %CI)	Extreme heat OR (95 %CI)	Extremely negative TCN OR (95 %CI)	Extremely positive TCN OR (95 %CI)
CVD	83.8 %	33.0	1.530 (1.484, 1.577)	1.001 (0.998, 1.004)	1.040 (1.001, 1.080)	0.891 (0.864, 0.918)
HD	82.0 %	32.1	1.592 (1.529, 1.658)	1.011 (0.998, 1.024)	1.028 (0.977, 1.083)	0.907 (0.870, 0.945)
IHD	86.1 %	34.1	1.554 (1.403, 1.721)	1.000 (0.994, 1.006)	0.941 (0.831, 1.065)	0.982 (0.892, 1.080)
Stroke	86.7 %	34.4	1.378 (1.260, 1.507)	1.003 (0.981, 1.026)	1.090 (0.990, 1.200)	0.895 (0.829, 0.965)
Arrhythmia	83.2 %	32.7	1.423 (1.262, 1.604)	1.004 (0.976, 1.033)	0.956 (0.827, 1.106)	0.808 (0.721, 0.906)

Abbreviation: TCN, temperature change in neighboring days; CVD, Cardiovascular disease; HD, Hypertensive disease; IHD, ischemic heart disease. Notes: † Minimum percentile of temperature distributions for emergency department visits. Extreme cold = 2.5<sup>th</sup> percentile of temperature distribution; extreme heat = 97.5<sup>th</sup> percentile of temperature distribution. Extremely negative TCN = 2.5<sup>th</sup> percentile of TCN distribution; extremely positive TCN = 97.5<sup>th</sup> percentile of TCN distribution.

### 3.2. Regression results

The cumulative exposure-response curves for hourly temperature and the risk of total and cause-specific CVD consistently showed an inverse J-shaped relationship, with risk increased for both low and high temperature, particularly at low temperature (Fig. 1). The impact of cold on HD appeared to be the most pronounced, with extreme cold increasing the risk of HD by 59.2 %, IHD by 55.4 %, CVD



**Fig. 2.** Overall lag structure of extreme cold and extreme heat and temperature change in neighboring days for total and cause-specific CVD. Abbreviation: TCN, temperature change in neighboring days; CVD, Cardiovascular disease; HD, Hypertensive disease; IHD, ischemic heart disease. Notes: The mean risk estimations are represented by the solid blue lines, while the 95 % confidence intervals shown as shaded blue areas. Extreme cold = 2.5<sup>th</sup> percentile of temperature distribution; extreme heat = 97.5<sup>th</sup> percentile of temperature distribution. Extremely negative TCN = 2.5<sup>th</sup> percentile of TCN distribution; extremely positive TCN = 97.5<sup>th</sup> percentile of TCN distribution. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

by 53.0 %, arrhythmia by 42.3 %, and stroke by 37.8 %, compared to the corresponding optimal temperature (Table 1). In contrast, exposure to heat was only slightly associated with an increased risk of CVD (Fig. 1), with an OR of 1.001 (95 % CI: 0.998, 1.004) for extreme heat (Table 1).

The lag structure of the association between extreme cold and the risk of total and cause-specific CVD generally delayed for approximately 18 h, peaked at approximately 40 h after exposure, and then gradually attenuated in the following hours (Fig. 2). In contrast, the risks of CVD associated with extreme heat peaked at the hour of exposure (lag 0 h) (Fig. 2). The lag patterns for cause-specific CVD generally mirrored those observed for CVD (Fig. 2).

For TCN, we observed that exposure to negative TCN increased the risk of CVD, HD, and stroke, while decreasing the risk of IHD and arrhythmia (Fig. 1). However, the effects of HD and stroke were not found to be statistically significant. Specifically, compared to the reference TCN, the ORs for CVD, HD and stroke at extremely negative TCN were 1.040 (95 % CI: 1.001, 1.080), 1.028 (95 % CI: 0.977, 1.083), and 1.090 (95 % CI: 0.990, 1.200), respectively (Table 1). Additionally, we found no evidence of an association between extremely positive TCN exposure and CVD (Table 1).

The effects of extremely negative TCN on the risk of total and cause-specific CVD were most pronounced on the day of exposure (lag 0 day) and lasted for approximately 1 day (Fig. 2). In contrast, the risks associated with extremely positive TCN delayed and peaked around 2 days after exposure (Fig. 2).

### 3.3. Results of subgroup analysis

In the stratified analyses, we found that the risk of CVD was consistent across age, sex, and season for both extreme temperatures and TCNs (Fig. S1, Fig. S2). However, individuals admitted to high-ranked hospitals exhibited higher susceptibility to CVD after exposure to extreme cold or extremely negative TCN (Fig. S1, Fig. S2). Additionally, residents of Zhoushan city demonstrated a higher risk of CVD associated with extreme heat or extremely negative TCN (Fig. S1, Fig. S2).

### 3.4. Results of sensitivity analysis

Regardless of whether we adjusted for individual air pollutants, included all pollutants simultaneously in the models, or excluded TCN from the main model, the results were not materially different from the main findings (Fig. S3, Fig. S4).

## 4. Discussion

Among over 1 million ED visits for CVD, we found that exposure to both cold and heat was associated with increased risk of ED visits for CVD, HD, IHD, stroke, and arrhythmia, with cold showing more pronounced effects. The most significant risks of extreme cold on CVD typically occurred around 40 h after exposure, while the effects of extreme heat were most pronounced at the time of exposure (lag 0 h). Additionally, declines in ambient temperature between neighboring days were linked to a higher risk of CVD, whereas sudden rises in temperature from the previous day were associated with a lower risk. The risk associated with extremely negative TCN peaked on the day of exposure, and the risk associated with extremely positive TCN peaked two days later after exposure.

We found that both cold and heat were associated with increased risk of CVD, with cold showing more pronounced effects. Although no study directly comparable, our findings align with previous studies that used ambient temperature and CVD on a daily basis (Tian et al., 2016; Bai et al., 2018; Zhao et al., 2018; Rodrigues et al., 2019; Fan et al., 2023; Kim et al., 2023). For example, a recent meta-analysis of 159 studies reported a 1.2 % increase in CVD-related morbidity for each 1 °C decrease in temperature (Fan et al., 2023). Similarly, a time series study from New York City showed that exposure to heat was associated with increased risk of hospital admissions for CVD (Lin et al., 2009).

We found that the effects of extreme cold peaked about 40 h after exposure, whereas the effects of extreme heat were more immediate. (Bhaskaran et al., 2012; Rowland et al., 2020). Our findings were consistent with most previous studies (Dang et al., 2016; Burkart et al., 2021; Kim et al., 2023); however, they were contrast with a study using the Chinese Cardiovascular Association Database-Chest Pain Center, which included 1,046,773 acute myocardial infarction patients. That study found that the association between extreme cold and acute myocardial infarction occurred immediately on the same day of exposure (Jiang et al., 2022).

In addition to ambient temperature, we found that negative TCN is linked to a higher risk of CVD, HD, and stroke, consistent with findings from previous studies (Chen et al., 2022a; Zha et al., 2022; Zhang et al., 2022a). The heightened risk may be attributed to the physiological effects of sudden temperature drops, such as increased blood viscosity and the potential to trigger infections, both of which are established risk factors for CVD (Liu et al., 2015; Zhang et al., 2024). Previous studies have documented the link between exposure to diurnal temperature range and temperature variability and CVD using time-series analyses (Rahman et al., 2022; Tang et al., 2022). However, our study adds to the limited evidence on the effect of inter-day temperature variations on CVD. We further showed that acute exposure to extremely negative TCN may trigger total and all-cause CVD risk within hours after exposure rather than days later.

Additionally, we found no evidence of an association between extremely positive TCN and CVD. This finding contrasts with previous studies (Guo et al., 2011; Zhan et al., 2017). For example, a study of 106 US communities found that exposure to extremely positive TCN was associated with elevated CVD mortality, with a relative risk of 1.52 (95 % CI: 1.40, 1.65) over a lag of 0–21 days (Zhan et al., 2017). Similarly, another study reported that rising temperature between consecutive days increased CVD mortality risk in Brisbane, a temperature decline between days was linked to increased CVD mortality in Los Angeles (Guo et al., 2011). The disparate effects of TCN on CVD risk may be attributed to differences in climate, population characteristics, sample size, and study design. The

underlying reasons to explain the mechanism linked TCN with CVD remain unclear. One hypothesis is that temperature fluctuations may weaken immunity, making individuals more susceptible to respiratory infections, which could in turn affect the circulatory system (Liu et al., 2015; Zhang et al., 2024).

We found that individuals admitted to high-ranked hospitals were more susceptible to temperature fluctuations. This may reflect that those with CVD treated in such hospitals often have more severe and complex conditions, more likely to access comprehensive healthcare services, and have higher health awareness, all of which increased the susceptible to temperature fluctuations.

Several hypotheses have been proposed to explain the potential biological mechanisms by which exposure to non-optimal temperature and sudden temperature drops between neighboring days may increase the risk of CVD. First, exposure to cold can lead to peripheral vasoconstriction, elevated arterial pressure, increased heart rate, inflammation, and oxidative stress. These physiological changes collectively increase cardiac workload while simultaneously reducing coronary blood flow, which can elevate the risk of CVD (Carder et al., 2005; Davidkiovová et al., 2014; Ni et al., 2022). In contrast, exposure to heat may increase the risk of coronary events due to thermoregulatory dysfunction and excessive fluid loss. This can result in increased blood viscosity, cholesterol, platelet count, blood concentration, coagulability, heart rate, and blood pressure (Keatinge et al., 1986; Nawrot et al., 2005; Stewart et al., 2017). Additionally, exposure to heat may reduce high-density lipoprotein levels while increasing low-density lipoprotein levels, further exacerbating CVD risks (Halonen et al., 2011). Furthermore, sudden drops in ambient temperature can stimulate skin receptors and increase in renal diuresis and lead to increased blood viscosity by increasing blood pressure, platelet count, and red blood cell count (Liu et al., 2015; Zhang et al., 2024). These alterations in blood composition place additional stress on the heart, heightening the risk of thrombus formation and subsequent CVD events (Fan et al., 2023).

The limitations of our study should be acknowledged. First, we used hourly ambient temperature data from fixed-site monitoring stations as a proxy for personal exposure, which might introduce some degree of exposure misclassification. Additionally, the potential for exposure misclassification may be amplified because we matched environmental data to hospital addresses, rather than the residential addresses of patients. However, this kind of exposure misclassification is nondifferential and bias our findings toward null of no association (Jiang et al., 2022). Second, our analyses were limited to nine hospitals in Zhejiang Province. Our findings may not be generalizable to other Chinese cities or countries.

## 5. Conclusions

This multi-center case-crossover study indicated that exposure to cold, heat, and sudden temperature decline were associated with an increased risk of total and cause-specific CVD. The most significant risks of extreme cold on CVD typically occurred around 40 h after exposure, while the effects of extreme heat were most pronounced at the time of exposure (lag 0 h). Additionally, declines in ambient temperature between neighboring days were linked to a higher risk of CVD, and the risk associated with extremely negative TCN peaked on the day of exposure. These findings suggest that exposure to non-optimal temperature and TCN may increase the risk of ED visits for total and cause-specific CVD shortly after exposure, especially due to cold and negative TCN.

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None.

## CRedit authorship contribution statement

**Kun Yuan:** Writing – original draft, Visualization, Software, Resources, Methodology, Investigation, Formal analysis, Data curation. **Xin Lv:** Writing – review & editing. **Yangchang Zhang:** Writing – review & editing. **Ruiyi Liu:** Writing – review & editing. **Tian Liang:** Writing – review & editing. **Zhenyu Zhang:** Writing – review & editing. **Wangnan Cao:** Writing – review & editing. **Lizhi Wu:** Writing – review & editing, Supervision. **Shengzhi Sun:** Writing – review & editing, Validation, Supervision, Funding acquisition, Conceptualization.

## Declaration of competing interest

None.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.uclim.2024.102197>.

## Data availability

Data will be made available on request.

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