



Air temperature variability and high-sensitivity C reactive protein in a general population of China

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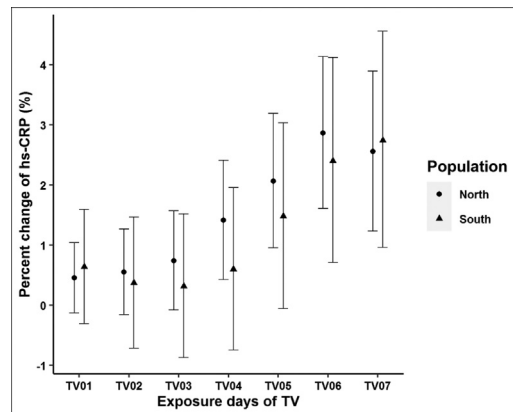
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HIGHLIGHTS

- Statistical significance between temperature variation and high-sensitivity C reactive protein (hs-CRP) were observed.
- Temperature variation significantly increased the level of hs-CRP, especially for female, obesity and elderly population.
- Lipoprotein(a) was the largest mediator for the above association.
- More attention should be paid to unstable weather in the global climate change context.

GRAPHICAL ABSTRACT

There is significant association between inter- and intra-day temperature variation and hs-CRP in different climate zones.



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ABSTRACT

Background: Along with global climate change, the relationship between temperature variability (TV) and cardiovascular hospitalization and deaths have been well established. However, limited studies were conducted to reveal the underlying mechanism for TV-related cardiovascular diseases.

Objectives: In the current study, a novel TV calculation, taking account for both interday and intraday TV as well as lag effects, was used to investigate the effect of short-term TV on the level of high-sensitivity C reactive protein (hs-CRP), which is a crucial preclinical predictor for cardiovascular disease (CVD).

Results: Among the 11,623 Chinese population (46.0% male; mean age 49.8 years), the average hs-CRP was 1.4 mg/L (standard deviation 1.6 mg/L). Statistical significance between TV and hs-CRP was observed for different TV exposure days (TV01-TV07) in adjusted model, with highest effect for TV06. Specifically, per 1 °C increase in TV06 led to 2.241% (95%CI: 1.552%–2.935%) increase in hs-CRP. Female, obesity and elderly population were more susceptible to TV. The largest mediator for the association of TV and hs-CRP was lipoprotein(a), accounting

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for 8.68%, followed by smoking status (4.78%), alcohol use (3.95%) and systolic BP (3.20%).

Conclusion: Short-term TV will significantly increase the level of hs-CRP, suggesting hs-CRP to be the potential biologic mechanisms underlying the cardiovascular effects of TV. And more attention should be paid to unstable weather in the global climate change context. Further developing efficient public health policies on climate change may benefit for global health.

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1. Introduction

Along with the global climate change, both the average temperature and variability of temperature are predicted to increase substantially (Stocker, 2014). The adverse effect of both air temperature (Chen et al., 2018) and temperature variability (TV) on cardiovascular hospitalization and death have received greater attention both in China and other countries (Guo et al., 2016; Hu et al., 2019; Zhao et al., 2018). However, the exact mechanisms of these associations have yet been well understood. Numerous studies have reported that the preclinical change of systemic inflammation biomarkers are included in the mechanisms to advance cardiovascular diseases (Cai et al., 2016; Kuh et al., 2019; Mason and Libby, 2015). High-sensitivity C reactive protein (hs-CRP), as a crucial circulating biomarker of systemic inflammation, has been recognized as a strong predictor for adverse cardiovascular events (Dong et al., 2019; Lin et al., 2018). Despite advances in linking the daily mean temperature and hs-CRP (Basu et al., 2017; Hong et al., 2012; Sartini et al., 2017a; Wu et al., 2017), TV, as an important index of climate change, have been scarcely studied to investigate the relationship with hs-CRP, so as to reveal the underlying mechanisms pathways of TV-related cardiovascular morbidity and mortality. To our knowledge, only a few of studies in western developed countries (Meier-Ewert et al., 2001; Rudnicka et al., 2007) and Korea (Hong et al., 2012) have documented both maximum and minimum daily temperature were linked with the increase of hs-CRP, revealing unstable temperature had adverse effect on systemic inflammation, though their findings are inconsistent.

More importantly, these associations have rarely been determined in China (Wu et al., 2017), where the climate characteristics may vary with other countries. Furthermore, few of the existing studies have reported the effect of both intraday and interday TV, whereas ample evidence had documented the non-neglectful impact of intraday and interday of TV on cardiovascular health, including China (Cheng et al., 2019; Zhao et al., 2019b). A better understanding for TV on the preclinical change may have public health implications, especially for susceptible population.

To address the question of interest, based on the China-CVD study with more than 10,000 individuals in 12 provinces of China, we use a novel method to calculate TV by including both intraday and interday of TV as well as lag effects and investigate the magnitude and cumulative effect of TV in different exposure days on the level of hs-CRP as part of mechanism leading to cardiovascular morbidity and mortality.

2. Methods

2.1. Study design and participants

During the baseline survey of the China-CVD study, general population in 12 provinces in China, including northern, southern, eastern, northeast, southeast and northwest regions, were recruited based on the economic and social development level so as to represent different parts of China using a stratified multistage random sampling. After excluding those who were not local residents, or cannot cooperate well with our investigation (such as working outside for a long time, suffering from serious psychological diseases), all general participants aged 35 to 64 years from 2009 to 2010 were invited to participant our study. Finally, a total of 14,046 inhabitants were invited and 11,623 participated in our survey; the response rate was 82.75%. Detailed methods

used in the survey have been described previously (Hao et al., 2013). The 12 provinces included North regions (Beijing, Heilongjiang, Shanxi, Shannxi, Xinjiang, Inner Mongolia) and South regions (Shanghai, Sichuan, Yunnan, Jiangsu, Guangdong, Tibet). This research was approved by the Fuwai hospital Ethics Review Board (approval number: 81373070). All procedures were explained to participants who then read and signed informed consent forms.

2.2. Measurements

2.2.1. Hs-CRP and blood lipid

Blood samples were collected after 10 h of fasting state at the first visit in our study and analyzed in the same core clinical laboratory (Beijing CIC Clinical Laboratory, Beijing, China). The data of hs-CRP and blood lipid were from baseline examination using transmission turbidimetry (Advia 2400 autoanalyser, Sciences, Munich, Germany) with a measurement range of 0–42,000 mg/L, with an interassay variation coefficient of 2.51%. Hs-CRP values >10 mg/L were excluded because they may have resulted from severe infection, major trauma, or chronic inflammatory diseases (Basu et al., 2017; Hong et al., 2012). More details and applications can be found in our previous studies (Dong et al., 2019).

2.2.2. Meteorological data

The newly released meteorological dataset contains over 2400 observations in China (Fig. 1). The time resolution is daily and the earliest record goes back to 1 January 1951. After excluding the stations with more than five missing-value days in a month, we retain 2163 stations. For more applications, one could find them in our recent study (Hu et al., 2017). In this paper, we use daily mean surface air temperature, maximum temperature, minimum temperature, relative humidity and sea level pressure from this dataset to conduct our analysis. And its applications could be found in our recent studies (Hu et al., 2017). Those weather data were assigned to each subject of current study according to his/her residential districts and the documented date of the baseline survey. Considering the slight difference of air temperature between neighboring districts, the weather data in Putuo district of Shanghai, Hantai district of Shannxi, Jingyang district of Sichuan were replaced by their nearest districts, that is Jiading district of Shanghai, Chenggu of Shannxi and Mianzhu districts of Sichuan, respectively.

2.2.3. Calculation of TV

In the current study, a composite index accounting for both intraday and interday TV as well as the lag effects of TV was used to estimate the association of TV and health outcomes. TV was calculated as the standard deviation (SD) of the minimum and maximum air temperatures during the exposure days. For example, the TV for the current day's (lag0) and preceding 1 days' exposure (lag1) were calculated as follows: $TV_{01} = SD(\text{maximum temperature}_{lag0}, \text{minimum temperature}_{lag0}, \text{maximum temperature}_{lag1}, \text{minimum temperature}_{lag1})$.

2.2.4. Risk factor definition

A standardized questionnaire was administered by trained staff to obtain information on demographic characteristics and socioeconomic factors through face-to-face interviews, including home address, age, sex, education, smoking status and other health characteristics. Height was measured without shoes using a standard right-angle device and a fixed measurement tape (to the nearest 0.5 cm). Body weight without heavy clothing was measured using an OMRON body

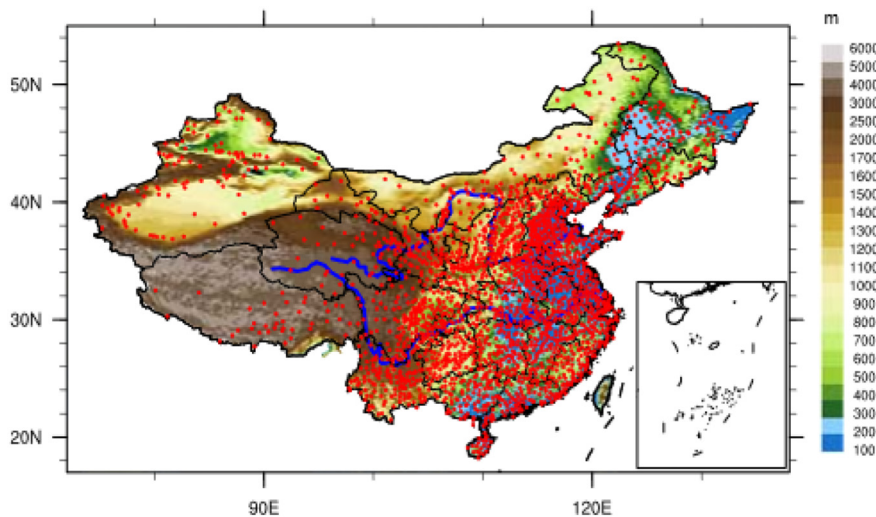


Fig. 1. The distribution of stations (red dots) in a new high-resolution dataset used in this study. Superimposed on elevation (blue-grey shading; m). Blue lines mark the Yellow and Yangtze Rivers.

fat and weight measurement device (V-body HBF-371, OMRON, Kyoto, Japan). Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m) (kg/m^2). According to the criteria from the guidelines for prevention and control of overweight and obesity in Chinese adults (Chen and Lu, 2004), normal weight, overweight/obesity were defined as $\text{BMI} < 24.0 \text{ kg}/\text{m}^2$ and $\geq 24.0 \text{ kg}/\text{m}^2$, respectively. Current smokers were defined as the use of at least 20 packets of cigarettes in their lifetime or smoking 1 cigarette/day at least for 1 year. Current drinkers were defined as drinking once per week (Dong et al., 2019; Hao et al., 2013). Metabolic syndrome was defined according to revised NCEP ATP III for Asian-Americans (Grundy et al., 2005). Dyslipidemia was defined as total glyceride $\geq 2.26 \text{ mmol}/\text{L}$ or total glyceride $\geq 6.22 \text{ mmol}/\text{L}$ or high density lipoprotein cholesterol $< 1.04 \text{ mmol}/\text{L}$ or low density lipoprotein Cholesterol $\geq 4.14 \text{ mmol}/\text{L}$ or lipid lowering medicine use (Joint Committee on the revision of guidelines for the prevention and treatment of adult dyslipidemia, 2016). Survey seasons were divided as warm season (from April to September) and cold season (from October to March) (Kang et al., 2019).

2.3. Statistical analysis

In our study, continuous variables were summarized using means \pm standard deviation (SD) and compared using the Student's *t*-test. Categorical variables were summarized using numbers (percentages) and compared using Chi-square test.

Hs-CRP were \log_{10} transformed to normal distribution and to stabilize variance. We included the log-transformed hs-CRP in the regression models as response variables, the TV in different exposure days were the independent variables. The multivariable model was estimated using general linear models (GLM) with normal distribution and identity-link to assess the hs-CRP changes with corresponding 95% confidence intervals (CIs) related with TV. In consideration of the effects of season and the current mean temperature, two independent indicators of TV, we included these two indicators as confounders in the model (Onozuka and Hagihara, 2017). The following other potential confounders were considered: gender, age, BMI, air temperature, air humidity, air pressure, current smoker, alcohol use and seasons (warm vs. cold season). We stratified all analyses by regions (North and South regions). And all results were expressed as the percent change per 1 °C SD increase in TV using the following formula $[(\exp^{\beta}-1) * 100\%]$ (Sartini et al., 2017a).

To explore the susceptible population, we repeated the analyses stratified by gender (male vs. female), age group (age < 50 years vs.

age > 50 years) and obesity status ($\text{BMI} < 24 \text{ kg}/\text{m}^2$ vs. $\text{BMI} \geq 24 \text{ kg}/\text{m}^2$). Moreover, we studied the robustness of the effects by performing several sensitivity analyses. Firstly, we additionally adjusted our model for education level, urbanity, BP-lowering medication, diabetes mellitus and family history of cardiovascular diseases with the same lag as temperature. Furthermore, we excluded Zhejiang, Shannxi and Sichuan districts to avoid measurements bias for TV.

We hypothesized that the association between TV and hs-CRP could be mediated by metabolic risk factors (e.g. blood pressure (Hong et al., 2012), blood lipid (Basu et al., 2017)) and lifestyles. Thus, following the method used in recent studies (Ahmad et al., 2018; Lee et al., 2003), we calculated the percent of the associations of TV and hs-CRP explained by the following potential mediators as $[1 - (\beta_{\text{cm}}/\beta_{\text{c}})] \times 100\%$, where β_{cm} was the regression coefficient in the adjusted model including mediators, β_{c} was the regression coefficient in the adjusted model without including mediators.

For all the statistical tests, a two-tailed $P < 0.05$ was considered statistically significant. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Characteristics of study population

A total of 11,623 participants were included, the mean age of participants was 49.8 years, 46.0% were males, 29.5% were current smokers, and 29.9% were urban residents. North regions had higher BMI, hypertension and education level, while south regions had higher proportion of male, smoking and alcohol consumption, with higher air temperature and humidity ($P < 0.05$). The TV01 was $5.6 \text{ }^\circ\text{C}$ (SD 2.1) and substantial larger in north regions than south regions ($6.4 \text{ }^\circ\text{C}$ vs. $4.8 \text{ }^\circ\text{C}$). The average hs-CRP level was $1.4 \text{ mg}/\text{L}$, with higher level in north regions (Table 1).

3.2. Short-term exposure to TV and hs-CRP

Figs. 2 and 3 showed the crude and full adjusted model of TV. The crude model showed all investigated TV indicators were consistently positively associated with hs-CRP level among whole population. People in south regions were more sensitive to short-term TV than those in north regions. Though the association between TV and hs-CRP in full adjusted model lower than that in crude model, TV remained an independent significant factor after adjustment for gender, age, BMI, air temperature, air humidity, air pressure, current smoker, alcohol use

Table 1
Descriptive statistics of the enrolled individual characteristics.

Characteristics	Overall	North regions	South regions	P value
Number of participants, No.	11,623	5654	5969	–
Male	5344 (46.0)	2524 (44.6)	2820 (47.2)	<0.05
Urbanity	3475 (29.9)	1458 (25.8)	2017 (33.8)	<0.05
Age (years), Mean ± SD	49.8 ± 8.0	50.2 ± 8.0	49.4 ± 8.1	>0.05
BMI (kg/m ²), Mean ± SD	24.4 ± 3.6	25.2 ± 3.7	23.6 ± 3.4	<0.05
Overweight or obesity	6498 (55.9)	3673 (65.0)	2825 (47.3)	<0.05
Current smoker	3431 (29.5)	1599 (28.3)	1832 (30.7)	<0.05
Alcohol consumption	2134 (18.4)	704 (12.5)	1430 (24.0)	<0.05
Hypertension	4537 (39.0)	2485 (44.0)	2052 (34.4)	<0.05
Educated to middle school or higher	6172 (53.1)	3342 (59.1)	2830 (47.4)	<0.05
Family history of CVD	6756 (58.1)	3562 (63.0)	3194 (53.5)	<0.05
Diabetes mellitus	1088 (9.4)	698 (12.4)	390 (6.5)	<0.05
Air temperature (°C), Mean ± SD	11.2 ± 12.9	3.8 ± 13.0	20.0 ± 4.7	<0.05
Air humidity (%), Mean ± SD	70.3 ± 16.7	69.7 ± 18.2	71.1 ± 14.6	<0.05
TV (°C), Mean ± SD				
TV01	5.6 ± 2.1	6.4 ± 2.3	4.8 ± 1.5	<0.05
TV02	5.5 ± 1.8	6.3 ± 1.9	4.6 ± 1.2	<0.05
TV03	5.4 ± 1.7	6.3 ± 1.6	4.5 ± 1.2	<0.05
TV04	5.4 ± 1.5	6.3 ± 1.3	4.5 ± 1.1	<0.05
TV05	5.4 ± 1.4	6.3 ± 1.2	4.5 ± 1.0	<0.05
TV06	5.5 ± 1.4	6.4 ± 1.1	4.6 ± 0.9	<0.05
TV07	5.5 ± 1.3	6.5 ± 1.0	4.6 ± 0.9	<0.05
hs-CRP (mg/L), Mean ± SD	1.4 ± 1.6	1.5 ± 1.7	1.2 ± 1.4	<0.05

BP: blood pressure. TV: Temperature variability. hs-CRP: high-sensitivity C reactive protein. SD: standard deviation. TV01-07 were the SD in air maximum and minimum temperature of current days and previous 1–7 days before hs-CRP collected. Data are presented with number (percentage) unless indicated.

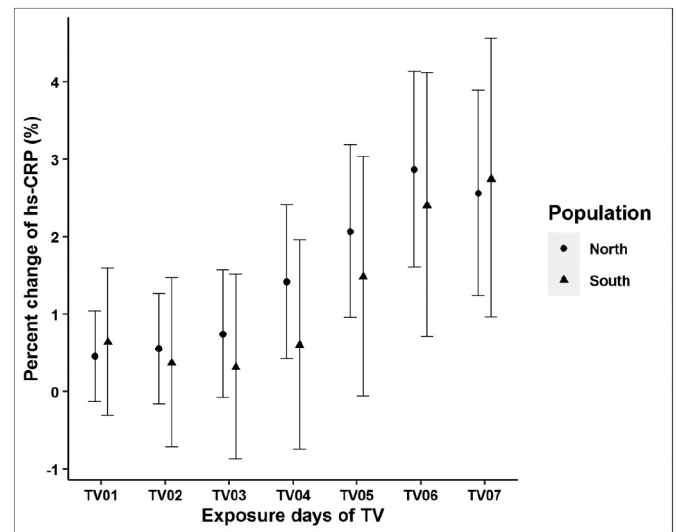


Fig. 3. Percent change (95% confidence interval) in hs-CRP associated with 1 °C increase in TV on different exposure days by different population. TV: Temperature variability. TV01-07 were the SD in air maximum and minimum temperature of current days and previous 1–7 days before hs-CRP collected. The model was adjusted for gender, age, BMI, air temperature, air humidity, air pressure, current smoker, alcohol use and survey seasons.

and survey seasons. The prolonged exposure of TV was observed to be associated with higher effect on hs-CRP, with highest effect in TV06. Specifically, per 1 °C increase in the TV06 led to 2.241% (95%CI: 1.552%–2.935%) increase in hs-CRP. In north regions, significance increase of hs-CRP were observed for TV04, TV05, TV06 and TV07, the highest effect estimates appeared at TV06. In south regions, all exposure days were significantly related with hs-CRP elevation, except for TV01, TV07 showed strongest association (Figs. 2 and 3).

3.3. Effect modification and Sensitivity analyses

Selected TV modifications and sensitivity analyses are shown in Fig. 4 and Table 2. When we performed the analyses stratified by gender (male vs. female), age (<50 years vs. ≥50 years) and BMI (<24 kg/m² vs. ≥24 kg/m²), the increase in hs-CRP level in response to increase of TV was much larger in female, those with BMI ≥24 kg/m² and elderly population than their counterparts. Specifically, female participants showed an increase in hs-CRP of about 1.007%–2.968% in all TV indicators, participants with BMI ≥24 kg/m² were observed to response for all TV indicators, ranging from 0.621%–3.344% elevation of hs-CRP. Only TV06 and TV07 effects were observed significantly associated with hs-CRP in men, young and BMI less than 24 kg/m² population.

Excluding Shanghai, Shannxi and Sichuan provinces did not alter the results substantially, with a slight larger effect after additionally adjusting for education level, urbanity, BP-lowering medication, diabetes mellitus and family history of cardiovascular diseases (Table 2).

3.4. Proportion of Reduction of hs-CRP Explained by Potential Mediators

We estimated the proportion of TV07 in hs-CRP that was explained by potential mediators (Fig. 5). Lipoprotein(a) made the largest contribution (accounting for 8.68%), followed by smoking status (4.78%), alcohol use (3.95%), systolic BP (3.20%), dyslipidemia (2.74%) and vegetable consumption (0.91%).

4. Discussion

This is the first study to examine the effect of TV on hs-CRP in China. Taking into account the non-neglectful effect of both interday and intraday variability, the current study revealed that TV were positively related with hs-CRP even after controlling for the effect of air

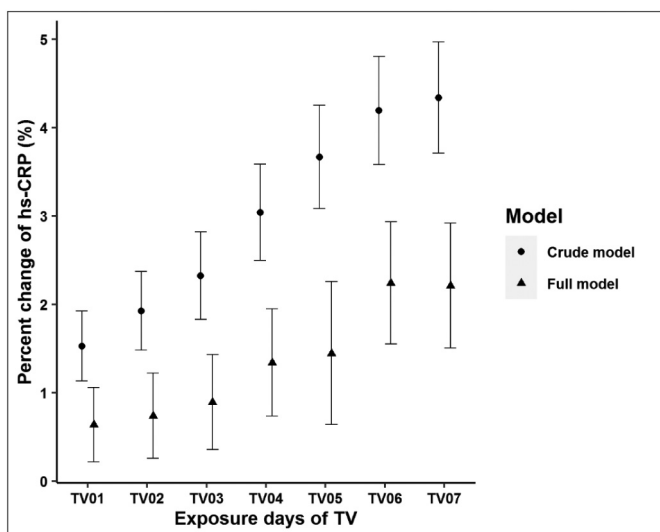


Fig. 2. Percent change (95% confidence interval) in hs-CRP associated with 1 °C increase in TV on different exposure days in crude and full adjusted models. TV: Temperature variability. TV01-07 were the SD in air maximum and minimum temperature of current days and previous 1–7 days before hs-CRP collected. The full model was adjusted for gender, age, BMI, air temperature, air humidity, air pressure, current smoker, alcohol use and survey seasons.

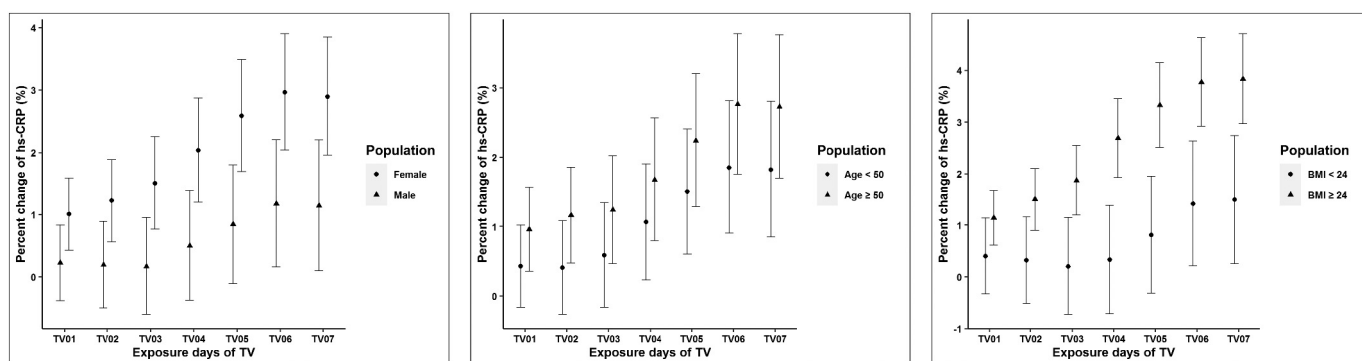


Fig. 4. Percent change (95% confidence interval) in hs-CRP associated with 1 °C increase in TV on different exposure days among different population. TV: Temperature variability. hs-CRP: high-sensitivity C reactive protein. TV01-07 were the SD in air maximum and minimum temperature of current days and previous 1–7 days before hs-CRP collected. The model was adjusted for gender, age, BMI, air temperature, air humidity, air pressure, current smoker, alcohol use and survey seasons. Data are presented with percent change (95% confidence interval).

temperature. The difference existed in different exposure durations and regions. Generally, for both north and south population, long exposures to TV had larger effect on hs-CRP, with the highest effect on TV06. People in south regions were more sensitive to short-term TV than those in north regions. In susceptible populations, such as female, elderly and obesity population, our findings indicated that prolonged exposure in TV may lead to additional risks for cardiovascular mortality, revealing a possible mechanism for the association between TV and CVD events in time-series studies.

Most prior studies have documented that the TV between neighboring days and hourly TV all increased the risk for cardiovascular hospitalization and mortality (Cheng et al., 2017; Guo et al., 2017; Hu et al., 2019; Zhang et al., 2018; Zhao et al., 2018). The prolonged exposure of TV was frequently reported to be associated with adverse outcomes of cardiovascular disease (Hu et al., 2019). For example, a study involving multi-countries observed higher effect at 0–7 days in some countries (Guo et al., 2016). Another study in Zhejiang province of China also reported 0–7 days exposure of TV had strongest effect on all-cause mortality in rural population (Hu et al., 2019). However, the association of symptoms and preclinical changes associated with TV have been less explored.

hs-CRP as the most significant predictor of future cardiovascular events (Hong et al., 2012), though previous studies have explored the relationship between daily mean temperature and hs-CRP (Hong et al., 2012; Rudnicka et al., 2007) in different counties, such as South Korea and the UK, to date, there were limited studies assessing the association between TV and hs-CRP. Previous studies involving multi-regions with different climatology (Basu et al., 2017; Hong et al., 2012; Sartini et al., 2017b), revealed diurnal temperature (e.g. intra-day TV) was linked with the increase of hs-CRP, and thus increase CVD risk. For example, a study included 57,409 subjects in Korea reported per 1 °C increase in minimum temperatures was related with 1.818×10^{-2} mg/dL increase of hs-CRP (Hong et al., 2012). Our study first assess that the unstable weather-not only for intraday TV but also

interday TV were positively associated with the increase of hs-CRP, which are generally consistent with the linearly positive associations between TV and cardiovascular events reported in a number of time-series studies (Cheng et al., 2017; Guo et al., 2017; Hu et al., 2019; Zhang et al., 2018; Zhao et al., 2018). The greater cumulative effect associated with longer term intraday TV can indicate more serious inflammation triggered by repeated exposures to TV. The results may help to explain the increased risk of cardiovascular events associated with TV.

The direction of our study was consistent with previous observational studies on hs-CRP related with daily mean temperature. Rupa et al. (Basu et al., 2017) enrolled 2306 midlife women aged 40–52 years reported per 5.6 °C decrease for mean temperature was linked with 3.7% decrease for hs-CRP; a recent study in China, including forty health undergraduate students, also revealed a 10 °C decrease in daily mean temperature at 2-d moving average was associated with increases of 2.5% for systemic inflammation, including hs-CRP (Wu et al., 2017). Comparing with prior studies assessing the effect of mean temperature on hs-CRP, our studies found a relative greater effect for TV on hs-CRP, reflecting the temperature indicator fully capturing the rapid heating and cooling of air temperature within a few days may be a better indicator representing acute weather instability (Zhao et al., 2019a).

A study has evidenced the TV-related acute elevation in hs-CRP levels are biologically plausible, which revealed rapid increase of CRP within hours (Pepys and Hirschfield, 2003). Though the mechanism of such relationship is unclear, our results indicated that blood lipid, blood pressure and lifestyle change, including smoking and alcohol use may involve in the pathways of TV on hs-CRP (Gronlund et al., 2014; Son et al., 2012). Additionally, intraday temperature variation was reported to change autonomic nervous functions, which may indirectly increase the cardiovascular workload, such as blood pressure

Table 2

Sensitivity Percent change (95% confidence interval) in hs-CRP associated with 1 °C increase in TV.

Indicators	Full model	Sensitivity Model 1	Sensitivity Model 2
TV 01	0.636 (0.215, 1.059)	0.315 (−0.176, 0.808)	1.116 (0.684, 1.551)
TV 02	0.737 (0.257, 1.220)	0.349 (−0.220, 0.922)	1.422 (0.920, 1.926)
TV 03	0.892 (0.354, 1.433)	0.464 (−0.179, 1.111)	1.709 (1.144, 2.278)
TV 04	1.340 (0.734, 1.950)	0.940 (0.199, 1.686)	2.122 (1.491, 2.756)
TV 05	1.445 (0.638, 2.257)	1.445 (0.638, 2.257)	2.482 (1.811, 3.158)
TV 06	2.241 (1.552, 2.935)	1.877 (1.024, 2.738)	2.892 (2.185, 3.604)
TV 07	2.211 (1.507, 2.919)	1.817 (0.941, 2.700)	2.808 (2.087, 3.533)

Sensitivity model 1 was excluding Putuo, Hantai and Jingyang districts. Sensitivity model 2 was additionally adjusted for education level, urbanity, BP-lowering medication, diabetes mellitus and family history of cardiovascular diseases.

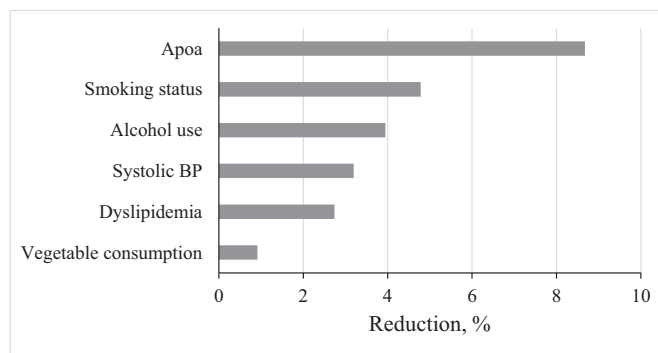


Fig. 5. Percentage reduction in hs-CRP associated with TV explained by potential risk mediators. ApoA: lipoprotein(a).

(Lim et al., 2012), and may precipitate acute atherosclerotic events (Lim et al., 2012; Steinvil et al., 2009). In line with our results, several studies reported that female, obesity and elderly population are more vulnerable to sudden changes in daily temperature due to potential lower thermoregulatory responses or weaker immunity (Cheng et al., 2014; Qiu et al., 2013; Williams et al., 2012). Increasing awareness of unstable weather may also play an important role in preventing temperature-related CVD-morbidity. Also, more research involving different study populations and climatology are needed to confirm our findings and further reveal the potential mechanics for the TV-related elevation of hs-CRP.

This study had several strengths. Firstly, the current study with a large-scale population study in China, was first to use a novel approach to provide ample evidence of the relationship between TV in different exposure's days with hs-CRP levels in various regions and susceptible populations, revealing the impact under the potential pathways of TV-related cardiovascular diseases. Secondly, our TV exposure assessment method, which had very high spatial resolution, substantially improved the accuracy of ambient TV estimation. There are some potential limitations of this study as well. Firstly, the current study was conducted in only 12 sites in China, unable to explore the relationship between TV and hs-CRP in various climatology. Secondly, we failed to adjust for other important risk factors, such as air pollution and indoor temperature. These factors may have additional effects on hs-CRP and may induce certain bias. Thirdly, the current study used station monitoring data to estimate TV which may result in measurement bias, if possible, personal-monitoring strategies for exposure measurements may provide more accurate estimate for TV.

5. Conclusion

Using a large population in China, this study supports our hypothesis that short-term TV increases circulating levels of hs-CRP. Our findings contribute to a better understanding about the pathophysiologic plausibility behind the effect of short-term TV on the cardiovascular events that could be investigated in future prospective cohort studies. Susceptible patients might benefit from our findings by taking possible precautions to reduce risk related to TV exposures.

CRedit authorship contribution statement

Yuting Kang, Haosu Tang, Zuo Chen, Zengwu Wang and Gang Huang: contributed to the acquisition, analysis, or interpretation of data for the work. **Xin Wang, Linlin Jiang, Zengwu Wang and Runlin Gao:** contributed to the conception or design of the work. **Yuting Kang, Gang Huang:** drafted the manuscript. **Haosu Tang, Su Wang, Linfeng Zhang, Congyi Zheng, Zengwu Wang, Runlin Gao:** critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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. Supplementary data

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References

- Ahmad, S., Moorthy, M.V., Demler, O.V., Hu, F.B., Ridker, P.M., Chasman, D.I., et al., 2018. Assessment of risk factors and biomarkers associated with risk of cardiovascular disease among women consuming a mediterranean diet. *JAMA Netw. Open* 1, e185708.
- Basu, R., Wu, X., Malig, B.J., Broadwin, R., Gold, E.B., Qi, L., et al., 2017. Estimating the associations of apparent temperature and inflammatory, hemostatic, and lipid markers in a cohort of midlife women. *Environ. Res.* 152, 322–327.
- Cai, J., Meng, X., Wang, C., Chen, R., Zhou, J., Xu, X., et al., 2016. The cold effects on circulatory inflammation, thrombosis and vasoconstriction in type 2 diabetic patients. *Sci. Total Environ.* 568, 271–277.
- Chen, C., Lu, F.C., 2004. The guidelines for prevention and control of overweight and obesity in chinese adults. *Biomed. Environ. Sci.* 17 (Suppl:1).
- Chen, R., Yin, P., Wang, L., Liu, C., Niu, Y., Wang, W., et al., 2018. Association between ambient temperature and mortality risk and burden: time series study in 272 main chinese cities. *Bmj* 363, k4306.
- Cheng, J., Xu, Z., Zhu, R., Wang, X., Jin, L., Song, J., et al., 2014. Impact of diurnal temperature range on human health: a systematic review. *Int. J. Biometeorol.* 58, 2011–2024.
- Cheng, J., Xu, Z., Bambrick, H., Su, H., Tong, S., Hu, W., 2017. The mortality burden of hourly temperature variability in five capital cities, Australia: time-series and meta-regression analysis. *Environ. Int.* 109, 10–19.
- Cheng, J., Xu, Z., Bambrick, H., Su, H., Tong, S., Hu, W., 2019. Impacts of heat, cold, and temperature variability on mortality in Australia, 2000–2009. *Sci. Total Environ.* 651, 2558–2565.
- Dong, Y., Wang, X., Zhang, L., Chen, Z., Zheng, C., Wang, J., et al., 2019. High-sensitivity c reactive protein and risk of cardiovascular disease in China-cvd study. *J. Epidemiol. Community Health* 73, 188–192.
- Gronlund, C.J., Zanobetti, A., Schwartz, J.D., Wellenius, G.A., O'Neill, M.S., 2014. Heat, heat waves, and hospital admissions among the elderly in the United States, 1992–2006. *Environ. Health Perspect.* 122, 1187–1192.
- Grundy, S.M., Cleeman, J.I., Daniels, S.R., Donato, K.A., Eckel, R.H., Franklin, B.A., et al., 2005. Diagnosis and management of the metabolic syndrome: an american heart association/national heart, lung, and blood institute scientific statement. *Circulation* 112, 2735–2752.
- Guo, Y., Gasparrini, A., Armstrong, B.G., Tawatsupa, B., Tobias, A., Lavigne, E., et al., 2016. Temperature variability and mortality: a multi-country study. *Environ. Health Perspect.* 124, 1554–1559.
- Guo, Y., Gasparrini, A., Armstrong, B.G., Tawatsupa, B., Tobias, A., Lavigne, E., et al., 2017. Heat wave and mortality: a multicountry, multicomunity study. *Environ. Health Perspect.* 125, 087006.
- Hao, G., Wang, Z., Zhang, L., Chen, Z., Wang, X., Guo, M., et al., 2013. Prevalence of microalbuminuria among middle-aged population of China. *Angiology* 66, 49–56.
- Hong, Y.C., Kim, H., Oh, S.Y., Lim, Y.H., Kim, S.Y., Yoon, H.J., et al., 2012. Association of cold ambient temperature and cardiovascular markers. *Sci. Total Environ.* 435–436, 74–79.
- Hu, K., Xie, S.-P., Huang, G., 2017. Orographically anchored el niño effect on summer rainfall in Central China. *J. Clim.* 30, 10037–10045.
- Hu, K., Guo, Y., Yang, X., Zhong, J., Fei, F., Chen, F., et al., 2019. Temperature variability and mortality in rural and urban areas in Zhejiang province, China: an application of a spatiotemporal index. *Sci. Total Environ.* 647, 1044–1051.
- Joint Committee on the revision of guidelines for the prevention and treatment of adult dyslipidemia, 2016. Chinese guidelines on prevention and treatment of dyslipidemia in adults. *Chin. Circulat. J.* 35, 390–419.
- Kang, Y., Han, Y., Guan, T., Wang, X., Xue, T., Chen, Z., et al., 2019. Clinical blood pressure responses to daily ambient temperature exposure in China: an analysis based on a representative nationwide population. *Sci. Total Environ.* 705 135762 pages.
- Kuh, D., Cooper, R., Sattar, N., Welsh, P., Hardy, R., Ben-Shlomo, Y., 2019. Systemic inflammation and cardio-renal organ damage biomarkers in middle age are associated with physical capability up to 9 years later. *Circulation* 139, 1988–1999.
- Lee, C.D., Folsom, A.R., Blair, S.N., 2003. Physical activity and stroke risk: a meta-analysis. *Stroke* 34, 2475–2481.
- Lim, Y.-H., Kim, H., Kim, J.H., Bae, S., Hong, Y.-C., 2012. Effect of diurnal temperature range on cardiovascular markers in the elderly in Seoul, Korea. *Int. J. Biometeorol.* 57, 597–603.
- Lin, J.S., Evans, C.V., Johnson, E., Redmond, N., Coppola, E.L., Smith, N., 2018. Nontraditional risk factors in cardiovascular disease risk assessment: updated evidence report and systematic review for the us preventive services task force. *Jama* 320, 281–297.
- Mason, J.C., Libby, P., 2015. Cardiovascular disease in patients with chronic inflammation: mechanisms underlying premature cardiovascular events in rheumatologic conditions. *Eur. Heart J.* 36, 482–489c.

- Meier-Ewert, H.K., Ridker, P.M., Rifai, N., Price, N., Dinges, D.F., Mullington, J.M., 2001. Absence of diurnal variation of c-reactive protein concentrations in healthy human subjects. *Clin. Chem.* 47, 426–430.
- Onozuka, D., Hagihara, A., 2017. Associations of day-to-day temperature change and diurnal temperature range with out-of-hospital cardiac arrest. *Eur. J. Prev. Cardiol.* 24, 204–212.
- Pepys, M.B., Hirschfield, G.M., 2003. C-reactive protein: a critical update. *J. Clin. Invest.* 111, 1805–1812.
- Qiu, H., Yu, I.T., Tse, L.A., Tian, L., Wang, X., Wong, T.W., 2013. Is greater temperature change within a day associated with increased emergency hospital admissions for heart failure? *Circ. Heart Fail.* 6, 930–935.
- Rudnicka, A.R., Rumley, A., Lowe, G.D.O., Strachan, D.P., 2007. Diurnal, seasonal, and blood-processing patterns in levels of circulating fibrinogen, fibrin d-dimer, c-reactive protein, tissue plasminogen activator, and von willebrand factor in a 45-year-old population. *Circulation* 115, 996–1003.
- Sartini, C., Barry, S.J., Whincup, P.H., Wannamethee, S.G., Lowe, G.D., Jefferis, B.J., et al., 2017a. Relationship between outdoor temperature and cardiovascular disease risk factors in older people. *Eur. J. Prev. Cardiol.* 24, 349–356.
- Sartini, C., Whincup, P.H., Wannamethee, S.G., Jefferis, B.J., Lennon, L., Lowe, G.D., et al., 2017b. Associations of time of day with cardiovascular disease risk factors measured in older men: results from the british regional heart study. *BMJ Open* 7, e018264.
- Son, J.Y., Lee, J.T., Anderson, G.B., Bell, M.L., 2012. The impact of heat waves on mortality in seven major cities in Korea. *Environ. Health Perspect.* 120, 566–571.
- Steinvil, A., Berliner, S., Bromberg, M., Cohen, M., Shalev, V., Shapira, I., et al., 2009. Micro-inflammatory changes in asymptomatic healthy adults during bouts of respiratory tract infections in the community: potential triggers for atherothrombotic events. *Atherosclerosis* 206, 270–275.
- Stocker, T.F., 2014. *Climate Change 2013: The Physical Science Basis: Working Group I Contribution to the Fifth Assessment Report of the Intergovernmental Panel on Climate Change*. Cambridge University Press, New York.
- Williams, S., Nitschke, M., Sullivan, T., Tucker, G.R., Weinstein, P., Pisaniello, D.L., et al., 2012. Heat and health in Adelaide, South Australia: assessment of heat thresholds and temperature relationships. *Sci. Total Environ.* 414, 126–133.
- Wu, S., Yang, D., Pan, L., Shan, J., Li, H., Wei, H., et al., 2017. Ambient temperature and cardiovascular biomarkers in a repeated-measure study in healthy adults: a novel biomarker index approach. *Environ. Res.* 156, 231–238.
- Zhang, Y., Yu, Y., Peng, M., Meng, R., Hu, K., Yu, C., 2018. Temporal and seasonal variations of mortality burden associated with hourly temperature variability: a nationwide investigation in England and Wales. *Environ. Int.* 115, 325–333.
- Zhao, Q., Coelho, M., Li, S., Saldiva, P.H.N., Hu, K., Abramson, M.J., et al., 2018. Spatiotemporal and demographic variation in the association between temperature variability and hospitalizations in Brazil during 2000–2015: a nationwide time-series study. *Environ. Int.* 120, 345–353.
- Zhao, Q., Coelho, M., Li, S., Saldiva, P.H.N., Hu, K., Abramson, M.J., et al., 2019a. Temperature variability and hospitalization for cardiac arrhythmia in Brazil: a nationwide case-crossover study during 2000–2015. *Environ. Pollut.* 246, 552–558.
- Zhao, Q., Li, S., Coelho, M., Saldiva, P.H.N., Hu, K., Huxley, R.R., et al., 2019b. Temperature variability and hospitalization for ischaemic heart disease in Brazil: a nationwide case-crossover study during 2000–2015. *Sci. Total Environ.* 664, 707–712.