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Long-term temperature variability and the incidence of cardiovascular diseases: A large, representative cohort study in China☆

Yuting Kang [a], Haosu Tang [b, c], Linfeng Zhang [a], Su Wang [b, c], Xin Wang [a], Zuo Chen [a], Congyi Zheng [a], Ying Yang [a], Zengwu Wang [a, *], Gang Huang [b, c], Runlin Gao [d], for the China hypertension survey investigators

[a] *Division of Prevention and Community Health, National Center for Cardiovascular Disease, National Clinical Research Center of Cardiovascular Disease, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, Peking Union Medical College & Chinese Academy of Medical Sciences, Beijing, 102308, China*

[b] *State Key Laboratory of Numerical Modeling for Atmospheric Sciences and Geophysical Fluid Dynamics, Institute of Atmospheric Physics, Chinese Academy of Sciences, Beijing, 100029, China*

[c] *University of Chinese Academy of Sciences, Beijing, 100049, China*

[d] *Department of Cardiology, Fuwai Hospital, Peking Union Medical College & Chinese Academy of Medical Sciences, Beijing, 100037, China*

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A B S T R A C T

In the context of global climate change, far less is known about the impact of long-term temperature variability (TV), especially in developing countries. The current study aimed to estimate the effect of long-term TV on the incidence of cardiovascular disease (CVD) in China. A total of 23,721 individuals with a mean age of 56.15 years were enrolled at baseline from 2012 to 2016 and followed up during 2017−2019. TV was defined as the standard deviation of daily temperatures during survey years and was categorized into tertiles (lowest≤ 8.78 °C, middle = 8.78−10.07 °C, highest ≥ 10.07 °C). The Cox proportional hazards regression was used to estimate the multivariable-adjusted hazard ratio (HR) between TV and CVD. During the median follow-up of 4.65 years, we ascertained 836 cases of incident CVD. For per 1 °C increase in TV, there was a 6% increase of CVD (HR = 1.06 [95% confidence interval (CI): 1.01−1.11]). A significant positive trend was observed between CVD risk and increasing levels of TV compared to the lowest tertile [HR = 1.34 (95% CI: 1.13−1.59) for the medium tertile, HR = 1.72 (95% CI: 1.35−2.19) for the highest tertile, P_{trend} < 0.001]. Exposure to high TV would lose 2.11 disease-free years for the population aged 35−65 years and 66 CVD cases (or 7.95% cases) could been attributable to TV higher than 8.11 °C in the current study. The current findings suggested that long-term TV was associated with a higher risk of CVD incidence, it is needed to reduce the TV-related adverse health effect.

1. Introduction

Cardiovascular diseases (CVD), ranked the first death cause in China, accounting for more than 40% of death. With the improvement of medical services, the age-standardized mortality rate fell by 28.7% from 2011 to 2016 in China (Liu et al., 2019). However, along with longevity, the burden of non-fatal CVD, as well as age-standardized rates of years lived with disability (YLD), is substantially increasing (James et al., 2018). It is necessary to understand the relevant risk factors for mitigating CVD morbidity and mortality, thus to improve disease-free years and survival into older ages.

Along with global warming intensifies, temperature variability (TV) characterized by extreme heat waves and cold spells, was predicted to become more frequent and more severe in the future (Stocker, 2014; Sun et al., 2018). The epidemiological linkage between short-term TV and CVD mortality hospitalization is increasingly evidenced in China (Hu et al., 2019a; Hu et al., 2019b; Tian et al., 2019). These findings implied that the intensifying climate change, such as TV, emerges as a novel risk factor for human CVD health.

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* Corresponding author. Division of Prevention and Community Health, National Center for Cardiovascular Disease, National Clinical Research center of Cardiovascular Disease, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, Peking Union Medical College & Chinese Academy of Medical Sciences. No. 15 (Lin), Fengcunxili, Mentougou District, Beijing, 102308, China.

E-mail address: wangzengwu@foxmail.com (Z. Wang).

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However, time-series studies, by their nature, were poorly designed for addressing the health question of TV on both life expectancy and disease incidence over longer time frames. A few studies explored the effect of long-term TV on CVD mortality in the USA (Shi et al., 2016; Zanobetti et al., 2012) and New England (Shi et al., 2015), but far less is known about such associations in developing countries, including China.

China, due to the vast territory and varied terrain, has a great diversity of climate, further studies in such countries with different climates and socioeconomic and demographic conditions will help for comprehensively understanding the risk of TV. Previously, we explored the association between short-term TV and high-sensitivity C reactive protein (Kang et al., 2020). In the current study, we for the first time combined the update and accurate ambient temperature data with a large-scale prospective cohort data to investigate the effect of TV on CVD and further estimate the CVD-free years associated with long-term TV, which may provide important evidence regarding the potential impact of climatic factors on CVD development in developing countries.

2. Methods

2.1. Study design and participants

During October 2012 and December 2016, a stratified multistage random sampling method was used in the Chinese Hypertension survey (CHS) to select nearly 0.5 million nationally representative participants aged ≥15 years from 31 provinces in China. More detail of CHS could be found in the previous publication (Wang et al., 2018b). Then, 16 cities and 17 counties were selected from the selected cities/counties of CHS using simple random sampling (7 cities and 7 counties from the Eastern region, 6 cities and 6 countries from the Middle region, and 3 cities and 4 countries from the Western region) (Wang et al., 2018a). 35,000 participants aged ≥35 years were randomly selected from the eligible sites. Finally, 30,036 individuals, with complete important baseline information, including sex, name, and valid blood sample, were followed up from 2017 to 2019. The overall rate of follow-up was 87.65%. After exclusions of 3709 participants who drop out in the 5-years follow up, 2330 participants with prior CVD history, 276 with missing data on important risk factors, such as smoking and education, finally, 23,721 participants entered the final analysis (Figure A1). We compared the characteristics of the included and excluded subjects in Supplementary Table A.1. Before recruitment, each participant provided written informed consent. The study was approved by the Ethics Committee of Fuwai Hospital.

2.2. Health outcomes

Trained health care staff from each site interviewed the participants to ascertain disease status and vital information to identify fatal and non-fatal CVD events. Meanwhile, hospital records and death certification were also obtained. CVD incidence included coronary heart disease (CHD), stroke, chronic heart failure, and death due to other CVD. CHD were defined as non-fatal CHD (experienced at least one of the following diseases or treatments: myocardial infarction, treatment by coronary artery bypass graft surgery, or percutaneous coronary intervention) and fatal CHD (fatal myocardial infarction and other coronary deaths). Stroke were defined as non-fatal and fatal stroke, including subarachnoid hemorrhage, intracerebral hemorrhage, ischemic stroke, unspecified stroke.

2.3. Ambient temperature

The daily mean ambient temperature from 2012 to 2016 used in the present study was derived from the European Centre for Medium-Range Weather Forecasts (ECMWF) fifth-generation global atmospheric reanalysis (ERA5) (https://www.ecmwf.int/en/forecasts/datasets/reanalysis-datasets/era5), which is widely deemed as one of the best atmospheric reanalysis datasets. Produced by Copernicus Climate Change Service at ECMWF, this dataset has a horizontal resolution of 0.25 ° × 0.25 °. Bilinear interpolation was used to interpolate the daily ambient temperature according to participants' residential addresses in baseline. The goodness of fit (R^2) and root mean square error (RMSE) were used for accuracy assessment by cross-validation, the results showed bilinear interpolation is in well compliance with meteorological stations observations ($R^2 = 0.975$, RMSE = 0.124 °C), more detailed information about validation with meteorological stations observations and other interpolation methods were shown in Supplementary methods.

Long-term TV was calculated as the standard deviation (SD) of the daily mean temperatures at baseline survey year, and residential districts and the survey date in baseline were used for assigning weather data to each participant.

2.4. Covariate measurements

2.4.1. Air pollution exposure assessment

The annual average concentrations of fine particulate matter of diameter ≤2.5 μm ($PM_{2.5}$), sulfur dioxide, and ozone from 2013 to 2016 were obtained from a newly-released high-resolution Chinese air quality reanalysis dataset at a high spatial (15 km) and temporal (1 h) resolution (Tang et al., 2020), which is developed by assimilating over 1000 surface air quality monitoring sites from China National Environmental Monitoring Centre. Assessments by the cross-validation method and independent observations suggest this dataset has high accuracy. Like the daily ambient temperature above, the $PM_{2.5}$, sulfur dioxide, and ozone data were also interpolated to each subject via the bilinear interpolation method. The annual exposure at baseline survey year was assigned to each participant by residential districts and the survey date in the baseline.

2.4.2. Other covariates

During the baseline survey, health information was obtained by trained interviewers using a standard protocol. Height and body weight were measured by a standard right-angle device (to the nearest 0.5 cm) and OMRON body fat and weight measurement device (V-body HBF-371, OMRON, Kyoto, Japan), respectively, and were used for the calculation of body mass index (BMI). BMI was divided as normal BMI (BMI < 24.0 kg/m^2) and high BMI (BMI ≥ 24.0 kg/m^2) (Chen and Lu, 2004) for subgroup analysis. In the past month, participants who had a history of smoking or drinking at least once per week were defined as current smoking or alcohol use, respectively (Dong et al., 2019). Years of education level were divided as ≤ 6 and ≥ 7 years. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or use of antihypertensive medication within two weeks. We collected blood samples of each participant after at least being fasting state for 8 h, the analysis of lipid was done using enzymatic methods with an autoanalyzer in the same core laboratory (Beijing Adicon Clinical Laboratories, Inc, Beijing, China). Dyslipidemia was defined according to guidelines of dyslipidemia in China (dyslipidemia, 2016). Diabetes mellitus was defined as fasting plasma glucose ≥7 mmol/dL and/or diabetes mellitus diagnosed by physicians before and/or use of hypoglycemic medication within two weeks (Wang et al., 2018b).

To adjust the difference in socio-economic level across sites, county-level annual education and per capita gross domestic product (GDP) were also collected from multi-sources, such as statistic yearbooks, demographic census of China at 2000, national bureau of statistics and China national knowledge infrastructure.

2.5. Statistical analysis

In our study, baseline participants characteristics were presented by TV tertiles, continuous variables and categorical variables were summarized using means ± SD and numbers (percentages), and were compared using the analysis of variance F-test and *Chi*-square test, respectively.

Long-term TV was divided into tertiles (tertile 1 ≤ 8.78 °C, tertile 2 = 8.78−10.07 °C, tertile 3 ≥ 10.07 °C), with the lowest tertile as the reference group. We tested the linear trend between CVD and TV by including the median values of tertiles of TV into the model as a continuous variable, and the Wald test was used for testing the statistical significance. TV on a continuous scale was also estimated with CVD incidence. We applied Cox proportional hazards models to estimate the association between long-term TV and incident of CVD, and output hazard ratio (HR) and 95% confidence intervals (CIs). After applying the change in estimate methods combining with directed acyclic graphs for selecting confounders, the following potential confounders were considered: sex (male and female), age (continuous variable), BMI (continuous variable), current smoker (no and yes), alcohol use(no and yes), education level (≤6 year and ≥7 years), urbanity (urban and rural), hypertension (no and yes), diabetes mellitus (no and yes), dyslipidemia (no and yes) and annual mean temperature, which was line with previous studies (Huang et al., 2019; Sun et al., 2018; Yang et al., 2020).

After adjusting for the above potential confounders, we also applied a SAS macro (Version: RCS_REG V1.0) for the restricted cubic splines (RCS) model with TV as a continuous variable, the model worked to output the HRs (95%CI) for TV by comparing with individuals exposure to median TV (Desquilbet and Mariotti, 2010). Likelihood ratio test was used for nonlinear associations. Linear models were used when the nonlinearity test showed no significance.

We repeated the analysis stratified by sex, age, BMI, urbanity, regions, hypertension, diabetes mellitus, and dyslipidemia for modification effect, and explored the possible interactions. Moreover, we tested the robustness of the effects by conducting sensitivity analysis. Firstly, the following different TV indicators were included in the model to estimate association with incidence of CVD: monthly TV, seasonal TV (warm and cold season were divided as from April to September and from October to March) (Kang et al., 2019), and TV of Lag 2, 3, 5 years. During follow-up, we also collected the residential mobility information by asking participants “Have they changed home address during follow-up period” using a questionnaire. We conducted a sensitivity analysis by removing participants whose address changed during follow up to assess the potential effect from those movers. Furthermore, we additionally adjusted for occupation (employed, retired, students, or unemployed), anti-hypertensive medicines, and $PM_{2.5}$, sulfur dioxide, and ozone in our models. County-level averaged years of education, together with per GDP, were used as the predictors of socio-economic status (SES) and included in sensitivity models adjusting for the difference between counties.

Lastly, CVD-free years loss was calculated using the trapezium rule to estimate the reduced disease-free years for high TV (Liu et al., 2018; Liu et al., 2020). Specifically, CVD-free years loss were estimated as the differences of areas under the survival curves between lower and higher TV exposure based on Cox proportional hazards models with age as the timescale by the following equation: CVD-free diseases years $= \int_{\text{baseline age}}^{90} \{s_i(u) - s_{ref}(u)\}du$, where $s_i(u)$was the survival probability at age u for higher TV, and $s_{ref}(u)$was the survival probability at age u for lower TV. High or low TV was dichotomously defined as higher or lower than the median of long-term TV.

We also estimated the population-attributable fraction (PAF) of CVD related to TV by the following formula for a continuous variable, attributable cases = baseline prevalence*[exp(β *Δx)-1]* population at risk, PAF = attributable cases/overall cases, where baseline prevalence is the CVD prevalence among participants exposed to counterfactual exposure; β is the coefficient of TV-CVD association, respectively; Δx is the difference between the observed TV and the counterfactual exposure (Lin et al., 2017; Lin et al., 2016; Lin et al., 2018). Overall cases are the total CVD cases. We chose the concentration corresponding to the lowest tertile of exposure as a counterfactual exposure distribution.

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

3. Results

3.1. Summary statistics

A total of 23,721 participants were entered into the final analysis, and the numbers of participants included and excluded at each stage in the study were shown in a flow chart (Figure A1). Table A1 showed that the excluded population tended to be more elderly, obese, hypertensive, and urban population. Fig. 1 presents a map of China with the annual mean TV of ambient temperature, showing that north regions had greater TV than south regions.

Over a median follow up of 4.65 years (maximum 6.75 years), we documented 836 CVD events (incidence rate: 762.21 cases per 100,000 person-years) (Table 1). The mean (SD) age of participants was 56.15 (13.08) years old, and 46.31% were men, with the mean of the long-term TV exposure 9.82 °C. Population with higher TV were more likely to have higher BMI, higher education level, higher prevalence of hypertension and diabetes, and higher incidence for CVD, they also tended to a resident in urban, and exposure to greater $PM_{2.5}$ level ($P < 0.05$).

3.2. Association of long-term exposure to TV with CVD incidence

The crude model showed long-term TV was positively associated with the incidence of CVD in the Chinese population aged 35 years or older (Table 2). After adjustment for sex, age, BMI, current smoker, alcohol use, education level, urbanity, hypertension, diabetes mellitus, dyslipidemia, and annual mean temperature, the association between CVD incidence and TV became more prominent. Specifically, for each 1 °C increase in the long-term TV, we observed a 6% (HR: 1.06, 95%CI: 1.01−1.11) increase in CVD incidence risk. A significant positive trend was observed between CVD incidence and levels of TV, the lowest tertile with an HR = 1.34 (95% CI: 1.13−1.59) for the medium tertile and an HR = 1.72 (95% CI: 1.35−2.19) for the highest tertile ($P_{trend} < 0.001$). For CHD, the HR was 1.80 (95%CI: 1.32−2.46) for median and 2.19 (95%CI: 1.40−3.41) for highest tertile, with HR of 1.07 per 1 °C increase in TV with a marginally significant association. Stroke also exhibit significantly positive effects on high TV. There was a 1.10 times risk for stroke associated with a 1 °C increase in TV.

The restricted spline model with 2 degrees of freedom showed that the response-reaction curve between long-term TV exposure

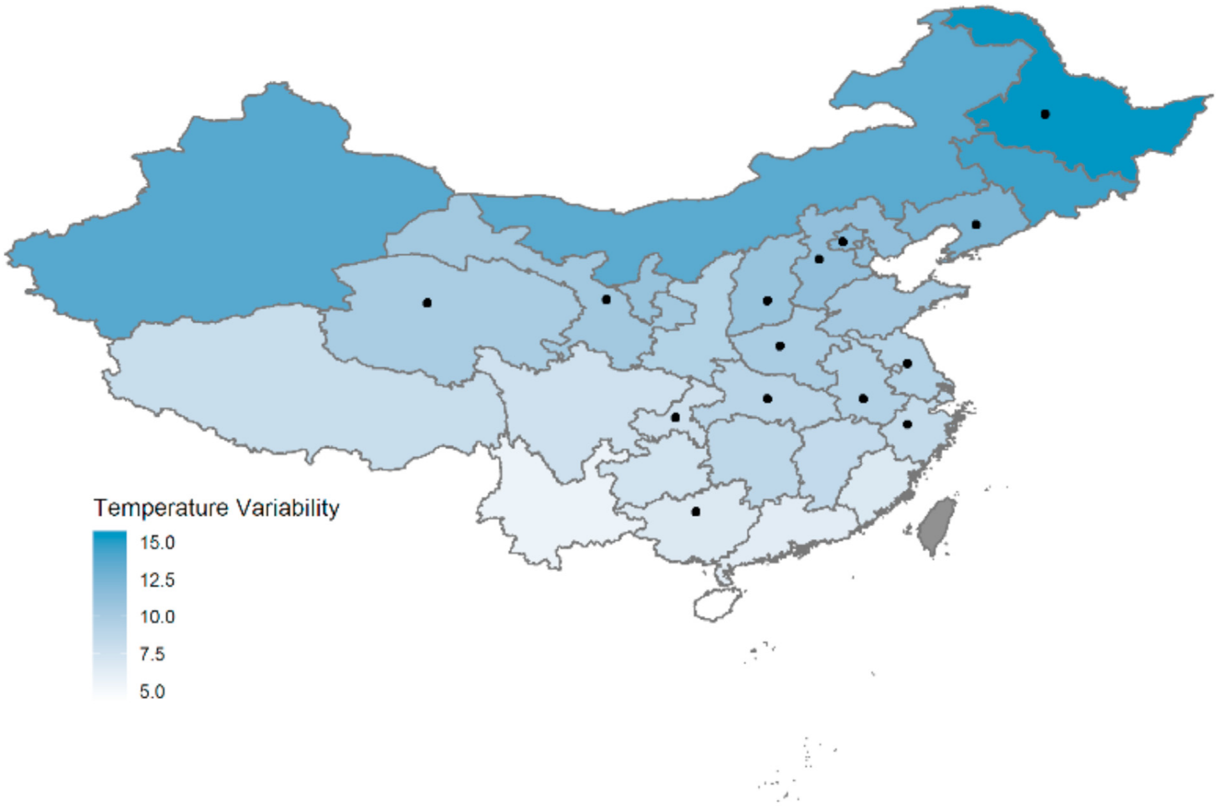

Fig. 1. The temperature variability between 2012 and 2016 in China and 14 survey sites distribution. Black dot denote provinces where study participants resided at baseline. No data was represented in Taiwan.

Table 1
Descriptive statistics of the enrolled individual characteristics.

Characteristics	Total Cohort	TV Tertiles			*P* value
		T1 (<8.74)	T2 (8.74–10.07)	T3 (≥10.07)	
Number of participants, No.	23,721	7632 (32.17)	8218 (34.64)	7871 (33.18)	–
CVD events					
Follow up years	4.62 ± 0.94	4.69 ± 0.89	4.58 ± 0.89	4.61 ± 0.94	
Cases (%)	836 (3.52)	231 (3.03)	287 (3.49)	318 (4.04)	–
Person-years	109,681.21	35,764.13	37,634.70	36,282.38	–
Incidence rate (per 100,000 person years)	762.21	645.90	762.59	876.46	–
Male	10,985 (46.31)	3527 (46.21)	3868 (47.07)	3590 (45.61)	0.176
Age (years), Mean ± SD	56.15 ± 13.08	57.03 ± 13.35	55.84 ± 13.26	55.61 ± 12.59	<0.001
BMI (kg/m^2), Mean ± SD	24.53 ± 3.48	23.76 ± 3.31	24.51 ± 3.40	25.28 ± 3.56	<0.001
High BMI	12,803 (53.97)	3413 (44.72)	4444 (54.08)	4946 (62.84)	<0.001
Educated to middle school or higher	11659 (49.15)	2416 (31.66)	3914 (47.63)	5329 (67.70)	<0.001
Current smoker	6012 (25.34)	2090 (27.38)	1863 (22.67)	2059 (26.16)	<0.001
Alcohol consumption	4734 (19.96)	1707 (22.37)	1412 (17.18)	1615 (20.52)	<0.001
Urban	10,502 (44.27)	1379 (18.07)	4862 (59.16)	4261 (54.14)	<0.001
Hypertension	9310 (39.25)	2862 (37.50)	3051 (37.13)	3397 (43.16)	<0.001
Diabetes mellitus	2462 (10.38)	700 (9.17)	776 (9.44)	986 (12.53)	<0.001
Dyslipidemia	8824 (37.20)	2927 (38.35)	2805 (34.13)	3092 (39.28)	<0.001
$PM_{2.5}$ (μg/m^3), Mean ± SD	52.09 ± 15.86	44.71 ± 9.31	50.46 ± 15.00	60.95 ± 17.48	<0.001
Annual temperature (°C), Mean ± SD	13.16 ± 5.05	17.85 ± 1.77	11.12 ± 5.59	10.74 ± 3.14	<0.001
Long-term TV (°C), Mean ± SD	9.82 ± 1.87	8.11 ± 0.56	9.45 ± 0.35	11.86 ± 1.72	<0.001

CVD, cardiovascular diseases; BMI, body mass index; $PM_{2.5}$, particulate matter of diameter ≤2.5 μm; SD, standard deviation; TV, temperature variability; T1 indicated TV < 8.78 °C, T2 between 8.78 and 10.07 °C and T3 ≥ 10.07 °C. Long-term TV were the annual SD of the mean temperature in baseline survey date. Incidence rate: per 100,000 person years. Data are presented with number (percentage) unless indicated.

and CVD incidence was monotonic and almost linear across the range of TV in the study population, the non-linear association test showed $P = 0.083$ for CVD (Fig. 2).

3.3. *Stratified analysis and effect modification*

The stratified analysis revealed a similar association across all subgroups, whereas the population in urban regions and with

Table 2
Hazard Ratio and 95% confidence intervals for long-term temperature variability on the incidence of cardiovascular diseases.

Incidence diseases	TV per 1 °C increment	TV Tertiles			P_{trend}
		T1	T2	T3	
CVD					
No. of events	836	231	287	318	–
Person-years	109,681.21	35,764.13	37,634.70	36,282.38	–
Incidence rate	762.21	645.90	762.59	876.46	–
Crude model	1.03 (1.00, 1.07)	1.00 [Reference]	1.18 (0.99, 1.40)	1.47 (1.15, 1.88)	0.001
Full model	1.06 (1.01, 1.11)	1.00 [Reference]	1.34 (1.13, 1.59)	1.72 (1.35, 2.19)	<0.001
CHD					
No. of events	255	62	78	115	–
Person-years	111,467.00	36,297.42	38,282.54	36,887.04	–
Incidence rate	228.77	170.81	203.75	311.76	–
Crude model	1.05 (0.99, 1.12)	1.00 [Reference]	1.18 (0.85, 1.65)	1.45 (0.92, 2.29)	<0.001
Full model	1.07 (0.98, 1.16)	1.00 [Reference]	1.80 (1.32, 2.46)	2.19 (1.40, 3.41)	<0.001
Stroke					
No. of events	499	141	170	188	–
Person-years	110,951.68	36,297.42	38,282.54	36,887.04	–
Incidence rate	449.75	388.46	444.07	509.66	–
Crude model	1.04 (1.00, 1.09)	1.00 [Reference]	1.14 (0.91, 1.43)	1.55 (1.12, 2.13)	0.018
Full model	1.10 (1.03, 1.16)	1.00 [Reference]	1.30 (1.05, 1.62)	1.81 (1.32, 2.48)	<0.001

CVD, cardiovascular diseases; CHD, coronary heart diseases; TV, temperature variability. Incidence rate: per 100,000 person-years. T1 indicated TV < 8.78 °C, T2 between 8.78 and 10.07 °C and T3 ≥ 10.07 °C. The HRs (95% CIs) of full model were the results after adjustment of sex, age, BMI, current smoker, alcohol use, education level, urbanity, hypertension, diabetes mellitus, dyslipidemia and annual mean temperature.

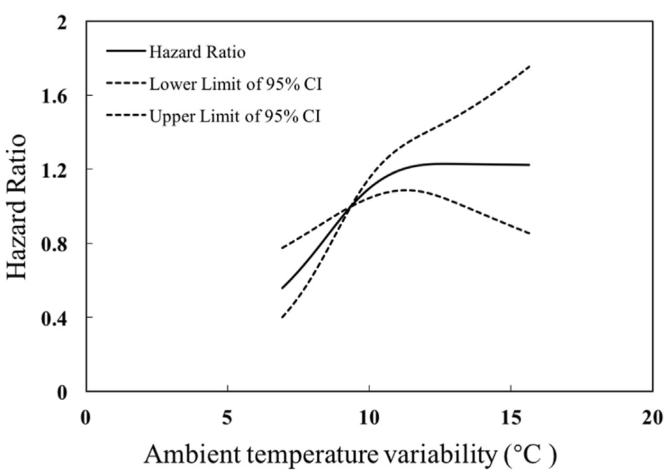

Fig. 2. Exposure-response relations between long term exposure to temperature variability and incidence of cardiovascular diseases among Chinese adults, using a natural spline function with two degrees of freedom. Hazard ratios were estimated by comparing to a reference value of 9.33 °C (the median of temperature variability exposure). Solid line represents point estimate and dashed lines represent 95% confidence intervals. CI, confidence intervals.

dyslipidemia had a greater significant effect of TV than their counterparts ($P < 0.05$) (Table 3).

3.4. The loss of disease-free years due to TV

Additionally, exposure to high TV may speed up CVD incidence (Fig. 3). In comparison to TV < 9.33 °C, the population between 35 and 65 years old, would develop CVD 2.11 years earlier when exposure to TV ≥ 9.33 °C. For CHD and stroke, population exposure to TV ≥ 9.33 °C would lose 1.11 CHD-free years and 2.89 stroke-free years, respectively (Fig. 3).

3.5. Sensitivity analysis

In the sensitivity analysis, the effect estimates of TV exposure on CVD did not change substantially when included different lagging exposure years, deleted movers, and further adjustment for occupation, anti-hypertensive medicine, annual $PM_{2.5}$, sulfur dioxide, ozone, mean county-level per capita GDP, and education level. Significantly positive associations were observed for longer TV with the incidence of CVD, such as lag02, lag 03, and lag 05 years TV. After further adjustment for occupation, anti-hypertensive medicine, annual $PM_{2.5}$, sulfur dioxide, ozone, mean county-level per capita GDP, and education level, the HR was 1.05 associated with per 1 °C increase of long-term TV (Fig. 4).

Table 3
Hazard Ratio and 95% confidence intervals with per 1 °C increment in temperature variability on incidence of cardiovascular diseases in the stratified analysis.

Subgroups	Incidence rate	Hazard Ratio (95% *CI*)	$P_{interaction}$
Sex			0.661
Men	955.12	1.05 (0.99, 1.12)	
Women	597.81	1.12 (1.04, 1.21)	
Age			0.056
< 65 years	325	1.12 (1.03, 1.22)	
≥ 65 years	1907.85	1.06 (1.00, 1.12)	
BMI			0.931
Normal	793.66	1.05 (0.99, 1.13)	
High	735.59	1.10 (1.03, 1.18)	
Urbanity			0.014
Urban	752.87	1.20 (1.09, 1.33)	
Rural	769.57	1.03 (0.97, 1.09)	
Hypertension			0.442
Without	410.67	1.07 (0.99, 1.16)	
With	1323.71	1.08 (1.02, 1.14)	
Diabetes mellitus			0.359
Without	703.58	1.06 (1.00, 1.11)	
With	1278.56	1.18 (1.05, 1.32)	
Dyslipidemia			0.048
Without	698.26	1.04 (0.98, 1.11)	
With	867.22	1.13 (1.05, 1.21)	

CVD, cardiovascular diseases; BMI, body mass index; HR, hazard ratio; CI, confidence intervals. Incidence rate: per 100,000 person-years. The reference was low TV. The HRs (95% CIs) of full model were the results after adjustment of sex, age, BMI, current smoker, alcohol use, education level, urbanity, hypertension, diabetes mellitus, dyslipidemia and annual mean temperature. $P_{interaction}$ indicated P value of the interaction effect between subgroup and TV.

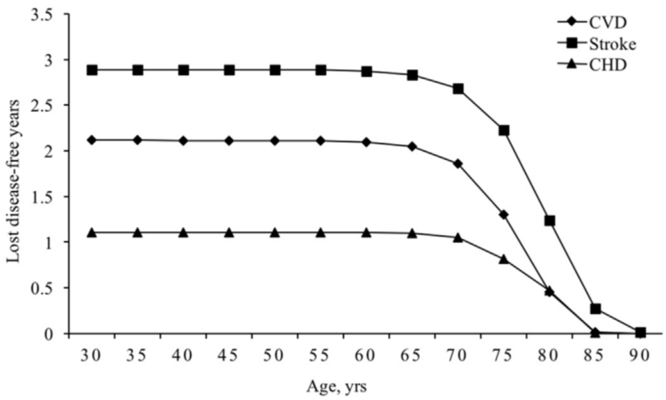

Fig. 3. Loss disease-free years up to 90 years old associated with high temperature variability. CVD, cardiovascular diseases; CHD, coronary heart diseases. High TV indicated TV ≥ 9.33 °C.

3.6. The attributable burden associated with TV

The PAF due to TV higher than 8.11 °C was 7.98% (95% CI: 1.30%–14.82%) for CVD, 9.17% (95% CI: 0%, 21.60%) for CHD, and 12.98% (95% CI: 3.80%–21.19%) for stroke incidence, respectively. It was estimated that 66 (95% CI: 3–124) cases for CVD, 23 (95% CI: 0–55) for CHD and 65 (95%CI: 3–15) for stroke could been attributable to TV higher than 8.11 °C, respectively (Table 4).

4. Discussion

Although the short-term effect of TV on human health have been widely explored in time-series studies, there are few data on the long-term effects of TV which is also a non-negligible profile of climate change. Our results provided evidence that long-term exposure to ambient TV was associated with elevated risk for CVD incidence, even after controlling for multiple potential confounders. The above results were robust when sensitivity analyses were done, including different lagging exposure years and further adjustment for other potential confounders. We also first estimated that exposure to high TV would lose 2.11 years disease-free years and 66 CVD cases (or 7.98% cases) could been attributable to TV higher than 8.11 °C. The current study supported related public health strategies for better CVD health management in China.

Long-term TV, however, unlike time-serious study, has been scarcely studied for its potential health effects. In the current study, the incident risk of CVD elevated 6% with each 1 °C increase for long-term TV. A New England study enrolling 2.7 million residents from Medicare data between 2000 and 2008, showed that each 1 °C increase in TV was related to 1.3% and 4.1% increases in all-cause mortality in summer and winter, respectively (Shi et al., 2015). A study by Shi et al. including 13 million Medicare beneficiaries in the Southeastern USA from 2000 to 2013, reported a 1 °C increase in TV was related to 0.80% and 0.41% increase in mortality during summer and winter, respectively (Shi et al., 2016). In another cohort study including elderly patients from 135 U.S cities, after adjusting for individual risk factors, the risk of myocardial infarction mortality increased 3.8% with per 1 °C increment in summer TV

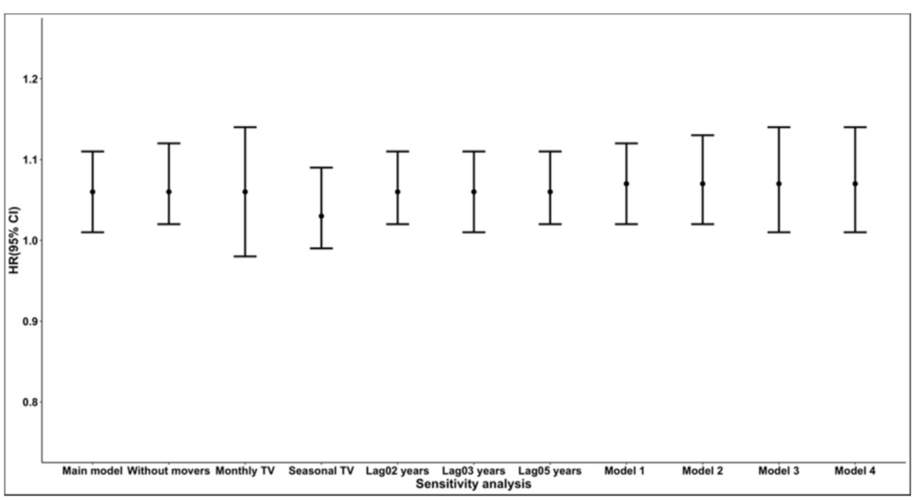

Fig. 4. Hazard Ratio and 95% confidence intervals with per 1 °C increment in temperature variability on incidence of cardiovascular diseases in the sensitivity analysis TV: temperature variability. CVD: cardiovascular diseases. Annual TV without movers were the baseline TV restricted to participants who did not move during follow up. Monthly, seasonal TV were the SD of the mean temperature in baseline survey month and season, respectively. The lag 02 years, lag 03 years and lag 05 years TV were the SD of the mean temperature in baseline survey year and previous 1, 2, 4 years, respectively. Model 1 were further adjusting for occupation and anti-hypertensive medicine based on full model. Model 2 were further adjusting for occupation, anti-hypertensive medicine and annual $PM_{2.5}$ based on full model. Model 3 were further adjusting for occupation, anti-hypertensive medicine and annual $PM_{2.5}$, sulfur dioxide, and ozone based on full model. Model 4 were further adjusting for occupation, anti-hypertensive medicine and annual $PM_{2.5}$, sulfur dioxide, and ozone, annual county-level per capita gross domestic product, annual county-level education level based on full model.

Table 4
Estimated attributable risk and the number of cardiovascular events attributable to temperature variability.

Events	No. of events	Attributable fraction (95% CI), %	Cases attributable to TV (95% CI)
CVD	836	7.95 (1.30, 14.82)	66 (3, 124)
CHD	255	9.17 (0, 21.60)	23 (0, 55)
Stroke	499	12.98 (3.80, 21.19)	65 (3, 15)

CVD, cardiovascular diseases; CHD, coronary heart diseases; TV, temperature variability; CI, confidence intervals. Counterfactual exposure corresponded to the lowest tertile concentration of TV (mean: 8.11, SD: 0.56) in this population.

(Zanobetti et al., 2012). A recent cross-sectional study in Pakistan found that TV was positively related to the incidence of acute myocardial infarction with regression coefficients of 0.12 (Khowaja et al., 2019). In the current study, we observed a relatively greater effect of TV on the incidence of CVD, which helps to enrich our understanding of the health effects of TV, especially for developing countries.

The underlying mechanics for TV on CVD have not been fully understood. Several studies have shown that the adverse effect of the TV may relate with the disturbance of normal physiological thermoregulation, which may subsequently lead to autonomic active nervous functions triggered, indirectly resulting in the increased cardiovascular workload, such as heart rate, blood pressure and thus further to precipitate potential atherosclerotic CVD (Lim et al., 2012). Some mechanistic studies also showed that unstable temperatures could alter the blood cholesterol levels (Yang et al., 2018), plasma fibrinogen concentrations (Rudnicka et al., 2007), platelet viscosity (Schauble et al., 2012), and high-sensitivity C reactive protein (Kang et al., 2020), which may exacerbate CVD. Besides, increased TV tend to impede the adaptation to local climate and thus may increase the risk for adverse health outcomes, including CVD (Sun et al., 2018).

The current study also found that individuals with dyslipidemia were at higher risk for elevated TV, indicating that people suffering from impaired vascular health, such as atherosclerosis, may have greater harmful effects with TV. Identifying subgroups that might be particularly vulnerable to TV is of value for adopting preventive strategies and reducing harmful health effects. Our results highlighted, in the context of global climate change, more attention should be paid to develop related preventive measures to reduce the harmful health effects of TV, more studies focusing on assessing the health burden of TV in different climate zones and socioeconomic levels should be conducted in the future.

4.1. Strength and limitation

The current study, with representative general Chinese adults aged 35 years and older, was the first to examine the impacts of TV on CVD incidence in developing countries. As one of the few studies to investigate the association between long-term TV on health outcomes, our findings provided a better understanding of the impacts of climate change, especially for TV. Secondly, with high spatial resolution in our TV assessment, the accuracy in ambient TV estimation was improved substantially in the current study. There were also several potential limitations to the present work. Firstly, personal temperature exposure, which means the individual's perception of temperature, may be influenced by not only the ambient temperature but also humidity and wind chill, which were not available in the current study. Second, the classification of participant characteristics was only obtained at baseline and therefore could not be included in the study as time-dependent covariates. Thirdly, we failed to collect information on air condition and indoor temperature, thus we were not able to fully adjust potential confounders. Additionally, missed air pollution in 2012 may result in measurement bias, although less than 1% of participants were in 2012 and the sensitivity showed no significant change for adjusting air pollution. Regarding the complexities on the epidemiological association between CVD incidence and long-term TV in subgroup analysis and sensitivity analysis, such as the indoor air condition use, future studies should be conducted to reveal related association and underlying mechanics.

5. Conclusion

In conclusion, this prospective cohort study added considerable strength to the evidence of a significant association for long-term exposures to TV on CVD incidence. The findings informed that the TV emerges as a key factor for the potential health impacts of climate change, more attention should be paid to public health organizations to better understand the health risks of TV, especially for the susceptible population.

The presentation of previous work related with current study

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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

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2021.116831.

Authors' contributions

Kang Yuting: Conceptualization, Methodology, Formal analysis, Software, Writing – original draft preparation. Tang Haosu, Zhang Linfeng and Wang Su: Data curation, Formal analysis, Software. Wang Xin and Chen Zuo: Visualization, Investigation. Zheng Congyi, Yang Ying, Gao Runlin and Huang Gang: Software, Validation. Wang Zengwu: Conceptualization, Funding acquisition, Writing-Reviewing and Editing.

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