Heatwave warnings mitigate long-term cardiovascular diseases risk from heat-related illness: a real-world prospective cohort study

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Summary

Background Global warming is intensifying, exacerbating associated health issues. Heat-related illness, a critical risk during heatwaves, significantly impacts public health, yet its long-term health effects remain poorly understood. We established a cohort to investigate these health impact and explore the mitigative role of heatwave warnings.

Methods Our cohort study enrolled 9,658,745 participants free of cardiovascular disease (CVD) at baseline from 1332 hospitals and 922 primary care centres in Shenzhen, China. The cohort was observed and followed up from January 1, 2017, to July 31, 2023. We utilized Cox proportional hazards model to analyse CVD incidence among participants who had heat-related illness versus those who did not, and further assessed causal relationship using instrumental variable approach. We employed stratified logistic regression to explore the protective effects of heatwave warning policies.

Findings Among 9,658,745 participants followed up to 6 years, 238,278 (2.47%) developed CVD. People who developed CVD were generally older, male, with a higher degree of education, and with more hospital admissions before baseline. Heat-related illness was associated with CVD, with a hazard ratio of CVD 2.526 (95% CI = 2.301–2.773) among patients with heat-related illness compared with those without heat-related illness, and instrumental variable approach analysis suggested causation. Issuing heatwave warnings reduced hospital admissions for heat-related illness (OR [95% CI] = 0.902 [0.832–0.977]) and future CVD risk (OR [95% CI] = 0.964 [0.946–0.982]). The mitigative role of heatwave warnings suggested delayed effect, with mitigative effect at greatest magnitude one to two days after issuance for heat-related illness admission and three to four days for CVD.

Interpretation Our study suggested that heat-related illness has significant long-term impacts on future CVD incidence, which can be mitigated by heatwave warnings.

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Keywords: Heat-related illness; Cardiovascular disease; Instrumental variable; Heatwave warnings

Research in context

Evidence before this study

We searched all databases in Web of Science for epidemiological studies, using keywords such as "high temperature", "heatwave", "heat-related disease", "Heat-related illness"; "heat stroke"; "heatstroke"; "warning", and "long-term health effects". Epidemiological studies have reported associations between short-term exposure of heat and various disease outcomes, including cardiovascular disease (CVD). Heat-related illness, the most classic and severe adverse health effect of heatwaves, has been linked to long-term cardiovascular consequences and an ongoing risk of mortality, as reported in some regional, hospital-based, and small-sample retrospective studies. Addressing heatwaves is a critical public health challenge. Despite worldwide efforts such as heat early warning systems to combat heatwaves, there is a lack of empirical research assessing their long-term health benefits.

Added value of this study

This real-world, prospective cohort study of 9 million participants arose from 20 million residents in China. This study shows an increase in the long-term CVD risk associated with heat-related illnesses, which can be mitigated by heatwave warnings.

Implications of all the available evidence

The long-term health impacts of heatwaves are severe and warrant attention. Protecting populations by reducing exposure to heatwaves and preventing heat-related illness is an effective strategy to avoid long-term adverse cardiovascular outcomes. Thus, heatwave warnings are low-cost, high-return measures that can enhance public health benefits; nations and regional organizations are encouraged to implement and sustain these efforts long-term.

Introduction

Heatwaves are becoming more frequent and intense, resulting in increased projections of global human mortality and morbidity. At the current 10-year average temperature increase of 1.14 °C (°C) above pre-industrial levels, people now face twice as many heatwave days—defined as periods of at least two consecutive days with temperatures above the 95th percentile from a longer historical reference period.[1] In 2019, 365,000 deaths were linked to short-term exposure to heat with cardiovascular disease (CVD) being the predominant cause.[2] Heat-related illness, a severe condition caused by prolonged exposure to heatwaves, occurs when the body's core temperature exceeds 40 °C.[3] The acute hazards of heat-related illness are clear: within hours, it can precipitate cellular damage and disrupt organ function, potentially leading to multi-organ failure and fatality.[2,4] The evidence for the long-term health effects of heat-related illness on populations is limited. Some studies have observed that heatstroke impacts long-term cardiovascular[5] and patient survival.[6–8] However, potential confounding factors and a limited sample size limit the extrapolation of these findings, particularly for the warming Western Pacific region, highlighting the urgent need for research on long-term heatwaves exposure and cardiovascular disease.[9,10]

To mitigate the hazards of heatwave, heat early warning systems, served as a key public health strategy for managing extreme heat, have been established in multiple countries.[11–14] Prior research has explored relationships between heat early warning systems and heatwave-related health benefits. A study from Shanghai, China, found that 50% of heat-related illnesses and 58.2% of heat-related deaths occurred on days without heat-health warning systems, highlighting the effectiveness of these systems. However, these studies primarily rely on descriptive statistics and lack of extensive epidemiological analysis, failing to investigate the long-term health benefits of heat early warning systems. To date, a comprehensive cohort study examining the long-term health effects of heatwaves and the mitigating impact of heat early warning systems remains missing.

Therefore, in this study, we established a cohort by linking meteorological data and policy measures with individuals' health outcomes. We analysed data from over nine million individuals to evaluate the long-term impact of heat-related illness on CVD caused by extreme high temperatures. Additionally, we employed instrumental variables (IVs) to assess the causal relationship between heat-related illness and CVD. Furthermore, we investigated both short-term and long-term health benefits of heat early warning systems. Our study focuses on the prolonged impact of heat-related illness on the population and the substantial long-term benefits of heatwave warnings, highlighting the risks of global warming and providing preventive strategies for governmental policies and actions.

Methods

Study design and population

This cohort arose from over 20 million residents in Shenzhen, China. We collected individual-level anonymised health records from 922 primary care centres,

and 1332 hospitals and independent outpatient departments of hospitals, which nearly encompassed all primary care centres and hospitals in the city. We linked the health profiles of residents in hospitals or primary care centres to medical visit and mortality records using personal identification numbers. We excluded unmatched records, including those with missing personal identification numbers or errors that rendered matching impossible. For covariates with missing data, we did not perform deletions or imputations but instead created a new category to represent missing values. Records of individuals whose primary residence was not in Shenzhen were also excluded. This cohort study included participants who (1) were age more than 18 years, and (2) had health profiles available in hospitals or primary care centres from January 1, 2017, to July 31, 2023, and (3) had at least two medical records in hospitals or primary care centres, with time span of medical records above 1 year. The baseline was set one year after the first available medical record, with cohort observation period beginning at this point and extending until the last medical record.[15] The exclusion criteria included (1) participants with missed key information such as age and sex or unclear diagnostic information; (2) and participants with any occurrences of CVD or deaths with one year prior to baseline to avoid left-truncated bias. Finally, our cohort study enrolled a total of 9,658,745 participants free of CVD at baseline. The inclusion and exclusion process of participants is detailed in the flowchart (Appendix p 22). The Tsinghua University Science and Technology Ethics Committee (Medicine) has approved this study (Project No: 20230065). Previously collected, anonymized, and de-identified administrative data were accessed on a secure, offline platform, which is exempt from requiring additional informed consent of individuals for secondary analyses.

Exposure and outcomes

The primary exposure variable was diagnosis of heat-related illness in inpatient or outpatient records. We included all types of heat-related illness, including heatstroke and sunstroke, heat syncope, heat cramp, heat exhaustion, heat fatigue, heat oedema and other effects of heat and light lead to heatstroke (the International Classification of Diseases, Tenth Revision: 2016 [ICD-10] from T67.0 to T67.9, Appendix p 8). We adopted a time-varying survival analysis to calculate person-years. Upon experiencing heat-related illness, individuals contributed person-years to the exposed group; if not, they contributed to the non-exposed group. If participants have outpatient or hospital records for heat-related illnesses within one year after their first medical record, they are defined as part of the exposed group and followed up starting from one year after the first medical record.

Outcomes included the first occurrence of CVD or CVD death, which were coded by ICD-10 (Appendix p 8). Available diagnostic information for CVD was collected from outpatient and inpatient records across all primary centres and hospitals. CVD outcomes exclude primary hypertension (I10), hypertensive renal disease (I12), and secondary hypertension (I15), which were controlled as covariates due to their commonality. We considered the following subtypes of CVD: stroke (I60–I69), atherosclerosis (I70), rheumatic heart diseases (I00–I09), myocarditis and cardiomyopathy (I40–I43), coronary heart disease (I21–I25), conductive heart disease (I44–I49), angina pectoris (I20), and other cardiovascular diseases (I11, I13–I14, I16–I19, I26–I39, I50–I59, I71–I99).

Covariates

In total, we included 11 covariates and 61 terms in the analysis. Covariates of the study included four main categories[16]: (1) demographic information, including age, sex, education, occupation, and marital status; (2) health and medical information, including type of health insurance, establishment of electronic health records, hospital type, and the number of hospital admissions in the first year before the baseline; (3) baseline medical history, including cancers (C00–C97), diabetes (E10–E14), hypertension (I10, I12, I15), pulmonary conditions (J12–J18, J40–J47, J60–J70), renal conditions (N00–N20, N25–N29), obesity (E66), mental disorders (F00–F99), fever (A68, R50), and gastrointestinal diseases (K29, ICD code in Appendix p 8); (4) and baseline medication history, encompassing angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, anticholinergics, anticonvulsants, diuretics, tricyclic antidepressants, amphetamines, benzodiazepines, antipsychotics, antihistamines, and additive substances like alcohol, opioids, and cocaine.

Instrumental variable

Instrumental variable methods, can be applied in epidemiology to address unmeasured confounding, with weather variables, such as rainfall and temperature, commonly used as IVs in research on economic productivity, social behaviours, and infectious disease transmission.[17–20] Here, we applied an instrumental variable analysis to explore the causal relationship between heat-related illness and CVD.[21,22] We randomly selected summer hospital admissions in summer (June, July, August) and divided them into heat-related illness and non-heat-related illness groups, including 7,037,241 participants. We matched heat-related illness cases with non-heat-related illness cases by admission date. We used daily average dew point temperature at the admission date as IVs.

Instrumental variables are defined by three assumptions: (1) relevance, meaning the variable is associated with exposure; (2) exclusion restriction, meaning the variable affects the outcome only through exposure; and (3) independence, meaning the variable is independent of confounders. In this study, dew point

temperature on heat-related illness admission date is an appropriate IV. First, daily dew point temperature is empirically associated with the heat-related illness and CVD. Unsuitable heat weather triggers thermoregulatory mechanisms that cause immediate physiological changes, including fluctuations in blood pressure, heart rate, and platelet activation, which can lead to end-organ failure, inflammation, and potentially long-term health risks.[23–27] Second, dew point temperature on a specific admission date is unlikely to affect CVD occurrence in the future via other pathways. However, the exclusion and independence assumptions cannot be directly verified. As Karl Popper's falsification methodology suggests, scientific theories or hypotheses cannot be definitively proven true through verification but can only be falsified through testing. We have not found any empirical evidence to suggest that temperature on a given day directly leads to subsequent long-term CVD risk, other than through heat-related illness. Moreover, there is limited empirical evidence suggesting that other potential confounders are directly related to temperature on a given day, heat-related illness admissions, and subsequent CVD incidence. We further assessed the balance of covariates across different dew point temperature categories (Appendix pp 9–11), observing a more even distribution of patient-level covariates within the categories defined by our IVs than in the overall sample, indicating instrumental variable analysis could reduce bias.[22]

For instrumental variable analysis, we conducted a two-stage residual inclusion estimation framework.[28,29] We first measured the association between heat-related illness and dew point temperature, adjusting for covariates and calculated residuals. We then used these residuals in a Cox proportional hazards model to estimate hazard ratio (HR) between heat-related illness and CVD, adjusting for the same covariates. Detailed model formulations, assumptions, and the selection and justification of IVs are detailed in the Supplementary Methods section of the Appendix pp 2–7.

Heat early warning system

Meteorological Bureau of Shenzhen Municipality (http://weather.sz.gov.cn/qixiangfuwu/yujingfuwu/lishiyujingchaxun/index.html) and Shenzhen Centre for Disease Control and Prevention (http://www.shenzhencdc.cn/rdzt/rlzs/index.html) issue early heatwave warnings to the public through websites and social media applications. The criteria for issuing a warning are that the local weather in Shenzhen is sultry, and the highest temperature within 24 h will rise to 35 °C or has already reached above 35 °C. The temperature on the day of heatwave issuance ranged from 24 °C to 27 °C range. Length of heatwave warnings, based on meteorological forecasts, range from 1 to 18 days in duration, according to 2017–2023 data (Appendix p 23).

Statistical analysis

We utilized the Cox proportional hazards model to analyse the impact of heat-related illness on CVD, adjusting for demographic information, health and medical information, medical history, and medication history. Additionally, subgroup analysis was conducted to access the interaction effects of heat-related illness with sex, age, occupation, and the number of hospital admissions before baseline. Cause-specific hazard approach was used by treating non-CVD deaths as censored events to handle potential competing risks. We constructed a directed acyclic graph (DAG) to clarify the relationships between heat-related illness admission, covariates, and cardiovascular disease outcomes (Appendix p 24).

Furthermore, we restricted the analysis to participants with summer hospital admissions to conduct a time-invariant survival analysis. We calculated Kaplan–Meier estimates to compare CVD incidence between the heat-related illness and non-heat-related illness groups, using the log-rank test. For instrumental variable analysis, we conducted a two-stage residual inclusion estimation framework.[28] From this model, we determined the residual for each participant by calculating the difference between the model-predicted probability of heat-related illness and non-heat-related illness patients. In the second-stage model, we specified a Cox proportional hazards model to estimate the association between heat-related illness and CVD, adjusting for residuals from the first stage and all similar covariates.

We also explored the relationships between heatwave warnings and the risk of heat-related illness and CVD, stratified by a 1 °C dew point temperature interval on the admission date. For the same temperature interval, we compared patients admitted on days with heatwave warnings to those admitted one day before the warning (i.e., reference) to evaluate the impact of heatwave warnings. Moreover, we examined the delayed effect of heatwave warnings and health outcomes: for heatwave warnings that lasted multiple days, we compared the heat-related illness admission and subsequent CVD occurrence among patients admitted after the one, two, three, four, and more than five days of continuous heatwave warnings, with those admitted one day before the warnings were issued (i.e., the reference).

Sensitivity analyses were conducted to assess the robustness of models by (1) adjusting different covariates; (2) redefining study population by focusing on individuals admitted only during the summer; (3) creating a new category or removing observations with missing covariates; (4) employing daily maximum average temperature as another IV; (5) and redefining stratification interval, including every 1 °C or 0.5 °C for dew point temperature, and every 1 °C for daily maximum temperatures. All statistical tests were two-sided, performed in R version 4.3.1, and conducted at a 0.05 significance level.

Role of the funding source

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Results

Among 9,658,745 participants with an average follow-up of 2.01 years (standard deviation 1.2) and up to 6 years of follow-up, 238,278 (2.47%) developed CVD. People who developed CVD were generally older, male, with higher degree of education, and having more hospital admissions before baseline (Table 1, Appendix pp 15–17). The Kaplan–Meier estimates showed that there was a statistically significance difference of CVD incidence between heat-related illness and non-heat-related illness patients ($p < 0.001$, Fig. 1). After adjusting for covariates, the HR of all CVD among patients with heat-related illness compared with those without heat-related illness was 2.526 (95% CI = 2.301–2.773, Fig. 2). Moreover, compared to those without heat-related illness, HRs of stroke, atherosclerosis, rheumatic heart diseases, myocarditis or cardiomyopathy, and other heart diseases in patients with heat-related illness were 2.260 (95% CI = 1.788–2.857), 1.514 (95% CI = 1.207–1.899), 2.206 (95% CI = 1.329–3.661), 2.895 (95% CI = 1.602–5.231), 2.538 (95% CI = 1.875–3.435), respectively (Fig. 2, $p < 0.001$).

In instrumental variable analysis, we found a statistically significant association between the IV and heat-related illness, but no significant association with CVD (HR [95% CI] = 1.002 [0.997–1.006], $p = 0.475$) (Table 2). A likelihood ratio test comparing models with and without the IV showed an F-statistic of 344 ($p < 0.001$; Table 2). Additionally, we reported the distribution of exposure, outcome, and other potential confounders stratified by IV. The results showed a more balanced distribution of covariates across IV-defined categories compared to the overall sample (Appendix pp 9–11). All the above results suggest that dew point temperature serves as a useful instrumental variable for assessing the relationship between heat-related illness and CVD. Heat-related illness was causally associated CVD (HR [95% CI] = 10.829 [1.202–97.511], $p = 0.034$) according to two-stage residual instrument variable model (Table 2). We also employed the daily maximum average temperature as an alternative IV, which produced consistent results, demonstrating a significant association between heat-related illness and CVD (HR [95% CI] = 12.461 [1.763–88.087], $p = 0.011$; Appendix pp 12–14, 19). We further conducted computer simulations with random sham data and used an oversampling method with real-word cohort dataset, finding that the primary reason for the incomplete consistency between the instrumental variable and adjusted Cox estimates is the imbalance in the proportions of the exposed and non-exposed groups (Appendix p 15, 24).

Subgroup analysis showed in Fig. 3 that female heat-related illness patients had a higher risk of CVD compared with the male heat-related illness patients (male, HR [95% CI] = 2.217 [1.956–2.514]; female, HR [95% CI] = 3.053 [2.436–3.825]; p for interaction <0.001). Middle-aged patients (45–65 years) had a lower risk of developing CVD compared to those aged less than 45 years (45–65 years group, HR [95% CI] = 1.863 [1.465–2.368]; 18–45 years group, HR [95% CI] = 3.165 [2.804–3.573]; p for interaction <0.001). Patients with more than five hospital admissions before baseline had a higher risk of CVD compared to those with fewer than five admissions (>5 times, HR [95% CI] = 2.557 [1.748–3.741]; 0–5 times, HR [95% CI] = 1.733 [1.337–2.248], p for interaction = 0.006). Compared with light physical activity occupation group, there was no statistical significance among other different occupation groups (all p for interaction >0.05).

Heat-related illness admission was associated with dew point temperature (Table 2, Fig. 4). Stratified by one degree interval of dew point temperature, compared with days prior to heatwave warning, issuing heatwave warning was associated with reduced heat-related illness-related hospital admission (OR [95% CI] = 0.902 [0.832–0.977]) and subsequently reduced future CVD risk (OR [95% CI] = 0.964 [0.946–0.982]) (Fig. 5a). Moreover, there was no differences in the effect of heatwave warnings by sex, occupation, or baseline health status (all $p > 0.05$), but younger individuals showed greater long-term cardiovascular benefits from the warnings (p for interaction <0.001, Appendix p 26).

For heatwave warnings that last multiple days, preventive effects of heatwave warning were significant after one to two days of continuous heatwave warnings for heat-related illness (OR [95% CI] = 0.835 [0.724–0.963], 0.767 [0.658–0.893]), and after three to four days for CVD (OR [95% CI] = 0.826 [0.787–0.867], 0.875 [0.833–0.919]), indicating a delayed effect (Fig. 5b–c).

Sensitivity analyses confirmed the robustness of our results after (1) adjusting for various covariates (Appendix pp 27–28), (2) redefining the study population to focus exclusively on individuals admitted during the summer (Appendix pp 29–30), (3) removing observations with missing covariates (HR [95% CI] = 2.691 [2.203–3.288]); (4) using daily maximum average temperature as an additional instrumental variable for causal inference (Appendix p 19), and (5) revising stratification factors for assessing warning policies (Appendix p 20).

Discussion

In this cohort study of more than nine million patients, heat-related illness admission was associated with

Characters	Non-CVD (N = 9,420,467)	CVD (N = 238,278)	Overall (N = 9,658,745)
Age, (years)[a]			
Mean (Standard Deviation)	30.60 (18.2)	45.54 (20.3)	30.96 (18.4)
Sex, n (%)[a]			
Male	4,566,391 (48.5)	131,466 (55.2)	4,697,857 (48.6)
Female	4,854,076 (51.5)	106,812 (44.8)	4,960,888 (51.4)
Occupation, n (%)[a]			
Civil Servant	3479 (0.0)	144 (0.1)	3623 (0.0)
Professional and technical personnel	50,141 (0.5)	1549 (0.7)	51,690 (0.5)
Clerical and related staff	383,054 (4.1)	14,650 (6.1)	397,704 (4.1)
Service and sales worker	284,081 (3.0)	7911 (3.3)	291,992 (3.0)
Farmer	9231 (0.1)	396 (0.2)	9627 (0.1)
Production and transportation worker	82,556 (0.9)	2554 (1.1)	85,110 (0.9)
Other unclassified workers	130,524 (1.4)	4941 (2.1)	135,465 (1.4)
Unemployed and retired	2,708,378 (28.8)	56,921 (23.9)	2,765,299 (28.6)
Other[d]	4,358,888 (46.3)	107,257 (45.0)	4,466,145 (46.2)
Missing[e]	1,410,135 (15.0)	41,955 (17.6)	1,452,090 (15.0)
Education, n (%)[b]			
Graduate	52,840 (0.6)	1202 (0.5)	54,042 (0.6)
Undergraduate	461,816 (4.9)	13,495 (5.7)	475,311 (4.9)
Junior college education	667,271 (7.1)	18,233 (7.7)	685,504 (7.1)
Secondary vocational education	444,809 (4.7)	14,137 (5.9)	458,946 (4.8)
General higher education	874,088 (9.3)	25,579 (10.7)	899,667 (9.3)
General primary education	1,428,725 (15.2)	38,191 (16.0)	1,466,916 (15.2)
Primary school education	760,026 (8.1)	19,960 (8.4)	779,986 (8.1)
Other[d]	2,690,931 (28.6)	46,772 (19.6)	2,737,703 (28.3)
Missing[e]	2,039,961 (21.7)	60,709 (25.5)	2,100,670 (21.7)
Marital status, n (%)[a]			
Unmarried	6,210,512 (65.9)	134,146 (56.3)	6,344,658 (65.7)
Married	1,618,088 (17.2)	78,376 (32.9)	1,696,464 (17.6)
Widow	12,756 (0.1)	1695 (0.7)	14,451 (0.1)
Divorce	13,492 (0.1)	875 (0.4)	14,367 (0.1)
Other[d]	996,181 (10.6)	14,152 (5.9)	1,010,333 (10.5)
Missing[e]	569,438 (6.0)	9034 (3.8)	578,472 (6.0)
First admission selection, n (%)			
Primary health centre	3,747,621 (39.8)	78,835 (33.1)	3,826,456 (39.6)
Hospital outpatient	4,777,004 (50.7)	117,973 (49.5)	4,894,977 (50.7)
Hospital inpatient	895,842 (9.5)	41,470 (17.4)	937,312 (9.7)
Electronic health records, n (%)			
Non-registered	6,348,494 (67.4)	147,903 (62.1)	6,496,397 (67.3)
Registered	2,273,444 (24.1)	54,275 (22.8)	2,327,719 (24.1)
Missing[e]	798,529 (8.5)	36,100 (15.2)	834,629 (8.6)
Health insurance, n (%)			
Urban employee basic medical insurance	1,125,100 (11.9)	34,146 (14.3)	1,159,246 (12.0)
Urban resident basic medical insurance	627,607 (6.7)	20,388 (8.6)	647,995 (6.7)
New rural cooperative medical scheme	7296 (0.1)	262 (0.1)	7558 (0.1)
Poverty alleviation	513 (0.0)	11 (0.0)	524 (0.0)
Commercial health insurance	1698 (0.0)	42 (0.0)	1740 (0.0)
Fully funded by government	2794 (0.0)	68 (0.0)	2862 (0.0)
Fully self-funded	1,528,175 (16.2)	36,513 (15.3)	1,564,688 (16.2)
Other social insurance	142,918 (1.5)	3936 (1.7)	146,854 (1.5)
Other[d]	4,152,861 (44.1)	108,486 (45.5)	4,261,347 (44.1)
Missing[e]	1,831,505 (19.4)	34,426 (14.4)	1,865,931 (19.3)

(Table 1 continues on next page)

Characters	Non-CVD (N = 9,420,467)	CVD (N = 238,278)	Overall (N = 9,658,745)
(Continued from previous page)			
Hospital admissions before baseline[c]			
Mean (Standard Deviation)	7.3 (7.4)	12.3 (11.7)	7.4 (7.6)
Median [25%, 75%]	5.0 [3.0, 9.0]	9.0 [5.0, 16.0]	5.0 [3.0, 10.0]
Disease history, n (%)[c]			
Cancer	225,660 (2.4)	4477 (1.9)	230,137 (2.4)
Diabetes	386,519 (4.1)	31,989 (13.4)	418,508 (4.3)
Hypertension	929,521 (9.9)	86,736 (36.4)	1,016,257 (10.5)
Pulmonary conditions	1,774,909 (18.8)	38,692 (16.2)	1,813,601 (18.8)
Renal conditions	215,040 (2.3)	5626 (2.4)	220,666 (2.3)
Obesity	22,286 (0.2)	783 (0.3)	23,069 (0.2)
Mental disorders	30,708 (0.3)	1667 (0.7)	32,375 (0.3)
Fever	502,465 (5.3)	7786 (3.3)	510,251 (5.3)
Gastroenteritis	1,494,128 (15.9)	37,337 (15.7)	1,531,465 (15.9)
Medication history, n (%)[c]			
ACE inhibitors	13,738 (0.1)	1050 (0.4)	14,788 (0.2)
Angiotensin receptor blockers	55,110 (0.6)	2990 (1.3)	58,100 (0.6)
β-Blockers	28,495 (0.3)	3004 (1.3)	31,499 (0.3)
Anticholinergics	53,759,(0.6)	733 (0.3)	54,492 (0.6)
Anticonvulsants	24,549 (0.3)	656 (0.3)	25,205 (0.3)
Diuretics	18,421 (0.2)	1081 (0.5)	19,502 (0.2)
Tricyclic antidepressants	802 (0.0)	20 (0.0)	822 (0.0)
Benzodiazepines	34,956 (0.4)	1369 (0.6)	36,325 (0.4)
Antipsychotics	5644 (0.1)	122 (0.1)	5766 (0.1)
Antihistamines	88,466 (0.9)	884 (0.4)	89,350 (0.9)
Substances like alcohol, opioids, and cocaine	35,646 (0.4)	729 (0.3)	36,375 (0.4)
Heat-related illness exposure, n (%)			
Yes	6900 (0.1)	442 (0.2)	7342 (0.1)
No	9,413,567 (99.9)	237,836 (99.8)	9,651,403 (99.9)
Follow-up time (years)			
Mean (Standard Deviation)	2.02 (1.2)	1.84 (1.2)	2.01 (1.2)
Median [25%, 75%]	2.1 [1.0, 2.9]	1.7 [0.9, 2.7]	2.1 [1.0, 2.9]

CVD, cardiovascular disease (ICD-10 code: I00–I09, I11, I12, I14, and I16–I99); ACE, Angiotensin-converting enzyme. [a]Sex, occupational classification, and marital status was based on the National Standard of People's Republic of China "Classification and Codes of Basic Personal Information (GB/T 6565–2009)." [b]Education refers to an individual's highest level of academic achievement, based on the National Standard of People's Republic of China "Codes for record of formal schooling (GB/T4658-2006)". [c]Hospital admissions before baseline, disease history, and medication history refers to the number of outpatient or inpatient admissions, specific diagnostic information from medical records, and medication records, respectively, for individuals in the cohort before the baseline (the first year after each individual's initial admission record). Medical history including cancers (C00–C97), diabetes (E10–E14), hypertension (I10, I12, I15), pulmonary conditions (J12-J18, J40-J47, J60-J70), renal conditions (N00–N20, N25–N29), obesity (E66), mental disorders (F00–F99), fever (A68, R50), and gastrointestinal diseases (K29); medication history containing encompassing angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, anticholinergics, anticonvulsants, diuretics, tricyclic antidepressants, amphetamines, benzodiazepines, antipsychotics, antihistamines, and additive substances like alcohol, opioids, and cocaine. [d]"Other" referred to individuals who did not fit into any other relevant categories. In the statistical analysis, these unknown variables were uniformly assigned a value of 90. [e]"Missing" referred to instances where the demographic information was either left blank or marked as unclear. In the statistical analysis, these missing entries were uniformly assigned a value of 99.

Table 1: **Characters of study population.**

significantly higher risks of developing CVD compared with people who never had heat-related illness admissions. Further instrumental variable analyses supported the causal effect of heat-related illness on CVD. Female, younger individuals (18–45 years), and patients with more than five hospital admissions before baseline had a higher risk of developing CVD. Moreover, patients admitted on days with heatwave warnings exhibited lower risks of heat-related illness and subsequent CVD development, compared to those admitted one day before heatwave warnings. This study suggests that heat-related illness significantly impacts individuals' long-term health, and such effect can be mitigated by heatwave warnings.

To date, there is a limited number of studies on the long-term cardiovascular complications associated with heatstroke.[9] A retrospective follow-up study found that patients who experienced heatstroke had a 388% increased incidence of CVD, with a particularly notable 171% increase in acute myocardial infarction and a 450% increase in acute ischemic stroke.[5] Our result found heat-related illness patients had a 153%

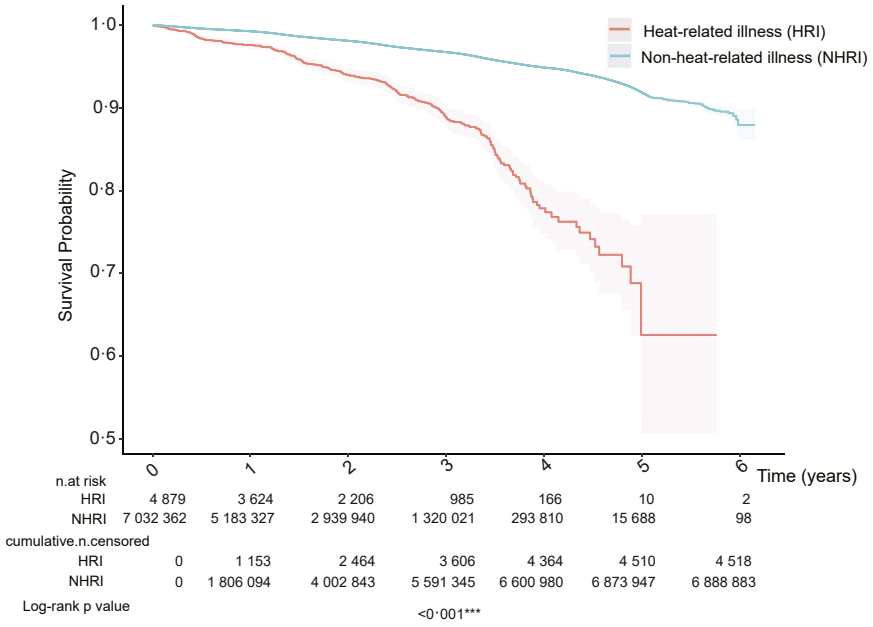


Fig. 1: **The Kaplan–Meier estimates of heat-related illness and non-heat-related illness participants that restricted to those with summer hospital admissions**. The red curve and shaded area represent the survival curve and 95% confidence interval for heat-related illness patients. The light blue curve and shaded area represent the survival curve and 95% confidence interval for non-heat-related illness patients. The survival probability here specifically refers to the probability of not developing CVD outcomes. A log-rank test was used to examine the differences in survival curves between the heat-related illness and non-heat-related illness groups.

increased hazard ratio of CVD, 190% increased of myocarditis or cardiomyopathy, and 126% increased of stroke, which was consistent with previous studies, but the risk of specific diseases was found to be lower. This difference can plausibly be explained by varying patient inclusion criteria: our study encompassed all types of heat-related illness patients (ICD-10 code: T67.0-T67.9), whereas the previous study specifically selected only those diagnosed with heatstroke and sunstroke (ICD-10 code: T67.0) for their study group. Compared to other

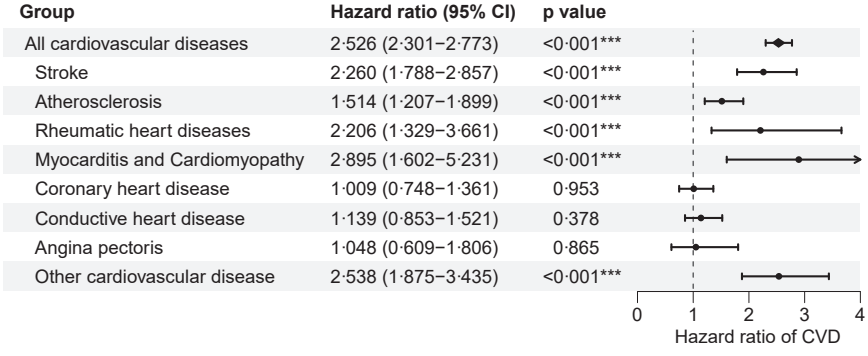


Fig. 2: **The hazard ratios of CVD in patients with heat-related illness compared with those without heat-related illness**. CVD, cardiovascular disease (ICD-10 code: I00–I09, I11, I12, I14, and I16–I99). The association of heat-related illness with all CVD and subgroups were estimated by time-varying Cox regression models, which adjusted for age, sex, education, occupation, and marital status, type of health insurance, hospital type, and establishment of electronic health records, the number of hospital admissions in the first year before the baseline, medical histories, and medication histories. Specially, we employed the Cox proportional hazards model using the coxph function from the survival package in R. The Efron method was used to handle ties, which adjusts the partial likelihood function to account for ties. The diamond represents HR for all CVD. Each dot represents a point estimate of the HR for subgroups. Error bars represent 95% CI. The horizontal dashed line represents the HR equal to 1, which is indicative of no effect. Each line connecting the error bars illustrates the range of HR values. *** means p values < 0.001.

Stage	Coefficient	Estimates	Hazards ratio (CI 95%)	p values
Stage1: Heat-related illness—IV + covariates[a,b]				
	TemperatureNS1	0.458	–	0.007**
	TemperatureNS2	0.771	–	<0.001***
	TemperatureNS3	0.898	–	0.016*
	TemperatureNS4	1.184	–	<0.001***
CVD–IV + covariates[c]				
	Temperature	0.002	1.002 (0.997, 1.006)	0.475
Stage2: CVD–Heat-related illness + covariates + residuals[d]				
	Heat-related illness	2.382	10.829 (1.202, 97.511)	0.034*

CVD, cardiovascular disease (ICD-10 code: I00–I09, I11, I12, I14, and I16–I99). * means p values <0.05 and p ≥ 0.01, ** means p values <0.01, and p ≥ 0.001. *** means p values <0.001. [a]In Stage 1, we used instrumental variables (dew point temperature) to estimate endogenous variable (heat-related illness) by logistic model. Given the nonlinear associations between temperature and heat-related health outcomes, we estimated the association of temperature with heat-related illness using natural cubic splines, with knots placed at the minimum, maximum and 25th (25 °C), 75th (26.5 °C) and 90th (27.1 °C) percentiles of the city-specific distribution of daily temperatures. The term TemperatureNS1 is the first basis of temperature's spline. The covariates included age, sex, education, occupation, and marital status, type of health insurance, hospital type, and establishment of electronic health records, the number of hospital admissions in the first year before the baseline, medical histories, and medication histories. Then, we calculated individuals' deviance residuals. [b]In the first stage of the the two-stage residual inclusion (2SRI) framework, dew point temperature was used as the instrumental variable (IV) to predict heat-related illness. The model aimed to remove any endogeneity in the relationship between heat-related illness and cardiovascular disease. A likelihood ratio test was performed to compare models with and without the IV, resulting in an F-statistic of 344 (p < 0.001). This indicates that dew point temperature is a strong and valid instrument for predicting heat-related illness in this context. [c]The dew point temperature, as an instrumental variable, is not directly related to CVD, meeting a key condition for instrumental variable analysis. [d]In stage 2, we used the endogenous variable (heat-related illness), the same covariates as in stage 1, and individuals' deviance residuals to fit the Cox model and assess the causal association between heat-related illness and CVD. Specially, in this analysis, we employed the Cox proportional hazards model using the coxph function from the survival package in R. The Efron method was used to handle ties, which adjusts the partial likelihood function to account for ties. Robust standard errors were not applied, and the default control parameters ensured appropriate convergence criteria and iteration limits.

Table 2: **Instrumental variable analysis by two-stage residual inclusion estimation framework.**

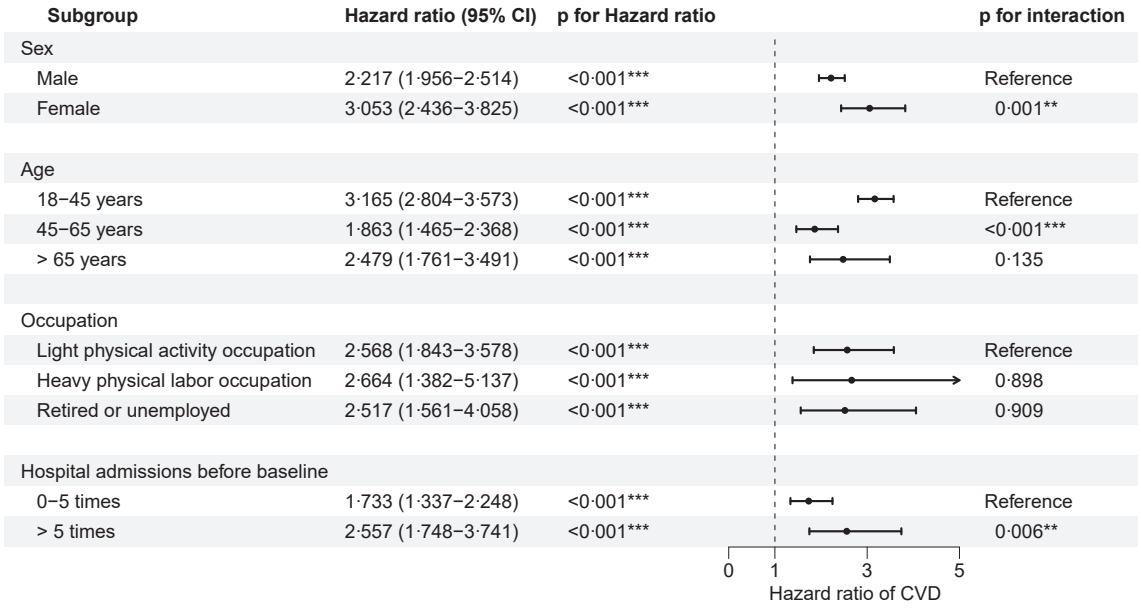
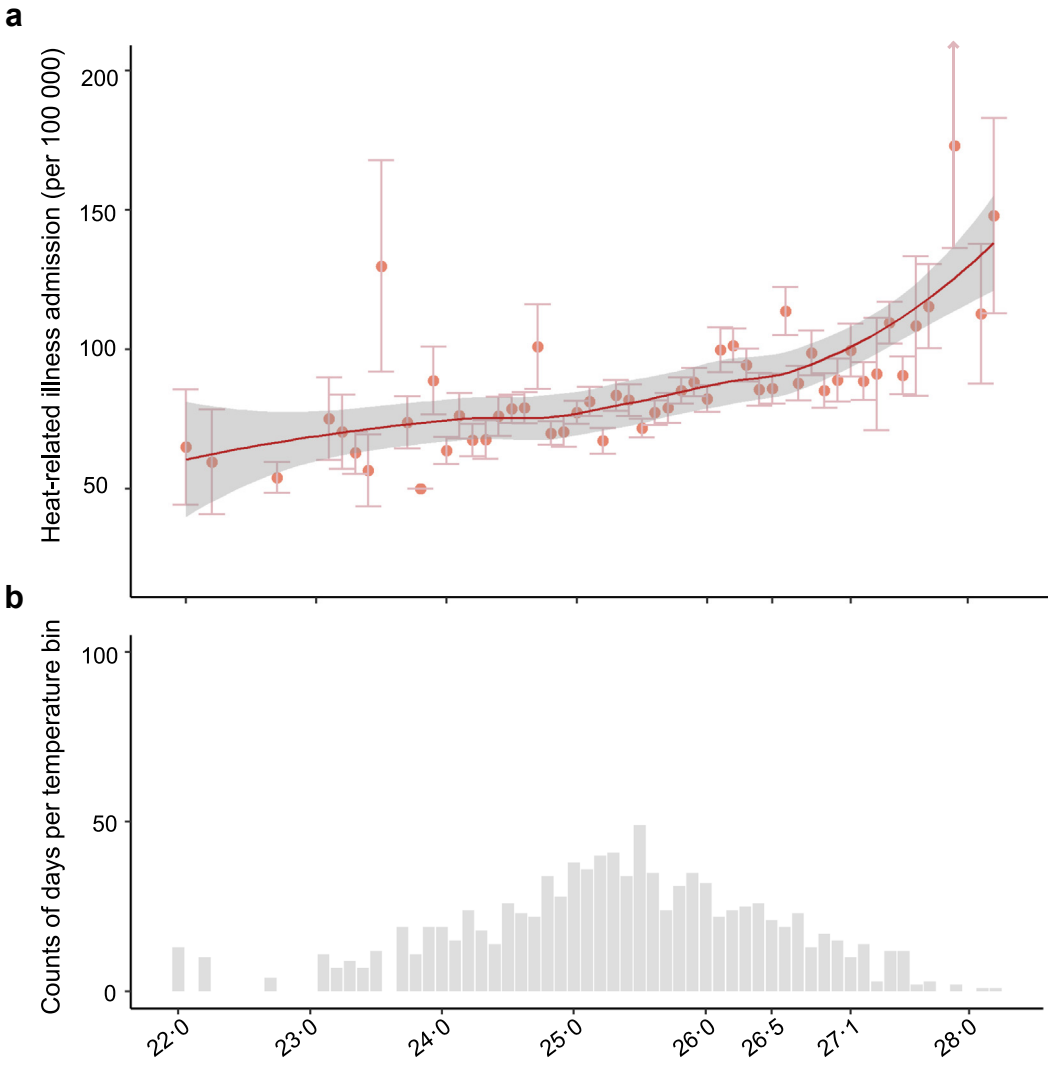


Fig. 3: **Subgroup analysis of risks of CVD in patients with heat-related illness relative to those without heat-related illness.** CVD, cardiovascular disease (ICD-10 code: I00–I09, I11, I12, I14, and I16–I99). The 'Hazard ratio (95% CI)' and 'p for Hazard ratio' indicate the CVD risk and p-value for each subgroup. The 'p for interaction' represents the p-value for the relative risk of a subgroup compared to the reference group. In the sex subgroup, for example, the hazard ratios for male and female heat-related illness patients were 2.217 (1.956–2.514) and 3.053 (2.436–3.825), respectively. The p for interaction is 0.001, indicating that female heat-related illness patients had a higher risk of developing CVD compared to male heat-related illness patients. The interaction effect calculation follows previous literature (BMJ 2003; 326:219), where the difference between two estimates has a standard error calculated as the square root of the sum of the squares of the individual standard errors. Subgroup analysis using time-varying Cox regression models, which adjusted for age, sex, education, occupation, and marital status, type of health insurance, hospital type, and establishment of electronic health records, the number of hospital admissions in the first year before the baseline, medical histories, and medication histories. Then, we calculated individuals' deviance residuals. Specially, we employed the Cox proportional hazards model using the coxph function from the survival package in R. The Efron method was used to handle ties, which adjusts the partial likelihood function to account for ties. Each dot represents a point estimate of the HR for subgroups. Error bars represent 95% CI. The horizontal dashed line represents the HR equal to 1, which is indicative of no effect. Each line connecting the error bars illustrates the range of HR values. ** means p values < 0.01, and p ≥ 0.001. *** means p values < 0.001.



c

Group	<= 25·0°C	25·0°C-26·5°C	26·5°C-27·1°C	> 27·1°C
Heat-related illness, n	911	2 431	825	712
All participants, n	1 979 235	3 562 213	910 785	680 129
Admission per 100 000	48·454	68·198	90·499	104·577
p value for trend		<0·001***		

***Fig. 4:* The association of heat-related illness admission with temperature and the number of days in each temperature bin during the summer of observation period.** (a) Linear fitting curve between temperature and daily heat-related illness admission. Red dots show the incidence of heat-related illness for each 0.1 °C temperature bin, and error bars denote 95% CIs. (b) The number of days in each temperature bin during the summer of observation period (January 2017 to July 2023). (c) Description and trend analysis of heat-related illness incidence across temperature intervals. Chi-squared trend test was used to examine the trend between heat-related illness admissions and temperature intervals.

heat-related illnesses, heatstroke had more severe disease progression, accompanied by more severe physiological and pathological damage. Similarly, in a military cohort study, patients with severe heat illness exhibited a 40% increased risk of all-cause mortality, with a particularly heightened risk of 70%–120% for

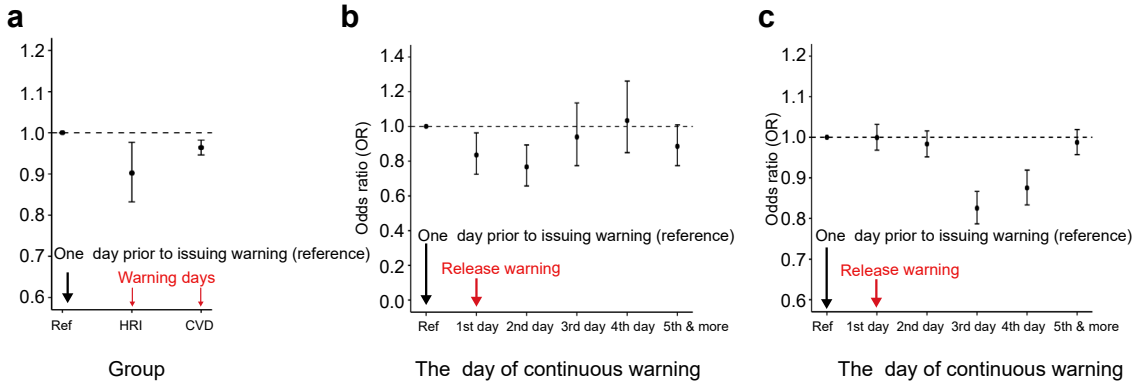


Fig. 5: **Preventive effects of heatwave warning**. (a) Odds ratio for heat-related illness and CVD risk after heatwave warning; Ref refers to the reference day, which is one day before a heatwave warning is issued. Each 1 °C interval of dew point temperature was used in stratified logistic regression to compare heat-related illness admission or subsequence CVD occurrences on days with heatwave warnings against the reference day. (b–c) Odds ratio for heat-related illness risk and CVD after heatwave warning group by the length of the warning. HRI, heat-related illness (ICD10: T67) CVD, cardiovascular disease (ICD-10 code: I00–I09, I11, I12, I14, and I16–I99). Ref also refers to the reference day, which is one day before a heatwave warning is issued. Heatwave warnings can last several days, categorized into the first day, second day, third day, fourth day, and fifth day or beyond. Notably, each of these days includes the presence of a warning. Each 1 °C interval of dew point temperature was used in stratified logistic regression to compare heat-related illness admission (b) or subsequence CVD occurrences (c) on each of these days against the reference day. All stratified logistic regression models were adjusted for age, sex, education, occupation, and marital status, type of health insurance, hospital type, and establishment of electronic health records, the number of hospital admissions in the first year before the baseline, medical histories, and medication histories. Each dot represents a point estimate of the OR. Error bars represent 95% CI. The horizontal dashed line represents the OR equal to 1, which is indicative of no effect. Each line connecting the error bars illustrates the range of OR values.

cardiovascular diseases, compared to controls.[6] Our large-sample, whole-population cohort study aligned with results of existing studies, altogether suggesting increased risk of subsequent CVD among people ever experienced heat-related illness.

The mechanisms underlying the cardiovascular complications of heat-related illness are not entirely known. Data in mouse model indicated that a single episode of exertional heatstroke led to long-term cardiovascular complications due to myocardial abnormalities and metabolic disorders.[30] The metabolic disorders were also found in a heatstroke mouse model and human experiment of heat exposure.[31,32] Moreover, unsuitable heat weather provoked thermoregulatory mechanisms, leading to a series of immediate physiological changes such as fluctuations in blood pressure and heart rate,[23] vasodilation, and sweating.[24] These changes triggered platelet activation and a prothrombotic state due to haemoconcentration, accompanied by immediate increases in circulating red cells, white blood cells, and platelets. These conditions could lead to end-organ failure and the production of heat-shock proteins,[25] as well as cumulations in inflammatory blood markers like C-reactive protein reactive oxygen species, and interleukin-6,[26,27] potentially posing long-term health risks.

Subgroup analysis showed that female was a vulnerable population of developing CVD after heat-related illness incidence. A significantly higher risk of ischemic heart disease was found in female diagnosed with heatstroke in a previous study.[33] Heatstroke mouse models suggested that female mice showed significantly more pronounced metabolic dysfunction and histological changes than male mice, potentially causing long-term cardiovascular complications.[30] We also found that younger heatstroke patients had a higher CVD risk than older heatstroke patients. This phenomenon could be partly explained that older individuals have different behaviours in terms of lifestyle or access to healthcare, which might help mitigate the impact of heatstroke on the risk of CVD. Furthermore, our findings suggested that the relative risk for developing CVD was higher among patients with more than five hospital admissions compared with patients who less than five times. Individuals who experienced more hospital admissions often had multiple underlying health conditions and generally poorer health, factors that heightened their risk of developing CVD.

Establishing heat early warning systems to mitigate the health impacts of heatwaves is an important primary prevention strategy worldwide. However, to our knowledge, few evidence existed to quantify the health benefits of heat early warning systems. Our study first suggested that heat early warning systems were associated with a reduction in heat-related illness hospital admissions (OR [95% CI] = 0.902 [0.832–0.977]) and subsequently a decreased future risk of CVD (OR [95% CI] = 0.964 [0.946–0.982]). This mitigating effect could potentially be explained by government interventions and individual adaptive behaviours. For example, the

Shenzhen government has implemented innovative measures such as the District Cooling System to combat increasing urban temperatures for climate change adaptation, thereby improving comfort in public areas and reducing heat-related health risks.[10] For individuals, they may change behaviours accordingly after heatwave warning. A questionnaire study revealed that over 80% of people chose to reduce outdoor activities and increase the use of indoor cooling devices.[34]

There are limitations in our study. Firstly, if an individual who was already enrolled in our cohort sought medical care outside of Shenzhen, we may not have collected their information. However, we excluded participants with a permanent residential address outside of Shenzhen and participants with time span of medical records less than 1 year, and chose the last inpatient or outpatient information as follow-up endpoint to control the selection bias.[15] Secondly, Shenzhen is an emerging, immigrant city with predominantly young population, with an average age of 31 years old in this study, leading to limit the generalizability of our study to populations in other cities. However, in our sensitive analysis, we found excluding age as a covariate yielded consistent results. Thirdly, further study requires population with precise individual-level heat exposure measurements, and broader geographical coverage. Fourth, the low proportion of the exposed group (patients with heat-related illnesses) led to wider confidence intervals in our causal inference 2SRI model. Moreover, our study may have left truncation bias, as those with outcomes in the first year after their initial medical record were excluded. However, after redefining cohort entry and running a sensitivity analysis, the association between heat-related illness and CVD remained consistent. Finally, this study is limited to a predominantly the Chinese Han population, and future research should include multi-ethnic and minority groups to enhance generalizability. Our study also has some strengths. This study was a large-scale, whole-population, and real-world cohort study, which covered nearly all individuals of over nine million with medical needs in a megacity. We included participants' medical history and medication use at baseline, which reduced bias compared to previous studies. Additionally, this study used instrumental variables to enhance the casual association between heat-related illness and subsequence CVD risk. Lastly, this study firstly quantified the health implications of heatwave warning policy, which suggested policymakers that significant public health benefits can be achieved through the timely implementation of relevant policies.

This investigation identified heat-related illness admission as significant CVD risk factors, offering new insights into CVD control. Firstly, prioritizing early intervention to address the risks associated with heatwave exposure, thereby utilizing primary preventive measures to reduce both heat exposure and heat-related illness incidence, ultimately aiming to lower CVD risks. Secondly, the study underscored the importance of monitoring individuals with a history of heat-related illness, recommending targeted CVD screenings as a secondary preventive measure.

In conclusion, our study suggested that heat-related illness significantly increased the long-term risk of CVD. By utilizing dew point temperature as an instrumental variable, our research suggested the causal relationship between heat-related illness and CVD. Furthermore, we found that heatwave warnings mitigated both heat-related illness and subsequent CVD risks. This study not only underscores the importance of prioritizing early intervention to reduce heat-related illness, but also provides actionable recommendations for CVD prevention and management.

Contributors

Qi Huang: Conceptualization, Methodology, Data curation, Formal analysis, Visualization, Validation, Writing-original draft, and Writing review & editing. Limei Ke: Conceptualization, Methodology, Visualization, Validation, Writing-original draft, and Writing—review & editing. Linfeng Liu: Conceptualization, Methodology, Validation, Data curation, Writing–review & editing. Yuyang Liu: Resources, Data curation, Project administration, and Software. Yanjun Li: Validation, Data curation, Writing—review & editing. Guoqing Feng: Methodology, and Writing—review & editing. Bo Yin: Methodology, and Writing—review & editing. Wenxin Xiang: Methodology, and Writing—review & editing. Jiarun Li: Investigation, and Writing—review & editing. Keyi Lv: Formal Analysis, and Writing—review & editing. Miao Wang: Project administration. Qiannan Tian: Data curation, and Project administration. Liqun Wu: Data curation, Project administration, and Writing-review & editing. Xiaofeng He: Data curation, and Project administration Wannian Liang: Resources, Conceptualization, Methodology, and Project administration. Huatang Zeng: Resources, Supervision, Conceptualization, Methodology, Project administration, and Writing-review & editing. Jiming Zhu: Resources, Conceptualization, Project administration, and Writing-review & editing. Kuiying Gu: Resources, Conceptualization, Supervision, Project administration, and Validation. Qian Di: Resources, Conceptualization, Methodology, Conceptualization, Supervision, Project administration, Validation, and Writing-review & editing. Qi Huang, Limei Ke, and Linfeng Liu verified the data. Yuyang Liu, Xiaofeng He, Liqun Wu and Huatang Zeng accessed the raw data. Qi Huang and Qian Di had the final responsibility for the decision to submit the article for publication.

Data sharing statement

We welcome collaboration from over the world to maximize the usage of this Shenzhen population-based multi-disease cohorts. Cohort data are inaccessible for public download due to data safety and privacy concerns. However, researchers interested in our cohorts can submit research proposals to Wannian Liang and Qian Di.

Declaration of interests

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

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2025.101468.

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