Heat exposure and cardiovascular health outcomes: a systematic review and meta-analysis

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Summary

Background Heat exposure is an important but underappreciated risk factor contributing to cardiovascular disease. Warming temperatures might therefore pose substantial challenges to population health, especially in a rapidly aging population. To address a potential increase in the burden of cardiovascular disease, a better understanding of the effects of ambient heat on different types of cardiovascular disease and factors contributing to vulnerability is required, especially in the context of climate change. This study reviews the current epidemiological evidence linking heat exposures (both high temperatures and heatwaves) with cardiovascular disease outcomes, including mortality and morbidity.

Methods In this systematic review and meta-analysis, we searched PubMed, Embase, and Scopus for literature published between Jan 1, 1990, and March 10, 2022, and evaluated the quality of the evidence following the Navigation Guide Criteria. We included original research on independent study populations in which the exposure metric was high temperatures or heatwaves, and observational studies using ecological time series, case crossover, or case series study designs comparing risks over different exposures or time periods. Reviews, commentaries, grey literature, and studies that examined only seasonal effects without explicitly considering temperature were excluded. The risk estimates were derived from included articles and if insufficient data were available we contacted the authors to provide clarification. We did a random-effects meta-analysis to pool the relative risk (RR) of the association between high temperatures and heatwaves and cardiovascular disease outcomes. The study protocol was registered with PROSPERO (CRD42021232601).

Findings In total, 7360 results were returned from our search of which we included 282 articles in the systematic review, and of which 266 were eligible for the meta-analysis. There was substantial heterogeneity for both mortality (high temperatures: I^2=93·6%, p<0·0001; heatwaves: I^2=98·9%, p<0·0001) and morbidity (high temperatures: I^2=98·8%, p<0·0001; heatwaves: I^2=83·5%, p<0·0001). Despite the heterogeneity in environmental conditions and population dynamics among the reviewed studies, results showed that a 1°C increase in temperature was positively associated with cardiovascular disease-related mortality across all considered diagnoses. The overall risk of cardiovascular disease-related mortality increased by 2·1% (RR 1·021 [95%CI 1·020–1·023]), with the highest specific disease risk being for stroke and coronary heart disease. A 1°C temperature rise was also associated with a significant increase in morbidity due to arrhythmias and cardiac arrest and coronary heart disease. Our findings suggest heat exposure leads to elevated risk of morbidity and mortality for women, people 65 years and older, individuals living in tropical climates, and those in countries of lower-middle income. Heatwaves were also significantly associated with a 11·7% increase in risk of mortality (RR 1·117 [95% CI 1·093–1·141]), and increasing heatwave intensity with an increasing risk (RR 1·067 [95% CI 1·056–1·078] for low intensity, 1·088 [1·058–1·119] for middle intensity, and 1·189 [1·109–1·269] for high intensity settings).

Interpretation This review strengthens the evidence on the increase in cardiovascular disease risk due to ambient heat exposures in different climate zones. The widespread prevalence of exposure to hot temperatures, in conjunction with an increase in the proportion of older people in the population, might result in a rise in poor cardiovascular disease health outcomes associated with a warming climate. Evidence-based prevention measures are needed to attenuate peaks in cardiovascular events during hot spells, thereby lowering the worldwide total heat-related burden of cardiovascular disease-related morbidity and death.

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Introduction

Extreme heat affects human health, and rising temperatures will probably have adverse consequences as the climate changes.[1] High temperature, among the well-documented effects of climate change on human health, has been included as a risk factor in the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2019, accounting for 11·7 million years of healthy

Research in context

Evidence before this study

The link between ambient heat exposure and adverse cardiovascular health outcomes is well documented. Heat stress can lead to severe health effects due to acute exacerbation of existing illnesses. Heat exposure also places an increased strain on the heart and can lead to heat exhaustion or heat stroke if the internal body temperature is not adequately regulated by the cardiovascular system. Previous epidemiological studies have shown consistent findings on the effects of heat exposure on cardiovascular mortality, whereas results regarding associations between heat exposure and cardiovascular morbidity vary between studies and locations. Despite the importance of geographical variations in climate in contextualising the risk associated with temperature-related mortality and morbidity, the magnitude of the risk of cardiovascular disease associated with heat exposure has not been systematically analysed across different global climate zones. To fill this knowledge gap, we present a systematic review and meta-analysis quantifying the effects of ambient heat exposure on cardiovascular disease mortality and morbidity.

Added value of this study

To our knowledge, the present review is the first to investigate the cardiovascular disease health effects of ambient heat exposure across different Köppen-Geiger climate zones. The meta-analysis of 266 studies that met our inclusion criteria revealed that a 1°C rise in temperature was associated with a 2·1% increase in cardiovascular disease-related mortality and 0·5% increase in cardiovascular disease-related morbidity. A consistent positive association was found across all considered cardiovascular disease diagnoses in mortality, with the strongest effects shown due to stroke (3·8%) and coronary heart diseases (2·8%). We found that high temperatures increased the risk of morbidity due to arrhythmias and cardiac arrest (1·6%), and that the greatest risk of morbidity was out-of-hospital cardiac arrest (2·1%). Heatwaves were also associated with negative cardiovascular disease health outcomes. The risk of heatwaves on cardiovascular disease-related mortality increased significantly by 11·7%, with an increased effect as heatwave intensity increased. Additionally, we found higher high temperature risk estimates among individuals living in tropical climates than in other climate zones examined, suggesting that the risk is not uniformly distributed in different climatic regions and is associated with local conditions

Implications of all the available evidence

Despite the heterogeneity in environmental conditions and population dynamics among the reviewed studies, the evidence to date supports a strong link between elevated ambient temperature and cardiovascular disease health outcomes. Findings indicate that underlying regional climate conditions need to be accounted for when assessing the risk of heat-related cardiovascular disease-related mortality and morbidity, as well as characteristics of the population and disease subgroups. Increasing temperatures in conjunction with an increase in the proportion of older people in the population might result in a rise in poor cardiovascular health outcomes associated with climate change. Our findings suggest the need for evidence-based prevention measures that could attenuate peaks in cardiovascular events during hot spells and decrease the heat-related burden of cardiovascular disease-related disability and death worldwide.

life (disability-adjusted life years [DALYs]) lost globally.[2] Heat exposure has been implicated as an important risk factor contributing to cardiovascular disease and associated mortality.[3–6] Internationally, cardiovascular disease is the leading cause of disease burden, accounting for one-third of all deaths, and is a major contributor to disability.[7] Globally, there has been a steady increase in DALYs due to cardiovascular disease since 1990, and years lived with disability (YLDs) doubled from 17·7 million in 1990 to 34·4 million in 2019.[7]

Unusually high temperatures can exacerbate existing health conditions, and cause illness and death.[8] Although heat exposure can be a risk to all, older people and those with impaired cardiovascular health are particularly at risk of mortality and morbidity associated with heat.[5,8] It is predicted that, because the background prevalence of cardiovascular disease will substantially increase due to population growth and ageing, so will the probable adverse effects associated with ambient heat exposure, especially in low-income and middle-income countries (LMICs).[7] Effects will probably vary according to population, society, and lifestyle characteristics, and factors relating to the extent of human physiological adaptation. We therefore need a better understanding of the association between heat and cardiovascular disease outcomes and variations in effects according to local environments and climates across different climate zones.[4,9] Taken together, these findings emphasise the need to study the effects of ambient heat exposure on cardiovascular health in different climate zones and geographical regions.

Previous reviews have explored the risk of heat-associated cardiovascular disease morbidity[4–6,10–12] and mortality,[3,5,6,11,12] and shown the probable non-linear association of the effects. Consistent findings have been reported on the positive associations between heat exposure and cardiovascular disease mortality. For example, a meta-analysis of 25 studies[3] reported that elevated temperatures were associated with a 1·3% increase in cardiovascular disease mortality. Another meta-analysis[5] found evidence of an association between temperature rise and cardiovascular disease-related mortality among older people (older than 65 years), although assessments of the risk of bias (RoB),

and of the strength of included evidence in the reviewed studies were poor. More recently, a 2019 meta-analysis summarising the evidence of the effect of heatwaves on cardiovascular disease found a significant 15% increase in cardiovascular disease mortality.[6] By contrast, the association between heat and cardiovascular disease morbidity varies between studies and locations. For example, no association between high temperatures and cardiovascular disease morbidity was found in one meta-analysis done using data from a small number of studies,[10] but another found evidence of a positive association among people older than 65 years.[5] The 2019 meta-analysis,[6] however, found no association with cardiovascular disease morbidity during heatwaves and the authors suggested the need for more research to examine how heatwave intensity affects cardiovascular disease risk. Additionally, despite the possible effects of climate variability on the associations being discussed in most previous studies, no study has assessed the risk of heat-related cardiovascular disease considering differences in climate zones.

We therefore systematically review and quantitatively synthesise the available epidemiological evidence concerning the effects of heat exposure (both high temperatures and heatwaves) on cardiovascular disease outcomes with an up-to-date literature search, and assess the quality and strength of the evidence. Further, we examine population susceptibility to cardiovascular disease outcomes resulting from heat exposure and do an extended meta-analysis considering the possible geographical variability classified by Köppen-Geiger climate zones.[13]

Methods

Search strategy and selection criteria

In this systematic review and meta-analysis, we searched PubMed, Embase, and Scopus databases using key terms "cardiovascular disease", "stroke", "heart disease", or "vascular disease" for health outcomes, paired with "climate change", "weather", "temperature", or "heat" for exposures. The complete search strategy used for each database were initially developed by JL and BMV, and was finalised upon consultation with the university librarian (appendix p 5). Peer-reviewed studies published in English between Jan 1, 1990, and May 20, 2021, were identified. An update of the search was done on March 10, 2022 to include studies published shortly before this Review was finalised. We also screened reference lists of included articles and relevant reviews for any remaining studies. Retrieved articles were imported into Endnote (version X8.2).[14]

Specifically, we included studies that explored heat effects on cardiovascular disease outcomes and that met the following criteria: original articles with an independent study population; high temperatures or heatwaves as the exposure metric; and observational studies using ecological time series, case crossover, or case series study designs comparing risks over different exposures or time periods. Reviews, commentaries, grey literature, and studies that examined only seasonal effects without explicitly considering temperature were excluded. Our Population-Exposure-Comparators-Outcomes (PECO) framework[15] is described in the panel.

Panel: **Population-Exposure-Comparators-Outcomes framework**

Population
- epidemiological studies assessing cardiovascular disease risk among the general population

Exposure
- ambient heat exposures (high temperatures and heatwaves) as defined by the original studies

Comparators
- a comparable population with the same heat exposures, or the same population at a time in which it was not exposed to the relevant ambient heat

Outcomes
- both mortality and morbidity (hospital admissions, emergency department visits, and ambulance call-outs) due to cardiovascular disease (ICD-10 I00-I99)

ICD-10=International Classification of Diseases tenth edition.

Two investigators (JL and BMV) did double-blind independent initial screenings of articles (title, abstract, and full-text) using Rayyan QCRI.[16] Information on the selected studies was entered into a customised spreadsheet (including author, year, location, study period, analytical methods, exposure measurements, outcomes, confounding factors, and findings), and cross-checked by JL and BMV. We analysed summary estimates from each study. The risk estimates were derived from texts, tables, supplemental materials, and graphical data using WebPlotDigitizer (version 4.5).[17] If insufficient information was included in the articles, authors were contacted by email to provide clarification.

We followed the Navigation Guide framework specifically for systematic reviews of observational studies in environmental health[18] to assess the evidence. Appraisal involved three steps: RoB assessment in each study, assessment of the quality of evidence across studies, and evaluating the strength of evidence across studies. Each stage of appraisal was independently done by JL and BMV. Each component rating was discussed to reach an agreement, with differences reconciled by consulting with AH and PB. A detailed description of the criteria for the assessments is provided in the appendix (pp 6–9). The study protocol was registered with PROSPERO (CRD42021232601)[19] and follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (appendix pp 3–4).[20]

See Online for appendix

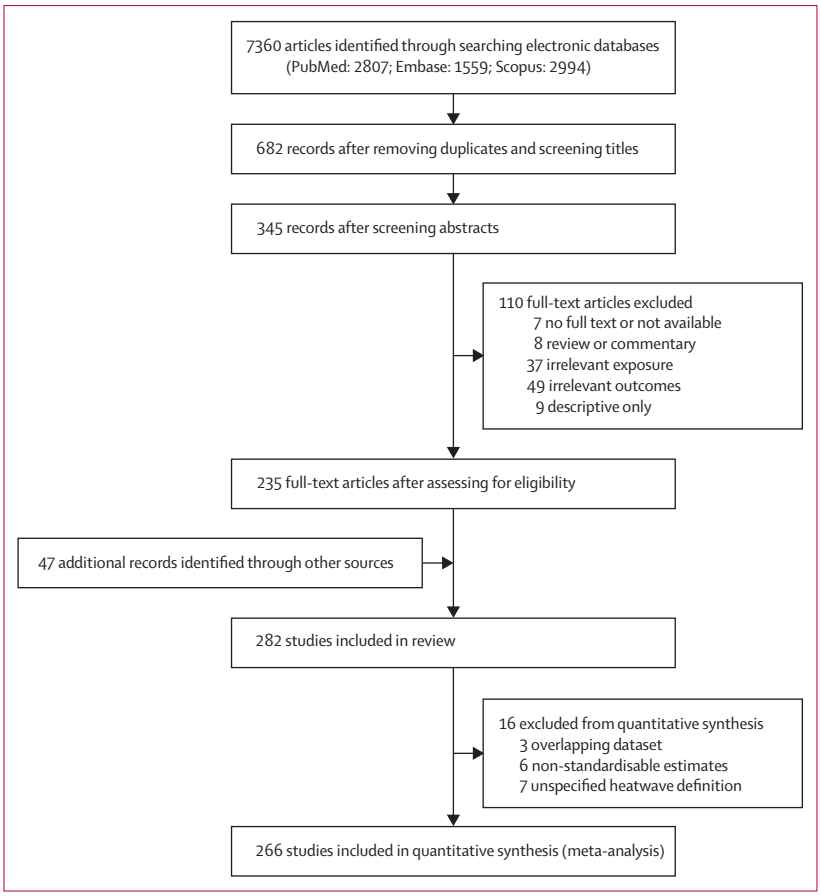

Figure 1: **Flowchart of assessment of eligible studies**

Data analysis

We used random-effects meta-analysis using the DerSimonian-Laird[21] method with studies that provided relative risk (RR) estimates, or effect estimates that could be converted to RR (eg, percentage change or excess risk, incidence rate ratio, and odds ratio). We converted high temperature exposure effect estimates to a standardised increment (1°C) of high temperature, assuming a log-linear exposure-response relationship (ie, a constant RR per unit increase in temperature above the defined reference temperature, which was reported in each study).[22] Given the strong correlation between temperature metrics and their similar predictive ability, we pooled the estimates regardless of the exposure metrics.[23] Due to varying heatwave definitions used in studies, we categorised heatwave definitions into three groups based on intensity as low intensity ($heatwave_{low}$; 90th to 93rd percentile of a specified temperature threshold), middle intensity (HW_{middle}; 94th to 96th percentile), and high intensity (HW_{high}, 97th to 99th percentile).[24] If studies reported multiple effect estimates for the same heatwave-intensity group, percentile-based RRs, different groups, or outcomes (ie, emergency department visits, hospital admissions, and ambulance call-outs), we did a fixed-effect meta-analysis to yield one overall estimate.[22] If studies reported multiple lag RRs, we selected the lag associated with the maximum risk to do the meta-analysis.[25] We computed the pooled RRs using both country-specific and city-specific or region-specific estimates as applicable. Subgroup analyses were done where possible to investigate population vulnerability stratified by age, sex, and national income level (classified by the World Bank data).[26] To enable investigation of the possible effects of climate variability on heat-related cardiovascular risks, we added coordinates to each city or region-specific estimate using Google maps to determine the climate zone location following the Köppen-Geiger climate zones (a classification system that divides climates into five main groups: A [tropical], B [dry], C [temperate], D [continental], and E [polar]).[13]

Heterogeneity was assessed using Cochrane *Q* (in which $p<0·10$ was deemed significant), and categorised as low (≤25%), moderate (26–74%), or high (≥75%) using I^2 statistics.[27] Additionally, we evaluated the consistency of pooled effect sizes using an 80% prediction interval (PI)[28] that provides an estimate of the 80% interval, within which the true RR for a future study will lie. Heterogeneity was indicated when the 80% PI included the null effect and was twice the 95% CI.[28] Potential publication bias was assessed by Egger's test, funnel plots,[29] and the trim-and-fill method.[30] Further, meta-regressions to explain between-study heterogeneity were done considering latitude, longitude, annual mean temperature, national income level, and climate zones.[22]

Sensitivity analyses were done by separating studies by temperature metrics, study design (time series or case crossover), RoB rating, seasonality (warm season or whole year), lag effects, and air pollution adjustment, modelling approach (non-linear or linear) specifically for high temperature exposure, and by durations for heatwaves. We did leave-one-out analysis to examine the influence of individual estimates on the pooled RRs. Statistical analyses were done using R statistical software (version 2.4–0) and Stata (version 15.0).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Database searches yielded 7360 studies and 47 additional articles were identified through reference lists or the updated search. After removing duplicates and screening titles, we assessed 682 abstracts and reviewed 345 relevant studies for full-text eligibility assessment. Ultimately, we identified 282 studies that fulfilled the inclusion criteria for the systematic review (figure 1). Of these, 203 (72%) studies assessed high temperatures effects, 72 (26%) studies examined heatwaves effects, and seven (2%) assessed both high temperatures and heatwaves (appendix pp 10–21).

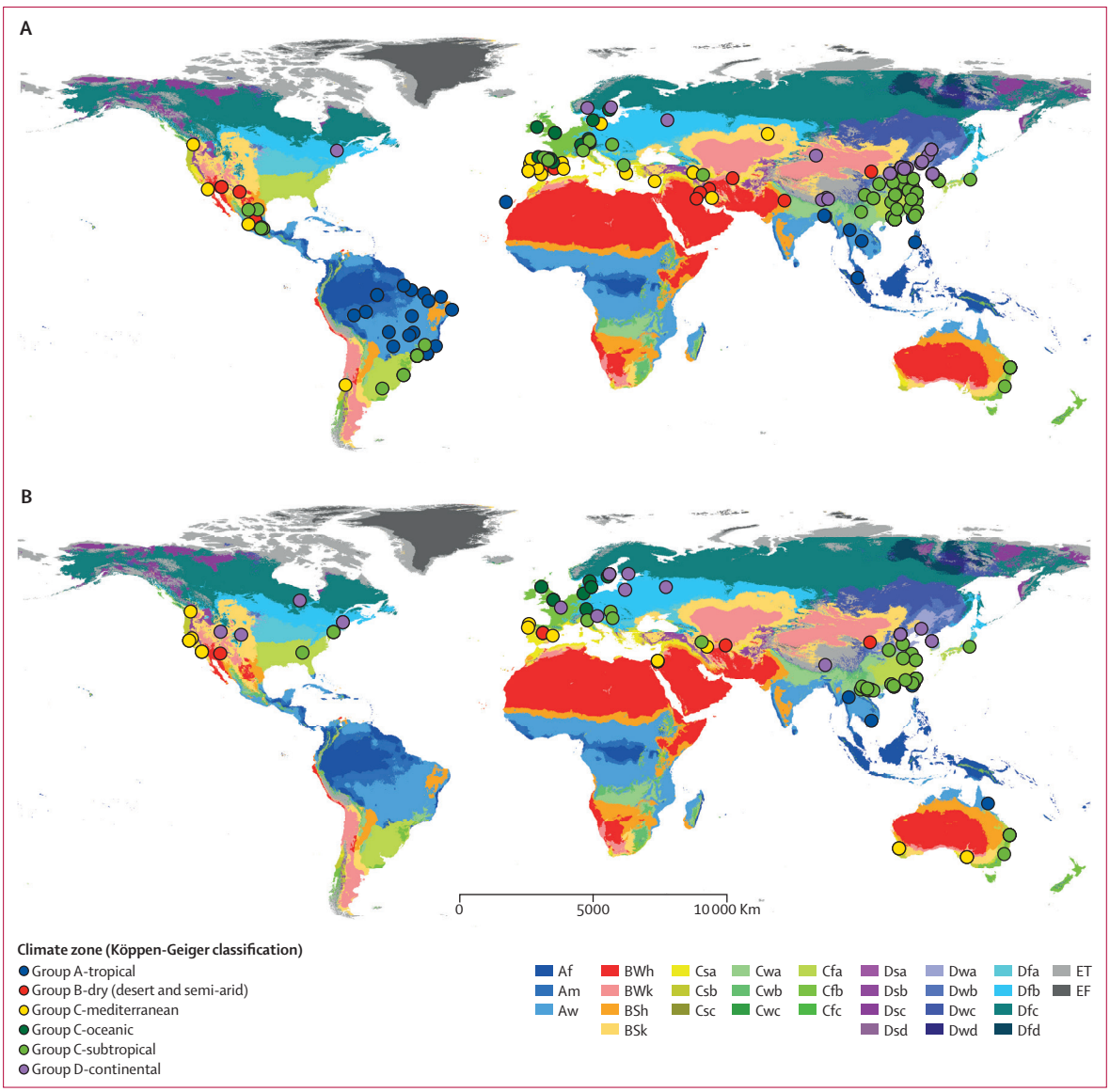

Figure 2: **Geographical distribution of the 311 city-specific or region-specific cardiovascular disease mortality (A) and cardiovascular disease morbidity (B) estimates included in the meta-analysis by climate zone**

Af=tropical rainforest climate. Am=tropical monsoon climate. Aw=tropical savanna climate. BWh=hot desert climate. BWk=cold desert climate. BSh=hot semi-arid climate. BSk=cold semi-arid climate. Csa=hot-summer Mediterranean climate. Csb=warm-summer Mediterranean climate. Csc=cold-summer Mediterranean climate. Cwa=monsoon-influenced humid subtropical climate. Cwb=subtropical highland climate or Monsoon-influenced temperate oceanic climate. Cwc=cold subtropical highland climate or Monsoon-influenced subpolar oceanic climate. Cfa=humid subtropical climate. Cfb=temperate oceanic climate. Cfc=subpolar oceanic climate. Dsa=Mediterranean-influenced hot-summer humid continental climate. Dsb=Mediterranean-influenced warm-summer humid continental climate. Dsc=Mediterranean-influenced subarctic climate. Dsd=Mediterranean-influenced extremely cold subarctic climate. Dwa=Monsoon-influenced hot-summer humid continental climate. Dwb=Monsoon-influenced warm-summer humid continental climate. Dwc=Monsoon-influenced subarctic climate. Dwd=Monsoon-influenced extremely cold subarctic climate. Dfa=hot-summer humid continental climate. Dfb=warm-summer humid continental climate. Dfc=subarctic climate. Dfd=extremely cold subarctic climate. ET=tundra climate. EF=ice cap climate.

For the meta-analysis, 16 (6%) studies were excluded: three due to overlapping datasets, six due to only providing a percentile temperature threshold, and seven due to using unspecified heatwave definitions (appendix pp 28–45). The remaining 266 studies were deemed suitable for quantitative synthesis. These included 142 studies in which the health outcome was cardiovascular mortality (103 high temperature studies, 37 heatwave studies, and two high temperature and heatwave studies), 122 reporting morbidity (91 high temperature studies, 26 heatwave studies, and five high temperature and heatwave studies), and 12 studies reporting both mortality and morbidity (five high temperature studies and seven heatwaves studies). The

	k	Relative risk (95% CIs)	80% prediction interval	I^2, p value	Egger's p value
Mortality*					
Cardiovascular disease (I00-I99)	151	1·021 (1·020–1·023)	(1·012–1·030)	93·6%, p<0·0001	p<0·0001
Hypertensive diseases (I10-I15)	6	1·032 (0·998–1·066)	(0·969–1·094)	79·4%, p<0·0001	p=0·52
Coronary heart diseases (I20-I25)	30	1·028 (1·020–1·036)	(1·001–1·054)	90·4%, p<0·0001	p=0·40
Acute coronary syndrome (I21-I22)	8	1·035 (1·017–1·052)	(1·000–1·069)	75·6%, p<0·0001	p=0·69
Heart failure (I50)	6	1·028 (1·014–1·041)	(1·005–1·050)	37·9%, p=0·15	p=0·67
Stroke (I60-I69)	34	1·038 (1·031–1·045)	(1·016–1·060)	78·7%, p<0·0001	p=0·02
Others, including cardiac arrest	4	1·021 (1·003–1·040)	(0·984–1·059)	78·1%, p=0·003	p=0·78
Sex					
Mal	19	1·016 (1·009–1·022)	(1·000–1·032)	91·8%, p<0·0001	p=0·53
Female	20	1·021 (1·012–1·030)	(0·998–1·044)	94·2%, p<0·0001	p=0·45
Age (years)					
0–64	24	1·009 (1·004–1·014)	(0·997–1·022)	85·9%, p<0·0001	p=0·51
≥65	46	1·017 (1·016–1·019)	(1·013–1·021)	94·4%, p<0·0001	p<0·0001
Climate zone (Köppen classification)					
Group A (tropical)	27	1·041 (1·030–1·052)	(1·014–1·067)	78·0%, p<0·0001	p<0·0001
Group B (dry)	15	1·029 (1·015–1·043)	(0·995–1·062)	89·7%, p<0·0001	p=0·03
Group C (mediterranean)	19	1·032 (1·021–1·043)	(1·001–1·062)	95·6%, p<0·0001	p=0·54
Group C (oceanic)	15	1·018 (1·011–1·024)	(1·002–1·033)	91·5%, p<0·0001	p=0·27
Group C (subtropical)	95	1·019 (1·017–1·021)	(1·011–1·027)	90·3%, p<0·0001	p<0·0001
Group D (continental)	41	1·031 (1·025–1·037)	(1·008–1·054)	92·3%, p<0·0001	p=0·002
National income level					
High income	64	1·020 (1·018–1·022)	(1·012–1·028)	96·0%,p<0·0001	p=0·001
Upper-middle income	83	1·026 (1·022–1·029)	(1·010–1·041)	88·9%, p<0·0001	p<0·0001
Lower-middle income	4	1·112 (1·040–1·183)	(0·956–1·267)	73·6%, p=0·01	p=0·02

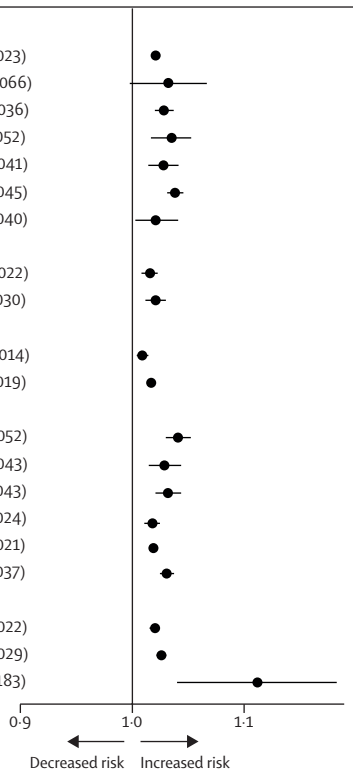

Figure 3: **Findings from a random-effects meta-analysis showing change in RR and 95% CIs for cardiovascular disease mortality in different groups, corresponding to a change per 1°C increase in temperature**
RR=relative risk. k=the number of effect estimates. *Codes relate to International Classification of Diseases tenth edition.

study locations varied and included 311 city-specific or region-specific estimates (figure 2). These study locations fell into four Köppen-Geiger climate zones: tropical, dry, temperate (ie, Mediterranean, oceanic, and subtropical), and continental.[31]

Among the 266 studies included in the meta-analysis, 201 examined the effects of high temperatures on cardiovascular disease. Analysis of pooled estimates showed that every 1°C increase in temperature was significantly associated with a 2·1% increase in cardiovascular disease-related mortality (RR 1·021 [95% CI 1·020–1·023]; figure 3) and a 0·5% increase in morbidity (1·005 [1·003–1·008]; figure 4). Cause-specific analyses showed positive associations between high temperatures and cardiovascular disease-related mortality across all groups considered, apart from hypertensive diseases (figure 3). Higher mortality risks were attributable to stroke (RR 1·038 [95% CI 1·031–1·045]), coronary heart diseases (1·028 [1·020–1·036]), and heart failure (1·028 [1·014–1·041]). For morbidity, we found significant protective effect for hypertensive diseases (0·949 [95% CI 0·928–0·970]), and the greatest positive effect was found for out-of-hospital cardiac arrest (1·021 [1·010–1·032]; figure 4).

A greater risk of cardiovascular disease-related mortality was observed in those 65 years or older than in those younger than 65 years (p=0·03). Additionally, people living in tropical climate zones were more vulnerable to cardiovascular disease-related mortality due to high temperatures than those in other climate zones examined, albeit with non-significant differences, and those living in LMICs were more vulnerable to cardiovascular disease-related mortality due to high temperatures than those living in high-income and upper-middle-income countries; however, caution should be taken when interpreting the result due to the small number of effect estimates included (n=4; appendix p 57).

The 79 reviewed heatwave studies included varying temperature indices (eg, maximum, minimum, and mean temperature), heatwave intensities (absolute or relative threshold temperature), and durations (ranging from 1 to 20 days) to define a heatwave (appendix pp 28–45). Risk estimates from 73 studies were used to pool the overall effects of heatwave into low-intensity, middle-intensity, and high-intensity groups. The overall pooled RR of heatwaves on cardiovascular disease-related mortality was 1·117 (95% CI 1·093–1·141; table 1). We

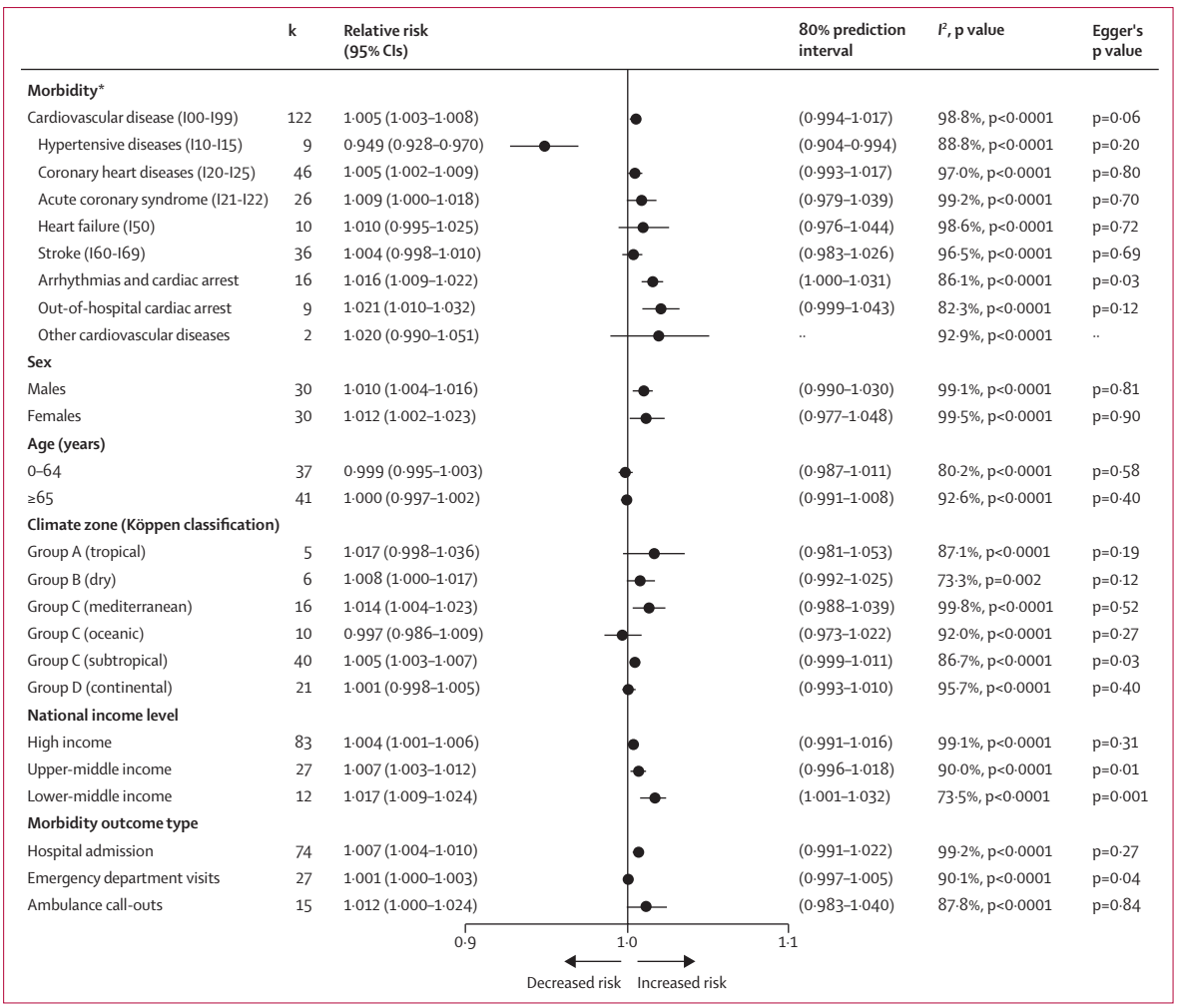

Figure 4: **Findings from a random-effects meta-analysis showing change in RR and 95% CIs for cardiovascular disease morbidity in different groups, corresponding to a change per 1°C increase in temperature**

RR=relative risk. k=the number of effect estimates. *Codes relate to International Classification of Diseases tenth edition.

found that the increase in cardiovascular disease-related mortality was associated with the level of heatwave intensity: as the heatwave intensity increased the pooled risk effects also increased. Compared with mortality, a lower and non-significant overall pooled RR was observed for the association between heatwaves and cardiovascular disease-related morbidity (1·008 [95% CI 0·998–1·017]; table 1; forest plots are shown in the appendix [pp 47–48]). In subgroup analyses, heatwaves were associated with an increased risk of mortality in both age groups (0–64 years: RR 1·057 [95% CI 1·015–1·099]; ≥65 years: RR 1·147 [1·061–1·232]), and mortality increased with heatwave intensity in people 65 years and older (low intensity RR 1·094 [95% CI 1·047–1·141]; middle intensity RR 1·106 [1·035–1·177]; and high intensity RR 1·233 [1·071–1·394]). Morbidity in those 65 years and older also increased as heatwave intensity increased (low intensity RR 0·975 [95% CI 0·920–1·030]; middle intensity RR 1·029

	k	RR (95% eCIs)	80% PI	I^2, p value
Mortality				
$Heatwave_{overall}$	60	1·117 (1·093-1·141)	(1·002-1·233)	98·9%, p<0·0001
$Heatwave_{low}$	21	1·067 (1·056-1·078)	(1·040-1·095)	90·2%, p<0·0001
$Heatwave_{middle}$	18	1·088 (1·058-1·119)	(1·008-1·169)	82·6%, p<0·0001
$Heatwave_{high}$	21	1·189 (1·109-1·269)	(0·937-1·441)	99·3%, p<0·0001
Morbidity				
$Heatwave_{overall}$	40	1·008 (0·998-1·017)	(0·980-1·035)	83·5%, p<0·0001
$Heatwave_{low}$	8	0·985 (0·971-1·000)	(0·962-1·010)	61·6%, p=0·01
$Heatwave_{middle}$	16	1·016 (0·993-1·040)	(0·962-1·071)	83·7%, p<0·0001
$Heatwave_{high}$	16	1·014 (0·998-1·030)	(0·983-1·045)	78·3%, p<0·0001

k=the number of effect estimates. RR=relative risk. eCI=empirical confidence interval. PI=prediction interval.

Table 1: **Random-effects meta-analysis estimates of the RR and 95% eCIs and heterogeneity for the risk of cardiovascular-associated morbidity and mortality by heatwave intensity**

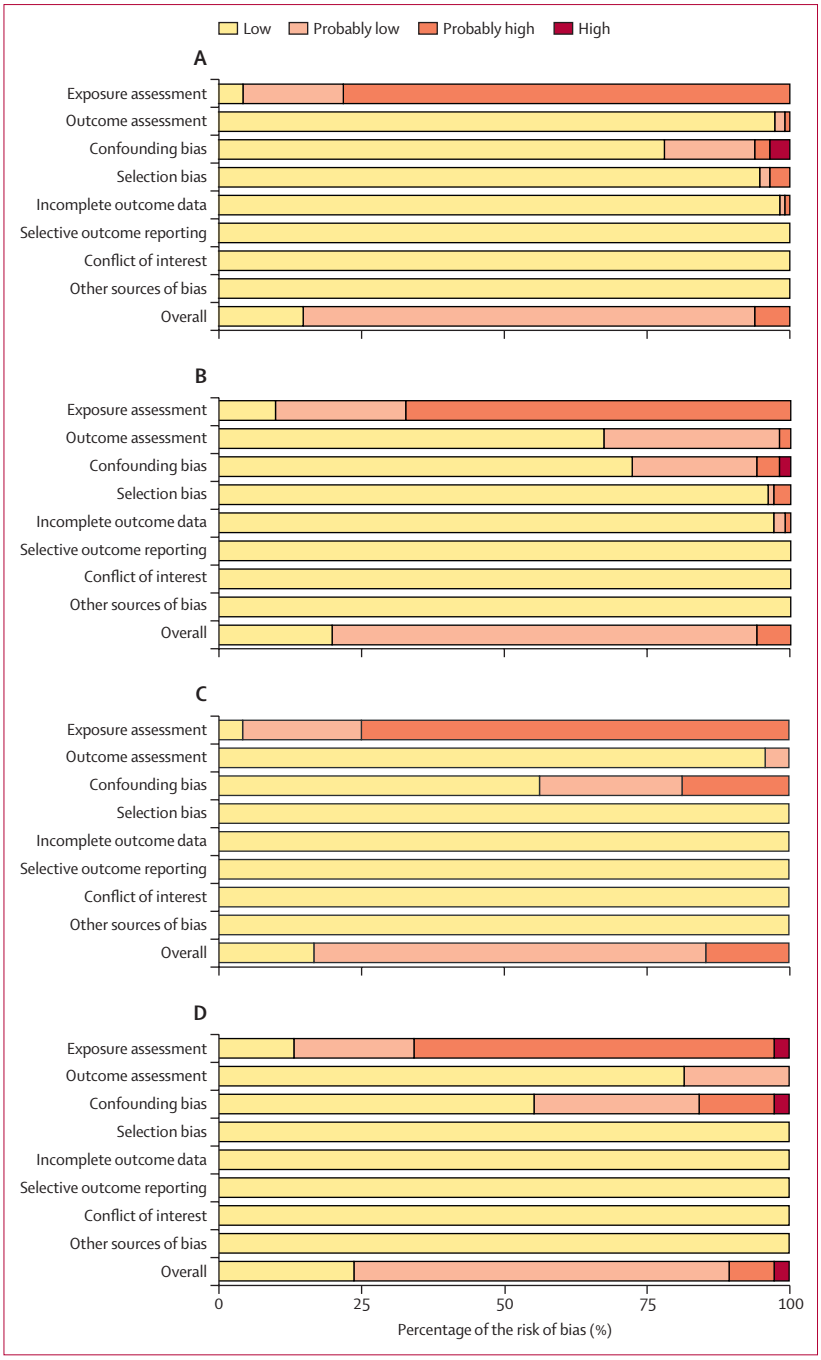

Figure 5: **Weighted bar plots indicating the percentage of the risk of bias judgements within each bias domain across reviewed studies of high temperatures and cardiovascular disease mortality (A), high temperatures and cardiovascular disease morbidity (B), heatwaves and cardiovascular mortality (C), and heatwaves and cardiovascular morbidity (D)**

	High temperature studies		Heatwave studies	
	Mortality	Morbidity	Mortality	Morbidity
Initial rating	Moderate	Moderate	Moderate	Moderate
Downgrade factors				
Risk of bias across studies	0	0	0	0
Indirectness	0	0	0	0
Inconsistency	0	–1	0	–1
Imprecision	0	0	0	0
Publication bias	0	0	0	0
Upgrade factors				
Large magnitude of effect	0	0	0	0
Dose response	+1	+1	+1	+1
Confounding minimises effect	0	0	0	0
Resulting rating	High	Moderate	High	Moderate

0=no downgrade or upgrade. –1=downgrade. +1=upgrade. Detailed information is presented in the appendix pp (52–54).

Table 2: **Rating of quality and strength of the body of evidence of influence of high temperature and heatwaves on cardiovascular mortality and morbidity**

[0·980–1·078]; and high intensity RR 1·126 [0·997–1·255]; appendix pp 28–45).

The details of the RoB assessment criteria, and individual studies assessed for each domain, are in the appendix (pp 62–199); in summary, we assessed the overall RoB of individual studies according to the key components of exposure, outcome, and confounding bias. Of the 282 included studies, 258 (91%) were rated with low risk or probably low risk of bias. 23 (8%) studies were rated as probably high risk of bias, and one study (<1%) was rated as high risk of overall bias (figure 5; appendix pp 49–51).

The rationale of the assessment of the quality and strength of evidence is presented in the appendix (pp 52–54). In brief, we assigned a priori an initial rating of moderate quality for evidence derived from observational studies, according to recommendations elsewhere.[32] The overall quality of evidence for studies on effects of heat exposures on cardiovascular disease-related mortality was not downgraded for any factors, even though heterogeneity was indicated by I^2 (high temperatures: I^2=93·6%, p<0·0001; heatwaves: I^2=98·9%, p<0·0001), and studies on cardiovascular disease-related morbidity were downgraded for inconsistency due to the significant heterogeneity indicated by both I^2 (high temperatures: I^2=98·8%, p<0·0001; heatwaves: I^2=83·5%, p<0·0001) and 80% PIs.[28] We upgraded the quality rating of a study if an exposure–response gradient was evident. The overall quality of evidence was upgraded to high for the studies assessing the risk of heat exposure associated with cardiovascular disease-related mortality, and moderate for the cardiovascular disease-related morbidity studies (table 2). Additionally, we found no substantial differences in the pooled RRs for the associations between heat exposures and cardiovascular disease-associated health outcomes in either the leave-one-out analysis (high temperature mortality RR 1·021–1·022; high temperature morbidity RR 1·004–1·006; heatwaves mortality RR

1·094–1·124; heatwave morbidity RR 1·002–1·010) or the sensitivity analyses (ie, variations of the pooled effect estimates are within the 80% PI in which a future study RR will lie [appendix pp 58–61]). The series of sensitivity analyses indicated consistency in the direction and magnitude of the associations in the reviewed studies (appendix pp 58–61). We therefore concluded that future studies would be unlikely to cause the meta-analysis effects to be null or insignificant. The assessment of the strength of evidence suggested that there was sufficient evidence (ie, chance, bias, and confounding were ruled out with reasonable confidence regarding the observed positive association[32]) that heat exposures adversely affect both cardiovascular disease-associated mortality and morbidity (appendix pp 52–54).

Discussion

This study provides an updated synthesis of the effects of both high temperature and heatwaves on the risk of cardiovascular disease-related mortality and morbidity. Our review of 282 studies strengthened evidence of increased cardiovascular disease health risks related to heat exposures, and provides new evidence that the cardiovascular disease risks vary geographically and are dependent on underlying climate conditions. The meta-analysis of 266 studies showed that for every 1°C increase in temperature above reference temperatures there is an associated 2·1% increase in cardiovascular disease-related mortality and a 0·5% increase in cardiovascular disease-related morbidity. Although positive associations were observed across all cardiovascular disease diagnoses in mortality, stronger risks were shown with stroke (3·8% increased risk) and coronary heart diseases (2·8% increased risk). For morbidity, increased risks were related to arrhythmias and cardiac arrest (1·6%), and out-of-hospital cardiac arrest presented the greatest increased risk (2·1%). Additionally, during heatwaves, the risk of cardiovascular disease-related mortality significantly increased by 11·7%, with the risk increasing as heatwave intensity increased.

The heat effects on poor cardiovascular outcomes relate to the multiple physiological pathways that initiate human cardiovascular responses to passive heat stress and exogenous heat gain. These pathways leading to heat-induced impairment of cardiovascular health are overlapping and complex, with potential systemic effects. Briefly, when heat gain exceeds the capacity of the body to lose heat, a series of pathological events can eventually result in cardiovascular impairment.[8,33] Increased sweating and skin blood flow can lead to water loss and dehydration and increase the risk of stroke. The accompanying decrease in plasma volume and increase in the concentration of red blood cells and other blood constituents, together with an increase in blood viscosity and an elevated cholesterol concentration, might cause thromboembolism, leading to increased risk of ischemic stroke and heart disease.[34] Thermal stress has been shown to increase the risk of cardiovascular dysfunction such as hypertension, heart rate disturbances, and ischemic heart disease.[35] Vasodilation of peripheral blood vessels reduces systolic blood pressure and so decreases coronary blood flow, leading to the risk of arrhythmias and cardiac arrest.[36] Additionally, a heat-induced elevated heart rate and cardiac contractility can increase myocardial oxygen consumption, which might also pose a threat of fatal arrhythmias.[37]

Our results support and update the findings of previous reviews associating high temperatures[5,38–40] and heatwaves[3,6,38] with cardiovascular disease-related mortality. We also found associations with cardiovascular disease-related morbidity, and our findings are in line with a 2016 meta-analysis that reported a 1% increased risk associated with elevated temperatures and a 6·1% increased risk for heatwaves.[4] However, some meta-analyses and original epidemiological studies reported either weak or no apparent associations between increased temperature and cardiovascular disease-related morbidity.[41–45] This might be explained by a variety of indicators being used in morbidity studies, including hospital admissions, emergency department visits, and ambulance attendances. Moreover, differences in effect estimates exist even for the same heat-associated cardiovascular disease outcome depending on the type of health outcome indicators the study used;[6] this might be a plausible explanation for the observed difference in associations for hypertensive mortality and morbidity. Furthermore, studies based on morbidity data might have underestimated the true heat effects if patients had difficulty accessing health-care services during extreme temperatures.[46] On the other hand, patients who die during heatwaves might be inpatients in hospitals (particularly hospitals without air conditioning), or those with acute cardiovascular disease conditions might die before being admitted to hospital for medical treatment,[47] and this might explain the observed higher overall effect on mortality than on morbidity and the high out-of-hospital morbidity for conditions such as cardiac arrest.

Inter-study heterogeneity was detected, indicating inherent differences between the studies, in aspects such as study areas and population structures, study designs, and statistical models used. Meteorological variables (wind speed, air pressure, and relative humidity) and air pollutants were considered and adjusted for as confounders in most of the included studies. However, different covariates included in analyses might also contribute to the heterogeneity of the results. The series of sensitivity analyses indicated consistency in the direction and magnitude of the associations in the reviewed studies (appendix pp 58–61). Additionally, heterogeneity was not reduced in any of these associations (in either the main analysis or sensitivity analyses), indicating that other unmeasured factors might be contributing to the heterogeneity, warranting future research.

The significant, higher mortality risk of heat impacts on people aged 65 years and over than those younger

than 65 years are evident from our findings. Older people usually exhibit low physiological tolerance to heat. In addition to age-related physiological changes in thermoregulation, the cardiovascular capacity of the human body naturally declines with age.[48] During heat exposure, older individuals generally respond with attenuated sweat gland outputs, reduced blood flow to the skin, smaller increases in cardiac output, and decreased redistribution of blood from the splanchnic and renal circulations.[49] Moreover, people 65 years and older tend to have a higher rate of pre-existing conditions than younger people (eg, hypertension, diabetes mellitus, hyperlipidaemia, and coronary artery disease), and associated medication use, which might also explain the observed increased risk of cardiovascular disease outcomes in response to heat.[50]

The importance of estimating exposure–response effects in different climate regions has been previously identified.[4] In this study, our subgroup analyses showed higher risk estimates of cardiovascular disease outcomes among individuals living in tropical climates than in those living in other climate zones examined, suggesting that the risk is not uniform.[51] This finding might be explained by the higher extreme heat frequency and lower interannual variability in tropical regions than other climate regions.[52] The variations in heat-related cardiovascular disease risks between regions might also be associated with differences in humidity at high temperatures.[9] Future studies investigating these geographical variations by population structure, socioeconomic status, and public health intervention capacity are needed. Additionally, for every 1°C increase in temperature, the pooled effect estimates for cardiovascular disease-related mortality and morbidity were higher in countries with lower national income, although LMICs are often in warmer regions than high-income countries.[53]

This systematic review of 282 studies included diverse populations and study areas. A key strength of this review is that it addresses the gaps in knowledge about the quantitative effects of high temperatures and heatwaves (stratified by intensity) on cardiovascular disease health outcomes in different climate zones. The studies have been assessed on the basis of best practice guidelines developed specifically for environmental health research, and several sensitivity analyses attest the robustness of our findings.[54]

Limitations should be acknowledged. Firstly, we only considered peer-reviewed literature published in English. Secondly, the Peer Review of Electronic Search Strategies (PRESS) checklist was not adopted for peer-review of search strategies,[20] and tools (such as Medline Transpose) were not used to translate search terms between databases. However, our search strategy was developed using recognised search guides and in consultation with an academic librarian, which might have enabled us to retrieve the most relevant studies. Thirdly, although we included studies from several countries with diverse climates, there were a low number of estimates in some subgroups. For example, only a few were from LMICs and tropical areas that might have increased susceptibility to the effects of a warming climate. Despite our efforts to account for the differences between climate zones, caution should be taken when interpreting these pooled effect estimates owing to the high observed heterogeneity that indicates the possible unaccounted factors within each climate zone. Moreover, many primary studies reviewed did not include data on modifying factors such as pre-existing cardiovascular disease illness, comorbidities, and use of medication.

As the global temperature rises, the population ages, and cardiovascular disease incidence and prevalence increases worldwide, tailored strategies for preventing the negative effects of ambient heat on cardiovascular disease can have a substantial effect on heat-related health burdens. However, data are sparse on interventions specifically aimed at reducing cardiovascular disease-related health risks from heat,[55] the effectiveness of the interventions, and whether they can be adequately received by the most vulnerable groups (eg, those with low education levels, people who are homeless, and people older than 65 years).[56,57] Another challenge is in determining a threshold at which hot weather conditions become sufficiently harmful to human health to warrant intervention.[56,58] To support this effort, collaboration should be enhanced between local government bodies, public health professionals, primary health-care providers, and cardiologists, in heat-health planning, research, education, and advocacy campaigns on global climate and health. Moreover, future studies improving understanding of the impact of ambient heat exposure on cardiovascular disease health that consider the differences in underlying climate pattern and age structure, and which involve the monitoring of health status and risks of heart disease before the onset of summer, are warranted.

In summary, this study provides updated evidence regarding the elevated risk of cardiovascular disease-related mortality and morbidity due to heat exposures and indicates avenues for future research. Findings also highlight that underlying regional climate conditions need to be accounted for when assessing the risk of heat-related cardiovascular disease health outcomes, as well as societal lifestyle factors, population characteristics, and disease subgroups. Findings from this review have important implications for the evaluation of current risks of adverse cardiovascular disease effects during hot weather and future health-care prevention strategies and resource allocation for high-risk populations. As rising temperatures already confer an increased risk of quantifiable and avoidable cardiovascular disease events in the general population, implementation of policy measures to achieve a zero-carbon emission economy should be a high priority.

Contributors

JL was involved in the literature search, figure creation, study design, data collection, data analysis, data interpretation, and writing of the

manuscript. BMV was involved in the literature search, figure creation, data collection, data interpretation, and reviewing and revising of the manuscript. AH oversaw the meta-analysis design, execution, statistical analysis, data interpretation, and was involved in the reviewing and revising of the manuscript. PB was involved in all stages of the project, including conception, design, data analysis, data presentation, interpretation, reviewing, and revising of the manuscript. JL, BMV, and AH accessed and verified the underlying data. All authors confirm that they had full access to all the data in the study and accept responsibility for submission for publication. All authors made substantial contributions to discussions of the content and reviewed or edited the manuscript before submission.

Declaration of interests

We declare no competing interests.

Data sharing

This manuscript makes use of publicly available data from published studies; therefore, no original data are available for sharing.

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