Global and Regional Cardiovascular Mortality Attributable to Non-optimal Temperatures over Time:

Samuel Hundessa PhD[a], Wenzhong Huang MSc[a], Qi Zhao PhD[b], Yao Wu MSc[a], Bo Wen MSc[a], Barrak Alahmad PhD[c], Ben Armstrong PhD[d], Antonio Gasparrini PhD[d,e,f], Francesco Sera MSc[g], Shilu Tong PhD[e,h,i,j], Joana Madureira PhD[k], Jan Kyselý PhD[l,m], Joel Schwartz PhD[n], Ana Maria Vicedo-Cabrera PhD[o,p,q], Simon Hales PhD[r], Amanda Johnson PhD[a], Shanshan Li PhD[a], Yuming Guo PhD[a] on behalf of the MCC Collaborators*

Departments and institutions with which the authors are affiliated:

[a]Climate, Air Quality Research Unit, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia, [b]Department of Epidemiology, School of Public Health, Cheeloo College of Medicine, Shandong University, Jinan, China, [c]Department of Environmental Health, Harvard T.H. Chan School of Public Health, Harvard University, Boston, MA, USA, [d]Department of Public Health Environments and Society, London School of Hygiene & Tropical Medicine, London, United Kingdom, [e]Centre on Climate Change & Planetary Health, London School of Hygiene & Tropical Medicine, London, United Kingdom, [f]Centre for Statistical Methodology, London School of Hygiene & Tropical Medicine, London, United Kingdom, [g]Department of Statistics, Computer Science and Applications "G. Parenti", University of Florence, Florence, Italy, [h]School of Public Health and Social Work, Queensland University of Technology, Brisbane, Australia, [i]School of Public Health and Institute of Environment and Human Health, Anhui Medical University, Hefei, China, [j]Shanghai Children's Medical Centre, Shanghai Jiao-Tong University, Shanghai, China, [k]Environmental Health Department, Instituto Nacional de Saúde Dr Ricardo Jorge, Porto, Portugal, [l]Institute of Atmospheric Physics, Czech

Academy of Sciences, Prague 141 00, Czech Republic, [m]Faculty of Environmental Sciences, Czech University of Life Sciences, Prague, Czech Republic, [n]Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, MA, USA, [o]Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland, [p]Oeschger Center for Climate Change Research, University of Bern, Bern, Switzerland, [q]Department of Public Health Environments and Society, London School of Hygiene and Tropical Medicine, London, United Kingdom, [r]Department of Public Health, University of Otago, Wellington, New Zealand.

FUNDING SUPPORT AND AUTHOR DISCLOSURES: This study was supported by the Australian Research Council (DP210102076) and the Australian National Health and Medical Research Council (APP2000581). WH was supported by the China Scholarship Council (number 202006380055). SL was supported by an Emerging Leader Fellowship of the Australian National Health and Medical Research Council (number APP2009866); QZ was supported by the Program of Qilu Young Scholars of Shandong University, Jinan, China; JK and AU by the Czech Science Foundation (project number 22-24920S); ST by the Science and Technology Commission of Shanghai Municipality (grant number 18411951600); AG by the Medical Research Council-UK (Grant IDs: MR/V034162/1 and MR/R013349/1), and the EU's Horizon 2020 project, Exhaustion (grant ID 820655). FS by the Medical Research Council UK (grant ID MR/R013349/1), the Natural Environment Research Council UK (grant ID NE/R009384/1), and the EU's Horizon 2020 project, Exhaustion (grant ID 820655); and YG by the Leader Fellowship (number APP2008813) of the Australian National Health and Medical Research Council. Statistics South Africa kindly provided the mortality data but had no other role in the study. The authors have declared that they do not have any relevant relationships to disclose regarding the contents of this paper.

ADDRESS FOR CORRESPONDENCE:

Professor Yuming Guo, School of Public Health and Preventive Medicine, Monash University, 553 St Kilda Road, Melbourne, VIC 3004, Australia. Tel: +61 3 9905 6100. E-Mail: yuming.guo@monash.edu.

Professor Shanshan Li, School of Public Health and Preventive Medicine, Monash University, 553 St Kilda Road, Melbourne, VIC 3004, Australia. Tel: +61 3 9905 6102. E-Mail: shanshan.li@monash.edu

ABSTRACT

BACKGROUND. The association between non-optimal temperatures and cardiovascular mortality risk is recognized. However, a comprehensive global assessment of this burden is lacking.

Objectives: Assess global cardiovascular mortality burden attributable to non-optimal temperatures, and investigate spatiotemporal trends.

METHODS. Using daily cardiovascular deaths and temperature data from 32 countries, we employed a three-stage analytical approach. Firstly, we estimated location-specific temperature-mortality associations, considering non-linearity and delayed effects. Secondly, we developed a multivariate meta-regression model between location-specific effect estimates and five meta-predictors. Thirdly, we estimated cardiovascular deaths associated with non-optimal, cold, and hot temperatures for each global grid (55km x 55km resolution) and explored temporal trends during 2000-2019.

RESULTS. Globally, 1,801,513 (95% eCI: 1,526,632 – 2,202,831) annual cardiovascular deaths were associated with non-optimal temperatures, constituting 8.86% (95% eCI: 7.51% – 12.32%) of total cardiovascular mortality (26 deaths per 100,000 population). Cold-related deaths accounted for 8.20% (6.74 – 11.57%), while heat-related deaths were 0.66% (0.49%–0.98%). The mortality burden varied significantly across regions, with the highest excess mortality rates observed in Central Asia and Eastern Europe. From 2000 to 2019, cold-related excess death ratios decreased, while heat-related ratios increased, resulting in an overall decline in temperature-related deaths. South-eastern Asia, Sub-Saharan Africa and Oceania observed the greatest reduction, while Southern Asia experienced an increase. The Americas and several regions in Asia and Europe showed fluctuating temporal patterns.

CONCLUSION. Non-optimal temperatures substantially contribute to cardiovascular mortality, with heterogeneous spatiotemporal patterns. Effective mitigation and adaptation strategies are crucial, especially given the increasing heat-related cardiovascular deaths amidst climate change.

KEYWORDS. cardiovascular death, non-optimal temperatures, excess death, death ratio, global burden of disease

CONDENSED ABSTRACT

Non-optimal temperatures substantially contribute to cardiovascular mortality worldwide. We conducted a comprehensive global assessment, estimating that about 1.8 million cardiovascular deaths annually are associated with non-optimal temperatures, representing 8.86% of total cardiovascular mortality. Most deaths (8.20%) were cold-related, while 0.66% were heat-related. Substantial spatiotemporal variations were observed, with the highest excess mortality rates in Central Asia and Eastern Europe. From 2000–2019, overall temperature-related deaths declined by 0.33 percentage points, notably reducing in South-eastern Asia and Sub-Saharan Africa but increasing in Southern Asia. Despite the decline, slight increase in heat-related cardiovascular deaths emphasizes the need for effective climate change adaptation strategies.

Key Words: cardiovascular deaths, non-optimal temperatures, excess death, death ratio, global burden of disease

ABBREVIATIONS AND ACRONYMS

7CVD = cardiovascular diseases

eCI = confidence intervals

GDB = global burden of diseases

GDP = gross domestic product

ICD = international classification of diseases

MCC = multi-country multi-city

MMT = minimum mortality temperature

UN = united nations

INTRODUCTION

Human activities, primarily the emissions of greenhouse gases, undeniably exert a significant influence on global warming. This influence becomes apparent when considering that the average global surface temperature rose to 1.1°C above the pre-industrial level during 2011-2020, largely due to these activities.[1] This temperature increase has led to heightened frequency and severity of extreme weather events,[1-3] exposing a growing number of individuals to temperature extremes.[4] Non-optimal temperatures, defined as those falling above or below the minimum-risk exposure level, have consistently been associated with morbidity and mortality.[5, 6] Studies indicated that both hot and cold temperatures are associated with an increased risk of death.[7-10] While several studies have investigated the global association between non-optimal temperatures and all-cause mortality.[9, 11-13], there is limited evidence specifically addressing the cardiovascular mortality burden attributable to non-optimal temperatures.

Despite substantial public health advancements in cardiovascular disease (CVD) prevention since the mid-20th century, it remains the leading cause of death globally. In 2019, cardiovascular disease was responsible for an estimated 17.9 million deaths, constituting 32% of global deaths that year.[14] According to Global Burden of Disease (GBD) 2019 study, the number of cardiovascular deaths steadily increased from 12.1 million to 18.6 million between 1990 and 2019.[15] This trend is expected to escalate in the coming years due to ongoing global warming and greater susceptibility of individuals with multiple risk factors for CVD.[16, 17]

Evidences indicate the association between non-optimal temperatures and cardiovascular disease and mortality.[18-21] However, previous studies have often been confined to single countries or regions, hindering global generalizability due to geographical heterogeneity in environmental conditions and population dynamics. The 2023 GBD study made progress in quantifying the global burden of cardiovascular disease mortality attributed to non-optimal temperatures.[16] However, its reliance on data from only nine countries hinders extrapolation to a global scale. Moreover, the study overlooked spatiotemporal variations in temperature-mortality relationships, potentially underestimating temperature-attributable mortality. Addressing this, Alahmad et al. conducted a study, providing more inclusive analysis.[22] However, estimating mortality burden at smaller scales allows for a more detailed understanding, and enabling more effective and targeted intervention strategies. Utilizing three-stage meta-analytical models in environmental epidemiology, we aim to estimate global and regional burden of cold and hot temperatures on cardiovascular mortality and investigate spatiotemporal trends in recent decades.

METHODS

Data sources

We obtained daily counts of cardiovascular deaths and corresponding daily temperature data from the latest version of the Multi-Country Multi-City (MCC) Collaborative Research Network dataset, spanning from January 1, 1969, to December 31, 2019. The MCC dataset has been detailed in our previous studies.[9, 22] Additionally, we augmented the cardiovascular death data included in the MCC dataset by obtaining more detailed cardiovascular mortality information for Australia, New Zealand, and Brazil. This additional data, were aggregated by date and location, using the pertinent administrative boundaries for each country or territory. The combined dataset encompassed global cardiovascular deaths (ICD-9, codes 390-459) & 10th (ICD-10, codes I00-I99) for 1847 locations across 32 countries or territories (Online Appendix Table 1).

Daily mean temperature data were identical to those used in our previous global study.[13] In summary, Daily Temperature data (2000-2019) gridded at 55km × 55km resolution were obtained from the Global Daily Temperature dataset. This data was utilized to compute both the average and the range of annual mean temperatures for each grid cell. Country-level annual Gross Domestic Product (GDP), and Population data from the Global Carbon Project were used to calculate grid-specific GDP per capita. Climate zones were assigned to each grid cell using the Koppen-Geiger climate classification.[23] Country-specific annual cardiovascular mortality rates were derived from the World Bank. This study was approved by the Monash University Human Research Ethics Committee.

STATISTICAL ANALYSIS. We applied a three-stage analytical approach to estimate the burden of cardiovascular mortality related to non-optimal temperatures. A detailed description of this approach can be found in previous MCC studies.[9, 13] *First*, we estimated the association between daily mean temperature and cardiovascular mortality for each study location. This involved utilizing quasi-Poisson regression combined with a distributed lag non-linear model (DLNM).[24] The temperature variable was modelled with a natural cubic spline, featuring three internal knots placed at the 10^{th}, 75^{th}, and 90^{th} percentiles of the city-specific temperature distribution. The lag effects of the temperature on cardiovascular mortality were modelled with an intercept and three internal knots, evenly spaced values in the log scale as in previous studies.[9, 13] We used a 21-day lag to fully capture the delayed effects of temperature and mortality displacement. A natural cubic spline for time with 8 degrees of freedom per year was utilized to control for long-term trends and seasonality. An indicator for the day of the week was also included to account for fine temporal patterns.[9, 13] We conducted this analysis in five-year intervals of the epidemiological data period to account for potential change in the historical temperature-mortality relationship over time.

Second, we developed a multivariate meta-regression model linking the reduced cumulative association for each location with five location-specific meta-predictors. These predictors included the yearly average of mean temperature, temperature range, climate zones (Online Figure 1)[23], an indicator of continents, and GDP per capita. These predictors were found to explain the heterogeneity in temperature-mortality relationships across locations.[9, 25] The meta-regression model included random effect to account for differences between locations, and time to adjust for the historic temperature-mortality relationship.[26]

Third, we estimated the temperature-cardiovascular mortality association for each grid per day, using the fitted meta-regression model and the grid-specific meta-predictors. These associations were then used to calculate the number of grid-specific daily excess deaths related to non-optimal temperatures. Specifically, we calculated grid-specific daily excess deaths associated with non-optimal temperatures, using the following formula:

$$Ed_{it} = (RR_{it}\text{-}1) \text{ x } D_i,$$

where Ed_{it} is grid-level daily excess cardiovascular deaths, RR_{it} is the cumulative relative risk predicted from the third stage of modelling, in grid *i*, on day *t*. D_i is average daily deaths count in grid *i,* which was derived from the annual cardiovascular death rate of the country where the grid cell was situated, along with the population within that particular grid cell.[13] Similar to previous studies[9, 13, 22], we set reference values to grid-specific minimum mortality temperatures (MMT), representing the temperature at which the mortality risk is at its lowest.[9] This value relates to human adaptability to local climate conditions, reflecting the temperature most conducive to human physiology.[27] The analyses were restricted to grids with a minimum of one cardiovascular death count per year to enhance the model stability.

We totalled daily excess cardiovascular deaths per grid cell, obtaining annual global, continental, and regional values based on United Nations (UN) Statistics Division (M49) criteria.[28] Considering demographic factors, we calculated the annual excess cardiovascular mortality ratio and rate per 100,000 population. Globally and across all regions, we calculated the temporal change in the temperature-related excess cardiovascular mortality ratio over five 4-year periods, using the earliest period (2000-2003) as a baseline. The presentation includes the excess cardiovascular mortality burden attributable to non-optimal, cold, and hot temperatures, along with their 95% eCIs, stratified by global, continental, and UN regions. Furthermore, we provided mortality burden associated with extreme heat (>=97.5th percentile) and extreme cold (<=2.5th percentile) temperatures.[9] We used Monte Carlo simulations, running 500 iterations to estimate uncertainty in mortality burden by drawing values from coefficients, variances, and covariances from the meta-regression model. To account for the spatial relationships between neighbouring grids we employed ordinary kriging (using residual from mixmeta model) and integrated a random component into the uncertainty measure, particularly in calculating the empirical confidence interval.[29]

The strength of the results, was measured by conducting sensitivity analyses (Supplementary Table 2) by changing the parameters of the knots and lag days. Specifically, we modelled the exposure-response relationship with 4 knots at the 10th, 50th, 75th, and 90th percentiles, and alternatively, with 5 knots at the 5th, 25th, 50th, 75th, and 95th percentiles. We also changed the maximum lag periods to 24 and 28 to examine the effect of temperature on mortality.

All data organisation and analyses were carried out using R software, version 4.4.3, with the *dlnm* and *mixmeta* packages used to fit the distributed lag non-linear model and multivariate meta-regression, respectively.[24]

RESULTS

We estimated the cardiovascular mortality burden related to non-optimal temperatures during 2000-2019. Our findings indicate that, globally, an estimated 1,801,513 (95% eCI: 1,526,632 – 2,202,831) cardiovascular deaths per year were associated with non-optimal temperatures (Table

1). Of these, 1, 666, 814 (95% eCI: 1, 369, 292 – 2, 351,730) deaths were linked to cold temperatures and 134, 699 (95% eCI: 100,165–199, 769) to hot temperatures. More than half (57%) of all excess deaths occurred in Asia, followed by Europe (21%), Africa (11.97%), Americas (9.29%), and Oceania (less than 1%). This distribution largely held true for cold-related deaths, with the highest proportions again concentrated in Asia and Europe, and the lowest in Oceania. However, a different pattern emerged for heat-related deaths. Asia still held the top position, but Africa saw a higher percentage compared to Europe. In summary, Asia suffered the highest proportion of excess cardiovascular deaths linked to both heat and cold, while Oceania had the fewest. A detailed overview of temperature-related excess deaths is presented in Figure 1A-C. Our analysis indicated that 8. 86% (95% eCI: 7.51% – 12.32%) of global cardiovascular deaths were associated with non-optimal temperatures. Among these deaths, 8.20 % (95% eCI: 6.74% – 8.83%) were related to cold temperatures and 0.66% (95% eCI: 0.49% – 0.98%) to hot temperatures. When calculating the global excess cardiovascular death rate, cold temperatures accounted for 24.17 (19.86 – 34.10) and heat for 1.95 (1.45 – 2.89) deaths per 100, 000 population. Extreme temperatures, both cold or heat contributed only a small fraction: 1.53% (1.45–1.79%), and 0.50% (0.45–0.66%), respectively, occurring on few days (Online Appendix Table 3 and 4).

Excess cardiovascular death ratios and rates varied considerably across regions (Table 2 and Figure 2A-C). The highest regional excess cardiovascular death rate was found in Central Asia, followed by Eastern Europe, and Western Asia. Of note, the cold-related death rate observed in Central Asia was more than four times the global average. Eastern Europe and Western Asia also faced significant cold-related death burdens, exceeding the global average by over three times in Eastern Europe. Interestingly, the pattern for heat-related deaths differed. Central Asia, Western Asia, and other regions in Oceania saw the highest rates. Notably, Central Asia had the highest excess cardiovascular death rates related to both cold and heat (Table 2). The grid-specific distribution of cardiovascular death ratio and rates are shown in Online Figure 2.

Between 2000-2003 and 2016-2019, the cold-related global excess death ratio declined by 0.53 percentage points (95% eCI: -0.73, - 0.74). Conversely, the hot-related excess death ratio increased by 0.20 (0.15 – 0.28) percentage points. When the combined cold and hot non-optimal temperatures-related excess death ratio was assessed for the same periods, a net decline of 0.33 percentage points was observed (Online Appendix Table 5, 6 and 7). Across regions, cold-related cardiovascular deaths declined, except in South Asia. Americas, most regions of Asia and Europe had fluctuating trends (Central Illustration). The biggest decline in total deaths was in South-eastern Asia, Sub-Saharan Africa, and Oceania. Heat-related deaths increased, considerably as a fraction of its initial low value in most regions, especially Central Asia, and North America. Europe and Asia showed unstable patterns. Net cardiovascular mortality ratio (black line) greatly declined in Sub-Sharan Africa, Oceania, Eastern Europe and Southeast Asia, but increased in Southern Asia. Americas, most regions of Asia, and Europe saw fluctuating trends. Detailed spatial changes are shown in Figures 2D-2F. Most grids observed declined cold-related deaths in North America, Europe, Eastern and South-eastern Asia, and sub-Saharan Africa near the equator. Heat-related deaths slightly rose in tropical/subtropical zones. Online Figure 2 show the change in the mortality burden estimates in terms of rates for hot, cold, and non-optimal temperature exposure at the grid level.

DISCUSSION

NON-OPTIMAL TEMPERATURES-RELATED CVD MORTALITY BURDEN. We estimated the global burden of cardiovascular mortality associated with non-optimal temperatures. at a spatial resolution of 55km × 55km, and investigated temporal changes from 2000 to 2019. Our findings indicated that globally, 1, 801, 513 cardiovascular deaths yearly were linked to non-optimal temperatures over the two-decades, comprising 8.86% of total global cardiovascular deaths, or 26 excess cardiovascular deaths per 100,000 people. More excess deaths were associated with cold temperatures (8.20%) than hot ones (0.66%). Between 2000-2003 and 2016-2019, a global net excess death ratio declined by 0.33 percentage points. Notably, cold-related excess death fell by 0.53 percentage points, while hot-related death increased by 0.20 points. Temporal and geographical variations were evident in the temperature-related cardiovascular mortality burden for both hot and cold temperatures.

Despite several studies have explored the associations between non-optimal temperatures and cardiovascular mortality,[18-21] none have specifically quantified the cardiovascular mortality burden attributed to non-optimal temperatures globally, using established statistical approaches. By employing multi-country MCC data from 1,847 locations and a state-of-the-art three-stage unified analytical strategy, our study revealed a cardiovascular mortality burden (8.86%) associated with non-optimal temperatures, predominantly driven by cold temperatures (8.20%) compared to hot temperatures (0.66%). These findings align with prior researches.[9, 13, 16], which consistently reports a higher burden of cold-related cardiovascular deaths compared to hot-related deaths, both nationally and globally. For example, a study conducted in China found that 11.62% of excess cardiovascular deaths were attributed to cold temperatures, while the ratio for hot-related deaths was 2.71%.[21] Similarly, a global study reported that 8.5% of all-cause excess mortality was linked to cold temperatures, compared to 0.9% associated with heat.[13] While our study notes as slightly lower burden of heat-related cardiovascular mortality compared to previous findings, it shows a slight upward trend, which align with reports of increasing heat-related cardiovascular deaths.[16]

These findings highlight the need for global communities and governments to address both cold and heat-related mortality burdens when planning for climate change adaptation.

Several biological mechanisms explain the link between non-optimal temperatures and cardiovascular health. Heat exposure increases skin blood flow, sweating, and change heart rate, and elevated blood viscosity. It disrupts core temperature regulation, increase the risk of coronary events, metabolic activity and oxygen consumption.[30] Heat-induced fluid shifts can disrupt electrolyte balance, exacerbating arrhythmias.[31] These responses are rapid and consistent with the sharp risk increase above the optimum temperature (Online Figure 3 and 4), which was associated with a comparatively low burden attributable to high temperature. Cold exposure rises blood viscosity, vasoconstriction, and muscle tone, raising blood pressure and cardiac oxygen demand.[32, 33] These responses can persist longer[32], and contribute to mortality risks with a pattern that is smooth and approximately linear, with most of the attributable deaths occurring on moderately cold days.

GEOGRAPHICAL VARIATIONS IN NON-OPTIMAL TEMPERATURE-RELATED CVD MORTALITY. Our study revealed significant geographical disparities in non-optimal temperature-related cardiovascular mortality. Central Asia and Eastern Europe had the highest rates for both cold and hot temperatures, aligning with a previous related study.[13] These disparities are likely due to differences in climate, environmental exposure, pre-existing cardiovascular disease prevalence, and baseline mortality rates. Eastern Europe's continental climate[23] with lower temperatures may explain its high burden of cold-related mortality. This aligns with the region's high cardiovascular mortality rate, as reported in the 2015 Global Burden of Disease study.[34] Notably, some countries like Latvia and Romania have double the EU's average, further contributing to the trend. Our previous multi-country study also estimated that Eastern Europe has the highest regional heat-related mortality rates in Europe.[13] Despite these, there was no substantial increase in the net cardiovascular mortality burden in Eastern Europe during the study period. In Central Asia, the region's dry climate (60%) and significant recent temperature increases likely contributed to its observed heat-related burden.[35] The high cold-related burden aligns with previous findings linking cold temperatures to increased mortality in tropical regions. For example, a comparable study found a high cold-related mortality rate in Sub-Saharan Africa, known for its hot and dry tropical climates.[13] The association between cold temperatures and high mortality burdens in hot climatic regions may seem unexpected, given the generally warmer weather. However, the population's susceptibility to cold effects in hot climates suggests acclimatization to local conditions, where temperature deviations-whether cold or hot-can lead to health risks. Additionally, factors beyond climate characteristics may contribute to the observed cold-related mortality burden in Central Asia. Studies highlight unusually high cardiovascular disease prevalence and rate in Central Asia, ranking second in estimated age-standardized prevalence of ischemic heart disease in 2015 and having the highest cardiovascular mortality rate globally.[34]

CHANGE IN TEMPERATURE-RELATED CVD MORTALITY BURDEN. Our study also identified temporal variation in the non-optimal temperature-related global cardiovascular mortality burden between 2000 and 2019. Over this period, there was a substantial decrease in the cold-related global excess deaths ratio and a slight increase in the heat-related excess death ratio, resulting in a net decline of 0.33 percentage points. This observation was consistent with our previous MCC study which reported a net decline of 0.30 percentage points in all-cause temperature-related deaths.[13] These results imply that the overall temperature-related mortality burden might slightly decrease with climate change. However, the heat-related mortality burden is expected to rise in the long term under ongoing global warming. Nevertheless, there is a regional difference, with the ratio of cold-related deaths decreasing substantially or fluctuating in most UN regions, except in Southern Asia. Our previous global estimates of all-cause mortality indicated a similar trend in the mortality ratio in the region.[13] Thus, local countries should consider the public health impact of low temperatures when developing climate mitigation and adaptation strategies. Conversely, the heat-related death ratio notably increased as a fraction of its initial low value in most regions, coinciding with the change in annual mean temperature during the study period (Online Figure 5). The highest regional increase in the heat-related excess death ratio occurred in Central Asia, Northern America, and Other regions in Oceania, despite a considerable reduction in the ratio of cold-related cardiovascular deaths in the same period in the region. Furthermore, all regions experienced a substantial increase in heat-related mortality burden during the most recent four years of the study period (2016-2019), emphasizing the public health implications associated with rising global surface temperatures.[1] Ongoing warming is expected to increase mortality burden, especially in tropical and subtropical climate zones, including areas with high population densities, such as central and southern parts of America and Southeast Asia.[36] Increased temperatures and associated mortality in these regions could potentially have substantial public health impacts.

This study has several strengths. To the best of our knowledge, this is the largest study to date quantifying the cardiovascular mortality burden attributable to non-optimal temperatures and exploring spatiotemporal trends globally. The analysis employed a high spatial resolution to enhance the ability to identify geographical variations and reduce the risk of exposure misclassification. Utilizing a well-established statistical model based on the largest dataset ever collected, the study assessed temperature-cardiovascular mortality associations. Encompassing 1,847 locations spanning 32 countries across five continents, this study includes areas characterized by diverse climates, demographics, socioeconomics, and public health services. and provided the estimate for global grids possessing approximately 6.9 billion individuals, representing 98.5% of the global population during the study period (2000-2019). This ensures global representativeness of our findings. Our study provides a robust evidence base for comprehending climate change's role in global cardiovascular mortality trends across regions. These findings aid regional and national governments in developing tailored policies to protect populations from temperatures-related health risks.

STUDY LIMITATION. This study also has some limitations. The grid-level temperature-related mortality burden was estimated using country-level death rates, due to the absence of mortality data for each grid cell. As a result, all grids within the same country were assumed to have identical mortality rates. The study incorporated five meta-predictors in the meta-regression model, to help account for heterogeneity in temperature-mortality associations across locations.[9, 36] However, there may be another factor contributing to geographic variation in the mortality burden not accounted for. For example, population age structure, underlying health conditions, air pollution, and adaptation strategies. We were not able to consider this information because such data were not available for a sufficient number of locations. Although the grid system applied in the present study included the majority of the world's population, we were not able to estimate the temperature-related mortality burden in the least populated grids, which had insufficient numbers of cardiovascular deaths. We used standardised ICD codes, including cardiac arrest, but they may also include non-cardiac conditions.

CONCLUSIONS

Non-optimal temperatures substantially contribute to cardiovascular mortality burden, with notable increase in heat-related deaths over the past two decades. However, this burden varies spatially and temporally. Our findings provide an evidence base for developing and implementing effective strategies aimed at mitigating the public health consequences of non-optimal temperatures, with a particular focus on the escalating impact of heat-related conditions in the context of global warming.

Clinical Perspectives

Clinical in Systems-Based Practice: A substantial portion of cardiovascular mortality can be attributed to both cold and hot temperatures, yet there exists considerable spatial and temporal variability.

Translational Outlook: Prospective studies are required to investigate the collective impact of population age distribution and environmental exposure on cardiovascular mortality.

REFERENCES

1. Mukherji A, Thorne P, Cheung W, et al. Synthesis Report of The IPCC Sixth Assessment Report (AR6). Intergovernmental Panel on Climate Change; 2023.
2. Romanello M, McGushin A, Di Napoli C, et al. The 2021 report of the Lancet Countdown on health and climate change: code red for a healthy future. *The Lancet*. 2021;398:1619-1662.
3. Rummukainen M. Changes in climate and weather extremes in the 21st century. *Wiley Interdisciplinary Reviews: Climate Change*. 2012;3:115-129.
4. Organization WH. Heat and Health. Geneva World Health Organization 2018 1 June 2018.
5. Burkart KG, Brauer M, Aravkin AY, et al. Estimating the cause-specific relative risks of non-optimal temperature on daily mortality: a two-part modelling approach applied to the Global Burden of Disease Study. *Lancet*. 2021;398:685-697.
6. Murray CJ, Aravkin AY, Zheng P, et al. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *The lancet*. 2020;396:1223-1249.
7. Kovats RS, Hajat S. Heat stress and public health: a critical review. *Annu Rev Public Health*. 2008;29:41-55.
8. Cheng J, Xu Z, Bambrick H, Su H, Tong S, Hu W. Impacts of heat, cold, and temperature variability on mortality in Australia, 2000-2009. *Sci Total Environ*. 2019;651:2558-2565.
9. Gasparrini A, Guo Y, Hashizume M, et al. Mortality risk attributable to high and low ambient temperature: a multicountry observational study. *Lancet*. 2015;386:369-375.
10. Liu J, Varghese BM, Hansen A, et al. Heat exposure and cardiovascular health outcomes: a systematic review and meta-analysis. *Lancet Planet Health*. 2022;6:e484-e495.

11. Chen R, Yin P, Wang L, et al. Association between ambient temperature and mortality risk and burden: time series study in 272 main Chinese cities. *BMJ*. 2018;363:k4306.

12. Vicedo-Cabrera AM, Tobias A, Jaakkola JJK, et al. Global mortality burden attributable to non-optimal temperatures. *Lancet*. 2022;399:1113.

13. Zhao Q, Guo Y, Ye T, et al. Global, regional, and national burden of mortality associated with non-optimal ambient temperatures from 2000 to 2019: a three-stage modelling study. *Lancet Planet Health*. 2021;5:e415-e425.

14. Cardiovascular Diseases Factsheet [Internet]. World Health Organization. 2021. Available from: https://www.who.int/en/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds).

15. Roth GA, Mensah GA, Johnson CO, et al. Global burden of cardiovascular diseases and risk factors, 1990–2019: update from the GBD 2019 study. *J Am Coll Cardiol*. 2020;76:2982-3021.

16. Al-Kindi S, Motairek I, Khraishah H, Rajagopalan S. Cardiovascular Disease Burden Attributable to Non-Optimal Temperature: Analysis of the 1990-2019 Global Burden of Disease. *Eur J Prev Cardiol*. 2023.

17. Sung F-C, Wang Y-C, Huang L-Y. Climate Warming and Cardiovascular Mortality in 2040–2050 in Taiwan. *Epidemiology*. 2011;22:S20.

18. Shrikhande SS, Pedder H, Röösli M, et al. Non-optimal apparent temperature and cardiovascular mortality: the association in Puducherry, India between 2010 and 2020. 2022.

19. Urban A, Davídkovová H, Kyselý J. Heat- and cold-stress effects on cardiovascular mortality and morbidity among urban and rural populations in the Czech Republic. *Int J Biometeorol*. 2014;58:1057-1068.

20. Wei J, Wang P, Xia F, et al. Time trends in cardiovascular disease mortality attributable to non-optimal temperatures in China: An age-period-cohort analysis using the Global Burden of Disease Study 2019. *Front Public Health*. 2022;10:1075551.

21. Yang J, Yin P, Zhou M, et al. Cardiovascular mortality risk attributable to ambient temperature in China. *Heart*. 2015;101:1966-1972.

22. Alahmad B, Khraishah H, Royé D, et al. Associations between extreme temperatures and cardiovascular cause-specific mortality: results from 27 countries. *Circulation*. 2023;147:35-46.

23. Peel MC, Finlayson BL, McMahon TA. Updated world map of the Köppen-Geiger climate classification. *Hydrology and earth system sciences*. 2007;11:1633-1644.

24. Gasparrini A. Distributed Lag Linear and Non-Linear Models in R: The Package dlnm. *J Stat Softw*. 2011;43:1-20.

25. Zanobetti A, O'Neill MS, Gronlund CJ, Schwartz JD. Susceptibility to mortality in weather extremes: effect modification by personal and small-area characteristics. *Epidemiology*. 2013;24:809-819.

26. Musekiwa A, Manda SO, Mwambi HG, Chen DG. Meta-Analysis of Effect Sizes Reported at Multiple Time Points Using General Linear Mixed Model. *PLoS One*. 2016;11:e0164898.

27. Tobías A, Hashizume M, Honda Y, et al. Geographical Variations of the Minimum Mortality Temperature at a Global Scale: A Multicountry Study. *Environ Epidemiol*. 2021;5:e169.

28. Division US. Methodology–standard country or area codes for statistical use (M49).

29. Masselot P, Mistry M, Vanoli J, et al. Excess mortality attributed to heat and cold: a health impact assessment study in 854 cities in Europe. *Lancet Planet Health*. 2023;7:e271-e281.

30. Keatinge WR, Coleshaw SR, Easton JC, Cotter F, Mattock MB, Chelliah R. Increased platelet and red cell counts, blood viscosity, and plasma cholesterol levels during heat stress, and mortality from coronary and cerebral thrombosis. *Am J Med*. 1986;81:795-800.

31. Liu C, Yavar Z, Sun Q. Cardiovascular response to thermoregulatory challenges. *Am J Physiol Heart Circ Physiol*. 2015;309:H1793-1812.

32. Keatinge WR, Coleshaw SR, Cotter F, Mattock M, Murphy M, Chelliah R. Increases in platelet and red cell counts, blood viscosity, and arterial pressure during mild surface cooling: factors in mortality from coronary and cerebral thrombosis in winter. *Br Med J (Clin Res Ed)*. 1984;289:1405-1408.

33. Woodhouse PR, Khaw KT, Plummer M, Foley A, Meade TW. Seasonal variations of plasma fibrinogen and factor VII activity in the elderly: winter infections and death from cardiovascular disease. *Lancet*. 1994;343:435-439.

34. Roth GA, Johnson C, Abajobir A, et al. Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. *J Am Coll Cardiol*. 2017;70:1-25.

35. Lioubimtseva E, Cole R, Adams J, Kapustin G. Impacts of climate and land-cover changes in arid lands of Central Asia. *J Arid Environ*. 2005;62:285-308.

36. Gasparrini A, Guo Y, Sera F, et al. Projections of temperature-related excess mortality under climate change scenarios. *Lancet Planet Health*. 2017;1:e360-e367.

FIGURE TITLE AND LEGENDS

FIGURE 1 Average annual excess cardiovascular deaths. The excess deaths were calculated at a spatial resolution of 55km × 55km for the period spanning 2000 to 2019. **(A)** all non-optimal temperatures-related, **(B)** cold-related, and **(C)** heat-related.

FIGURE 2 Average annual excess cardiovascular mortality ratios and change per decade. The excess death ratios were calculated for each grid (cell size 55km × 55km). Panels **(A-C)** represent excess mortality ratios, while panels **(D-F)** depict changes in the mortality ratio per decade compared to the baseline (2000-2003) average.

CENTRAL ILLUSTRATION Cardiovascular mortality burden and trends by region (2000-2019). (A) average excess mortality ratio (%) per region during 2000- 2019, **(B)** Mortality ratio change per 4-years periods compared to baseline (2000-2003) average. The y-axis represents change in percentage points. Other regions in Oceania refers to regions in Oceania, excluding Australia and New Zealand.

TABLE 1 Annual average excess cardiovascular mortality, related to non-optimal temperatures, during 2000-2019, by continent and region.

	Excess cardiovascular mortality					
	All non-optimal (95% eCI)	**Regional percentage (%)**	**Cold-related (95% eCI)**	**Regional percentage (%)**	**Heat-related (95% eCI)**	**Regional percentage (%)**
Global	**1,801,513 (1,526,632-2 202,831)**	**100.00**	**1,666,814 (1,369,292-2,351,730)**	**92.52**	**134,699 (100, 165-199,769)**	**7.48**
Americas	**167,301 (106,270-278, 173)**	**9.29**	**154,410 (88,752-267,046)**	**8.57**	**12,891 (4,884-24,677)**	**0.72**
Northern America	89,503 (56,365-139,996)	4.97	83,298 (49,865-133,985)	4.62	6,205 (4,035-10,231)	0.34
Latin America and the Caribbean	77,798 (48,063-141,919)	4.32	71,112 (39,006-135,118)	3.95	6,686 (185-15 045)	0.37
Africa	**215,632 (118,646-409,701)**	**11.97**	**196,411 (97,304-382,771)**	**10.90**	**19,221 (2,575-47,139)**	**1.07**

Northern Africa	83,518 (49,461-138,730)	4.64	77,675 (44,809-132,153)	4.31	5,842 (2,405-11,387)	0.32
Sub-Saharan Africa	132,114 (70,721-272,059)	7.33	118,736 (53,870-252,766)	6.59	13,378 (4,633-36,075)	0.74
Asia	**1,026,923 (967,420-1,285,784)**	**57.00**	**941,844 (867,846-1,191,959)**	**52.28**	**85,079 (75,590-109,946)**	**4.72**
Central Asia	74,982 (64,703-96,600)	4.16	69,929 (59,409-91,058)	3.88	5,053 (4,371-6,954)	0.28
Eastern Asia	462,313 (428,245-563,170)	25.66	433,352 (396,558-529,594)	24.05	28,961 (25,993-38,868)	1.61
South-eastern Asia	53,639 (48,525-68,564)	2.98	46,036 (41,633- 61,381)	2.56	7,603 (4,378-10,063)	0.42
Southern Asia	325,662 (303,476-418,001)	18.08	291,168 (267,589-381,038)	16.16	34,494 (28,975-45,780)	1.91
Western Asia	110,328 (69,348-180,118)	6.12	101,359 (59,486-169,486)	5.63	8,969 (5,341-15,042)	0.50
Europe	**385,569 (266,084-593,821)**	**21.40**	**368,656 (242,478-575,876)**	**20.46**	**16,913 (12,318-28,004)**	**0.94**
Eastern Europe	267,056 (190,621-408,500)	14.82	255,076 (176,607-393,021)	14.16	11,979 (8,906-20,190)	0.66

Northern Europe	27,752 (16,584-43,248)	1.54	26 976 (15,591-42,453)	1.50	776 (482-1,449)	0.04
Southern Europe	45,908 (27,625-73,413)	2.55	43,443 (24,540-70,769)	2.41	2,465 (1,664-4,200)	0.14
Western Europe	44,853 (27,276-70,274)	2.49	43,161 (25,051-68,579)	2.40	1,692 (1,089-2,973)	0.09
Oceania	**6, 088 (6,015-8 466)**	**0.34**	**5,493 (5,313-7,838)**	**0.30**	**595 (489-851)**	**0.03**
Australia and New Zealand	4,414 (4,129-5,821)	0.25	4,243 (3,925- 5,627)	0.24	172 (157-248)	0.01
Other regions in Oceania*	1,673 (1,528-3,048)	0.09	1,250 (992-2,660)	0.07	423 (295-634)	0.02

eCI= empirical confidence interval. *Regions in Oceania except for Australia and New Zealand.

TABLE 2 Cardiovascular mortality ratio, and rate related to non-optimal temperatures during 2000-2019, by continent and region.

	Excess cardiovascular death ratio (%) (95% eCI)			**Excess cardiovascular death rate per 100, 000 population (95% eCI)**		
	All non-optimal	**Cold**	**Heat**	**All non-optimal**	**Cold**	**Heat**
Global	**8.86 (7.51-12.32)**	**8.20 (6.74-11.57)**	**0.66 (0.49-0.98)**	**26.12 (22.14-36.29)**	**24.17 (19.86-34.10)**	**1.95 (1.45-2.89)**
Americas	**10.16 (6.46-16.90)**	**9.38 (5.39-16.22)**	**0.78 (0.30-1.50)**	**17.87 (11.35-29.72)**	**16.50 (9.48-28.53)**	**1.38 (0.52-2.64)**
Northern America	16.48 (10.38-25.77)	15.34 (9.18-24.67)	1.14 (0.74-1.88)	25.82 (16.26-40.38)	24.02 (14.38-38.65)	1.79 (1.16-2.95)
Latin America and the Caribbean	7.054 (4.35-12.87)	6.45(3.53-12.25)	0.61 (0.02-1.36)	13.20 (8.16-24.08)	12.07 (6.62-22.93)	1.135 (0.03-2.55)
Africa	**6.32 (3.48-12.01)**	**5.76 (2.85-11.22)**	**0.56 (0.07-1.38)**	**20.69 (11.39-39.32)**	**18.85 (9.34-36.73)**	**1.84 (0.25-4.52)**
Northern Africa	8.233 (4.87-13.67)	7.657 (4.41-13.03)	0.58 (0.24-1.12)	39.42 (23.34-65.47)	36.66 (21.15-62.37)	2.757 (1.14-5.37)

Sub-Saharan Africa	5.513 (2.95-11.35)	4.95 (2.24-10.55)	0.56 (0.19-1.51)	15.91 (8.52-32.72)	14.30 (6.48-30.45)	1.612 (0.56-4.35)
Asia	**7.86 (7.41-9.85)**	**7.21 (6.64-9.13)**	**0.65 (0.58-0.84)**	**24.79 (23.35-31.03)**	**22.73 (20.95-28.77)**	**2.05 (1.82-2.65)**
Central Asia	14.25 (12.29-18.36)	13.29 (11.29-17.31)	0.96 (0.83-1.32)	122.51 (105.72-157.83)	114.25 (97.07-148.77)	8.256 (7.14-11.36)
Eastern Asia	9.81 (9.09-11.95)	9.1 (8.42-11.24)	0.62 (0.55-0.83)	29.75 (27.56-36.24)	27.89 (25.52-34.08)	1.864 (1.67-2.50)
South-eastern Asia	2.707 (2.44-3.46)	2.323 (2.10-3.09)	0.38 (0.22-0.51)	8.96 (8.11-11.45)	7.69 (6.954-10.25)	1.27 (0.73-1.681)
Southern Asia	6.597 (6.14-8.47)	5.898 (5.42-7.72)	0.69 (0.58-0.93)	19.23 (17.92-24.69)	17.19 (15.81-22.51)	2.037 (1.71-2.70)
Western Asia	12.216 (7.68-19.94)	11.22 (6.58-18.76)	0.99 (0.59-1.67)	46.69 (29.35-76.22)	42.89 (25.173-71.72)	3.796 (2.26-6.37)
Europe	**18.09 (12.49-27.87)**	**17.3 (11.38-27.02)**	**0.79 (0.58-1.31)**	**52.19 (36.02-80.38)**	**49.9 (32.82-77.95)**	**2.29 (1.67-3.79)**

Eastern Europe	18.787 (13.41-28.47)	17.94 (12.42-27.65)	0.84 (0.62-1.42)	90.81 (64.82-138.90)	86.73 (60.052-133.64)	4.073 (3.03-6.87)
Northern Europe	17.258 (10.31-26.89)	16.776 (9.69-26.40)	0.48 (0.3-0.90)	27.91 (16.68-43.49)	27.13 (15.67-42.69)	0.78 (0.48-1.46)
Southern Europe	16.13 (9.71-25.79)	15.264 (8.62-24.86)	0.87 (0.58-1.48)	29.50 (17.75-47.18)	27.92 (15.77-45.48)	1.584 (1.07-2.69)
Western Europe	16.99 (10.33-26.62)	16.35 (9.49-25.98)	0.64 (0.41-1.13)	23.65 (14.38-37.06)	22.76 (13.21-36.16)	0.892 (0.54-1.568)
Oceania	**8.33 (8.23-11.58)**	**7.51 (7.27-10.72)**	**0.81 (0.67-1.16)**	**16.83 (16.63-23.41)**	**15.19 (14.69-21.67)**	**1.64 (1.35-2.35)**
Australia and New Zealand	13.04 (12.19-17.19)	12.53 (11.59-16.62)	0.51 (0.46-0.73)	16.37 (15.31-21.58)	15.73 (14.55-20.86)	0.636 (0.58-0.92)
Other regions in Oceania*	4.263 (3.89-7.76)	3.184 (2.53-6.78)	1.08 (0.75-1.62)	18.19 (16.61-33.14)	13.59 (10.78-28.92)	4.602 (3.20-6.89)

eCI= empirical confidence interval. *Regions in Oceania except for Australia and New Zealand.