Stroke

ORIGINAL CONTRIBUTION

Extreme Temperatures and Stroke Mortality: Evidence From a Multi-Country Analysis

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BACKGROUND: Extreme temperatures contribute significantly to global mortality. While previous studies on temperature and stroke-specific outcomes presented conflicting results, these studies were predominantly limited to single-city or single-country analyses. Their findings are difficult to synthesize due to variations in methodologies and exposure definitions.

METHODS: Within the Multi-Country Multi-City Network, we built a new mortality database for ischemic and hemorrhagic stroke. Applying a unified analysis protocol, we conducted a multinational case-crossover study on the relationship between extreme temperatures and stroke. In the first stage, we fitted a conditional quasi-Poisson regression for daily mortality counts with distributed lag nonlinear models for temperature exposure separately for each city. In the second stage, the cumulative risk from each city was pooled using mixed-effect meta-analyses, accounting for clustering of cities with similar features. We compared temperature-stroke associations across country-level gross domestic product per capita. We computed excess deaths in each city that are attributable to the 2.5% hottest and coldest of days based on each city's temperature distribution.

RESULTS: We collected data for a total of 3 443 969 ischemic strokes and 2 454 267 hemorrhagic stroke deaths from 522 cities in 25 countries. For every 1000 ischemic stroke deaths, we found that extreme cold and hot days contributed 9.1 (95% empirical CI, 8.6–9.4) and 2.2 (95% empirical CI, 1.9–2.4) excess deaths, respectively. For every 1000 hemorrhagic stroke deaths, extreme cold and hot days contributed 11.2 (95% empirical CI, 10.9–11.4) and 0.7 (95% empirical CI, 0.5–0.8) excess deaths, respectively. We found that countries with low gross domestic product per capita were at higher risk of heat-related hemorrhagic stroke mortality than countries with high gross domestic product per capita (P=0.02).

CONCLUSIONS: Both extreme cold and hot temperatures are associated with an increased risk of dying from ischemic and hemorrhagic strokes. As climate change continues to exacerbate these extreme temperatures, interventional strategies are needed to mitigate impacts on stroke mortality, particularly in low-income countries.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: climate change ■ extreme cold ■ hemorrhagic stroke ■ ischemic stroke ■ temperature

Nonoptimal temperatures, hot and cold, contribute significantly to global mortality and are responsible for ≈5 million deaths each year.[1] They could account for 13% of cardiovascular deaths[2] and 5.2% of global stroke deaths.[3] These figures come from studies that analyzed all-cause, cardiovascular, or stroke deaths. Each stroke subtype presents with its own unique pathology, necessitating specialized attention. Yet, studies on the impact of extreme temperatures on specific stroke subtypes were not as conclusive.

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Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.123.045751.

For Sources of Funding and Disclosures, see page XXX.

Stroke is available at www.ahajournals.org/journal/str

Nonstandard Abbreviations and Acronyms

eCI	empirical confidence intervals
GDP	gross domestic product
ICD	International Classification of Disease
MCC	Multi-Country Multi-City
MMT	minimum mortality temperature
RR	relative risk

A search on the association between ischemic stroke and ambient temperatures yields conflicting results, with some studies finding no significant association and others noting marginal links with both hot and cold temperatures.[4–7] Studies on hemorrhagic stroke suggest a slight protective effect from higher temperatures, but no consistent relationship with cold temperatures was identified.[5,6] The existing literature on the relationship between temperature and different stroke subtypes primarily consists of single-city or single-country studies.[8] Collectively, these single-city studies are susceptible to publication bias. Further synthesis of the existing evidence is challenged by the range of statistical methods and study designs used. For example, true effects may be obscured when modeling approaches do not consider the complex nonlinear temperature relationships (ie, the U-shape relationship, where both extreme cold and hot temperatures can be detrimental).[9]

To address these research gaps, we built a multinational, multiregional stroke-specific mortality database and analyzed it with a standardized statistical framework capable of handling complex temperature modeling. In this analysis, we investigate the 2 most common causes of stroke, ischemic and hemorrhagic, and their associations with extreme hot and cold temperatures.

METHODS

Data Collection

The Multi-Country Multi-City (MCC) network, established in 2013[10] (website: http://mccstudy.lshtm.ac.uk/), constitutes one of the largest environmental health consortia of its kind, with researchers from >49 countries around the globe. We contacted investigators from each country to extract specific stroke deaths from governmental and regional death registries. Data collection in each country followed a unified protocol where investigators were instructed to extract the statistical underlying cause of death only if it was coded using the ninth or tenth revisions of the *International Classification of Diseases* (*ICD-9*/*ICD-10*). The World Health Organization defines the underlying cause of death as "the disease or injury which initiated the train of morbid events leading directly to death."[11] *ICD-9* and *ICD-10* codes for any cerebrovascular accident were 430 to 438 and I60 to I69, respectively. We narrowed the extraction to include only deaths from hemorrhagic stroke (*ICD-9*, 430–432; *ICD-10*, I60–I62) or ischemic stroke (*ICD-9*, 433–434; *ICD-10*, I63–I66). Sources of stroke mortality in each country are provided in the Table. The data were for the years 1979 to 2019, although not all cities had data for the entire period. Institutional approvals were obtained by each MCC participant in their respective country. This article follows the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines. Data were collected within the MCC network under a data sharing agreement and cannot be made publicly available. Researchers can refer to MCC participants, who are listed as coauthors of this article, for information on accessing the data for each country.

When available, temperature data for each location were gathered from ground-monitoring stations. In cities that had >1 weather station, we took the average across all stations for each day. In cities without ground-monitoring temperature data, we used downscaled climate reanalysis models for predicting temperature each day.[12] Details of the MCC environmental data and sources have been extensively described previously.[2,13] City-level climate zones and country-level gross domestic product (GDP) per capita were obtained from the Köppen-Geiger climate classification[14] and the World Bank,[15] respectively.

Statistical Analysis

The methodology for our statistical analysis largely relies on a protocol we previously outlined in detail.[2] We implemented a priori 2-stage statistical analysis to examine stroke-specific deaths using a case-crossover design. By design, the unit of analysis becomes the day and not the individual person, effectively eliminating any possible time-invariant confounding from individual characteristics such as age, gender, smoking, and co-morbidity, among others.[16] We first fitted a conditional quasi-Poisson regression for counts of daily mortality in each city. Compared with standard Poisson regression, a quasi-Poisson distribution accounts for overdispersion in the count data. We then fitted a 3-way interaction among year, month, and day of the week.[17] The indicator variables from the interaction terms are not estimated; rather, they are eliminated from the likelihood terms by conditioning on the sum of events in each stratum—a computationally efficient alternative to the conditional logistic case-crossover analysis.[17] Lagged temperature association with mortality in each city was modeled nonlinearly using distributed lag nonlinear models.[18] This technique combines 2 functions to model the risk across predictor and lag spaces. The 2 functions were represented by a quadratic B-spline with 3 internal knots placed at the 10th, 75th, and 90th temperature percentiles of each location[19] and a natural splines with 3 internal knots equally spaced in the log scale over a period of 14 lag days. In the second stage, the cumulative risk from each city was pooled using mixed-effect meta-analysis.[20] We used meta-predictors (fixed and random effects) to account for potential effect modification and clustering of cities with similar features. As in previous analyses,[2] we included 3 fixed-effect predictors: city-level average summer temperature, city-level average winter temperature, and country-level GDP per capita. The model included 2 levels of random effects where cities are nested within country-specific climate zones, allowing cities in the same country and climate zone to borrow information from each other. The country-specific and overall pooled effect estimates were predicted from the meta-regression model. We reported a significance test (*P* value) for predictors using an extended version of the Wald F test. The best linear unbiased predictions were then extracted for each

Table. Descriptive Statistics of the Official National and Regional Registries for Stroke Mortality and Temperature Data Sets in 25 Countries

Country	Stroke data source	Years	Cities	Ischemic stroke	Hemorrhagic stroke	Temp. mean (°C)	Temp. SD (°C)
Brazil	Ministry of Health	1997–2018	9	146 180	97 044	23.4	4.2
Canada	Canadian Mortality Database	1986–2015	26	92 448	56 242	6.8	10.9
Costa Rica	Instituto Nacional de Estadística y Censos	2000–2017	1	655	516	22.7	1.1
Cyprus	Causes of Death Database, Health Monitoring Unit, Ministry of Health	2004–2017	5	3954	981	20.4	6.2
Ecuador	Instituto Nacional de Estadística y Censos	2013–2019	2	3857	4806	21.0	5.4
Estonia	Estonian Causes of Death Registry	1997–2018	8	23 637	5385	6.2	8.9
Finland	Statistics Finland	1987–2018	1	10 302	5791	5.9	9.0
Guatemala	Instituto Nacional de Estadística, Unidad de Estadística de Salud	2009–2018	1	1162	916	19.4	1.6
Italy	Regional mortality registry of the Lazio Region	2006–2015	4	2110	8315	16.3	7.4
Japan	Ministry of Health, labor and Welfare	1979–2015	47	1 845 428	1 584 972	15.2	8.6
Kuwait	National Center for Health Information, Ministry of Health	2000–2016	1	4432	1937	27.1	9.8
Moldova	National Center for Health Management	2001–2010	1	2289	5581	10.8	9.8
Panama	Instituto Nacional de Estadística y Censo, Centro de Información Estadística.	2013–2016	1	118	219	28.1	1.1
Paraguay	Ministerio de Salud Pública y Bienestar Social, Dirección General de Información Estratégica en Salud	2004–2019	1	995	1248	23.3	5.3
Philippines	Philippine Statistics Agency	2006–2010	4	14 738	12 476	28.2	1.4
Portugal	Statistics Portugal	1990–2018	6	69 742	26 810	16.3	5.4
South Africa	Statistics South Africa	1997–2013	51	337 559	45 655	18.0	5.4
Spain	Spain National Institute of Statistics	2000–2018	6	51 033	25 615	17.1	6.6
Switzerland	Federal Office of Statistics (Switzerland)	1995–2016	8	39 057	10 705	10.5	7.5
Taiwan	Department of Health in Taiwan	2008–2016	3	10 544	11 079	24.1	5.1
Thailand	Ministry of Public Health	1999–2008	55	25 996	76 675	27.6	2.4
United Kingdom	Office of National Statistics	1990–2016	70	203 401	87 947	10.5	5.3
Uruguay	Ministerio de Salud Publica	2001–2018	1	14 565	6558	18.6	5.6
United States	National Center for Health Statistics	1985–2006	209	534 701	373 350	14.1	10.1
Vietnam	Provincial Department of Health, Ho Chi Minh	2010–2013	1	5066	3444	28.5	1.4
Total		1979–2019	522	3 443 969	2 454 267		

city. Using the best linear unbiased prediction, we identified the minimum mortality temperature (MMT), which is the temperature of the least number of stroke deaths in each city. We then calculated the cumulative relative risk (RR) across all lag days comparing any given temperature to the MMT. We reported the RR of extreme heat and cold cut points as the 99th and 1st percentiles of each city's distribution of temperatures, respectively. For a specific day and corresponding temperature, the attributable number of deaths refers to the cumulative impact of temperature on mortality aggregated at the log-RR across lag days up to 14 days. This is an extension to calculate excess deaths in distributed lag nonlinear model frameworks.[21] We then reported excess ischemic and hemorrhagic stroke deaths from all nonoptimal temperatures and from a range of extreme hot and cold days by summing the contributions for the coldest and hottest 2.5% of the days based on the temperature distribution within each city. In other words, in any given city, the extreme heat range was defined as all days where the temperature exceeded the 97.5th percentile for that city. Similarly, the extreme cold range was defined as all days where the temperature was below the 2.5th percentile of that city. We reported proportion of excess deaths as the number of additional deaths for every 1000 deaths. The 95% empirical CIs (eCI) around excess deaths estimates were computed from Monte Carlo simulations assuming a multivariate normal distribution of the best linear unbiased prediction of reduced coefficients.

In post hoc analyses, we explored additional meta-variables that could modify the temperature-stroke relationship beyond what is explained by GDP per capita and average summer/winter temperature. This secondary analysis examined variables including: (1) city-level SD of annual temperature, (2) country-level human development index (HDI), (3) city-level average motorized time travel to health care facilities,[22] (4) city-level SD of motorized time travel to health care facilities,[22] and (5) city-level Global Gridded Relative Deprivation Index.[23] These metrics collectively capture additional meteorologic dynamics, socioeconomic factors, health care accessibility, and community-specific health vulnerabilities.

RESULTS

We collected data on a total of 3 443 969 ischemic stroke and 2 454 267 hemorrhagic stroke deaths from 522 cities in 25 countries (Table). Mortality data covered overlapping time periods that ranged from January 1, 1979 (Japan) to December 31, 2019 (Paraguay and Ecuador).

There were similar features in exposure-response curves for ischemic and hemorrhagic strokes (Figure 1). Both types of strokes exhibited a U-shaped relationship with a higher risk of death at both high and low temperatures. The pooled RR of death from extreme cold (at the first percentile versus MMT) was higher for hemorrhagic stroke (1.49 [95% CI, 1.40–1.58]) than ischemic stroke (1.34 [95% CI, 1.27–1.41]). On the contrary, the pooled RR of death from extreme heat (at the 99th percentile versus MMT) was greater for ischemic stroke (1.13 [95% CI, 1.06–1.20]) than for hemorrhagic stroke (1.02 [95% CI, 1.00–1.05]). The MMT for ischemic stroke (81st percentile) was substantially higher compared with hemorrhagic stroke (97th percentile), which left a high risk of death for only very hot days. The actual temperatures of the MMT for each country are provided in Table S1.

Out of every 1000 ischemic stroke deaths, the coldest 2.5% of days contributed to 9.1 excess deaths (95% eCI, 8.6–9.4), while the hottest 2.5% of days accounted for 2.2 excess deaths (95% eCI, 1.9–2.4). For hemorrhagic stroke, the coldest 2.5% of days resulted in a larger contribution of 11.2 excess deaths per 1000 hemorrhagic stroke deaths (95% eCI, 10.9–11.4). In contrast, the hottest 2.5% of days resulted in 0.7 excess deaths per 1000 hemorrhagic stroke deaths (95% eCI, 0.5–0.8), translating to roughly 7 excess deaths for every 10 000 hemorrhagic stroke deaths. Country-by-country estimates of excess ischemic and hemorrhagic stroke deaths are shown in Figure 2 and Table S2. Excess deaths from all nonoptimal hot and cold temperatures (not just the coldest and hottest 2.5% of days) are provided in Table S3. Effect sizes of RRs of death in each country are provided in Table S4.

Our analysis of meta-predictors is presented in Figure 3. We found that country-level GDP per capita modifies the relationship between temperature and hemorrhagic stroke mortality (P=0.02). In contrast, we found no significant effect of the modification of GDP per capita on the temperature-ischemic stroke mortality relationship (P=0.26). Specifically, countries with lower GDP per capita demonstrated a higher risk of heat-related hemorrhagic stroke deaths compared with countries with higher GDP per capita (RR, 1.08 [95% CI, 1.02–1.15] versus 1.00 [95% CI, 0.99–1.01]). Conversely, the heat-related ischemic stroke mortality risk did not significantly differ between countries of high (RR, 1.11 [95% CI, 1.05–1.17]) and low (RR, 1.17 [95% CI, 1.05–1.29]) GDP per capita. Cold temperatures were associated with a high risk of both ischemic and hemorrhagic stroke mortality in countries with a lower GDP per capita. Pooled RRs of stroke mortality from heat and cold stratified by GDP per capita are provided in Table S5. Furthermore, cities that experience extremely cold winters and hot summers have a high risk of hemorrhagic stroke mortality. The impact of summer and winter temperatures on ischemic stroke mortality produced mixed results that were hard to interpret.

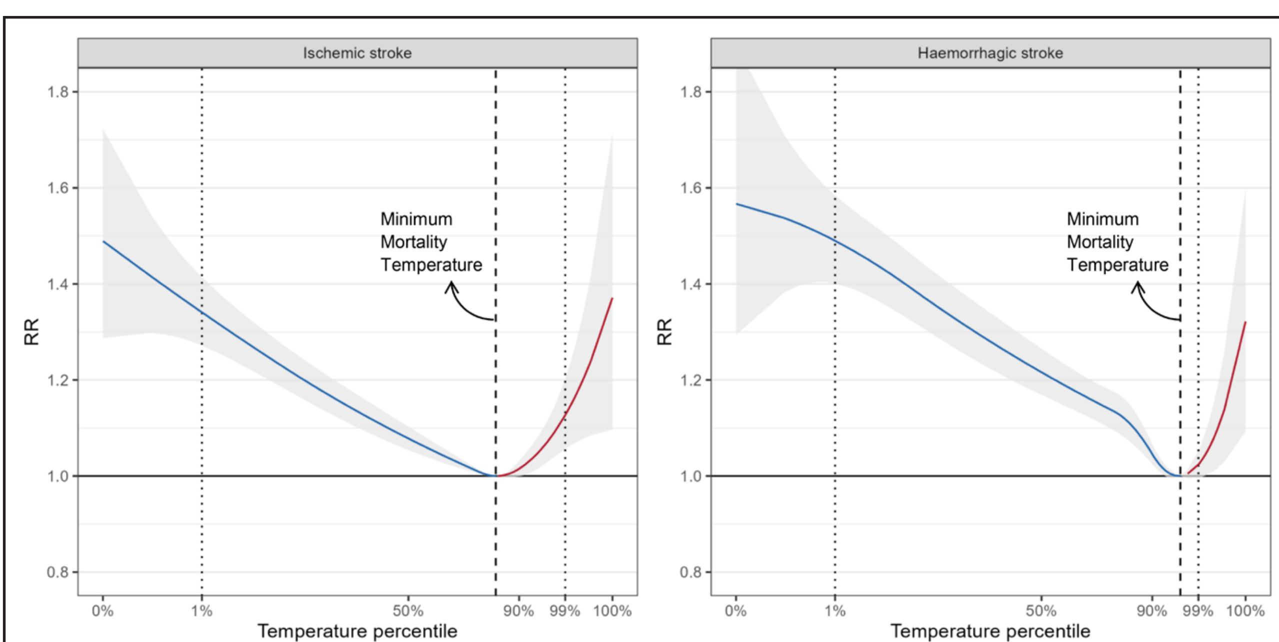


Figure 1. Pooled exposure-response relationships between overall temperature percentiles and relative risk (RR) of ischemic and hemorrhagic stroke mortality from 522 cities in 25 countries.

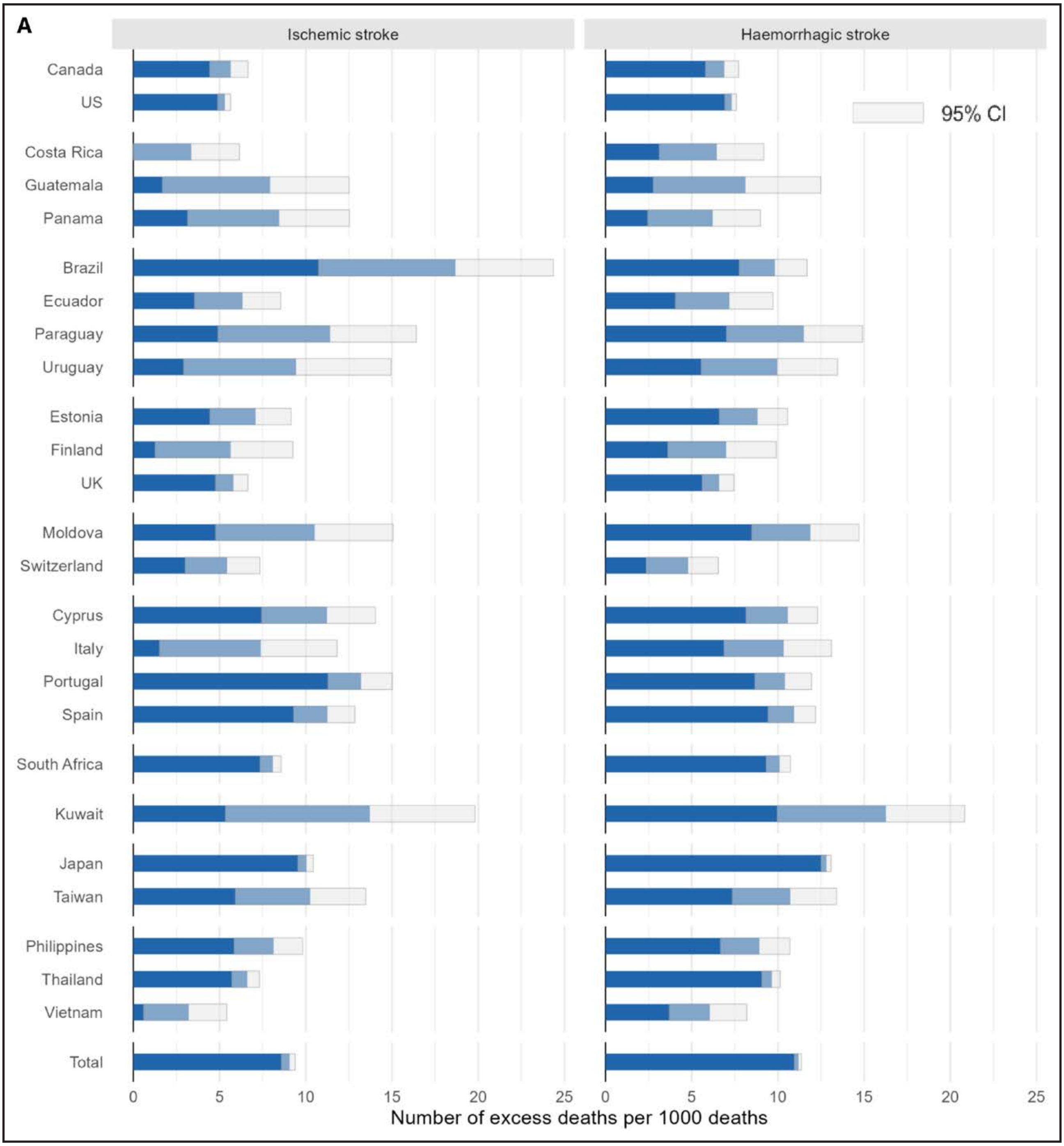
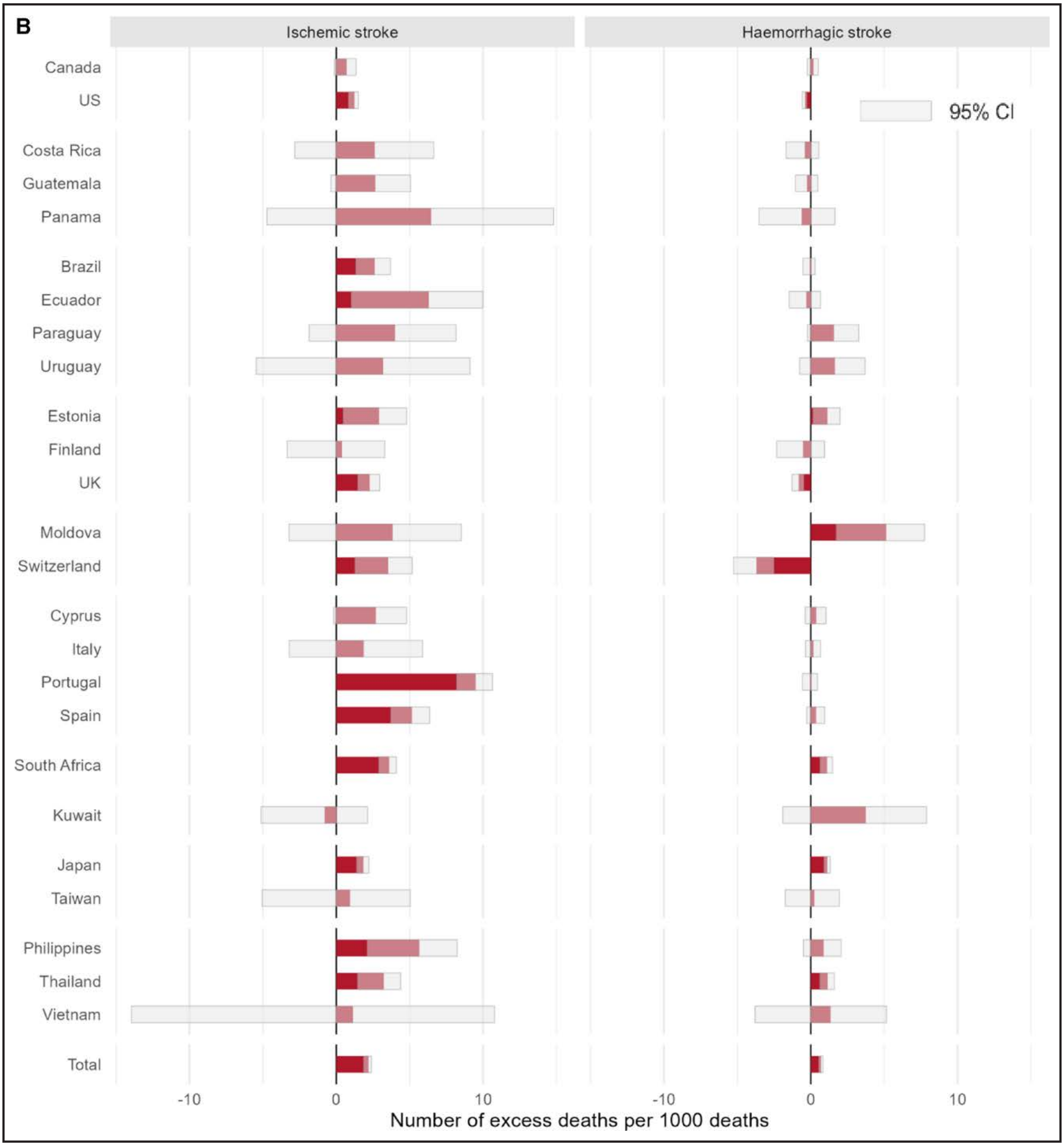


Figure 2. Proportion of excess deaths for every 1000 hemorrhagic and ischemic stroke deaths.
The results are shown for (**A**) extremely cold days (lower than the 2.5th percentile of temperature) and (**B**) extremely hot days (higher than the 97.5th percentile of temperature). (*Continued*)

Post hoc analyses of additional meta-predictors showed no significant (*P*>0.10) effect measure modification by city-level SD of annual temperature, country-level human development index, city-level average motorized time travel to health care facilities, city-level SD of motorized time travel to health care facilities, or deprivation index (results not shown).

DISCUSSION

This study comes from what we think is the largest multinational investigation into stroke-specific mortality risk and extreme temperatures. Previous large-scale environmental health investigations used a catch-all outcome such as any stroke mortality, which does not capture



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distinct pathologies for different types of strokes. We analyzed >3.4 million ischemic stroke deaths and 2.4 million hemorrhagic stroke deaths across 522 cities in 25 countries using the same statistical analysis protocol (ie, applied universally to all cities and countries). We found that both extreme hot and cold temperatures contribute to an increased mortality risk from both ischemic and hemorrhagic strokes. However, the estimated impact of these temperature extremes differed between stroke types. Notably, extreme cold temperatures presented a more pronounced association with the risk of death from hemorrhagic stroke compared with ischemic stroke. In contrast, extreme heat was associated with substantially increased deaths from ischemic stroke, while the estimated risk of death from hemorrhagic stroke was lower. Analysis stratified by GDP per capita showed that low-income countries may bear a higher burden of heat-related hemorrhagic stroke mortality.

Previous estimates of the relationship between ischemic stroke and ambient temperatures have shown

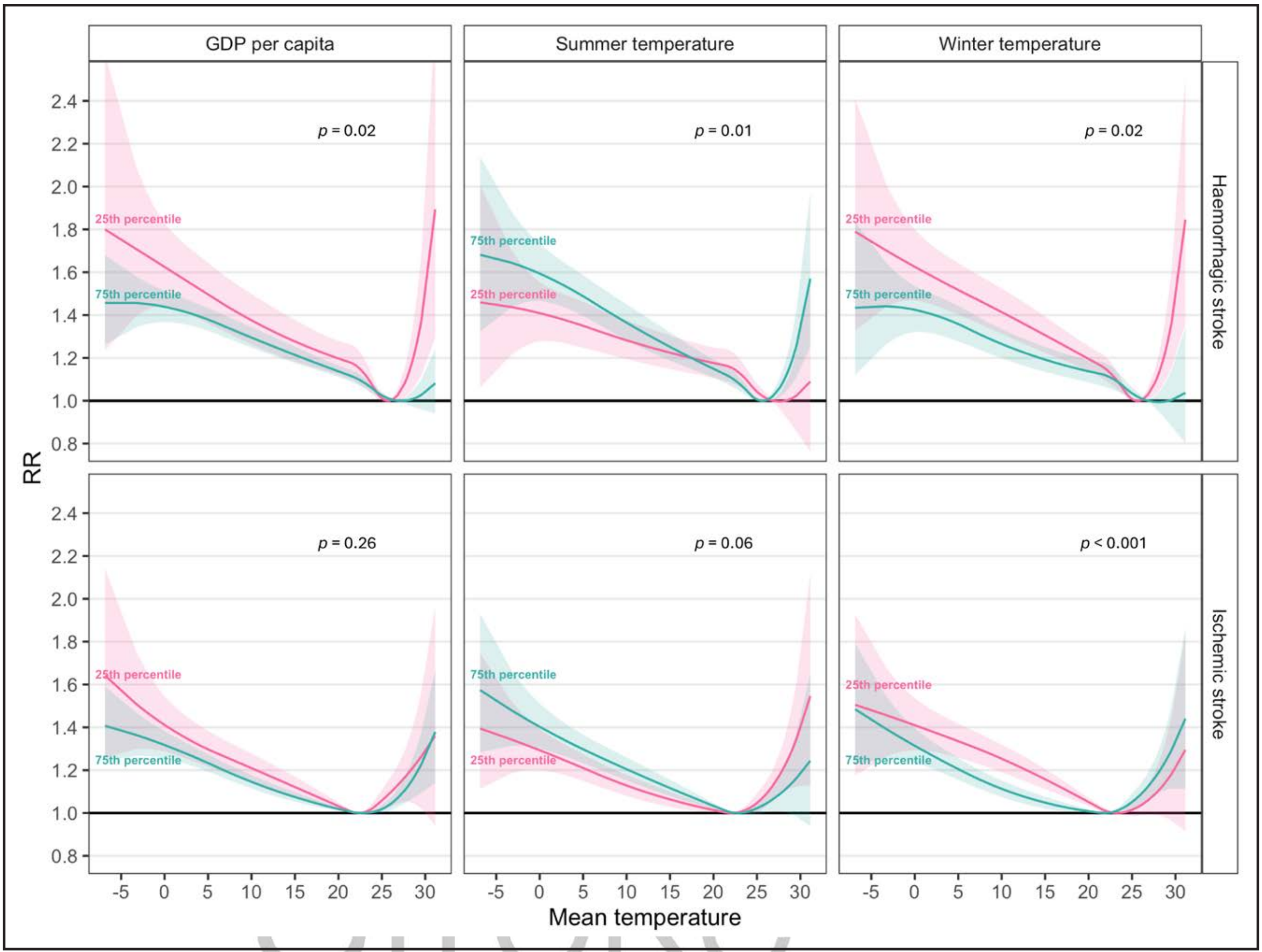

Figure 3. Pooled exposure-response relationships between overall temperatures (in °C) and relative risk (RR) of ischemic and hemorrhagic stroke mortality after stratifying by the 25th and 75th percentile of country-level gross domestic product (GDP) per capita (75th, higher GDP countries; 25th, lower GDP countries), city-level mean summer temperature (75th, warmer summers cities; 25th, cooler summers cities), and city-level mean winter temperature (75th, warmer winters cities; 25th, cooler winters cities).

conflicting results. In a systematic review and meta-analysis (8 studies, 290 154 patients) conducted by Wang et al,[4] no significant relationship was seen between extreme temperatures and ischemic stroke admissions. Similarly, after adjusting for potential confounders, Zorrilla-Vaca et al[6] did not find a significant association between the incidence of ischemic stroke and low temperatures. However, Lian et al,[5] in another systematic review (20 studies, 2 070 923 events), found that both hot and cold temperatures were marginally associated with an increased risk of ischemic stroke. With regards to hemorrhagic stroke, a meta-analysis by Lian et al[5] found that higher temperatures were associated with modest protective effects (−1.9% [95% CI, −2.8 to −0.9%], for every 1 °C increase). No association was found between hemorrhagic stroke and cold ambient temperatures. Zorrilla-Vaca et al[6] and Wang et al[4] found no association between ambient temperatures and hemorrhagic stroke in their respective meta-analyses. In this multi-country study, we had higher statistical power to disentangle different risks and investigate effect modifiers on the most common causes of stroke with minimal risk of publication bias.

Despite advancements in stroke prevention and treatment, stroke was the second-leading cause of death in 2019, accounting for 11.6% of total deaths worldwide.[24] Stroke incidence and mortality burden disproportionately affect low- and middle-income countries, where patients are typically younger. The Global Burden of Disease's investigation into the global burden of stroke noted that the age-standardized mortality rate for stroke was 3.6× higher in low-income countries compared with high-income countries.[24] In this study, we found evidence for effect measure modification in countries with low GDP per capita, where extreme hot temperatures were associated with increased risk of hemorrhagic stroke mortality compared with countries with high GDP per capita, but the risk of ischemic stroke mortality was not associated with increased risk. Colder temperatures in low GDP per capita countries were associated with an increased risk of both ischemic and hemorrhagic stroke deaths compared with estimated effects in high GDP per capita countries; however, the evidence was suggestive and not conclusive. We tested whether motorized time travel to a health care facility could partially explain this difference, but we found no evidence of effect measure modification by this variable. We hypothesize that countries with high GDP per capita may have an increased ability to mitigate exposure to extreme temperatures (eg, indoor cooling and heating) and a decreased rate of outdoor work. Additionally, low-income countries might have limited resources to detect, treat, and manage risk factors for hemorrhagic stroke. This includes potential shortcomings in providing timely surgical intervention for specific types of hemorrhagic strokes, rendering these populations more vulnerable to the adverse effects of extreme temperatures.

Extreme temperatures can cause several physiological changes that can lead to ischemic and hemorrhagic strokes. Extreme cold results in a decreased core body temperature, which can result in increased sympathetic activity, vasoconstriction, increased skeletal muscle tone to conserve heat, and high blood pressure.[25,26] Hypertension increases the risk of both ischemic and hemorrhagic strokes.[27] Hypothermia is associated with an increased risk of bleeding. Perioperative evidence shows that even mild hypothermia (<1 °C) increases blood loss by ≈16% (4%–26%) and increases the need for blood transfusion.[28] Cholesterol crystallization from cold exposure may also increase in atherosclerotic plaques, leading to a risk of plaque rupture, which increases the risk of ischemic stroke.[29] On the contrary, extreme heat can result in an elevated body temperature, leading to volume depletion, sympathetic activation, and increased oxygen consumption, eventually leading to tachycardia.[30] In individuals with preexisting cardiovascular disease, the hypermetabolic state can lead to ischemia or plaque rupture.[31] Hyperthermia causes dehydration, which leads to an abnormally high concentration of red blood cells.[32] This can lead to a hypercoagulable state, which can increase the risk for thrombosis and, as a result, ischemic stroke.[30] High temperatures can also affect cellular endothelial and protein function, especially the chaperone family of heat shock proteins, leading to systemic inflammation, which contributes to the progression of both ischemic and hemorrhagic stroke.[33,34]

Even as age-standardized rates of stroke mortality decreased, the absolute number of stroke-related deaths increased by 43% between 1990 and 2019.[24] Our findings indicate that out of every 1000 ischemic stroke deaths, 11 can be attributed to the most extreme hot and cold days. A similar estimate was found for hemorrhagic stroke mortality. Though our study may not generate direct evidence for clinical practice, we encourage professional stroke societies and the scientific community to devote further research and attention to emerging environmental risk factors such as extreme temperatures and to identify gaps for future intervention studies. Given the escalating impact of climate change on extreme temperatures, we foresee a widening disparity in stroke mortality between high- and low-income countries, as the latter are likely to bear a larger share of climate effects without effective mitigation strategies.

This study has several limitations. First, the pooled results should not be interpreted as global estimates. There are many countries and regions in the world that were not included in our analysis. In particular, we anticipate that the effects of temperature on stroke mortality may be heightened in regions with high average temperatures and low economic resources. Our data are underrepresented in low-income countries, especially in South Asia, Africa, and the Middle East, and largely reflects urban settings. Second, our data were limited to only fatal ischemic and hemorrhagic strokes. Studying the incidence of nonfatal strokes (ie, hospitalization) will provide further understanding of the actual burden of temperature and stroke on disability and health care systems. Third, hemorrhagic stroke mortality was a composite outcome for 3 categories: nontraumatic subarachnoid hemorrhage (*ICD-10*, I60), nontraumatic intracerebral hemorrhage (*ICD-10*, I61), and other and unspecified nontraumatic intracranial hemorrhage (*ICD-10*, I62). We were not able to collect these subtypes of hemorrhagic stroke mortality. Additionally, although they cannot be confounders, individual-level characteristics such as age, sex, and education were not examined as effect measure modifiers in our study. Our initial data collection protocol was primarily centered on broader, aggregate counts, and as a result, these detailed individual-level demographics were not collected. Finally, our temperature exposure data were based on monitoring stations and climate reanalysis data and not on the actual perceived microenvironment temperature (eg, inside homes). Differences in activity patterns, housing conditions, and occupational exposure (eg, outdoor workers) impact the relationship between personal exposures and the ambient temperatures analyzed in this study.

CONCLUSIONS

The public health burden from extreme hot and cold temperatures is substantial. Extreme temperatures increase the risk of hemorrhagic and ischemic stroke deaths. As climate change is driving more extreme temperatures and weather events, urgent attention to clinical care, adaptation, and mitigation is needed to minimize the risk of death from stroke, especially in low-income countries.

ARTICLE INFORMATION

Received November 8, 2023; final revision received March 27, 2024; accepted April 9, 2024.

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Sources of Funding

This study was supported by the Kuwait Foundation for the Advancement of Science (Grant ID: CB21-63BO-01), the Medical Research Council-UK (Grant ID: MR/V034162/1), the European Union's Horizon 2020 Project Exhaustion (Grant ID: 820655), the Swiss National Science Foundation (Grant ID: TMSGI3_211626), and the National Institutes of Health (Grant ID: R01ES034038).

Disclosures

Dr Garshick receives grant support from the US Department of Veterans Affairs and is an author for UpToDate. Dr Zanobetti receives grant support from the National Institutes of Health. Dr Bell receives grant support from US Environmental Protection Agency, National Institutes of Health, High Tide Foundation, Health Effects Institute, Yale Women Faculty Forum, Environmental Defense Fund, Wellcome Trust Foundation, Yale Climate Change and Health Center, Robert Wood Johnson Foundation, Hutchinson Postdoctoral Fellowship, and Institute of Physics. The other authors report no conflicts.

Supplemental Material

Tables S1–S5

APPENDIX

Multi-Country Multi-City (MCC) Network Group author list:

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