

# Geographical Variations of the Minimum Mortality Temperature at a Global Scale

## A Multicountry Study

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**Background:** Minimum mortality temperature (MMT) is an important indicator to assess the temperature-mortality association, indicating long-term adaptation to local climate. Limited evidence about the geographical variability of the MMT is available at a global scale.

**Methods:** We collected data from 658 communities in 43 countries under different climates. We estimated temperature-mortality associations to derive the MMT for each community using Poisson regression with distributed lag nonlinear models. We investigated the variation in MMT by climatic zone using a mixed-effects meta-analysis and explored the association with climatic and socioeconomic indicators.

**Results:** The geographical distribution of MMTs varied considerably by country between 14.2 and 31.1 °C decreasing by latitude. For climatic zones, the MMTs increased from alpine (13.0 °C) to continental (19.3 °C), temperate (21.7 °C), arid (24.5 °C), and tropical (26.5 °C). The MMT percentiles (MMTPs) corresponding to the MMTs decreased from temperate (79.5th) to continental (75.4th), arid (68.0th), tropical (58.5th), and alpine (41.4th). The MMTs increased by 0.8 °C for a 1 °C rise in a community's annual mean temperature, and by 1 °C for a 1 °C rise in its SD. While the MMTP decreased by 0.3 centile points for a 1 °C rise in a community's annual mean temperature and by 1.3 for a 1 °C rise in its SD.

**Conclusions:** The geographical distribution of the MMTs and MMTPs is driven mainly by the mean annual temperature, which seems to be a valuable indicator of overall adaptation across populations. Our results suggest that populations have adapted to the average temperature, although there is still more room for adaptation.

**Keywords:** Minimum mortality temperature; Climate; Adaptation; Time-series; Distributed lag nonlinear models; Multi-city; Multi-country

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## Background

Studies on the temperature-mortality association have focused on quantifying the increase in risk due to heat and cold<sup>1,2</sup> and its determinants.<sup>3</sup> The temperature-mortality relationship has been described as a J- or U-shaped curve, where the minimum is the temperature at which the risk of mortality is lowest.<sup>1,2,4</sup> Consequently, the minimum mortality temperature (MMT) is an important indicator to characterize associations between temperature and health, in particular regarding long-term

## What this study adds

The minimum mortality temperature (MMT) is an important indicator of the relationship between temperature and mortality. It indicates the adaptability to climate, but little is known about its geographical changes in the global distribution. This article investigates the geographic differences of the MMT on a global scale and studies the influence of geographical, climatic, and socioeconomic factors. The results indicate that although there is still more room for adaptation, populations have adapted to the average temperature.

adaptation to climate. The MMT and how it varies across cities with different climates has been investigated only at the local level in some countries,<sup>4-6</sup> but a comprehensive evaluation has not been performed so far.

Adaptation could offset some of the mortality from higher temperatures by shifting the MMT to higher values. Although MMT is essential to estimate the future health impact of global-heating, little is known about the geographical variation of the MMT distribution at a global scale and the underlying factors that could explain the variation of MMTs. Identifying correctly these factors that play a key role on MMTs would help developing and implementing population-based effective adaptation strategies.

In this context, the Multi-City Multi-Country (MCC) Collaborative Research Network (<http://mccstudy.lshtm.ac.uk/>) provides the opportunity to investigate geographical variations in MMTs at a global scale. We aimed to estimate MMTs using data from hundreds of communities across various countries under different climates and to study the geographical, climatic, and socioeconomic determinants of the MMT. To our knowledge, this is the most extensive study ever conducted using daily mortality and temperature data to determine geographical variations in MMTs.

## Methods

### Data collection

Data collection has been described in previous studies using the MCC Collaborative Research Network dataset.<sup>1-3,7-9</sup> In this study, we used daily time-series data from 658 communities in 43

countries worldwide (eFigure 1; <http://links.lww.com/EE/A152>). The study periods largely overlapped, ranging from 1 January 1984 to 31 December 2016. The data included observed daily mortality for all causes or nonexternal causes (International Classification of Diseases 9th Revision, ICD-9: 0-799, and 10th Revision, ICD-10: A00-R99) and daily mean temperature, for each community. Additional details on data collection are provided in eTable 1; <http://links.lww.com/EE/A152>.

We also collected data on community-specific geographical (latitude and geographical region), climatic (annual mean temperature and its SD, and climate zone using Köppen's climate classification<sup>10</sup>), and socioeconomic (gross domestic product per capita [GDP]) indicators. In particular, GDP was collected from the OECD Regional Database at the smallest geographical level available using the value averaged across multiple years compatible with our dataset.<sup>3</sup>

### Statistical analysis

We first performed a community-specific time-series analysis using generalized linear models with quasi-Poisson family. The model includes a natural cubic spline of time with 8 degrees of freedom per year to control for seasonal and long-term trends and indicator variables for the day of the week. We modeled the temperature-mortality association with distributed-lag nonlinear models. Specifically, we used a natural cubic spline with three internal knots placed at the 10th, 75th, and 90th percentiles of location-specific temperature distributions and the lag-response curve with a natural cubic spline with three internal knots placed at equally spaced values in the log scale. The lag period extended to 21 days. The modeling choices were based in previous MCC

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Data have been collected within the MCC (Multi-City Multi-Country) Collaborative Research Network (<https://mccstudy.lshtm.ac.uk/>) under a data sharing agreement and cannot be made publicly available. The R code for the analysis is available from the first author.

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studies addressing the temperature-mortality association.<sup>2,3,11</sup> These studies already conducted the corresponding sensitivity analyses to assure the robustness of results. We identified the MMT from each estimated spline curve representing the overall cumulative exposure-response (the net effect summed across lags), together with an approximate parametric bootstrap estimator of its confidence interval and standard error.<sup>6</sup> In previous studies, we had noted that in locations with low mortality counts and/or short time-series, the MMT could be one of the imprecisely estimated tails of the exposure-response curve.<sup>6</sup> To avoid this situation, we constrained the identification of the MMT to the 1st–99th percentile range. We also calculated the MMT percentile (MMTP), defined as the percentile of the temperature distribution corresponding to the MMT.

In a second stage, we pooled the city-specific MMTs and MMTPs by country, geographical region and climatic zone using an extended random-effects meta-analysis,<sup>12</sup> and quantified the heterogeneity using the  $I^2$  statistic.<sup>13</sup> We explored the association between MMT, and MMTP, and the communities' geographical, climatic, and socioeconomic characteristics by including the absolute value of latitude, annual mean temperature, its SD, and GDP simultaneously as fixed-effects predictors in the meta-analytical models. We also evaluated the linearity of the associations comparing the log-likelihood between the linear and nonlinear fit. The models were specified as a two-level hierarchical random-effects meta-regression, with communities and countries as two nested levels of random-effects<sup>12</sup>; thus, accounting for heterogeneity across both. The temperature-mortality association and MMTs have been suggested different by climatic zones implying population adaptation to the local climate.<sup>4,14</sup> Therefore, we ran stratified models to get specific estimates by climatic zone and tested for effect modification using a likelihood ratio test between nested models estimated by maximum likelihood with and without interaction terms. Statistical analyses were performed in R software (version 3.6.2).

## Results

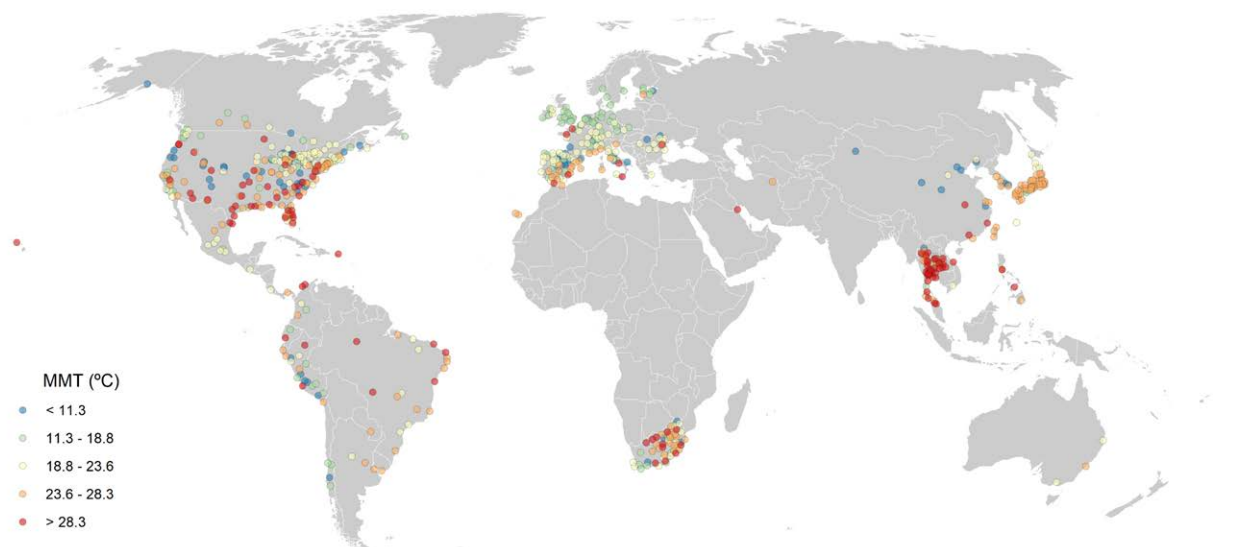
In 21 of the 658 communities analyzed, the MMT corresponded to the minimum value of the exposure-response curve, whereas in 34, the MMT corresponded to the maximum. After constraining to the 1st–99th percentile range, only six communities remained with an MMT at the minimum value of the exposure-response curve and eight communities at the maximum. These few communities showed a monotonic increase

or decrease of the exposure-response curve, so the 1st–99th percentile constraint merely increases the MMT estimate from the minimum value of the temperature distribution to the 1st percentile or decreases from the maximum to the 99th percentile. eFigure 2; <http://links.lww.com/EE/A152> shows the overall cumulative exposure-response curves in 43 communities, as the capital city or the largest city/area for each country, illustrating the wide range of relationships in estimating the MMT and its confidence interval.

The geographical distribution of the MMTs varied considerably worldwide (Figure 1). Country pooled MMTs ranged from 14.2 to 31.1 °C (eFigure 3; <http://links.lww.com/EE/A152>), and the MMT distribution showed an increasing north-to-south pattern in all the geographical regions (Figure 2). The MMT and MMTP distributions by country are reported in the eTables 2 and 3; <http://links.lww.com/EE/A152>, respectively. Similarly, for the climatic zones, the MMTs increased from alpine (13.0 °C) to continental (19.3 °C), temperate (21.7 °C), arid (24.5 °C), and tropical (26.5 °C). The MMTP distribution also showed large variation (Figure 3), and the country pooled MMTPs ranged from 5.3th to 98.7th (eFigure 4; <http://links.lww.com/EE/A152>). Conversely, for the climatic zones, the MMTPs tended to decrease from temperate (79.5th) to continental (75.4th), arid (68.0th), tropical (58.5th), and alpine (41.4th) (Figure 4).

We observed very large geographical heterogeneity in the MMT distribution ( $I^2 = 96.1\%$ ), which was substantially reduced after adjusting for the geographical, climatic and socioeconomic indicators in the meta-regression model ( $I^2 = 44.6\%$ ) (Table 1). Annual mean temperature and its SD were found to be associated independently with MMT but not latitude and GDP (eFigure 5; <http://links.lww.com/EE/A152>). MMTs increased by 0.8 °C for a mean annual temperature increase of 1 °C, and by almost 1 °C for an SD rise of 1 °C (Table 1). MMTPs also had large heterogeneity ( $I^2 = 90.2\%$ ) that was reduced after adjusting for predictors ( $I^2 = 68.7\%$ ). MMTPs were reduced when the mean annual temperature and its SD increased. Latitude and GDP were not found either to be associated with MMTP. We evaluated the linearity of the associations without observing evidence of departure from linearity.

We further explored these associations by climatic zones (Table 1). An average increase in annual mean temperature of 1 °C was associated with MMT increases of 0.8 °C in temperate, 0.9 °C in tropical, 1.1 °C in continental, and 1.7 °C in arid climates ( $P$  value for effect modification = 0.190). Estimates for Alpine climate were not possible to derive because there



**Figure 1.** Geographical distribution of the MMT (°C) in the 658 communities analyzed.

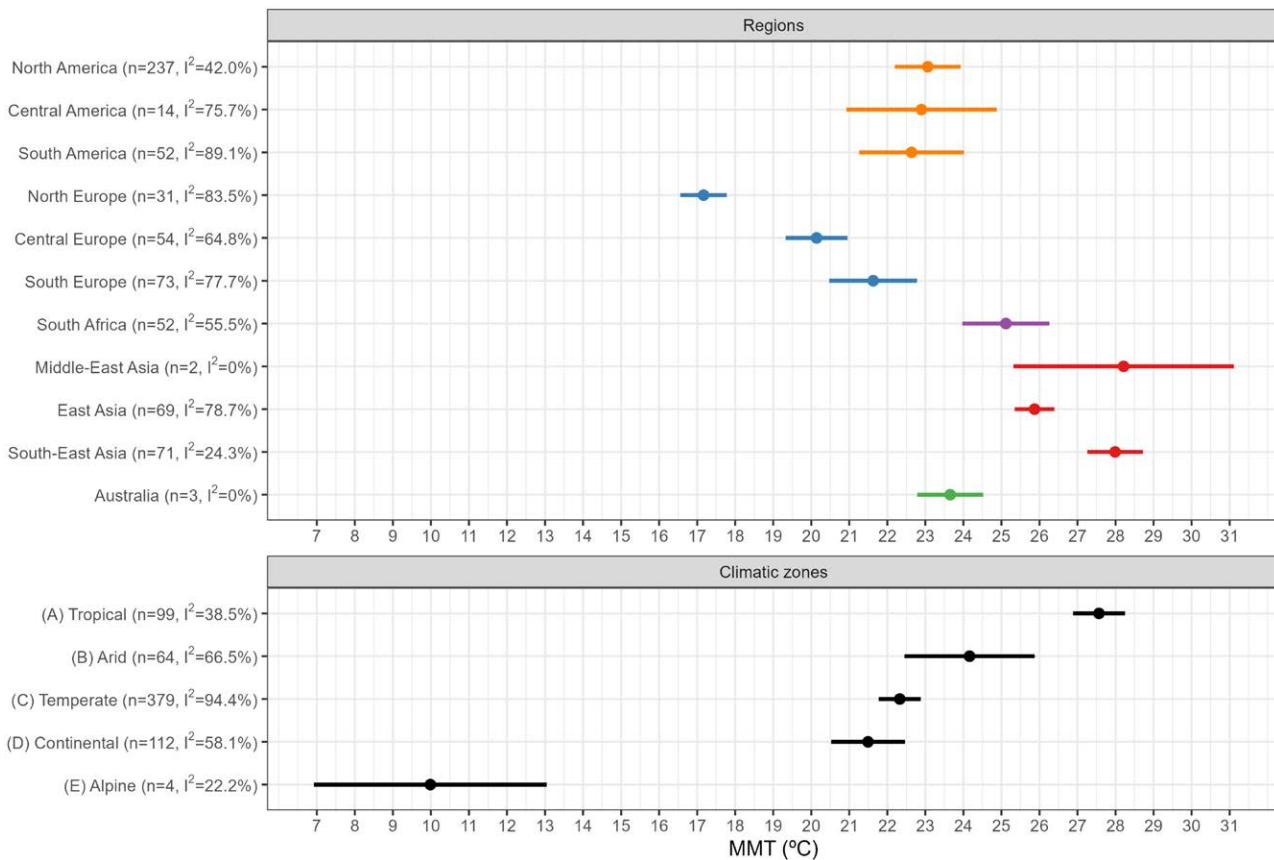


Figure 2. Pooled MMT (°C) by geographical region and Köppen's climate classification.

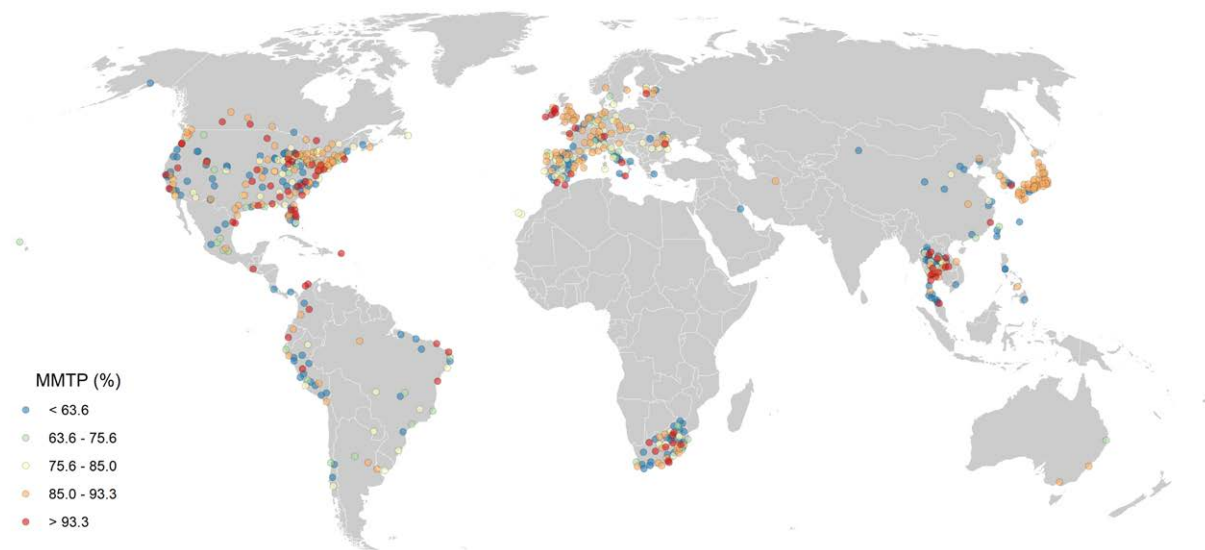


Figure 3. Geographical distribution of the MMTP (%) in the 658 communities analyzed.

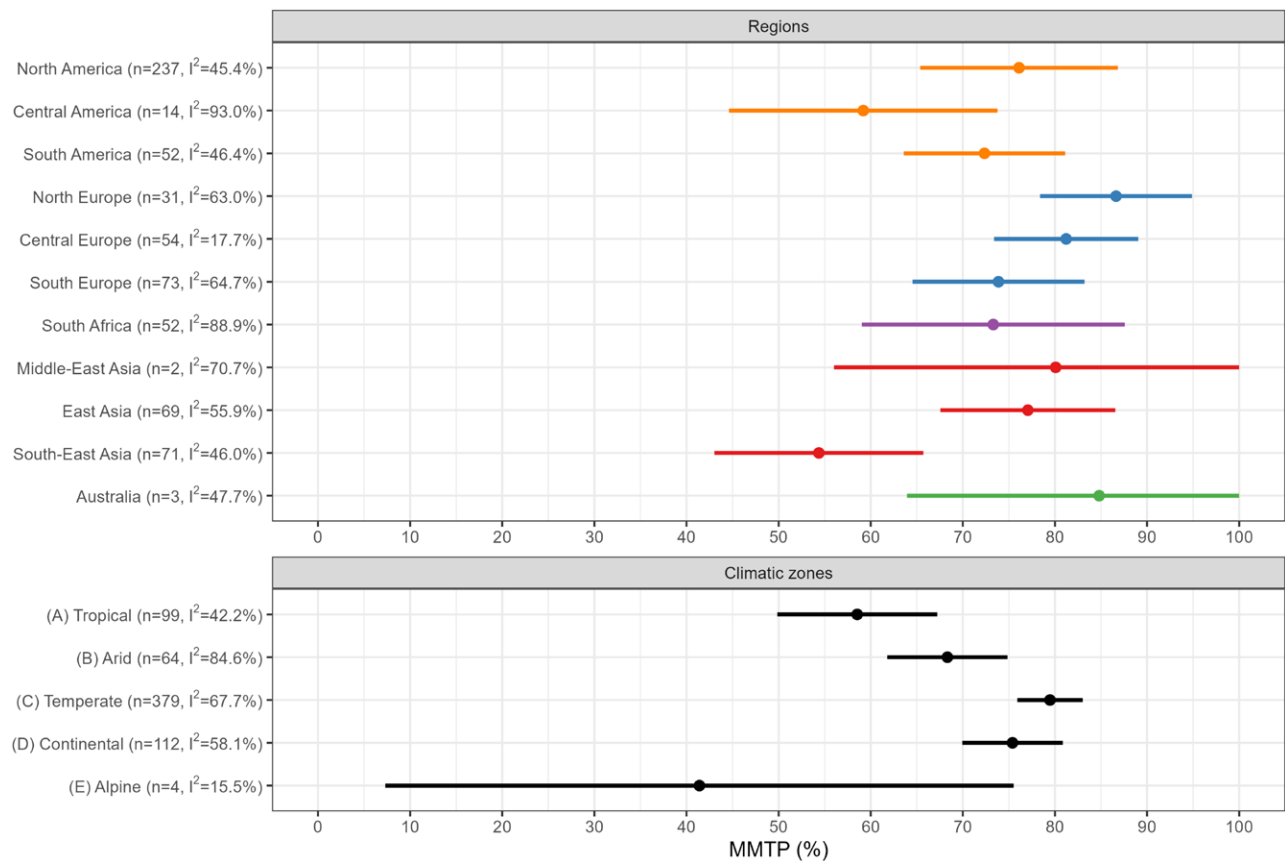
were only four cities included. For the temperature's SD, an average increase of 1 °C was associated with an increase in MMT of 0.3 °C in arid climate, 0.6 °C in tropical, 0.8 °C in temperate, and 1.1 °C in continental climates (*P* value for effect modification = 0.288).

### Discussion

In this study, we investigated variations in MMT at a global scale and its geographical, climatic, and socioeconomic determinants.

Overall, we found that increases in local annual mean temperature and its SD were associated with higher MMTs and lower MMTPs.

Extreme high temperatures have increased in frequency and intensity, which in turn is increasing heat-related mortality.<sup>15</sup> It is reasonable to assume that, to some extent, people and societies can adapt to gradual increases in average temperatures. MMT is often regarded as an indicator of climate adaptation. If the absolute value of the MMT was fixed and all other factors were held constant, higher temperatures would shift the relative



**Figure 4.** Pooled MMTP (%) by geographical region and Köppen's climate classification.

MMT (MMTP) to a lower percentile of the temperature distribution.<sup>16</sup> Similarly, if the MMTP was fixed at a specific percentile of temperature distribution, warmer climates would tend to increase the absolute value of the MMT.<sup>17</sup> Complete adaptation can be determined by a unitary MMT-mean temperature association (i.e., when MMT increases on average 1 °C for a mean rise of 1 °C of the mean annual temperature) and no variation in MMTP dependent on the mean temperature. Our results of increased local annual mean temperature associated with higher MMT indicates that populations have adapted to the average temperature to a certain degree, but the negative association of MMTP with mean annual temperature suggests that this adaptation is incomplete. The exceedance over the MMT-temperature unitary association observed in continental (1.1 °C) and arid (1.7 °C) climates may be explained by contributions of factors other than adaptation processes such as demographic, infrastructural characteristics, and socioeconomic development or people's behavior that are unrelated to the responses to average temperature. Some of the overadaptation processes such as an overuse of air conditioning could be also an explanation.<sup>18</sup> Although the unitary increase in MMT with mean temperature observed cross-sectionally indicates long-term adaptation, it does not imply that the same result will be observed over time in the future. Moreover, the positive association between MMT and the temperature SD in temperate and continental climates suggests that populations living in areas with larger temperature variations and distinct seasonal temperature changes may be more resilient to higher temperatures and, therefore, have higher MMTs than other populations.

These findings may help in understanding the mechanism of long-term adaptation to climate at the population level. Keatinge et al.<sup>19</sup> stated that populations in Europe had adjusted successfully to mean summer temperatures and heat-related

risk of mortality was reported to be declining over time<sup>20,21</sup> suggesting adaptation to elevated temperatures. Since a warming trend has been observed, it may be possible to determine how fast populations and societies adapt to the changing climate, by evaluating changes in MMT.<sup>5</sup> Curriero et al.<sup>4</sup> reported that the MMT was associated with latitude in a multicity study conducted in 11 cities of the Eastern United States, and similarly, Baccini et al.<sup>22</sup> in 15 European cities. However, the latitude may not be a useful climatic index, because, for example, altitude can also affect climate, and areas with same latitude and altitude can have different climates.<sup>5</sup> In fact, we did not find evidence of an association between MMT and latitude once the other meta-predictors, in particular mean temperature, were accounted for. More recently, Yin et al.<sup>23</sup> reported that the most frequent temperature was a better indicator for fitting MMT. However, the authors collected data from previously published studies which provided MMT estimates and derived the most frequent temperature in the same period, but did not use temperature data from the weather stations used to estimate the MMT in the original studies, which could cause uncertainties. Similarly, the authors also acknowledged the different parameter specifications from the published studies was a limitation, especially when empirical MMTs derived from the observed exposure-response curves were combined with those from using best linear unbiased curves.<sup>2</sup>

The MMT for all-cause mortality is a function of cause-specific MMTs and cause composition. For example, the shape of the association between temperature and cardiovascular disease mortality is in general J- or U-shaped,<sup>24-26</sup> whereas that for infectious disease mortality shows various patterns such as inverse U-shaped or reverse-J-shaped.<sup>27,28</sup> This suggests that cause-composition should be an important driver of variation in the MMTs.

**Table 1.** Associations between the MMT (°C) and MMTP (%) with geographical, climatic, and socioeconomic indicators, from random-effects meta-regression analysis

	MMT (°C)			MMTP (%)		
	b	(95% CI)	I <sup>2b</sup>	b	(95% CI)	I <sup>2b</sup>
Overall			44.6			68.7
Latitude (×10°)	-0.30	(-0.76, 0.16)		4.28	(0.26, 8.30)	
Annual mean temperature (°C)	0.81	(0.73, 0.88)		-0.21	(-0.92, 0.50)	
SD temperature (°C)	1.06	(0.90, 1.22)		-1.26	(-2.45, -0.07)	
GDP (×10,000 US\$)	-0.05	(-0.48, 0.39)		1.17	(-1.74, 4.07)	
Climatic zones <sup>a</sup>						
(A) Tropical (n = 99)			26.3			42.3
Latitude (×10°)	-0.59	(-2.17, 1.00)		-8.49	(-28.02, 1.10)	
Annual mean temperature (°C)	0.91	(0.43, 1.39)		-0.32	(-5.89, 5.24)	
SD temperature (°C)	0.58	(-0.58, 1.76)		6.56	(-5.98, 19.11)	
GDP (×10,000 US\$)	0.24	(-1.00, 1.48)		0.93	(-11.84, 13.70)	
(B) Arid (n = 64)			55.3			83.4
Latitude (×10°)	-2.39	(-0.86, 5.64)		15.11	(-2.02, 32.24)	
Annual mean temperature (°C)	1.67	(1.01, 2.32)		2.73	(0.02, 5.45)	
SD temperature (°C)	0.27	(-0.95, 1.48)		-5.39	(-11.04, 0.26)	
GDP (×10,000 US\$)	-1.34	(-4.19, 1.41)		2.48	(-10.21, 15.16)	
(C) Temperate (n = 379)			45.5			63.6
Latitude (×10°)	-0.15	(-0.70, 0.41)		2.96	(-0.94, 6.85)	
Annual mean temperature (°C)	0.83	(0.73, 0.93)		-0.41	(-1.18, 0.36)	
SD temperature (°C)	1.06	(0.88, 1.25)		-0.74	(-1.90, 0.42)	
GDP (×10,000 US\$)	-0.26	(-0.78, 0.25)		-0.48	(-3.09, 2.13)	
(D) Continental (n= 112)			33.4			53.1
Latitude (×10°)	-0.58	(-1.95, 0.78)		1.57	(-5.01, 8.17)	
Annual mean temperature (°C)	1.13	(0.70, 1.57)		1.44	(-1.24, 3.00)	
SD temperature (°C)	0.65	(0.18, 1.12)		-1.61	(-3.67, 4.48)	
GDP (×10,000 US\$)	0.62	(0.11, 1.12)		3.18	(0.41, 5.96)	

<sup>a</sup>Köppen climate classification. Estimates for (E) Alpine climate were not possible to derive because there were only four cities included.

<sup>b</sup>I<sup>2</sup> indicates the residual heterogeneity.

Our study has several methodological strengths. To our knowledge, this is the largest study ever conducted using daily mortality and temperature data to determine geographical variations in the MMT at a global scale. This has allowed us to consider the full range of the temperature-mortality association to estimate the MMT distribution, and its determinants, by climate region. Likewise, the availability of estimating the standard errors for the MMTs enabled us to allow for precision and so make the meta-analysis of MMT more powerful and robust. The major difficulty was handling MMTs that were apparently at minimum or maximum temperatures, where exposure-response curves are imprecise, mainly in small cities.<sup>6</sup> Unlike previous studies,<sup>2,7,9</sup> we did use empirical estimates, instead of best linear unbiased prediction, to obtain independent estimates for each community that might reflect the geographical variability properly in the MMTs distribution. However, our ad-hoc procedure of constraining the identification of the MMT to the 1st–99th percentile range worked well in our dataset. Only a small number of communities reported the MMT at the extreme tails of the mean daily temperature distribution, 0.9% at the minimum and 1.2% at the maximum. Most of the communities with an MMT at the minimum temperature show a wide thermal variation during the year, ranging from 40 to 60 °C between the warmer and colder months. On the other hand, those with an MMT at the maximum temperature showed two differentiated patterns; communities with humid climates, either temperate or continental, with a broad thermal variation during the year, or communities in a tropical climate with a slight thermal variation, of less than 8 °C between the warmer and colder months.

We also acknowledge limitations in our study. As quoted in preceding MCC studies, we could not rule out the potential influence of changes in humidity, influenza epidemics or public holidays due to the lack of data.<sup>1,8</sup> However, a previous study including a subset of the current MCC dataset showed an

absence of a positive association of humidity with daily mortality.<sup>29</sup> Others also showed no changes in the temperature-mortality association when fitting humidity<sup>1</sup> and influenza epidemics<sup>30</sup> in sensitivity analyses. Although public holidays should be controlled for in studies on air pollution and health outcomes,<sup>31</sup> as both are related to holidays, the temperature does not seem to be affected by public holidays, therefore not affecting the temperature-mortality association. However, the current model fit including the adjustment by day of the week could partly address the impact of public holidays. We were not able to differentiate between the different types of adjustments, that is, physiological, behavioral, cultural, society-based, and technology-driven adjustments. This is a common limitation in epidemiological studies of long-term adaptation to climate and weather. Although caution is needed to avoid oversimplification in interpreting the results, these findings are nevertheless valuable in that they allow assessment of the overall adaptation across different populations. We did not address how the temperature-mortality association might change by sex and age, which could provide further insight into the different levels of adaptation in the population.<sup>32</sup> Our dataset is also limited in covering communities in low-income countries that might be the most affected by climate change.<sup>33,34</sup> Several studies have reported that MMT could continue to rise with increasing temperatures at the local level, in Stockholm,<sup>17</sup> and nationwide, in France<sup>35</sup> and Japan,<sup>36</sup> suggesting partial adaptation to increasing temperatures as one potential explanation for their findings. However, in our study, we did not explore the time-varying distribution of MMTs, only focusing on the geographical variations. This limited view could be masking the impact of changes in socioeconomic factors, such as GDP, that could directly influence long-term adaptation to climate, especially in some of rapidly developing countries included in this analysis. Therefore, this important issue will be part of future research at a global scale using the dataset collected within the MCC Collaborative Research Network.

In conclusion, our results suggest that the geographical distribution of MMTs and MMTPs is mainly driven by the mean annual temperature. Although adaptation is a complex phenomenon, mean annual temperature seems to be a useful measure in its overall assessment across different populations. Our results also suggest that populations have adapted to the average temperature to some extent, although there is more room for further adaptation. This indicates that extreme and relatively fast changes in climate can result in additional environmental stress and related health effects.

## References

- Guo Y, Gasparrini A, Armstrong B, et al. Global variation in the effects of ambient temperature on mortality: a systematic evaluation. *Epidemiology*. 2014;25:781–789.
- 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.
- Sera F, Armstrong B, Tobias A, et al. How urban characteristics affect vulnerability to heat and cold: a multi-country analysis. *Int J Epidemiol*. 2019;48:1101–1112.
- Curriero FC, Heiner KS, Samet JM, Zeger SL, Strug L, Patz JA. Temperature and mortality in 11 cities of the eastern United States. *Am J Epidemiol*. 2002;155:80–87.
- Honda Y, Kabuto M, Ono M, Uchiyama I. Determination of optimum daily maximum temperature using climate data. *Environ Health Prev Med*. 2007;12:209–216.
- Tobías A, Armstrong B, Gasparrini A. Brief report: investigating uncertainty in the minimum mortality temperature: methods and application to 52 Spanish cities. *Epidemiology*. 2017;28:72–76.
- Gasparrini A, Guo Y, Hashizume M, et al. Temporal variation in heat-mortality associations: a multicountry study. *Environ Health Perspect*. 2015;123:1200–1207.
- Vicedo-Cabrera AM, Sera F, Guo Y, et al. A multi-country analysis on potential adaptive mechanisms to cold and heat in a changing climate. *Environ Int*. 2018;111:239–246.
- Gasparrini A, Guo Y, Hashizume M, et al. Changes in susceptibility to heat during the summer: a multicountry analysis. *Am J Epidemiol*. 2016;183:1027–1036.
- Köppen W. *Grundriss der Klimakunde. (Zweite, verbesserte Auflage der Klimata der Erde.)*. Walter de Gruyter & Co.; 1931.
- Lee W, Bell ML, Gasparrini A, et al. Mortality burden of diurnal temperature range and its temporal changes: a multi-country study. *Environ Int*. 2018;110:123–130.
- Sera F, Armstrong B, Blangiardo M, Gasparrini A. An extended mixed-effects framework for meta-analysis. *Stat Med*. 2019;38:5429–5444.
- Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21:1539–1558.
- Evangelopoulos D, Analitis A, Giannakopoulos C, Katsouyanni K. Does climatic zone of birth modify the temperature-mortality association of London inhabitants during the warm season? A time-series analysis for 2004–2013. *Environ Res*. 2021;193:110357.
- IPCC. Climate Change 2014: Synthesis Report. Contribution of Working Groups I, II and III to the Fifth Assessment Report of the Intergovernmental Panel on Climate Change [Core Writing Team, Pachauri RK and Meyer LA, eds]. Geneva, Switzerland: IPCC; 2014.
- Gosling SN, Hondula DM, Bunker A, et al. Adaptation to climate change: a comparative analysis of modeling methods for heat-related mortality. *Environ Health Perspect*. 2017;125:087008.
- Åström DO, Tornevi A, Ebi KL, Rocklöv J, Forsberg B. Evolution of minimum mortality temperature in Stockholm, Sweden, 1901–2009. *Environ Health Perspect*. 2016;124:740–744.
- Sera F, Hashizume M, Honda Y, et al. Air conditioning and heat-related mortality: a multi-country longitudinal study. *Epidemiology*. 2020;31:779–787.
- Keatinge WR, Donaldson GC, Cordioli E, et al. Heat related mortality in warm and cold regions of Europe: observational study. *BMJ*. 2000;321:670–673.
- Bobb JF, Peng RD, Bell ML, Dominici F. Heat-related mortality and adaptation to heat in the United States. *Environ Health Perspect*. 2014;122:811–816.
- Achebak H, Devolder D, Ballester J. Heat-related mortality trends under recent climate warming in Spain: a 36-year observational study. *PLoS Med*. 2018;15:e1002617.
- Baccini M, Kosatsky T, Analitis A, et al; PHEWE Collaborative Group. Impact of heat on mortality in 15 European cities: attributable deaths under different weather scenarios. *J Epidemiol Community Health*. 2011;65:64–70.
- Yin Q, Wang J, Ren Z, Li J, Guo Y. Mapping the increased minimum mortality temperatures in the context of global climate change. *Nat Commun*. 2019;10:4640.
- 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.
- Zhang Y, Li S, Pan X, et al. The effects of ambient temperature on cerebrovascular mortality: an epidemiologic study in four climatic zones in China. *Environ Health*. 2014;13:24.
- Hurtado-Díaz M, Cruz JC, Texcalac-Sangrador JL, et al. Short-term effects of ambient temperature on non-external and cardiovascular mortality among older adults of metropolitan areas of Mexico. *Int J Biometeorol*. 2019;63:1641–1650.
- Barreca AI, Shimshack JP. Absolute humidity, temperature, and influenza mortality: 30 years of county-level evidence from the United States. *Am J Epidemiol*. 2012;176(suppl 7):S114–S122.
- Sewe M, Rocklöv J, Williamson J, et al. The association of weather variability and under five malaria mortality in KEMRI/CDC HDSS in Western Kenya 2003 to 2008: a time series analysis. *Int J Environ Res Public Health*. 2015;12:1983–1997.
- Armstrong B, Sera F, Vicedo-Cabrera AM, et al. The role of humidity in associations of high temperature with mortality: a multicountry, multicity study. *Environ Health Perspect*. 2019;127:97007.
- Lee WH, Lim YH, Dang TN, et al. An investigation on attributes of ambient temperature and diurnal temperature range on mortality in five east-asian countries. *Sci Rep*. 2017;7:10207.
- Bhaskaran K, Gasparrini A, Hajat S, Smeeth L, Armstrong B. Time series regression studies in environmental epidemiology. *Int J Epidemiol*. 2013;42:1187–1195.
- Mari-Dell’Olmo M, Tobías A, Gómez-Gutiérrez A, et al. Social inequalities in the association between temperature and mortality in a South European context. *Int J Public Health*. 2019;64:27–37.
- Mora C, Dousset B, Caldwell IR, et al. Global risk of deadly heat. *Nat Clim Change*. 2017;7:501–506.
- Schleussner C-F, Lissner TK, Fischer EM, et al. Differential climate impacts for policy-relevant limits to global warming: the case of 1.5°C and 2°C. *Earth System Dynamics*. 2016;7:327–351.
- Todd N, Valleron AJ. Space-time covariation of mortality with temperature: a systematic study of deaths in France, 1968–2009. *Environ Health Perspect*. 2015;123:659–664.
- Chung Y, Yang D, Gasparrini A, et al. Changing susceptibility to non-optimum temperatures in Japan, 1972–2012: the role of climate, demographic, and socioeconomic factors. *Environ Health Perspect*. 2018;126:057002.