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ABSTRACT

Background: The evidence and method are limited for the associations between mortality and temperature variability (TV) within or between days.

Objectives: To develop a novel method to calculate TV, and to investigate the TV-mortality associations using a large multi-country dataset.

Methods: We collected daily data of temperature and mortality from 372 locations in 12 countries/regions (Australia, Brazil, Canada, China, Japan, Moldova, South Korea, Spain, Taiwan, Thailand, UK, and USA). We calculated TV by standard deviation of minimum and maximum temperatures during the exposure days. Two-stage analyses were used to assess the relation between TV and mortality. Firstly, a Poisson regression model allowing over-dispersion was used to estimate the community-specific TV-mortality relation, after controlling for potential confounders. In the second stage, a meta-analysis was used to pool the effect estimates within each country.

Results: There was a significant association between TV and mortality in all countries, even after controlling for the effects of daily mean temperature. In stratified analyses, TV was still significantly associated with mortality in cold, hot, and moderate seasons. Mortality risks related to TV were higher in hot areas than cold areas when using short TV exposure (0–1 days), while TV-related mortality risks were higher in moderate areas than cold and hot areas when using longer TV exposure days (0–7 days).

Conclusions: Results indicate that more attention should be paid to unstable weather conditions in order to protect health. These findings may have implications for developing public health policies for managing health risks of climate change.

INTRODUCTION

Time series data on daily air pollution concentrations, weather conditions, and daily measures of health outcomes (e.g., mortality or hospital admissions), have been used to assess how environmental factors may contribute to short-term (days to weeks after the environmental exposure) increases in mortality/morbidity (Bhaskaran et al. 2013; Samet et al. 2000). To date, numerous time series analyses have shown that both cold and hot temperatures are associated with increased risks for a number of health outcomes (Basu and Samet 2002; Basu 2009; Ye et al. 2012). These findings have important implications for understanding the health effects of climate change (Field 2012). However, as climate change increases both the average values and the variability of temperature (Stocker 2014), the health impacts of unstable weather are still unclear (Zanobetti et al. 2012). People may adapt to the usual temperature, but may not to the variable temperature. Thus, further evidence is needed for assessing health impacts of temperature variability locally, regionally and globally.

Currently, two indices, intra-day temperature variability (TV) (e.g. diurnal temperature range) and inter-day TV (e.g. temperature change between neighbouring days), have been used to assess the associations between short-term unstable weather and population health (Guo et al. 2011a; Lin et al. 2013; Qiu et al. 2013; Yang et al. 2013). In addition, some studies have used standard deviation of summer daily mean temperature to represent summer long-term TV (Shi et al. 2015; Zanobetti et al. 2012). This is also one type of inter-day variability. All studies assessed the relationships between health outcomes and intra-day and inter-day variability separately. However, because the unstable weather is a continuous process, impacts on health may be better captured by considering the intra-day and inter-day variability together when assessing the associations between TV and population health.

In addition, most previous studies of unstable weather and health risks were from one city, one region, or one country, and used different methods. This makes it difficult to compare the findings directly. We have recently established a Multi-Country multi-City (MCC) Collaborative Network to assess impacts of weather on mortality globally (Gasparrini et al. 2015a; Gasparrini et al. 2015b; Guo et al. 2014). In this study, we developed a novel method to calculate TV including both intra-day and inter-day TV, and examined the TV-mortality associations using the MCC data.

METHODS

Data Collection

The MCC data set has been described in previous publications (Gasparrini et al. 2015a; Gasparrini et al. 2015b; Guo et al. 2014). In brief, we obtained daily counts of all cause/non-accidental deaths and weather conditions in 372 communities from twelve countries/regions: Australia (3 cities during 1988-2008), Brazil (18 cities during 1997–2011), Canada (26 cities during 1986-2009), China (6 cities during 2002-2007), Japan (47 prefectures, 1972-2012), Moldova (4 cities, 2001–2010), South Korea (7 cities during 1992–2010), Spain (51 cities during 1990-2010), Taiwan (3 cities during 1994–2007), Thailand (62 provinces during 1999-2008), United Kingdom (10 regions during 1993-2006), and USA (135 cities during 1985-2006). Daily weather data included daily minimum, mean and maximum temperatures, and relative humidity.

The locations are displayed by Figure 1. Supplemental Material provides the details for data collection and Table S1 shows the list of locations.

Calculation of temperature variability

Evidence shows that the associations between both intraday and inter-day temperature variability and health outcomes last for several days (Lin et al. 2013; Yang et al. 2013), which suggests that the impacts of temperature variability on health should be a continuous process. However, these associations were assessed separately, which makes difficult to assess the overall effects of temperature variability. In addition, putting intraday and inter-day temperature variability into the same model might make the model unstable and lead to invalid effect estimates, because there might be strong collinearity between intraday and inter-day temperature variability particularly when considering the lag effects. In this study, we developed a composite index of intra-day and inter-day TV, by computing the standard deviation (SD) of minimum and maximum temperatures (MinTemp and MaxTemp) during the exposure days. For example, TV for preceding two days' exposure was calculated by TV_{0-1}=SD ($MinTemp_{lag0}$, $MaxTemp_{lag0}$, $MinTemp_{lag1}$, $MaxTemp_{lag1}$). TV for preceding three days' exposure was calculated by TV_{0-2}=SD ($MinTemp_{lag0}$, $MaxTemp_{lag0}$, $MinTemp_{lag1}$, $MaxTemp_{lag1}$, $MinTemp_{lag2}$, $MaxTemp_{lag2}$). This method has ability to account for both intra-day and inter-day TV, as well as the lag effects of TV.

Data analysis

Analytic plan

The TV-mortality association was investigated with a two-stage analytic approach using time series data from the 372 communities in the twelve countries/regions. In the first stage, we applied a time series model to each community's data in order to estimate the city-specific TV–mortality relationship. These estimated relationships were then pooled in the second stage at the country level with a meta-analysis. This approach was described in previous publications (Gasparrini et al. 2012; Gasparrini and Armstrong 2013).

First stage of analysis

In the first stage, we used a regression model to obtain community-specific estimates assuming a quasi-Poisson distribution allowing for over-dispersed death counts, which follows a standard analytical approach for time-series data (Bhaskaran et al. 2013). We used linear function for TV, as previous studies suggest that diurnal temperature range has linear effect on health and both large decrease and increase in temperature between neighbour days increase risks of health outcomes. The long-term trend and seasonality was controlled for using a natural cubic spline with 7 degrees of freedom per year for time. A categorical variable was used to control for the confounding effect of day of the week. We also controlled for the non-linear and delayed effect of daily mean temperature using a distributed lag non-linear model (Gasparrini et al. 2010). A natural cubic spline with 4 degrees of freedom was used for daily mean temperature, while a natural cubic spline with 4 degrees of freedom was used to capture the lags over time up to 21 days. We placed three internal knots at equally-spaced temperature percentiles (25th, 50th, and 75th) and two internal knots at equally spaced log-values of lag (approximately 1.4, and 5.5

days), respectively, plus intercept. The choice of 21 days for the lag period was motivated by previous studies showing that effects of cold temperature were more delayed and spread over the previous weeks of exposure, while the effects of hot temperatures were more acute and were based on the same day and previous few days of exposures (Gasparrini and Armstrong 2013; Guo et al. 2014). We controlled for daily mean temperature rather than daily minimum and maximum temperatures, as daily mean temperature represents the exposure throughout whole day and night and corresponds to the daily count of deaths.

We assessed several exposure days' TV, separately, for example preceding 2 days (same day and 1 day before, 0–1 days), preceding 3 days (same day, 1 and 2 days before, 0–2 days), to preceding 8 days (0–7 days), to understand which exposure days' TV was associated with mortality risks.

We calculated the community-specific effect estimates of death associated with one inter-quantile range (IQR, for each community) increase of TV, because most communities had non-overlapping ranges of TV (See Supplemental Material, Table S1). Also, a sensitivity analysis looking at the effect per 1˚C increase in TV showed that it is more heterogeneous than the effect per IQR change in TV in the meta-analysis. The values of IQR for each community are shown in Supplemental Material Table S1.

To examine whether the effects of TV on mortality differed by different seasonal characteristics, we conducted stratified analyses for the cold season (four coldest months), the hot season (four hottest months), and the moderate season (except cold and hot seasons), by an interactive term between TV and seasons (as a categorical variable) in the community-specific regression model. We defined cold season as four months with lowest monthly mean temperatures for each community, hot season as four months with highest monthly mean temperatures, moderate season as four months except hot and cold seasons.

Second stage of analysis

At the second stage, a meta-analysis was used to pool the community-specific effect estimates obtained from the first-stage model. The meta-analyses were fitted using a random effects model by maximum likelihood, and was applied in each country, obtaining national pooled estimates.

Studies have reported that people may have ability to adapt to their local climate. In order to understand whether the associations between TV and mortality are different by climate (for example, whether warm/cold locations have higher effect estimates for TV-mortality associations than cold/warm locations), we divided 372 communities into 4 groups (cold, moderate cold, moderate hot, and hot areas) by the quantiles (≤25th, 25th–50th, 50th –75^{th,} and >75th) of their annual mean temperatures during study period (each community has one value of annual mean temperature) (See Supplemental Material Figure S1). Meta-analyses were used to pool the community-specific effect estimates obtained from the first-stage model for these four groups.

The TV-mortality associations were expressed as the Percent increase (and 95% confidence interval) in mortality associated with an increase in IQR (for each community) of TV.

Sensitivity analyses were performed on the parameters for the community-specific model to test the robustness of our results. We changed lag days to 28 days to examine whether using 21 lag days was sufficient to control for the temperature effects on mortality. We modified the degrees of freedom for temperature (3–6 *df*). We included relative humidity into the analyses. We also included heat waves and cold spells into the analyses, as they might be responsible for increases in TV. The heat waves were defined as temperature above 95th percentile of daily mean temperature for that community with duration ≥2 days, while the cold spells were defined as temperature below 5th percentile of daily mean temperature with duration ≥2 days. We also controlled for daily minimum and maximum temperatures instead of daily mean temperature respectively, using the same distributed lag non-linear model, to check whether daily minimum and maximum temperatures confound the associations between TV and mortality.

In addition, an approach called generalization of Granger causality (Flanders et al. 2011) was used to check the possibility of residual confounding and potential cause-effect association between TV and mortality. In brief, we examined the associations between daily mortality and future 1–7 days' TV. If this future exposure is associated with mortality, it is an indication of a residual confounding with the model. If there is no association between this future exposure and mortality, it means that there is no residual confounding and there is cause-effect relationship between TV and mortality.

R software (version 3.0.1, R Development Core Team 2009) was used for data analysis. The "dlnm" package was used to create the distributed lag non-linear model (Gasparrini et al. 2010) and the "mvmeta" package to fit the meta-analyses (Gasparrini et al. 2012).

This study was approved by the Behavioural & Social Sciences Ethical Review Committee, University of Queensland.

RESULTS

This study included 372 communities, and covered the period 1972 to 2012, with different years of data for different regions (Table 1). The total death counts were over 83 million. Thailand had the hottest climate pattern, while Canada had the coldest one. Supplemental Material Table S1 shows that the daily average counts of death, average temperatures, and TV varied greatly by community.

It is clear that the associations between of TV (associated with one IQR increase) and mortality with adjustment for the effects of daily mean temperature (Figure 2A) were lower than those without adjustment for the effects of temperature (Figure 2B) during all exposure days in all countries/regions. In addition, the highest effect estimates appeared on different exposure days in different countries. For the models controlling for the effects of daily mean temperature, the highest effect estimates appeared at 0–7 days of exposure for Australia, Japan, Korea, Spain, and USA; 0–1 days for Brazil, Thailand, and UK; 0–4 days for China. Canada had the same effect estimates on all type of exposure days. The effect estimates varied by community (results not shown).

In general, there were positive associations between TV and mortality in all seasons in all countries (Table 2). The effect estimates for TV-mortality associations were higher in moderate season than hot and cold seasons for all countries, except for Thailand and Moldova. The effect estimates in moderate season range from an increase of 0.39% in UK to 1.45% in China in mortality associated with an IQR increase in TV. Supplemental Material Table S2 shows the associations between TV and mortality on different exposure days in three seasons. In brief, the effect estimates varied by exposure days, for example, when we used 0–1 days' TV exposure, cold season had higher effect estimates for TV-mortality associations than those in hot and cold seasons in Brazil, China and Thailand.

Figure 3 shows the pooled relationships between TV and mortality in cold, moderate cold, moderate hot, and hot areas. The effect estimates for TV-mortality associations were higher in hot areas than cold, moderate cold, and moderate hot areas when using short exposure days (0–1 and 0–2 days). However, the effect estimates were greater in moderate cold and moderate hot areas than cold and hot areas when using longer exposure days (0–5, 0–6, and 0–7 days).

Our results were robust to a changed lag structure of 28 days for temperature, modified degrees of freedom for temperature (3–6 *df*), and inclusion of relative humidity into the analyses (results not shown). When we included heat waves and cold spells into the models, the results were similar. When we calculated the effects per 1˚C increase in TV (See Supplemental Material, Figure S2), the patterns (e.g., lag effect) of mortality risks did not change for all the countries/regions while the magnitude of mortality risks were lower than those using IQR increase. Although replacing daily mean with maximum and minimum temperatures in our model did not qualitatively change the evidence for an association of TV with mortality (Figure S3), we were unable to control for daily maximum and minimum temperatures at the same time, as they have very strong collinearity. Thus, we could not fully control for the residual confounding from extreme minimum and maximum temperatures, so it is also possible that the association of TV with mortality reflects adverse effects of the more extreme maximum or minimum temperatures that high diurnal temperature range, and hence TV, would imply.

Our generalization of Granger causality analysis shows that there is no association between daily mortality and future 7 days' TV exposure (See Supplemental Material, Figure S4). This reassures that there is little residual confounding in our models and strengthens evidence for a cause-effect relationship between TV and mortality.

DISCUSSION

This study examined TV-mortality associations using consistent methods for 372 communities across twelve countries/regions, including countries from both developing and developed regions with different climate patterns (i.e., tropical, subtropical and temperate). We developed a novel method to calculate TV by taking into account both intra-day and inter-day variability. We found that, in all countries/regions, TV was associated with an increased risk of deaths, even after controlling for the main effects of temperature. The associations between TV and mortality appeared in different exposure days in different countries. In general, TV-mortality associations varied with season. People were more sensitive to acute exposure of TV in warm areas than cold areas, while they were more sensitive to long exposure of TV in cold areas than hot areas.

Our findings are generally consistent with previous studies on intra-day or inter-day TV (Lin et al. 2013; Qiu et al. 2013; Yang et al. 2013). However, those prior studies examined the intra-day or inter-day TV separately, and did not consider the delayed effects of intra-day or inter-day TV (Lin et al. 2013; Qiu et al. 2013; Yang et al. 2013). Additionally, they did not fully account for the lagged effects of temperature, even though some studies controlled for the confounding effect of daily mean temperature on the same day of death. Actually, the effects of cold temperature include the lagged effects after several weeks of exposure, while the effects of hot temperatures relate to more recent days of exposure (Gasparrini and Armstrong 2013; Guo et al. 2011b). If the main effects of temperature were not controlled fully, the estimates of TV on mortality could be overestimated, as our findings showed in Figure 1.

Much evidence from the physiology literature has shown that people can have difficulty with thermoregulation and acclimatization to extreme cold and hot temperatures (Buguet 2007; Epstein and Moran 2006; Nixdorf-Miller et al. 2006), and that the automatic thermoregulation system cannot fully adapt to unstable weather (Kan et al. 2007; Liang et al. 2009). The thermoregulatory system of the human body might not efficiently respond to sudden changes (drops or increases) in temperature within a very short interval of time (Martinez-Nicolas et al. 2015). People may feel uncomfortable for sudden intraday and inter-day changes in temperature, as they don't prepared well for this temperature variability not only physiologically but also regarding behavioural patterns (Garrett et al. 2009; Garrett et al. 2011). Unstable temperatures have been associated with increases in heart rate, blood pressure, blood cholesterol levels, plasma fibrinogen concentrations, peripheral vasoconstriction, platelet viscosity, autonomic control of the heart, and reducing the immune system's resistance (Ballester et al. 1997; Carder et al. 2005; Garrett et al. 2009; Garrett et al. 2011; Halonen et al. 2010, 2011a, b; Martinez-Nicolas et al. 2015). These alterations may trigger cardiovascular and respiratory events. In addition, considering the characteristics of the present study, it is not possible to identify the most sensitive groups to TV. Most probably, the older population segments may be those most vulnerable to TV, due to their progressive decrease in thermoregulatory ability associated with aging and the higher prevalence of comorbidities.

We found that different countries had different patterns in the TV-mortality associations. For example, after controlling for the effects of daily mean temperature, the associations between TV and mortality were more acute in Brazil, Thailand, and UK than in Australia, China, Japan, Korea, Spain, and USA. Also, the evidence on the impacts of TV in different seasons is not consistent by country. Some countries had highest effect estimates in moderate season, while others had highest effect estimates in cold season or hot season. It appears that people living in hot areas were more sensitive to acute TV exposure than those in cold areas, while people living in moderate areas were more sensitive to long TV exposure than those in hot and cold areas. These differences may be caused by people adapting to their local climates via a range of physiological, behavioural, and technological adaptations (Nielsen et al. 1993). Clearly, further studies are needed to fully assess the reasons underlying the variation.

This study has several strengths. This is the first study to calculate TV accounting for both intra-day and inter-day variability. We developed a novel method to calculate TV using the standard deviation of current day's and preceding days' minimum and maximum temperatures. We used a large multi-country, multi-city dataset and followed consistent procedures and definitions. The same statistical method was used for each community, which makes it possible to compare the results directly. In addition, the TV-mortality associations were assessed in models after controlling for the non-linear and delayed effects of daily temperature using flexible distributed lag non-linear models. Additionally, a range of sensitivity analyses were performed to test the robustness of our results.

This study also has some limitations. As other similar time series studies, we used the data on temperature from fixed sites, rather than individual exposure, which will create measurement errors in exposure to some extent. However, these measurement errors are likely to be random, which would usually result in an underestimation of the relative risks (Guo et al. 2013). There are no sufficient data to address reasons for the variation in TV-mortality associations across communities. In addition, our data set did not include age or cause-specific mortality, so we investigated only all cause/non-accidental mortality.

CONCLUSIONS

Our findings provide strong evidence that TV is associated with increased risks of mortality in different countries. These findings may have implications for assessing TV-related health risks and developing public health policies to minimise the health consequences of unstable weather conditions. Our findings also suggest that projecting health risks of climate change should take into account both the impacts of temperature increases and TV. However, more comprehensive epidemiological studies across the globe are needed, as our results show that the health effects of temperature variability vary greatly among different countries and climate zones.

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Table 1: Summary of the study periods, number of deaths, and mean temperatures in the 12 countries/regions.

Country/ Region	Period	No. communities	No. deaths	Mean temperature (˚C)
Australia	1988-2009	3	1,184,154	18.1
Brazil	1997-2011	18	3,435,535	24.2
Canada	1986-2009	26	2,989,901	6.8
China	2002-2007	6	558,959	18.4
Japan	1972-2012	47	33,511,400	15.1
Korea	1992-2010	7	1,511,996	13.7
Moldova	2001-2010	4	59,906	10.7
Spain	1990-2010	51	3,480,531	15.5
Taiwan	1994-2007	3	688,394	24.0
Thailand	1999-2008	62	1,827,853	27.6
UK	1990-2012	10	11,636,089	10.3
USA	1985-2006	135	22,896,409	14.9

Table 2: Percent change (95% CI) in mortality associated with an IQR (inter-quartile range for each community) increase in 0–7 days' temperature variability (°C) in cold season (four coldest months), hot season (four hottest months), and moderate season (except cold and hot seasons), after controlling for the main effect of temperature.

Country	Percent increase in mortality (%)		
	Cold season	Hot season	Moderate season
Australia	0.84 (-0.12, 1.82)	0.79 (0.20, 1.39)	0.85 (0.19, 1.51)
Brazil	0.47 (0.06, 0.89)	0.39 (-0.07, 0.84)	0.54 (0.14, 0.95)
Thailand	0.14 (-0.50, 0.78)	0.27 (-0.39, 0.93)	0.26 (-0.09, 0.62)
China	0.86 (0.18, 1.54)	0.93 (0.01, 1.86)	1.45 (0.49, 2.41)
Taiwan	0.20 (-0.36, 0.77)	0.20 (-0.14, 0.54)	0.86 (0.13, 1.61)
Korea	0.80 (0.47, 1.12)	0.85 (0.52, 1.19)	0.89 (0.57, 1.21)
Japan	0.72 (0.64, 0.80)	0.78 (0.70, 0.86)	1.08 (0.99, 1.16)
Spain	0.45 (0.16, 0.75)	0.49 (0.26, 0.72)	0.86 (0.60, 1.11)
Moldova	3.08 (-6.89, 14.11)	2.76 (-2.83, 8.67)	3.10 (-5.84, 12.88)
UK	0.28 (0.10, 0.46)	0.34 (0.06, 0.62)	0.39 (0.14, 0.65)
USA	0.67 (0.55, 0.80)	0.47 (0.37, 0.56)	0.82 (0.71, 0.93)
Canada	0.57 (0.29, 0.85)	0.30 (0.06, 0.54)	0.61 (0.34, 0.88)

Figure legends

Figure 1: Locations of study areas and their mean values of 0–1 days' temperature variability (°C). The map is freely downloaded from the "maps" package of R software.

Figure 2: Percent change (95% CI) in mortality associated with an IQR (for each community) increase in temperature variability (°C) on different exposure days, (A) after controlling for the effect of daily mean temperature, (B) without controlling for the effect of temperature.

Figure 3: Percent change (95% CI) in mortality associated with an IQR (for each community) increase in temperature variability (°C) on different exposure days in cold, moderate cold, moderate hot and hot areas, after controlling for the effect of daily mean temperature.

Figure 1.

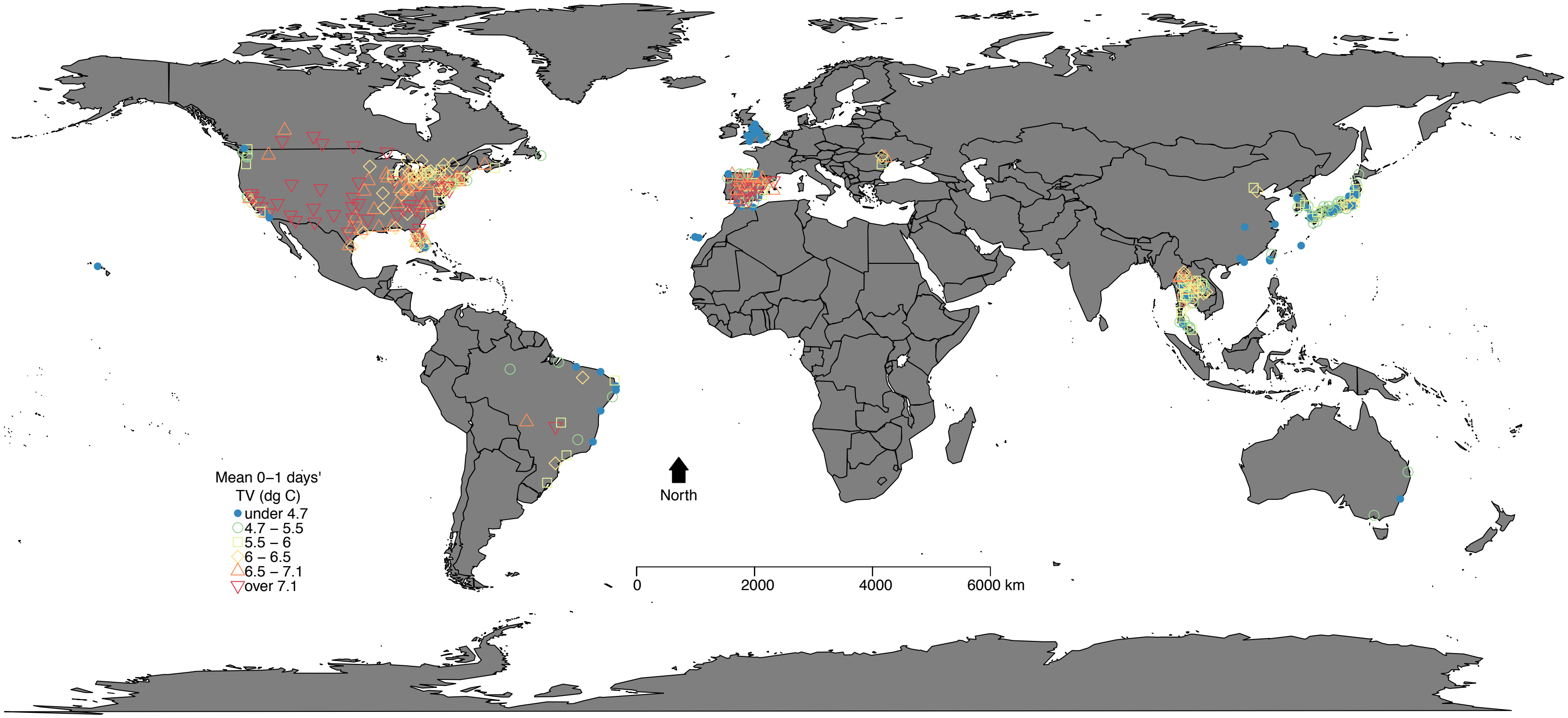
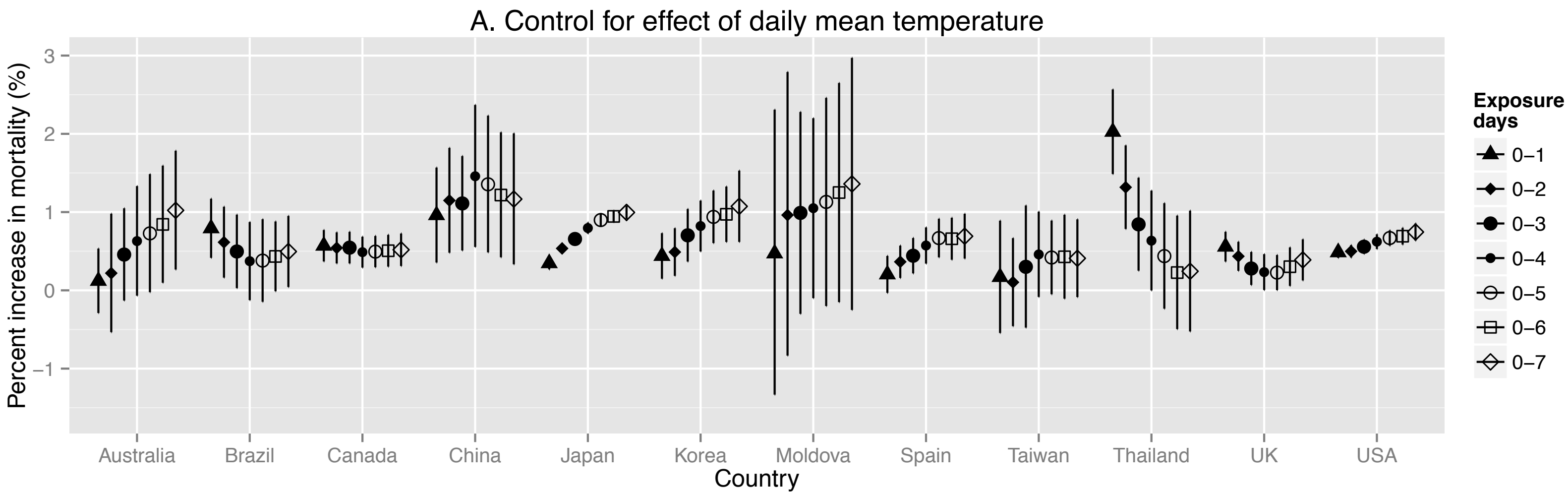

Mean 0–1 days'
TV (dg C)
under 4.7
4.7 – 5.5
5.5 – 6
6 – 6.5
6.5 – 7.1
over 7.1
North
0
2000
4000
6000 km

Figure 2.


A. Control for effect of daily mean temperature
Percent increase in mortality (%)
3
2
1
0
−1
Australia
Brazil
Canada
China
Japan
Korea
Moldova
Spain
Taiwan
Thailand
UK
USA
Country
Exposure days
0−1
0−2
0−3
0−4
0−5
0−6
0−7

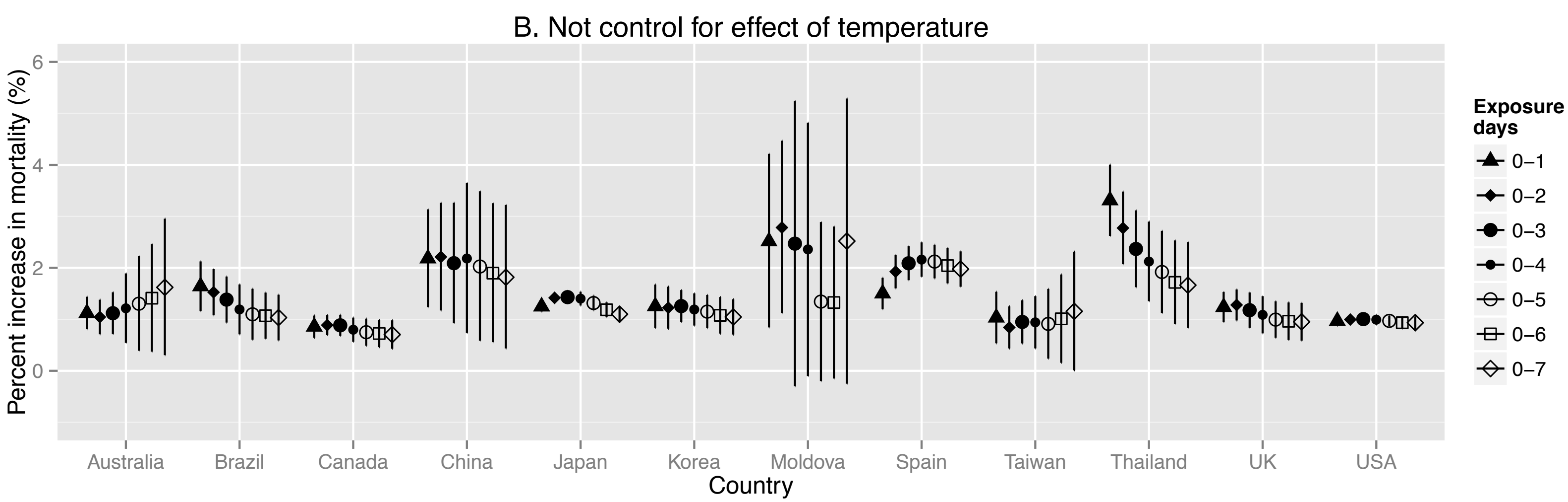
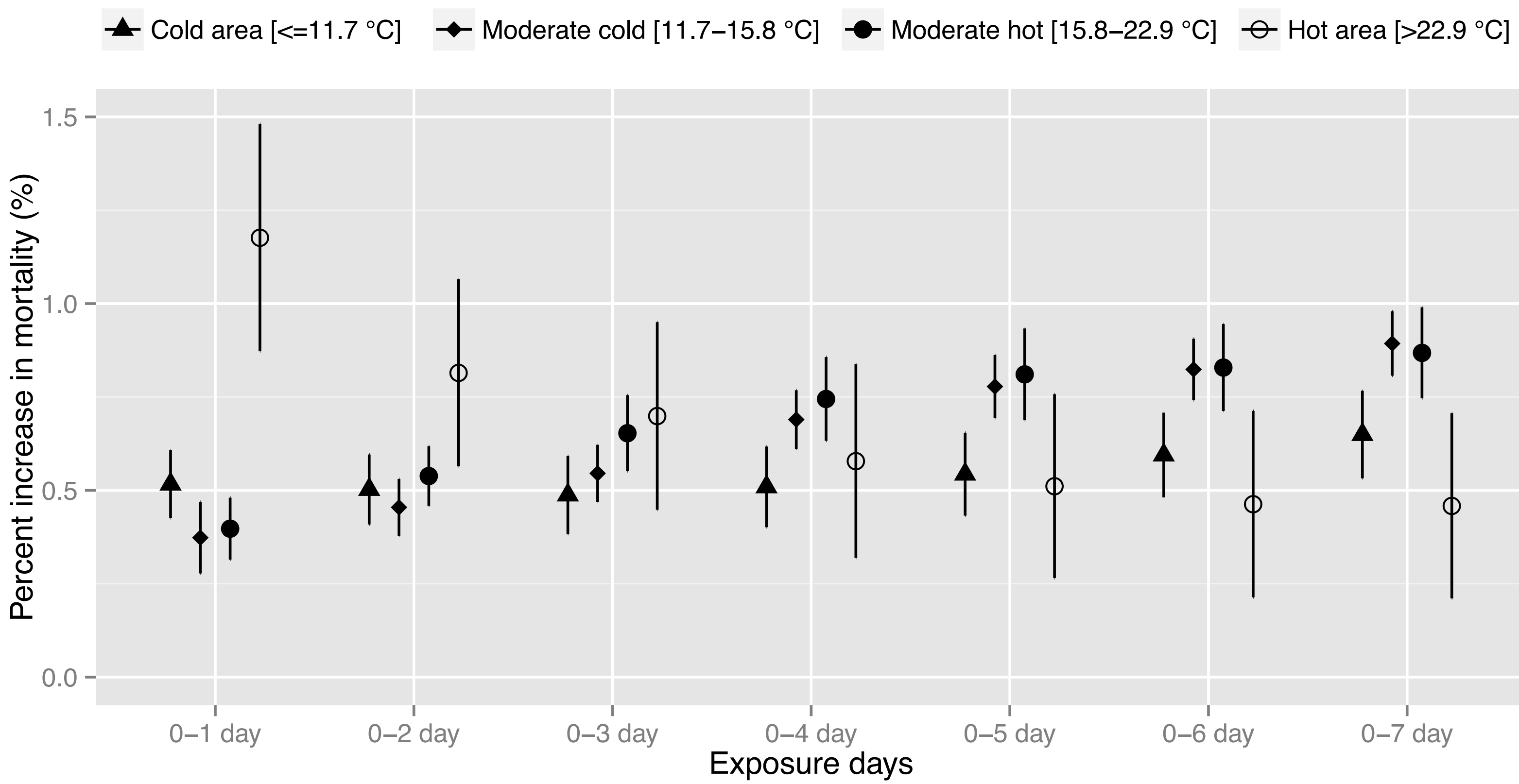

B. Not control for effect of temperature
Percent increase in mortality (%)
6
4
2
0
Australia
Brazil
Canada
China
Japan
Korea
Moldova
Spain
Taiwan
Thailand
UK
USA
Country
Exposure days
0−1
0−2
0−3
0−4
0−5
0−6
0−7

Figure 3.


Cold area [<=11.7 °C]
Moderate cold [11.7–15.8 °C]
Moderate hot [15.8–22.9 °C]
Hot area [>22.9 °C]
Percent increase in mortality (%)
1.5
1.0
0.5
0.0
0–1 day
0–2 day
0–3 day
0–4 day
0–5 day
0–6 day
0–7 day
Exposure days