보건학박사 학위 논문

온도 및 온도 변동성과 사망과의 관계 연구:

시간 변동성, 교호 작용 및 불확실성 추정

Investigation for the temperature-mortality and temperature variability-mortality associations:

Temporal variation, Interaction, and Uncertainty estimation.

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서울대학교 보건대학원

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이환희

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이 논문을 보건학박사 학위논문으로 제출함

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You can't have any idea what it's like always to hear such a giant marching behind you.

Johannes Brahms

Abstract

Investigation for the temperature-mortality and temperature variability-mortality associations:

Temporal variation, Interaction, and Uncertainty estimation.

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Climate change is a major issue in public health and epidemiology fields, and its health impacts have been studied greatly in recent decades. Extreme temperature, and sudden temperature change (i.e. temperature variability) have been regarded as major variables of climate change, and air pollution also has been raised as a crucial health risk factor related to climate change. Rich previous studies reported the association between health and these variables. Some aspects, such as time-varying association, effect modification, synergism, and estimation uncertainty, have not been fully studied, although they are substantially important in measuring the health impacts of climate change. During my PhD research, I have mainly investigated the temporal changes in weather-mortality relationships, the plausible modifiers of weather-related mortality, and statistical methodologies that address uncertainties in estimating weather-related mortality. The PhD thesis contains previously published or submitted research papers during my PhD coursework, and provides epidemiological and statistical evidences that: 1) mortality burden due to extreme temperatures (heat and cold, both) and temperature variability might not decrease or increase in the near future, 2) hot temperature might be a major modifier of the temperature variability-mortality association, and 3) advanced statistical approaches are needed to estimate the temperature-related mortality. In final, all topics suggested in the thesis and future research issues were discussed. I believe these researches might suggest meaningful implications in assessing health risks under climate change.

Keywords: Climate change, Extreme temperature, Health risk assessment, Statistical methodology, Temperature variability

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Contents

Preface

This PhD thesis is composed of published or submitted research papers. The paper contains three main parts: Background, Research, and Further discussion. The aim is to organize my research activity during the master and PhD coursework, and to suggest future research topics in epidemiological and statistical perspectives.

The Background includes a summary of pervious research topic about health impacts of temperature, and temperature variability. The Research part contains two chapters: temperature-mortality and temperature variability-mortality associations (Section 2.1) and uncertainty estimation using statistical methodologies (Section 2.2).

The Section 2.1 consist of two specific chapters: Section 2.1.1 illustrates the temporal changes in weather-mortality association. Section 2.1.2 shows the interactions in the weather-mortality association.

The Section 2.2 includes the Bayesian approach that estimating uncertainties of minimum mortality temperature and temperature-related risks on mortality, and contains the modified time-series regression approach to estimate mortality risk due to temperature variability separated from absolute temperature, and to compare the mortality burden between absolute temperature and temperature variability.

The Further discussion section contains discussion about all topics suggested in the thesis, and future research issues.

Backgrounds

1.1. Extreme temperature and health

Extremely cold and hot temperatures are prominent threats to human health. Previous researches have reported that the positive association between extreme temperature and mortality in Asia (Y. Chung et al. 2015; Ha and Kim 2013; Kim et al. 2006; Lee et al. 2017; Xie et al. 2013), Europe (Hajat et al. 2002; Huynen et al. 2001; Kyselý and Kříž 2008; Le Tertre et al. 2006), America (Anderson and Bell 2009; Barnett et al. 2012; Bobb et al. 2014; Curriero et al. 2002; Wu et al. 2014), and Australia (Tong et al. 2012; Tong et al. 2014; Tong et al. 2015). In recent years, multi country-scale studies found that the association is widely observed in many countries, although the estimated temperature-related risks are quite heterogeneous depending on countries (Gasparrini et al. 2015b; Guo et al. 2014; Guo et al. 2017).

The extreme temperature-mortality relationship is more evident in people with cardiovascular or respiratory diseases (Y. Chung et al. 2015; Lee et al. 2017b; Stafoggia et al. 2006), the elderly (Hajat et al. 2007; Medina-Ramón and Schwartz 2007), and females (Hajat et al. 2007; Rooney et al. 1998). Numerous underlying medical and biological mechanisms have been reported to define the increased risk of mortality associated with extreme temperature. Substantial evidence from the physiology literature has reported that people have difficulty with acclimatization and thermoregulation to extreme cold and hot temperature (Buguet 2007; Epstein and Moran 2006). Regarding cardiovascular mortality, a high temperature is related to the burden of cardiovascular-related motility. An increase in temperature causes blood vessels to dilate, increasing the cardiac output and risk of decompensating heart failure; it also raises platelet counts, blood viscosity, and cholesterol levels. These influences might cause or trigger death from coronary and cerebral thrombosis (Greenberg et al. 1983; Keatinge et al. 1984). Cold temperature is one of the factors that causes blood vessels to become narrow, increasing blood pressure and heart rate (Group 1997). Increases in blood pressure, fibrinogen concentrations, and blood viscosity, in instances of lower temperature, suggest that cold induces cardiovascular stress and may be prevalent in the entire population (Brennan et al. 1982; Neild et al. 1994). One of the underlying reasons for death due to cardiovascular disease appears to be thrombosis due to hemoconcentration in the cold (Neild et al. 1994).

Under the climate change, extreme temperatures have more significance. The Intergovernmental Panel on Climate Change (IPCC) recently reported greenhouse gases will evidently increase the earth's temperature and predicted climate change would cause frequent weather pattern instability (Solomon 2007; Stocker 2014). Further, recent studies found that the shift of the polar vortex over the last several decades, which could lead to increasing extreme cold and hot weather events in mid-latitude regions (Cohen et al. 2014; Wallace et al. 2014; Zhang et al.

2016). Therefore, investigating the impacts of extreme temperature on human health is crucial to establishing better public health strategies (Meehl and Tebaldi 2004).

1.2. Indices of extreme temperatures

Continuous scale-temperature

Ambient temperature measured with continuous scale were used to estimate the risk related to extreme hot and cold temperature. Researchers have reported that there exists a nonlinear association between temperature and mortality, characterized by U- or J- shaped association (B. Armstrong 2006; Y. Chung et al. 2015; Gasparrini et al. 2015b). One important feature in the temperature-mortality association is the minimum mortality temperature (MMT, i.e. optimal temperature), which is defined as the temperature at which the lowest mortality is achieved. The MMT has been regarded as a threshold point in describing the population susceptibility (Guo et al. 2014) to temperature because the mortality risk becomes increased as temperature increases or decreases from the MMT. Therefore, the MMT has often been used as a reference temperature to quantify the relative risk (RR) related to cold or hot temperatures in many previous studies (Chung et al. 2018; Gasparrini et al. 2015b; Guo et al. 2014).

The heat risk was defined as RR comparing the MMT and 99th, 97.5th, or 95th percentiles of temperature, and cold risk was defined as RR comparing the MMT and 1st, 2.5th, or 5th percentiles of temperature (Gasparrini et al. 2015b; Guo et al. 2014; Lee et al. 2017). Although the continuous scale temperature has a great advantage to reflect complex patterns of the temperature-mortality relationship, it has limitation to reflect duration of extreme temperatures during consecutive days, to estimate optimal alarming point based on attributable mortality burden due to existence of extreme temperature (difference of mortality burden attributed to extreme temperature occurrence versus. non-occurrence).

Heat wave and cold spell

In order to assess the intensity and duration effect of extreme temperature, heat wave and cold spell (or cold wave) indices have been used in previous studies (Anderson and Bell 2009; Anderson and Bell 2011; Barnett et al. 2012; Fouillet et al. 2008; Gasparrini and Armstrong 2011; Guo et al. 2017; Huynen et al. 2001; Lee et al. 2018c; Robinson 2001; Tong et al. 2012; Tong et al. 2014; Tong et al. 2015; Wang et al. 2016; Xu et al. 2016). Although defining both

heat waves and cold spells have not been standardized yet, numerous studies have used relative thresholds based on each community's mean temperature to define heat wave and cold spell, rather than absolute thresholds (Anderson and Bell 2009; Åström et al. 2013; Guo et al. 2017; Lee et al. 2018c; Tong et al. 2012; Tong et al. 2014; Tong et al. 2015; Wang et al. 2016), because the relative scale thresholds enable to reflect regional acclimatization considering each community's normal temperature (Guo et al. 2017), and to facilitate comparing result of each community (Lee et al. 2018c).

In general, in order to define the duration day of heat wave or cold spell, two or more consecutive days provided more accurate statistical estimates (Tong et al. 2014) and the duration effect of extreme temperature was less relevant to increased mortality (Gasparrini and Armstrong 2011; Guo et al. 2017; Lee et al. 2018c).

1.3. Temperature variability

Temperature variability (intra-day or inter-day temperature change) is a well-known weather-related risk factor for human health. Numerous studies conducted in Asia and America have described a positive association between temperature variability and mortality (Cao et al. 2008; Kan et al. 2007; Lim et al. 2014; YH Lim et al. 2012; Tam et al. 2009; Yang et al. 2013), and in recent days, multi-country studies reported the association is widely observed in many countries, although the associations are quite heterogeneous depending on countries or climatic conditions (Guo et al. 2016; Lee et al. 2018a). Further, it has been reported that the temperature variability-mortality associations are influenced by individual, environmental, and socio-economic risk factors and vary depending on a cause of mortality (Kan et al. 2007; Lee et al. 2018d; Y-H Lim et al. 2012; Yang et al. 2013).

Biological mechanisms through which temperature variability might affect mortality, have been described in previous medical and epidemiological studies (Garrett et al. 2009; Garrett et al. 2011; Greenberg et al. 1983; Martinez-Nicolas et al. 2015; Qiu et al. 2013). Sudden changes in short-term temperature may cause physiological health problems (Garrett et al. 2009; Garrett et al. 2011). And unstable weather or temperature changes can lead to the onset of cardiovascular events brought on by increased workload, and influence the respiratory system by triggering inflammatory nasal responses (Ballester et al. 1997; Carder et al. 2005; Graudenz et al. 2006; Hashimoto et al. 2004; Imai et al. 1999; Luurila 1980). These mechanisms have been suggested as potential causes of increasing human mortality (Buguet 2007).

In addition, temperature variability has been an important index in climate change, because it has been anticipated to increase under climate change (Solomon 2007). However, recent studies have reported that climate change factors (greenhouse gases, urbanization, and aerosols) have led to a global decline in the diurnal temperature range, one of representative index of temperature variability, during the twentieth century because the nocturnal minimum temperatures have increased faster than the maximum temperatures (Braganza et al. 2004; Makowski et al. 2008). Furthermore, another study found that the variability of low-frequency global mean surface air temperature will likely decrease under climate warming. They suggested that the reduction in high-latitude surface albedo variability by a climatological reduction in albedo was a major reason for this reduction in global mean surface air temperature variability (Brown et al. 2017).

As the decrease in temperature variability, health impacts due to temperature were also assumed to decline in climate change (Yang et al. 2013). However, recent studies reported that high temperature might increase in the temperature variability-related mortality risk, and the temperature variability-mortality relationship increased during the recent decades (Lee et al. 2018a; Lee et al. 2018d). Thus, the health impacts of temperature variability under climate change should be discussed in future research.

1.4. Indices of temperature variability

There are various indicies to measure tempearture variability in this research field. As a relatively classical indicies, diurnal temperature range (DTR, i.e. intra-day temperature change), defined as the intra-day difference between maximum and minimum temperatures, has been widely used in previous studies (Braganza et al. 2004; Cao et al. 2008; Kan et al. 2007; Lee et al. 2017; Lee et al. 2018a; Liang et al. 2009; Y-H Lim et al. 2012; Tam et al. 2009; Vutcovici et al. 2014; Yang et al. 2013). In addition, the change in mean temperature between two neighboring days (i.e. inter-day temperature change) was also used (Lee et al. 2018a; Lin et al. 2013; Zhan et al. 2017).

However, because the indicators are limited to include the intra- and inter-day variability altogether, the studies assessed the association between mortality and intra- and inter-day variability separately, although the variability of temperature has continuously influenced to death during consecutive days. To complement this limitation of previous indices, a recent study developed a new index to calculate temperature variability including both intra- and inter-day variations by calculating the standard deviation of minimum and maximum temperatures during

the adjacent exposure days (Guo et al. 2016). The study showed a significant temperature variability-related mortality in multiple countries using the new index.

1.5. Interaction between temperature and temperature variability

The investigating modifier of weather-mortality association need to be discussed importantly in epidemiological perspectives, because considering the modifiers not only contributes to more efficient public health interventions, but also can be a key factor to estimate the temporal variations in the weather-related mortality (Knol and VanderWeele 2012).

Surprisingly, despite the fact that humans are exposed simultaneously to extreme temperature and temperature variability, which have similar biological mechanisms that lead to death, effect modification and interactive relationship of the co-exposure has been far less studied (Lee et al. 2018d). Some studies have shown season-specific association between temperature variability and mortality (Kan et al. 2007; Y-H Lim et al. 2012; Zhou et al. 2014), with some evidence of higher temperature variability-related mortality risks in the warmer season.

However, the previous studies have used a season or a binary indicator (e.g., warm and cold seasons) to examine the temperature modification and did not consider a flexible lag-pattern of temperature variability-mortality association. More sophisticated approach (e.g., including a flexible statistical terms in the model) would be merited to investigate the complex modification pattern of temperature on the temperature variability-related mortality and complement potential limitations of the previous studies. Hence, a few studies have attempted investigating the multiplicative effect modification between temperature and temperature variability (Lee et al. 2018d; Yang et al. 2013); the report showed that temperature variability-related mortality is modified by temperature level.

In addition, people are generally exposed to these two variables at the same time and these variables have similar biological mechanisms, which can lead to death, therefore mortality risks related to the co-exposures to temperature and temperature variability should be assessed simultaneously. To the best of our knowledge, there is no study estimating the interaction between high temperature and temperature variability on mortality. The interaction is a more suitable public health measure than the use of the effect modification measures only (Blot and Day 1979; Rothman et al. 1980). Further, to investigate the synergism between high temperature and temperature variability, additive interaction between the two variables should be studies in further. And, as we described above, although temperature variability may

decrease under climate change (Braganza et al. 2004; Makowski et al. 2008), there exists an interactive role of temperature to change the temperature variability-mortality association, it is uncertain what would be the net effect of climate change on the temperature variability-related health risk. Therefore, future research should more investigate the issues in the future.

1.6. Changing susceptibility to temperature and temperature variability

Previous studies have reported temporal decline in the susceptibility to heat extremes during recent decades in Asia (Chung et al. 2017; Ha and Kim 2013; Lee et al. 2018c), and America (Barnett 2007; Bobb et al. 2014; Gasparrini et al. 2015a; Petkova et al. 2014). Most of the studies have suggested usage of air conditioner, advances in household and public health intervention, economic growth, and adaptation to climatic warming are major plausible reasons of the temporal change (Barnett 2007; Bobb et al. 2014; Chung et al. 2017; Coates et al. 2014; Gasparrini et al. 2015a).

However, a few studies that have assessed the cold extremes-related mortality risk over time have showed mixed results, with some reporting a reduction in risk (Carson et al. 2006; Christidis et al. 2010), and other reporting no change or increase in risk (Åström et al. 2013; Chung et al. 2017; Lee et al. 2018c). A recent study conducted in Japan suggested that aging demography, relative humidity increase, and economic depression might be related with increase in risks due to extreme cold (Chung et al. 2018).

Besides, some studies reported that mortality burdens due to extreme temperatures were changed after considering both the time-varying temperature distribution and temperature-related mortality, compared to estimates only considering the time-varying temperature-related mortality (Lee et al. 2018b; Vicedo-Cabrera et al. 2018). In particular, a study reported that deaths attributed to extreme hot temperature raised after 2010, although the corresponding RR of extreme hot temperature decreased during the same period (Lee et al. 2018b). The study suggested the total mortality burden due to extreme heat may increase in climate change as frequency of extreme heat increase, despite human may adapt to warming.

In addition, recent studies reported the temporal increase in the mortality burden due to temperature variability during recent decades, and suggested that the temporal increase might be related with climate change (Lee et al. 2018a; Lee et al. 2018d). As we discussed above, since

high temperature might increase the temperature-variability association, the modification pattern should consider to predict mortality burden related to temperature variability in future study.

Therefore, in order to assess the mortality burden due to climate change, temporal changes in distribution of exposure variable and temporal changes in the relationship between the exposure variable and mortality should become key issues to avoid over/underestimated impacts of extremes and unstable weathers under climate change (Lee et al. 2018c).

1.7. Statistical modelling

Non-linearity

Unlike air pollution and temperature variability, the exposure-response association between death and temperature were generally reported as non-linear: U, V, or J-shape (Curriero et al. 2002; Hajat et al. 2007). As a classical approach, a V-shape threshold exposure-response association was applied in modelling the temperature-mortality relationship (Muggeo and Hajat 2008; Muggeo 2008). This approach was simple and easy to interpret results, however it had limitation to reflect complex non-linear relationship between temperature and mortality. Hence, spline functions (e.g. natural cubic spline, or B-spline) were more generally used to capture temperature-mortality association in the research field.

In addition, one more non-linear association exists in environmental variable-related mortality relationship: lagged effect of exposure. Generally, exposure to environmental variables generate delayed effect. In previous researches, heat showed the highest mortality at lag 0-1 day and the risk was delayed up to 7 to 9 days, and cold showed the highest mortality at lag 1-4 day and the risk was delayed up to 10 to 21 days (Gasparrini et al. 2010; Guo et al. 2014). Further, temperature variability generally showed about 10 days lagged association with mortality, and air pollution effect on mortality also lasted during 2-4 days (Burkart et al. 2013; Kan et al. 2007; Lee et al. 2018a; Stafoggia et al. 2008). Simplest approach to consider the lagged association is moving average across the corresponding lag days, however the approach has limitation to reflect non-linear lagged association (Gasparrini et al. 2010). Thus, in order to capture the non-linear delayed association between exposure and response, a distributed lag linear model was widely used (Almon 1965; Ben Armstrong 2006; Schwartz 2000).

Nevertheless, a distributed lag linear model also have a crucial limitation: it only can consider the linear exposure-response relationship. Hence, in order to overcome this limitation, Ben Armstrong and Antonio Gasparrini developed a new flexible model: a distributed lag non-linear

model (DLNM) (Gasparrini et al. 2010). This methodology can flexibly capture both non-linear exposure-response and non-linear lagged association, and now the approach is a nearly standard approach to estimate environmental exposure-related mortality association.

Minimum mortality temperature

In temperature-related mortality association estimated using DLNM, one important feature is the minimum mortality temperature (MMT), which is defined as the temperature at which the lowest mortality is achieved. The MMT has been regarded as a threshold point in describing the population susceptibility to temperature because the mortality risk becomes increased as temperature increases or decreases from the MMT (Chung et al. 2018; Guo et al. 2014). Therefore, the MMT has been also called as an optimal temperature, and it has often been used as a reference temperature to quantify the relative risk (RR) related to cold or hot temperatures in many previous studies (Chung et al. 2018; Gasparrini et al. 2015b; Guo et al. 2014; Lee et al. 2018b).

The typically used approach for estimating the MMT is to determine the MMT as the temperature at which mortality is minimized in the estimated temperature-mortality curve, however this approach provides a point estimate but the corresponding uncertainty is not quantified. Hence, a previous proposed a Monte Carlo simulation to calculate standard errors and the confidence interval for the MMT (Tobías et al. 2016), however , the statistical property of the methods and how the uncertainty in the MMT affects the estimation of the RR referenced with the MMT were not fully studied (Lee et al. 2017a). Therefore, a previous study proposed a modified Monte Carlo simulation with prior information to estimate the uncertainty of MMT and the RR referenced with the MMT, and showed that the uncertainty and prior information of MMT should be considered if the corresponding exposure-response curves are not complete U or V shape (like inverse J or sector shape) (Lee et al. 2017a).

Non-identifiable issue between temperature and temperature variability

Identifiability is a rising issue in temperature and temperature variability research, because it was quite difficult to distinguish whether high temperature variability lead to death or whether absolutely higher/lower temperature lead to death (Lee et al. 2017; Vicedo-Cabrera et al. 2016). Let's suppose yesterday's daily mean temperature was raised from 25˚C to 35˚C today, and a person died at today. Then, it is quite difficult to distinguish whether the person who died today was due to a rapid temperature change (10˚C in a day), or whether it was caused by an absolute

hot temperature today (35˚C).

In order to separate the effects of the two variables, a previous study adjusted absolute temperature using DLNM and MMT in estimating the temperature variability-mortality association, and did not consider the delayed effect of temperature variability on death (Vicedo-Cabrera et al. 2016). Another study applied two-step regression (residual adjustment) approach to distinguish absolute temperature and temperature variability effects on mortality (Lee et al. 2017). Both studies showed that the overall effects of absolute temperature were generally higher than those of temperature variability: however the effect of temperature variability was still related significantly to death, after considering the absolute temperature effect.

1.9. Summary of my researches in the PhD thesis

Section 2.1. Temperature-mortality and temperature variability-mortality associations

Section 2.1.1. The temporal changes in weather-mortality association

1) I studied the temporal changes in mortality risk related to heat wave and cold spell in 53 communities in Korea and Japan.

2) I studied the temporal changes in mortality burden due to DTR in 308 communities in 10 countries.

Section 2.1.2. The interactions in the weather-mortality association

1) I studied interactive role of temperature on the DTR-related mortality in 57 communities in Korea, Japan, and Taiwan.

2) I studied synergic association (additive scale interaction) between heat and temperature variability on mortality in 57 communities in Korea, Japan, and Taiwan.

Section 2.2. Uncertainty estimation in weather-mortality association

1) I studied the uncertainty estimation of MMT, heat and cold risks on mortality using Bayesian simulation method.

2) I studied the two-step regression approach to distinguish mortality risk related to temperature variability from absolute temperature.

Research

2.1. Temperature-mortality and temperature variability-mortality associations

2.1.1. The temporal changes in weather-mortality association

In this section, I investigated the temporal changes in weather-mortality association: the temporal changes in the impact of heat wave and cold spell on mortality during 1992-2015 in 53 communities in Korea and Japan (**Research 1**), and the attributable risk fraction of diurnal temperature range (DTR) and its temporal change for 308 cities of 10 countries (**Research 2**).

Research 1.

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Title: Temporal Changes in Mortality Impacts of Heat wave and Cold spell in Korea and Japan.

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Abstract

Investigating how well people adapt to heat waves and cold spells has been an important issue under climate change. Also, most of previous studies focused only on the mortality risks for heat waves or cold spells for certain time period not considering its temporal changes and increasing frequencies. This study investigated the change in risks of mortality from heat waves and cold spells over time, and estimated the temporal changes in mortality burden attributed to heat waves and cold spells in Korea and Japan. We collected time-series data covering mortality and weather variables from 53 communities in the two countries from 1992 to 2015. Two-stage time-series regression with a time-varying distributed lag model and meta-analysis was used to assess the impacts of heat waves and cold spells by period (1990s, 2000s, and 2010s). In total population, the risks of heat waves have decreased over time; however their mortality burden increased in the 2010s compared to the 2000s with increasing frequency. On the other hand, the risk and health burden of cold spells have increased over the decades. Our findings showed that the future mortality burden of heat waves and cold spells might not decrease, when considering their changes in risks and frequencies.

Key words: Heat wave; Cold spell; Climate change; Mortality burden; Time-varying model;

Abbreviations: Attributable risk fraction (ARF), Distributed lag non-linear model (DLNM), Relative risk (RR).

Introduction

Heat waves and cold spells are prominent threats to human health. Many studies have reported that the positive association between extreme weather and mortality (Analitis et al. 2014; Anderson and Bell 2009; Barnett et al. 2012; Huynen et al. 2001; Le Tertre et al. 2006; Semenza et al. 1996; Xie et al. 2013). A recent study found that 48-74% of the world's population will suffer from heat waves in 2100 (Mora et al. 2017), and other studies discovered the shift of the polar vortex over the last several decades, which could lead to increasing cold spells in mid-latitude regions (Cohen et al. 2014; Wallace et al. 2014; Zhang et al. 2016). The Intergovernmental Panel on Climate Change also reported that global warming will increase the extremes of temperature (Meehl and Tebaldi 2004; Solomon 2007). Therefore, anticipating the effects of increasing occurrence of heat waves and cold spells on human health is crucial to establishing better public health strategies (Meehl and Tebaldi 2004).

In order to assess the health burden due to climate change, temporal changes in the relationship between the extreme temperatures and mortality have become key issues in recent days (Chung et al. 2017; Gasparrini et al. 2015a). Relevant studies have reported temporal decline in the association between extreme heat and mortality, due to adaptation (Barnett 2007; Bobb et al. 2014; Coates et al. 2014; Davis et al. 2003; Guo et al. 2012; Ha and Kim 2013; Petkova et al. 2014). In addition, a recent multi-country study showed that the heat-mortality association decreased over the last decades, and the decline was more pronounced in the United States and Japan (Gasparrini et al. 2015a). Another study also reported that a decline in the heat-mortality association in summer (June to September) over time in three Northeast Asian countries (Korea, Japan, and Taiwan), and this decreasing trend was more pronounced in respiratory mortality, compared to all-cause mortality (Lee et al. 2018).

In addition, as record-breaking cold spells have occurred in recent years in the United States (Screen and Simmonds 2014) and East Asian countries (Ap 2016; British Broadcasting Corporation 2016), the importance of research on the impacts of cold spells on climate change has been on the rise. However, relatively fewer studies (Huynen and Martens 2015; Kalkstein and Greene 1997) focused on changes in the association between cold extremes and mortality over time (Åström et al. 2013; Chung et al. 2017; Vicedo-Cabrera et al. 2018), than heat-mortality association. A previous study reported that the population in Northeast Asia mal-adapted to cold temperature during the 1990s and 2000s (Chung et al. 2017). In addition, another study showed that the temporal trends in attributable risk for cold temperature (higher than the location-specific minimum mortality temperature) varied by country (Vicedo-Cabrera et al. 2018). However, to the best of our knowledge, there is no research investigating the temporal changes in cold spell-related mortality during recent years in Asian countries.

Moreover, many previous studies have been limited in assessing the health burden of climate change, because most of them only denoted a temporal change in risk ratio of exposure (e.g., relative risk [RR]) (Bobb et al. 2014; Davis et al. 2003; Gasparrini et al. 2015a). Since the risk ratio does not consider the change in the distribution of extreme weather events, it could result in under- or over-estimation of mortality burden due to extreme events. A recent study showed that although the risk of mortality from heat decreased during recent decades in Japan, the mortality risk attributed to heat increased in the 2000s (2003-2012), compared to the 1970s (1972-1981), due to increased frequency of hot days in summer (Lee et al. 2018). The study also showed that erroneous conclusion regarding anticipating the future health impacts of heat temperature can be derived when only the risk of heat was considered, and suggested that the index for future health impacts considering the frequency and risk of heat should be used accordingly. Another study also reported that the time-trend of mortality burdens attributed to temperature, considering yearly-varying temperature distribution and the risks associated with temperature together, could be different from those estimated considering only considering risk changes (Vicedo-Cabrera et al., 2018).

Therefore, this study aimed 1) to estimate the temporal changes in the risks (RRs) of heat waves and cold spells on mortality in Korea and Japan, 2) to evaluate the temporal changes in the mortality burdens of heat waves and cold spells considering changes in their frequency during the study period, 3) to examine whether the changes in 1) and 2) are different in three regions (Korea, Japan-north, and Japan-south) separated by country and regional climates.

Methods

Data

This study includes time-series data for weather variables and all-cause mortality (as a daily mortality count) for 53 communities in two Northeast Asian countries: Korea (6 cities during 1992–2015), and Japan (47 prefectures during 1992–2015). Figure S1 shows the geographical locations of 53 communities (divided into Korea, Japan-north, and Japan-south, which include 6, 24, and 23 communities; Japan-north and Japan-south was divided with the annual mean temperature within the range of 9.25-15.4°C (corresponding to 0-50th percentiles) and of 15.4-23.3°C (corresponding to 50-100th percentiles), respectively. Weather variables included daily mean temperatures (°C), and daily mean relative humidity (%). For each community, weather variables were measured from a single monitor station. The weather variables were originally hourly measured and 24-hour average value were obtained for each community. Mortality data were obtained from the Korea National Statistics Office (Korea) and the Ministry of Health &

Welfare of Japan (Japan), and weather data were obtained from the Korea Meteorological Office (Korea) and the Japan Meteorological Agency (Japan).

Definitions of Heat wave and Cold spell

In this study, daily mean temperature was used as an indicator of exposure to identify the effects of heat waves and cold spells on mortality. We defined heat waves as daily mean temperature above 95th (heat wave$_{>95\%}$), 97th (heat wave$_{>97\%}$), and 99th (heat wave$_{>99\%}$) percentiles of the temperature distribution with two or more consecutive days for each community during its study period. Also, we defined cold spells as daily mean temperature below 5th (cold spell$_{<5\%}$), 3rd (cold spell$_{<3\%}$), and 1st (cold spell$_{<1\%}$) percentiles of the temperature distribution with two or more consecutive days for each community during its study period. Although defining both heat waves and cold spells have not been standardized yet, numerous studies have used relative thresholds based on each community's mean temperature to define heat wave and cold spell (Anderson and Bell 2011; Åström et al. 2013; Guo et al. 2017; Tong et al. 2015; Tong et al. 2014; Wang et al. 2016). This enables to reflect regional acclimatization considering each community's normal temperature (Guo et al. 2017), and facilitates comparing result of each community. We only used duration of two or more consecutive days to define heat wave and cold spell, because previous studies reported that definitions of heat wave and cold spell with two or more consecutive days provided more accurate statistical estimates (Tong et al. 2014) and the duration effect of extreme temperature was less relevant to increased mortality (Guo et al. 2017). And all days with temperature above (or below) the threshold vales for a given heat wave (or cold spell) definitions with two duration days were defined as heat wave (or cold spell) days (Guo et al. 2017).

Statistical analysis

The heat wave analyses were limited to the June to September (four hottest adjacent months), and the analyses for cold spell were limited to the December to March (four coldest adjacent months). The analyses for heat wave and cold spell were performed by individual model. The heat wave- and cold spell-mortality associations were analyzed using a two-stage time-series approach. In the first stage analysis, we applied a time-varying distributed lag model to estimate community-specific heat wave- and cold spell-mortality relationships with a linear interaction between year and exposures. The second-stage pooled these community-specific associations by meta-analysis. Those analytical approaches were referenced by previous studies (Gasparrini et

al. 2015a; Gasparrini et al. 2015b; Guo et al. 2016).

First stage analysis

The first-stage used a generalized linear model with quasi-Poisson distribution. Firstly, we fitted the model to estimate heat wave- and cold spell-mortality associations respectively, with a year-interaction term for each community with the following specifications. The primary exposures, represented by binary indicators for heat waves and cold spells, were included using a distributed lag model structure. We used a basis function; a natural cubic spline including an intercept with two interval knots at equally spaced log values of lag days (up to 10 days for heat waves, and 21 days for cold spells) to capture flexible lag effects of heat waves and cold spells on mortality. We used a linear interaction term between year and basis to estimate the time-varying association between two exposures and mortality. And, to reflect consecutive days of December to March, we newly defined a "year" variable as the periods from December of previous year to March of the following year in cold spell analyses. For example, the period from December 2010 to March 2011 was re-defined as the 2011.

We also controlled the daily mean relative humidity (%) with cross-basis of distributed lag nonlinear model structure; a natural cubic B-spline with two internal knots (33.3rd, and 66.7th percentiles of location-specific relative humidity) for humidity dimension and a natural cubic B-spline with an intercept and two equally spaced knots on the log scale for lag dimension (up to 7 days). Seasonality was adjusted using a natural cubic B-spline with 4 degrees of freedom (df) for day of the hot (for heat wave) and cold (for cold spell) season within a year, respectively. Long-term trend was also controlled using a natural cubic B-spline of time on day with equally spaced knots and approximately 1 df every 10 years. The choices of lag days and modelling assumptions were referenced by previous extreme temperature-mortality studies (Gasparrini et al. 2015b; Guo et al. 2017).

From the first-stage analysis, we obtained four coefficients of the basis to represent the exposure-response relationships over the lags for each community by three decades. We defined three decades according to years of study period: the 1990s (1992-1999), the 2000s (2000-2009), and the 2010s (2010-2015), and obtained four coefficients for exposure-response associations over the lags for the centering years (1999.5, 2004.5, and 2012.5; the median years of each decade) of each of the three decades for each community. We reduced coefficients for each decade to a single coefficient respectively, which represents the overall lag-cumulative exposure-response associations (log values of relative risks of heat wave and cold spell). Also, we obtained four coefficients for an interaction between year and the basis, reduced those to a

single overall cumulative community-specific interaction coefficient. The community-specific associations were used in the second-stage analysis. The first-stage analyses were performed using R statistical software and the *dlnm* package.

Second stage analysis

The community-specific associations (the lag-distributed association represented by four coefficients, and the overall cumulative association by a single coefficient) were pooled for each decade separately, using multivariate and univariate random effect meta-analysis. We pooled the estimates by each decade, separately for Korea, Japan-north, and Japan-south using meta-regression with an indicator for regions. And the univariate random effect meta-analyses also were used to derive the best linear unbiased prediction (BLUP) of the overall cumulative exposure-response for each community. Additionally, the multivariate random effect meta-analyses (Gasparrini et al. 2012) were used to pool the lag-distributed association in total population and for each sub-region, respectively. The second-stage meta-analyses were performed using R software and the *mvmeta* package.

Mortality attributable risk fraction of heat wave and cold spell

From the second-stage analysis, we derived the decade-specific overall lag-cumulative RR at heat wave (or cold spell) days, compared to non-heat wave (or non-cold spell) days, to estimate the attributable deaths and fraction in the next 10 days (or 21 days for cold spells), using a previously described method (Gasparrini and Leone 2014). We used the overall lag-cumulative RRs corresponding to each heat wave (or cold spell) day by each decade to compute the daily attributed number of deaths by decades, as the product of the day's deaths and the daily attributable risk (= (RR-1)/RR) of the day.

The attributable number of deaths caused by heat waves (or cold spells) across by decades (the 1990s, 2000s, and 2010s) are given by the sum of the contributions from all the days of each decade, and its ratio with the total number of deaths during each decade provides the decade-specific the attributable fractions (ARFs, %). Furthermore, we inferred empirical 95% confidence interval using Monte Carlo simulations, with normal distribution assumption of the BLUP. These procedures for calculating the ARFs and their confidence intervals were described in previous researches (Gasparrini et al. 2015b). We described the detailed computation procedures in Supplementary Materials (Appendix 1.Details on the calculation of attributable risk fraction).

Testing the significance of temporal risk changes

The community-specific year-interaction coefficients for heat wave- and cold spell-mortality associations were pooled separately using univariate random-effect meta-analysis. We tested whether the interaction between year and heat wave (or cold spell) is significant (H_0: the lag-cumulative year-heat wave (or cold spell) interaction coefficient is zero). We used the pooled interaction coefficient, and applied univariate Wald test to examine if the pooled coefficient is not equal to zero. Additionally, in order to test whether there is a difference between the ARFs of the 2010s and the ARFs of the other decades (1990s and 2000s, respectively), we also applied Wald test between the corresponding ARFs (H_0: a difference between two ARFs is zero), based on independence hypothesis: the ARFs of two different decades were independently distributed. Mean and standard error of the ARFs for each decade were derived from the Monte Carlo simulations, described in above (a part for calculating an empirical confidence interval of the ARF).

Added effect of heat wave and cold spell

We also examined whether heat waves and cold spells had added effect on mortality after considering the effect of single day temperature. All other variables from first-stage model were maintained, only the temperature was controlled by using a cross-basis function in distributed lag non-linear model (Gasparrini et al. 2010). We modeled the temperature-response relationship using a natural cubic B-spline with three internal knots (placed at the 25th, 50th, and 75th percentiles of location-specific temperature distributions), lag-response (heat wave models: up to 10 days, cold spell models: up to 21 days) curve with natural cubic B-spline with two (cold spell models: three) internal knots placed at equally spaced values on the log scale. Procedures for second-stage analysis were maintained to pool the estimates of added effects of heat waves and cold spells.

Sensitivity analysis

In order to test the sensitivity of our results to the modeling parameters and assumptions described above, we calculated ARFs by decades with changing lag days (7 and 14 days for heat waves, and 14 and 28 days for cold spells), df for seasonality (df=3 and 5), df for long term trend (df=2), and duration days (three or more consecutive days). Additionally, we tried to

report that how our main results change when the relative humidity, which is the prominent confounder on the heat wave (or cold spell)-related mortality, was not adjusted.

Results

The average and total number of heat waves and cold spells by decades (the 1990s, 2000s, and 2010s) are displayed in Table 1. In the total population, the yearly-average number of heat wave$_{>95\%}$ days decreased in the 1990s to 2000s, and increased in the 2010s (634.2 in the 1990s, 615.4 in the 2000s, and 1,002 in the 2010s). The yearly-mean number of cold spell$_{<5\%}$ days in the total population increased during the 1990s to 2010s (468.5 in the 1990s, and 709.5 in the 2010s). The yearly-averaged numbers of heat wave and cold spell days during 1992 to 2015 are displayed in Figure S2. Similar trends are shown in all other definitions for heat wave and cold spell, and for all sub-regions. Community-specific descriptive statistics, including death counts and temperature distribution during June to September (Table S1) and December to March (Table S2) are also shown in the Supplementary Materials. The community-specific counts for heat waves and cold spells during the whole study periods are reported in Figure S3.

Table1. Yearly averaged and total number of heat wave and cold spell defined by each three types of intense days in 53 communities of Korea and Japan.

Region (# of community)	Period	Yearly averaged number of days (Total number of days)					
		Heat wave$_{>95\%}$	Heat wave$_{>97\%}$	Heat wave$_{>99\%}$	Cold spell$_{<5\%}$	Cold spell$_{<3\%}$	Cold spell$_{<1\%}$
Total population (53)	Whole	718.3 (17,240)	386.1 (9,267)	100.4 (2,409)	558.8 (13,411)	292 (7,008)	72.4 (1,738)
	1990s (92-99y)	634.2 (5,074)	346.6 (2,773)	101 (808)	468.5 (3,748)	248.4 (1,987)	58.8 (470)
	2000s (00-09y)	615.4 (6,154)	290.6 (2,906)	60.1 (601)	540.6 (5,406)	277.1 (2,771)	71.6 (716)
	2010s (10-15y)	1,002 (6,012)	598 (3,588)	166.7 (1,000)	709.5 (4,257)	375 (2,250)	92 (552)
Japan-north (24)	Whole	323.1 (7,754)	174.2 (4,182)	43.7 (1,048)	253.3 (6,080)	133.6 (3,206)	34.2 (820)
	1990s (92-99y)	281.8 (2,254)	155.1 (1,241)	44.8 (358)	202.5 (1,620)	112.6 (901)	31.2 (250)
	2000s (00-09y)	247.9 (2,479)	114 (1,140)	25.8 (258)	253.3 (2,533)	127.6 (1276)	32.9 (329)
	2010s (10-15y)	503.5 (3,021)	300.2 (1,801)	72 (432)	321.2 (1,927)	171.5 (1029)	40.2 (241)
Japan-south (23)	Whole	314.5 (7,549)	167.6 (4,022)	44.2 (1,062)	240.2 (5,766)	123.3 (2959)	29.5 (709)
	1990s (92-99y)	264.8 (2,118)	139.6 (1,117)	38.6 (309)	210.4 (1,683)	111.6 (893)	24.8 (198)
	2000s (00-09y)	302.7 (3,027)	144.8 (1,448)	29.5 (295)	230.7 (2,307)	118 (1,180)	30.3 (303)
	2010s (10-15y)	400.7 (2,404)	242.8 (1,457)	76.3 (458)	296 (1,776)	147.7 (886)	34.7 (208)
Korea (6)	Whole	80.7 (1,937)	44.3 (1,063)	12.5 (299)	65.2 (1,565)	35.1 (843)	8.7 (209)
	1990s (92-99y)	87.8 (702)	51.9 (415)	17.6 (141)	55.6 (445)	24.1 (193)	2.8 (22)
	2000s (00-09y)	64.8 (648)	31.8 (318)	4.8 (48)	56.6 (566)	31.5 (315)	8.4 (84)
	2010s (10-15y)	97.8 (587)	55 (330)	18.3 (110)	92.3 (554)	55.8 (335)	17.2 (103)

Figure 1 (A) shows the RRs of heat waves (temperature unadjusted) by decades in the total population and according to regions with the results for the statistical test. The RRs of all heat waves significantly decreased during the study period in the total population (all *P*-values< 0.001). The significant-decreasing RR patterns were similar in Japan-north. However, in Japan-south and Korea, the RRs for heat waves did not significantly decrease over time (*P*-value>0.05), except for heat wave$_{>95\%}$ in Japan-south. The corresponding community-specific RRs of heat waves by decades are reported in Figure S4. And the pooled lag-response curves of heat waves by decades in the total population are represented in Figure S6, it showed the highest RR at lag 0 days, and the RR decreased over lags with indications of delay up to 2-3 days, for all heat wave definitions. In addition, we could not find significant added effects of heat waves (Figure 1 (B); temperature adjusted), except for heat wave$_{<99\%}$ for each decade.

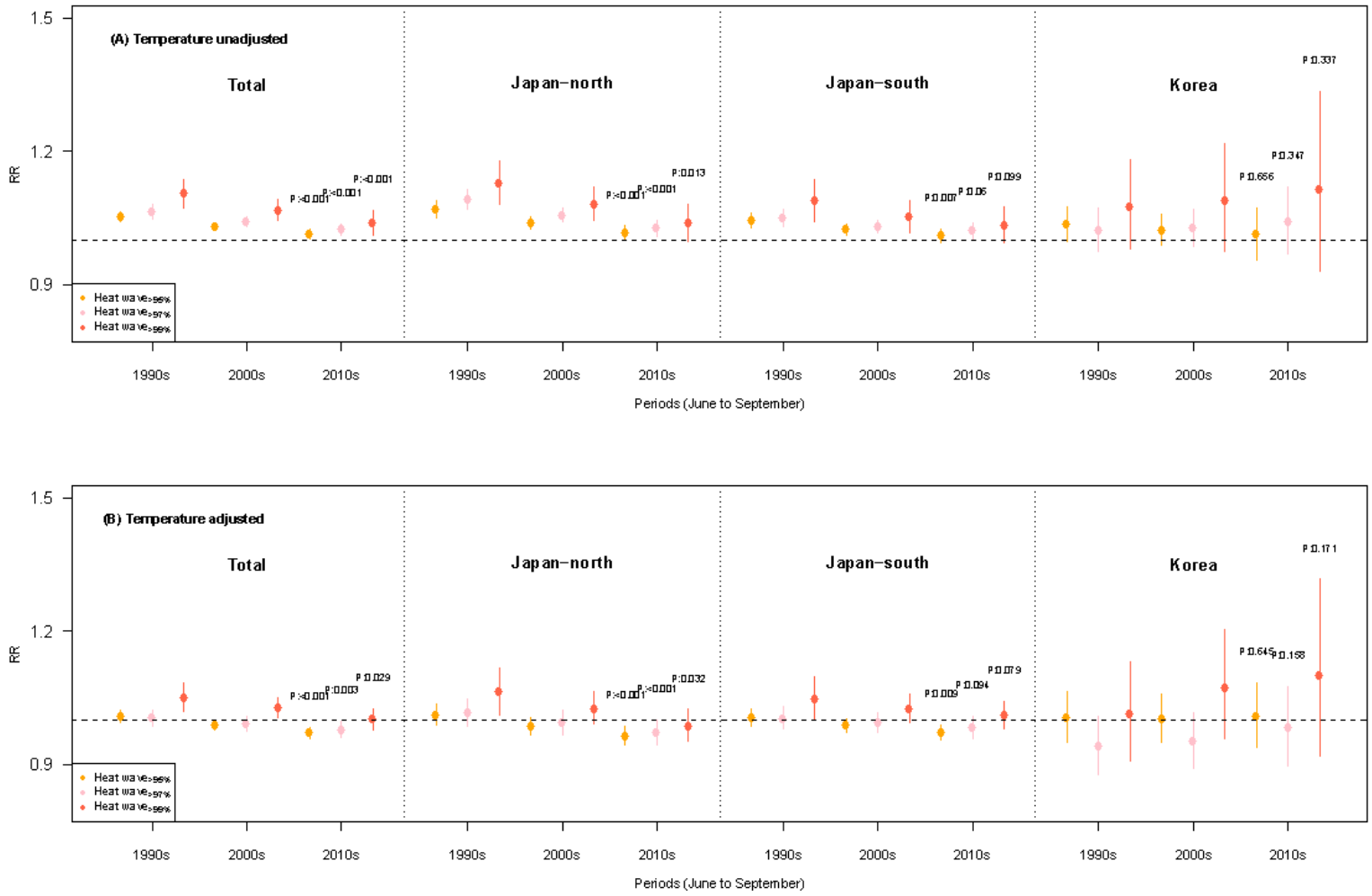

Figure 1. Temporal changes in cumulative relative risks (RR) of heat waves on mortality by decades (the 1990s: 1992-1999, 2000s: 2000-2009, and 2010s: 2010-2015) in the total population and by the three regions, with results from Wald type tests (H_0: the year-heat wave (or cold spell) interaction coefficient is zero; P: P-value). (A): overall effects of heat waves, (B) added effects of heat waves after controlling for the effects of daily mean temperature.

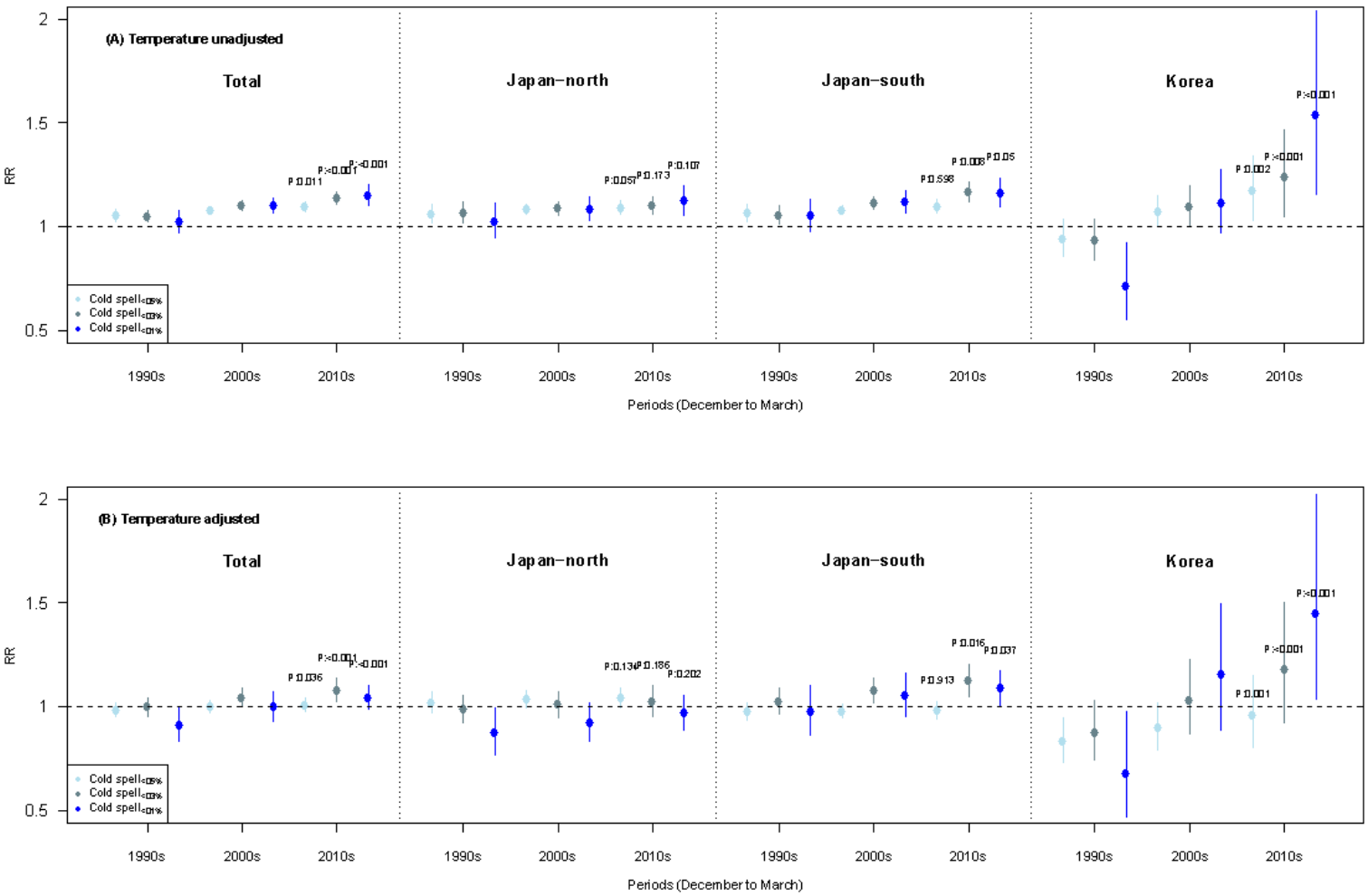

Figure 2. Temporal changes in cumulative relative risks (RRs) of cold spells on mortality by decades (the 1990s: 1992-1999, 2000s: 2000-2009, and 2010s: 2010-2015) in the total population and by the three regions, with results from Wald type tests (H_0: the year-heat wave (or cold spell) interaction coefficient is zero; P: P-value). (A): overall effects of cold spells, (B) added effects of cold spells after controlling for the effects of daily mean temperature.

On the other hand, as shown in Figure 2 (A), the RRs for all cold spells (temperature unadjusted) significantly increased (all *P*-values: <0.05) in the total population during the study period. In particular, the RR of the highest intensity cold spell (cold spell$_{<1\%}$) increased more rapidly over time in Japan-south (RR: from 1.05 in the 1990s to 1.16 in the 2010s) and Korea (RR: from 0.71 in the 1990s to 1.54 in the 2010s), than in Japan-north (RR: from 1.02 in the 1990s to 1.12 in the 2010s). Cold spell$_{<3\%}$ showed a similar time-pattern of RR as cold spell$_{<1\%}$. The corresponding community-specific RRs of cold spells by decades are reported in Figure S4, while the pooled lag-response curves of cold spells by decades in the total population are represented in Figure S6. It showed the highest RR at lag 1-3 days, and the RR decreased over lags with indications of delay up to 15-20 days for all intensities of cold spells. In addition, we could not find significant added effects of cold spells (Figure 2 (B); temperature adjusted) for each decade.

Temporal changes in ARFs due to heat waves and cold spells are shown, and the statistical test results for the ARF changes in the 2010s compared to other periods (H_0: the heat wave ARFs of the 1990s or 2000s are equal to that of the 2010s) are presented in Figure 3. In the total population, the ARF of heat wave$_{>95\%}$ declined significantly in the 2010s (0.31%) compared to 1990s (0.64%) with *P*-value <0.001. The ARF in the 2010s also decreased compared to the 2000s (0.39%), although this difference was not statistically significant (*P*-value=0.152). On the other hand, the ARFs of heat wave$_{>97\%}$ and heat wave$_{>99\%}$ in 2010s (0.34% and 0.22%, respectively) has increased compared with those of the 2000s (0.27% with *P*-value=0.078, and 0.12% with *P*-value=0.001, respectively). These increased patterns for heat wave$_{>97\%}$ and heat wave$_{>99\%}$ ARFs was more prominent in Japan-south and Korea. These trends were considered to be related to the increasing frequency of heat waves in the 2010s, compared to the 2000s (Table 1). The corresponding attributable number of deaths due to heat waves are displayed in Table S3.

Changes in mortality ARF to cold spell over time and the corresponding statistical test results (H_0: the cold spell ARFs of the 1990s or 2000s are equal to those of the 2010s) are also reported in Figure 3. In the total population, the ARFs of all definitions for cold spell significantly increased in the 2010s (1.44% for cold spell$_{<5\%}$, 1.13% for cold spell$_{<3\%}$, and 0.38% for cold spell$_{<1\%}$, with all corresponding *P*-values <0.001) compared to both the ARFs of the 2000s and 1990s. These decreasing trends over time have been observed to be consistent in all sub-regions. These ARF time trends were presumed to reflect both the increase in cold spell RR (Figure 2) and the increase in frequency of cold spells during the study period (Table 1). The corresponding attributable number of deaths due to cold spells is displayed in Table S3, and the community-specific ARF of heat wave and cold spell by decades are reported in Figure S5.

Figure 4 shows interaction coefficients (BLUPs for interaction coefficient from second-stage

analysis) between year and heat wave$_{>99\%}$ (top left) and cold spell$_{<1\%}$ (bottom left). Although some communities had positive interaction coefficients, most communities showed a decreasing trend of the heat wave-mortality association (log value of RR) over time. This declining pattern was more pronounced in the Japan-south. On the other hand, increasing trends of log valued RR for cold spells were found across all regions in both countries; this increasing trend was more pronounced in Korea and Japan-south. In addition, Figure 4 also contains the differences in ARF of heat waves (top right) and cold spells (bottom right) in the 2010s compared to the 2000s. In considerable number of communities in Korea and Japan-south, the ARFs of heat wave showed increasing trends in the 2010s, although the communities showed temporal decreases in the corresponding RRs. On the other hand, the ARFs of cold spell increased in the 2010s in most communities compared to the 2000s. Figure S7-8 represent the corresponding figures with different heat wave and cold spell definitions, and similar trends were observed as Figure 4.

In the sensitivity analysis, our main conclusions were robust to the choice of model conditions (Table S4). When the modeling specifications were changed, the results were generally consistent, suggesting that the ARFs of heat waves increased in the 2010s compared to the 1990s, except for heat wave$_{<95\%}$. The ARFs for all cold spells increased during the study period. In addition, we found that the risk of both exposures decreased after relative humidity adjustment, although the decrease was too small to affect the significance of the overall exposure-response relationship (Table S5).

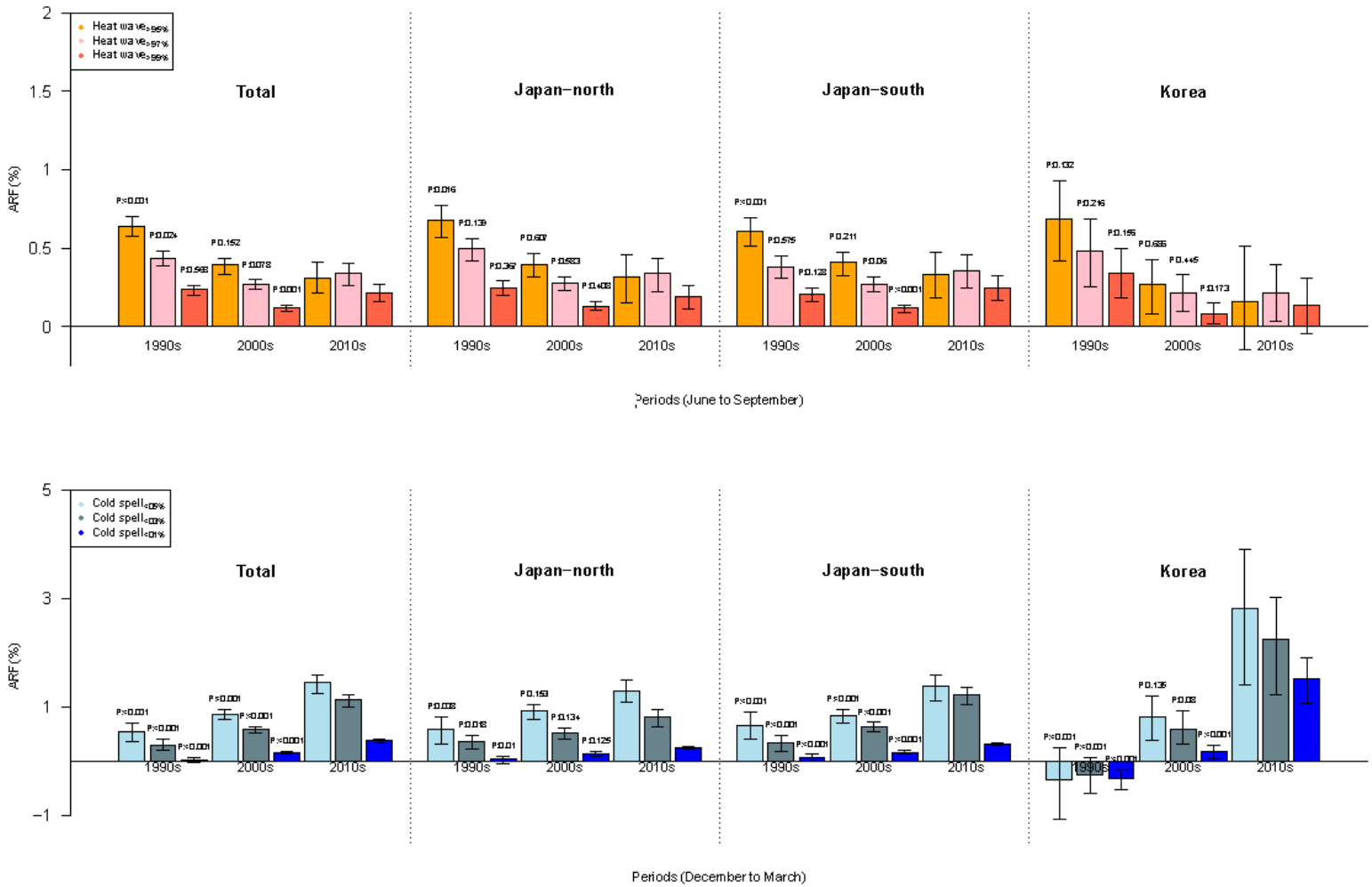

Figure. 3. Temporal changes in mortality attributable risk fraction (ARF) of heat wave (top) and cold spell (bottom) by decades (the 1990s: 1992-1999, 2000s: 2000-2009, and 2010s: 2010-2015) in the total population and by the three regions with results from Wald type tests (H_0: the ARF in the 1990s (or in the 2000s) is the same as the ARF in the 2010s; P: P-value).

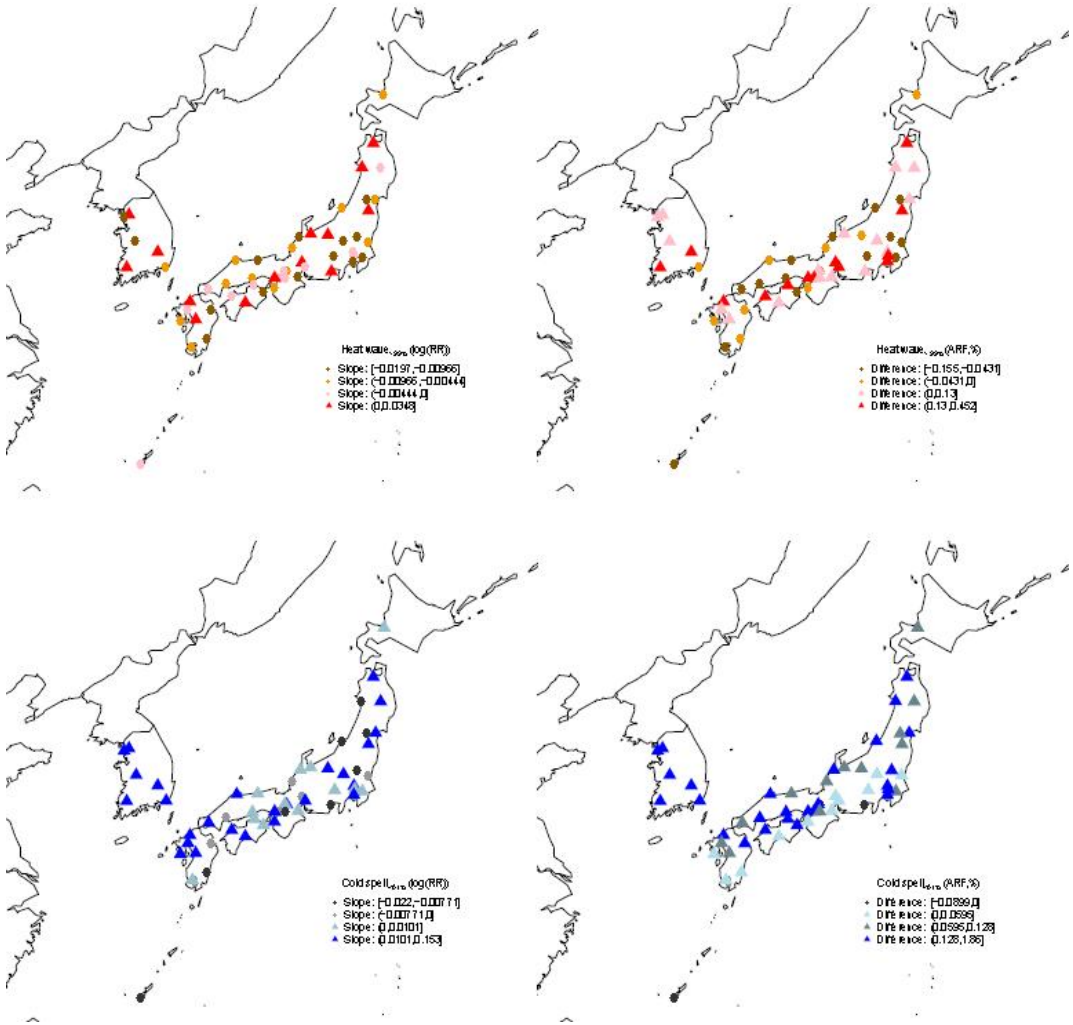

Figure 4. Geographical distribution of year-interaction coefficients for the heat wave$_{>99\%}$- and cold spell$_{<1\%}$-mortality association, and differences of mortality attributable risk fractions (ARF) of heat wave$_{>99\%}$ and cold spell$_{<1\%}$ between the 2010s (2010-2015) and 2000s (2000-2009).

Discussion

In this study, we observed that the average number of heat waves and cold spells increased in the 2010s compared to the 2000s in Korea and Japan. This study also provides evidence of temporal decreases in the RRs of heat waves for all intensities of heat wave in the total population. On the other hand, most RRs for cold spells significantly increased during the study period in the total population, and more pronounced increases were observed in Japan-south and Korea. Taking into account the time-varying RRs and frequencies of extreme events, the ARFs of both heat waves and cold spells increased in the 2010s, compared to those in the 2000s, except for low intense heat wave (heat wave$_{<95\%}$). These results were related to increased frequencies of heat waves and cold spells in the 2010s compared to the 2000s.

The results of our study show a temporal decrease in RR patterns of heat waves, which can be interpreted as an adaptation. This finding has been described in previous studies. A previous study showed that the risk of heat temperature has declined during recent decades in multiple countries (Gasparrini et al. 2015a). Other studies reported that the excess mortality during the 2006 heat wave was markedly lower than the predicted mortality estimated from the model using summer temperature data from 1975–2003 in France (Fouillet et al. 2008), and also described that heat-related mortality rates declined over time, with 41.0 averaged-excess heat-related deaths per year in the 1960s and 10.5 in the 1990s for 28 metropolitan areas in the U.S. (Davis et al. 2003). Increasing air conditioning prevalence, physiological acclimatization, demographic or socioeconomic factors, and improvements in housing have been suspected as the drivers of these decreasing patterns (Fouillet et al. 2008; Gasparrini et al. 2015a; Kyselý and Kříž 2008). In addition, prevention plans, such as heat-surveillance systems and other public health interventions, have presented as one of the possible reasons of the reduced heat effects on mortality (Kovats and Kristie 2006). However, this topic should be more discussed in further, and the corresponding prevention plans should be developed continuously to minimize the effect of extreme heat temperatures.

On the other hand, relatively few studies have described the temporal changes in the cold-mortality association, and the results were still mixed. Åström et al. (2013) showed that the number of cold extremes increased in 1980-2009 (251) compared to 1900-1929 (220); however, the RR of cold extremes did not statistically relate with the increase in frequency (Åström et al. 2013). Also, Chung et al. reported that cold-related mortality remained constant over decades (from 1972) and slightly increased in the late 2000s. In another previous study, Vicedo-Cabrera et al. (2018) showed that the temporal pattern of ARF for cold were heterogeneous among 10 countries, unlike the pattern of ARF for heat which declined over time in most countries (Vicedo-Cabrera et al. 2018). In that study, the ARF due to cold in the 2000s decreased

compared to the 1990s in Japan, which can be interpreted differently with our results. However, the differences should be interpreted with caution. Although there are some differences in the study period and analytic conditions used in each study, we believe the most important difference lies in the definition of "cold." Whereas the "cold" can be interpreted as cold spell days in our study, Vicedo-Cabrera et al. defined the "cold" day as all temperatures higher than the minimum mortality temperature and calculated the ARF during all the cold days. However, their study also reported that the risk of extreme cold (1st percentile vs. percentile of minimum mortality temperature) increased over time in Japan (RR: 1.364 in 1985, 1.371 in 2012), therefore the results of both studies might be similar if similar definition for "cold" was used.

Furthermore, the reason why the risks of cold spell have increased over time should be more discussed. A recent study in 15 metropolitan cities in three Northeast Asian countries suggested "acclimatization" as a hypothesis of mal-adaptation to cold (Chung et al. 2017). The study represented prior studies which showed that people in warmer weather were generally more sensitive to cold temperature (Anderson and Bell 2009; Guo et al. 2014), and suggested that the trend of warmth could make people more vulnerable to cold temperatures. In our study, the RRs of cold spells increased during the study period, and the increasing trend was more prominent in Japan-south which has a relatively hotter climate than Japan-north. Therefore, although limited evidence, our findings may support the acclimatization hypothesis related to cold spells. And also, our results implicate the need for more interventions for cold spell in both Asian countries. Despite technological advancements (such as early warning system), the increasing cold spell effect suggests that researchers will need to focus on the causes and countermeasures for temporal increase in cold spell effects.

The temporal trend of heat wave/cold spell-mortality association were generally consistent both with time-constant percentiles and with time-dependent percentiles used to define the threshold temperature points of heat wave and cold spell (Figure S9). The thresholds of heat wave and cold spell were similar between the 1990s and 2000s; however they were substantially different in the 2010s, as a result of warmer temperature distribution (Table S6). We selected the time-constant threshold percentiles as the main approach, because the time-constant percentiles took into account the average threshold points across the entire study period. However, further discussions are needed as to whether the definition of time-constant percentiles should be applied in the studies for anticipating future impacts of heat waves and cold spells, because the time-constant percentiles approach might have a limitation in reflecting acclimatization to a warming climate, as the study period would be longer. In addition, the fact that the temporal risk trends were maintained even after considering the varying threshold points by period may indicate that there might be non-climatic factors (such as lifestyle and technological

advancements) that could affect adaptation to extreme temperatures (Vicedo-Cabrera et al. 2018). These factors should be importantly considered to find suitable definitions for heat wave and cold spell in the future, and we believe that further studies are needed to find the optimal heat wave and cold spell definitions taking into account the various factors.

The interesting finding of our study was that the temporal change pattern of ARF differed with the changes in RR. In particular, the RRs of heat waves$_{<97\%}$ and heat wave$_{<99\%}$ in the 2010s decreased, compared to those in the 2000s (Figure 1 (A)); however, those ARFs in the 2010s increased, compared to the 2000s (Figure 3). This result indicates that the health burden of heat wave may increase with future climate change, even with the population partly adapted to heat wave. Most previous studies evaluating the temporal changes in the health impact of extreme events only focused on RR (Bobb et al. 2014; Carson et al. 2006; Gasparrini et al. 2015a). However, this could cause a misunderstanding of the future health burden of extreme temperature, unless the increasing frequency is considered. Since extreme weather events are expected to be increase with climate change (Meehl and Tebaldi 2004; Solomon 2007), our study suggests that ignoring the temporal changes would result in considerable over/underestimated impacts of heat wave/cold spell under climate change.

We performed analyses to detect the added effects of heat wave and cold spell by decomposing the effects of heat wave and cold spell into temperature and added effects, and found that heat wave and cold spell nearly did not have added effects on mortality (Figure 1 (B), and Figure 2 (B), except for highly intense heat wave (heat wave$_{>99\%}$) and cold spell (cold spell$_{<1\%}$). These results are consistent with previous studies conducted to estimate the added effect of extreme events (Barnett et al. 2012; Gasparrini and Armstrong 2011). However, we reported the effects of heat wave and cold spell without separation with main temperature effect, for two major reasons. First, it was for concise interpretation of heat wave and cold spell impact. Warning systems also do not distinguish the concepts of main temperature and duration effects (Robinson 2001). Second, it is controversial to describe the effect of heat wave and cold spell as a part of temperature effects, and the complexity of heat wave (or cold spell) effects is still insufficient to be accounted for by concepts of the main effect of heat (or cold) and added effect of sustained heat (or cold) (Xu et al. 2016). For those reasons, many previous studies selected the modelling approach to estimate the effect of heat wave and cold spell without decomposing the main and added effects (Åström et al. 2013; Guo et al. 2017; Tong et al. 2015; Tong et al. 2012; Xu et al. 2016).

Furthermore, our study can support the formulation of a definition of heat wave based on local climatic conditions (Figure S4). Firstly, in most communities, we found that the heat wave RR of mortality was significant at the 95th percentile of community-specific temperature, increased

at the 97th percentile and sharply rose at the 99th percentile during the entire study period. This trend is consistent with the results of previous studies (Guo et al., 2017; Tong et al., 2015; Tong et al., 2014), and implies that a more effective heat wave alert is needed as daily temperature increases. However, some communities in Kyushu (the island in the southernmost part of the four major islands in Japan: Fukuoka, Nagasaki, Kumamoto, etc. in Figure S4) showed a decreasing trend of heat wave RR (or did not increase) at the 99th centile, compared to the RR at the 97th centile. We assumed that the reversed pattern might have arisen from regional acclimatization (Anderson and Bell, 2009; Guo et al., 2017), and that adaptation to extreme hot temperature may be more crucial in the hottest area than other areas (Guo et al., 2017). Therefore, the cut-off for the definition of heat wave in the hottest region should be set lower than that of other regions. In addition, our results also imply that the definition for heat wave needs to be modified over time, because the heat wave RR at the 99th centile was lower than that at the 97th or 95th centiles in a considerable number of communities in the 2010s. This trend can be related to avoidance of the outdoors due to the weather forecast or use of air conditioner on extremely hot days during the recent period (Gasparrini et al., 2015). Thus, in order to establish a more efficient heat wave warning system, a lower cut-off of heat wave definition should be considered than in the past.

Unlike the heat wave, our results suggest that a slightly different approach seems necessary to define cold spell (Figure S4). In Japan-north and Korea, many communities showed higher cold spell RRs at the 5th and 3rd centile than the RR at the 1st centile in the 1990s; however, the RR at the 1st centile was higher than that at other centiles in the 2010s. On the other hand, in a substantial number of communities in Japan-south, there was no distinct pattern between cold spell RR and cut-off points in the 1990s; however, they showed higher RRs for cold spell at the 3rd centile than that at the 1st percentile after 2010, similar to the results obtained in the 1990s for Japan-north. Although there may be several plausible explanations for these temporal patterns (such as changes in outdoor/indoor activities, income level, or public health interventions), we conjecture that the acclimatization to warming climate may be a possible hypothesis. As described above, people in warmer weather were generally more vulnerable to cold (Anderson and Bell 2009; Guo et al. 2014); thus, the temporal warming climate could make people became more sensitive to the high-intensity of cold spell. However, since there was no consistent pattern among all communities and in many communities of Japan-south, the cold spell RR at the 1st centile was still less than the RR at the 3rd centile; thus, this hypothesis should be discussed comprehensively in further studies. Nevertheless, the results of the study support the need for regional- and period-specific cold spell definitions in order to develop effective warning systems across the communities. After 2010, a more high-level cold spell

warning system was needed as daily temperature declined in Japan-north and Korea, and the alert for mild-cold spell (5th and 3rd centiles) may be more efficient than the alarm for extreme cold spell (1st centile) in Japan-south.

Finally, we acknowledge several limitations in our study. First, age-specific heat wave- and cold spell- mortality relationships could not be considered. Because differential adaptations to heat according to age were also reported in a previous study (Bobb et al. 2014), the age-specific analysis should be conducted in future studies. Second, our study did not consider air pollution which could be a confounder of temperature, because the data were not available. Third, the current findings cannot be interpreted as being representative of other communities and countries with different socioeconomic characteristics and climatic conditions, because this study was conducted in only two Northeast Asian countries (Korea and Japan). Therefore, future studies should strive to overcome these limitations by expanding the study populations and data collection.

Conclusion

We examined the temporal changes in the impact of heat wave and cold spell on mortality during 1992-2015 in 53 communities in Korea and Japan. As a result, the pooled RRs of heat waves decreased in the 2010s in the total population, while the RRs of cold spells increased in the 2010s, compared to other decades. These results support the evidence that the population in the two countries were adapted to heat waves; however the population had maladapted to cold spells during recent decades. In addition, we observed the increases in averaged frequency of heat waves and cold spells in the 2010s compared to the 2000s in the total population, and the ARFs of heat waves and cold spells also showed increasing trend during the same period as results of considering increases in their frequency. These findings suggest that the health burden of extreme events can increase with climate change even if the population adapts to extreme events gradually. Furthermore, we expect that our study can attribute to advanced public health policies and multinational efforts aimed at reducing extreme weather events.

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Supplementary Materials

The Supplementary Materials file can be downloaded from the URL (https://www.sciencedirect.com/science/article/pii/S0160412017322882)

OR the file also is available on request to the first author (jleehwan33@gmail.com).

Research 2

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Title: Mortality Burden of Diurnal Temperature Range and Its Temporal Changes: A Multi-Country Study

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ABSTRACT

Although diurnal temperature range (DTR) is a key index of climate change, few studies have reported the health burden of DTR and its temporal changes at a multi-country scale. Therefore, we assessed the attributable risk fraction of DTR on mortality and its temporal variations in a multi-country data set. We collected time-series data covering mortality and weather variables from 308 cities in 10 countries from 1972 to 2013. The temporal change in DTR-related mortality was estimated for each city with a time-varying distributed lag model. Estimates for each city were pooled using a multivariate meta-analysis. The results showed that the attributable fraction of total mortality to DTR was 2.5% (95% eCI: 2.3–2.7%) over the entire study period. In all countries, the attributable fraction increased from 2.4% (2.1–2.7%) to 2.7% (2.4–2.9%) between the first and last study years. This study found that DTR has significantly contributed to mortality in all the countries studied, and this attributable fraction has significantly increased over time in the USA, the UK, Spain, and South Korea. Therefore, because the health burden of DTR is not likely to reduce in the near future, countermeasures are needed to alleviate its impact on human health.

Keywords: Diurnal temperature range, Attributable mortality risk fraction, Time-varying Effect, Climate Change.

Abbreviations: Attributable risk fraction (ARF), Distributed Lag Non-linear Model (DLNM).

Introduction

Diurnal temperature range (DTR, i.e., the intra-day temperature change) is a well-known weather-related risk factor for human health. Numerous studies have described a positive association between DTR and mortality (Cao et al. 2009; Lim et al. 2015; Tam et al. 2009; Vutcovici et al. 2014; Yang et al. 2013) and have reported that people who are elderly, less educated, female, or have cardiovascular or respiratory disease are more susceptible to DTR than others (Kan et al. 2007b; Lim et al. 2012a; Yang et al. 2013). In addition, because DTR has been reported as an important meteorological indicator closely related to global climate change (Braganza et al. 2004; Kan et al. 2007b; Yang et al. 2013), an in-depth investigation of the DTR-mortality relationship is important to comprehensively assess the future health impact of climate change.

Biological mechanisms through which a sudden change in absolute temperature might affect mortality have been described in previous medical and epidemiological studies (Garrett et al. 2009; Garrett et al. 2011; Greenberg et al. 1983; Keatinge et al. 1984; Martinez-Nicolas et al. 2015; Qiu et al. 2013). Sudden changes in within-day temperatures may cause physiological health problems (Garrett et al. 2009; Garrett et al. 2011); unstable weather or temperature changes can lead to the onset of cardiovascular events brought on by increased workload. This can affect the respiratory system by triggering inflammatory nasal responses (Ballester et al. 1997; Carder et al. 2005; Graudenz et al. 2006; Hashimoto et al. 2004; Imai et al. 1999; Luurila 1980). These mechanisms have been suggested as potential causes of increasing human mortality (Buguet 2007; Guo et al. 2016).

Based on this biological evidence, previous studies have tried to estimate the risk of DTR on mortality (Lim et al. 2015; Tam et al. 2009; Vutcovici et al. 2014). However, most previous studies assessed the risk of DTR using only relative risk (RR), not the attributable risk fraction, which can quantify the mortality burden. Furthermore, because a majority of the previous studies were conducted in single cities or single countries and used different statistical methods (Kan et al. 2007b; Lim et al. 2012a; Yang et al. 2013), results of these studies might have limited applicability on a multi-country scale.

Most previous studies estimated the risk of DTR on mortality using historical data (Kan et al. 2007b; Lim et al. 2012a), and the estimated impact of DTR was assumed to be consistent over time. However, this assumption might not be suitable for predicting the health impact of climate change because several factors, including intrinsic biological (e.g., disease/nutrition status) and extrinsic factors (e.g., forecast and infrastructure improvements, local environment, or social system conditions), can modify the population's vulnerability to absolute temperature and rapid

temperature change within a day (Gasparrini et al. 2015a; Linares et al. 2014; Wu et al. 2014). Therefore, it is important to assess temporal change in the DTR-related mortality relationship to examine whether people are adapted or mal-adapted to DTR.

In this study, we assessed the percent increases in risks and the attributable risk fraction of DTR for 308 cities of 10 countries. We examined whether the excessive risks and attributable risk fractions changed during the study period. We used a Multi-Country Multi-City (MCC) Collaborative Network to assess the impact of weather on mortality using a multi-country data set referenced in previous papers (Gasparrini et al. 2015a; Gasparrini et al. 2016; Guo et al. 2014; Guo et al. 2016).

Material and methods

Data

Time-series data covering mortality and weather variables were collected from 385 locations in 10 countries: Canada (26 cities, 1986–2011), the United States (USA) (135 cities, 1985–2006), Brazil (18 cities, 1997–2011), Colombia (5 cities, 1998–2013), the United Kingdom (UK) (10 regions, 1990–2012), Ireland (6 regions, 1984–2007), Spain (51 cities, 1990–2010), Japan (47 prefectures, 1972–2012), South Korea (7 cities, 1992–2010), and Australia (3 cities, 1988–2009). For convenience of interpretation, the location is described as "city" in this study. The daily mortality count is the daily count of death for all causes. If a daily count of all causes of death was not available for a city, then death for non-external causes (ICD-9: 0-799, ICD-10: A00-R99) was used instead. The DTR was chosen as the exposure index, computed from monitoring stations as the difference between the daily maximum and daily minimum temperatures. Detailed information regarding data collection is provided in the Supplementary Material (Data details).

First-stage time series model

The first-stage time series model was divided into a two-step procedure. First, a time-series regression was applied, based on a generalized linear model using a quasi-Poisson distribution with parameters for DTR, the day of week, the seasonal long-term trend, the inter-day temperature change (the change in mean temperature between two neighboring days), and absolute temperature. We modeled the DTR-response curve with a linear function and the lag-response curve with two internal knots placed at equally spaced values on a log scale using a

natural cubic B-spline with 14 days of lag. The inter-day temperature change was adjusted in the same way as DTR. We also modeled the temperature-response relationship using a quadratic B-spline with three internal knots (placed at the 10th, 75th, and 90th percentiles of location-specific temperature distributions) and a lag-response (up to 21 days) curve with natural cubic B-spline with three internal knots placed at equally spaced values on the log scale. This modeling approach was used in a previous multi-country temperature-mortality study using a distributed lag non-linear model (DLNM) (Gasparrini et al. 2010; Gasparrini et al. 2015b). Seasonal trends were adjusted using a natural cubic B-spline of time with eight degrees of freedom (df) per year (df=8), and the day of week was included as an indicator variable. Results of the first stage estimated the association between DTR and mortality for each city.

Time varying distributed lag non-liner model

The DLNMs, described in the first-stage analysis, assumed that the exposure-lag-response associations between DTR and mortality in each location were constant across the whole study period. We also applied a time-varying DLNM with a linear interaction (Gasparrini et al. 2015a; Gasparrini et al. 2016) between DTR and year. Using the time-varying DLNM, we derived coefficients representing the exposure-lag-response association for the first and last year of the study period for each city. The set of four coefficients (the entire period, the first year, and the last year for each location) were reduced to one coefficient that modeled the overall cumulative associations between DTR and mortality. The sets of four coefficients were used to determine the lag-response relationships at the 99th percentile of the DTR reference at 0 ºC DTR.

Second stage meta-analysis

We pooled one parameter of the overall cumulative exposure-response relationship and the four parameters of the lag-response relation. Multivariate random-effect meta-regression was used to pool the parameters by country. We used indicators of country as predictors in the meta-regression to country-pooled estimates and city-specific predicted parameters (Best Linear Unbiased Prediction, BLUP). The overall pooled coefficient (only for calculating excessive relative risk for all countries together) was estimated by meta-analysis without predictors. All analyses were performed using R software (version 3.3.1) packages dlnm and mvmeta (Gasparrini 2011; Gasparrini et al. 2012; Gasparrini et al. 2010).

Attributable mortality risk faction

Overall cumulative relative risk estimated from BLUP for each city was used to compute the attributed number of deaths and the fraction of deaths over the following 14 days at each location. The total number of deaths attributed to DTR was calculated as the sum of all days in the series when DTR contributed to death and its ratio with the total number of deaths; this provides the 'total attributable fraction' (Gasparrini and Leone 2014). We also computed the time-varying attributable risk of DTR based on the BLUP for each city from the time-varying DLNM. Although time-dependent distributions of DTR and death could be used to estimate time-varying attributable risk, we used DTR and the mortality distribution for the entire period because we did not find a clear difference between DTR distributions for the first and last three years of the series for each city (Table 1).

Sensitivity analysis

In order to test the sensitivity of our results to the modeling parameters and assumptions described above, we changed lag days for DTR (21 days), inter-day temperature changes (10 and 21 days), and the df of lag knots for DTR (df=5), and we analyzed the first results. We also assessed sensitivity to controlling for humidity (only for six countries that had relative humidity data), air pollution (Korea: O_3 and PM10), flexibility of long-term trend (df=7 and 9), and absolute temperature using various knot percentiles and changing lag days (14 and 28 days).

Results

Descriptive statistics of mortality, absolute temperature, and the distribution of DTR are in Table 1. Figure 1 displays the geographical distributions of the 308 cities within the 10 countries included in the analyses and the corresponding annual averaged DTR (˚C). The data set included 85 912 372 deaths. Variability in DTR was observed among countries over the entire study period, with mean values ranging from 6.7 ˚C (Ireland, six cities) to 10.9 ˚C (USA, 135 cities). Table 1 also lists the DTRs and absolute temperature distributions during the first and second halves of the study period for each country. As expected, the mean temperature increased slightly over time, although we did not detect a clear temporal pattern in the DTR values. City-specific descriptive statistics are reported in Supplementary Table S1.

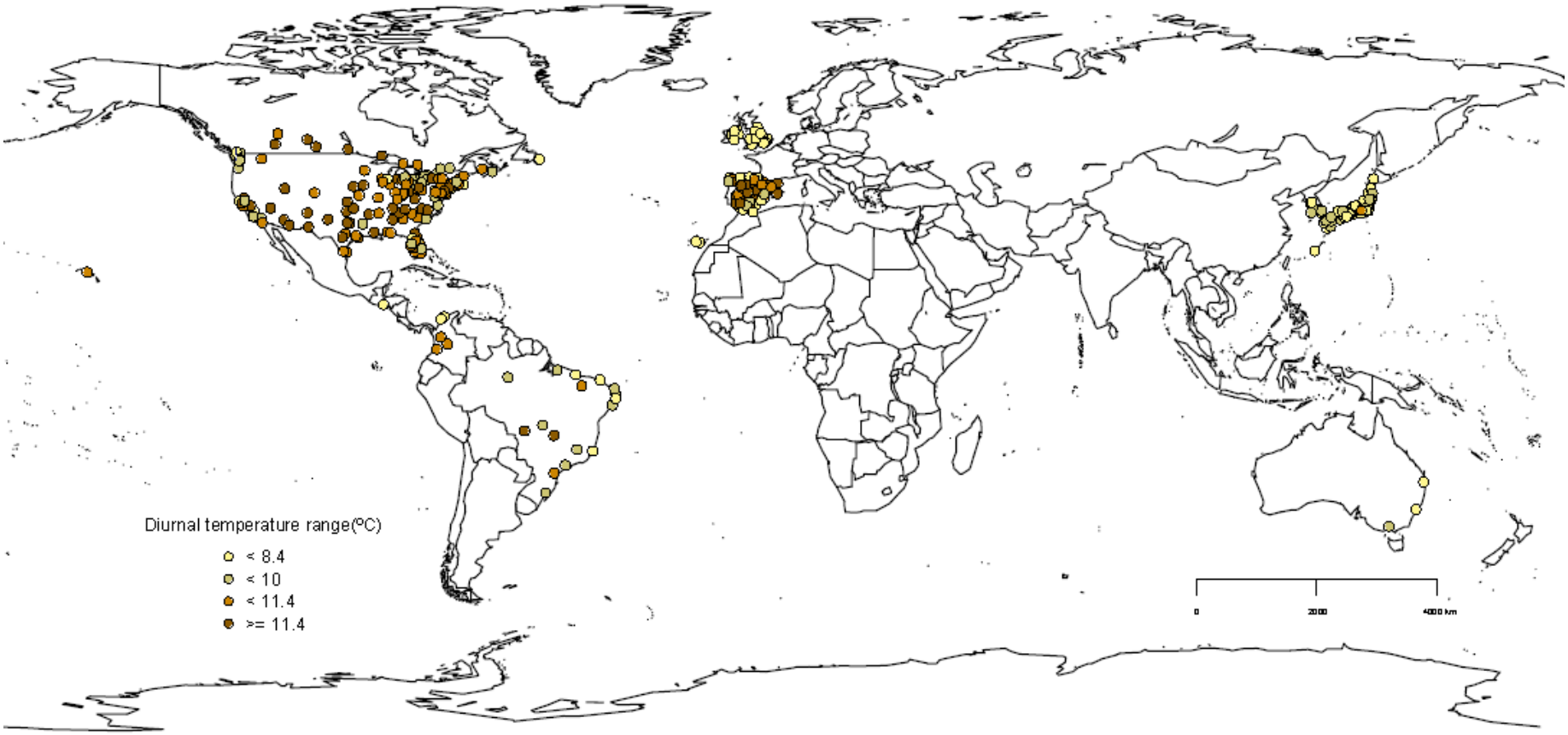

Figure. 1. Geographical locations of study cities and their annual mean values of diurnal temperature range (DTR, °C).

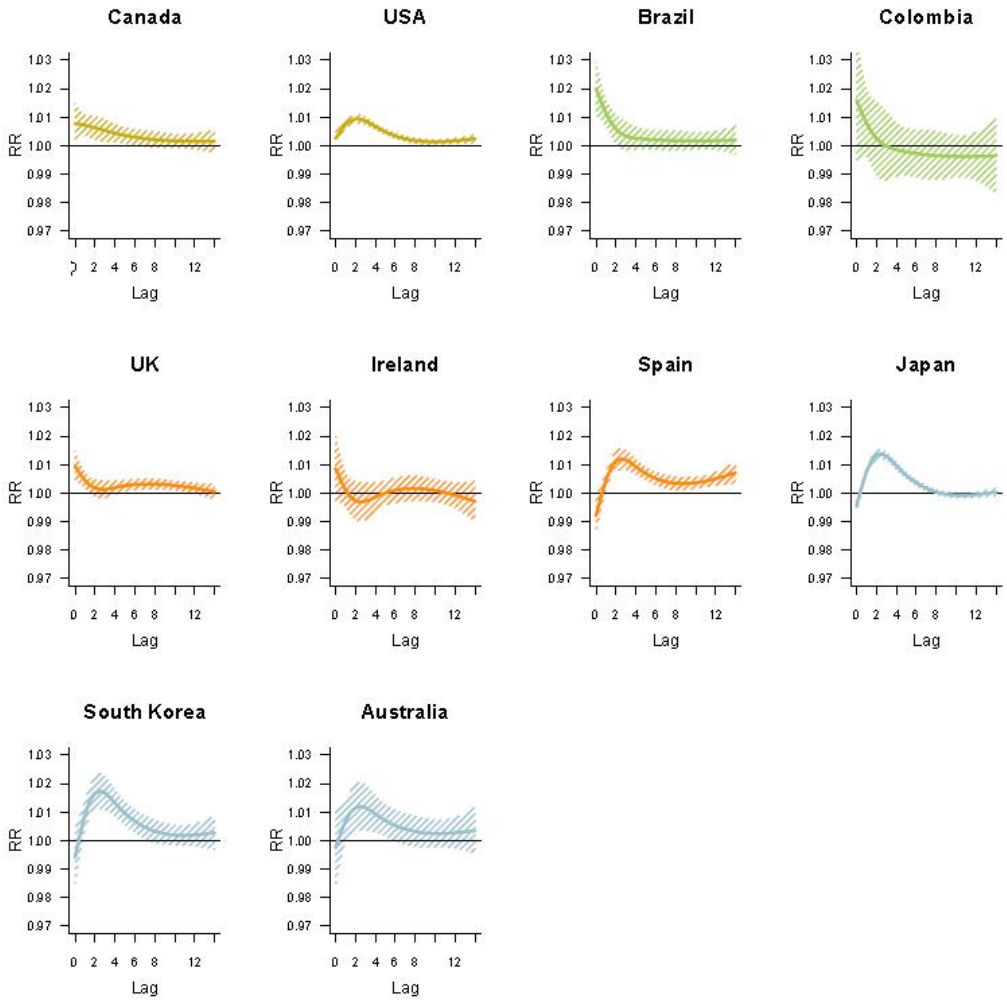

Figure. 2. Lag-response relationship between diurnal temperature range (DTR) and mortality predicted for the overall study periods of 10 countries; RR: relative risk. USA: United States, UK: United Kingdom.

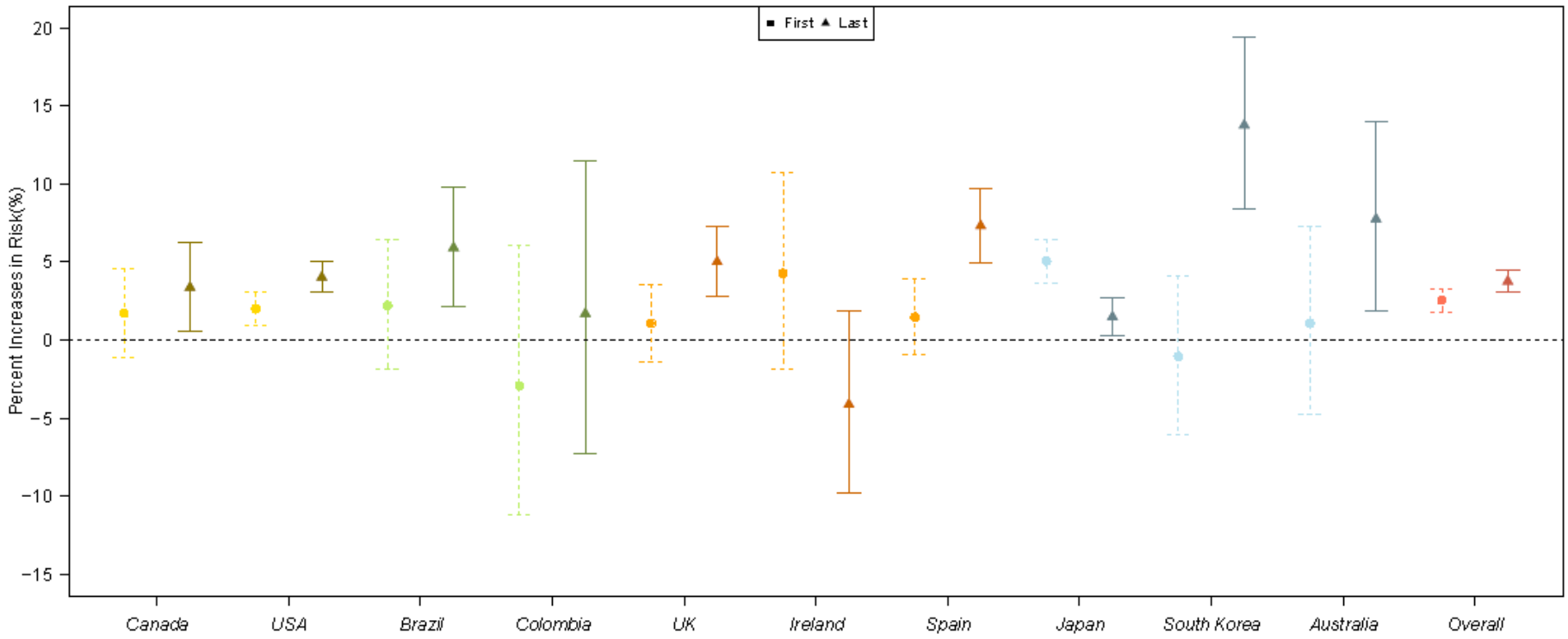

Figure. 3: Temporal changes in percent increases in risk (%) between the first (First) and the last (Last) year of country-specific study periods; USA: United States, UK: United Kingdom.

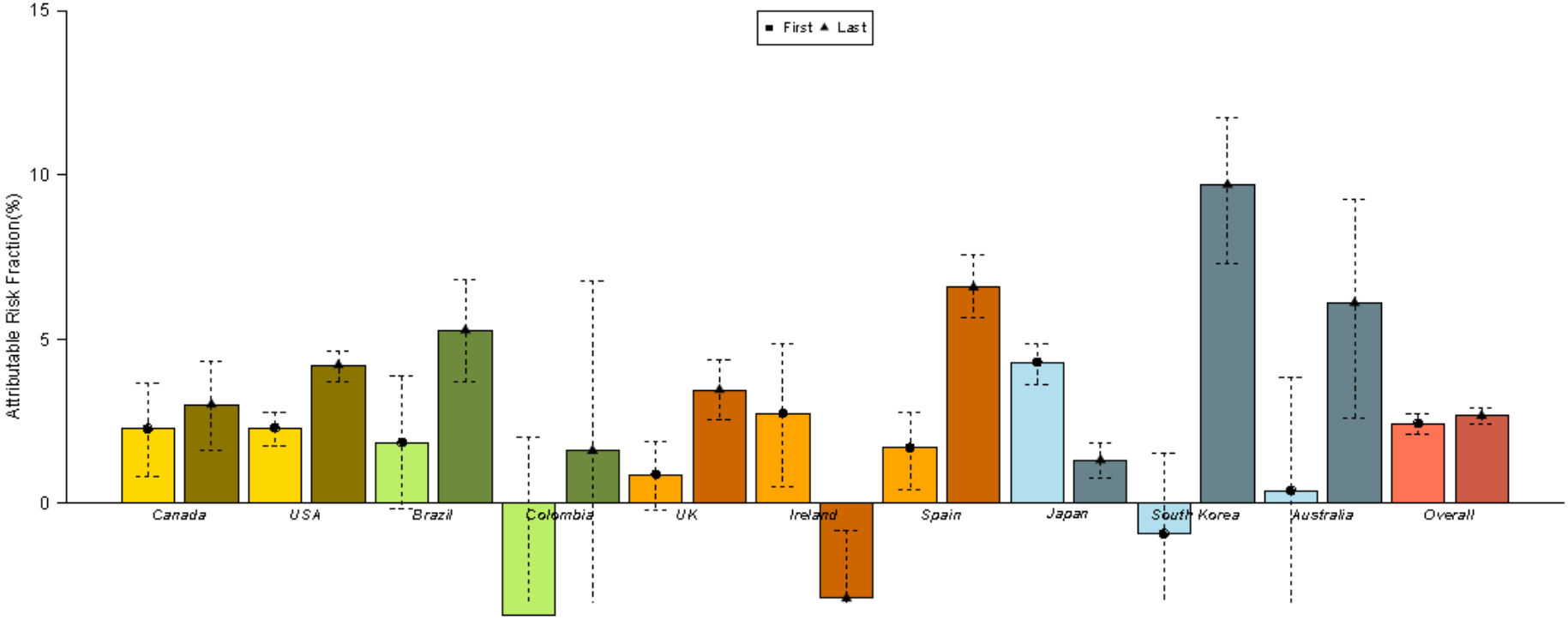

Figure. 4. Temporal changes in attributable risk fraction (%) between the first (First) and the last (Last) year of country-specific study periods; USA: United States, UK: United Kingdom.

Table 1. Descriptive statistics by country. Including distribution of diurnal temperature range in first 3 years (First) and last 3 years (Last) of country-specific study periods. USA: United States of America, UK: United Kingdom.

Country (# of city)	Time Period	Total Deaths	Study Period (year)	Absolute temperature (°C)	Diurnal temperature range (°C)					
				Mean	Mean	10%	25%	50%	75%	90%
Canada	Whole	2,989,901	1986-2011	6.8	10	4.4	6.6	9.7	13	15.9
(26)	First			7	10.1	4.5	6.7	9.8	13	16
	Last			6.9	9.9	4.4	6.4	9.4	12.9	16.1
USA	Whole	22,896,409	1985-2006	14.8	10.9	5.6	7.8	10.6	13.9	16.7
(135)	First			14.7	11	5.6	7.8	10.6	13.9	17.2
	Last			15.1	10.7	5.6	7.8	10.6	13.3	16.1
Brazil	Whole	3,435,502	1997-2011	24.2	9	5.4	6.8	8.6	10.7	13.2
(18)	First			24.1	8.8	5.1	6.6	8.4	10.6	13.1
	Last			24.3	9.1	5.5	7	8.6	10.7	13.4
Colombia	Whole	956,539	1998-2013	23.4	9	5.8	7	8.8	10.8	12.4
(5)	First			23.1	8.9	5.6	6.8	8.7	10.8	12.5
	Last			23.5	8.9	6.1	7.2	8.7	10.4	12.1
UK	Whole	1,2075,786	1990-2012	10.3	7.3	3.8	5.2	6.9	9.1	11.3
(10)	First			10.1	7.3	3.8	5.1	6.9	9.1	11.3
	Last			10.1	7.5	3.9	5.3	7	9.4	11.7
Ireland	Whole	1,058,215	1984-2007	9.7	6.7	3.4	4.8	6.4	8.3	10.3
(6)	First			8.9	6.8	3.6	4.9	6.5	8.4	10.4
	Last			10.3	6.9	3.6	4.9	6.6	8.5	10.5
Spain	Whole	3,480,531	1990-2010	15.5	10.6	4.9	7	10	13.8	17
(51)	First			15.1	10.7	5	7.2	10.2	13.8	17.2
	Last			15.5	10.4	4.8	6.8	9.8	13.6	17
Japan	Whole	3,6113,897	1972-2012	15.1	8.4	4.2	6	8.2	10.6	12.8
(47)	First			14.4	8.8	4.4	6.3	8.6	11	13.3
	Last			15.5	8.2	4.1	5.9	8	10.2	12.4
South Korea	Whole	1,727,642	1992-2010	13.7	8.2	4.1	5.9	8	10.2	12.7
(7)	First			13.5	8	3.8	5.6	7.7	10.1	12.5
	Last			13.8	8.3	4.3	5.9	8	10.3	12.7
Australia	Whole	1,177,950	1988-2009	18.1	8.2	4.4	5.9	7.8	10	12.4
(3)	First			18.1	7.8	4.1	5.6	7.3	9.5	11.9
	Last			18.7	8.1	4.5	5.8	7.6	10	12.6

The percent increases in risks and attributable mortality risk fractions of DTR estimated from the model with no interaction (i.e., the average throughout the study period) are reported in Table 2. Percent increases in risks of DTR (per 10 ˚C) were highest in South Korea (6%, 95% CI: 3–9.1%), Spain (4.4%, 3–5.8%), and Brazil (4.2%, 1.7-6.7%). Colombia (-1.2%, -6.3–4.1%) and Ireland (0.3%, -3–3.8%) showed the lowest percent increases in risk of DTR, although both were not significant. Table 2 also displays the total percentage of deaths attributable to DTR (reference at minimum DTR of each city, 2.5% with 95% empirical confidence interval (95% eCI): 2.3–2.7%). Similar with percent increases in risk, most of the country-specific estimated attributable risks were statistically significant. The risk fraction was highest in Korea (4.5%, 3–5.9%) and Spain (4.2%, 3.5–4.9%). The fractions were lowest in Colombia (-1.5%, -5.1–2.1%) and Ireland (0.2%, -1.2–1.4%).

Table 2. Percent increases in risk (per 10°C) and attributable risk fraction (%) of diurnal temperature range on mortality by country. USA: United States of America, UK: United Kingdom.

Country	Percent Increases in Risk (%, 95% CI)	Attributable Risk Fraction (%, 95% eCI)
Canada	2.6 % (0.9 , 4.2)	2.7 % (1.8 , 3.5)
USA	2.9 % (2.3 , 3.6)	3.2 % (2.9 , 3.5)
Brazil	4.2 % (1.7 , 6.7)	3.7 % (2.6 , 4.9)
Colombia	-1.2 % (-6.3 , 4.1)	-1.5 % (-5.1 , 2.1)
UK	2.9 % (1.5 , 4.4)	2.1 % (1.6 , 2.7)
Ireland	0.3 % (-3 , 3.8)	0.2 % (-1.2 , 1.4)
Spain	4.4 % (3 , 5.8)	4.2 % (3.5 , 4.9)
Japan	3.1 % (2.3 , 3.9)	2.7 % (2.4 , 3)
South Korea	6 % (3 , 9.1)	4.5 % (3 , 5.9)
Australia	4.2 % (0.7 , 7.9)	3.3 % (1.1 , 5.3)
Overall	3.1 % (2.7 , 3.5)	2.5 % (2.3 , 2.7)

eCI: empirical confidence interval.

Figure 2 displays the country-pooled lag-response associations at the 99th percentile of DTR referenced at 0 ˚C. The coldest (Canada, Ireland, and UK) and warmest (Brazil and Colombia) countries showed the highest RR at lag 0 and lasted to a lag of 4–7 days. Other countries, which had moderate temperatures, had the highest RR in approximately 1–3 lag days and were limited to a lag of 7–14 days. The corresponding city-specific lag-response is displayed in Supplementary Fig. S1.

Results from an analysis of the temporal variation in the percent increases in risk of DTR are

illustrated in Fig. 3. Table 3 displays the temporal variation of estimates per year and test results for linear interaction (null hypothesis is the pooled interaction term is zero; the null hypothesis is that no temporal change occurred). The percent increase in risk of DTR increased from 2.5% (95% CI: 1.8–3.3%) to 3.8% (95% CI: 3.1–4.5%) between the first and last periods. Except for Ireland and Japan, all countries showed patterns of increasing percent increases in DTR risk, with -2.9–5% in the first year and 1.5–13.8% in the last year of the data. The temporal increase of percent increases in DTR risk were significant (P-value<0.05) for the USA, the UK, Spain, and South Korea (Table 3). Country-pooled temporal changes in the lag-response relationship are displayed in Supplementary Fig. S2. A comparison between the curves suggested that a longer lag-association and smaller harvesting effect were present in most countries.

Table 3. Variation of excessive relative risk (per 10°C) and attributable fraction (%) of diurnal temperature range on mortality per a year, and p-value of the test. USA: United States of America, UK: United Kingdom.

		Variation (per year)		
Country	**Study Period (Years)**	**Percent Increases in Risk**	**Attributable Risk Fraction**	**p-value***
Canada	26	0.06 %	0.03 %	0.4384
USA	22	0.09 %	0.09 %	0.0209
Brazil	15	0.25 %	0.23 %	0.2243
Colombia	16	0.29 %	0.31 %	0.6583
UK	23	0.17 %	0.11 %	0.0344
Ireland	24	-0.35 %	-0.23 %	0.0989
Spain	21	0.28 %	0.23 %	0.0025
Japan	41	-0.09 %	-0.07 %	<0.0001
South Korea	19	0.78 %	0.56 %	<0.0001
Australia	22	0.3 %	0.26 %	0.1543

* Significant test on temporal change by Wald type test of the pooled reduced coefficient of the year-interaction terms. The null hypothesis is that no change in year occurred.

Figure 4 and Table 3 display the temporal variation in the attributable mortality risk fraction of DTR. Overall, the attributable risk fraction of DTR to deaths increased from 2.4% (95% eCI: 2.1-2.7%) to 2.7% (2.4-2.9%) between the first and last periods. The increase in the attributable risk fraction of death overtime was observed in all countries except Japan (0.07% decrease per year) and Ireland (0.23% decrease per year). Korea (0.56% per year) and Colombia (0.31% per year) showed the fastest increase in the risk fraction of death, whereas Canada (0.03% per year), the USA (0.09% per year,) and the UK (0.11% per year) showed the slowest increase over time.

Corresponding city-specific estimates are reported in the Supplementary Material (Supplementary Table S2). The main conclusions were found to be robust based on the sensitivity analysis (Supplementary Table S3).

Discussion

Our findings showed that DTR is responsible for an increasing mortality risk (3.1%, 95% CI: 2.7–3.5%) and fraction of deaths (2.5%, 95% eCI: 2.3–2.7%) in all the countries studied. South Korea and Spain showed the highest percent increase in risk (6% and 4.4%, respectively) and attributable risk fractions (4.5% and 4.2%, respectively). This study also provides evidence of the incremental health impact of DTR during the last few decades. Except for Japan and Ireland, an increasing pattern of percentile increases in risks (3.8% in the last year of the study periods, compared with 2.5% in the first year) was observed, and the attributable risk fraction showed the same temporal pattern (2.7% in the last year of the study period, compared with 2.4% in the first year).

This study is comparable to a recent temperature variability-mortality association study in the MCC Collaborative Network (Guo et al. 2016). Both studies were based on a similar multi-country data set and addressed the significant association between temperature variability and mortality, even after controlling for the main effect of absolute temperature. Guo et al. developed a new composite index of intra- and inter-day temperature variability using a standard deviation of minimum and maximum temperatures during the exposure days, and found the temperature variability-mortality relationship varied with exposure days (0–7 days), countries (twelve countries/regions with 372 communities), and season (cold, hot, and moderate). Meanwhile, our study focused on the association between intra-day temperature variability and mortality, using a classical meteorology index (DTR) and flexible statistical method, which considered a flexible lag-response structure of DTR. In addition, our study included data from 308 cities in 10 countries with more than 15 years of study data to estimate the temporal changes in the DTR-mortality association. We also found an overall increase in the health burden of DTR on mortality during recent decades.

Our finding suggested that the DTR effects on mortality were higher in warmer countries (Brazil, Australia, and Spain) compared to colder countries (Canada, Ireland, and the UK), although Korea and Colombia were exceptions. These findings are consistent with previous studies, such as multi-country studies that reported that the effect of temperature variability with short exposure durations (0–1 and 0–2 days) on mortality is higher in hot area (>22.9˚C) than other areas (cold, moderately cold, and moderately hot areas) (Guo et al. 2016). Studies from

the USA also showed a higher DTR effect in southern areas (percent change of non-accidental mortality per one unit of DTR 0.24–0.31%) than other regions (0.22–0.27%) (Lim et al. 2014). Studies in China also showed a similar trend of a relatively higher and more significant effect of DTR in warmer cities (Guangzhou and Shanghai) than colder cities (Anshan and Xi'an, although Tangshan is an exception).

To specifically assess the association between the DTR effects and the annual mean of absolute temperature, we fitted a weighted regression model (Supplementary Fig. S3) to our data; a city-specific BLUP of the DTR coefficient (i.e., log of relative risk estimated from the second stage analysis) was used as a response variable, annual mean temperature was used as an explanatory variable, and inversed city-specific variances of the DTR coefficient were used as weights. We observed a significantly positive linear association between the DTR effect and the annual mean temperature from the weighted regression model (P-value=0.01). This result can be interpreted as evidence to support the hypothesis that there may be an impact on mortality from the positive interactions between long-term temperature and DTR.

The synergism effect of the DTR and long-term temperature on mortality may be due to many factors. One mechanism may be aggravation. Hot temperatures can disturb normal physiological thermoregulation, including changes in blood viscosity, plasma cholesterol levels, and the red blood cell count (Keatinge et al. 1986). Increasing DTR may also impact mortality by lowering the thermoregulatory system and negatively affecting the heart rate, heart rate variability, blood platelets, red blood cells, and blood viscosity (Keatinge et al. 1984; Lim et al. 2012b). Because warm countries are exposed to hot weather more often, the DTR effect in warm areas can be amplified by the increase in the biological burden. Another hypothesis is that the effect of the DTR is higher in warm areas because people in warm and moderately warm areas are more likely to keep their windows open and spend more time outdoors, which may increase exposure to DTR, thus increasing the effects of DTR. However, our results only suggested the aggravation hypothesis; further research should be conducted to find the causal relationship between DTR and annual mean temperature on mortality.

Our research found that the effect of DTR on mortality changed across time. We speculate several plausible explanations. The first hypothesis is deterioration by climate change, suggested in the previous paragraph. We found higher risk and greater risk increases in hot cities. This finding suggests that climate change may increase the risk of DTR. Secondly, an aging population may also be a crucial factor, as numerous studies have revealed that elderly people are more susceptible to DTR (Kan et al. 2007a; Lim et al. 2012a; Yang et al. 2013), and the populations of developed and developing countries included in our research are aging (Börsch-Supan 2008; Faunce 2008).

In the results (Table 3), we found that the increasing rate of the DTR effect on mortality was higher in warmer countries (percent increase in risk per year was 0.25–0.3% for Brazil, Colombia, Spain, and Australia) compared to other countries (-0.35–0.17%)(except for Korea (0.78%)). These results suggested that there may be an association between long-term temperature and the increasing mortality rate for the DTR effect. Our study did not consider this relationship because of data limitations and the disparity in study periods. As well, some confounding factors need to be considered to understand this association between temperature and the DTR effect. If there is a positive correlation between warming and the effect of DTR, then the degree of climate warming by country should be considered as a confounding variable. The rate and extent of aging in each country should also be investigated. Furthermore, each country has disparate weather forecasting systems, accessibility to medical care, public health services, national income, and social infrastructure, all of which can affect the mortality burden of DTR. Therefore, these variables should be considered comprehensively, and additional research on this topic is needed.

Although not found in our study, prior studies have reported that climate change factors (greenhouse gases, urbanization, and aerosols) have led to a global decline in the DTR during the twentieth century because the nocturnal minimum temperatures have increased faster than the maximum temperatures (Braganza et al. 2004; Makowski et al. 2008). In addition, Brown et al. (2017) found that the variability of low-frequency global mean surface air temperature (GMST) will likely decrease under climate warming. They suggested that the reduction in high-latitude surface albedo variability by a climatological reduction in albedo was a major reason for this reduction in GMST variability (Brown et al. 2017b). However, it is still unclear how this decline in the DTR will affect human health, and how the extend and intensity of the DTR variation will change depending on the climate and geographical conditions. Previous studies reported that the DTR values in some regions have not declined during past decades despite the global reduction (Easterling et al. 1997). Brown et al. (2017) found that local surface air temperature variability in tropical and subtropical land areas can increase with climate change (Brown et al. 2017). Also, given that increasing nocturnal temperatures can affect mortality and the distribution of DTR simultaneously, a confounding effect of the nocturnal temperatures needs to be considered to estimate the effect of DTR on death. Even if the effect of increasing nocturnal minimum temperature is partly considered in our study by controlling the daily averaged temperature, there is a limitation to controlling the effect of nocturnal temperature due to lack of data. Therefore, future research should be conducted using various climate conditions with longer study periods and more detailed weather data.

As described earlier, although DTR and absolute temperature may affect human health in

diverse ways, because both have a mechanism that negatively affects human health, the effect of absolute temperature and temperature variability on mortality has been an interesting topic of environmental research. In addition, comparing the health effects of two variables has important implications for understanding human health in a climate change context (which can increase both the average values and the variability of temperature)(Guo et al. 2016; Stocker 2014; Vicedo-Cabrera et al. 2016). Recent studies asserted that DTR has a lesser effect than absolute temperature on mortality (Lee et al. 2017; Vicedo-Cabrera et al. 2016). Our results also suggest a lesser effect of DTR on mortality when compared with the total attributable mortality fraction of absolute temperature from a previous study (Gasparrini et al. 2015b). The total fraction of DTR attributed to mortality (2.5%) was much smaller than the fraction for total absolute temperature (7.71%) (Gasparrini et al. 2015b). However, our results may differ from the conclusions of previous studies (Chen et al. 2007; Kan et al. 2007a; Lim et al. 2015; Tam et al. 2009; Yang et al. 2013) that used modeling strategies that did not fully control the flexible lag structure of absolute temperature. The estimates of DTR on mortality could be overestimated unless the main effects of temperature are fully adjusted because the effect of absolute temperature is delayed up to several weeks after exposure. Hence, we contend that our modeling approach provides more appropriate results for estimating the health effects of DTR when compared with previous studies.

In this study, more acute DTR-mortality relationships (highest RR at 0 lag days) were observed in warmer and colder countries (Brazil, Colombia, Canada, Ireland, and the UK). In contrast, delayed DTR-mortality relationships (highest RR at 2–4 lag days) were observed in moderate temperature countries. Although this study did not study this difference, we speculate that the specific factors are related to physiological, technological, and behavioral adaptations to the climate.

A key strength of our study is the use of a large multi-country, multi-city data set with different demographic distributions, climate conditions, and socio-economic characteristics. To the best of our knowledge, our study is the largest of its kind including 308 locations and more than 85 million deaths from 10 countries. Our study also is the first and the largest study of time-varying DTR-related mortality, and the use of a uniform statistical framework across all cities makes the results directly comparable. In addition, unlike previous studies that have quantified the association using RR (Kan et al. 2007b; Vicedo-Cabrera et al. 2016; Yang et al. 2013), our study used the attributable mortality burden of DTR. Because the attributable fraction considers the distribution and risks of each variable, the attributable fraction is a suitable measure to estimate the mortality burden of the exposure variable and to establish corresponding public health strategies.

However, our study had some limitations that must be acknowledged. First, our findings are not globally representative because regions of Africa and large countries in Europe and Asia (such as France, Russia, and India) were not included in this study. Second, the data did not include age- or gender-specific mortality rates, which could be explored in future research. We could only identify the association between DTR and all-causes of mortality and not the causal effect of DTR on mortality. Future studies should strive to overcome these limitations by expanding the study population and modifying the study design.

Conclusions

In summary, this study found that there was a significant effect of DTR on mortality across all countries, and provided evidence that the effect of DTR was higher in warmer regions. Although our estimated attributable mortality fraction of DTR was smaller than risk fractions of absolute temperature from a previous multi-country study (Gasparrini et al. 2015b), it was higher than risk fractions of extreme heat and cold temperatures. In addition, although the risks and contributions of DTR to mortality varied for each country, it increased at the multi-country scale with significant increases estimated for the USA, the UK, Spain, and South Korea; we found non-significant increments for Canada, Brazil, Colombia, and Australia. The estimates of DTR-related mortality increased throughout the study period in all countries, which could be interpreted as maladaptation to DTR. This indicates that the health burden of DTR is not likely to decrease in the near future. Hence, we suggest that public-health policies and climate change research that have so far focused on the effects of extreme heat should be extended to account for the health burden of DTR and its temporal variations.

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Supplementary Materials

The Supplementary Materials file can be downloaded from the URL (https://www.sciencedirect.com/science/article/pii/S0160412017313570)

OR the file also is available on request to the first author (jleehwan33@gmail.com).

2.1.2. The interactions in the weather-mortality association

In this section, I investigate the interactive association between temperature and temperature variability on mortality. **Research 3** reported the effect modification (one way interaction) of temperature on diurnal temperature range (DTR)-related mortality in 57 communities of Korea, Japan and Taiwan. **Research 4** reported the synergic association between high temperature and temperature variability (TV index) on mortality in same study region with Research 3.

Research 3

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Title: The Interactive Effect of Diurnal Temperature Range and Temperature on Mortality in 57 communities in Northeast Asia; a multi-country study

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Abstract

Background: The diurnal temperature range (DTR) represents temperature variability within a day and has been reported as a potential risk factor for mortality. Previous studies attempted to identify the role of temperature in the DTR–mortality association but results are inconclusive. This study aims to investigate the interactive effect of temperature and DTR on mortality using a multi-country time-series analysis.

Methods: We collected time-series data for mortality and weather variables for 57 communities of three countries (Taiwan, Korea, and Japan) in Northeast Asia (1972-2012). Two-stage time-series regression with a distributed lag nonlinear model and meta-analysis was used to estimate the DTR-mortality association changing over temperature strata (six strata were defined based on community-specific temperature percentiles). We first investigated the whole population and then, the sub-populations defined by temperature distribution (cold and warm regions), sex, and age group (people aged <65 and ≥65 years), separately.

Results: The DTR–mortality association changed over temperature strata. The relative risk (RR) of mortality for 10°C increase in DTR was larger for high temperature strata compared with cold temperature strata (e.g., RR = 1.050 (95% CI: 1.040, 1.060) at extreme-hot stratum and RR = 1.040 (95% CI: 1.031, 1.050) at extreme-cold stratum; extreme hot and cold strata were defined as the days with daily mean temperature above 90th and below 10th percentiles each community's temperature distribution). Such increasing pattern was more pronounced in cold region and in people aged ≥65 years.

Conclusions: We found evidence that the DTR-related mortality may increase as temperature increases.

Keywords: Diurnal temperature range, Temperature, Interactive effect, Mortality

Introduction

The diurnal temperature range (DTR), which is defined as the difference between the maximum and minimum temperatures within a day, is a well-known risk factor for human mortality (Kan et al. 2007; Lee et al. 2017; Yang et al. 2013). Numerous studies have reported a positive association between the DTR and mortality (Cao et al. 2009; Lim et al. 2015; Tam et al. 2009; Vutcovici et al. 2014; Yang et al. 2013). The Intergovernmental Panel on Climate Change recently reported that an anthropogenic climate change is expected to increase unstable weather patterns (Solomon 2007), which suggests that the mortality risk related with temperature variability may become more crucial in the future. The DTR is one of the representative indices for temperature variability, and careful investigation of the DTR-related mortality risk becomes important as it helps assessing the future health impact of climate change more accurately (Braganza et al. 2004; Yang et al. 2013).

In most of previous analysis of the DTR-related mortality risk, temperature has been typically considered as a control variable and simply adjusted in the risk estimation model (Lim et al. 2012; Vicedo-Cabrera et al. 2016; Yang et al. 2013). Potentially, temperature may influence the DTR–mortality association and investigating the changing association by temperature may improve our understanding the interactive effect of DTR and temperature on mortality. In the recent decades, the DTR has decreased as nocturnal minimum temperatures have risen faster than the maximum temperatures (Braganza et al. 2004; Makowski et al. 2008). Such decrease may suggest the DTR-related health risk is anticipated to decrease (Yang et al. 2013). However, if there exists an interactive role of temperature to change the DTR-mortality association, it is uncertain what would be the net effect of climate change on the DTR-related health risk.

Previous studies examined if the DTR-related mortality varies by temperature, and results are mixed. Some studies suggested that the DTR-related risk increase during warmer seasons in Korea (Lim et al. 2012) and six European and American cities (Vicedo-Cabrera et al. 2016). Meanwhile, other studies found that the DTR has smaller effects on non-accidental mortality during warmer days, compared to colder days in China (Kan et al. 2007; Yang et al. 2013; Zhou et al. 2014). These studies were conducted in a single city or a country and used different statistical methods, thus making the comparison among studies difficult. Moreover, the studies investigated the role of temperature using seasons (e.g., spring, summer, etc.) or binary temperature categories (e.g., hot and cold) (Kan et al. 2007; Lim et al. 2015; Vicedo-Cabrera et al. 2016), which limits a flexible and refined investigation of the complex interactive role of temperature affecting the DTR-related mortality.

The present study investigated the interactive effect of temperature and DTR on mortality in 57

communities in three countries in Northeast Asia. We used a flexible and powerful statistical approach; a two-stage time-series analysis with a distributed lag nonlinear model (DLNM) and meta-analysis. The DLNM flexibly characterized the delayed association between DTR and mortality to change over temperature strata. The meta-analysis pooled city-specific associations gaining more power to detect the interactive effects. To our knowledge, this is the largest study investigating the interaction of temperature and DTR pooling information over multiple communities in multiple countries.

Methods

Data

Daily time-series data were obtained for weather variables and all-cause mortality for 57 communities in three countries: Taiwan (3 cities during 1994–2007), Korea (7 cities during 1992–2010), and Japan (47 prefectures during 1972–2012). Figure 1 shows the geographical locations of 57 communities divided into cold and warm regions, which include 29 and 28 communities with the annual mean temperature within the range of 8.82-15.3°C (corresponding to 0-50th percentiles) and of 15.3-25.2°C (corresponding to 50-100th percentiles), respectively. Weather variables included daily maximum, mean and minimum temperatures (°C), and daily mean relative humidity (%). For each community, weather variables were measured either from a single monitor or from multiple monitors. If measured from multiple monitors, the measurements were averaged across all monitor stations. The primary exposure, DTR, was calculated as the difference between the daily maximum and minimum temperatures for each community. In order to conduct sex-specific and age-specific analysis, we stratified the total mortality counts by sex and two age group (people aged <65 and ≥65 years). In addition, we obtained data for air pollution including daily mean concentrations of ozone (μg/m^3) and PM_{10} (μg/m^3) for 10 communities (7 cities in Korea and 3 cities in Taiwan). Air pollution data were also measured from multiple monitors, and community-specific data were obtained by averaging across all monitors. Detailed information about data collection is provided in Appendix 1 in Supplemental Materials.

Statistical analysis

The DTR-mortality association and the change of association by temperature were analyzed using a two-stage time-series approach. The first stage estimated the community-specific DTR-mortality relationship changing over temperature strata. The second stage pooled the

community-specific associations for each temperature stratum by meta-analysis. The modeling framework is briefly described below, with more mathematical details available in Appendix 2 in Supplemental Materials.

First stage analysis

The first stage used a generalized linear model with quasi-Poisson distribution. For each community, we fit the model with the following specifications. Long-term trend and seasonality were adjusted using a natural cubic B-spline of time with 8 degrees of freedom (df) per year, and day of the week was included as indicator variables. The primary exposure, DTR was included using a distributed lag nonlinear model (DLNM) structure. We used a cross-basis (CB); a linear term for DTR-mortality association and a natural cubic B-spine with two equally spaced knots on the log scale for lag-mortality relation with maximum lag of 14 days. These choices of model specifications were based on a previous study investigating the effect of DTR on mortality in multiple countries (Lee et al. 2018a). To examine whether the DTR-mortality association changes over temperature strata, we included interaction terms between the CB of DTR and categorical variables for temperature strata. We defined six strata according to the community-specific temperature percentiles: below the 10th percentile (extreme-cold), 10-25th percentile (cold), 25–50th percentiles (moderate-cold), 50–75th percentiles (moderate-hot), 75-90th percentile (hot), and above the 90th percentile (extreme-hot). Similar approach was used in previous studies regarding the interactive effect of temperature and air pollution on mortality (Roberts 2004; Stafoggia et al. 2008). In addition, we adjusted for daily mean temperature using a DLNM structure with a CB; a quadratic B-spline with three internal knots (10th, 75th, and 90th percentiles of location-specific temperatures) for temperature dimension and a natural cubic B-spine with an intercept and three equally spaced knots on the log scale for lag dimension (up to 21 days). Similar approach of the CB specification for daily mean temperature was used in previous multi-country temperature-mortality studies (Gasparrini et al. 2010; Gasparrini et al. 2015). Finally, we controlled for the daily mean relative humidity (at lag 0) as a linear term.

From the first stage analysis, we firstly obtained four coefficients of the CB to represent the lag-distributed DTR-mortality association for each temperature stratum in each community. To obtain the lag-cumulative association between DTR and mortality, we reduced them to a single coefficient which represents the association as log of relative risk per unit change in DTR. The community- and stratum-specific associations were used in the second stage analysis. The first stage analyses were performed using R statistical software and the *dlnm* package.

Second stage analysis

The community-specific associations (both lag-distributed association represented by four coefficients and lag-cumulative one by a single coefficient) were pooled for each temperature stratum separately using univariate and multivariate meta-analysis. We firstly pooled the estimates over the whole population (57 communities) using a random intercept meta-analysis. Then, we also obtained region-specific pooled estimate using a meta-regression with region indicator as a meta-predictor. Residual heterogeneity for the association was tested and quantified by the Cochran Q test and I^2 statistic. The second stage analyses were performed using R software and the *mvmeta* package.

Testing for the interaction

We tested for the interaction between DTR and temperature in both the first and the second stage modeling. In the first stage, we compared the models with and without the interaction between the CB of DTR and temperature strata for each community. In the second stage, we pooled the community-specific coefficients for the interaction terms and a multivariate Wald test was applied to examine if any of the pooled coefficients is not equal to zero. Additionally, observing that the linearly increasing trend in the DTR-related risk as temperature increases, we considered a linear interaction instead of the interaction with temperature strata. We tested for the linear interaction both the first and the second stage modeling.

Sensitivity analysis

We performed sensitivity analyses to examine the consistency of the results. We changed the maximum lag (10 days and 21 days) for DTR and changed the maximum lag for mean temperature to 28 lag days. The df and knot choices were also modified for the adjustment of mean temperature. In addition, we adjusted for heat waves and cold spells as they may confound the DTR-mortality relationship. Heat waves and cold spells were defined as periods of >2 days with daily mean temperatures that exceeded the 95th percentile or were below the 5% percentile of community-specific temperature, respectively. Long-term time trend was controlled with df as 7 or 9 per year. Finally, using the data only for 10 communities (Taiwan and Korea), we conducted the two-stage analysis with and without the adjustment of the two air pollutants (PM_{10} and O_3) separately as a linear term of the current day mean concentration in the first stage model.

Results

Table 1 shows descriptive statistics for mortality and weather variables for each country (community-specific summary statistics are available in Table S1). The data includes 38,609,201 deaths from all causes in the 57 communities. Each country showed a broad range of DTR and mean temperature. The distribution of DTR was similar between Korea and Japan while the range of DTR was smaller in Taiwan. The temperature distribution was also similar between Japan and Korea while Taiwan showed much narrower range of temperature. Figure 1 displays the geographical locations of 57 communities divided into cold and warm regions.

Figure 2 shows the pooled lag-cumulative association between DTR and mortality (the relative risk (RR) per 10°C change in DTR) for each temperature stratum in total population (A) and stratified by region (B), by sex (C) and by age group (D). Positive associations between DTR and mortality were shown for almost all temperature strata in both the total population and all of the sub-populations. The DTR-related mortality risks were higher for cold region, females, and people aged ≥65 years over all temperature strata compared with warm region, males, and people aged <65 years, respectively. In total population, the DTR-related mortality risk was observed to increase for higher temperature strata. The highest RR was shown at extreme-hot stratum (1.050; 95% CI: 1.040, 1.060) and the lowest RR was at cold stratum (RR: 1.038; 95% CI: 1.030, 1.046). Such increasing pattern was shown in all of the sub-populations, being more obvious in cold region and in people aged ≥65 years. Figure S1 shows community-specific results which were generally consistent with the pooled results with some variation among communities.

The changing association was tested in both the first and the second stage modeling. The first stage test indicated that there may exist an interaction between DTR and temperature strata in many communities (p-value (1) in Table S2). The second stage test also indicated that the pooled interaction may be true in total population (p-value=0.028) and many of the sub-populations (p-value=0.029 and 0.325 in cold and warm regions, p-value=0.044 and 0.058 in males and females, and p-value=0.016 and 0.514 in people aged ≥65 and <65 years, respectively). Testing a linear versus strata-based interaction showed an evidence that the linear interaction may be enough in most of the communities (p-value (2) in Table S2). Finally, evidences were shown that the linear interaction may be true in many of the communities (p-value (3) in Table S2), and in total population and all of the sub-populations (p-values <0.001).

Table 1. Summary statistics for mortality and weather variables for each country.

Country	Number of communities	Periods	Total Deaths	DTR (ºC)					Daily mean temperature (ºC)					
				Min	25%	50%	75%	Max	Min	25%	50%	75%	Max	ρ*
Taiwan	3	1994-2007	767,662	0.8	5.5	7.1	8.7	17.9	8.1	20.5	25.1	27.9	33	0.104
Korea	7	1992-2010	1,727,642	0.5	5.9	8	10.2	24.3	-15.7	5.8	14.8	21.8	33	-0.057
Japan	47	1972-2012	36,113,897	0.5	6	8.2	10.6	24.7	-14.1	7.7	15.6	22.2	33.8	-0.020
Total	57	1972-2012	38,609,201	0.5	6.0	8.2	10.5	24.7	-15.7	7.7	15.9	22.4	33.9	-0.028

*** ρ**: Pearson correlation coefficient between DTR and absolute temperature.

Figure 3 shows the pooled lag–distributed association between DTR and mortality over temperature strata in total population and in cold and warm regions. The lag-distributed association showed a distinct pattern by temperature strata. In total population, extreme-cold stratum showed the highest RR (1.015 with 95% CI: 1.009, 1.021) at lag 0 day and the RR decreased over the lags with an indication of delay up to 7 to 9 days. Cold and moderate-cold strata showed a similar pattern but the highest RR (1.011 with 95% CI: 1.009, 1.013) was at 2–3 days. Meanwhile, hot to extreme-hot strata showed the highest RR (hot strata: 1.006 with 95% CI: 1.002, 1.009, extreme-hot strata: 1.005, 95% CI: 1.001, 1.009) at lag 0 followed by a longer delay up to 14 days. Such lag–distributed association pattern was also observed in cold and warm regions (Figure 3), in males and females (Figure S2), and in people aged ≥65 years (Figure S3). Exceptionally, in people aged <65 years, the association was not delayed long in all temperature strata (Figure S3).

Finally, our overall conclusions were robust to sensitivity analyses (Table S3). With the modeling specifications changed, results were generally consistent, suggesting that the risk of mortality related to DTR is larger at higher temperature strata. In addition, we found that the adjustment of air pollutants (PM_{10} and O_3) had small impact on the increasing pattern in DTR-related risk over temperature strata, although it amplified the effect of DTR. Table S4 reports the statistics for residual heterogeneity from the second stage model with and without the region indicator included. In all of the temperature strata, we found indications for residual heterogeneity (p-value of Cochran Q test: <0.001-0.0032, and I^2: 37.2-57.1%) in meta-analysis both with and without the region indicator included.

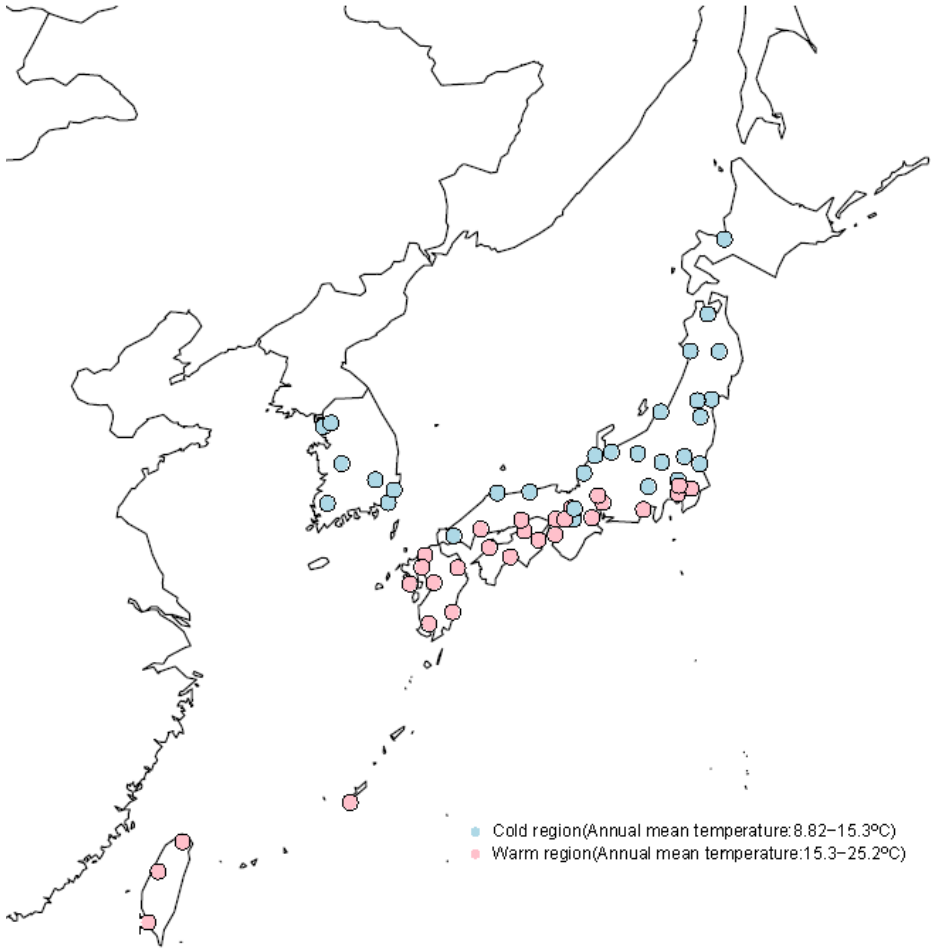

Figure 1. Geographical locations of 57 communities in Taiwan, Korea, and Japan in Northeast Asia. Cold and warm regions include the communities with annual mean temperature belonging to the range of 8.82–15.3ºC and 15.3-25.2ºC, respectively.

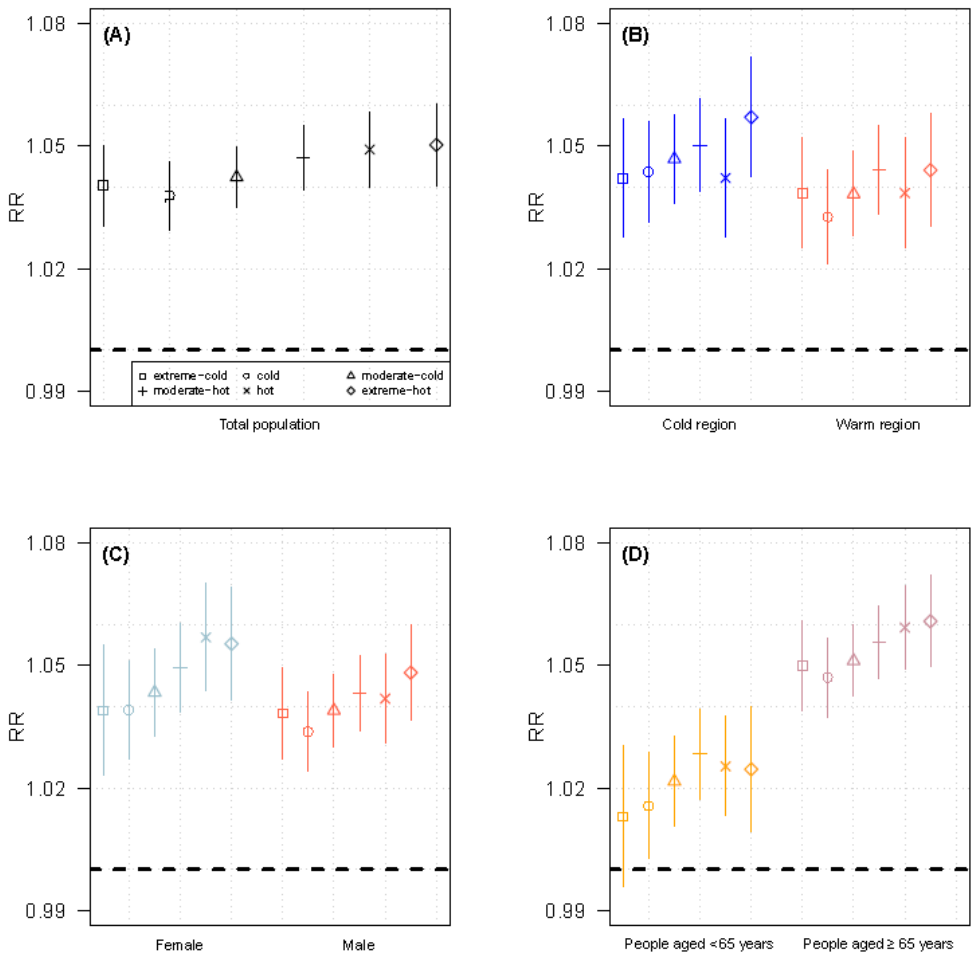

Figure 2. Pooled lag-cumulated associations between diurnal temperature range (DTR) and mortality by temperature strata in total population (A) and in subpopulations defined by temperature distribution (cold and warm regions) (B), sex (C), and age group (people aged <65 and ≥65 years) (D). The y-axis indicates the lag-cumulated relative risk of mortality per 10°C change in DTR. Cold and warm regions include the communities with annual mean temperature belonging to the range of 8.82 - 15.3ºC and to 15.3 - 25.2ºC, respectively.

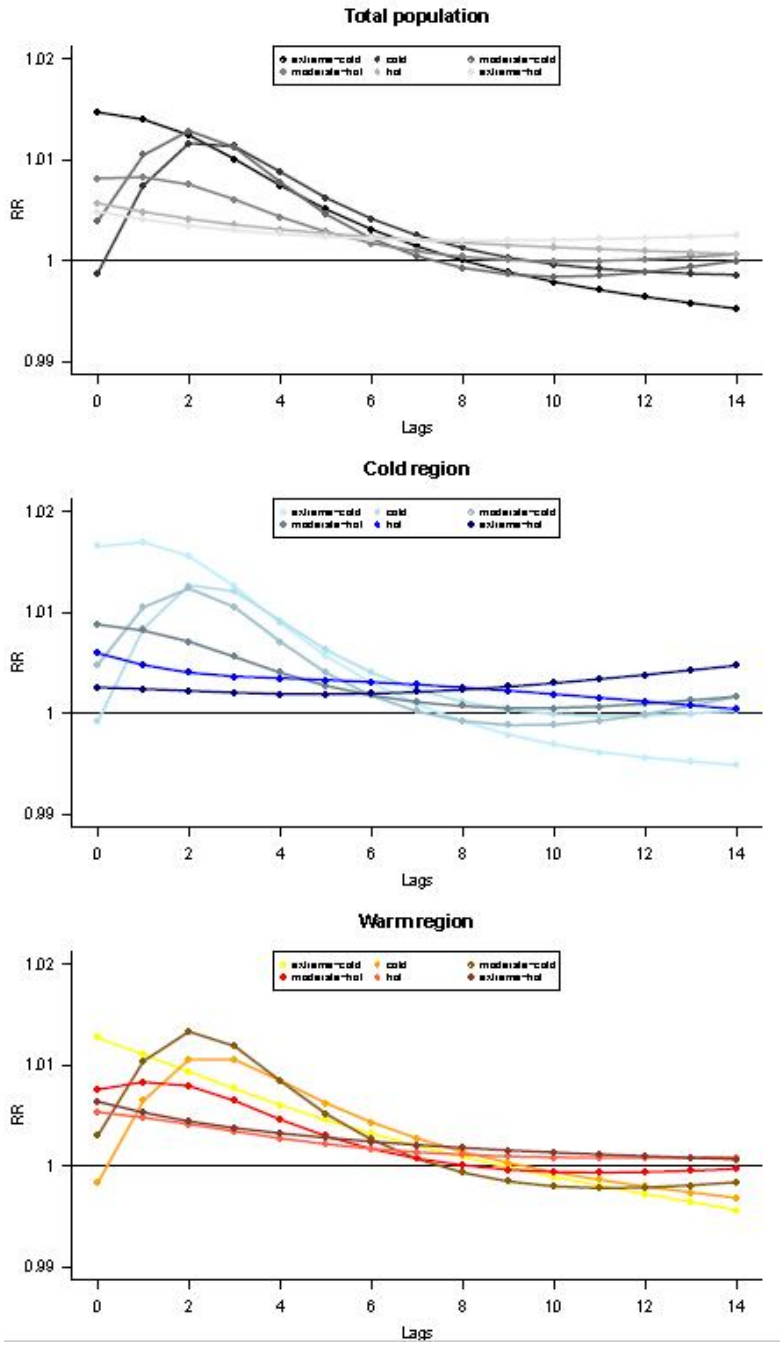

Figure 3. Pooled lag-distributed associations between diurnal temperature range (DTR) and mortality by temperature strata in total population and cold and warn regions. The y-axis indicates the relative risk of mortality per 10°C change in DTR. Cold and warm regions include the communities with annual mean temperature belonging to the range of 8.82 - 15.3ºC and to 15.3 - 25.2ºC, respectively.

Discussion

This study investigated the interactive effect of DTR and temperature on mortality in 57 communities of three countries in Northeast Asia. We found that the DTR-related mortality risk increased by temperature level, suggesting that there may exist an interaction between DTR and temperature. Results showed that such interactive effect was observed in all of the subpopulations defined by temperature distribution, sex, and age group, and was more obvious in cold region than in warm region, and in people aged ≥65 years than in people aged <65 years.

Our findings provide important implications for the role of temperature on the mortality impact of DTR. The DTR has decreased over decades under climate change and the decreased health effects related to DTR has been predicted (Yang et al. 2013). However, our results indicate that the DTR-related mortality in the future may be uncertain considering the interactive effect of DTR and temperature. The uncertainty is also related to whether or not people have adapted to DTR and temperature overtime. A considerable number of studies have reported evidences about temporal decrease of heat-related mortality risk, potentially explained by human adaptation and vulnerability changes (Chung et al. 2017; Davis et al. 2003; Gasparrini et al. 2015; Lee et al. 2018b). In contrast, there is limited evidence for the temporal change in the DTR-related mortality risk. One recent study reported that a non-decreasing trend in the DTR effect on mortality during recent decades, and proposed a hypothesis that the temporal variation may be related with climate change (Lee et al. 2018a). Given the lack of evidence on the temporal change and on the interaction with temperature, further studies should be conducted on these topics to provide more practical information for predicting the future health effects of DTR under climate change.

The interactive effect between DTR and temperature on mortality is supported by several plausible explanations. The first hypothesis is deterioration. Extremely hot temperatures and sudden temperature changes have a similar biological mechanism in disrupting normal physiological thermoregulation (Buguet 2007; Epstein and Moran 2006; Kan et al. 2007; Liang et al. 2009) and affecting plasma viscosity, heart rate, blood pressure, blood cholesterol levels, oxygen uptakes, and the immune system (Garrett et al. 2009; Garrett et al. 2011; Halonen et al. 2010, 2011; Ockene et al. 2004). In other words, heat-related stress exacerbates cardiovascular and respiratory health conditions, which may make people more susceptible to the DTR. Another hypothesis is that, the effect of the DTR is higher during moderate and hot days because of air ventilation (i.e., “ventilation effect”) (Stafoggia et al. 2008). It is possible that the higher DTR effect during moderate and hot days are related to increased exposure in that period or to better exposure measurement, because people are more likely to spend time outdoors and keep their windows open, and exposure measurement by

outdoor station better reflect actual individual exposure. Previous studies suggest evidence of the ventilation effect on PM_{10}-mortality association (Sarnat et al. 2000; Stafoggia et al. 2008). However, there is no individual level research related with DTR effect on mortality, for which further studies are deserved.

In this study, more short-term DTR–mortality relationships (the RR is delayed up to 7-9 days) were observed in extreme-cold to moderate-cold strata. Meanwhile, more delayed DTR–mortality relationships were observed in moderate-hot to extreme-hot strata (the RR is delayed up to 10-14 days). Such longer delay shown in hot temperature strata seems to be a major reason for the observed larger lag-cumulative risk of DTR than in cold temperature strata. This suggests the DTR-related mortality risk shows different delay depending on temperature, for which our study is limited to provide a plausible explanation. Future research is merited to identify the related factors or the mechanism that explain the differential delay.

In this study, the six temperature strata were defined based on the temperature in relative scale (i.e., community-specific temperature percentiles). Previous multi-country studies on the temperature-mortality association have used this relative-scale approach as it accounts for regional acclimatization. Our study population includes 57 communities of three countries with different climate conditions (i.e., temperature climate for Korea, microthermal to sub-tropical climate for Japan, and sub-tropical or tropical climate for Taiwan), though they all belong to Northeast Asia. Therefore, we applied the relative-scale approach as in many of the temperature-mortality studies to reflect the acclimatization in investigating the interactive role of temperature in DTR-related mortality.

The key strength of the present study is that it is the largest study to examine the interactive effect of DTR and temperature on mortality. This study includes a multi-country dataset; 57 communities in three countries in Northeast Asia. Also, our unified statistical modeling framework (i.e., two-stage time series analysis with a DLNM and multivariate meta-analysis) makes the results directly comparable among communities and allows for gaining power to detect the interactive effects pooling the information. In addition, using the DLNM, we modeled a flexible delayed effect of DTR on mortality changing over temperature (Gasparrini et al. 2010), which has not been done in previous studies. We also adjusted for a flexible effect of temperature differently from other previous studies, and thus our estimated RRs for the DTR were relatively smaller than those of the previous studies (Kan et al. 2007; Lim et al. 2012; Yang et al. 2013).

We acknowledge several limitations in this study. First, the current findings cannot be generalized to other communities than our study population, Northeast Asia. Previous studies showed that regional characteristics such as different climates and socio-economic indicators affect the population

susceptibility to weather stressors, and thus further research targeting on other communities like the US or European countries should add evidence to generalize our results. Second, our study is limited to carefully investigate the potential role of air quality in the interactive effect of DTR and temperature. As a partial evidence, our sensitivity analysis using the data for 10 communities of Korea and Taiwan showed adjusting for PM_{10} or O_3 did not change our conclusion on the interactive effect. Further examination should be made with the whole study population and other air pollutants to firmly support this finding. Third, our study can only suggest interactive associations, but can neither suggest any casualty nor identify specific factors or potential mechanisms that may underlie the interactive effect. Fourth, we did not consider temporal changes in the DTR-mortality association. Temperature-mortality studies reported that the association varies over time, (Barnett 2007; Gasparrini et al. 2015; Lee et al. 2018b) and a recent DTR-related mortality study represented the mortality risk of DTR has changed overtime (Lee et al. 2018a). Hence future study should consider the temporally changing association between DTR and mortality, and the role of temperature in that variation.

This study provides evidences of the changing association between DTR and mortality by temperature. Because DTR and temperature are well-known risk factors for mortality, a careful identification of their interactive effect on mortality will improve our understanding on the risk of mortality related to climate and contribute to the projection of future health risk under climate change.

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Supplementary Materials

The Supplementary Materials file is available on request to the first author (jleehwan33@gmail.com).

Research 4

This research paper is under review

Title: Synergic Association between Heat and Temperature Variability on Mortality in 57 Communities in Northeast Asia: a Multi country study

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Abstract

Background: High temperature and temperature variability (TV) have been reported as prominent risk factors of mortality. Previous studies investigated the modification of TV-mortality association by temperature; however, the synergism (additive interaction) between the two variables was far less studied.

Objectives: This study aimed to assess the synergic effect between high temperature and TV on mortality using a multi-country time-series analysis.

Methods: We collected time-series data for mortality weather variables for 57 communities of three countries (Japan, Korea, and Taiwan) in Northeast Asia (1972-2015). TV was defined as the standard deviation of the minimum and maximum temperatures during adjacent exposure days, and temperature was defined as daily mean temperature. Quasi-Poisson time-series regression and meta-analysis were used to estimate the additive interaction between high temperature and TV. The additive interaction was measured by relative excess risk due to interaction (RERI) index. We calculated the RERI using relative risks (RR) of the $99^{th}/10^{th}$, $90^{th}/90^{th}$, and $99^{th}/90^{th}$ percentiles of temperature metric/TV, where risk at the $90^{th}/10^{th}$ percentiles of temperature metric/TV was the reference category.

Results: This study suggests that there may exist synergism between high temperature and TV in the total population (95% lower confidence interval of all RERIs >0 or near 0). The synergism was more obvious in cardiovascular-related deaths than in respiratory-related deaths, and in people aged ≥65 years than in people aged <65 years.

Discussion: We found evidence of synergic effect between high temperature and TV on mortality. Our study provides evidence of the need to build an effective alarm system and public health policies considering both weather variables.

Introduction

Numerous epidemiologic studies have reported associations between high temperature and daily mortality (Gasparrini et al. 2015; Guo et al. 2014; Lee et al. 2017a; Vicedo-Cabrera et al. 2018). The association is widely observed in many countries, although the estimated temperature-related risks are quite heterogeneous depending on countries (Gasparrini et al. 2015; Guo et al. 2014). The relationship is more evident in people with cardiovascular or respiratory diseases (Lee et al. 2017a; Stafoggia et al. 2006), the elderly (Medina-Ramón and Schwartz 2007), and females (Rooney et al. 1998).

Temperature variability (hereafter, TV) has also been studied as a risk factor of increased mortality in many countries (Guo et al. 2016; Lee et al. 2018a; Lee et al. 2018b; Yang et al. 2018), and the TV-related mortality risks are stronger in females, less-educated people, elderly persons, and people who have cardiovascular or respiratory diseases (Kan et al. 2007; Lim et al. 2012; Yang et al. 2013). Further, a recent study reported that the within-day TV-related mortality risk increased in recent decades in many countries; which may lead to increased health burden due to TV, in the near future (Lee et al. 2018a).

Surprisingly, despite the fact that humans are exposed simultaneously to high temperature (heat) and TV, which have similar biological mechanisms that lead to death, synergistic relationship of the co-exposure has been far less studied (Lee et al. 2018b). Some studies have shown season-specific association between TV and mortality (Kan et al. 2007; Lim et al. 2012; Zhou et al. 2014), with some evidence of higher TV-related mortality risks in the warmer season. A few studies have attempted investigating the multiplicative effect modification between temperature and TV (Lee et al. 2018b; Yang et al. 2013); the report showed that TV-related mortality is modified by temperature level. However, the modification of the temperature-mortality association by TV and the synergistic effects of the simultaneous exposures of the two variables (i.e. interaction on the additive scale) on mortality have been rarely studied.

Measuring interaction on the additive scale is known as the most appropriate approach for assessing the public health importance of interactions (Blot and Day 1979; Knol and VanderWeele 2012; Saracci 1980). The additive interaction is more useful in resource allocation and in targeting specific populations for public health policy than the multiplicative interaction (Knol and VanderWeele 2012; VanderWeele 2009), because it indicates which subpopulation is more vulnerable to the risk factor in a quantitative perspective. Specifically, investigations into the synergic association between heat and high-level TV can provide valuable information concerning estimated health burden due to extreme weather events under climate change, and can suggest practical evidence required to build an effective warning system.

The present study aimed to investigate the synergic effect between high temperature and TV in 57 communities of three countries in Northeast Asia. In order to measure the synergism, the relative excess risk due to interaction (RERI) index was used (Knol and VanderWeele 2012). We used a multi-staged approach to: 1) investigate the interaction between high temperature and TV: TV was defined as the standard deviation of the minimum and maximum temperatures during adjacent exposure days (Guo et al. 2016); 2) estimate the differences in mortality risk-related high temperature by TV levels, and differences in mortality risk-related TV by temperature levels; 3) calculate RERI and examine whether the synergism between the two variable exists.

Methods

Data

Daily time-series data were obtained for weather variables and all-cause mortality for 57 communities of three countries: Japan (47 prefectures during 1972–2015), Korea (seven cities during 1992–2015), and Taiwan (three cities during 1994–2014). Weather variables included the daily maximum, mean, and minimum temperatures (°C); and daily mean relative humidity (%). For each community, weather variables were measured either from a single monitor or from multiple monitors. If measured from multiple monitors, the measurements were averaged across all monitor stations. In order to conduct cause-specific and age-specific analyses, we stratified the total mortality counts by causes of death and age (total population, cardiovascular diseases, respiratory diseases, and age [<65 and ≥65 years], respectively). The causes of death were classified using the codes of the International Classification of Disease Revisions (ICD) 8–10 as follows: cardiovascular-related death (ICD8, 390-458; ICD9, 390-459; ICD10, I00-I99) and respiratory-related death (ICD8 and ICD9, 460-519; and ICD10, J00-J99). In addition, we obtained data on air pollution including the daily mean concentrations of ozone ($\mu g/m^3$) and PM_{10} ($\mu g/m^3$) for 10 communities (seven cities in Korea and three cities in Taiwan). Air pollution data were also measured using multiple monitors; and community-specific data were obtained by averaging across all monitors. See Supplemental Material, detailed information about data collection in Appendix 1.

Statistical modelling

For each community, we modeled the non-linear temperature-mortality relationship and the linear TV-mortality relationship using quasi-Poisson regression model as follows:

$$Y_t \sim quasi - Poisson(\mu_t)$$

$$\ln(\mu_t) = \beta_0 + ns(TEMP_t, df = 7) + TV_t + factor(DOW_t)$$

$$+ns(TIME_t, df = 7/yr) + ns(HUM_t, df = 3) + ns(TEMP, df = 7): TV_t \quad (1)$$

where Y_t=death count on day *t*, μ_t=expected mortality count on day *t*, β_0=model intercept, $TEMP_t$= temperature metric on day *t*, TV_t=TV on day *t*, DOW_t=categorical variable for day of week on day *t*, $TIME_t$=time on day *t*, and HUM_t=mean relative humidity on day *t*. The *ns()* indicates natural cubic splines with degrees of freedom denoted as *df*. $ns(TEMP, df = 7): TV_t$ represents the interaction term between temperature metric and TV. We defined an temperature as a daily mean temperature. These model specifications were based on a previous environmental time-series study conducted in a similar study region (Chung et al. 2015; Chung et al. 2017). In the main analyses, we used TV as the standard deviation of the minimum and maximum temperatures for two consecutive days (lag0-1 days), including both intra-day and inter-day variability. Correspondingly, we defined the temperature metric as a 2-day moving average of temperature in model (1).

From the temperature-mortality associations estimated from model (1) for each community, we defined heat effect as the relative risk (RR) comparing the 90th and 99th percentiles of temperature metric for each community (Chung et al. 2015; Chung et al. 2017), and high-level TV effect as RR comparing the 10th and 90th percentiles of TV for each community, to simplify the interpretation about interaction on the additive scale. Hence, $ns(TEMP_t, df = 7)$ and TV_t in model (1) were centered at each 90th percentile of temperature metric and 10th percentile of TV for each community. From these frameworks, we obtained each of the seven coefficients of the basis function to represent the temperature metric-mortality curves at the 10th and 90th percentiles of TV in each community as well as the eight coefficients to represent the TV-mortality curve by temperature metric in each community.

We pooled each community-specific effect estimates (the temperature metric-mortality relationships at two TV levels and TV-mortality relationship by temperature metric) to generate an overall estimate across all communities, using multivariate meta-analysis with a random intercept.

Testing for changes in RR

We performed the following two-fold statistical testing for RR differences on the additive scale: First, we investigated changes in estimated heat RRs between the 10th and 90th percentiles of TV

('Heat RR at 90th percentile of TV - Heat RR at 10th percentile of TV'). Second, we also investigated changes in high-level TV RRs between the 90th and 99th percentiles of temperature metric ('High-level TV RR at 99th percentile of temperature metric – High-level TV RR at 90th percentile of temperature metric'). In these procedures, each pooled temperature-mortality by two TV levels and the pooled TV-mortality associations by temperature were used; and the corresponding P-values were calculated by Wald test (H_0: two log-scaled RRs are equal).

Relative excess risk due to interaction (RERI)

Suppose there is an interaction between A and B (the two interest exposure variables) on mortality count, where A and B are dichotomous. Let RR_{10} be RR for exposure to A only, RR_{01} be RR for exposure to B only, and RR_{11} be RR for co-exposure to both A and B, where no A and B exposures is the reference category. Then, we can derive RR_{11}-RR_{10}-RR_{01}+1 as the additive interaction using RR, referred to as the "RERI" (Knol and VanderWeele 2012; VanderWeele 2009). The RERI>0 implies a positive interaction between A and B on the additive scale, and synergism between the two exposures (Knol and VanderWeele 2012).

In our case, since the two exposures of interest (temperature and TV) are continuous variables, reference points are needed to define categorical exposure levels. As described above in the "*Statistical modelling*" section, we defined the heat-related risk as RR comparing the 90th and 99th percentiles of temperature metric, and also defined the high-level TV risk as RR comparing the 10th and 90th percentiles of TV. Then, the RR_{10} can be interpreted as RR of the 99th percentile of temperature metric and 10th percentile of TV exposures; the RR_{01} can be interpreted as RR of the 90th percentile of temperature metric and 90th percentile of TV exposures; and RR_{11} can be interpreted as RR of the 99th percentile of temperature metric and 90th percentiles of TV exposures, where risk at the 90th percentile of temperature metric and the 10th percentile of TV is the reference category. Then, the estimated RERI from this procedure can be interpreted as the synergic association between high temperature and TV on mortality.

We obtained community-specific parameters for log-scaled RR_{10}, RR_{01}, and RR_{11} from model (1) respectively. In addition, we obtained calculated community-specific RERIs and its empirical variance estimates. The community-specific empirical variances were calculated by the Monte Carlo sampling (1,000 simulated values for each community), as proposed in a previous study (Lee et al. 2017b). The three log-scaled RRs and RERIs were pooled across all communities using univariate meta-analysis with a random intercept. All the pooled RRs were reported as percentile increase (= [RR-1]*100 %) in mortality-related risk. From the meta-analysis for RERI, we also obtained the community-specific best linear unbiased predictor (BLUP) of RERI.

All the analytic procedures were repeated by sub-populations (causes of mortality, and age groups) with an individual model. We also evaluated the corresponding country-specific estimates in all the meta-analyses for all-causes death, using country indicator as a meta-predictor.

Association between RERI and community-specific meta-variables

We applied random effect meta-regression to examine the relationship between RERI and community-specific meta-variables in the total population, and included community-specific average temperature, average TV, average relative humidity, latitude, longitude, and country, as meta-variables using a single predictor model and multi-predictor models. From the single predictor meta-regression model, the association between RERI and each meta-variable, was estimated, as the change in RERI per unit change. Additionally, residual heterogeneity was tested and quantified by the Cochran Q test and I^2 statistics from the meta-regression models. We conducted the meta-regressions for the total population.

Sensitivity analysis

The sensitivity of modeling assumptions was tested by changing the lag periods (lag0-2 and lag0-3; both moving average temperature and standard deviation during consecutive lag days), degrees of freedoms for the temperature-mortality association (df=6 and 7), and seasonality and long term trend adjustments (df=6/per year and 8/per year). Further, using the data from the 10 communities (Taiwan and Korea) only, we conducted sensitivity analyses with and without adjustment for the two air pollutants (PM_{10} and O_3) separately as a linear term of the current day mean concentration in the first stage model. These assessments were implemented using all-cause mortality only.

Results

Table 1 shows the descriptive statistics for death and weather variables for each country (community-specific summary statistics are available in Table S1). The data included 42,768,307 all causes from the 57 communities. Each country showed a broad range of temperature (daily mean temperature) and TV. During the entire study period, Taiwan had the highest average of temperature (23.6ºC) while Korea had the lowest average of temperature (13.9ºC). The distribution of TV was similar among all countries. Figure S1 displays the

geographical locations of the 57 communities divided into three average temperature groups (Figure S1 A) and three average TV groups (Figure S1 B).

Table 1. Summary statistics for mortality and weather variables for each country.

Country	# of communities	All-causes	Cardiovascular	Respiratory	People aged ≥65 years	Daily mean temperature (ºC, Range*)	Temperature variability (ºC, Range)	Relative humidity (%, Range)
Japan	47	39,943,041	13,631,353	5,028,310	30,884,771	15.1 (8.9-22.9)	5.1 (3-6.4)	70 (62.2-77)
Korea	7	1,662,422	389,601	106,215	1,071,598	13.9 (12.7-15)	5.3 (4.5-6)	63.9 (57.9-69.2)
Taiwan	3	1,162,844	262,747	110,976	745,649	23.6 (23.1-24.2)	4.6 (4.3-4.9)	74.9 (74.7-75)

*Range indicates minimum and maximum of community-specific averages for each variable.

Temperature variability (TV) was calculated as standard deviation of minimum and maximum temperatures during the two adjacent exposure days (lag 0-1 day).

Table 2. Statistics for residual heterogeneity (P-values from Cochran Q-test and I^2 statistics) and estimates (coefficients for each meta-variables with 95th confidence of intervals) from the second-stage random-effects meta-analysis and meta-regression models for relative excess risk due to interaction (RERI).

Model	Meta-variable	Increase*	95% CI	Q-test (P-value)	I^2
Intercept-only				0.58	1%
Single predictor (continuous variable)	Average temperature (ºC)	-0.5	(-1,-0.1)	0.75	1%
	Average temperature variability (TV, ºC)	0.3	(-1.7,2.2)	0.55	1%
	Average relative humidity (%)	-0.1	(-0.4,0.2)	0.58	1%
	Latitude (º)	0.5	(0.2,0.9)	0.81	1%
	Longitude (º)	0.4	(0.1,0.6)	0.82	1%
Single predictor (indicator variable)	Korea	-1.6	(-6.9,3.8)	0.53	1%
	Taiwan	-2.1	(-11.3,7.1)		
Multiple predictors	All predictors			0.76	1%

*RERI increase per one unit of meta-variable increase.

Figure 1 shows the pooled temperature metric-mortality associations (referenced at the 90th percentile of temperature metric) by two TV levels (10th and 90th percentile of TV) in the total population (A) and stratified by causes of death (B-C) and age group (D-E). In the total population, the heat-related mortality risks (comparing the 99th and 90th percentiles of temperature metric) at the 90th percentile of TV were higher than the risks at the 10th percentile of TV (2.7% increase in RR with P-value <0.001). Such increasing pattern was shown in all sub-populations, being more obvious in cardiovascular-related deaths (4.6% increase in RR with P-value <0.001) and in people aged ≥65 years (3.2% increase in RR with P-value <0.001), compared with respiratory-related deaths and people aged <65 years, respectively. Corresponding country-specific results are displayed in Figure S2; and Japan showed a more evident interaction pattern (2.7% increase in RR with P-value <0.001) in all-causes death, than the other two countries.

Figure 2 displays the pooled TV-mortality associations (comparing 90th and 10th percentiles of TV) by temperature levels in the total population (A) and stratified by causes of death (B-C) and age group (D-E). The TV-related mortality risks at the 99th percentile of temperature metric were higher in the total population, compared to the risks at the 90th percentile of temperature metric (2.1% increase in RR with P-value <0.01). Such interactive pattern was shown in all of the sub-populations, being more obvious in cardiovascular-related deaths (3.2% increase in RR with P-value <0.01) and in people aged ≥65 years (2.4% increase in RR with P-value <0.001), compared with other sub-populations. Corresponding country-specific results are displayed in Figure S3, and the interactive pattern for all-causes mortality was more pronounced in Japan (2.2% increase in RR with P-value <0.01).

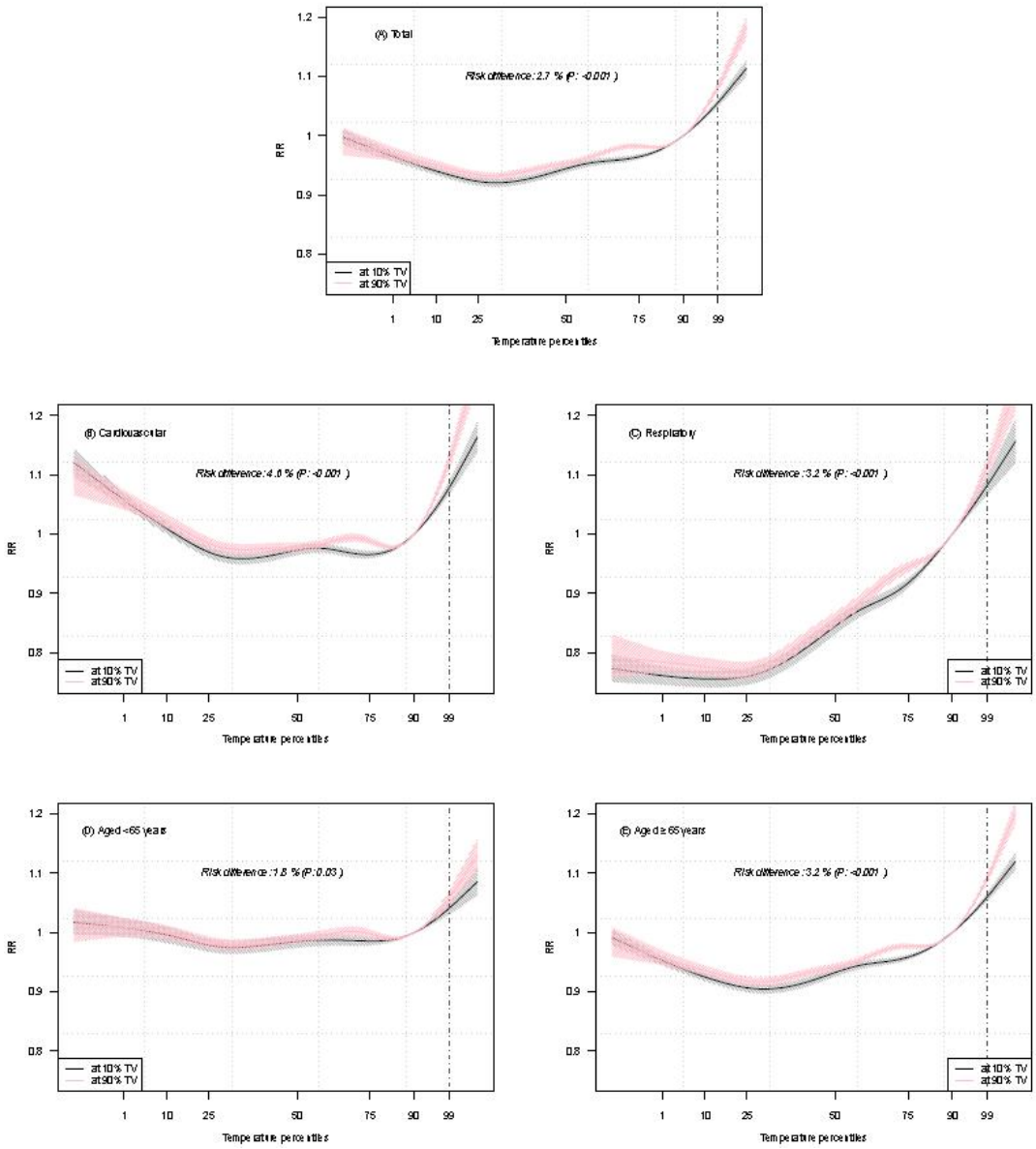

Figure 1. The pooled temperature metric-related mortality by two temperature variability (TV) levels (10th and 90th percentages of TV) with 95% confidence intervals for the total (A) and each sub-populations (B-E). The vertical dashed lines represents the 99th percentiles of the temperature metric (2 day moving average of temperature). Risk differences: relative risks (RRs) of 99th percentile temperature metric at the 90th percentage TV – RRs of 99th percentile temperature metric at 10th percentage TV. Wald type test was used as a significance test on the risk differences (P-values).

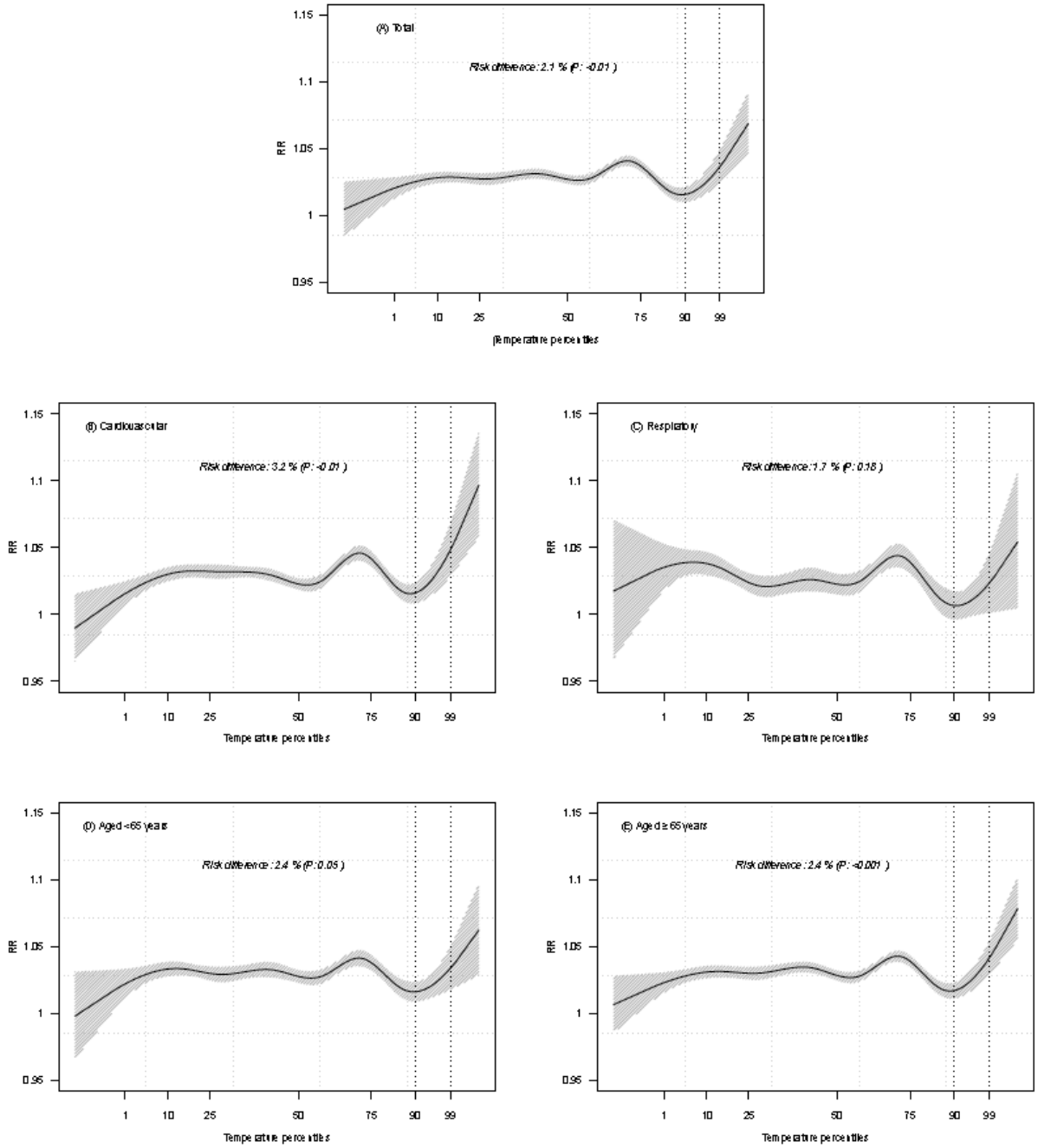

Figure 2. The pooled temperature variability (TV)-related mortality by temperature metric (2 day moving average of temperature) with 95% confidence intervals for the total (A) and each sub-populations (B-E). The vertical dashed lines represents the 90th and 99th percentiles of the temperature metric. The curves were computed for the TV corresponding to the 90th percentile vs 10th percentile of TV). Risk differences: relative risks (RRs) of TV at the 99th percentage temperature metric – RRs of TV at 90th percentage temperature metric. Wald type test was used as a significance test on the risk differences (P-values).

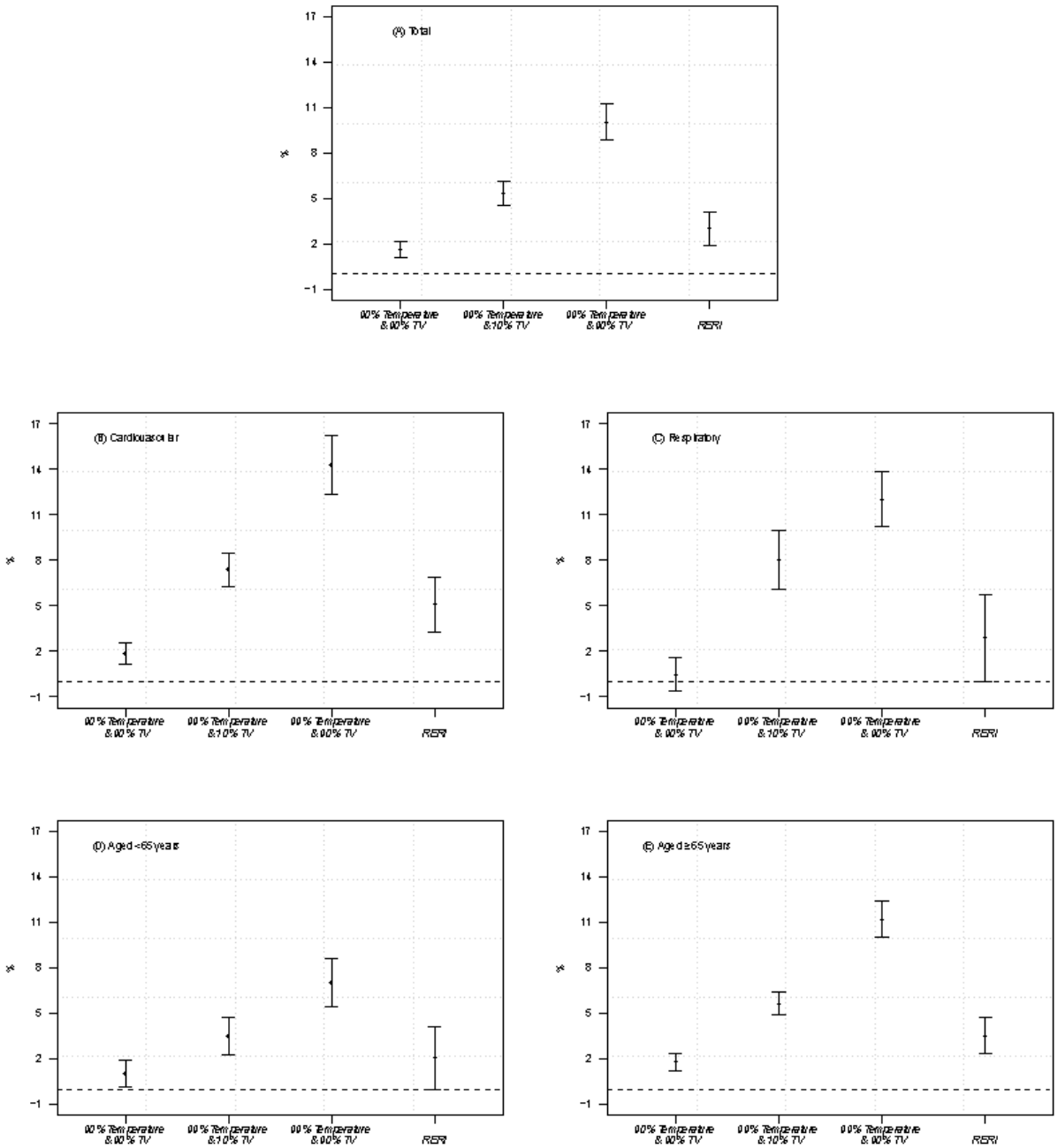

Figure 3. The pooled relative risks by temperature and temperature variability (TV) levels and relative excess risk due to interaction (RERI) in the total population (A) and for each sub-populations (B-E), where risk at the 90th percentile of temperature metric (2 day moving average of temperature) and the 10th percentile of TV is the reference.

Figure 3 illustrates the pooled percentile increases in mortality risk and RERI by high temperature and TV levels in the total population (A), stratified by causes of death (B-C) and age group (D-E), where risk at the 90th percentile of temperature metric and the 10th percentile of TV is the reference. In the total population and all sub-populations, mortality risks increased in both heat and high-level TV, and the synergic association between the two variables may be true (95% lower confidence interval of RERIs >0 or near 0). Further, the synergic association was highest in cardiovascular-related deaths (RERI: 5.1%), and was more pronounced in the total population (RERI: 3.0%), and people aged ≥65 years (RERI: 3.5%), compared to respiratory-related deaths (RERI: 2.9%) and people aged <65 years (RERI: 2.1%), respectively. Corresponding country-specific results for all-causes mortality are displayed in Figure S4. The most evident synergic pattern was observed in Japan.

The associations between RERI and community-specific meta-variables in the total population are reported in Table 2. The table summarizes the estimated increment in RERI per unit increase in each of the meta-variables. RERIs were higher for communities with colder average temperature, and higher latitude and longitude. However, we could not find a meaningful association between community-specific RERI and other meta-variables. In addition, we found indications of residual homogeneity (P-values from Q test: 0.53-0.82 and I^2 statistics: 1%) in all meta-regression models with and without the meta-variables, and the country indicator had the greatest reduction in heterogeneity. Figure S5 displays the community-specific RERI for all-causes mortality, with the corresponding geographical locations.

Our overall conclusions were robust based on the sensitivity analyses. With the modeling specifications changed (Figures S6-7: each 0-2 and 0-3 lag days for both exposures, Table S2: degree of freedoms for temperature-mortality curve and long-term trend and seasonality, and air pollution adjustments), results in the total population were generally consistent, suggesting that the synergic association between heat and high-level TV exists.

Discussion

The study aimed to investigate the effect of the synergic association between high temperature and TV on mortality using data from 57 communities in three Northeast Asian countries. This study revealed an additive interaction between heat and high-level TV in the total population and all sub-populations, categorized by death causes and age groups. The synergism was more obvious in cardiovascular-related deaths than in respiratory-related deaths, and in people aged ≥65 years than in people aged <65 years. The spatial variations in synergic effects were associated with average temperature and geographical locations.

There are several plausible biological mechanisms for synergism between high temperature and TV. Both heat and sudden temperature change can disrupt the normal immune system and physiological thermoregulation, including changes in blood viscosity, plasma cholesterol level, and red blood cell count (Bull 1980; Keatinge et al. 1986); and can cause inflammatory reactions in the cardiovascular and respiratory systems (Garrett et al. 2009; Halonen et al. 2010; Lee et al. 2017a). Moreover, these two variables can induce renal disorders, which are known to be affected by electrolyte and water imbalances, as a consequence of hyperthermia and dehydration (Hansen et al. 2008).

We showed that the TV-mortality association increased with high temperature, and the findings are generally consistent with previous studies. A nationwide study in Japan reported that the associations between diurnal temperature range (intra-day TV) and mortality were generally higher when it is extremely hot (>95th percentile of daily mean temperature) than at other temperature strata, for all-causes and for the five types of cardiovascular-related deaths (Lee et al. 2018b). Another study in six metropolitan cities in Korea also showed a higher effect of intra-day TV on non-accidental deaths during the summer (from June to August) and fall (from September to November), compared to winter (December to February). However, we could not find any previous paper reporting on the temperature-related mortality changed by TV.

Furthermore, the reason why the synergic effect between high temperature and TV was greater for communities with colder average temperature should be more discussed. We supposed an acclimatization to local climate as a plausible hypothesis of the association between synergic effect and local average temperature, based on the previous studies which showed that people in colder weather were generally more sensitive to high temperature (Anderson and Bell 2009; Guo et al. 2014). Further, in our results, the heat-related mortality risks were generally higher than the high-level TV risks (see Figure 1-2), hence the synergic relationship between two variables might be more affected by changes in heat-related risks. In addition, association with latitude and longitude could be explained in relation to average temperature; in our study area, higher longitude community showed higher latitude in general. Thus, the synergic effect between high temperature and TV may increase in colder community, and the corresponding community-specific prevention plans should be investigated to minimize the synergic effect.

A key strength of the present study is the estimation and statistical testing of additive interaction between high temperature and TV. Most previous studies reported on only the one-way multiplicative effect modification: the TV-related mortality modified by temperature levels (Lee et al. 2018b; Lim et al. 2012; Vicedo-Cabrera et al. 2016). However, people are generally exposed to these two variables at the same time and these variables have similar biological mechanisms, which can lead to death, therefore mortality risks related to the co-exposures to

temperature and TV should be assessed simultaneously. To the best of our knowledge, our study is the first to estimate the synergism between high temperature and TV on mortality. Further, another important strength is the usage of interaction on the additive scale. The additive interaction is a more suitable public health measure than the use of the multiplicative interaction measures only (Blot and Day 1979; Rothman et al. 1980). This is because multiplicative interaction is only calculated on the risk ratio scale and cannot reflect the quantitative risk difference, whereas, the multiplicative interaction can indicate a wrong subgroup for treatment (Knol and VanderWeele 2012). That is, despite the quantitative risk difference (RR_1-RR_0) was greater, the multiplicative interaction can lead to incorrect conclusions if the corresponding ratio increase (RR_1/RR_0) is small. In addition, based on the stratified analysis, synergic relationships were found to vary by causes of death and age group. These results can therefore be utilized towards establishing composite alarm systems considering both high temperature and TV, and to establish effective public health policies.

Furthermore, our findings can provide important approach to the prediction of health burden due to heat and high-level TV under climate change. Recent studies reported a temporal increase in the TV-related mortality risk in recent decades, and the temporal increment might be associated with warmer climate (Lee et al. 2018a). Since anthropogenic climate change is expect to increase the frequencies and intensities of hot and unstable weather (Stocker 2014), the consideration of the synergism between two variables may be indispensable to anticipate future health impacts of heat and high-level TV.

We acknowledge several limitations in this study. First, our findings cannot be generalized to other communities other than our study population, Northeast Asia. Climates and socio-economic indicators affect population susceptibility to weather stressors, and thus, further research targeting other communities should be conducted to support our results. Second, our study is limited to the careful investigation of the potential role of air quality on the interactive effect of high temperature and TV. For further evidence, our sensitivity analysis based on data from 10 communities in Korea and Taiwan showing adjustment for PM_{10} or O_3 did not change our conclusion. Third, we did not use a more flexible statistical method to capture the nonlinear lagged relationship with longer lag days (distributed lag non-linear model), because the lag days of heat is relatively short (lag 0-1 days) (Basu and Samet 2002; Guo et al. 2014) and we mainly focused on intra- and inter-day TV. Since the 2-day durations were not long enough for the nonlinear lag pattern, we believe that the usage of the flexible model may not bring out major changes in our main results. Furthermore, because of the discordance in lag days, we did not consider the interaction with cold, which is known to have longer lag days (14 to 28 days) (Guo et al. 2014). A previous US study also showed that TV during cold months (November to March)

was not related with the cold-mortality association (Medina-Ramón and Schwartz 2007).

We found evidence about the synergism between high temperature and TV with RERI index. The additive interaction between the two variables existed in the total population (P-value<0.001), and were more prominent in cardiovascular-related deaths than in respiratory-related deaths; in people aged ≥65 years than in people aged <65 years; and in colder areas than in warmer areas. Based on these findings, as a matter of importance, we suggest the need to build an additional warning system considering both high temperature and TV, and to establish effective public health interventions targeting specific populations.

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Supplementary Materials

The Supplementary Materials file is available on request to the first author (jleehwan33@gmail.com).

2.2. Uncertainty estimation in weather-mortality association

In this section, I assessed the statistical property of the statistical approach to estimate the minimum mortality temperature (MMT) via a simulation study, and proposed an alternative approach using Bayesian framework (**Research 5**). And, I suggested two-step regression approach to classify the mortality risks related to absolute temperature and temperature variability (**Research 6**).

Research 5

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Title: Monte Carlo estimation for the minimum mortality temperature in the temperature-mortality association study

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Abstract

Rich literature has reported that there exists a nonlinear association between temperature and mortality. One important feature in the temperature-mortality association is the minimum mortality temperature (MMT) which is regarded as a threshold point in describing the population susceptibility to temperature. The commonly used approach for estimating the MMT is to determine the MMT as the temperature at which mortality is minimized in the estimated temperature-mortality curve. Also, one recent study proposed a Monte Carlo simulation based approach to calculate the standard errors and the confidence interval for the MMT. However, the statistical property of these methods was not fully studied. Our research aims firstly to assess these methods in various types of the temperature-mortality association via a simulation study. Secondly, we suggest an alternative approach to provide a point and an interval estimates for the MMT, which may improve upon the previous approach if some prior knowledge is available on the MMT. We compare the previous and alternative methods through a simulation study and an application. In addition, as the MMT is often used as a reference temperature to calculate the RRs, we assess how the uncertainty in the MMT affects the estimation of the RR referenced with the MMT.

Introduction

Ambient temperature has been shown to be a risk factor for mortality in numerous epidemiological studies.(Armstrong 2006; Chung et al. 2015; Curriero et al. 2002; Gasparrini et al. 2015; Guo et al. 2014) Researchers have reported that there exists a nonlinear association between temperature and mortality, characterized by U- or J- shaped association.(Armstrong 2006; Chung et al. 2015; Gasparrini et al. 2015) One important feature in the temperature-mortality association is the minimum mortality temperature (MMT), which is defined as the temperature at which the lowest mortality is achieved. The MMT has been regarded as a threshold point in describing the population susceptibility (Guo et al. 2014) to temperature because the mortality risk becomes increased as temperature increases or decreases from the MMT. Therefore, the MMT has often been used as a reference temperature to quantify the relative risk (RR) related to cold or hot temperatures in many previous studies (Gasparrini et al. 2015; Guo et al. 2014).

Despite the importance of the MMT, little research has been conducted on statistical inference for the MMT. The commonly used approach for estimating the MMT is to determine the MMT as the temperature at which mortality is minimized in the estimated temperature-mortality curve (Gasparrini et al. 2015; Guo et al. 2014). This approach provides a point estimate but the corresponding uncertainty is not quantified. One recent study (Tobías et al. 2016) proposed a Monte Carlo simulation based approach to calculate the standard errors and the confidence interval for the MMT. The study applied the method to the data for 52 cities in Spain and showed that the uncertainty can be small or large depending on the estimated association pattern.

However, the statistical property of the aforementioned methods was not fully studied. Our research aims firstly to assess these methods in various types of the temperature-mortality association via a simulation study. Secondly, we suggest an alternative approach to provide a point and an interval estimates for the MMT, which may improve upon the previous approach if some prior knowledge is available on the potential range of the MMT. We compare the previous and alternative methods through a simulation study and an application. In addition, as the MMT is often used as a reference temperature to calculate the RRs, we assess how the uncertainty in the MMT affects the estimation of the RR referenced with the MMT.

In section 2, we describe the previous and alternative methods to calculate a point and an interval estimates for the MMT. In section 3, we conduct a simulation study to compare the methods in various types of the association. In section 4, applying the methods, we investigated the MMT for 135 cities in the US. Section 5 concludes with discussions.

Methods

First, we describe how to model the temperature-mortality association. Let Y_t be the daily death count on day t, with $\mathrm{t} = 1, \ldots, N$, and $\mathbf{x}_t = (x_t, x_{t-1}, \ldots, x_{t-L})'$ be the vector of daily mean temperatures on day t and over the previous L days. We model the association between Y_t and $\mathbf{x}_t$ using a generalized linear model (GLM) with splines.

$$Y_t \sim Quasi - Poisson(\mu_t)$$

$$\log(\mu_t) = \alpha + s(\mathbf{x}_t; \boldsymbol{\eta}) + \sum_{j=1}^{J} h_j(u_{jt}; \boldsymbol{\gamma}_j) \qquad (1)$$

where μ_t is the expected death count on day t, $\mathrm{s}(\cdot)$ is a flexible function characterized by parameter $\boldsymbol{\eta}$ to depict the nonlinear and lagged effects of temperature, u_{jt} is the j-th confounding variable measured on day t, $h_j(\cdot)$ is a flexible function to represent the (potentially nonlinear) effects of j-th confounding variable, and $\boldsymbol{\gamma}_j$ is the corresponding parameter. For s( ), we use the distributed lag nonlinear model (DLNM)(Gasparrini et al. 2010) where a cross-basis is used to describe the nonlinear and lagged dependency. Let $\phi_1(\cdot), \cdots, \phi_{v_x}(\cdot)$ be the basis to describe the temperature-mortality association and $\psi_1(\cdot), \cdots, \psi_{v_l}(\cdot)$ be the basis to depict the lag-mortality association. The DLNM is expressed as

$$s(\mathbf{x}_t; \boldsymbol{\eta}) = \sum_{j=1}^{v_x} \sum_{k=1}^{v_l} \mathbf{r}_{tj}' \mathbf{c}_k \eta_{jk}, \qquad (2)$$

where $\mathbf{r}_{tj} = \left(\phi_j(x_t), \cdots, \phi_j(x_{t-L})\right)'$ is the vector of $\mathbf{x}_t$ transformed through the j-th basis $\phi_j(\cdot)$ in the temperature dimension and $\mathbf{c}_k = \left(\psi_k(0), \cdots, \psi_k(L)\right)'$ is the vector derived by applying the k-th basis $\psi_k(\cdot)$ for lag dimension to the vector $(0, \cdots, L)'$. Then, $\boldsymbol{\eta} = (\eta_{11}, \ldots, \eta_{v_x v_l})'$ is the vector of coefficients for the cross-basis with the dimension $v_x \times v_l$. In order to estimate the lag-cumulated temperature-mortality association, $\boldsymbol{\eta}$ is reduced through the following transformation.(Gasparrini and Armstrong 2013)

$$\boldsymbol{\beta} = \mathbf{M}\boldsymbol{\eta}$$

$$\mathrm{V}(\boldsymbol{\beta}) = \mathbf{M}\, V(\boldsymbol{\eta})\, \mathbf{M}^T \qquad (3)$$

where $\mathbf{M} = \mathbf{1}'_{(L+1)}\mathbf{C} \otimes \mathbf{I}_{(v_x)}$ is a reducing matrix, $\boldsymbol{\beta} = (\beta_1, \beta_2, \ldots, \beta_{v_x})'$ is the reduced parameter, and $V(\boldsymbol{\beta})$ is the associated error (co)variance matrix. In $\mathbf{M}$,

$$\mathbf{C} = (\boldsymbol{c}_1, \cdots, \mathbf{c}_{v_l}) = \begin{pmatrix} \psi_1(0) & \psi_2(0) & \cdots & \psi_{v_l}(0) \\ \psi_1(1) & \psi_2(1) & \cdots & \psi_{v_l}(1) \\ \vdots & \vdots & \ddots & \vdots \\ \psi_1(L) & \psi_2(L) & \cdots & \psi_{v_l}(L) \end{pmatrix}, \quad (4)$$

and $\otimes$ is the notation of the Kronecker product. Then, $\boldsymbol{\beta}$ is the parameter to describe the lag-cumulated temperature-mortality association.

Next, we describe how to estimate the MMT and its uncertainty. Let $\widehat{\boldsymbol{\beta}}$ be the maximum likelihood estimate obtained from model (1) through (3). Given $\widehat{\boldsymbol{\beta}}$, the commonly used point estimate for the MMT is a solution of $\operatorname{argmin}(_x \boldsymbol{Q}_x \widehat{\boldsymbol{\beta}})$ where $\boldsymbol{Q}_x = \left(\phi_1(x), \cdots, \phi_{v_x}(x)\right)$ is the vector of basis variables by applying the basis for temperature to a particular temperature value *x*, and *x* ranges from minimum to maximum temperatures observed in the data. The solution can be the minimum or the maximum temperature, in which case it has been suggested to constrain the solution within the 1st – 99th percentiles of the temperature.[6] To quantify the uncertainty, a Monte Carlo simulation based method[6] can be used to derive the empirical distribution of the MMT. Based on the maximum likelihood principle,(Casella and Berger 2002) if the sample size is sufficiently large, it can be assumed that the true $\boldsymbol{\beta}$ follows a multivariate normal distribution with the mean as the estimate ($\widehat{\boldsymbol{\beta}}$) and the variance as the corresponding error (co)variance ($\mathrm{V}(\widehat{\boldsymbol{\beta}})$).(Gelman and Hill 2006; Hoff 2009) Then, one can simulate the true $\boldsymbol{\beta}$ and the true MMT through the following procedure.

$$sample\ \boldsymbol{\beta}_{(i)} \sim MVN\left(\widehat{\boldsymbol{\beta}}, \mathrm{V}(\widehat{\boldsymbol{\beta}})\right)$$

$$\theta_{(i)} = \operatorname{argmin}(_x \boldsymbol{Q}_x \boldsymbol{\beta}_{(i)}) \quad (5)$$

where (i) indicates i-th simulated sample, $\boldsymbol{\beta}_{(i)}$ are independent and identically distributed sample, and $\theta_{(i)}$ are the samples to approximate the empirical distribution of the true MMT. Then, the standard deviation of the distribution can serve as a standard error estimate and the empirical percentiles (e.g., the 2.5th - 97.5th percentiles) can be used as an interval estimate for the MMT. In fact, the empirical mean is an alternative point estimate for the MMT, which can be different from the solution of $\operatorname{argmin}(_x \boldsymbol{Q}_x \widehat{\boldsymbol{\beta}})$argmin solution.

Now, we describe an alternative procedure to estimate the MMT, which may improve upon the method described in the previous paragraph when a prior knowledge is available on the MMT. As the empirical distribution for the MMT is determined by the multivariate normal distribution with mean ($\widehat{\boldsymbol{\beta}}$) and (co)variance ($\mathrm{V}(\widehat{\boldsymbol{\beta}})$), the uncertainty for the MMT tends to be large if $\mathrm{V}(\widehat{\boldsymbol{\beta}})$ is large. In such case, adding some restrictions based on a prior knowledge for the MMT distribution may reduce the uncertainty. One way of doing so is to specify a prior distribution for the MMT and to combine it with the sampling procedure (5). A reasonable prior would be a Uniform distribution with a support (α_1, α_2), which is specified based on a prior knowledge about a potential range of the MMT. With such prior assumption, the sampling procedure (5) can simply be modified by discarding the samples of $\theta_{(i)}$ which do not fall within the range of (α_1, α_2). That is,

$$sample\ \boldsymbol{\beta}_{(i)}\ such\ that\ \ \alpha_1 \leq \mathrm{argmin}({}_x\, \boldsymbol{Q}_x \boldsymbol{\beta}_{(i)}) \leq \alpha_2$$

$$\theta_{(i)} = \mathrm{argmin}({}_x\, \boldsymbol{Q}_x \boldsymbol{\beta}_{(i)}) \qquad (6)$$

Then, the empirical mean and percentiles can serve as a point and an interval estimates for the MMT.

Finally, we describe how to estimate an RR with the MMT used as a reference temperature accounting for the uncertainty in the MMT. Given the Monte Carlo samples of $\boldsymbol{\beta}_{(i)}$ and $\theta_{(i)}$ obtained through procedure (5) or (6), one can calculate an RR comparing an arbitrary temperature value x and the MMT as

$$\boldsymbol{\zeta}_{(i)} = (\boldsymbol{Q}_x - \boldsymbol{Q}_{\theta_{(i)}})\boldsymbol{\beta}_{(i)}$$

$$\exp(\boldsymbol{\zeta}_{(i)}) = \boldsymbol{RR}_{(i)} \qquad (7)$$

where $\boldsymbol{\zeta}_{(i)}$ indicates the log of RR calculated using i-th sample of $\boldsymbol{\beta}_{(i)}$ and $\theta_{(i)}$ and $\boldsymbol{RR}_{(i)}$ is the i-th sample of the true RR. Then, a point and an interval estimates for the RR can be derived from the empirical distribution of the RR in the same way as previously. Often, interest is on the cold- or the heat- related RR. We define the cold- and heat- related RR as comparing the 1st percentile of temperature distribution and the MMT and comparing the 99th percentile and the MMT, respectively. Hereafter, we call these RRs as a cold- and heat- related RR.

Simulation

In this section, simulations were carried out to assess the performance of different methods in

estimating the MMT and the cold- and heat- related RR. The first method (Argmin1) is to use the solution of the $\text{argmin}({}_x \boldsymbol{Q}_x \widehat{\boldsymbol{\beta}})$ without any constraint as a point estimate for the MMT and to use the MMT estimate for calculating the RR. The second method (Argmin2) is the same as the first one except that the solution of the $\text{argmin}({}_x \boldsymbol{Q}_x \widehat{\boldsymbol{\beta}})$ is constrained within the 1st - 99th percentiles. The third method (Empirical1) is to use the empirical mean and the 2.5th – 97.5th percentiles as a point and an interval estimates for the MMT and to calculate the RR accouting for the MMT uncertainty without any prior knowledge combined. The fourth method (Empirical2) is the same as the third one except that the empirical distribution of the MMT is derived with some prior knowledge combined.

Data-generating and modeling

To generate the data, four different scenarios were considered for the temperature-mortality association: U-shape (Scenario 1), reverse J-shape (Scenario 2), rotated S-shape (Scenario 3) and sector shape (Scenario 4). Figure S1 displays the shape of the true RR curve and the true MMT. To obtain the model parameters for each scenario, we used part of the US data analyzed in the following section. For scenarios 1, 2, and 4, we fit eqation (1) for the data of New York with the temperature metric as 0-2 day moving average, 0-1 day moving average, and the current day value, respectively. For scenario 3, the same model was fit with 0-3 day moving average for the data of Ockland. For all scenarios, we controlled for the day of week using indicator variables and for the long-term and seasonal pattern using natural cubic spline with 8 degree of freedom for each year. For $s(\cdot)$, as we use moving average as temperature metric, we used one-dimensional basis (natural cubic B-spline with the knots placed at the 10th, 75th, and 90th percentiles). Once the parameters are estimated, the mortality data were generated from the fitted model using the covariates in the data for each scenario. Regarding the distribution for mortality, we considered Quasi-Poisson distribution with the overdispersion parameter set to be equal to the model fit.

For each scenario, we generated 1,000 replicates of the dataset. For each dataset, we fitted equation (1) and obtained the coefficient estimates. Because we use moving avearage as temperature metric, which is a special case of distributed lag nonlineear model, the coefficients in equation (1) can be considered as the reduced coefficients ($\boldsymbol{\beta}$) in equation (3). Using the coefficient estimates, we estimated the MMT and the cold- and heat- related RRs by four methods. For the Empirical2, we used Uniform prior for the MMT with the following support; the 70th - 95th percentiles of the temperature distribution for scenarios 1 and 3, the 40th - 65th percentiles for scenario 2, and the 1st - 10th percentiles for scenario 4. These prior ranges are indicated in Figure S1 and these priors were set assuming that we have some

knowledge about the true MMT. To compare the methods, we calculated mean bias (Bias) and root mean squared error (RMSE) for the point estimate and coverage probability (%CP) and mean length (Length) of the interval estimate for the MMT and the two kinds of RRs using the 1000 replicates.

Results

Table 1 reports the results in estimating the MMT by the four methods. Because Argmin1 and Argmin2 do not provide an interval estimate, the %CP and Length are not reported. In scenario 1, all four methods show small negative Bias and small RMSE (1.073 at maximum). In scenario 2, Argmin1 and Empirical1 show small positive Bias and relatively large RMSE (8.896 and 6.979, respectively) while Argmin2 and Empirical2 show small negative Bias and smaller RMSE (2.243 and 1.542, respectively). In scenario 3, Argmin1 and Empirical1 show large positive Bias and large RMSE (28.011 and 21.092, respectively) while Argmin2 and Empirical2 show small positive Bias and small RMSE (3.342 and 1.126, respectively). In scenario 4, Argmin1 and Empirical1 show relatively large positive Bias and large RMSE (8.686 and 6.259, respectively) while Argmin2 and Empirical2 show small Bias and small RMSE (3.592 and 1.504, respectively). The %CP is near or greater than 95% for both Empirical1 and Empirical2. However, the Length is much smaller for Empirical2 than for Empirical 1 in all scenarios. These results suggest that Argmin2 is a reasonable point estimator, though some bias may occur depending on the association shape, and Empirical1 provides an interval estimate with near 95% coverage while the length can be too large in some scenarios. If prior knowledge is available, the bias can be reduced with Empirical2 compared with Argmin2 and the length of the interval estimate becomes shorter with Empirical2 compared with Empirical1 still achieving the similar level (near 95%) of coverage probability.

Table 1. Mean Bias (Bias) and root mean squared error (RMSE) for the point estimate and the coverage probability (%CP) and mean length (Length) of the interval estimate in estimating the minimum mortality temperature (MMT) by four different methods (Argmin1, Argmin2, Empirical1, Empirical2) for each of the 4 scenarios; U-shape (Scenario 1), reverse J-shape (Scenario 2), rotated S-shape (Scenario 3) and sector shape (Scenario 4).

		Methods			
		Argmin1	**Argmin2**	**Empirical1**	**Empirical2**
Scenario 1 (True MMT=23.889)	**Bias**	-0.178	-0.183	-0.203	-0.203
	RMSE	1.046	1.073	0.859	0.836
	%CP			97.2%	96.4%
	Length			3.385	3.210
Scenario 2 (True MMT=11.274)	**Bias**	2.680	-0.245	4.197	-1.183
	RMSE	8.896	2.243	6.979	1.542
	%CP			96.4%	98.0%
	Length			10.415	5.631
Scenario 3 (True MMT=29.167)	**Bias**	16.486	0.512	16.683	0.776
	RMSE	28.011	3.342	21.092	1.126
	%CP			96.5%	96.4%
	Length			9.758	3.257
Scenario 4 (True MMT=-3.333)	**Bias**	4.359	0.099	4.340	-1.069
	RMSE	8.686	3.592	6.259	1.504
	%CP			95.4%	93.8%
	Length			7.816	6.097

Table 2. Mean Bias (Bias) and root mean squared error (RMSE) for the point estimate and the coverage probability (%CP) of the interval estimate in estimating the cold- and heat- related relative risk (RR) by four differennt methods (Argmin1, Argmin2, Empirical1, Empirical2) for each of the 4 scenarios; U-shape (Scenario 1), reverse J-shape (Scenario 2), rotated S-shape (Scenario 3) and sector shape (Scenario 4).

			Methods			
			Argmin1	**Argmin2**	**Empirical1**	**Empirical2**
Cold-related RR	**Scenario 1** (True RR=1.094)	**Bias**	-0.0002	0.0001	-0.0009	-0.0008
		RMSE	0.0093	0.0090	0.0094	0.0092
		%CP	94.2%	95.6%	94.9%	96.7%
	Scenario 2 (True RR=1.023)	**Bias**	-0.001	-0.0004	-0.004	-0.006
		RMSE	0.0069	0.0067	0.0073	0.0069
		%CP	95.4%	94.0%	95.7%	96.2%
	Scenario 3 (True RR=1.070)	**Bias**	-0.030	-0.005	-0.046	-0.022
		RMSE	0.0548	0.0287	0.0548	0.0250
		%CP	94.6%	93.5%	86.8%	99.7%
	Scenario 4 (True RR=1.000)	**Bias**	-0.008	-0.002	-0.013	-0.005
		RMSE	0.0126	0.0036	0.0155	0.0055
		%CP	95.8%	58.4%	70.3%	93.2%
Heat-related RR	**Scenario 1** (True RR=1.079)	**Bias**	-0.0005	-0.0005	-0.0006	-0.001
		RMSE	0.0062	0.0064	0.0062	0.0062
		%CP	96.0%	95.4%	95.5%	93.5%
	Scenario 2 (True RR=1.118)	**Bias**	-0.002	0.0001	-0.004	0.0005
		RMSE	0.0100	0.0084	0.0114	0.0050

		%CP	95.6%	95.0%	94.3%	99.9%
	Scenario 3 (True RR=1.015)	**Bias**	-0.027	-0.003	-0.044	-0.019
		RMSE	0.0548	0.0144	0.0632	0.0192
		%CP	95.6%	85.8%	89.2%	98.1%
	Scenario 4 (True RR=1.185)	**Bias**	-0.010	-0.0016	-0.016	-0.006
		RMSE	0.0205	0.0111	0.0232	0.0085
		%CP	96.2%	95.1%	90.0%	99.4%

Table 2 reports the results in estimating the cold- and heat-related RR by four different methods. For cold-related RR, both Bias and RMSE were small and the %CP was near 95% in scenario 1 and 2. In scenario 3, RMSE was relatively large and the %CP was low as 86.8% with Empirical1 but near 95% with other methods. In scenario 4, both Bias and RMSE was small but the %CP was low as 58.4% and 70.3% with Argmin2 and Empirical2. For heat-related RR, both Bias and RMSE were small and the %CP was near 95% in scenario 1 and 2. In scenario 3, RMSE was relatively large and the %CP was low as 85.8% and 89.2% with Argmin2 and Empirical1 but near 95% with Argmin1 and Empirical2. In scenario 4, RMSE was somewhat large and the %CP was low as 90% with Empirical1 but near 95% with other methods. In summary, in estimating the RR, Argmin1 seems to result in an appropriate coverage but may lead to large RMSE while Argmin2 may result in low coverage but small RMSE in various scenarios. Empirical1 can result in low coverage and large RMSE. However, Empirical2 seems to work robustly in various scenarios in both aspects of RMSE and coverage.

Application

In this section, we applied three methods (Argmin2, Empirical1, and Empirical2) to estimate the MMT and the cold- and heat-related RR in the temperature-mortality association for 135 cities in the US for the period of January 1, 1985 to December 31, 2006. We exclude Argmin1 because it only provides a point estimate and tends to lead to large RMSE. Daily mortality counts were obtained from the National Center for Health Statistics and non-external cause mortality counts were used (ICD-9: 0–799; ICD-10: A00–R99). Daily mean temperatures (24-hr mean) were obtained from the National Climate Data Center of the National Oceanic and Atmospheric Administration. These data were analyzed in a previous study (Gasparrini et al. 2015) and the city-specific descriptive statistics are reported in Table S1.

For each city, we fit equation (1) and (2) with the following modeling choices. For cross-basis, the quadratic B-spline method was used to investigate the nonlinear effect of temperature with the knots placed at the 10th, 75th, and 90th percentiles of the city-specific temperature distributions. For the lagged dependency, we used the natural cubic B-spline with an intercept and three internal knots (equally spaced values in the log scale) with 21 lag days. We controlled for the day of week using indicator variables and for the seasonal and long-term trends via a natural cubic B-spline of time with 8 degrees of freedom per year. These choices were based on the results in a previous study (Gasparrini et al. 2015). Because the city-specific modeling accompanies relatively large estimation error, we combined evidence across all cities using multivariate meta-regression (Gasparrini and Armstrong 2011) with city-specific average temperature and temperate range as meta-predictors and obtained the

best linear unbiased predictor (BLUP) $\widehat{\boldsymbol{\beta}}$ and the corresponding standard error for each city. Then, using the BLUP**,** we applied the three methods for estimating the MMT and the cold- and heat- related RR. For Empirical2, we assumed a uniform prior distribution with the support as 1st - 99th percentiles of city-specific temperature.

Figure 1 displays the point estimates for the MMT obtained by Argmin2, Empirical1, and Empirical2 and the interval estimates by the two empirical methods. The cities are ordered based on the length of the interval estimate calculated by Empirical1. Based on the MMT uncertainty patterns, it seems reasonable that we divide 135 cities into four categories; category 1 (from New York to Knoxville), category 2 (from Oakland to San Jose), category 3 (from Austin to Milwaukee), and category 4 (from Western Palm Beach-Boca Raton to Seattle). Such categorization also consists with the patterns of the RR curve shape presented in Figure S2 (the cities are in the same order as in Figure 1).

In category 1, cities show clear U-shape RR curve and small uncertainty in the MMT. Accordingly, the point estimates were close among the three methods and the interval estimates were similar between the two empirical methods. In category 2, cities show U-shape RR curve with a short right arm and a short bottom and small uncertainty in the MMT. Argmin2 tends to suggest a smaller value for the MMT estimate, Empirical1 suggests larger point estimate, and Empirical2 compromises between the Argmin2 and Empirical1 estimates. In category 3, the RR curve is mostly reverse J-shape or U-shape with a wide bottom and the MMT uncertainty become large. For the reverse J-shape curve, Empirical1 suggests the largest value for the MMT while Argmin2 and Empirical2 suggests somewhat smaller values. In category 4, cities show rotated S-shape or widely opened U-shape with large uncertainty on both arms. Empirical1 suggests extremely large uncertainty in the MMT covering almost the whole range of the temperature distribution. However, the uncertainty reduced largely by Empirical2 with the prior restriction, within the 1st – 99th percentiles.

Figure S3 shows the scatter plots for the point estimates of the MMT obtained by Argmin2 vs by Empirical1 and by Argmin2 vs by Empirical2. Between Argmin2 and Empirical1, large inconsistency was found particularly for the cities in category 4. However, the estimates were in general consistent between Argmin2 and Empirical2 (the right of Figure S3) though there are a few cities still showing different estimates between the two methods.

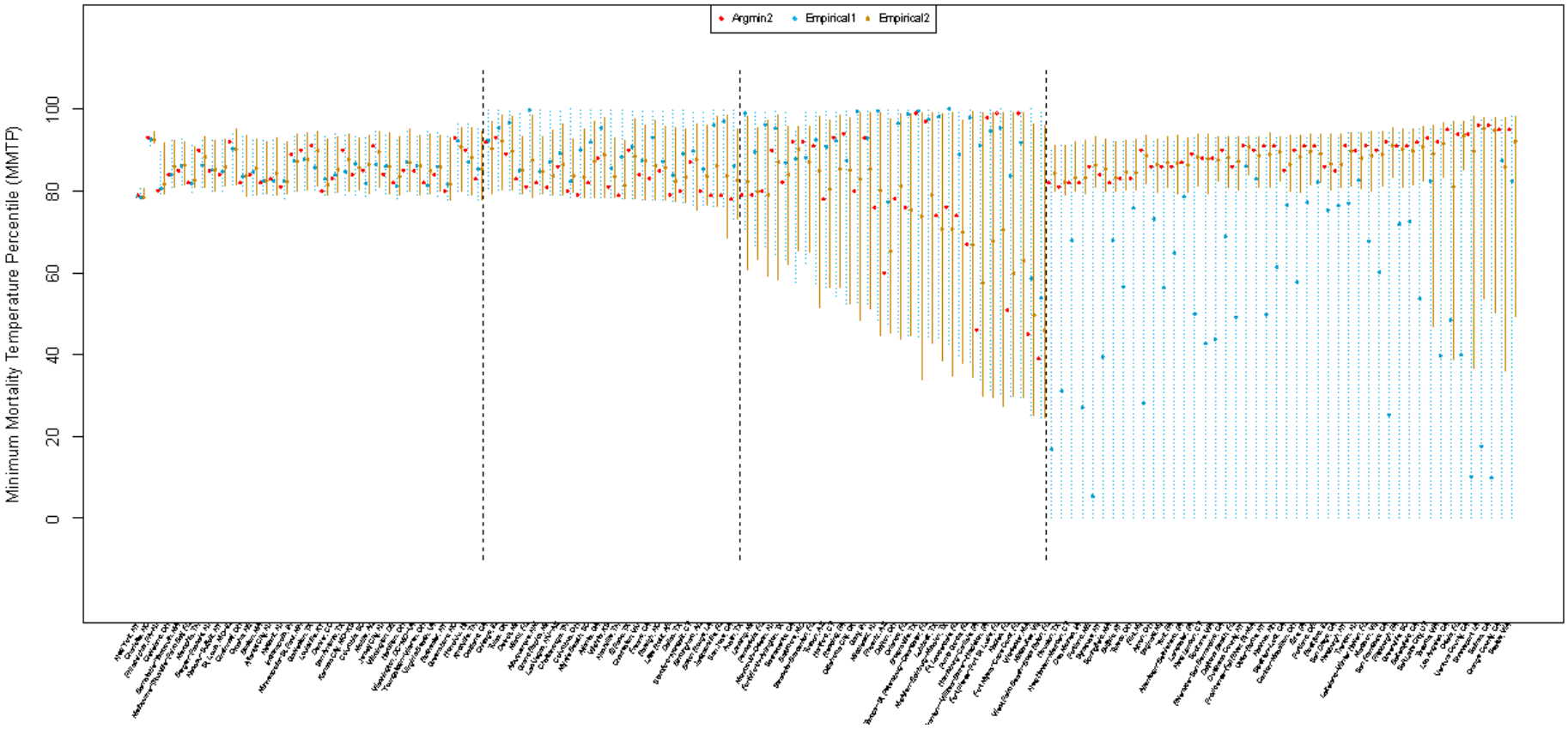

Figure 1. Estimated minimum mortality temperature (MMT) percentile for 135 cities in the US by three different methods; Argmin2 (red), Empirical1 (blue), Empirical2 (orange). Points indicate the point estimate and vertical solid/dashed bars indicate 95% empirical interval estimates. Cities are ordered according to the MMT uncertainty (the length of the interval estimates obtained by Empirical1). The cities are divided into 4 categories (indicated by black dashed vertical lines) with respect to the MMT uncertainty and temperature-mortality association types (refer to Figure S2).

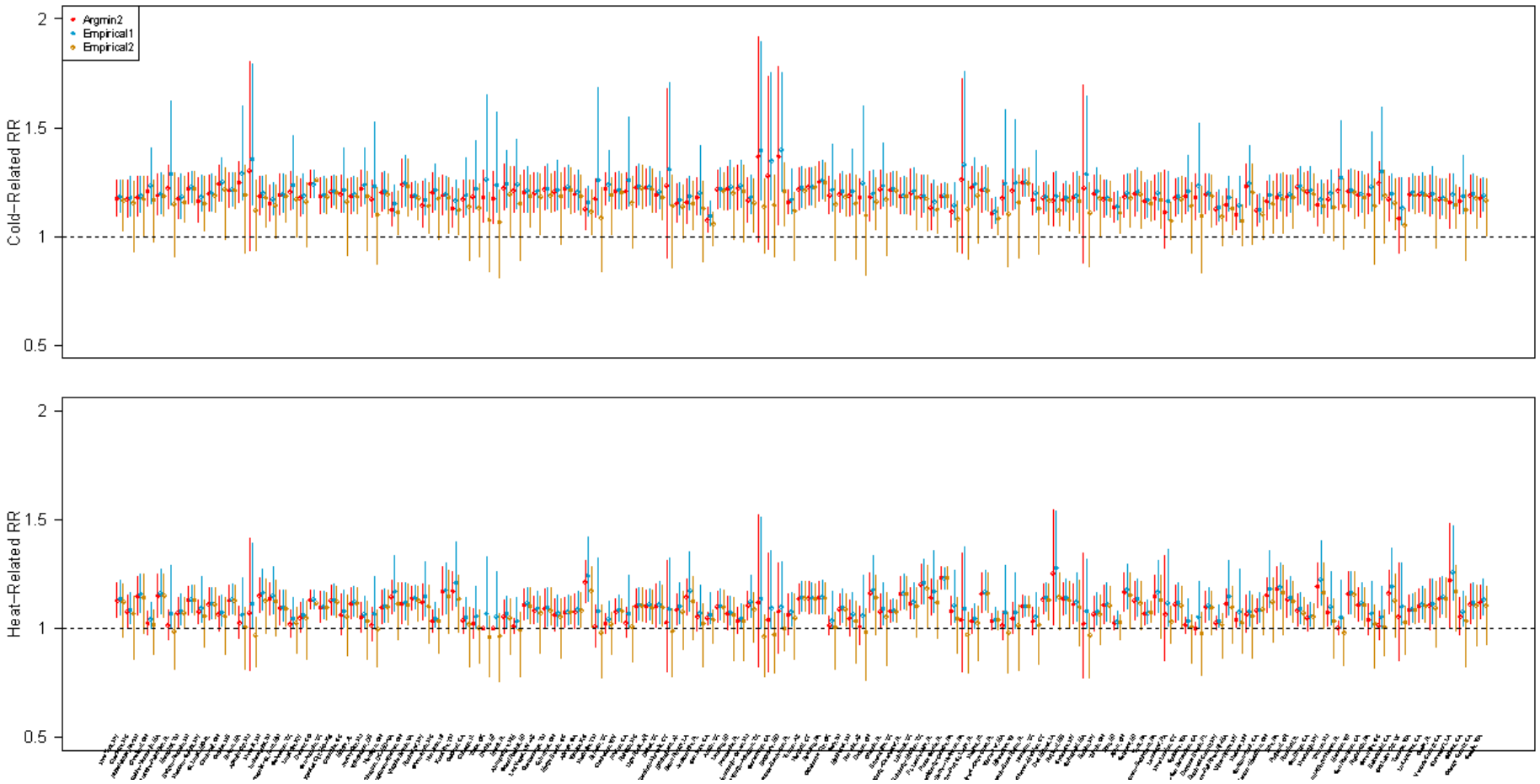

Figure 2. Estimated cold- and heat- related relative risk (RR) for 135 cities in the US by three different methods; Argmin2 (red), Empirical1 (blue), Empirical2 (orange). Points indicate the point estimate and vertical solid/dashed bars indicate 95% empirical interval estimates. Cities are ordered according to the MMT uncertainty (the length of the interval estimates obtained by Empirical1) as in Figure 1.

Figure 2 shows the point and interval estimates for the cold-related and heat-related RR calculated by the three methods. Differently from the MMT estimates, the point estimates were mostly consistent among the three methods. Such result is expected from the simulation study because different methods did not make much difference with respect to the point estimation. However, the intervals estimates calculated by Argmin2 and Empirical1 tend to stretch to the right while those computed by Empirical 2 tend to do to the left. Such result is consistent with simulation results in that the coverage for the RR were low with Argmin2 and Empirical1 as those intervals tend to exclude the true RR because of the right-skewness of the empirical distribution. Figure S4 shows the scatter plot for the RR estimates obtained by the three methods. In general, the point estimates were consistent between Argmin2 and Empirical1 while there are several discrepant points between Argmin2 and Empirical2.

Conclusion

In this research, we assessed the statistical property of the previously proposed statistical approach (Tobías et al. 2016) to estimate the MMT in various types of association via a simulation study. The method of using the solution of argmin function with some ad hoc restriction (i.e., within the 1st – 99th percentiles of the observed temperature distribution) (Argmin2 in this paper) turns out to be a reasonable point estimator for the MMT, though Bias or RMSE may be large in some scenarios. Also, the simulation-based method to calculate the confidence interval (Empirical2 in this paper) performs properly achieving near 95% coverage, though the length can be extremely large depending on the scenarios.

To improve upon the previous method, we suggested an alternative approach, which can be applied if some prior knowledge is available on the MMT. We suggested to combine the prior knowledge with the procedure of deriving the empirical distribution of the MMT and to use the empirical mean and percentiles (2.5^{th} to 97.5^{th} percentiles of the empirical distribution) as a point and an interval estimates for the MMT (named as Empirical2 in this paper). Simulation study showed that our proposed method works properly and robustly reducing the Bias and RMSE in point estimation and achieving near 95% coverage while shortening the length in interval estimation in all scenarios.

In addition, we examined how the uncertainty in the MMT would affect the RR estimation when the MMT is used as a reference temperature in calculating an RR. We derived the empirical distribution of the MMT-referenced RR through a sampling procedure similar to deriving the MMT distribution. Then, the empirical mean and percentiles are alternative point and interval estimates for the RR with the uncertainty in the MMT accounted for. Compared with the current approach (using only a single

point estimate for the MMT as a reference value in quantifying the RR and calculating the confidence interval based on the normal approximation), the simulation-based RR estimates, when prior knowledge is combined, were less biased with reduced RMSE and achieves appropriate level of coverage probability in all scenarios.

Although the method of combining prior knowledge with the inference showed better performance in estimating the MMT and the corresponding RR, one should be cautious about this methodology. If prior distribution is incorrectly specified, the whole inference can be seriously biased and invalid. To avoid such prior misspecification, one may use the prior information minimally setting the potential range as the 1st – 99th percentiles, which barely avoid the boundary values of minimum and maximum. In section 4, when investigating the MMT in the US, adding such minimal prior information reduced the uncertainty in the MMT by large amount particularly when the estimated association curves are unstable in terms of suggesting an MMT (e.g., category 4). In the previous study (Tobías et al. 2016), they applied an ad hoc restriction in obtaining a point estimate for the MMT, which is conceptually equivalent to incorporating some prior knowledge into the inference for the MMT. Alternatively, numerous researches have reported the varying types of the temperature-mortality association and suggested potential range of the MMT for different locations (Curriero et al. 2002; Gasparrini et al. 2015; Guo et al. 2014) and those studies or some other region-specific epidemiological research results could be referred to guide the prior specification.

Applying the methods to the US data, we found four categories in terms of the MMT uncertainty. For categories 1 and 2, the estimated temperature-mortality association is mostly U-shape with short or long arms on either side and with a short bottom. In these categories, the MMT uncertainty is small and estimated between the 75th through the 95th percentiles of the observed temperature distribution. For category 3, the association is mostly reverse J-shape with relatively long bottom on the right side and the MMT uncertainty was relatively large. The large uncertainty is induced by the long bottom of the association curve and it may be more appropriate to describe the MMT as a range, not a single point. The previous study (Tobías et al. 2016) also suggested to introduce this new concept of the minimum mortality temperature range. In category 4, the association is the rotated S-shape with the left arm curving down at the lowest temperature, for which the uncertainty is very large. Such uncertainty on the left arm is induced by the sparse data and causes the MMT uncertainty to unnecessarily cover the whole range of the temperature. In this case, it is suggested that adding restrictions on the range would lead to more reasonable inference on the MMT.

In summary, the Monte Carlo simulation-based approach to estimate the MMT either as a point or as an interval seems to be a reasonable approach, particularly when some prior restrictions are added to

reduce the uncertainty. The MMT uncertainty can also affect the estimation for the MMT-referenced RR and ignoring the MMT uncertainty in the RR estimation may lead to invalid results with respect to bias in point estimation and the nominal coverage in interval estimation.

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Supplementary Materials

The Supplementary Materials file can be downloaded from the URL (https://bmcmedresmethodol.biomedcentral.com/articles/10.1186/s12874-017-0412-7)

OR the file also is available on request to the first author (jleehwan33@gmail.com).

Research 6

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Title: An Investigation on Attributes of Ambient Temperature and Diurnal Temperature Range on Mortality in Five East-Asian Countries

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Abstract

Interest in the health effects of extremely low/high ambient temperature and the diurnal temperature range (DTR) on mortality as representative indices of temperature variability is growing. Although numerous studies have reported on these indices independently, few studies have provided the attributes of ambient temperature and DTR related to mortality, concurrently. In this study, we aimed to investigate and compare the mortality risk attributable to ambient temperature and DTR. The study included data of 63 cities in five East-Asian countries/regions during various periods between 1972 and 2013. The attributable risk of non-accidental death to ambient temperature was 9.36% (95% confidence interval [CI]: 8.98–9.69%) and to DTR was 0.59% (95% CI: 0.53–0.65%). The attributable cardiovascular mortality risks to ambient temperature (15.63%) and DTR (0.75%) are higher than the risks to non-accidental/respiratory-related mortality. We verified that ambient temperature plays a larger role in temperature-associated mortality, and cardiovascular mortality is susceptible to ambient temperature and DTR.

Introduction

In general, ambient temperature and sudden temperature change have been reported as the prominent causes of weather-related mortality (Gasparrini et al. 2015; Y. Guo et al. 2014; Vutcovici et al. 2014; Yang et al. 2013). Moreover, the Intergovernmental Panel on Climate Change (IPCC) recently reported greenhouse gases will evidently increase the earth's ambient temperature and predicted climate change would cause frequent weather pattern instability (e.g., rapid increase/decrease of temperature)(Solomon 2007). As a result, the importance of assessing the effect of ambient temperature and temperature change on health is heightened.

Some researchers have found that the exposure–response relationship of temperature presents a U- or V-shaped association (Gasparrini et al. 2015; Y. Guo et al. 2014), and previous studies have found epidemiological evidence that the risk of mortality increases when the temperature is extremely high or low (Basu and Samet 2002; Ye et al. 2012). In addition, many studies also reported the diurnal temperature range (DTR) (e.g., intra-day temperature change is an index representing sudden temperature change within a day, which is calculated by subtracting the minimum temperature from the maximum temperature) as one of the environmental risk factors of mortality (i.e., non-accidental, cardiovascular-related, and respiratory-related deaths) or morbidity (Curriero et al. 2002; Kan et al. 2007; YH Lim et al. 2012; Tam et al. 2009) in Asia (Cao et al. 2008; Luo et al. 2013) and North America(Lim et al. 2014; Vutcovici et al. 2014).

Although concerns about climate change have been numerous, including the increases in DTR, many epidemiological studies have separately reported on the health impact of the low/high temperature and DTR (Chung et al. 2015; Gasparrini et al. 2015; Kim et al. 2006; Vicedo-Cabrera et al. 2016). Even if these three measures (low temperature, high temperature, and DTR) are widely used indices of temperature variability, the complex correlational effects of temperature and its variability on mortality are still undetermined (Vicedo-Cabrera et al. 2016). Since people are exposed to ambient temperature and DTR simultaneously, studies also need to consider these effects concurrently.

In this study, we aimed to comprehensively investigate and compare the attributable risks of temperature and DTR on three specific causes of mortality, non-accidental, cardiovascular-related, and respiratory-related, among Asian countries/regions. We considered attributable risk fractions of temperature indices using an advanced statistical method, the distributed lag non-linear model (DLNM)(Gasparrini et al. 2010), and applied it to 63 cities in five East Asian countries/regions (Japan, South Korea [hereafter Korea], Chinese Taiwan, Vietnam, and the Philippines), which are exposed to different weather conditions.

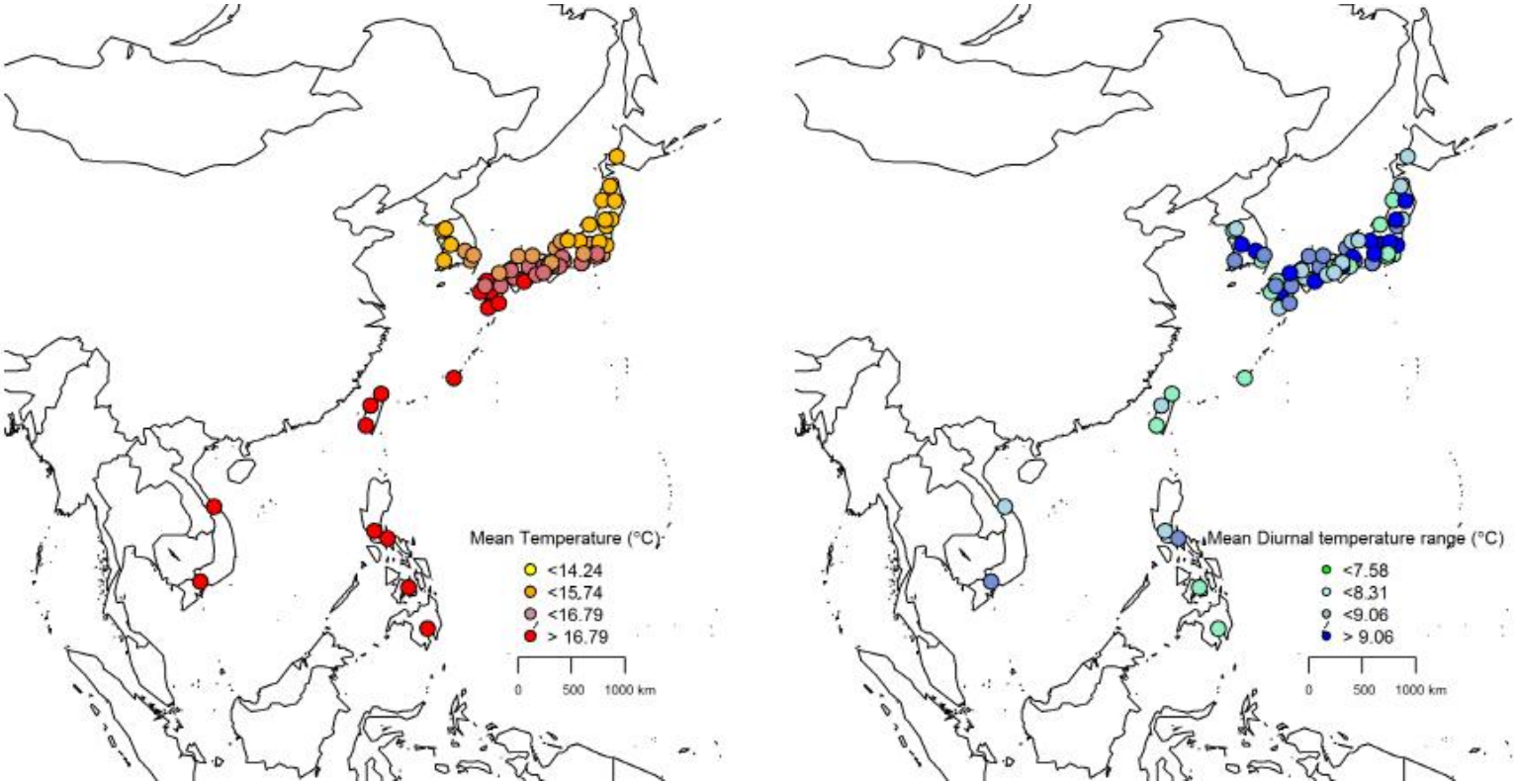

Figure 1. Geographic distributions of mean temperature and diurnal temperature range (DTR) for 63 locations in six East Asian countries/regions included in analysis. The darker colors means the higher mean temperature and diurnal temperature range. Packages "maps" and "mapdata" in R software (3.3.1 version, https://www.r-project.org/) were used.

Results

Fig. 1 shows the geographical distributions of the mean temperature and DTR for the 63 locations that were included in this study. We found trends for an association of low-latitude and high-latitude locations with a higher mean temperature and a higher mean DTR, respectively.

Table 1. Descriptive statistics by country/region; SD: Standard deviation

Country /Region	Number of Locations	Study-Periods	Temperature (°C ,SD)	Diurnal temperature range (°C ,SD)	Non-accidental Death	Cardiovascular related-Death	Respiratory related- Death
Japan	47	1972-2012	15.08 (8.61)	8.41 (3.30)	33,511,400	12,605,176	4,413,875
South Korea	7	1992-2010	13.72 (9.34)	8.19 (3.28)	1,511,961	435,457	91,135
Chinese Taiwan	3	1994-2007	24.03 (4.72)	7.10 (2.44)	688,394	164,911	63,180
Vietnam	2	2009-2013*	26.91 (3.48)	8.26 (2.61)	102,400	24,433	8,970
The Philippines	4	2003-2010	28.06 (1.43)	7.25 (2.10)	275,189	31,190	31,190
Total	63	1972-2013	15.34 (8.76)	8.36 (3.28)	36,089,344	13,317,378	4,608,350

*Two cities of Vietnam had different study periods: Ho chi minh city has 2010-2013 and Hue city has 2009-2013 each.

Table 1 shows the descriptive statistics for each country. There were 36,089,344 non-accidental deaths, 13,317,378 cardiovascular-related deaths, and 4,608,350 respiratory-related deaths across the five countries/regions. As we expected, each of the five East Asian countries/regions experienced a broad temperature range, such that the country-specific mean varied widely, from 13.72 °C in Korea to 28.06 °C in the Philippines. These temperatures represent the diverse climate conditions of the following regions: areas of northeast Asia (Japan, Korea), southeast subtropics (Chinese Taiwan), and southeast tropics (Vietnam, the Philippines). The average DTR was slightly higher in Northeast Asian countries/regions than in South Asian countries/regions, ranging from 7.10 °C in Chinese Taiwan to 8.36 °C in Japan.

Fig. 2 shows the overall cumulative exposure–response curves using the best linear unbiased predictions for three of the locations (Tokyo, Taipei, and Manila) that represent each climate condition. For non-accidental mortality, the minimum mortality percentile ranges were at approximately the 80th and 90th percentiles for Tokyo and Manila, whereas Taipei was at approximately the 57th percentile. In Tokyo, the relative risk (RR) increased gradually for cold and hot temperatures (lower and higher

than the minimum mortality temperature), and in Taipei, the RR increased more sharply for cold temperatures. However, in Manila, the RR of hot temperatures significantly increased. In Tokyo and Taipei, the RR increased more rapidly for extreme cold of cardiovascular-related mortality than of non-accidental mortality. In addition, the respiratory-related mortality in subtropical and tropical locations had sharply increased RRs for extreme cold and hot temperatures than for other cause-specific mortality. The corresponding temperature–non-accidental mortality curves and minimum mortality percentiles of the 63 locations are reported in the supplementary materials (Supplementary Fig. S1 and Supplementary Table S5, respectively). This tendency similarly appeared for overall regions.

The main results in Table 2 and Fig. 3 show the estimated attributable fraction by cause-specific mortality; calculations were performed separately for all-season temperature, two extreme temperatures, and DTR by country. Extreme cold and hot temperatures were defined as <2.5th percentile and >97.5th percentile of temperature distribution, respectively. Overall, the total fraction of non-accidental death by temperature was 9.36% (95% empirical confidence interval [eCI]: 8.98–9.69) and varied from 6.37% (95% eCI: 3.60–8.94) in the Philippines to 11.38% (95% eCI: 3.22–18.95) in Vietnam. Moreover, the total attributable fraction was the highest for cardiovascular-related death (15.63%; 95% eCI: 15.04–16.11) and the lowest for respiratory-related death (8.63%; 95% eCI: 6.93–9.39). Specifically, in non-accidental mortality, a relatively high fraction occurred with extreme cold (0.80%; 95% eCI: 0.77–0.83), while heat was responsible for a relatively small fraction (0.16%; 95% eCI: 0.14–0.18).

DTR had a significant but relatively small effect of 0.59% on non-accidental mortality (95% eCI: 0.53–0.65). Similar results were shown for cardiovascular-related and respiratory-related mortality. The total burden of cardiovascular-related death was 15.63% (95% eCI: 15.04–16.11), and 0.75% (95% eCI: 0.65–0.84) for temperature and DTR, respectively. In the same order, respiratory-related death showed a burden of 8.2% (95% eCI: 7.27–8.99) and 0.42% (95% eCI: 0.31–0.52) for temperature and DTR, respectively. Lag-response plots for DTR are described in Supplementary Fig. 2, and location-specific attributable fractions with three specific mortality are reported in Supplementary Table S2–S4.

Although the Cochran Q test provides evidence for heterogeneity in all the models, a substantial amount is explained by three predictors (average temperature, temperature range, and country indicators), as indicated by the drop in the I^2. The meta-regression of the temperature-response relationship had heterogeneity values (I^2) of 40.8% for non-accidental mortality, 26.8% for cardiovascular-related mortality, and 13.1% for respiratory-related mortality. The meta-regression of the DTR and response relation all had I^2 values of 1.0%. Although we used all three predictors to

modify the exposure–response association, heterogeneities based on single predictors or only the intercept were not significantly different for each model (see Supplementary Table S6).

Table 2. Attributable fractions of cause-specific mortality by country/region Empirical confidence interval), DTR: Diurnal temperature range.

		Attributable Mortality Fractions (95% eCI.)											
		Non-accidental				Cardiovascular-related				Respiratory-related			
Country /Region	**Periods**	**Temperature**	**Extreme cold**	**Extreme hot**	**DTR**	**Temperature**	**Extreme cold**	**Extreme hot**	**DTR**	**Temperature**	**Extreme cold**	**Extreme hot**	**DTR**
Japan	1972-2009	9.38 (9.01, 9.72)	0.82 (0.79, 0.85)	0.15 (0.14, 0.17)	0.58 (0.53, 0.63)	15.8 (15.29, 16.30)	1.15 (1.11, 1.18)	0.26 (0.24, 0.29)	0.73 (0.94, 0.82)	8.2 (7.27, 8.99)	0.9 (0.81, 0.96)	0.23 (0.21, 0.25)	0.43 (0.33, 0.52)
Korea	1992-2010	10.33 (7.86, 12.38)	0.47 (0.29, 0.62)	0.14 (0.06, 0.21)	0.8 (0.33, 1.26)	15.62 (11.70, 18.93)	0.79 (0.53, 1.00)	0.19 (0.05, 0.32)	0.9 (0.02, 1.73)	14.88 (5.77, 21.36)	0.39 (-0.34, 0.82)	0.5 (0.30, 0.66)	0.16 (-0.57, 0.86)
Chinese Taiwan	1994-2009	6.91 (5.41, 8.29)	0.99 (0.75, 1.18)	0.28 (0.16, 0.36)	0.05 (-0.18, 1.12)	11.64 (6.71, 16.05)	1.42 (1.11, 1.64)	0.26 (-0.01, 0.46)	1.21 (-0.15, 2.55)	10.11 (1.69, 16.59)	1.38 (0.85, 1.74)	0.85 (0.60, 1.05)	0 (-1.68, 1.79)
Vietnam	2009-2013	11.38 (3.22, 18.95)	0.13 (-0.37, 0.50)	0.9 (0.44, 1.27)	-1.02 (-5.70, 3.44)	21.38 (8.28, 31.49)	0.39 (-0.39, 0.79)	1.28 (0.50, 1.86)	0.1 (-4.27, 4.02)	30.44 (-456.47, 55.51)	-0.12 (-235.31, 1.20)	0.11 (-1.88, 0.23)	1.62 (-11.32, 12.78)
The Philippines	2006-2010	6.37 (3.60, 8.94)	0.36 (0.02, 0.59)	0.68 (0.52, 0.80)	1.28 (-0.10, 2.48)	2.86 (-4.88, 8.04)	0.01 (-0.71, 0.39)	0.31 (-0.01, 0.59)	0.84 (-1.12, 2.86)	15.16 (4.36, 23.17)	0.67 (-0.08, 1.41)	1.13 (0.74, 1.41)	1.23 (-1.49, 3.68)
Total		9.36 (8.98, 9.69)	0.8 (0.77, 0.83)	0.16 (0.14, 0.18)	0.59 (0.53, 0.65)	15.63 (15.04, 16.11)	1.13 (1.08, 1.16)	0.26 (0.24, 0.29)	0.75 (0.65, 0.84)	8.63 (6.93, 9.39)	0.89 (0.18, 0.93)	0.26 (0.23, 0.28)	0.42 (0.31, 0.52)

*Model for respiratory mortality in Vietnam could not be converged because of lack of `sample size.

* Extreme cold and extreme hot temperatures were defined as <2.5th and >97.5th percentiles of temperature distribution, respectively.

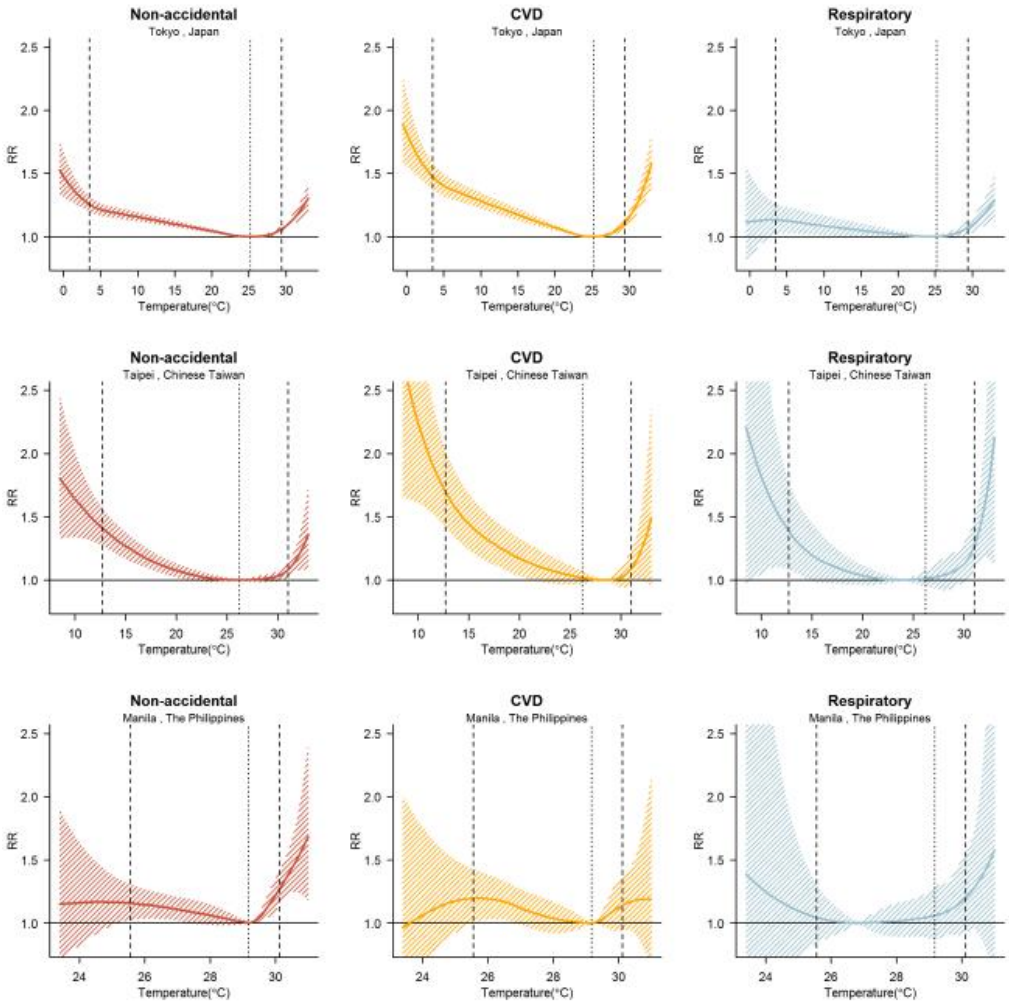

Figure 2. Cumulative exposure-response relations of total (non-accidental) morality in 63 east-Asia locations: Thick dashed lines are the 2.5th and 97.5th percentiles as cut offs. Light dashed lines are minimum mortality temperatures. Using city-specific distributed lag non-linear model.

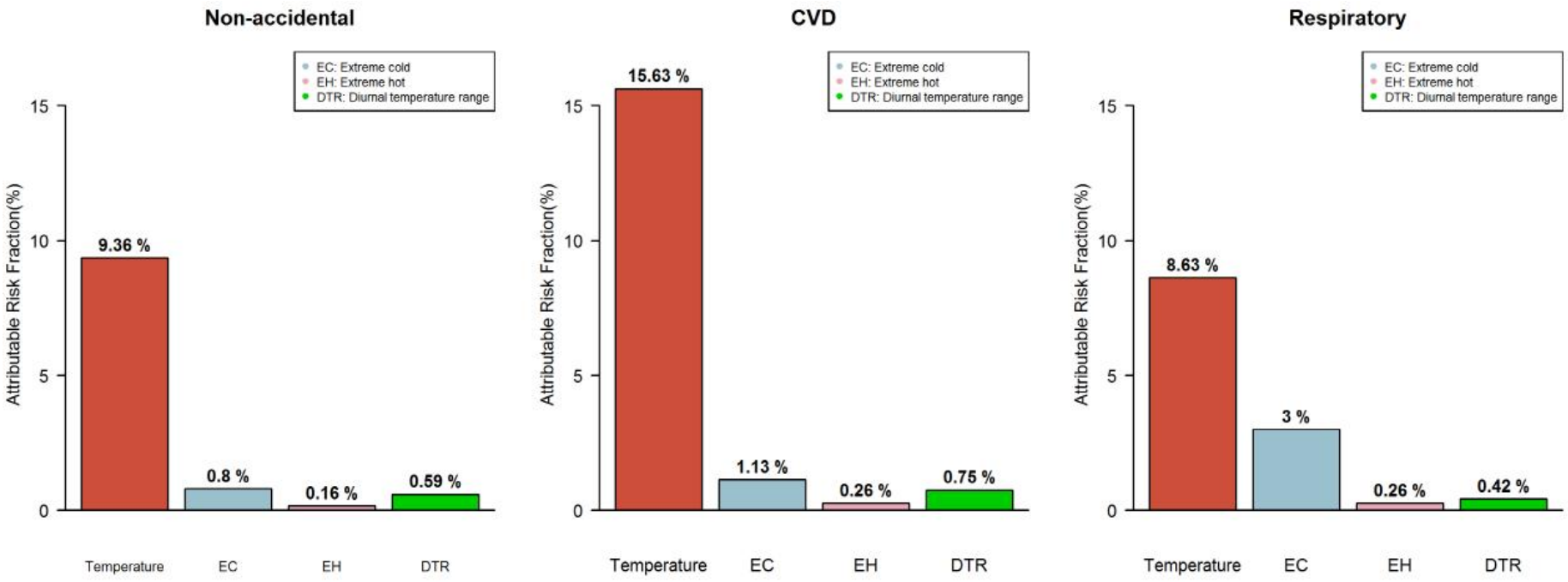

Figure 3. Attributable fractions of cause-specific mortality to overall temperature, extreme cold-hot temperature, and diurnal temperature range. Extreme cold and heat temperature were defined with < 2.5th and > 97.5th percentiles of temperature distribution.

Discussion

This study was conducted with the largest dataset to study the attributable fraction of temperature and temperature change on mortality risk. A total of 36,089,344 deaths from five East Asian countries/regions was also included. By analyzing five different countries/regions that have various climate conditions, demographics, and socioeconomic features, our study could provide evidence for an association between temperature variability and death in East Asia. Moreover, by analyzing cause-specific death, we can compare the extent to which the temperature variability indices are attributed to the different causes of death. Our findings show that ambient temperatures and DTR were significantly related to the attributable fractions of total, cardiovascular-related, and respiratory-related mortality in all five countries/regions over the duration of the study periods, and the contribution of the daily mean temperature was much greater than that of the DTR, with total temperature and DTR contributing 9.36% and 0.59% of the risk for non-accidental mortality, respectively. In addition, the influence of ambient temperature and DTR was the highest for cardiovascular-related mortality than for other types of mortality.

Our results are consistent with previous studies, although there were some limitations because the results possibly varied depending on study design, modeling framework, or risk measure. Gasparrini et al. reported the attributable all-cause deaths due to ambient temperature in East Asia as follows: 10.12% in Japan, 7.24% in Korea, and 4.75% in Chinese Taiwan (Gasparrini et al. 2015). Yang et al. described that 17.1% of cardiovascular disease mortality was attributable to ambient temperature in China.(Yang et al. 2015) Moreover, Yang et al. found that ambient temperature was responsible for 14.5% of stroke deaths for 16 large cities in China.(Yang et al. 2016) Focusing only on the extreme temperature, Gasparrini et al. showed the all-cause deaths attributed to extreme temperature in East Asia as follows: extreme cold, 0.77% and extreme heat, 0.18% in Japan, extreme cold, 0.35% and extreme heat, 0.21% in Korea, and extreme cold, 0.71% and extreme heat, 0.25% in Chinese Taiwan (Gasparrini et al. 2015). Moreover, similar and consistent tendency-attributable fractions were described, including Hajat and colleagues' work showing 0.37% to 1.45% of all-cause mortality fractions attributable to heat in three European cities (Hajat et al. 2006). In addition, the findings of previous studies in Asian countries/regions that focused on effects on mortality of DTR suggested a non-accidental mortality increase of 0.4–1.4%, cardiovascular-related mortality increase of 0.2–1.8%, and respiratory-related mortality increase of 0.7–1.5% per 1 °C incremental increase in DTR (Kan et al. 2007; YH Lim et al. 2012; Tam et al. 2009; Yang et al. 2013).

Whereas, in our study, after considering the daily mean temperature effect on mortality, ten units

of DTR (℃) was associated with about a 0.5–2% increase in excessive mortality risk. We supposed that previous studies overestimated the relative risk of DTR, because their model strategy did not consider any identifying association issues (both ambient temperature and DTR are derived using daily min and max temperature) arising when temperature indices were considered covariates or confounders during the modeling process. Actually, our results correspond with relatively new research describing excessive DTR mortality risks from -0.29% to 0.4% for six cities in Europe and the United States (Vicedo-Cabrera et al. 2016). However, although the researchers also applied a modeling framework that can adjust for identifying relationships using indicator variables, they could not assess the lag effects of DTR. In contrast, by using a two-step procedure, we ensured that the DTR effects considering lag structure were estimated after removing the overall effects of the daily temperature and seasons (Barnett et al. 2012).

Numerous assumptions and much of the evidence of underlying medical and biological mechanisms have been reported to define the increased risk of mortality associated with ambient temperature. Substantial evidence from the physiology literature has reported that people have difficulty with acclimatization and thermoregulation to extreme cold and hot temperature (Buguet 2007; Epstein and Moran 2006; Guo et al. 2016). Regarding cardiovascular mortality, a high temperature is related to the burden of cardiovascular-related motility. An increase in temperature causes blood vessels to dilate, increasing the cardiac output and risk of decompensating heart failure; it also raises platelet counts, blood viscosity, and cholesterol levels. These influences might cause or trigger death from coronary and cerebral thrombosis (Greenberg et al. 1983; Keatinge et al. 1984). Cold temperature is one of the factors that causes blood vessels to become narrow, increasing blood pressure and heart rate (Group 1997). Increases in blood pressure, fibrinogen concentrations, and blood viscosity, in instances of lower temperature, suggest that cold induces cardiovascular stress and may be prevalent in the entire population (Brennan et al. 1982; Neild et al. 1994). One of the underlying reasons for death due to cardiovascular disease appears to be thrombosis due to hemoconcentration in the cold (Neild et al. 1994).

Previous studies identified that the effect of DTR on death independently exist with ambient temperature (Kan et al. 2007; Yang et al. 2013), and a recent studies reported that the variability of temperature is significantly associated with increasing mortality in multi countries, even if daily mean (or maximum and minimum) temperature effect on mortality is also be considered (Guo et al. 2016). Our study consistently showed the independent DTR effect with temperature on mortality using daily mean temperature as a confounder variable. Much of the biological

evidences suggest that an abrupt change of temperature causes cardiovascular-related and respiratory-related death. Medical studies reported that weather changes might affect the human immune system (Bull 1980; Keatinge et al. 1984). In addition, Murayama and Luurila showed that the cardiovascular workload might be increased by sudden temperature changes (Luurila 1980; Murayma 1998) and rapid temperature change could also cause the onset of cardiovascular events by affecting workload, heart rate, and oxygen uptake(Liang et al. 2009). In respiratory diseases, Graudenz et al. (Graudenz et al. 2006) reported that rapid temperature changes may influence inflammatory nasal responses in rhinitis patients and were more strongly connected with elderly asthma patients.

However, the role of temperature in DTR-related mortality is still uncertain. A study in Korea suggested that the effects of DTR are increased during warmer seasons,(Y-H Lim et al. 2012) while Chinese studies have reported that DTR has lesser effects on non-accidental mortality during higher temperatures (Kan et al. 2007; Yang et al. 2013). Furthermore, global warming factors (greenhouse gases, urbanization, and aerosols) have led to decreases in the DTR during recent decades because the nocturnal minimum temperatures have increased faster than the maximum temperatures (Braganza et al. 2004). Therefore, the effect of decreasing DTR and increasing mean temperature on DTR-mortality should be further studied. Additionally, as a representative indicator of global warming, the effect of heat and cold waves on DTR-mortality also needs to be identified. We expect that in-depth studies will be conducted in various countries or regions that have different climates and alert systems for extreme weather events.

One of the strengths of the study is in its use of advanced statistical approaches, including multivariate random-effect meta-analysis and the distributed non-linear lag model, to estimate the temperature variability-mortality associations and pool effects across cities and countries/regions. Although the Cochran Q test provides evidence for residual heterogeneity in all the models, a substantial amount is explained by three meta-predictors (average temperature, temperature range, and country indicator), as indicated by the higher decrease in the I^2 statistics when three variables were included in the meta-regression. These methods have advantages in estimating the lag-exposure relation without strong assumptions about the lag structures. In addition, we used a two-step regression to avoid an identifying association (Vicedo-Cabrera et al. 2016) problem between temperature indices and to compare contributions of ambient temperature and DTR, more clearly. One major finding from this study is that ambient temperature accounted for a greater mortality fraction than DTR. Because the attributable fraction considers the distribution of each variable, we can suppose that the attributable fraction is a better measure than RR for comparing contributions of temperature indices. Besides, we also used cause-specific mortalities (cardiovascular-related and respiratory-related mortality)

including total mortality and found meaningful associations between temperature variability indices and cause-specific mortalities.

This study also has some limitations. First, we studied slightly different periods in each country, which could induce temporal variability of the estimates. Previous studies reported that temperature variability changed over time, especially DTR, which has decreased worldwide over the last several decades (Braganza et al. 2004; Makowski et al. 2008; Shahid et al. 2012). To adjust for the difference of time periods, we estimated the attributable fractions across the same long study period, from 1994 to 2007, of three countries/regions (i.e., Japan, Korea, and Chinese Taiwan) and found that the effect size was slightly attenuated but was not significantly different from the main findings with various study periods (see Supplementary Table S1). Second, we could not adjust for an influenza epidemic as a confounder in the model of respiratory-related death, which would allow for an overestimation or underestimation of attributable fractions. Because we only had an influenza epidemic variable for 10 cities in two countries/regions (Korea and Chinese Taiwan), we did not include influenza in our main results. Instead, we reported the attributable fractions of two countries/regions, adjusting for an influenza epidemic as shown in the supplementary materials, and the results were still robust. Third, ecological variables in this study (across multiple monitors in each city) were used to determine city-specific values, with the assumption of spatial homogeneity for a city (Chung et al. 2015). This assumption should be investigated more thoroughly by assessing the spatial patterns of each city. Fourth, the current findings cannot necessarily be interpreted as being representative of other cities and countries/regions with different climates, socioeconomic characteristics, and public health policy. In particular, the Japanese locations (47 prefectures) accounted for most of the locations and periods, potentially allowing for biased results. Therefore, future studies should strive to overcome these limitations by expanding the study populations through the monitoring of other cities and nations. In addition, we could not adjust for the humidity variable because of data limitation. Although such a contribution did not substantially affect the temperature-related mortality association, the humidity needs to be considered in future study as a confounder.

In summary, this study found a substantial impact on temperature and DTR on mortality in five Asian countries/regions. Overall, the ambient temperature and DTR are significantly associated with increases in mortality risk, and the ambient temperature on mortality as a major role. Moreover, cardiovascular-related mortality is the most susceptible to temperature and DTR than total/respiratory-related mortality. We hope our results can also support public health offices or researchers actively engaged in studies that consider the risk and health burden of ambient temperature and DTR on mortality.

Methods

This study included 63 cities; 3 cities in Chinese Taiwan for 1994–2007, 7 cities in Korea for 1992–2010, 47 prefectures in Japan for 1972–2009, 2 cities in Vietnam 2009-2013 and 4 cities in Philippines for 2003-2010. Daily mortality excluded accidental causes (hereafter referred to as a non-accidental mortality). Two specific causes (cardiovascular- and respiratory-related) of daily mortality were considered. Based on the International Classification of Diseases Revision 10 (ICD-10), non-accidental mortality as ICD-10 (A00-R99) cardiovascular-related mortality was defined as ICD-10 (I00-I99), and respiratory-related mortality was defined as ICD-10 (J00-J99). Only in Philippines, we used all-cause mortality instead of non-accidental mortality, because non-accidental mortality was not available. Weather variables included the daily mean, maximum, and minimum temperature (°C), Mortality counts and weather data for each city were obtained from different sources for some cities; air pollution data were only available for some years of the study periods(Chung et al. 2015). And source of the weather data and study periods are shown in supplementary materials (see Supplementary Table S7). A daily categorical variable for influenza epidemics was created assigning a value of 1 if the moving average of the daily number of influenza deaths per 1000 all-cause deaths over the previous week was ≥ 1; otherwise, a value of 0 was assigned. This way to adjust the influenza effect was also used in previous research (Chung et al. 2015).

We used a two-step regression approach analysis. In the first step, we fitted distributed lag non-linear model to consider the non-linear relationship between exposure-response and the non-linear delayed effect of exposure on response simultaneously, with every city with day of week, seasonal and long term trend, and temperature. Then we fitted a model to estimate extra effects of DTR. We used this two-step regression to ensure that the DTR effects were estimated after removing the overall effects of temperature and season. We used the following quasi-Poisson regression model for time-series analysis in each city firstly,

$$Y_t \sim quasiPoisson(\mu_t),\ t=1,\ \ldots T$$

$$\log(\mu_t) = \beta_0 + s(TEMP_t) + factor(DOW_t) + ns(TIME_t, df = 8\ per\ yr) \qquad (1)$$

where Y_t = death count on day *t*, μ_t = expected death count on day *t*, β_0 = intercept of the model, s($TEMP_t$)= basis of ambient temperature on day *t*. The quasi-Poisson likelihood was used to consider the over-dispersion (Gasparrini et al. 2015; Y. Guo et al. 2014). Specifically, we used the exposure-response curve with quadratic B-spline with three internal knots placed at 10th, 75th, and 90th percentiles of location-specific temperature distributions, and the lag-

response curve with a natural cubic spline with an intercept and three internal knots placed at equally spaced values in the log scale. This basis is referenced from previous study (Gasparrini et al. 2015). We extended the lag period to 28 days. DOW_t = categorical variable for day of week on day t, $TIME_t$ = time on day t using 8 degrees of freedom(df) per year In order to estimate the effects of DTR (difference between daily maximum and minimum temperature) in each city we used,

$$y_t \sim quasiPoisson(\mu_t{}^*), t = 1, \ldots \mathrm{T}$$

$$\log(\mu_t{}^*) = \log(\hat{\mu}_t) + DTR_t \qquad (2)$$

where $\mu_t{}^*$ is the predicted values from equation (1). We assumed the association between mortality and DTR as a linear, referenced from previous studies (Kan et al. 2007; Y-H Lim et al. 2012; YH Lim et al. 2012), so we applied an cross-basis function for DTR with exposure-response is linear and the lag-response curve with a natural cubic spline with an intercept and two internal knots placed at equally spaced values in the log scale. We extended the lag period for DTR to 14 days. This choice of lag days was motivated by previous studies reporting a delayed effect of DTR (Kan et al. 2007; Vutcovici et al. 2014; Yang et al. 2013). All processes of two step analysis were accomplished using R package *dlnm* (Gasparrini 2011). Sensitivity analyses were performed to test the consistency of the results with various modeling choices such as various lag days of temperature indices, degrees of freedom for indices and time trend, and adjustments for humidity and an influenza epidemic. The supplementary materials includes sensitivity analysis results (see Supplementary Table S1). The results of these sensitivity analyses indicate that our results are not dependent on the modeling assumptions.

Before we pooled the estimated city-specific results, we reduced the association to the overall temperature-mortality and DTR-mortality associations, cumulating the risk during lag periods by summing estimates of all lag periods from equation (1) and (2) (Gasparrini and Armstrong 2013). These associations were reduced to two summaries: the overall cumulative exposure-response relation and the lag-response relation specific to the 2.5th and 97.5th percentiles of temperature distributions and 99th percentiles of DTR distributions. This definitions have been previously reported (Gasparrini et al. 2012; Gasparrini and Armstrong 2013; Gasparrini et al. 2015). After reducing parameters, we pooled the estimated city-specific overall cumulative exposure-response associations and the city-specific lag-exposure associations using a multivariate meta-analysis. We obtained city-specific average temperature, temperature range and country indicators as meta-predictors in a multivariate meta-regression. We tested heterogeneity through a multivariate extension if indicated by the Cochran Q statistic and I^2 index (Gasparrini et al. 2012; Higgins and Thompson 2002) and these results are described in

Supplementary Table S6.

We used the fitted random-effect multivariate meta-regression models to derive the best linear unbiased prediction (BLUP) for the exposure-response and lag-response association respectively in each city. This process allows analysis of cities with a small population, small number of death counts, or short study periods, generally described by imprecise estimates (Gasparrini et al. 2015; Post et al. 2001). The second-stage analysis was accomplished with the R package *mvmeta* (Gasparrini et al. 2012). City-specific attributable fractions and minimum mortality temperature of each city were estimated from second-stage analysis are reported in supplementary materials. Minimum mortality temperature (an estimated temperature at which mortality was the lowest by the BLUP), used it the reference to calculate relative risks and attributable risk fraction for lag days.

The total attributable number for three different causes of death associated with temperature indices was obtained by the sum of the contributions from all the days of study, and we obtained the attributable fraction using the total attributable number ratio corresponding with the total number of deaths (Gasparrini et al. 2015). The fraction attributable to indices was calculated by summing the subsets corresponding to the days of minimum temperature to 0.25% (extreme cold), 97.5% to maximum temperature (extreme hot) and minimum to maximum DTR to reflect the total effect. We calculated the empirical confidence intervals (eCI.) using Monte Carlo simulations, with an assumption of multivariate normal distribution of the reduced BLUP coefficient. All these processes for analyzing attributable risk also have been used in previous studies (Gasparrini et al. 2015; Yuming Guo et al. 2014).

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Supplementary Materials

The Supplementary Materials file can be downloaded from the URL (https://www.nature.com/articles/s41598-017-10433-8)

OR the file also is available on request to the first author (jleehwan33@gmail.com).

Discussion

3.1. Research summary

The temporal changes in weather-mortality association

Research 1. I investigated the temporal changes in the impact of heat wave and cold spell on mortality during 1992-2015 in 53 communities in Korea and Japan. I found the temporal decreases in the RRs of heat waves in the total population. On the other hand, most RRs for cold spells significantly increased during the study period in the total population, and more pronounced increases were observed in southern Japan and Korea. In addition, we observed the increases in averaged frequency of heat waves and cold spells in the 2010s compared to the 2000s in the total population, and the attributable death risk due to heat waves and cold spells also showed increasing trend during the same period as results of considering increases in their frequency. These findings suggest that the mortality burden of extreme temperature events can increase in the future even if the population adapts to extreme events gradually.

Research 2. In this study, I assessed the percent increases in risks and the attributable risk fraction of DTR for 308 cities of 10 countries. I examined whether the excessive risks and attributable risk fractions changed during recent decades, and used a Multi-Country Multi-City (MCC) Collaborative Network dataset. I found that there was a significant effect of DTR on mortality across all countries, and provided evidence that the effect of DTR was higher in warmer regions. Furthermore, although the risks and contributions of DTR to mortality increased at the multi-country scale with significant increases estimated for the USA, the UK, Spain, and South Korea; non-significant increments for Canada, Brazil, Colombia, and Australia. The estimates of DTR-related mortality increased throughout the study period in all countries, which could be interpreted as maladaptation to DTR. This indicates that the health burden of DTR is not likely to decrease in the near future.

The interactions in the weather-mortality association

Research 3. This study investigated the interactive effect of DTR and temperature on mortality in 57 communities of three countries in Northeast Asia (Korea, Japan and Taiwan). I found that the DTR-related mortality risk increased by temperature level, suggesting that there may exist an interaction between DTR and temperature. Results showed that such interactive effect was observed in all of the subpopulations defined by temperature distribution, sex, and age group, and was more obvious in cold region than in warm region, and in older people (aged ≥65 years) than in younger people (aged <65 years). The DTR has decreased over decades under climate change and the decreased health effects related to DTR has been predicted. However, results of

the study may indicate that the DTR-related mortality in the future may be uncertain (or may increase) considering the interactive effect of DTR and temperature.

Research 4. The study aimed to investigate the synergic association between high temperature and temperature variability (TV) on mortality using data from 57 communities in three Northeast Asian countries (Korea, Japan and Taiwan). This study revealed an additive interaction between heat and high-level TV in the total population and all sub-populations, categorized by death causes and age groups. The synergism was more obvious in cardiovascular-related deaths than in respiratory-related deaths, and in older people (aged ≥65 years) than in younger people (aged <65 years). Based on these findings, the study suggest the need to build an additional warning system and public health interventions considering both high temperature and TV, and vulnerable populations.

Uncertainty estimation in weather-mortality association

Research 5. The study assessed the statistical property of the previously proposed statistical approach to estimate the minimum mortality temperature (MMT) in various types of association via a simulation study, and suggested an alternative approach, which can be applied if some prior knowledge is available on the MMT to improve upon the previous method. I suggested to combine the prior knowledge with the procedure of deriving the empirical distribution of the MMT and to use the empirical mean and percentiles (2.5^{th} to 97.5^{th} percentiles of the empirical distribution) as a point and an interval estimates for the MMT, and heat and cold RRs. Simulation study showed that the proposed method works properly and robustly reducing the Bias and RMSE in point estimation and achieving near 95% coverage while shortening the length in interval estimation in all scenarios.

Research 6. The study aimed to classify the mortality risks related to absolute temperature and temperature variability with two-step regression approach. Our findings show that ambient temperatures and temperature variability (diurnal temperature range) were significantly related to the attributable fractions of total, cardiovascular-related, and respiratory-related mortality in all five countries/regions over the duration of the study periods, and the contribution of the daily mean temperature was much greater than that of the temperature variability.

3.2. Discussions for issues in the thesis

The temporal changes in weather-mortality association

Above all, the possible reasons why the risks of extreme temperature events have changed over time should be more discussed. Numerous studies reported that that the risk of heat temperature has declined during recent decades in multiple countries (Gasparrini et al. 2015a; Fouillet et al. 2008; Davis et al. 2003; Chung et al. 2017; Vicedo-Cabrera et al. 2018), and suggested increasing air conditioning prevalence, physiological acclimatization, demographic or socioeconomic factors, and improvements in housing as the drivers of these temporal decreasing (Fouillet et al. 2008; Gasparrini et al. 2015a; Kyselý and Kříž 2008). In addition, prevention plans, such as heat-surveillance systems and other public health interventions, have presented as one of the possible reasons of the reduced heat effects on mortality over time (Kovats and Kristie 2006).

On the other hand, interestingly, the temporal pattern of cold-related mortality and temperature variability-related mortality were observed heterogeneous with the temporal pattern of heat-related mortality. A study conducted in Northeast Asia showed that cold-related mortality remained constant over decades (from 1972) and slightly increased in the late 2000s (Chung et al 2017). Another previous study showed that the temporal pattern of attributable risk fraction (ARF) for cold were heterogeneous among 10 countries (Vicedo-Cabrera et al. 2018). Further, my research (Research 1) showed that the mortality risk related to cold spell linearly increased in Japan and Korea after 1990s, and another my research (Research 2) also reported that the mortality risk and attributable deaths-related to temperature variability increased in multiple countries during the recent decades.

The main question in my researches was “Why the mortality risk related to cold and temperature variability did not decrease (or did increase) over time, unlike heat-related mortality risk?”. In particular, despite improvements in economic status, standard of living, health, and housing which have been suggested as the main factor of the decrease in temperature-mortality relationship, the cold-related mortality and the temperature-related mortality did not decrease during the recent decades in many countries. This is a quite contradictory phenomenon, and it may mean that there are the other major factors that affect contradictory to heat.

I and other previous studies have suggested a “warming climate” as a plausible hypothesis to explain increasing cold impacts (i.e. acclimatization to warming climate). Because populations in warmer climates was more/less sensitive to cold/heat (Anderson and Bell 2009; Lee et al 2018c; Gasparrini 2015b), thus a warming climate can lead population to become more/less

vulnerable to cold/heat. Most studies thus far have predicted that warmer weather may reduce the effects of extreme cold in the future (Carson et al. 2006; Kalkstein and Greene 1997). However, if the hypothesis is true, then the health impacts of cold can increase in the near future. Thus, the relationship between "warming climate" and temporal changes in the temperature-related mortality should be carefully monitored climate change progresses. Another hypothesis is a "reduced heat impacts on mortality". Previous studies showed that summer temperature-related mortality was higher in years with lower winter mortality, than in years with average or higher winter mortality (Qiao et al. 2015; Rocklöv et al. 2009; Stafoggia et al. 2009). By the same logic, if the impacts of temperature in the preceding summer were reduced, then cold-related mortality in the following winter could increase.

In addition, the "warming climate" also may affect to temporal increase in the temperature variability-related mortality. My previous researches (Lee et al. 2018a; Research 3 in the thesis) showed that the mortality risk-related to temperature variability increased at higher levels of temperature. As climate change is anticipated to increase the number of hot days, thus the future impacts of DTR could be underestimated if the effect of warmer temperatures is not considered. Therefore, association between warming climate and increase in the temperature variability-related mortality should be more investigated in the future researches.

Further, several aspects should be more investigated in the future study. First, increasing frequency of extreme cold and extreme temperature variability should be considered. Latest studies have discovered that the arctic warming is attributable for the increase in the frequency and intensity of cold extremes and extreme temperature variability in mid-latitude regions (Cohen et al. 2014; Wallace et al. 2014; Zhang et al. 2016). Second, community-specific geographical characteristics (latitude, longitude, or altitude) which may modify the mortality risk-related to temperature and temperature variability should be considered in estimation. Third, especially in multi-country study, community-specific weather season (e.g. dry, rainy season, and etc.), climates (e.g. tropical, continental, and etc.), unusual weather phenomenon (e.g. monsoon, squall, and etc.), and policy should be studied. Fourth, temporal changes in cause-specific death also should be considered. Previous studies reported that the proportion of respiratory deaths has increased in developed counties due to aging, dietary habits, etc., while cardiovascular-related disease deaths have decreased (Moran et al. 2014). Because cause of death is crucial modifiers of temperature-related mortality (Anderson et al. 2011; Chung et al. 2015) and temperature variability mortality (Lee et al. 2018a), thus changes in the cause of death may related to temporal changes in the temperature and temperature variability-related mortality risks. I have plan to implement these topics in further study.

The interactions in the weather-mortality association

Interaction between temperature and temperature variability provide important implications for estimating the mortality impacts of temperature variability under climate change. Previous studies have anticipated the temperature variability will increase in climate change (Solomon 2007; Stocker 2014), however a recent study reported that the variability of low-frequency global mean surface air temperature (GMST) will likely decrease in climate change (Brown et al. 2017), and suggested the reduction in high-latitude surface albedo variability as a major reason of the decrease in GMST variability. And also, intra-day temperature variability have been reported to decrease during the recent decades, because the nocturnal minimum temperatures have increased faster than the maximum temperatures by climate change factors, such as greenhouse gases, aerosols, and urbanization (Braganza et al. 2004; Makowski et al. 2008). Thus, according to these results, the health impacts of temperature variability can be expected to decline in future by exposure decrease (Yang et al. 2013). However, results of my studies (Research 3 and 4) imply that the association between temperature variability and mortality in the future may be increase considering the positive interaction with temperature, although the absolute value of temperature variability may decrease in climate change.

However, some perspectives should be considered to estimate health impact of temperature variability and interaction association between temperature and temperature variability on death. First, direction of temperature variability should be considered. In other words, temperature variation from heat to cold should be distinguished with those from cold to heat. The biological mechanism leading to death may vary depending on the direction of temperature variability (e.g. ischemic heart disease may related to being cold, and hemorrhagic disease may related to being hot), thus the direction of temperature variability should be crucial to assess the health impacts of temperature variability and interactive association with ambient temperature. However, the temperature variability indices developed so far (diurnal temperature range, temperature change between two neighboring days, and standard deviation among lag days) could not reflect the direction, therefore new temperature variability index should be developed in future study. Second, the temperature range (distribution) of each community should be considered to estimate the temperature variability-related mortality risk. Although some previous multi country studies reported that distribution of temperature variability was heterogeneous among climate conditions (Guo Y. et al. 2016; Lee et al. 2018a), the association between temperature range and mortality risks-related temperature variability have not been sufficiently studied. Third, like the temperature-related mortality, community-specific weather season, climates, unusual weather phenomenon, and policy should be considered in estimating the temperature variability-related mortality risk.

Uncertainty estimation in weather-mortality association

I suggested the Bayesian approach to reflect the uncertainty of minimum mortality temperature (MMT) to estimate the temperature-mortality association, and showed that the method of combining prior knowledge with the inference showed better performance in estimating the MMT and the corresponding temperature-mortality association. However, as described above, incorrect prior distribution may occur seriously biased and invalid estimation. Furthermore, the simulation method is based on multivariate normal distribution, thus inadequate sample also may cause biased and inaccurate estimation.

Therefore, in order to develop the suggested Bayesian method, various prior distribution of parameters should be applied, and the more complex method (e.g. Markov Chain Monte Carlo; MCMC) to derive posterior distribution shall be studied. Further, parametric approach, for example random effect model, can be applied to consider the uncertainty of MMT. In this thesis, I could not find an appropriate parametric approach. Given the advantage of parametric estimation (e.g. simple and fast calculation), the development of parametric approach will contribute greatly to infer the uncertainty of MMT and the corresponding mortality risk-related to temperature.

Further, the identifiability between temperature and temperature variability is highly difficult issue in the weather-mortality study. I adopted the two-stage regression which uses the predicted residual, however the method has limitation when covariates in the first-stage regression is not independent with the interesting variable in second-stage regression. The two-stage approach in Research 6 was not free from the limitation, thus the attributable mortality risks fraction due to DTR estimated from the second-stage regression could be biased. So far, no optimal methodology has been developed to address this identifiability problem. I'll try to develop the suitable statistical approach to identify the effects of temperature and temperature variability.

3.3. Implications for public health policy in Korea

I believe this thesis can be used in several points to advance public health policies of Korea.

Weather warning system

Currently, the major alarming systems related to extreme temperature/temperature variability provided by the Korea Meteorological Administration (KMA) are as following table:

Table 3.3.1 Alarming systems related to extreme temperature/temperature variability in Korea

Alarming	Description
Heat wave advisory	When the day's highest temperature is expected to be more than 33°C for more than 2 days.
Heat wave warning	When the day's highest temperature is expected to be more than 35°C for more than 2 days.
Cold spell advisory	From October to April, if one of the following is true 1) When the morning minimum temperature is lower than 3°C (by 10°C lower than the previous day), and 3°C lower than yearly normal value. 2) When the morning's lowest temperature is expected to be lower than -12°C for more than 2 days. 3) When serious damage is expected due to sudden low temperature phenomenon.
Cold spell warning	From October to April, if one of the following is true 1) When the morning minimum temperature is lower than 3°C (by 15°C lower than the previous day), and 3°C lower than yearly normal value. 2) When the morning's lowest temperature is expected to be lower than -15°C for more than 2 days. 3) When serious damage is expected due to sudden low temperature phenomenon.

Based on the results of Research 1, I suggest the heat wave/cold spell warning system using relative thresholds based on each community's temperature, because the approach may allow for regional acclimatization to the normal temperature of each community. In most communities in Research 1, the result (Figure 1) shows that the heat wave RR of mortality was significant at the 95th percentile of community-specific temperature, increased at the 97th percentile and sharply rose at the 99th percentile during the entire study period. This trend is consistent with the results of previous studies (Guo et al., 2017; Tong et al., 2015; Tong et al.,

2014). In addition, Korea showed similar cold spell RRs among the 5th, 3rd, and 1st percentiles (Figure 2). Communities in Korea had different temperature distribution, and 1-3rd and 95-99th percentile temperature points were also heterogeneous among communities (Table S1). These results denote the mortality risks of heat wave/cold spell are strongly associated with distribution of local temperature, and suggest that it may not be appropriate to apply the same criteria using absolute scale temperature across the country. In other words, in order to reduce the death due to heat wave/cold spell, the thresholds of heat wave/cold spell warning systems should be modified to take into account the local temperature distribution.

Further, despite numerous studies reported that high temperature variability was associated with increase in mortality risk (Guo et al. 2016; Lee et al. 2018a; Lee et al. 2018b; Yang et al. 2018), there is no independent KMA alarm system for temperature variability in Korea, until today. Only weather forecasts provide information about high diurnal temperature range (DTR) in the change of season. Research 2 shows the mortality risk related to DTR has been highly increased during the recent decades in Korea, and the absence of alarming system for high temperature variability may be associated the risk increase. Likewise, Research 3 showed that the DTR-related mortality is amplified in hot temperature. In addition to DTR, Research 4 shows the temperature variation between consecutive days may have an association with mortality risk, and the association also may increase in hot temperature, compared to moderate temperature. These results can support a necessity of new alarming system for high temperature variability in Korea, and the alarming system should be operated more importantly in hot weather that are even not covered by the weather forecast not.

Target population

Research 1-4, and 6 shows the mortality risks-related to extreme temperature and temperature variability are more pronounced in those who are elderly, have cardiovascular disease or respiratory disease, or local weather conditions (e.g. average temperature). Further, other previous studies also reported that the weather-related mortality risks are more obvious in female, those who are less educated, or low income (Kan et al. 2007; Lim et al. 2015; Lim et al. 2012; Chung et al. 2015; Medina-Ramón M and Schwartz J. 2007). These results show which populations are more vulnerable to extreme temperature and temperature variability, and provide a significant evidence for establishing target populations for effective policy enforcement.

In particular, “aging” should be considered crucially in the target population establishment. Korea's aging rate is increasing rapidly every year, meaning the number of people vulnerable to

extreme temperature and temperature variability is also increasing rapidly. A previous study reported that ignoring the demographic changes may lead to underestimate future risk of unstable weather in aging society (Lee and Kim 2016, 2017), and the proportion of respiratory patients which are more susceptible to temperature and temperature variability has increased in developed counties due to aging, dietary habits, etc. (Moran et al. 2014). Thus, the predictable aging should be considered crucially in estimating the health impacts of temperature and temperature variability, and in coping with climate change.

Furthermore, the increased usage of personalized devices (e.g. smartphone) in Korea facilitates to provide more detailed alarm system and public health services, if the users save their health status, such as disease, sex, age, and etc. in the personalized device. This increased use of personalized devices has greatly improved the accessibility of personal information, and health services should respond very aggressively to these changes. It can contribute hugely to reducing the weather-related health effects in the future.

Climate change responses: Cold

The question of how the impacts of extreme cold events would change in the future is a crucial issue of climate-health researches. Most of previous studies reported that milder winter conditions will lead to reduced mortality burden due to cold (Bennett et al. 2014; Hajat et al. 2014; Huynen and Martens 2015; Vardoulakis et al. 2014). Thus, relatively fewer studies focused on the health impact due to cold than heat (Åström et al. 2013; Chung et al. 2017; Vicedo-Cabrera et al. 2018), and also it may be true that the health issue of exteme heat has been getting more public and politic attention than cold in Korea.

However, Researh 1 shows that the average number of cold spells increased in the 2010s compared to the 2000s in Korea, and RRs for cold spells highly increased in Korea. Further, latest studies have discovered that the arctic warming is attributable for the increase in the frequency and intensity of cold extremes in mid-latitude regions (Cohen et al. 2014; Wallace et al. 2014; Zhang et al. 2016), and the phenomenon is related recent record breaking cold spells in Northeast Asia, including Korea. It means that the frequency and health susceptibility of cold extremes may temporally increase, and also imply that the health impacts of cold extremes may be amplified in the near future of Korea.

In addition, recent studies suggested “acclimatization” to warming climate as a hypothesis of mal-adaptation to cold (Chung et al. 2017; Lee et al. 2018a). The studies represented prior studies which showed that people in warmer weather were generally more sensitive to cold

temperature (Anderson and Bell 2009; Guo et al. 2014), and suggested that the trend of warmth could make people more vulnerable to cold temperatures. Therefore, since average temperature will increase by climate change, researchers and Korean government should more focus on the future health impacts of extreme cold, than present.

Climate change responses: Temperature variability

Findings in Research 2-4 provide important implications for estimating and counteracting the mortality impacts of temperature variability under climate change. Previous studies have anticipated the temperature variability will increase in climate change (Solomon 2007; Stocker 2014), however a recent study reported that the variability of low-frequency global mean surface air temperature (GMST) will likely decrease in climate change (Brown et al. 2017), and suggested the reduction in high-latitude surface albedo variability as a major reason of the decrease in GMST variability. And also, DTR have been reported to decrease during the recent decades, because the nocturnal minimum temperatures have increased faster than the maximum temperatures by climate change factors, such as greenhouse gases, aerosols, and urbanization (Braganza et al. 2004; Makowski et al. 2008). Thus, according to these results, the health impacts of temperature variability can be expected to decline in future by exposure decrease (Yang et al. 2013).

However, Research 2-4 imply that the association between temperature variability and mortality in the future may be uncertain considering the aging, and warming climate together, although the absolute value of temperature variability may decrease in climate change. Especially, since Korea showed higher temperature variability-related risk on mortality compared to other countries (Research 2-4), and increased temperature variability-related risk during the recent years (Research 2). Thus, the results may imply that the future association between temperature variability and mortality in the Korea possibly increase, considering the aging rate, and warming climate together, although the absolute value of temperature variability may decrease in climate change. Thus, careful investigation about temperature variability will contribute to improve effective health policies for reducing health impacts of temperature variability in Korea.

3.4. Epilogue

I believe my researches have contributed to environmental epidemiology study in three aspects:

First, I showed that the health impacts of cold and temperature variability have not diminished in recent years, and this phenomenon might be associated with warming climate. In addition, my researches also provided epidemiological evidences that, as the frequency increases, future mortality burden attributed to extreme heat may increase, even if population will be well-adapted to extreme heat. The results may suggest that more progressive actions are needed for climate change, and may provide implications for further researches. However, since all of my studies were based on historical data set, I will predict the future mortality burden due to extreme temperature and temperature variability using climate change scenario data in future researches.

Second, I investigated the indirect impacts of hot temperature, and verified interactive roles of hot temperature on the temperature variability-mortality association. These results may support to establish effective alarming systems and public health intervention, also can be used to anticipate the future health impacts of temperature variability. In future research, more specific interactive or modification patterns, such as three-way interaction among weather and air pollution variables, and effect modification of humidity in the temperature-mortality relationship, will be investigated.

Third, I showed that if uncertainty of minimum mortality temperature (MMT) is not taken into consideration, there may be a bias in estimating the heat- and cold-related risks on mortality compared to MMT. Furthermore, I suggested the Bayesian simulation approach with prior information of MMT should be useful to reduce the estimation bias, when the uncertainty of MMT is high. I will continuously focus on the advanced statistical methods for estimating the weather-health association.

Finally, I wish that the results of my researches will be used for people who are struggling to prevent climate change. Sadly, we don’t have much time.

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국문 초록

기후변화는 보건학 및 역학 연구에서 중요한 이슈이며, 기후 변화에 따른 건강 영향은 많은 연구들에서 논의되어 왔습니다. 극한 온도, 갑작스러운 온도 변화(온도 변동)는 기후 변화의 주요 변수로 알려져 왔으며, 대기 오염 또한 기후 변화와 연관된 주요 위험 요인으로 여겨지고 있습니다. 수많은 기존 연구에서 이들 변수들과 건강의 연관성이 보고되었습니다. 하지만, 시간 변동성(time-varying association), 교호작용(interaction), 추정 불안정성(estimation uncertainty)과 같은 주제들은 기후 변화의 건강 영향을 추정하는데 있어 매우 중요함에도 불구하고, 아직까지 충분히 논의되지 않았습니다. 저는 박사학위 과정 동안 기후-사망 관계의 시간 변동성, 기후-사망 관계의 교호작용 요인, 기후-사망 관계 추정의 불확실성을 반영한 통계 모형들에 대해 주로 연구하였습니다. 이 박사 학위 논문은 박사 학위 과정 중에 출판되었거나 심사 중인 연구들을 포함하고 있으며, 다음에 대한 역학 및 통계학적 근거들을 제시하였습니다: 1) 극한 온도 및 온도 변동성의 사망과 연관성이 있으며, 2) 그 연관성이 시간에 따라 변화하며, 3) 그 연관성에 영향을 미치는 수정 인자 혹은 교호작용이 존재하며, 4) 연관성 추정 시 발생되는 불안전성을 고려한 통계적 모형이 필요하다. 마지막으로, 본 학위 논문에서 다뤄진 주제와 미래에 연구될 주제들을 논의 하였습니다.

주요어: 건강 위험 평가, 극한 온도, 기후 변화, 온도 변동, 통계 모형

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