THE UNIVERSITY OF TSUKUBA

Spatial and Temporal short term effect of temperature on mortality: a time series analysis in some Asia cities

(死亡率に対する温度の時空間短期影響:

いくつかのアジアの都市における

時系列分析)

By

Tran Ngoc Dang

Graduate school of Comprehensive Human Sciences

A thesis submitted to the University of Tsukuba for the degree of Doctor of Philosophy in Human Care Sciences

January, 2017

The undersigned have examined the thesis entitled '**Spatial and Temporal short term effect of temperature on mortality: a time series analysis in some Asia cities**' presented by **TRAN NGOC DANG**, a candidate for the degree of **Doctor of Philosophy in Human Care Sciences**.

Prof. Yasushi Honda

Date | Supervisor name

Prof. Ichiro Okubo

Date | Committee member name

Prof. Nanako Tamiya

Date | Committee member name

Prof. Masahiro Hashizume

Date | Committee member name

Table of Contents

Declaration

I declare that this thesis is my own work, and that I have acknowledged all results and quotations from the published and unpublished work of other people

Abstract

Climate change and global warming have sparked a great interest in the research on the health effects of temperature in recent years. However, there are some limitations of current research on temperature-mortality relationship. Firstly, few studies have explored the effects of temperature on health in tropical or subtropical developing countries, particular in Vietnam (i.e. ranked 7th among the 10 countries most affected by climate change). Secondly, previous studies indicated that urban populations are more susceptible to the heat compared to non-urban population. There is, however, no study so far has directly quantified the magnitude of attributable deaths due to urban heat island (UHI) as well as the attributable deaths can be prevented by the increase of green space. Finally, some methodological issues remain to be addressed, such as the uncertainty in estimation of minimum mortality temperature (MMT). This PhD thesis aims to contribute to the solving of above deficits.

I wrote this thesis using a publication style based on three manuscripts.

Chapter 1 provides a literature review on the effect of climate change and health, specifically focus on the direct effect of climate change (i.e. temperature effect) on mortality. This chapter also summarizes time series regression, which has been widely used in examine temperature-mortality relationship, as well as address limitations of current evidence in the field. Then, it follows by aims and objectives of the study and significance of the study.

The three manuscripts are presented in chapter 2-4, each of them try to solve one-by-one limitation addressed in chapter 1. Basically, chapter 2 used the distributed lag non-linear model to investigate the relationship between temperature and mortality in Hue, a sub-tropical city of Vietnam. Chapter 3 directly quantifies the attributable deaths due to urban heat island effect in Ho Chi Minh City of Viet Nam using dynamic downscaling with a regional weather model. Chapter 4 proposes a method to estimate confidence interval of minimum mortality temperature (MMT) with application using Japanese data.

Chapter 5 gives some conclusions based on results of the three manuscripts and some directions for future researches.

List of tables

List of figures

Acknowledgements

I am grateful to my supervisors, Prof. Yasushi Honda, Prof. Ichiro Okubo, and Prof. Masahide Kondo for their professional guidance.

Prof. Yasushi Honda, my principal supervisor, gave me full freedom to realize and conduct PhD research topics with his utmost support. I am extremely indebted to him for the patience, wisdom, and kindness he showed to me during the past three years. He generously provided the budget for data collection as well as buying books related to research topics. These books with his signature on them will be precious gifts, good memories, and motivations in my life. Prof. Ichiro Okubo, and Prof. Masahide Kondo, my co-supervisor, spent a lot of time to give consultations in my research, even though they were very busy.

My sincere gratitude also goes to my lab-mates, who have being so close to me during PhD time. I will always remember the enjoyable time we spend together not only in doing research, but also in endless parties. With them my life in Japan is so far so comfortable.

I would like to thank the Japanese Government and the University of Tsukuba for providing me the "Monbukagakusho" scholarship to conduct my PhD study. I am also grateful to teachers who gave inspiring lesson to me during PhD courses.

The final thank you is to my family for their encouragement and care. They gave me unconditional love and support.

Publications

Publications relevant to the thesis

Dang TN, Seposo XT, Duc NHC, Thang TB, An DD, Hang LTM, Long TT, Loan BTH, Honda Y: **Characterizing the relationship between temperature and mortality in tropical and subtropical cities: a distributed lag non-linear model analysis in Hue, Viet Nam, 2009–2013**. *Global Health Action* 2016, **9**:10.3402/gha.v3409.28738

Other publications during PhD course

Dang TN, Naka I, Sa-Ngasang A, Anantapreecha S, Chanama S, Wichukchinda N, Sawanpanyalert P, Patarapotikul J, Tsuchiya N, Ohashi J: **Association of BAK1 single nucleotide polymorphism with a risk for dengue hemorrhagic fever**. *BMC medical genetics* 2016, 17(1):43.

Dang TN, Naka I, Sa-Ngasang A, Anantapreecha S, Chanama S, Wichukchinda N, Sawanpanyalert P, Patarapotikul J, Tsuchiya N, Ohashi J: **A replication study confirms the association of GWAS-identified SNPs at MICB and PLCE1 in Thai patients with dengue shock syndrome**. *BMC medical genetics* 2014, **15**:58.

Conference presentations

Oral presentation "**Short-term temperature effect on mortality: A distributed lag non-linear model analysis in Hue, Viet Nam, 2009-2013**", The 7th International Conference on Public Health among the Greater Mekong Sub-regional Countries (26-27, September, 2015).

Oral presentation "**Time trends of MMT: a multi-country study**", The 2nd International Symposium on Environmental Health, Seoul National University, Feb 14-16th, 201

Oral presentation "**Attributable deaths due to heat and cold: How did it change in Japan in 40 years?**" , Conference of International Society for Environmental Epidemiology and Interna- tional Society of Exposure Science - Asia Chapter 2016, Sapporo, Japan, June 26–29, 2016

Poster presentation "**Attributable deaths due to urban heat island effect in a mega city of Vietnam: an application of dynamic downscaling with a regional weather model**", Conference of International Society for Environmental Epidemiology – ISEE, Rome, Italy, September 1-4, 2016.

Chapter 1: Introduction

1.1 Background

1.1.1 Climate change, temperature and health

During the last century, our global climate is changing rapidly, due to anthropogenic greenhouse gas emissions. The Intergovernmental Panel on Climate Change has concluded that warming of the climate system is obviously from 1950s (Figure 1.1, upper). The planet's average temperature has increased by 0.74 °C from 1906 to 2005 (IPCC 2007b). During the past three decades, the global temperature increased significantly compared to that of previous decades (Figure 1.1, bottom). It is projected that climate change will increase the global average temperature not only by between 1.1 °C and 6.4 °C by 2100, but also to increase the frequency of extreme weather events (e.g., heat waves, cyclones and storms) (Medina-Ramon and Schwartz 2007).

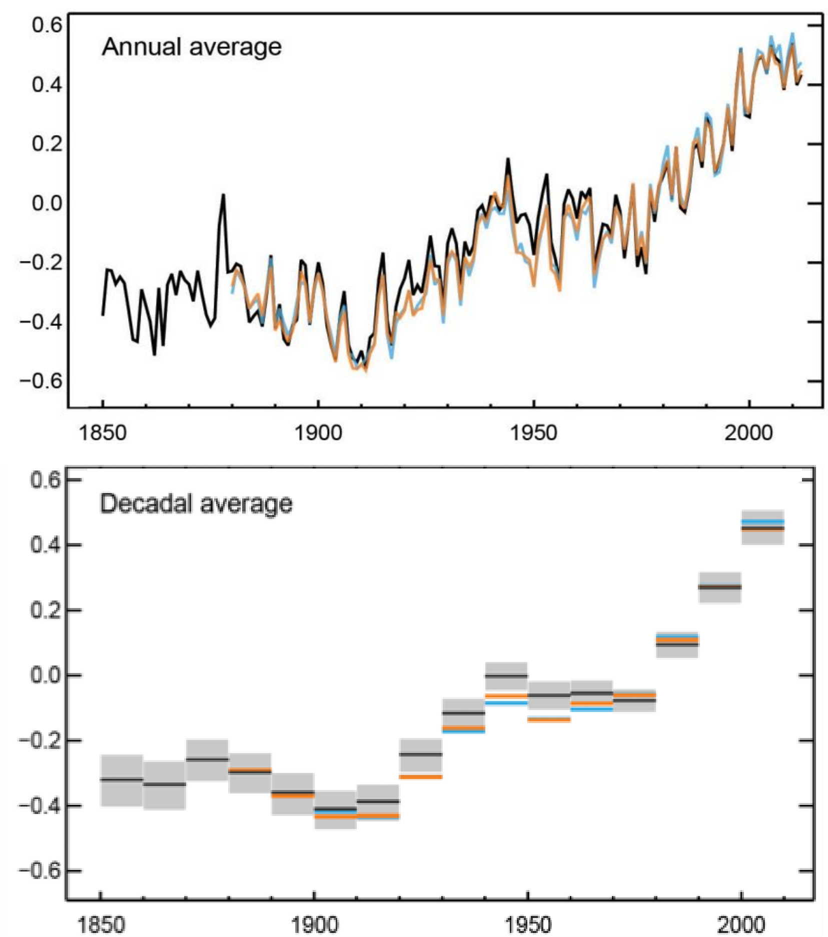

Figure 1.1 Globally averaged combined land and ocean surface temperatures (Smith, Woodward et al. 2014)

Climate change is a significant and emerging threat to public health in many countries worldwide (Smith, Woodward et al. 2014). Climate change affect population health through three main pathways: direct exposure, in-direct exposure, and through social and economic disruption (Figure 1.2). The direct pathway relates to changes in mortality or morbidity rates associated with exposure to temperature.

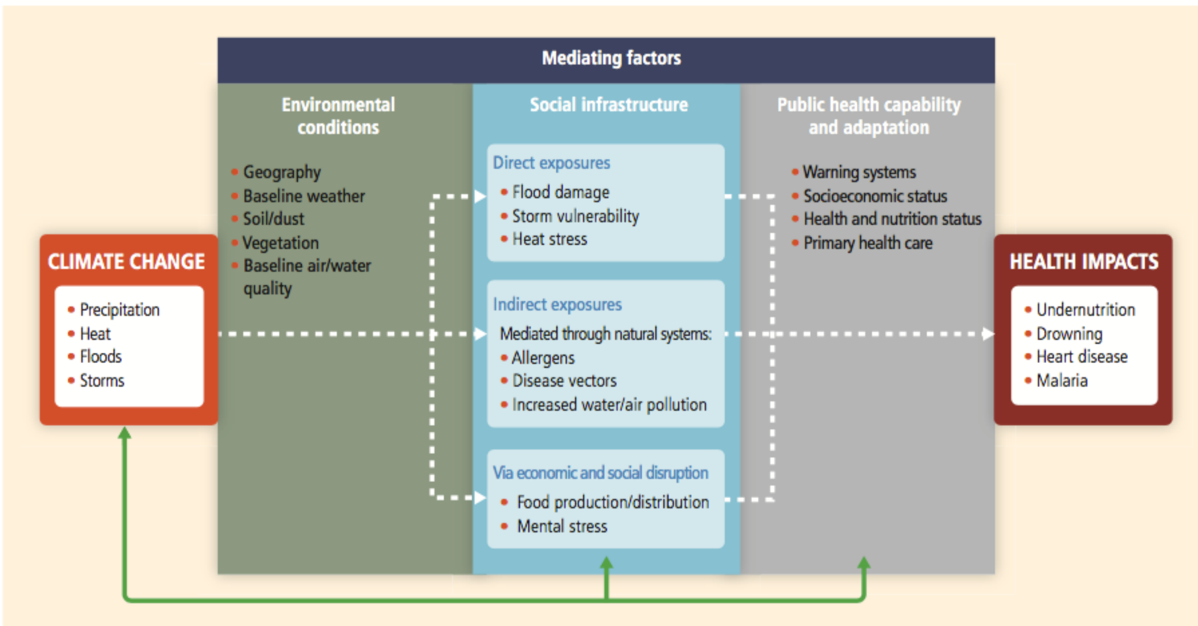

Figure 1.2. Schematic diagram of pathways by which climate change affects health (Smith, Woodward et al. 2014)

Several studies showed that many countries already experienced burdens of temperature-related mortality from current weather patterns. These studies showed that mortality tends to rise with increasing hot or cold temperatures from an optimum temperature value, therefore form a U-, V-, J-, reversed J-shape (or L-shape) (Figure 1.3) (Kalkstein and Greene 1997, Gellert 1998, McMichael, Wilkinson et al. 2008, Hajat, Vardoulakis et al. 2014, Tawatsupa, Dear et al. 2014)

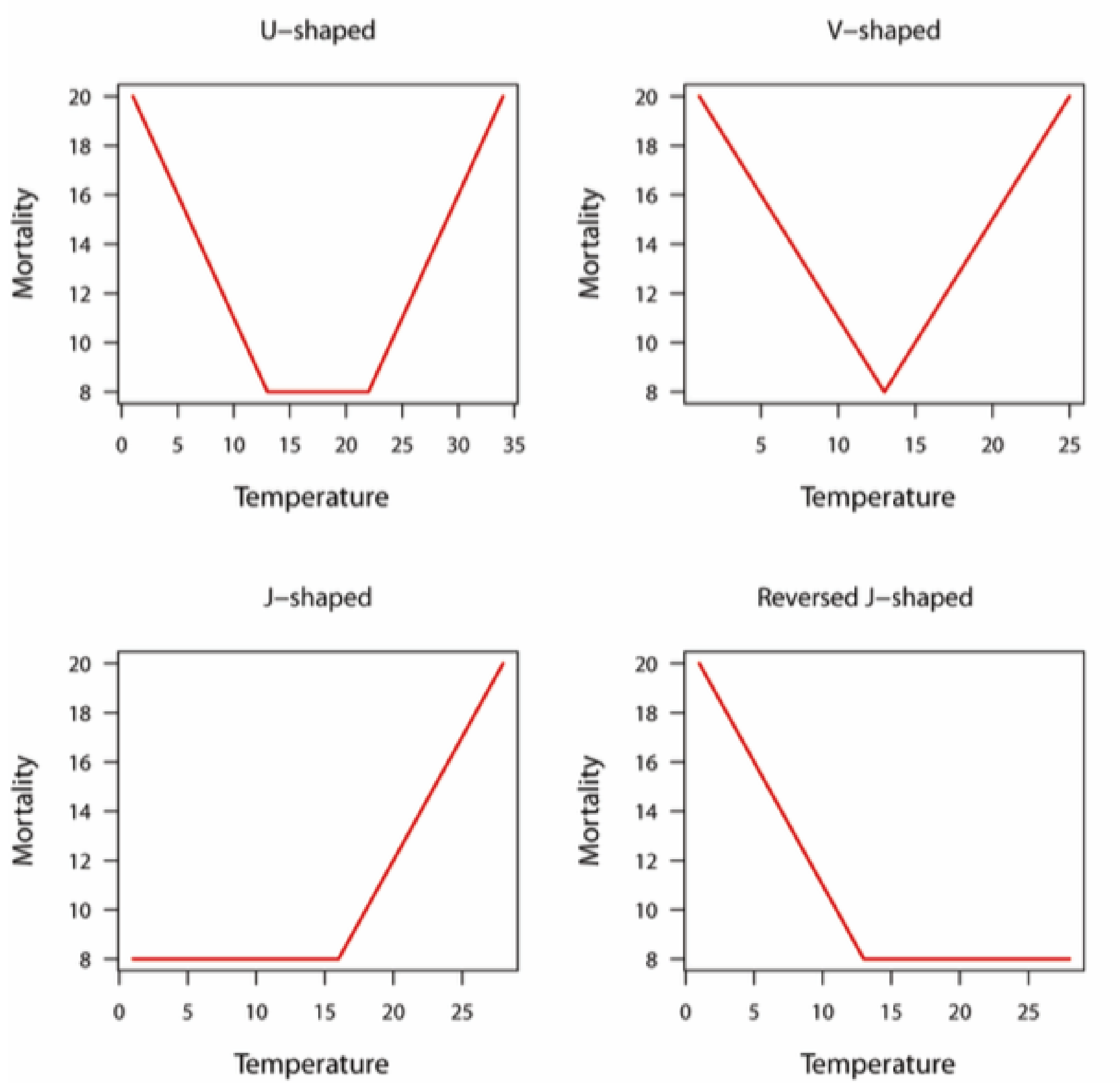

Figure 1.3. Common shapes of temperature and mortality relationship

(Guo 2012)

Many factors may modify the effects of temperature on human health, categorized into intrinsic and extrinsic factors (Kovats and Hajat 2008). The intrinsic factors (i.e. related to individuals aspects) include age (Filleul, Le Tertre et al. 2004), gender (Bell, O'Neill et al. 2008), chronic diseases (Stafoggia, Forastiere et al. 2006), Whereas, the extrinsic factors (i.e. related to environmental and behavioral aspects) include socio-economic disadvantage (Rey, Fouillet et al. 2009), housing (Vandentorren, Bretin et al. 2006), urban heat island effect (Goggins, Chan et al. 2012, Xu, Dadvand et al. 2013), access to air conditioning and availability of health care services (Kovats and Hajat 2008). Importantly, populations in developing countries are more sensitive to impacts of climate change, because they have limited adaptive capacity and more vulnerable people (Costello, Abbas et al. 2009).

Previous studies also indicated some levels of population adaptation to temperature effect by investigating the geographical and temporal variations in the temperature-mortality association. For example, people living in cities with milder summers were more susceptible to heat than people in cities with higher summer temperatures (i.e. spatial variation) (Medina-Ramon and Schwartz 2007). Interestingly, some studies reported a progressive reduction in heat-related mortality along the last century, despite the aging of populations (i.e. temporal variation) (Gasparrini, Guo et al. 2015, Todd and Valleron 2015). There are some factors that may contribute to this reduction trend, such as the improvements in social, environmental, behavioral, and health-care factors. Particularly, the increase of air conditioning is one of the main factors (Rogot, Sorlie et al. 1992, Curriero, Heiner et al. 2002, Medina-Ramon and Schwartz 2007, Ostro, Rauch et al. 2010, Gasparrini, Guo et al. 2015). In addition, some studies reported that heat waves occurring early in the summer are associated with a higher mortality risk than heat waves occurring later in the summer (Baccini, Biggeri et al. 2008), implicating a short-term adaptation of population to changing climate.

1.1.2 Time series analysis in environmental epidemiology

Time series methods have been hugely applied in environmental epidemiology during the last couple of decades to investigate the acute health effects of air pollution, and more recently outdoor temperature and other weather parameters (Armstrong 2006).

The data of time series in temperature and health study usually consists of a single observation for every day in a city or multiple cities. For each day (row) there is a temperature measurement (i.e. exposure) on that day, and the total number of deaths (i.e. outcome). In addition, the dataset may also contain daily measurements of potential confounders, for example ozone level and relative humidity. For a typical dataset, please consult an example in Figure 1.4 (London dataset)

Date	Ozone ($\mu g/m^3$)	Temperature (°C)	Relative humidity (%)	*n* deaths
1 Jan 2002	4.59	−0.2	75.7	199
2 Jan 2002	4.88	0.1	77.5	231
3 Jan 2002	4.71	0.9	81.3	210
4 Jan 2002	4.14	0.5	85.4	203
5 Jan 2002	2.01	4.3	93.5	224
6 Jan 2002	2.4	7.1	96.4	198
7 Jan 2002	4.08	5.2	93.5	180
8 Jan 2002	3.13	3.5	81.5	188
9 Jan 2002	2.05	3.2	88.3	168
10 Jan 2002	5.19	5.3	85.4	194
11 Jan 2002	3.59	3.0	92.6	223
12 Jan 2002	12.87	4.8	94.2	201

Figure 1.4 Example of time series dataset in temperature and heath study (London data) (Bhaskaran, Gasparrini et al. 2013)

The main aim of temperature and health study is to investigate an association between day-to-day variation in temperature and daily risk of death or other health outcomes (short-term effect). To do so, we often use time series regression with quasi-Poisson distribution to adjust for the over-dispersion of the outcome, while controlling for seasonality and long-term trend (Bhaskaran, Gasparrini et al. 2013). Figure 1.5 shows an example of time-series data of temperature and mortality in Ho Chi Minh City. In Figure 1.5 we can obviously see an association between temperature and mortality at short-term scale (e.g, in summer of year 2010 when temperature increased, the mortality counts also increased), while we also see the seasonality and long-term trend of temperature and mortality counts.

In addition, because the causal relationships between temperature, air pollutants, and mortality is complicated, adjusting for air pollutants or not in modelling temperature and mortality association is still a debate. For example, in previous studies Ozone was treated as a confounder, sometimes as an effect modifier, or as a co-exposure (Reid, Snowden et al. 2012). Though there is no simple solution for this debate, it is suggested that a Directed acyclic graphs (DAGs) could help to further clarify the role of air pollutants in temperature-mortality study.

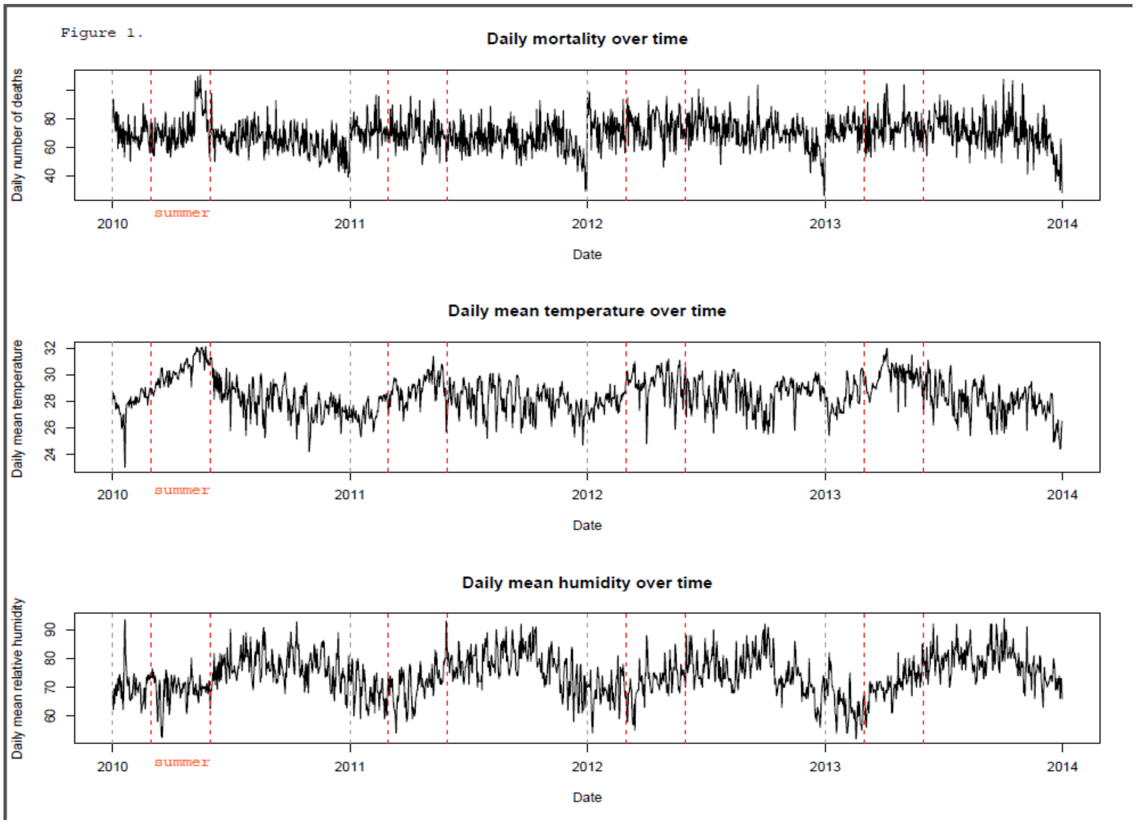

Figure 1.5 Time-series of mortality, temperature (°C) and relative humidity (%) in Ho Chi Minh City (2010-2013). The unit for temperature is Celsius (°C), and unit for relative humidity is percent (%)

The relationship between temperature and mortality has two main characteristics: non-linear relationship and lag effect. Previous studies showed a non-linear curve in temperature-mortality relationship (Basu and Samet 2002, Basu 2009). Meanwhile, lag effect means the temperature not only increases the risk of mortality at current day, but also persists for a period of time (from several days in heat effect to several weeks in cold effect) (Baccini, Biggeri et al. 2008, Muggeo and Hajat 2009). Recently, the non-linear relationship and lag effect can be modeled flexibly using distributed lag non-linear model (DLNM). This framework is firstly developed by Armstrong et.al (Armstrong 2006), following by an implementation of this framework into R, an open statistical software with several publications (Gasparrini, Armstrong et al. 2010, Gasparrini 2014). Since then, DLNM framework has been widely used in the field of temperature and health. Figure 1.6 shows an example of application of DLNM into temperature and health study.

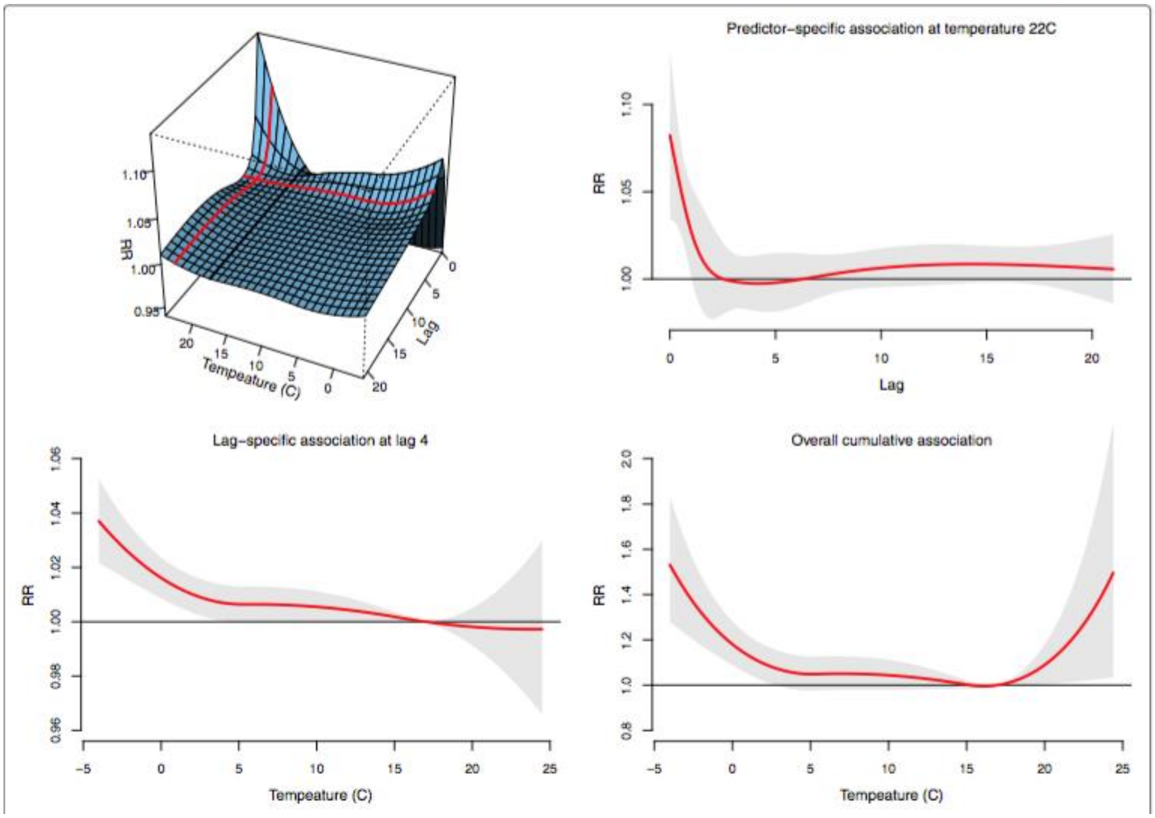

Figure 1.6 An example of application DLNM framework into temperature and health study (Gasparrini and Armstrong 2013)

1.1.3 Limitations of current evidences (temperature and health studies)

Global warming and other weather phenomena, such as El Niño, have sparked new interest in the weather-mortality relation. Most studies on exploring temperature-mortality relation, however, have been conducted in developed countries (i.e. North America, Europe), majority of which are temperate and cold climate regions (Hajat and Kosatky 2010). Meanwhile, very few studies have been done in tropical or subtropical developing countries (Mannig, Müller et al. 2013), particularly in Vietnam. According to Global Climate Index 2015, Vietnam ranked 7^{th} among the 10 countries most affected by climate change (Kreft, Eckstein et al. 2015). Over the last 50 years, the mean temperature of Vietnam has increased by 0.5-0.7^{0}C, and the sea level has risen by 20 cm.

Some evidence suggests that urban populations are more susceptible to heat compared to people living in non-urban areas (McGeehin and Mirabelli 2001). The main reason for that phenomenon is because of urban heat island (UHI) (Milojevic, Armstrong et al. 2016). However, no study so far has directly quantified the magnitude of attributable deaths due to urban heat island as well as the attributable deaths can be prevented by the increase of green space.

The temperature-mortality relationship has been described as a J- or U-, or V-shaped curve as common shapes (Figure 1.3), where a temperature, so called minimum mortality temperature (MMT), has a lowest risk of mortality. MMT is found to vary greatly by countries with different climate condition (Guo, Gasparrini et al. 2014, Honda, Kondo et al. 2014) and by time (Todd and Valleron 2015). This variation suggests some level of adaptation, but ability to characterize it is limited in previous studies by the absence of a method to describe uncertainty in estimated MMT. For example, one of the comment of reviewer in Todd et.al study is "I think it's a nice conclusion, but I'd like to see more to justify their conclusions—for example, confidence intervals or hypothesis testing" (Barrett 2015).

1.2 Aims and Objectives

This doctoral thesis aims to fill these gaps (stated in 1.1.3) by offering a multi-city assessment of the health effect of temperature in cities with different climate condition, including Vietnam (Hue and Ho Chi Minh City), and Japan (47 prefectures). Specific objectives are:

- To examine short term effect of temperature on mortality in Hue, a sub-tropical city of Vietnam using distributed lag non-linear model (DLNM).
- To investigate the urban heat island (UHI) effect on mortality in Ho Chi Minh city, Vietnam using dynamic downscaling with a regional weather model.
- To propose a novel statistical method to estimate MMT and its 95% confidence interval (CI). Then apply this method to explore the MMT movement in Japan with 40 years of data.

Each of the following chapter 2-4 will address one of the stated objectives above.

Chapter 2: Characterizing the relationship between temperature and mortality in tropical and subtropical cities: A distributed lag nonlinear model analysis in Hue, Viet Nam, 2009-2013

This chapter is based on the published report described below:

Dang TN, Seposo XT, Duc NHC, Thang TB, An DD, Hang LTM, Long TT, Loan BTH, Honda Y: **Characterizing the relationship between temperature and mortality in tropical and subtropical cities: a distributed lag non-linear model analysis in Hue, Viet Nam, 2009–2013**. *Global Health Action* 2016, **9**:10.3402/gha.v3409.28738

2.1 Abstract

Background: The short-term association between temperature and mortality was found to have U-, V-, or J shapes in developed temperate countries, however, in developing tropical/subtropical cities, it remains unclear.

Objectives: To investigate the relationship between temperature and mortality in Hue, a subtropical city in Viet Nam.

Methods: We collected daily mortality data from A6 system in Viet Nam with 6214 deceased persons between 2009 and 2013. A distributed lag nonlinear model (DLNM) was used to examine the temperature effects on all-cause, and cause-specific mortality by assuming negative binomial distribution for count data. We developed an objective-oriented model selection with four steps following the Akaike information criterion (AIC) rule (i.e. smaller AIC value is the better model).

Results: High temperature-related mortality was more associated with short lags, whereas, low temperature-related mortality was more associated with long lags. The low temperatures increased higher risk in all-category mortality compared to high temperatures. We observed elevated temperature-mortality risk in vulnerable groups such as: elderly people (high temperature effect, RR= 1.42, 95% CI=1.11–1.83; low temperature effect, RR=2.0, 95% CI=1.13–3.52), female (low temperature effect, RR=2.19, 95% CI=1.14–4.21), respiratory disease (high temperature effect, RR=2.45, 95% CI=0.91–6.63), and cardiovascular (high temperature effect, RR=1.6, 95% CI=1.15–2.22; low temperature effect, RR=1.99, 95% CI = 0.92 – 4.28).

Conclusions: In Hue, the temperature significantly increased risk of mortality, especially in vulnerable groups (i.e. elderly, female, people with respiratory and cardiovascular diseases). These findings may provide a foundation for developing adequate policies to address the effects of temperature on health in Hue City.

Keywords: high temperature effects, low temperature effects, hot effects, cold effects, time series regression

2.2 Introduction

Climate change is a significant and emerging threat to public health in many countries worldwide, which directly relates to a short-term increase in mortality rates during exposure to low or high temperature (Smith, Woodward et al. 2014). Most studies exploring the temperature-mortality relationship have been conducted in developed countries (i.e. North America, Europe) of which the majority are temperate and cold climate regions (Hajat and Kosatky 2010). Meanwhile, very few studies have been performed in tropical or subtropical developing countries (McMichael, Wilkinson et al. 2008, Mannig, Müller et al. 2013).

According to the Global Climate Index 2015, Viet Nam ranked 7th among the 10 countries most affected by climate change (Kreft, Eckstein et al. 2015). Unsurprisingly, 9 out of 10 of those countries were developing countries, and one country was a middle-income country. In a recent study by Guo et al. (Guo, Gasparrini et al. 2014) which assessed the global variation of high temperature and low temperature effects on mortality, the data set was collected and analyzed from 306 communities in 12 countries including Australia, Brazil, Thailand, China, Taiwan, Korea, Japan, Italy, Spain, United Kingdom, United States, and Canada, however, none of the 10 countries most affected by climate change mentioned above was included. This fact may cause an imbalance in assessing the impact of climate change on health.

In temperate and cold climate regions, the temperature-mortality relationship has been confirmed to have the usual U-, V-, or J-shapes (Baccini, Biggeri et al. 2008, Anderson and Bell 2009). However, the latest multi-country study showed an unusual so called L-pattern with a 0-21 lag period, where low temperature effects had a steeper slope and high temperature effects were almost flat (Gasparrini, Guo et al. 2015). Interestingly, these patterns only occurred in tropical or subtropical cities (**see Additional file 1, Figure S1**). The reason for the L-pattern being a characteristic in these tropical or subtropical cities remains unclear. In addition, some studies found that both high temperature and low temperature effects resulted in immediate increases in mortality in tropical and subtropical climate areas (Hashizume, Wagatsuma et al. 2009, Guo, Punnasiri et al. 2012). While other studies have observed that low temperature effects being delayed for several days to weeks in temperate and cold climate areas (Anderson and Bell 2009).

A better understanding of the temperature-mortality relationship in tropical/subtropical developing cities is crucial for the establishment of local intervention strategies against temperature effects, and contributes to projection studies on a global scale (Honda, Kondo et al. 2014). We therefore undertook time-series analyses coupled with DLNM to investigate the short-term (day-to-day variation) association between temperature and mortality in Hue, a subtropical city in Viet Nam. This is the first study in the field using daily mortality data in Viet Nam.

2.3 Materials and Methods

Study area:

Viet Nam is located between 8 and 24 degrees north of the equator, having remarkably different climates from the northern to the southern regions. According to the Kȍppen-Geiger classification, the climate of Southern Viet Nam (e.g., Ho Chi Minh City) can be classified as "tropical wet and dry climate - Aw" with the annual mean temperature above 18°C and a dry winter. On the other hand, the northern parts (e.g. Hanoi city) have a "humid subtropical - Cwa" climate, with the warmest month over 22°C, the coldest month between -3°C and 18°C and a dry winter (Peel, Finlayson et al. 2007). Hue is the capital city of Thua-Thien-Hue province in North-central Viet Nam, 71.7 km^2 in area and with a population of around 348000 in year 2013 (Committee) (14). The climate of Hue is "tropical monsoon climate - Am" under the Kȍppen-Geiger classification (Peel, Finlayson et al. 2007). Hue has a mild cold-wet winter and hot-dry summer with a rainy season from September to January and a dry season from March to August. The yearly average temperature is around 25°C, and yearly rainfall is approximately 3000 mm.

Mortality and weather data

Since 1956, mortality data in Viet Nam has been collected from the civil registration and vital statistics system. The quality of mortality data in this system, however, was very poor; the number of deaths especially was often incomplete and the cause of death inaccurate (Rao, Osterberger et al. 2010). Since 1992, a mortality data-collecting system based on the commune health center has been introduced in an official book named A6 (hereafter, namely A6 mortality reporting system) (Heath. 1992). Data from the A6 are collected at the commune health center level and then forwarded to the provincial and central levels. The quality of A6 mortality data is good enough as validated in a previous study (Stevenson, Ngoan le et al. 2012). In this study, daily mortality data from 27 community health centers in Hue was collected from the A6 mortality reporting system, from 2009-2013. The data included 6214 deceased persons with information about date of death, sex, age, and cause of death classified by the 10th Revision of the International Classification of

Disease (ICD10) code. The deceased person was, however, anonymous (only name abbreviations were used). We obtained permission from Thua-Thien-Hue provincial health department before collecting the data. Weather data was obtained from the National Oceanic and Atmospheric Administration's (NOAA) National Climate Data Center (NCDC). The necessary information included daily minimum, average, and maximum temperatures, dewpoint temperature, and relative humidity. We did not include air pollution levels in our model due to the data unavailability. However, some studies found that temperature effect was not confounded or modified due to air pollution exposure (Hales, Salmond et al. 2000, Rainham and Smoyer-Tomic 2003, Basu, Feng et al. 2008, Pinheiro, Saldiva et al. 2014).

Statistical model

We used a negative binomial coupled with a distributed lag nonlinear model (DLNM) to examine the short-term association (day-to-day variation) between temperature and all-cause mortality (i.e. the daily total number of death counts). Negative binomial distribution was employed to adjust for the Poisson over-dispersion of daily death count Y_t (23). In addition, DLNM was applied to describe the nonlinear effect of temperature (in the temperature-mortality dimension) and lag (in the lag-mortality dimension) simultaneously (Gasparrini, Armstrong et al. 2010). The general model is specified as follows:

$$Y_t \sim Negative\ binomial\ (\mu_t)$$

$$Log\ (Y_t) = \alpha + \beta_1 {*} T_{t,l} + \beta_2 {*}\ DOW_t + \beta_3 {*} NCS\ (time,\ df{=}i/year) + \beta_4 {*} NCS(relative\ humidity,\ df{=}3) + \beta_5 {*} NCS(dewpoint\ temperature,\ df{=}3) \quad (1)$$

where α is the intercept; t is the day of the observation; Y_t is daily all-cause death count on day t; $T_{t,l}$ is a matrix obtained by applying the "cross-basis" DLNM functions to temperature, β_1 is the vector of coefficients for $T_{t,l}$, and l is the lag days. According to previous studies, the natural cubic spline (NCS) with three degrees of freedom (df) was selected to control for potential confounding factors (i.e. daily average relative humidity and daily average dewpoint temperature) (Peng, Dominici et al. 2006, Guo, Punnasiri et al. 2012). *Time* is a continuous variable ranging from 1 on the starting day of observation to 1811 on the final day of observation within five years of data (2009-2013). To adjust for the long-term trend and seasonality, we used NCS smoothing for the *time* variable with *i* degrees of freedom per year. The day of the week on day t (DOW_t) was used to control for the effect of weekday on daily mortality (e.g. on the weekends, mortality tended to be higher than that on week days). After a series of steps for model selection (**Additional file 2**), the final model of temperature and all-cause mortality included 5 df per year of time variable (*i* value) for controlling seasonality and long-term trend, an “NCS –NCS” DLNM using 4 df for the temperature dimension and 5 df for the lag dimension with maximum lag equal to 28. The model checking procedure was carried out to check the fitness of this final model and can be found in **Additional file 3**. For the cause-, age-, and sex-specific analyses, the outcome variable, all-cause daily death count Y_t, was changed to cause-, age-, and sex-specific daily death count, whereas, the structure of predictors was the same as in the final model of all-cause mortality analysis. The cause-specific analysis included four categories: non-external (ICD10 code A00-R99), cardiovascular (ICD10 code I00-I99), respiratory (ICD10 code J00-J99) and cancer mortality (ICD10 code C00-D48). The external mortality was excluded due to very small number of deaths per day (0.2 daily mean). The age-specific analysis included two groups: 0-64 years old and >=65 years old (the 0-14 years old group was not separated due to the small daily deaths). Given the technical nature of the statistical model, we invite readers to refer to a previous publication by Bhaskaran et al. (Bhaskaran, Gasparrini et al. 2013).

Definition of high and low temperature effects: To quantify effects of temperature on mortality, we calculated relative risk (RR) of low temperature effect comparing the 1st temperature percentile (15.8oC) to 50th temperature percentile (26.3oC), and RR of high temperature effect comparing the 99th temperature percentile (32.4oC) to 50th temperature percentile, using the final DLNM model. RRs can be calculated at single lag (from lag 0 to lag 28), or can be can be calculated at cumulative lag (lag 0-2 for high temperature effect, and lag 0-28 for low temperature effect). For example, the cumulative RR of high temperature effect on mortality at lag 0-2 is estimated by $\exp((\beta 0 + \beta 1+ \beta 2)*(32.4-26.3))$, where βi are obtained by using a DLNM function of the average temperature with $i = 0, 1, 2$ previous days.

2.4 Results

Descriptive statistics

A total of 6214 all-cause deaths were recorded in the study period from 2009 to 2013, including 2215 (35.64%) from cardiovascular diseases and 1074 (17.28%) from cancer. The other main causes of death in the data were classified as malaise (ICD10 code R53), and cachexia (ICD10 code R64), which amounted to 1767 cases (accounting for 28.4% of all-cause deaths). These causes of death are, however, mainly associated with ageing condition. We decided to not examine the association between these specific causes with temperature, because we have already included the association analysis between age-specific mortality and temperature as specified in the statistical model section. The proportion of male deaths was slightly higher compared to that of female deaths (53.49% vs. 46.51%). The majority of the deceased were older than 65 years (65.5%). **Table 2.1** shows the descriptive statistics of daily mortality and daily weather conditions. On average, all-cause daily deaths amounted to three cases and ranged from 0 to 12 cases. The mean daily maximum temperature was 29.9°C, average temperature 25.7°C, and minimum temperature 21.7°C. These three temperature indicators were strongly associated with each other as shown in **Figure 2.1**.

Table 2.1. Summary statistics of daily weather conditions and daily mortality in Hue, Viet Nam, 2009-2013.

Variables	Mean	SD	Minimum	Percentile			Maximum
				25%	50%	75%	
Maximum temperature (°C)	29.9	5.5	15	26.2	31	34.2	42
Average temperature (°C)	25.7	4.1	14.4	23	26.3	28.9	33.9
Minimum temperature (°C)	21.7	3.1	12.7	19.8	22.8	24.2	27.5
Average dew point temperature (°C)	22.1	2.7	12.5	20.6	22.9	24.1	28.5
Average relative humidity (%)	81.9	12.7	21.9	75.8	85	91.1	100
All-cause mortality#	3.4	2.2	0	2	3	5	12
Cause-specific mortality#							
External cause	0.2	0.4	0	0	0	0	4
Non-external cause	3.2	2.1	0	2	3	4	12
Cardiovascular	1.2	1.2	0	0	1	2	7
Respiratory	0.1	0.3	0	0	0	0	2
Cancer	0.6	0.8	0	0	0	1	5
Sex-specific mortality#							
Male	1.8	1.5	0	1	2	3	10
Female	1.6	1.4	0	1	1	2	8
Age-specific mortality#							
0-14 years old	0.1	0.25	0	0	0	0	2
15-64 years old	1.1	1.1	0	0	1	2	7
>=65 years old	2.2	1.7	0	1	2	3	12

the unit of mortality is number of deaths per day

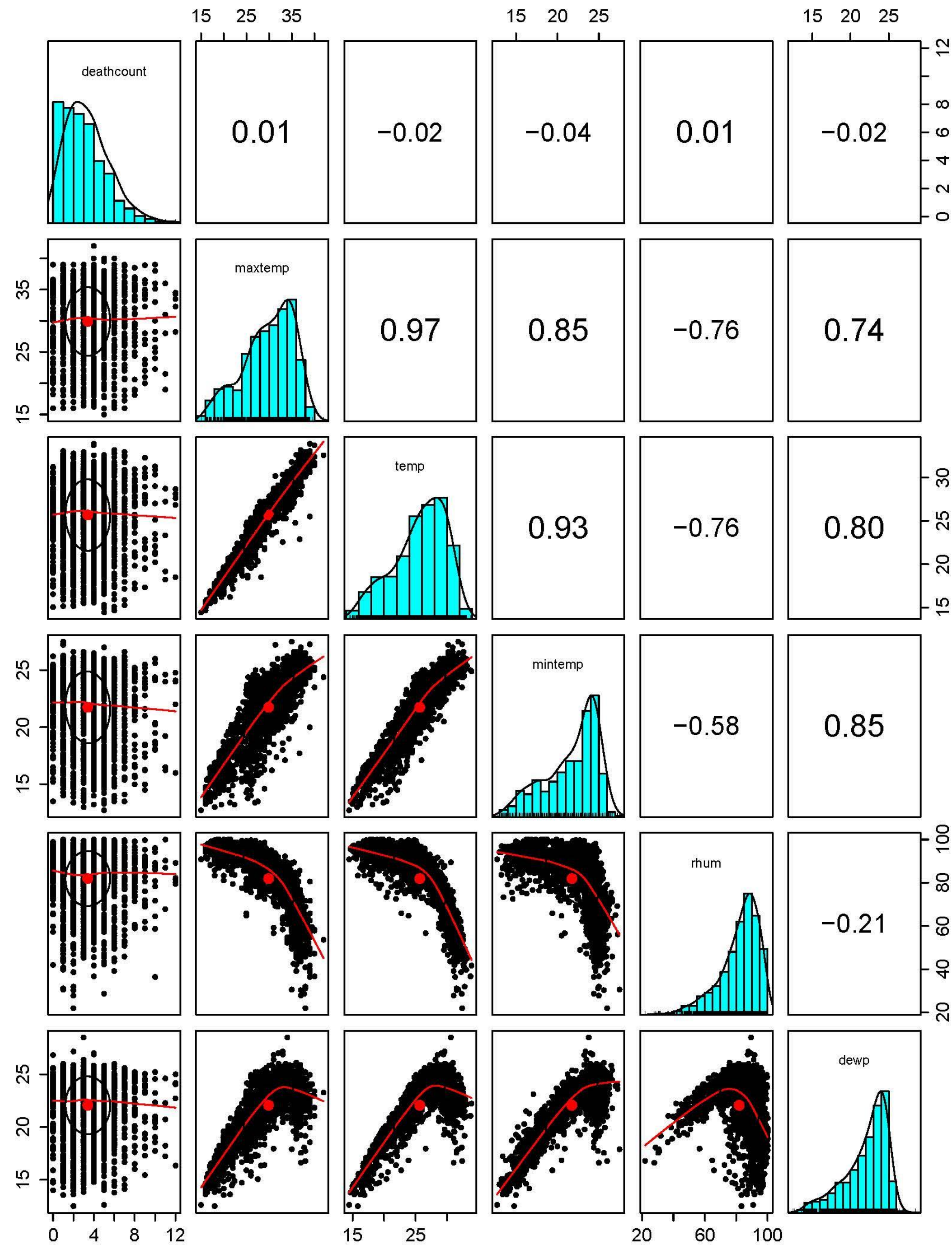

Figure 2.1. Histograms, scatter plots and correlation coefficients between weather conditions and mortality in Hue, Viet Nam, 2009-2013

Temperature-mortality relationship

The cumulative overall temperature effects on all-cause mortality at different lag periods are shown in **Figure 2.2**. In lags 0-1 and 0-2, the temperature-mortality relationship had a J-shaped pattern where only high temperatures increased the risks of mortality. In lags 0-3, 0-4 and 0-7, the relation appeared U-shaped wherein both high and low temperatures increased the risks of mortality. From lag 0-14 to lag 0-28, however, the pattern was L-shaped wherein only low temperatures significantly increased the risks. These results indicated that the high temperature-related mortality was more associated with short lags, whereas, low temperature-related mortality was more associated with long lags.

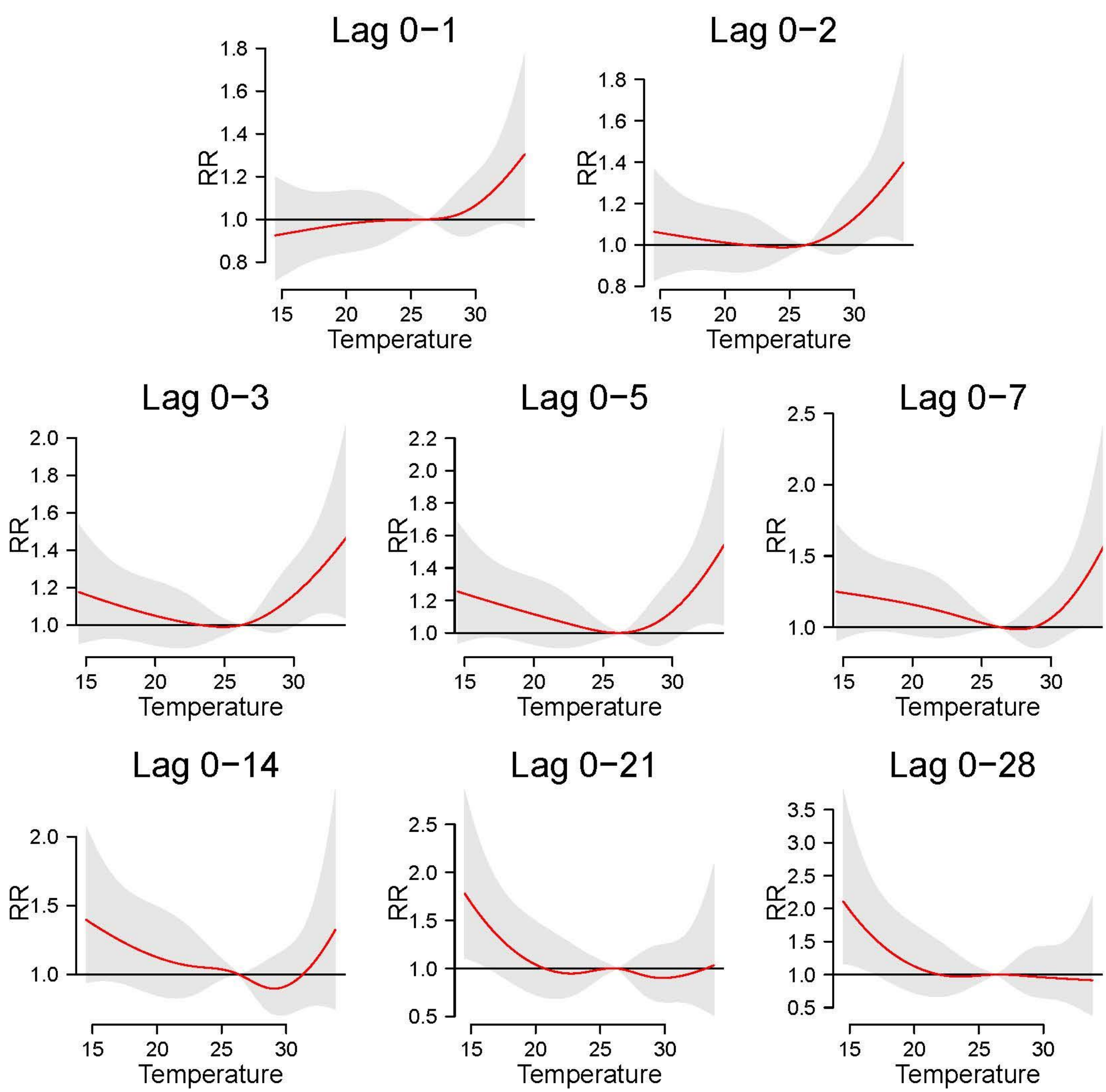

Figure 2.2. Cumulative overall temperature effects on all-cause mortality at different lag periods.

The final NCS-NCS model defined by DLNM cross-basis functions with 4 df for temperature dimension and 5 df for lag dimension. The reference was at the median of temperature. The red lines are the cumulative RRs, and grey regions are 95% confidence intervals.

Figure 2.3 shows the cumulative overall temperature effects on age-, and sex-specific mortality. There was no separate analysis for the 0-14 age group due to the small number of daily deaths. The elderly group (>=65 years old) displayed higher risk of mortality at both high and low temperatures compared to 0-64 years old group. The high temperature effects in short lags (lag 0-2) were similar between male and female. In contrast, the low temperature effects in long lags (lag 0-28) were more prominent among females compared to males. In the cause-specific analysis (**Figure 2.4**), we observed a similar pattern with that of all-cause analysis, wherein high temperature effects were observed in short lags and low temperature effects in long lags, respectively. The exception, however, was cardiovascular mortality where the high temperature effects manifested in short lags and lasted in long lags. The pattern of temperature-mortality in respiratory-related case at long lags was not clear. One of the possible explanations for that is the number of respiratory deaths per day are insufficient.

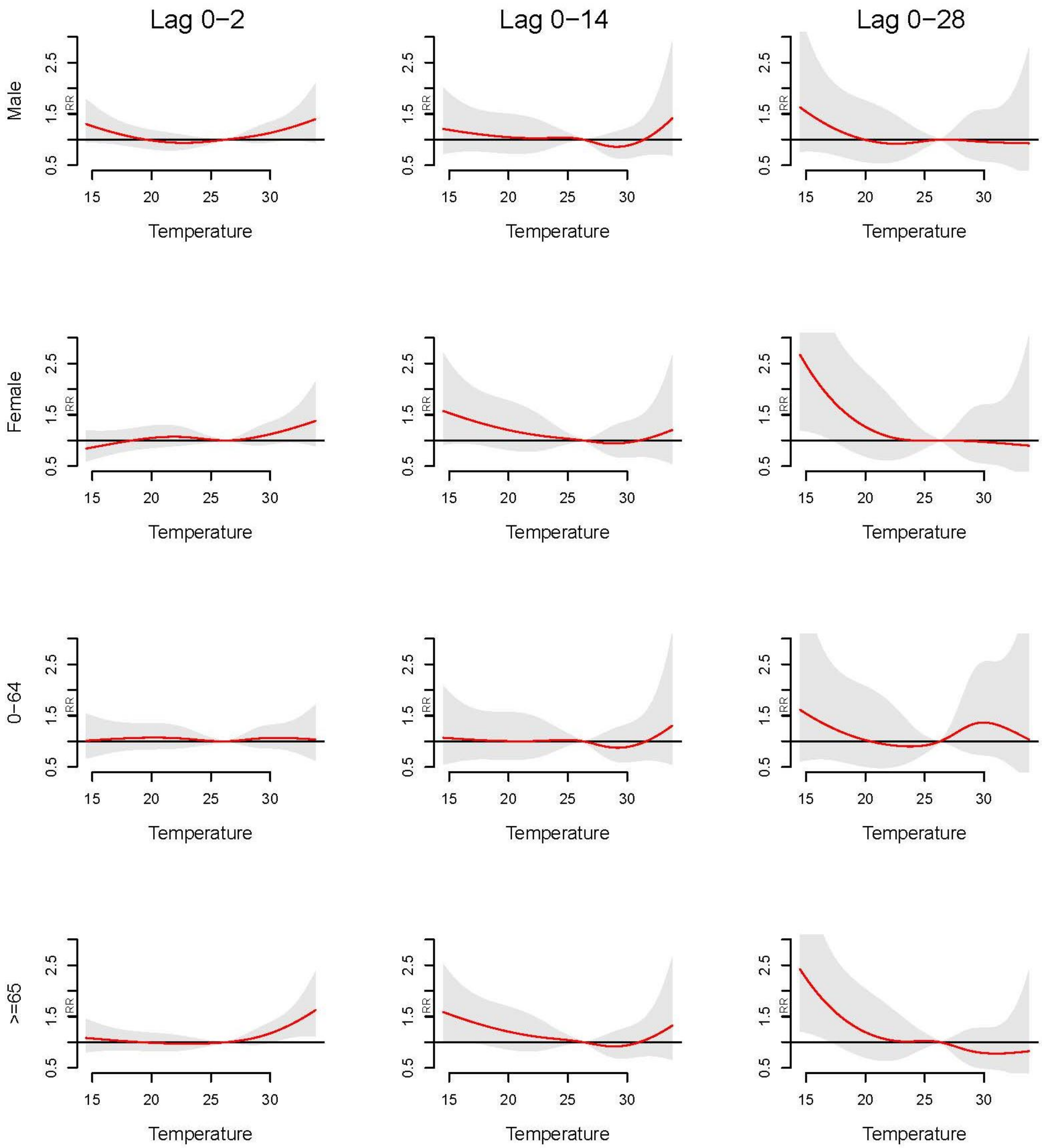

Figure 2.3. Cumulative overall temperature effects on age-, and sex-specific mortality.

Red lines are the cumulative RRs, and grey regions are 95% confidence intervals.

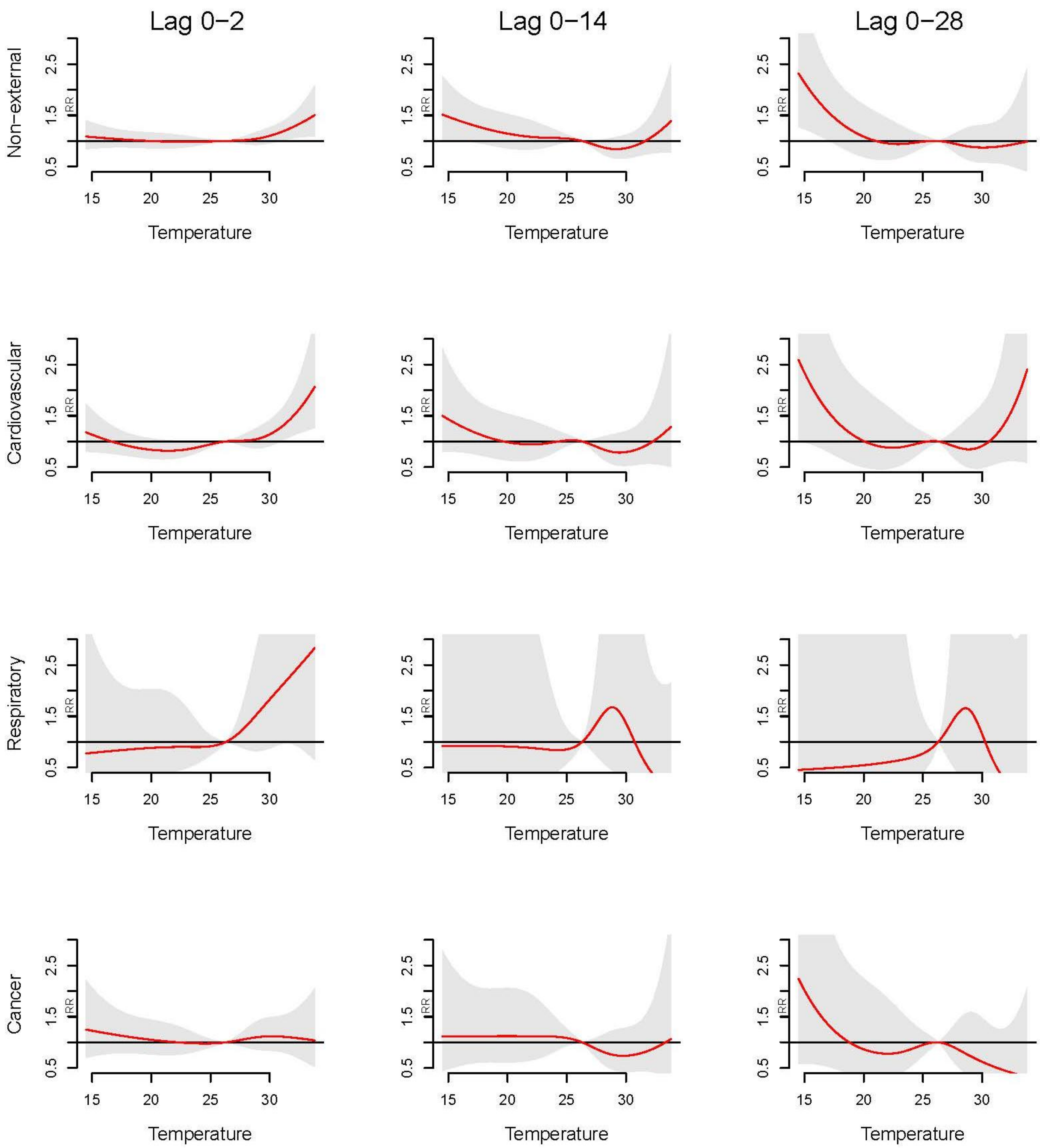

Figure 2.4. Cumulative overall temperature effects on cause-specific mortality.

Red lines are the cumulative RRs, and grey regions are 95% confidence intervals.

Figure 2.5 displays high and low temperature effects on all-cause and cause-specific mortality at single lag (please refer to "definition of high and low temperature effects" in methods section for more detail). Both high and low temperature effects caused an immediate increase in the risk of all-cause mortality as well as cause-specific mortality, with high temperatures being affected more acutely than low temperatures (high temperature effects occurred in day 0 vs. low temperature effects occurred after 2 days). In addition, high temperatures induced mortality displacement, while low temperatures did not show mortality displacement (except for cancer mortality where low temperatures also induced mortality displacement).

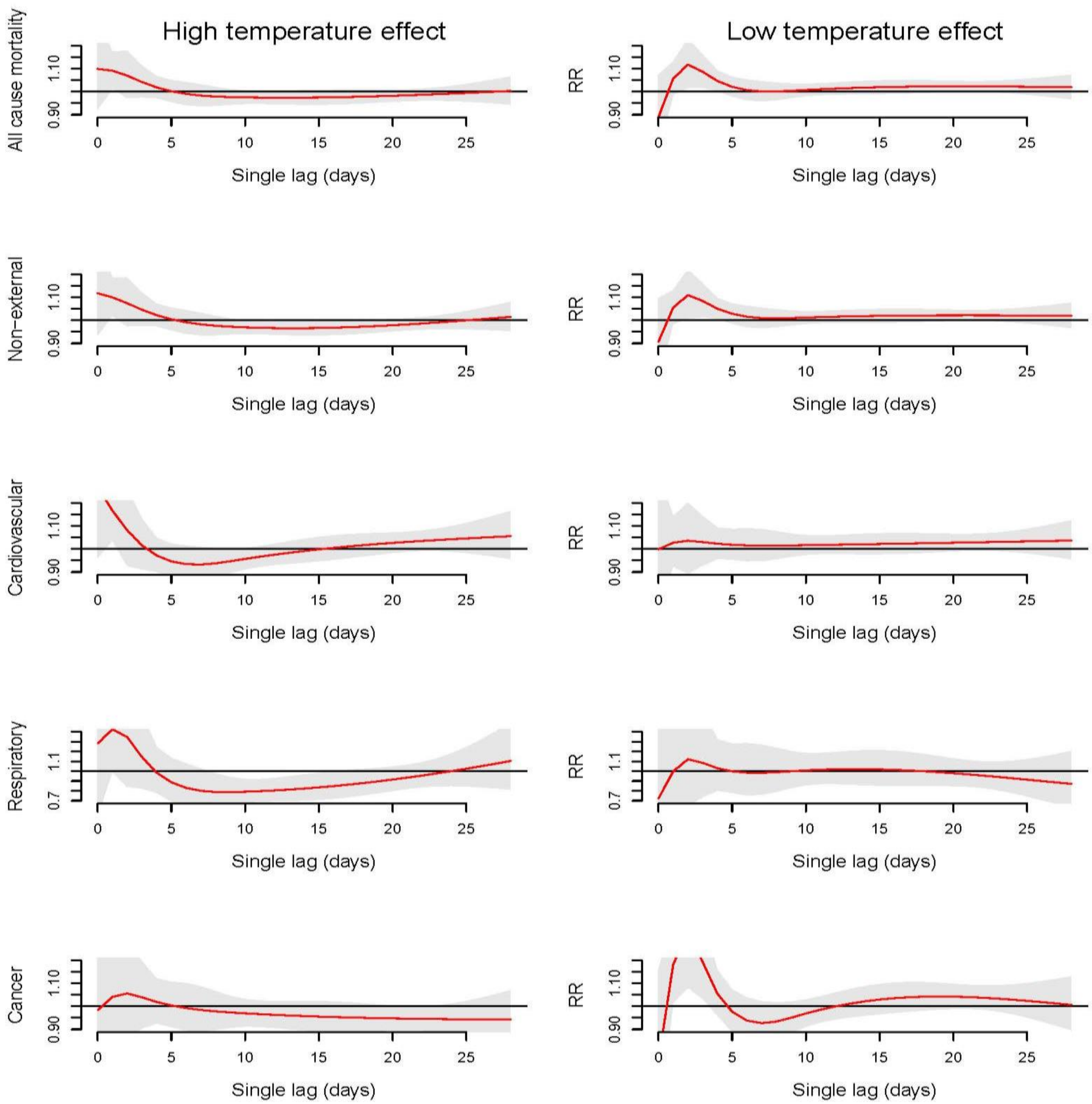

Figure 2.5. The lag structures of high and low temperature effects on all-cause and cause-specific mortality.

The high temperature effect (left) is the effect of the 99th temperature percentile (32.4°C) relative to the 50th temperature percentile (26.3°C). The low temperature effect is the effect of the 1st temperature percentile (15.8°C) relative to the 50th temperature percentile (26.3°C).The red lines are the RRs at single lag, and grey regions are 95% confidence intervals.

Table 2.2 shows the cumulative RRs of high temperature effect in lag 0-2, and low temperature effect in lag 0-28 in cause-, age-, and sex-specific mortality. In all-category mortality (i.e. including cause-, age-, and sex-specific mortality), the RRs of low temperature effect were higher than RRs of high temperature effect (except for respiratory disease). We observed elevated temperature-mortality risk in vulnerable groups such as: elderly people (high temperature effect, RR= 1.42, 95% CI=1.11–1.83; low temperature effect, RR=2.0, 95% CI=1.13–3.52), female (low temperature effect, RR=2.19, 95% CI=1.14–4.21), respiratory disease (high temperature effect, RR=2.45, 95% CI=0.91–6.63), and cardiovascular (high temperature effect, RR=1.6, 95% CI=1.15–2.22; low temperature effect, RR=1.99, 95% CI = 0.92 – 4.28).

Table 2.2. The cumulative effects of high and low temperatures on cause-, age-, and sex-specific mortality.

Statistic	**High temperature effect [a] (95%CI)**	**Low temperature effect [b] (95%CI)**
All–cause mortality	1.28 (1.04–1.58)*	1.78 (1.10–2.88)*
Cause–specific mortality		
Non–external	1.32 (1.07–1.63)*	1.88 (1.15–3.07)*
Cardiovascular	1.6 (1.15–2.22)*	1.99 (0.92–4.28)
Respiratory	2.45 (0.91–6.63)	0.47 (0.03–8.19)
Cancer	1.08 (0.69 – 1.68)	1.71 (0.58–5.05)
Sex–specific mortality		
Male	1.28 (0.99–1.67)	1.42 (0.77–2.63)
Female	1.27 (0.95–1.7)	2.19 (1.14–4.21)*
Age–specific mortality		
0–64 years old	1.05 (0.76–1.46)	1.43 (0.65–3.14)
>=65 years old	1.42 (1.11–1.83)*	2.0 (1.13–3.52)*

[a] High temperature effect is the cumulative RR comparing 99[th] temperature percentile (32.4°C) relative to 50[th] temperature percentile (26.3°C) in lag 0-2
[b] Low temperature effect is the cumulative RR comparing 1[st] temperature percentile (15.8°C) relative to 50[th] temperature percentile (26.3°C) in lag 0-28
* Significant at p value<0.05

2.5 Discussion

The study examined the temperature-mortality relationship in Hue, Viet Nam during the period 2009-2013. We found that the temperature-mortality cumulative overall curves changed through lag periods (**Figure 2.2**). Considering short lags, only high temperature effects were significant (formed a J-shape). However, considering long lags, only low temperature effects were significant (formed an L-shape). McMichael et al. (McMichael, Wilkinson et al. 2008) and Wu et al. (Wu, Xiao et al. 2013) found the same phenomenon happened in other tropical and subtropical cities. This phenomenon raised an important issue with regard to choosing the adequate lag periods for modeling the temperature-mortality relationship. For example, most studies chose lag 0-1 to model high temperature effects on mortality, and the authors found significant effects of high temperature on mortality (Hajat, Kovats et al. 2007). By restricting the study to short lags for high temperatures, however, other characteristics of high temperatures in long lags, such as mortality displacement, may not be fully described.

The cumulative effects of temperature on all-cause mortality had an L-shape in lags 0-14, 0-21 and 0-28 (**Figure 2.2**), which was induced by mortality displacement occurring in high temperatures (**Figure 2.5**). Mortality displacement refers to a phenomenon whereby excess daily deaths result from short-term displacement of the time of death (e.g. occurring in most frail individuals whose deaths have only been brought forward by a few days) (Basu 2009). Another study showed an L-shaped temperature-mortality relationship when quantifying the effect of temperature on mortality in Ha Noi (Xuan le, Egondi et al. 2014). Ha Noi is in the northeast of Viet Nam and has a similar tropical climate and temperature distribution to Hue. The study in Ha Noi, however, used monthly data, therefore the occurrence of mortality displacement could not be fully examined. In addition, other studies using daily mortality data in tropical/subtropical regions also showed an L-shaped pattern (Wu, Xiao et al. 2013, Bai, Cirendunzhu et al. 2014). The lag structures of these studies, nevertheless, had not been described in detail to confirm whether or not mortality displacement occurred. Basu et al. (Basu and Malig 2011) and Hajat et al. (Hajat, Armstrong et al. 2005) addressed the presence or absence of mortality displacement depending on several factors including the baseline health status of population (presence of chronic diseases), the population at risk (elderly people), and other local factors. Mortality displacement occurring in Hue is understandable, because a majority of deaths were attributed to chronic diseases (35.64% cardiovascular diseases and 17.28% from cancer diseases) and the proportion of the deaths in the elderly older than 65 years was quite high (65.5% of the total deaths).

Previous studies tried to project the impact of heat-related death on a global scale (Takahashi, Honda et al. 2007). As pointed out by Honda et al. (Honda, Kondo et al. 2014) the estimation of optimum temperature (OT) and the risk function of temperature on mortality in each area were needed to conduct the projection on a global scale. To estimate the OT, the temperature-mortality had to be assumed to have a V-shape (where the OT is the base of the V-shape). In Hue, however, and in other tropical/subtropical cities **(as shown in Additional file 1, Figure S1)**, the temperature-mortality relationship had an L-shape with long lags. Therefore, the spatial pattern of temperature-mortality should also be taken into account when projecting the impact of heat-related death on a global scale. Hajat et al. (Hajat and Kosatky 2010) and Seposo et al. (Seposo, Dang et al. 2015) showed a huge paucity of research on the effect of temperature on mortality in tropical/subtropical developing areas compared to temperate/cold developed areas. Thus, for a better heat-related death projection on a global scale, more studies from tropical/subtropical developing areas warrant further exploration.

In Hue, a subtropical city of Viet Nam showed higher mortality risk induced by low temperatures (in long lags) compared to high temperatures (in short lags) in all-category mortality (**Table 2.2**). Other studies in subtropical regions (i.e. Brisbane, Australia and Guangzhou, China) reported that mortality in winter was higher than in summer (Ou, Song et al. 2013, Chau and Woo 2015). In a multi-country study, Gasparrini et al. (Gasparrini, Guo et al. 2015) found that the attributable deaths were more pronounced for low than for high temperatures, and the differences in attributable deaths between low and high temperatures were even more distant in tropical or subtropical cities (**see Additional file 1, Figure S1**). These results suggest that population in subtropical region suffers more from low temperature effects than high temperature effects. Within the context of global warming, many previous studies focused on the high temperature effects rather than low temperature effects. However, this finding indicated that the government of Hue City should pay attention to both high and low temperature effects when developing health policies in order to reduce impact of temperature effects. In addition, the acute low temperature effects in this study (**Figure 2.5**) was also observed in other tropical/subtropical regions such as in Chiang Mai city, Thailand (Kòppen tropical wet and dry climate-Aw) (Guo, Punnasiri et al. 2012), Monterey, California (Kòppen-dry summer subtropical climate-Csb), Saō Paulo (Kòppen-humid subtropical climate-Cfa), Mexico (Kòppen-subtropical highland climate-Cwb) (McMichael, Wilkinson et al. 2008). These phenomena could be understood since people in tropical/subtropical regions were not well acclimatized to cold weather.

Regarding the age-specific analysis, the effects of both high and low temperature were greater among the elderly (>=65 years old) compared to 0-64 years old group (**Figure 2.3 and Table 2.2**). Numerous studies have provided similar evidence that the elderly population is among the most vulnerable groups (Basu 2009). Aging induces a decrease in thermoregulatory abilities, together with the increased prevalence of chronic diseases, which are likely contribute to vulnerability to temperature effects in elderly people (Gasparrini, Armstrong et al. 2012). We found that low temperature effects were more pronounced for females than for males, which is in light with Ou et al.'s study (Ou, Song et al. 2013). The high temperature effects, however, were not significantly different in females compared to males. So far the evidence that sex modifies the effects of high temperature on mortality depends on location and population (Basu and Ostro 2008). We also observed that the RR of high temperature was highest in respiratory mortality through it did not reach significant level (**Table 2.2**). One of the physiological mechanisms that triggers respiratory deaths induced by high temperatures is that high temperatures can affect the lung function of chronically-ill and older people (Worfolk 2000, D'Ippoliti, Michelozzi et al. 2010). It should be noted that the effects were observed in cardiovascular mortality in both high and low temperature (**Figure 2.4 and Table 2.2**). It implies that patients with cardiovascular disease should be taken care of during both hot and cold periods. Losing water and salt from sweating during exposure to high temperatures can cause haemoconcentration, which in turn leads to thrombosis. Moreover, exposure to low temperatures will slow down blood flow to the skin in order to preserve heat; increases blood cholesterol, levels of red blood cell counts and plasma fibrinogen. This will also induce thrombosis due to haemoconcentration (Carder, McNamee et al. 2005).

Selecting an appropriate model is crucial when examining the temperature effects on mortality, as it can affect the ability to make a prediction (Anderson and Bell 2009). In this study we proposed an objective-oriented DLNM approach based on the AIC rule in analyzing the temperature-mortality relationship rather than making strong prior assumptions. For example, choosing the df for time variable to control seasonality and long-term trend, choosing the best temperature indicators (i.e. maximum, average or minimum temperature), as well as choosing the best fit df for NCS-NCS in temperature dimension and lag dimension.

Our research contained some limitations, such as the lack of control for air pollution. The effect modification by air pollution, however, seems to be negligible, thus its inclusion might not really alter the relationship (Basu, Feng et al. 2008, Pinheiro, Saldiva et al. 2014). The information of A6 mortality data contained some missing values and the causes of death were misclassified in some cases (i.e. inconsistencies between the cause of death in text and ICD codes). In order to ensure the quality of mortality data, we sent our facilitators to every community health centers for random checking and collecting of missing values.

2.6 Conclusion

This is the first study using daily all-cause and cause-specific mortality data to examine the effects of temperature on mortality in Hue, Viet Nam. In Hue, high temperature-related mortality was more associated with short lags, whereas, low temperature-related mortality was more associated with long lags. Both high and low temperature effects occurred acutely, but low temperature effects lasted longer than high temperature effects and the high temperature effects induced mortality displacement. The low temperatures increased higher risk in all-category mortality compared to high temperatures. We observed that elderly people, females, patients with cardiovascular and respiratory disease were the most vulnerable groups affected by temperatures. These findings may provide a foundation for developing adequate policies to address the effects of temperature on health in Hue City.

2.7. Supplement material chapter 2

Please refer to the online version at:
http://www.globalhealthaction.net/index.php/gha/rt/suppFiles/28738

Chapter 3: Attributable deaths due to urban heat island effect in a mega city of Vietnam: an application of dynamic downscaling with a regional weather model

Authors:

Tran Ngoc Dang[1*], Doan Quang Van[2], Xerxes T. Seposo[1], Hiroyuki Kusaka[3], Yasushi Honda[4]

1.Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Japan

2.Graduate School of Life and Environmental Sciences, University of Tsukuba, Japan

3.Center for Computational Sciences, University of Tsukuba, Japan

4. Faculty of Health and Sport Sciences, University of Tsukuba, Tsukuba, Japan

* Contact person: ngocdangytcc@gmail.com

Declaration:

In this chapter I used some results from previous publication by Doan Quan Van and Hiroyuki Kusaka (Doan and Kusaka 2015), who are also co-author of this chapter. The full paper of Doan and Kusaka can be found at the Appendix 1.

This chapter is prepared as a "Research article" manuscript to be summited to a peer-review international journal.

3.1 Abstract

Introduction: Previous studies have examined the *intra-city* variation in heat-related mortality; of these, however, no study directly quantifies magnitude of the urban heat island (UHI) attributable risks to mortality. The purpose of this study is to investigate the attributable deaths due to UHI within Ho Chi Minh (HCM) city, a mega city of Vietnam using dynamic downscaling with a regional weather model.

Methods: The analysis consists of the following steps: (1) We used dynamic downscaled weather model to estimate spatial temperatures of each districts with in HCM city. (2) For each district we calculated mortality attributable fractions (AFs) due to total heat, extreme-heat, and mild-heat, following the previous method by Gasparrini et al. (3) The difference of AF due to total heat between central districts (centers) and outer districts (outers) is then calculated, which we define as AF due to UHI effect. (4) We then perform linear regression between AFs with green space percentage of each district.

Results: Overall, centers were hotter and drier compared to outers. The mean of average temperature of centers was 0.9^{o}C higher compared to outers (28.4^{o}C vs. 27.5^{o}C); whereas, the means of average relative humidity in centers and outers were 68.6%, and 75.1% respectively. In addition, number of hot days (average temperature >= 30^{o}C) was higher in centers compared to outers (108 days vs. 42 days). The AFs due to total heat, extreme-heat, and mild-heat were 1.42%, 0.3%, and 1.12% respectively in centers; and were 1%, 0.26%, and 0.74% respectively in outers. Therefore, the AF due to UHI effect was 0.42%. Every increase in 1 km^2 green space per 1,000 people can prevent 7.4 deaths attributable to heat in HCM city

Conclusions: The study found a difference in weather conditions, and AFs due to heat components between central districts and outer districts. The AF due to UHI effect in HCM city was substantial at 0.42%, and every km2 green space increase per 1,000 people can prevent 7.4 deaths due to heat. This information is valuable for authorities in considering how much the UHI effect on mortality may be minimized by implementing appropriate planning and intervention.

Chapter 4: Minimum Mortality Temperature (MMT) in Japan: How did it change in 40 years?

Author:

Tran Ngoc Dang[1*], Xerxes T. Seposo[1], Yasushi Honda[2]

1.Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Japan

2. Faculty of Health and Sport Sciences, University of Tsukuba, Tsukuba, Japan

* Contact person: ngocdangytcc@gmail.com

This chapter is prepared as a "Short communication" manuscript to be summited to a peer-review international journal.

4.1 Abstract

Background: Temperature-mortality relationship has described as J-, U-, V- shapes, in which the base of the shape is minimum mortality temperature (MMT). This study aims to propose a novel method to estimate the 95% confidence interval (CI) of MMT, and use that method to investigate direction as well as speed of MMT temporal movement in Japan using 40 years data.

Methods: The analysis consists of the following steps: (1) Divided Japanese data into four decades. For each decade we modeled prefecture temperature-mortality relationship using distributed lag non-linear model (DLNM). (2) For calculating MMT and empirical 95% CI of MMT, we used a simulation method with 1000 times repetition. (3) A linear model: MMT = α + β1*time (time=1 for first, =2 for the second decade, etc.) + β2*Tmax85 (85th maximum temperature percentile for each decade) is constructed to explore the speed of MMT movement as well as to predict MMT using Tmax85 variable.

Results: We successful estimated the 95% CI of MMT in each decades from 1973-2012 of 47 prefectures in Japan. In overall, the MMT moved to the right over 40 years in Japan, implies some level of adaptation to the heat. The linear model to estimate MMT from Tmax85, controlling for time trend of MMT is *MMT = 11.18 + 0.87*decade + 0.52*Tmax85*

Conclusions: The study found a increased trend of MMT in Japan, which indicates considerable adaptation to the heat. Our method is quite promising in estimation of uncertainty of MMT as well as estimation of MMT using Tmax85; it can be used to determine threshold for heat-health action plan, and the heat-related projection model.

Chapter 5: General discussions

5.1. Significance of the study

This thesis (hopefully) can contribute to literature in the field of temperature and health by main points below:

Chapter 2 characterized temperature and mortality relationship in Hue, a subtropical city in Vietnam using a flexible distributed lag non-linear model (DLNM). The results from chapter 2 could help to achieve a better understanding of the temperature-mortality relationship in tropical/subtropical developing cities, which is crucial for the establishment of local intervention strategies against temperature effects, and contributes to projection studies on a global scale.

Chapter 3, to the best of our knowledge, for the first time quantified the attributable deaths due to urban heat island, and provided information about the attributable deaths can be prevented by an increase of green space. Such kind of information would be valuable for authorities in implementing appropriate planning and intervention policy in order to mitigate the health effects of temperature. In addition, this study used dynamic downscaling with a regional weather model (WRF model) to estimate the climate condition (e.g. temperature, humidity) at the district levels within a city. This WRF model can overcome the limitation of previous studies, in which they usually use one weather station or average value of several weather stations in a city as a approximate of city-wide temperature (Guo, Barnett et al. 2013). More ever, so far the studies projecting heat related mortality at global scale have not yet considered the UHI effect in projection (Honda, Kondo et al. 2014). The results of chapter 3, however, showed a substantial UHI effect on mortality, which suggest that considering UHI can results a better projection in future studies.

Chapter 4 proposed a novel statistical method to estimate MMT and its 95% CI. This novel method is quite helpful because it help to justify the hypothesis testing of the adaptation level based on MMT in future studies. In addition, the method can be useful for determining the threshold of heat warning system because it consider the uncertainty of MMT. It is worth to notice that, recently Tobias et.al published a paper proposing a similar idea in estimating MMT uncertainty using Spanish data [http://www.ag-myresearch.com/2016_tobias_epidem.html]; through Tobias method and the method proposing here are independent at the time of discovery. In chapter 4, we also used this method to apply for Japan in order to understand the adaptation level to heat of Japanese in 40 years, and we provided a better equation to estimate MMT from Tmax85 when controlling for the time trend of MMT.

5.2. Future development

Research on projection impact of UHI on mortality

The study in chapter 3 contains several limitations. Therefore I am going to extend this study as below direction:

Firstly, the study only conducted in Ho Chi Minh City, which is a tropical city with rapid urbanization. Therefore, the results of this study may not generalize to other cold, temperate climate cities or cities have not the same pace of urbanization compared to Ho Chi Minh City. In a near future I want to explore this topic more using national-wide Japanese data.

Secondly, We did not identify vulnerable groups due to UHI effect in the study in chapter 3. An association study between UHI and cause-, sex-, age-, social-economic specific mortality is warranted to overcome this deficit.

Thirdly, so far we only evaluated the impact of currently UHI impact on mortality. However, by applying the same down scaled weather model, we intend to extend this study to evaluate the future impact of UHI.\

Finally, a cost-benefit of green space intervention is warranted for future study in order to fully evaluate the effectiveness of green space intervention in reducing heat-mortality.

Research on spatial minimum temperature mortality (MMT), and mortality attributable number and fraction

In chapter 4, we successful develop a method to estimate MMT and its 95% confidence interval. We also applied that method to explore the temporal variation of MMT in Japan using 40 year data. In a near future, I want to expand this topic by using Multi-Country Multi-City (MCC) data. MCC is an international collaborative research program on associations between weather and health (http://mccstudy.lshtm.ac.uk/). The MCC currently involves an international network of 27 researchers from various research institutions (including Prof. Yasushi Honda and me), and has an established protocol for data collection, data sharing, mode of collaboration and authorship agreement. The dataset currently comprises data on mortality, air pollution and weather variables for 410 locations within 18 countries around the world, including over 81 million deaths. In addition, a time lag between MMT movement and autonomous adaptation is warranted for future study

I also want to investigate the temporal variation of mortality attributable number (AN) and fraction (AF) due to heat and cold. The AN and AF are very much related to MMT, because as MMT they can indicate the autonomous adaptation to climate change. But by studying temporal variation of MMT, we can only explore the adaptation to the heat, whereas by studying AN and AF, we can explore both the adaptation to cold and the heat.

References

1. ADB. (2014). "Viet Nam: Ha Noi and Ho Chi Minh City Power Grid Development Sector Project." Retrieved September, 2016, from https://www.adb.org/sites/default/files/linked-documents/46391-001-ieeab-04.pdf.

2. Anderson, B. G. and M. L. Bell (2009). "Weather-related mortality: how heat, cold, and heat waves affect mortality in the United States." Epidemiology **20**(2): 205-213.

3. Armstrong, B. (2006). "Models for the relationship between ambient temperature and daily mortality." Epidemiology **17**(6): 624-631.

4. Baccini, M., A. Biggeri, G. Accetta, T. Kosatsky, K. Katsouyanni, A. Analitis, H. R. Anderson, L. Bisanti, D. D'Ippoliti, J. Danova, B. Forsberg, S. Medina, A. Paldy, D. Rabczenko, C. Schindler and P. Michelozzi (2008). "Heat effects on mortality in 15 European cities." Epidemiology **19**(5): 711-719.

5. Bai, L., Cirendunzhu, A. Woodward, Dawa, Xiraoruodeng and Q. Liu (2014). "Temperature and mortality on the roof of the world: a time-series analysis in three Tibetan counties, China." Sci Total Environ **485-486**: 41-48.

6. Barrett, J. R. (2015). "Increased Minimum Mortality Temperature in France: Data Suggest Humans Are Adapting to Climate Change" EHP **123**(7).

7. Basu, R. (2009). "High ambient temperature and mortality: a review of epidemiologic studies from 2001 to 2008." Environ Health **8**: 40.

8. Basu, R. (2009). "High ambient temperature and mortality: a review of epidemiologic studies from 2001 to 2008." Environmental Health **8**.

9. Basu, R., W. Y. Feng and B. D. Ostro (2008). "Characterizing temperature and mortality in nine California counties." Epidemiology **19**(1): 138-145.

10. Basu, R. and B. Malig (2011). "High ambient temperature and mortality in California: exploring the roles of age, disease, and mortality displacement." Environ Res **111**(8): 1286-1292.

11. Basu, R. and B. D. Ostro (2008). "A multicounty analysis identifying the populations vulnerable to mortality associated with high ambient temperature in California." Am J Epidemiol **168**(6): 632-637.

12. Basu, R. and J. M. Samet (2002). "Relation between elevated ambient temperature and mortality: a review of the epidemiologic evidence." Epidemiol Rev **24**(2): 190-202.

13. Bell, M. L., M. S. O'Neill, N. Ranjit, V. H. Borja-Aburto, L. A. Cifuentes and N. C. Gouveia (2008). "Vulnerability to heat-related mortality in Latin America: a case-crossover study in Sao Paulo, Brazil, Santiago, Chile and Mexico City, Mexico." Int J Epidemiol **37**(4): 796-804.

14. Bhaskaran, K., A. Gasparrini, S. Hajat, L. Smeeth and B. Armstrong (2013). "Time series regression studies in environmental epidemiology." Int J Epidemiol **42**(4): 1187-1195.

15. Cao, C., X. Lee, S. Liu, N. Schultz, W. Xiao, M. Zhang and L. Zhao (2016). "Urban heat islands in China enhanced by haze pollution." Nat Commun **7**.

16. Carder, M., R. McNamee, I. Beverland, R. Elton, G. Cohen, J. Boyd and R. Agius (2005). "The lagged effect of cold temperature and wind chill on cardiorespiratory mortality in Scotland." Occupational and Environmental Medicine **62**(10): 702-710.

17. Chau, P. H. and J. Woo (2015). "The Trends in Excess Mortality in Winter vs. Summer in a Sub-Tropical City and Its Association with Extreme Climate Conditions." PLoS ONE **10**(5): e0126774.

18. Committee, T. T. H. P. P. s. "Thành Phố Huế." Retrieved Jan, 2015, from https://www.thuathienhue.gov.vn/portal_ge/Views/LevDetail.aspx?OneID=14&TwoID=78&ThreeID=734.

19. Costello, A., M. Abbas, A. Allen, S. Ball, S. Bell, R. Bellamy, S. Friel, N. Groce, A. Johnson, M. Kett, M. Lee, C. Levy, M. Maslin, D. McCoy, B. McGuire, H. Montgomery, D. Napier, C. Pagel, J. Patel, J. A. de Oliveira, N. Redclift, H. Rees, D. Rogger, J. Scott, J. Stephenson, J. Twigg, J. Wolff and C. Patterson (2009). "Managing the health effects of climate change: Lancet and University College London Institute for Global Health Commission." Lancet **373**(9676): 1693-1733.

20. Curriero, F. C., K. S. Heiner, J. M. Samet, S. L. Zeger, L. Strug and J. A. Patz (2002). "Temperature and mortality in 11 cities of the eastern United States." American Journal of Epidemiology **155**(1): 80-87.

21. D'Ippoliti, D., P. Michelozzi, C. Marino, F. de'Donato, B. Menne, K. Katsouyanni, U. Kirchmayer, A. Analitis, M. Medina-Ramon, A. Paldy, R. Atkinson, S. Kovats, L. Bisanti, A. Schneider, A. Lefranc, C. Iniguez and C. A. Perucci (2010). "The impact of heat waves on mortality in 9 European cities: results from the EuroHEAT project." Environ Health **9**: 37.

22. Doan, Q. V. and H. Kusaka (2015). "Numerical study on regional climate change due to the rapid urbanization of greater Ho Chi Minh City's metropolitan area over the past 20 years." International Journal of Climatology.

23. Ekamper, P., F. V. Poppel, C. V. Duin and J. Garssen (2009). "150 Years of temperature-related excess mortality in the Netherlands." Demographic Research.

24. Filleul, L., A. Le Tertre, I. Baldi and J. F. Tessier (2004). "Difference in the relation between daily mortality and air pollution among elderly and all-ages populations in southwestern France." Environ Res **94**(3): 249-253.

25. Gabriel, K. M. and W. R. Endlicher (2011). "Urban and rural mortality rates during heat waves in Berlin and Brandenburg, Germany." Environ Pollut **159**(8-9): 2044-2050.

26. Gasparrini, A. (2014). "Modeling exposure-lag-response associations with distributed lag non-linear models." Stat Med **33**(5): 881-899.

27. Gasparrini, A. and B. Armstrong (2013). "Reducing and meta-analysing estimates from distributed lag non-linear models." BMC Med Res Methodol **13**: 1.

28. Gasparrini, A. and B. Armstrong (2013). "Reducing and meta-analysing estimates from distributed lag non-linear models." BMC Med Res Methodol **13**.

29. Gasparrini, A., B. Armstrong and M. G. Kenward (2010). "Distributed lag non-linear models." Stat Med **29**(21): 2224-2234.

30. Gasparrini, A., B. Armstrong and M. G. Kenward (2012). "Multivariate meta-analysis for non-linear and other multi-parameter associations." Stat Med **31**(29): 3821-3839.

31. Gasparrini, A., B. Armstrong, S. Kovats and P. Wilkinson (2012). "The effect of high temperatures on cause-specific mortality in England and Wales." Occup Environ Med **69**(1): 56-61.

32. Gasparrini, A., Y. Guo, M. Hashizume, P. L. Kinney, E. P. Petkova, E. Lavigne, A. Zanobetti, J. D. Schwartz, A. Tobias, M. Leone, S. Tong, Y. Honda, H. Kim and B. G. Armstrong (2015). "Temporal Variation in Heat-Mortality Associations: A Multicountry Study." Environ Health Perspect **123**(11): 1200-1207.

33. Gasparrini, A., Y. Guo, M. Hashizume, E. Lavigne, A. Zanobetti, J. Schwartz, A. Tobias, S. Tong, J. Rocklov, B. Forsberg, M. Leone, M. De Sario, M. L. Bell, Y. L. Guo, C. F. Wu, H. Kan, S. M. Yi, M. de Sousa Zanotti Stagliorio Coelho, P. H. Saldiva, Y. Honda, H. Kim and B. Armstrong (2015). "Mortality risk attributable to high and low ambient temperature: a multicountry observational study." Lancet **386**(9991): 369-375.

34. Gasparrini, A., Y. Guo, M. Hashizume, E. Lavigne, A. Zanobetti, J. Schwartz, A. Tobias, S. Tong, J. Rocklöv, B. Forsberg, M. Leone, M. D. Sario, M. L. Bell, Y.-L. L. Guo, C.-f. Wu, H. Kan, S.-M. Yi, M. d. S. Zanotti, S. Coelho, P. H. N. Saldiva, Y. Honda, H. Kim and B. Armstrong (2015). "Mortality risk attributable to high and low ambient temperature: a multi-country study." Lancet.

35. Gasparrini, A. and M. Leone (2014). "Attributable risk from distributed lag models." BMC Med Res Methodol **14**(1): 55.

36. Gellert, G. A. (1998). "Health and climate change: Modelling the impacts of global warming and ozone depletion." Nature **393**(6685): 534-534.

37. Goggins, W. B., E. Y. Y. Chan, E. Ng, C. Ren and L. Chen (2012). "Effect Modification of the Association between Short-term Meteorological Factors and Mortality by Urban Heat Islands in Hong Kong." PLoS ONE **7**(6): e38551.

38. Goggins, W. B., C. Ren, E. Ng, C. Yang and E. Y. Chan (2013). "Effect modification of the association between meteorological variables and mortality by urban climatic conditions in the tropical city of Kaohsiung, Taiwan." Geospat Health **8**(1): 37-44.

39. Goosse, H. (2015). Climate System Dynamics and Modelling, Cambridge University Press.

40. Guo, Y. (2012). ESTIMATING THE EFFECTS OF AMBIENT TEMPERATURE ON MORTALITY: METHODOLOGICAL CHALLENGES AND PROPOSED SOLUTIONS. Doctor of Philosophy, Queensland University of Technology.

41. Guo, Y., A. G. Barnett and S. Tong (2013). "Spatiotemporal model or time series model for assessing city-wide temperature effects on mortality?" Environ Res **120**: 55-62.

42. Guo, Y., K. Punnasiri and S. Tong (2012). "Effects of temperature on mortality in Chiang Mai city, Thailand: a time series study." Environ Health **11**: 36.

43. Guo, Y. M., A. Gasparrini, B. Armstrong, S. S. Li, B. Tawatsupa, A. Tobias, E. Lavigne, M. D. Z. S. Coelho, M. Leone, X. C. Pan, S. L. Tong, L. W. Tian, H. Kim, M. Hashizume, Y. Honda, Y. L. L. Guo, C. F. Wu, K. Punnasiri, S. M. Yi, P. Michelozzi, P. H. N. Saldiva and G. Williams

(2014). "Global Variation in the Effects of Ambient Temperature on Mortality A Systematic Evaluation." Epidemiology **25**(6): 781-789.

44. Habeeb, D., J. Vargo and B. Stone (2015). "Rising heat wave trends in large US cities." Natural Hazards **76**(3): 1651-1665.
45. Hajat, S., B. G. Armstrong, N. Gouveia and P. Wilkinson (2005). "Mortality displacement of heat-related deaths - A comparison of Delhi, Sao Paulo, and London." Epidemiology **16**(5): 613-620.
46. Hajat, S. and T. Kosatky (2010). "Heat-related mortality: a review and exploration of heterogeneity." J Epidemiol Community Health **64**(9): 753-760.
47. Hajat, S., R. S. Kovats and K. Lachowycz (2007). "Heat-related and cold-related deaths in England and Wales: who is at risk?" Occup Environ Med **64**(2): 93-100.
48. Hajat, S., S. Vardoulakis, C. Heaviside and B. Eggen (2014). "Climate change effects on human health: projections of temperature-related mortality for the UK during the 2020s, 2050s and 2080s." J Epidemiol Community Health.
49. Hales, S., C. Salmond, G. I. Town, T. Kjellstrom and A. Woodward (2000). "Daily mortality in relation to weather and air pollution in Christchurch, New Zealand." Aust N Z J Public Health **24**(1): 89-91.
50. Harlan, S. L., J. H. Declet-Barreto, W. L. Stefanov and D. B. Petitti (2013). "Neighborhood effects on heat deaths: social and environmental predictors of vulnerability in Maricopa County, Arizona." Environ Health Perspect **121**(2): 197-204.
51. Hashizume, M., Y. Wagatsuma, T. Hayashi, S. K. Saha, K. Streatfield and M. Yunus (2009). "The effect of temperature on mortality in rural Bangladesh--a population-based time-series study." Int J Epidemiol **38**(6): 1689-1697.
52. Heath., M. o. (1992). Decision No 822/BYT.QD to issue mortality reporting book A6/YTCS. Hanoi, Ministry of Health.
53. Honda, Y. (2007). "impact of climate change on human health in Asia and Japan." Global Environ Res **11**: 33-28.
54. Honda, Y., M. Kondo, G. McGregor, H. Kim, Y. L. Guo, Y. Hijioka, M. Yoshikawa, K. Oka, S. Takano, S. Hales and R. S. Kovats (2014). "Heat-related mortality risk model for climate change impact projection." Environ Health Prev Med **19**(1): 56-63.
55. Huang, C., A. G. Barnett, X. Wang, P. Vaneckova, G. FitzGerald and S. Tong (2011). "Projecting Future Heat-Related Mortality under Climate Change Scenarios: A Systematic Review." Environmental Health Perspectives **119**(12): 1681-1690.
56. IPCC (2007b). "Climate change 2007: synthesis report. Contribution of Working Groups I, II and III to the Fourth Assessment Report of the Intergovernmental Panel on Climate Change."
57. Kalkstein, L. S. and J. S. Greene (1997). "An evaluation of climate/mortality relationships in large US cities and the possible impacts of a climate change." Environmental Health Perspectives **105**(1): 84-93.

58. Kovats, R. S. and S. Hajat (2008). "Heat stress and public health: a critical review." Annu Rev Public Health **29**: 41-55.

59. Kreft, S., D. Eckstein, L. Junghans, C. Kerestan and U. Hagen (2015). GLOBAL CLIMATE RISK INDEX 2015. Who Suffers Most From Extreme Weather Events? Weather-related Loss Events in 2013 and 1994 to 2013**:** 1-31.

60. Kusaka, H., H. Kondo, Y. Kikegawa and F. Kimura (2001). "A Simple Single-Layer Urban Canopy Model For Atmospheric Models: Comparison With Multi-Layer And Slab Models." Boundary-Layer Meteorology **101**(3): 329-358.

61. Li, D. and E. Bou-Zeid (2013). "Synergistic Interactions between Urban Heat Islands and Heat Waves: The Impact in Cities Is Larger than the Sum of Its Parts." Journal of Applied Meteorology and Climatology **52**(9): 2051-2064.

62. Mannig, B., M. Müller, E. Starke, C. Merkenschlager, W. Mao, X. Zhi, R. Podzun, D. Jacob and H. Paeth (2013). "Dynamical downscaling of climate change in Central Asia." Global and Planetary Change **110, Part A**: 26-39.

63. McGeehin, M. A. and M. Mirabelli (2001). "The potential impacts of climate variability and change on temperature-related morbidity and mortality in the United States." Environ Health Perspect **109 Suppl 2**: 185-189.

64. McMichael, A. J., P. Wilkinson, R. S. Kovats, S. Pattenden, S. Hajat, B. Armstrong, N. Vajanapoom, E. M. Niciu, H. Mahomed, C. Kingkeow, M. Kosnik, M. S. O'Neill, I. Romieu, M. Ramirez-Aguilar, M. L. Barreto, N. Gouveia and B. Nikiforov (2008). "International study of temperature, heat and urban mortality: the 'ISOTHURM' project." Int J Epidemiol **37**(5): 1121-1131.

65. Medina-Ramon, M. and J. Schwartz (2007). "Temperature, temperature extremes, and mortality: a study of acclimatisation and effect modification in 50 US cities." Occup Environ Med **64**(12): 827-833.

66. Milojevic, A., B. G. Armstrong, A. Gasparrini, S. I. Bohnenstengel, B. Barratt and P. Wilkinson (2016). "Methods to Estimate Acclimatization to Urban Heat Island Effects on Heat- and Cold-Related Mortality." Environ Health Perspect **124**(7): 1016-1022.

67. Miron, I. J., J. J. Criado-Alvarez, J. Diaz, C. Linares, S. Mayoral and J. C. Montero (2008). "Time trends in minimum mortality temperatures in Castile-La Mancha (Central Spain): 1975-2003." Int J Biometeorol **52**(4): 291-299.

68. Muggeo, V. M. and S. Hajat (2009). "Modelling the non-linear multiple-lag effects of ambient temperature on mortality in Santiago and Palermo: a constrained segmented distributed lag approach." Occup Environ Med **66**(9): 584-591.

69. Ng, C. F. S., M. Boeckmann, K. Ueda, H. Zeeb, H. Nitta, C. Watanabe and Y. Honda (2016). "Heat-related mortality: Effect modification and adaptation in Japan from 1972 to 2010." Global Environmental Change **39**: 234-243.

70. Ostro, B., S. Rauch, R. Green, B. Malig and R. Basu (2010). "The Effects of Temperature and Use of Air Conditioning on Hospitalizations." American Journal of Epidemiology **172**(9): 1053-1061.

71. Ou, C.-Q., Y.-F. Song, J. Yang, P. Y.-K. Chau, L. Yang, P.-Y. Chen and C.-M. Wong (2013). "Excess Winter Mortality and Cold Temperatures in a Subtropical City, Guangzhou, China." PLoS ONE **8**(10): e77150.

72. Pain, S. (2016). "The rise of the urbanite." Nature **531**(7594): S50-51.

73. Peel, M. C., B. L. Finlayson and T. A. McMahon (2007). "Updated world map of the Köppen-Geiger climate classification." Hydrol. Earth Syst. Sci. **11**(5): 1633-1644.

74. Peng, R. D., F. Dominici and T. A. Louis (2006). "Model choice in time series studies of air pollution and mortality." Journal of the Royal Statistical Society Series a-Statistics in Society **169**: 179-198.

75. Petitti, D. B., D. M. Hondula, S. Yang, S. L. Harlan and G. Chowell (2015). "Multiple Trigger Points for Quantifying Heat-Health Impacts: New Evidence from a Hot Climate." Environ Health Perspect.

76. Pinheiro, S. d. L. L. d. A., P. H. N. Saldiva, J. Schwartz and A. Zanobetti (2014). "Isolated and synergistic effects of PM(10) and average temperature on cardiovascular and respiratory mortality." Revista de Saúde Pública **48**(6): 881-888.

77. Rainham, D. G. and K. E. Smoyer-Tomic (2003). "The role of air pollution in the relationship between a heat stress index and human mortality in Toronto." Environ Res **93**(1): 9-19.

78. Rao, C., B. Osterberger, T. D. Anh, M. MacDonald, N. T. K. Chúc and P. S. Hill (2010). "Compiling mortality statistics from civil registration systems in Viet Nam: the long road ahead." Bulletin of the World Health Organization **88**(1): 58-65.

79. Reid, C. E., M. S. O'Neill, C. J. Gronlund, S. J. Brines, D. G. Brown, A. V. Diez-Roux and J. Schwartz (2009). "Mapping community determinants of heat vulnerability." Environ Health Perspect **117**(11): 1730-1736.

80. Reid, C. E., J. M. Snowden, C. Kontgis and I. B. Tager (2012). "The role of ambient ozone in epidemiologic studies of heat-related mortality." Environ Health Perspect **120**(12): 1627-1630.

81. Rey, G., A. Fouillet, P. Bessemoulin, P. Frayssinet, A. Dufour, E. Jougla and D. Hemon (2009). "Heat exposure and socio-economic vulnerability as synergistic factors in heat-wave-related mortality." Eur J Epidemiol **24**(9): 495-502.

82. Rogot, E., P. D. Sorlie and E. Backlund (1992). "Air-conditioning and mortality in hot weather." Am J Epidemiol **136**(1): 106-116.

83. Seposo, X. T., T. N. Dang and Y. Honda (2015). "Evaluating the Effects of Temperature on Mortality in Manila City (Philippines) from 2006-2010 Using a Distributed Lag Nonlinear Model." Int J Environ Res Public Health **12**(6): 6842-6857.

84. Seto, K. C. and J. M. Shepherd (2009). "Global urban land-use trends and climate impacts." Current Opinion in Environmental Sustainability **1**(1): 89-95.

85. Shi, L., P. Liu, I. Kloog, M. Lee, A. Kosheleva and J. Schwartz (2016). "Estimating daily air temperature across the Southeastern United States using high-resolution satellite data: A statistical modeling study." Environ Res **146**: 51-58.

86. Smargiassi, A., M. S. Goldberg, C. Plante, M. Fournier, Y. Baudouin and T. Kosatsky (2009). "Variation of daily warm season mortality as a function of micro-urban heat islands." J Epidemiol Community Health **63**(8): 659-664.

87. Smith, C., S. Lindley and G. Levermore (2009). "Estimating spatial and temporal patterns of urban anthropogenic heat fluxes for UK cities: the case of Manchester." Theoretical and Applied Climatology **98**(1): 19-35.

88. Smith, K. R., A. Woodward, D. Campbell-Lendrum, D. D. Chadee, Y. Honda, Q. Liu, J. M. Olwoch, B. Revich and R. Sauerborn (2014). Human health: impacts, adaptation, and co-benefits. Climate Change 2014: Impacts, Adaptation, and Vulnerability. Part A: Global and Sectoral Aspects. Contribution of Working Group II to the Fifth Assessment Report of the Intergovernmental Panel of Climate Change. C. B. Field, V. R. Barros, D. J. Dokken et al. Cambridge, United Kingdom and New York, NY, USA, Cambridge University Press**:** 709-754.

89. Stafoggia, M., F. Forastiere, D. Agostini, A. Biggeri, L. Bisanti, E. Cadum, N. Caranci, F. de' Donato, S. De Lisio, M. De Maria, P. Michelozzi, R. Miglio, P. Pandolfi, S. Picciotto, M. Rognoni, A. Russo, C. Scarnato and C. A. Perucci (2006). "Vulnerability to heat-related mortality: a multicity, population-based, case-crossover analysis." Epidemiology **17**(3): 315-323.

90. Stevenson, M., D. V. Hung, T. H. Hoang, L. Mai Anh, T. Nguyen Thi Hong and N. Le Tran (2015). "Evaluation of the Vietnamese A6 Mortality Reporting System: All-Cause Mortality." Asia Pac J Public Health **27**(7): 733-742.

91. Stevenson, M. R., T. Ngoan le, D. V. Hung, N. T. Huong Tu, A. L. Mai, R. Q. Ivers and H. T. Huong (2012). "Evaluation of the Vietnamese A6 mortality reporting system: injury as a cause of death." Inj Prev **18**(6): 360-364.

92. Takahashi, K., Y. Honda and S. Emori (2007). "Assessing Mortality Risk from Heat Stress due to Global Warming." Journal of Risk Research **10**(3): 339-354.

93. Tawatsupa, B., K. Dear, T. Kjellstrom and A. Sleigh (2014). "The association between temperature and mortality in tropical middle income Thailand from 1999 to 2008." International Journal of Biometeorology **58**(2): 203-215.

94. Todd, N. and A. J. Valleron (2015). "Space-Time Covariation of Mortality with Temperature: A Systematic Study of Deaths in France, 1968-2009." Environ Health Perspect **123**(7): 659-664.

95. Tomlinson, C. J., L. Chapman, J. E. Thornes and C. J. Baker (2011). "Including the urban heat island in spatial heat health risk assessment strategies: a case study for Birmingham, UK." Int J Health Geogr **10**: 42.

96. Vandentorren, S., P. Bretin, A. Zeghnoun, L. Mandereau-Bruno, A. Croisier, C. Cochet, J. Riberon, I. Siberan, B. Declercq and M. Ledrans (2006). "August 2003 heat wave in France: risk factors for death of elderly people living at home." Eur J Public Health **16**(6): 583-591.

97. WHO (2014). Quantitative risk assessment of the effects of climate change on selected causes of death, 2030s and 2050s.

98. Wolf, T., W.-C. Chuang and G. McGregor (2015). "On the science-policy bridge: do spatial heat vulnerability assessment studies influence policy?" International journal of environmental research and public health **12**(10): 13321-13349.

99. Worfolk, J. B. (2000). "Heat waves: their impact on the health of elders." Geriatr Nurs **21**(2): 70-77.

100. Wu, W., Y. Xiao, G. Li, W. Zeng, H. Lin, S. Rutherford, Y. Xu, Y. Luo, X. Xu, C. Chu and W. Ma (2013). "Temperature-mortality relationship in four subtropical Chinese cities: a time-series study using a distributed lag non-linear model." Sci Total Environ **449**: 355-362.

101. Xu, Y., P. Dadvand, J. Barrera-Gomez, C. Sartini, M. Mari-Dell'Olmo, C. Borrell, M. Medina-Ramon, J. Sunyer and X. Basagana (2013). "Differences on the effect of heat waves on mortality by sociodemographic and urban landscape characteristics." J Epidemiol Community Health **67**(6): 519-525.

102. Xuan le, T. T., T. Egondi, T. Ngoan le, T. T. Toan do and T. Huong le (2014). "Seasonality in mortality and its relationship to temperature among the older population in Hanoi, Vietnam." Glob Health Action **7**: 23115.

103. Zhu, W., A. Lű and S. Jia (2013). "Estimation of daily maximum and minimum air temperature using MODIS land surface temperature products." Remote Sensing of Environment **130**: 62-73.

Appendix 1

The full paper of Doan Quan Van and Hiroyuki Kusaka can be found online at: http://onlinelibrary.wiley.com/doi/10.1002/joc.4582/full

Appendix 2

R code for the method to estimate uncertanty of MMT in chapter 4

The analysis divided in to 5 main parts, describe below:

Part 1: Data preparation (65yr, 47 prefectures, 40years)

load the 40 years Japanese data

```
#read the datafile: 65yr_47cities_ver3.csv
setwd("H:/o dia D may lab thay Honda/o E may tinh core i7_lab thay Hond
a/temp")
japan.40years <- read.csv("65yr_47cities_ver3.csv",header=T)
head(japan.40years)
```

the code chunk below is to load packages and atributable risk function

```
# CITIES
cities <- as.character(unique(japan.40years$cityname))
# LOAD THE FUNCTION attrdl
source("2014_gasparrini_BMCmrm_RcodeData/attrdl.R")
#LOAD PACKAGES
library(dlnm) ; library(mvmeta) ; library(splines);require(MASS);requir
e(lmtest);
library(tsModel); library(boot)
```

Specification of DLNM functions and create matrix to store the results

```
  # SPECIFICATION OF THE EXPOSURE FUNCTION
varfun = "bs"
vardegree = 2
varper <- c(10,75,90)
cenper <- 75

### simple DLNM
#varfun = "bs"
#df <- 3
#degree=2

# lag function
#lag <- 14
#lagnk <- 2
######

# SPECIFICATION OF THE LAG FUNCTION
lag <- 21
lagnk <- 3

# DEGREE OF FREEDOM FOR SEASONALITY
dfseas <- 8
```

```
#dfseas <- 4

# MODEL FORMULA
formula <- all~cb+dow+ns(time,df=dfseas*length(unique(year)))

regions <- data.frame(
  citycode = unique(japan.40years$citycode),
  cityname = cities)

# COEFFICIENTS AND VCOV FOR OVERALL CUMULATIVE SUMMARY
coef <- matrix(NA,nrow(regions),3+2,
               dimnames=list(cities))
vcov <- vector("list",nrow(regions))
names(vcov) <- cities
```

From now on we will analyze each decade data.

Analysis for decade 1 from 1973-1982

```
japan1<-japan.40years[japan.40years$decade==1,]
#japan1<-japan.40years[japan.40years$decade==2,]
#japan1<-japan.40years[japan.40years$decade==3,]
#japan1<-japan.40years[japan.40years$decade==4,]
attach(japan1)
# CREATE A LIST WITH THE CITY SERIES
dlist <- lapply(cities,function(x) japan1[japan1$cityname==x,])

# COMPUTE PERCENTILES
per <- t(sapply(dlist,function(x)
  quantile(x$Tmax,c(1,2.5,10,25,50,75,90,97.5,99)/100,na.rm=T)))
```

Part2. Obtaint the BLUP for each prefectures

```
# RUN THE LOOP

# LOOP
time <- proc.time()[3]
for(i in seq(length(dlist)))
{
  #i<-1
  # PRINT
  cat(i,"")

  # EXTRACT THE DATA
  data <- dlist[[i]]

  # DEFINE THE CROSSBASIS
  #argvar <- list(fun=varfun,degree=degree,df=df)
  #cb <- crossbasis(data$Tmax,lag=lag,argvar=argvar,arglag=list(knots=l
ogknots(lag,lagnk)))
```

```
  argvar <- list(fun=varfun,knots=quantile(data$Tmax,varper/100,na.rm=T
),       degree=vardegree,cen=quantile(data$Tmax,cenper/100,na.rm=T))

  cb <- crossbasis(data$Tmax,lag=lag,argvar=argvar,                 arg
lag=list(knots=logknots(lag,lagnk)))

  #summary(cb)

  # RUN THE MODEL AND OBTAIN PREDICTIONS
  model <- glm(formula,data,family=quasipoisson,na.action="na.exclude")
  pred <- crosspred(cb,model)

  # REDUCTION TO OVERALL CUMULATIVE
  red <- crossreduce(cb,model)
  coef[i,] <- coef(red)
  vcov[[i]] <- vcov(red)
}

# CREATE AVERAGE TEMPERATURE AND RANGE AS META-PREDICTORS
avgtmean <- sapply(dlist,function(x) mean(x$Tmax,na.rm=T))
rangetmean <- sapply(dlist,function(x) diff(range(x$Tmax,na.rm=T)))
########################################################################
#########
# META-ANALYSIS

mv <- mvmeta(coef~avgtmean+rangetmean,vcov,data=regions,control=list(sh
owiter=T))
summary(mv)

########################################################################
#########
# OBTAIN BLUPS

blup <- blup(mv,vcov=T)
```

Part3. Determine the MMT

```
# RE-CENTERING

# GENERATE THE MATRIX FOR STORING THE RESULTS
minperccity <- mintempcity <-tmax.dist<- rep(NA,length(dlist))
names(mintempcity) <- names(minperccity) <-names(tmax.dist)<- cities

# DEFINE MINIMUM MORTALITY VALUES: EXCLUDE LOW AND VERY HOT TEMPERATURE
for(i in seq(length(dlist))) {
  data <- dlist[[i]]
  predvar <- quantile(data$Tmax,1:99/100,na.rm=T)
  # REDEFINE THE FUNCTION USING ALL THE ARGUMENTS (BOUNDARY KNOTS INCLU
DED)
   #argvar <- list(x=predvar,fun=varfun,degree=degree,df=df, Bound=rang
```

```
e(data$Tmax,na.rm=T))

    argvar <- list(x=predvar,fun=varfun,                knots=quantile
(data$Tmax,varper/100,na.rm=T),degree=vardegree,                 Bound=
range(data$Tmax,na.rm=T),cen=quantile(data$Tmax,cenper/100,na.rm=T))

  bvar <- do.call(onebasis,argvar)
  minperccity[i] <- (1:99)[which.min((bvar%*%blup[[i]]$blup))]
  mintempcity[i] <- quantile(data$Tmax,minperccity[i]/100,na.rm=T)
}
```

Part 4. Plot overall cure and MMT for each decade

```
pdf("MMT_dlnmlag21.pdf",width=8,height=9)
xlab <- expression(paste("Temperature (",degree,"C)"))
par(mfrow=c(4,3))
for(i in seq(length(dlist))) {
  data <- dlist[[i]]
  # NB: CENTERING POINT DIFFERENT THAN ORIGINAL CHOICE OF 75TH
  #argvar <- list(x=data$Tmax,fun=varfun,degree=degree,df=df, cen=minte
mpcity[i])
  argvar <- list(x=data$Tmax,fun=varfun,degree=vardegree,
   knots=quantile(data$Tmax,varper/100,na.rm=T),cen=mintempcity[i])
  bvar <- do.call(onebasis,argvar)
  pred <- crosspred(bvar,coef=blup[[i]]$blup,vcov=blup[[i]]$vcov,
                    model.link="log",by=0.1)
  plot(pred,type="n",ylim=c(0,2.5),yaxt="n",lab=c(6,5,7),xlab=xlab,ylab
="RR",
       main=cities[i])
  ind1 <- pred$predvar<=mintempcity[i]
  ind2 <- pred$predvar>=mintempcity[i]
  lines(pred$predvar[ind1],pred$allRRfit[ind1],col=4,lwd=1.5)
  lines(pred$predvar[ind2],pred$allRRfit[ind2],col=6,lwd=1.5)
  #mtext(cities$countryname[i],cex=0.7,line=0)
  #axis(1,at=-8:8*5)
  axis(2,at=1:5*0.5)
  breaks <- c(min(data$Tmax,na.rm=T)-1,seq(pred$predvar[1],
                                          pred$predvar[length(pred$pre
dvar)],length=30),max(data$Tmax,na.rm=T)+1)
  hist <- hist(data$Tmax,breaks=breaks,plot=F)
  hist$density <- hist$density/max(hist$density)*0.7
  prop <- max(hist$density)/max(hist$counts)
  counts <- pretty(hist$count,3)
  plot(hist,ylim=c(0,max(hist$density)*3.5),axes=F,ann=F,col=grey(0.95)
,
       breaks=breaks,freq=F,add=T)
  axis(4,at=counts*prop,labels=counts,cex.axis=0.7)
  #mtext("N",4,line=-0.5,at=mean(counts*prop),cex=0.5)
  abline(v=mintempcity[i],lty=3)
  #abline(v=c(per[i,c("2.5%","97.5%")]),lty=2)
```

```
  abline(v=c(per[i,c("1%","99%")]),lty=2)
}

dev.off()
```

Part 5. MMT simulation

```
library(TTR)
library(MASS)
library(tsModel)
library(splines)
library(dlnm)
library(mvtnorm)

DLNM<-matrix(NA,47,4)
colnames(DLNM)<-c("MMT.temp","MMT.per","MMT95.per","MMT95.temp")

Test <- function (y){
  which.min (y)
}


n<-99
n.sims <- 1000
y.rep <- array (NA, c(n.sims, n))
test.rep <- rep (NA, n.sims)
test.rep2 <- matrix (NA, n.sims,47)

for (i in 1:47){

  data<-dlist[[i]]

  #define the pred variable according to Antonio
  predvar <- quantile(data$Tmax,1:99/100,na.rm=T)
  # REDEFINE THE FUNCTION USING ALL THE ARGUMENTS (BOUNDARY KNOTS INCLU
DED)
  argvar <- list(x=predvar,fun=varfun,
                 knots=quantile(data$Tmax,varper/100,na.rm=T),degree=va
rdegree,
                 Bound=range(data$Tmax,na.rm=T),cen=quantile(data$Tmax,
cenper/100,na.rm=T))
  bvar <- do.call(onebasis,argvar)
  X<-bvar
  #MMT
  mmt.per <- (1:99)[which.min((bvar%*%blup[[i]]$blup))]
  mmt.temp <- quantile(data$Tmax,mmt.per/100,na.rm=T)
  DLNM[i,1]<-mmt.temp
  DLNM[i,2]<-mmt.per

  ### SIMULATION
```

```
  for (s in 1:n.sims){
    X <- bvar
    newbeta<-rmvnorm(1,blup[[i]]$blup,blup[[i]]$vcov)
    y.hat <-  exp(X %*% t(newbeta))
    y.rep[s,] <- y.hat
    test.rep2[s,i] <- (1:99)[which.min(y.rep[s,])]
  }
}

for (i in 1:47) {
  data<-dlist[[i]]
  quant<-quantile(test.rep2[,i],c(0.025,0.975))
  quant.temp<-quantile(data$Tmax,quant/100,na.rm = T)

  simul.mmt.per <- round(median(test.rep2[,i]),1)
  simul.mmt.temp <- quantile(data$Tmax,simul.mmt.per/100,na.rm=T)

  DLNM[i,3]<-paste(simul.mmt.per,"(",round(quant[1],1),",",round(quant[
2],1),")")
  DLNM[i,4]<-paste(simul.mmt.temp,"(",round(quant.temp[1],1),",",round(
quant.temp[2],1),")")
}


pdf("MMTdist_decade1_1to99_lag21.pdf")
par(mfrow=c(4,3))

for (i in 1:47){
  hist(test.rep2[,i],main="Empirical Distribution of MMT%",
       xlab="Maximum temperature (oC)",
       breaks=100,freq=FALSE,xlim=c(1,99))

  mtext(regions[i,2],cex=0.8)
}
dev.off()
```