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Association between diurnal temperature range and mortality modified by temperature in Japan, 1972–2015: Investigation of spatial and temporal patterns for 12 cause-specific deaths

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ABSTRACT

Many previous literatures suggested that high temperature and diurnal temperature range (DTR) are prominent risk factors to increase risk of mortality. However, the role of effect modification of temperature on the DTR-related mortality is unclear. We examined whether temperature was an effect modifier on the DTR-mortality association and how the modification patterns differed by cause of deaths and different regional climates using a nationwide 47 prefecture data in Japan (1972–2015). We used a two-stage analysis. For the first stage, we used a time-series regression with a distributed lag model to estimate the DTR-mortality association according to five levels of temperature (extreme cold, cold, moderate, hot, and extreme hot days) for each prefecture stratified by twelve cause-specific deaths. Then, we applied a meta-analysis to pool the estimates across the 47 prefectures in Japan and separately by cooler vs. warmer regions. Our findings showed that the risk of mortality associated with DTR was strongly modified by temperature for all causes and cardiovascular deaths ($p < 0.001$) in the total population, suggesting that the influence of DTR on mortality increases at higher levels of temperature. These findings were consistent across warmer and cooler regions. Similar patterns were observed for respiratory and renal disease deaths which demonstrated the associations with DTR were the highest during extreme hot days, although it was statistically not significant and varied depending on the climate regions. Our findings suggest that the DTR-related mortality may be modified by daily mean temperature and the most elevated during extremely hot temperatures.

1. Introduction

Diurnal temperature range (DTR), defined as the intra-day difference between maximum and minimum temperatures, has been studied as a risk factor for increased mortality in many countries (Cao et al., 2009; Kan et al., 2007; Lim et al., 2012; Lim et al., 2015; Vutcovici et al., 2014; Yang et al., 2013). High and low temperature associated with increased mortality have also been well-documented by many epidemiological studies (Anderson and Bell, 2009; Gasparrini et al., 2015; Guo et al., 2014). It has been reported that these associations are influenced by individual, environmental, and socio-economic risk factors and vary depending on a cause of mortality (O'Neill et al., 2003; Stafoggia et al., 2006; Kan et al., 2007; Lim et al., 2012; Yang et al., 2013).

Although it is expected that climate change would largely influence temperature and temperature variability (Stocker, 2014), a few epidemiological studies have examined the role of temperature as an effect modifier on the DTR-related mortality (Kan et al., 2007; Lim et al., 2012; Vicedo-Cabrera et al., 2016; Yang et al., 2013). Some biological mechanisms could potentially support the effect modification of temperature on DTR-related mortality. Both sudden temperature change and extreme temperature are highly likely to disrupt normal physiological immune system, and they can also affect blood pressure, thermoregulation system, and oxygen uptake related to cardiovascular and respiratory diseases (Epstein and Moran, 2006; Liang et al., 2009; Garrett et al., 2011).

However, the previous findings for the modification role of temperature were inconsistent. Two Chinese studies reported that the DTR

Abbreviations: DLNM, Distributed lag non-linear model; DTR, Diurnal temperature range; IQR, Interquartile range; PI, Percentile increase

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had a higher influence on non-accidental mortality during cold days (Yang et al., 2013; Zhou et al., 2014), while another study suggested that the DTR-related mortality risks were elevated during warm seasons in South Korea (Lim et al., 2012). And a recent study in six European and US cities reported that the associations between temperature and DTR on mortality were inconsistent among their study locations (Vicedo-Cabrera et al., 2016). In addition, the most of previous studies have used a season or a binary indicator (e.g., warm and cold seasons) to examine the temperature modification and did not consider a flexible lag-pattern of DTR-mortality association. Thus, more sophisticated approach (e.g., including a flexible statistical terms in the model) would be merited to investigate the complex modification pattern of temperature on the DTR-related mortality and complement potential limitations of the previous studies.

One possible reason for the inconsistency is that the role of temperature on DTR-related mortality may differ by cause of death because of different biological mechanisms attributable to DTR and temperature exposure. A previous study reported that DTR has a significant impact on cardiovascular deaths during the whole period, while the effect on respiratory deaths was only found during days with < 23 °C (Kan et al., 2007). Another study also reported that the DTR-related mortality in high temperature (> 22 °C) were varied with causes of deaths (Yang et al., 2013). These results may indicate the temperature modification pattern may vary depending on the composition of deaths in study community, however the evidence is still insufficient to understand how temperature contributes to the DTR-mortality association and how the role of temperature differs by cause of deaths. More comprehensive investigations covering a broader range of causes of deaths at multiple locations are needed.

Therefore, in this study we aimed to examine the role of temperature on the DTR-mortality association as an effect modifier for twelve causes of death in all 47 prefectures in Japan. Also, we investigated if the effect modification differed between warmer vs. cooler regions and attempted to examine if the temporal changes in the DTR-related mortality has a potential link to the rising temperature over recent decades from 1972 to 2015. We conducted a two-stage analysis based on flexible statistical approaches using a distributed lag model and a meta-analysis.

2. Material and methods

2.1. Data

We collected prefecture-specific daily time-series of weather variables and cause-specific mortality for all 47 prefectures in Japan from 1 January 1972 to 31 December 2015. The weather data were derived from the Japan Meteorological Agency, including daily maximum, mean and minimum temperatures (°C), and daily mean relative humidity (%) measured at a monitoring site for each prefecture. We defined the DTR as the difference between maximum and minimum temperatures in a day. We also calculated the average of the mean temperature from the current day to the two preceding days. The choice of the 3-days moving average metric was based on the previous studies that showed the highest DTR-related mortality over the lag of 0–3 days (Kan et al., 2007; Yang et al., 2013; Lee et al., 2018). Then, the 3-days average temperature was categorized into five strata, consisting of below the 5th percentile (extreme cold days), 5–25th percentiles (cold), 25–75th percentiles (moderate), 75–95th percentiles (hot), and above the 95th percentile (extreme hot days) for each prefecture.

The mortality data were derived from the Ministry of Health, Labour and Welfare in Japan. We used the codes of International Classification of Disease Revision (ICD) 8–10 to define the twelve causes of deaths in our study: (1) all-cause, (2) total cardiovascular disease, (3) cerebrovascular disease, (4) cerebral hemorrhage, (5) cerebral infarction, (6) ischemic heart disease, (7) total respiratory disease, (8) pneumonia, (9) asthma, (10) chronic obstructive pulmonary diseases (COPD), (11) emphysema, and (12) renal disease. Details of the ICD codes were described in the Supplemental Material (Data details).

2.2. Statistical analysis

We used a two-stage statistical approach using meta-analysis. We firstly estimated a prefecture-specific DTR-mortality association and stratified the associations by the five strata of temperature. Then, the estimates were pooled across all prefectures and separately by cooler vs. warmer regions. In addition, we examined the temporal changes in DTR-related mortality by decades. All analyses were repeated by the specific causes of mortality.

All the DTR-mortality associations were presented as a percent increase (PI) per an interquartile range (IQR) increase in DTR. We used the R statistical software with the *dlnm* package for the first stage analyses and the *mvmeta* package for the second stage analyses (Gasparrini, 2011; Gasparrini and Armstrong, 2011). We interpreted all statistical tests with significant level (α) = 0.05.

2.2.1. First stage analysis

We performed a prefecture-specific analysis using a generalized linear model with quasi-Poisson distribution. A constrained distributed lag was used to estimate the association between DTR and mortality assumed as linear in which we fitted the lag-distributed estimates over 14 days using a natural cubic B-spline function with two equally spaced knots on the log scale. The model specifications were motivated by a previous study investigating the association between DTR and mortality in multiple countries (Lee et al., 2018). To estimate the stratum-specific DTR-mortality associations by temperature, we added interaction terms between the basis function for the DTR-mortality association and indicator variables for the temperature strata.

In addition, we adjusted for daily mean temperature as a cross-basis functional form using natural cubic B-splines for exposure-response relationship (with three internal knots at 25th, 50th, and 75th percentiles of prefecture-specific temperature) and for lag-response relationship (with an intercept and three equally spaced knots on the log scale) over the lag of 21 days. These modeling choices were based on the previous studies using a distributed lag non-linear model (Gasparrini et al., 2015; Guo et al., 2016). We also adjusted for the relative humidity on the current day as a nonlinear term by a natural cubic spline with three degrees of freedom and day-of-week as a categorical variable. Seasonality and long-term trend were controlled using a natural cubic B-spline of time (date) with eight degrees of freedom (df) per year.

2.2.2. Second stage analysis

From the first stage analysis, we obtained four coefficients representing the lag-distributed DTR-mortality association along the lags of 14 days stratified by each temperature strata for each prefecture. And we reduced the four coefficients to a single coefficient for each prefecture, which represents an overall lag-cumulative DTR-mortality association. We then pooled the prefecture-specific associations over the whole population (47 prefectures) for each temperature strata, separately using univariate (for the lag-cumulative coefficients) and multivariate (for the lag-distributed coefficients) random effect meta-analysis (Gasparrini and Armstrong, 2013). Additionally, we pooled the prefecture-specific associations in cooler and warmer climate regions using a meta-regression with a region indicator, defined by the median of the prefecture-specific annual mean temperature (ranged 8.89–15.8 °C for the cooler region with 24 prefectures and 15.8–22.9 °C for the warmer region with 23 prefectures) (Fig. S1).

2.2.3. Testing the significance of the modification by temperature

In parallel with the second stage analysis above, we did a significance test for the effect modification of temperature on DTR-related mortality. The interaction coefficients between DTR and the