The modifying effects of heat and cold wave characteristics on cardiovascular mortality in 31 major Chinese cities

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Abstract
Cardiovascular disease is the most common cause of death globally. Examining the relationship between the extreme temperature events (e.g. heat and cold waves) and cardiovascular mortality has profound public significance. However, this evidence is scarce, particularly those from China. We collected daily data on cardiovascular mortality and meteorological conditions from 31 major Chinese cities during the maximum period of 2007–2013. A two-stage analysis was used to estimate the effects of heat and cold waves, and the potential effect modification of their characteristics (intensity, duration, and timing in season) on cardiovascular mortality. Firstly, a generalized Poisson regression combined with distributed lag nonlinear model was used to evaluate city-specific effects. Then, the meta-analysis was performed to pool effect estimates at the national scale. Overall, cardiovascular mortality risk increased by 19.03% (95%CI: 11.92%, 26.59%) during heat waves and 54.72% (95%CI: 21.20%, 97.51%) during cold waves. The effect estimates varied by the wave’s characteristics. In heat wave days, the cardiovascular mortality risks increased by 3.28% (95%CI: −0.66%, 6.73%) for every 1 °C increase in intensity, 2.84% (95%CI: 0.92%, 4.80%) for every 1-d more in duration and −0.07% (95%CI: −0.38%, 0.24%) for every 1-d late in the staring of heat wave; the corresponding estimates for cold wave were 1.82% (95%CI: −0.04%, 3.72%), 1.52% (95%CI: 0.60%, 2.44%) and −0.26% (95%CI: −0.67%, 0.16%). Increased susceptibility to heat and cold waves was observed among patients with ischemic heart disease, females, the elderly, and those with lower education level. And consistent vulnerable populations were found for the effects of changes in cold and heat wave’s characteristics. The findings have important implications for the development of early warning systems and plans in response to heat and cold waves, which may contribute to mitigating health threat to vulnerable populations.

1. Introduction
Extreme temperature events (mainly heat and cold waves) caused significant adverse impact on mortality from plenty of diseases worldwide (Anderson and Bell 2009, Deschénes and Moretti 2009, Kysely et al 2009, Montero et al 2010, Ou et al 2013, Yang et al 2019). Although human being is anticipated to undergo more frequent extreme heat events but rarer extreme cold events in the context of global warming (Bucchignani et al 2017, Sun et al 2019, Gao et al 2020), the extreme cold events (e.g. cold waves)
will not stop to happen in coming decades (Meehl and Tebaldi 2004, Wang et al 2016). Moreover, cold was identified to induce a higher health burden than heat (Gasparrini et al 2015). Therefore, examining the relationship between heat and cold waves and mortality has profound public significance, as this evidence could help to prepare the public, especially those vulnerable populations, for sudden extreme temperature change.

Heat and cold waves present variations in their intensity, duration and timing, which may affect the health impact of heat and cold waves. Few papers have attempted to investigate the effect modification of characteristics of heat and cold waves (Anderson and Bell 2011, Barnett et al 2012, Son et al 2012, Tian et al 2013, Zeng et al 2014, Wang et al 2016). However, which characteristic of cold and heat waves dominates the modifying effects was inconsistent in these studies (Anderson and Bell 2011, Barnett et al 2012, Son et al 2012, Tian et al 2013, Zeng et al 2014, Wang et al 2016). For instance, Barnett et al (2012) observed higher health risk of the change in intensity of heat wave in 99 US cities, compared to the timing and duration of heat wave. However, Zeng et al (2014) reported relatively greater effect for the change in the duration of heat wave in four Chinese communities. Nevertheless, there is no nationwide investigation to quantify the modifying effects by characteristics of heat and cold waves in China, although the overall health impacts of heat waves or cold waves have been assessed (Zhou et al 2014, Chen et al 2019, Yang et al 2019). As the country with the largest population and the third largest land area worldwide, China is characterized by complicated population composition and large spatial heterogeneity in climate socio-demographic and cultural characteristics. A national study from China can help us fully explore spatial variations of health effects of heat/cold waves and identify the potential determinants.

Cardiovascular disease (CVD), which causes substantial health and economic burdens, is the most common cause of death globally (World Health Organization 2018). China has disproportionately high health burden caused by CVD. According to China CVD Report 2018, there were nearly 290 million patients with CVD and over 3 million deaths from CVD in 2016, which is worthy of plenty of public attention in China (Ma et al 2020). Furthermore, previous studies have reported that the health impacts of non-optimum weather conditions vary substantially among different subpopulation, which was mainly due to the difference in physiological responses or behavior modification (Yang et al 2015, 2019, Wang et al 2016, Chen et al 2019). Thus, research considering the vulnerabilities of subpopulations to cold and heat waves is highly needed.

Therefore, in the present study, a two-stage model strategy was employed to estimate the health effects of heat and cold waves and determine how the impacts change when heat and cold waves get more intense, longer and earlier in season across China during 2007–2013. Finally, subgroup analyses by specific causes and individual characteristics were conducted to identify vulnerable subpopulations.

2. Material and methods

2.1. Study sites

Thirty one provincial capitals in China (figure 1) were selected, with a maximum period of 2007 to 2013. The geographical boundary between south and north is the Qinling Mountains-Huaihe River line (figure 1). The detailed information for four climatic zones (alpine zone, temperate continental zone, temperate monsoon zone, and tropical and subtropical monsoon zone), and seven geographical zones (southwest, northwest, northeast, north, south, east, and central) was available in Supplemental figures S1 and S2 (available online at stacks.iop.org/ERL/15/105009/mmedia).

2.2. Data collection

Daily mortality data during 2007 to 2013 were collected from Chinese National Center for Chronic and Non-communicable Disease Control and Prevention. At least 1-year data were used for each city. The International Statistical Classification of Diseases (10th revision, ICD-10) was applied: CVDs (I00–I99), stroke (I60–I69), and ischemic heart diseases (IHD, I20–I25). Subgroup analyses were performed for different strata stratified by sex, age group (0–64 and 65 + years), educational level (primary school or lower, high school or higher), climatic zones and geographical zones. The daily weather data from all monitoring stations in 31 Chinese capital cities were collected from the China Meteorological Data Center (http://data.cma.cn/). The city-level values of meteorological variables were obtained by calculating the average value of all stations in each city per day. The records of daily air pollution index (API) were derived from the Chinese Ministry of Ecology and Environment (www.mee.gov.cn/). More detailed introduction of the data sources could be found elsewhere (Chen et al 2019, Yang et al 2019).

We identified heat and cold waves using the best definitions developed in our previous studies (Chen et al 2019, Yang et al 2019). Specifically, heat wave was defined as at least three consecutive days with daily maximum temperature ≥92.5th percentile and cold wave as at least two consecutive days with daily mean temperature ≤5th percentile. Moreover, we further characterized the extreme temperature event by its intensity (the difference between the daily temperature and city-specific thresholds), duration (0 on the first day of wave, 1 on the second day, 2 on the third day, and so on), and timing in season [difference in days between the occurrence date of a wave
and the beginning date of the cold season (November to March) or hot season (May to September)).

2.3. Statistical analysis

In this analysis, we conducted a two-stage analytical strategy to examine the effects of extreme temperature events and their characteristics on mortality (Guo et al 2016, Chen et al 2019, Yang et al 2019). As the daily counts of deaths from CVD, ischemic heart disease, and stroke presented strong over-dispersion which was tested by the nonparametric test (Böhning 1994), the quasi-Poisson generalized linear model (allowing for over-dispersion) combined with distributed lag nonlinear model was used to assess the lagged effects of cold and heat waves on mortality in each city (Gasparrini et al 2012). Then, the meta-analysis was performed to pool city-specific effects at the national level. The data analyzed was limited to hot seasons for the heat wave and cold seasons for the cold wave, respectively (Anderson and Bell 2011, Wang et al 2016).

2.3.1. First-stage analysis

2.3.1.1. Effect of extreme temperature event

In the first stage, we fitted a city-specific quasi-Poisson regression to estimate city-specific health effects of heat and cold waves, after controlling for the long-term trend and seasonality, daily relative humidity, atmospheric pressure, API, day of the week and public holidays. Akaike information criterion for quasi-Poisson (Q-AIC) was used to determine the optimal degrees of freedom (df) and parameters in models (available in Supplement Table S1). The regression model can be given as:

$$\log(\mu_t) = \alpha + \beta T_t \cdot (ETE_t) + \text{NS}(\text{Time}_t, 3/\text{year}) + \text{NS}(\text{API}_t, 3) + \gamma \text{Dow}_t + \nu \text{Holiday}_t + \text{NS}(\text{Hum}_t, 3) + \text{NS}(\text{Press}_t, 3)$$

where $t$ is the observation days; $\mu_t$ is the daily expected counts of CVD deaths on day $t$; $\alpha$ is the intercept; $\beta$, $\gamma$, and $\nu$ were vectors of regression coefficients; $ETE_t$ is the dummy variable that denotes the extreme temperature event (heat or cold wave) on day $t$, in which the value of 0 and 1 indicates days without and with extreme temperature event, respectively. Considering the potential harvesting effect and prolonged effect of heat and cold wave, cross-basis function $T_t \cdot (.)$ was applied for the heat and cold waves, with a linear function for exposure dimension and the natural cubic spline with two internal knot placed along equally-spaced log-values for lag dimension (Gasparrini et al 2012, Gasparrini and Armstrong 2013, Zhou et al 2014, Chen et al 2019). The maximum lag days of heat and cold wave valued 10 and 27 respectively, which were motivated by our previous studies (Chen et al 2019, Yang et al 2019). NS(.) means natural cubic spline. three degrees of freedom (df) per year was used for time variable $\text{Time}_t$ to adjust for the seasonal trend and long-term change. The df for natural splines of daily mean air pollution index (APIt), daily mean relative humidity (Humt), and daily mean atmospheric pressure (Press) were determined using the Akaike information criterion (AIC).
(Hum<sub>t</sub>) and daily mean atmospheric pressure (Press<sub>r</sub>) were set as 3 (Yang et al. 2012, Chen et al. 2019). The categorical variables which indicate public holidays (Holiday<sub>t</sub>) and day of the week (Dow<sub>r</sub>) were included (Yang et al. 2012, 2016, Chen et al. 2015, Zhang et al. 2017). Percent increase (PI) in mortality comparing days with heat and cold waves with regular days without events was calculated by \([\exp(\beta) - 1]*100\%\).

### 2.3.1.2. Health effects of characteristics of ETEs

To quantify the health effects of characteristics (intensity, duration, and timing) of extreme temperature events (heat and cold wave), we modeled the relationship between characteristics and mortality in days with heat waves and in days with cold waves, respectively. The characteristics variables of extreme temperature events were introduced simultaneously as linear terms into the models to quantify the percentage change in mortality with a unit increase of specific characteristics (Zeng et al. 2014). The model can be presented as:

\[
\text{Log}(\mu_i) = \alpha + \beta_1 \text{Intensity}_i + \beta_2 \text{Duration}_i
\]

\[+ \beta_3 \text{Timing}_i + \gamma \text{Dow}_i + \nu \text{Holiday}_i \]

\[+ \text{NS}(\text{API}_i, 3) + \text{NS}(\text{Hum}_i, 3) \]

\[+ \text{NS}(\text{Press}_r, 3) \]

\[= \alpha + \sum \beta_j x_j + \text{COVs} \]

where: \(x_j\) indicates characteristics of heat and cold waves (intensity, duration, and timing); \(\text{COVs}\) are the confounding factors with the same forms in section 2.3.2.1.

### 2.3.2. Second-stage analysis

A univariate random-effect meta-analysis model based on the restricted maximum likelihood was applied to pool city-specific estimates of heat and cold waves on cardiovascular mortality (Borenstein et al. 2010, Guo et al. 2013, Zhou et al. 2014, Yang et al. 2015, 2019, Chen et al. 2019). The random-effect meta-analysis was applied as the Q-tests for most analyses were statistically significant and \(I^2\) statistics were greater than 50\%, indicating high heterogeneity among cities (Huedo-Medina et al. 2006, Viechtbauer 2010, Yang et al. 2020).

Furthermore, a meta-regression was conducted to examine the possible determinants of spatial heterogeneity (Ma et al. 2015, Chen et al. 2019, Yang et al. 2019). A variety of city-level socioeconomic and meteorological factors were explored, including the unemployment rate, the number of hospital bed per 10,000 population, the number of hospital per 10,000 population, longitude, latitude, population, green space, population density, proportion of the elderly population, proportion of the illiterate, GDP (gross domestic product) per capita, mean temperature, diurnal temperature range, relative humidity and concentrations of particulate matter \(\leq 2.5 \mu g \text{m}^{-3}\) in aerodynamic diameter (PM<sub>2.5</sub>). The formula is given as follows:

\[\tilde{\beta}_i = \theta_0 + \theta_i x_i + v_i + \epsilon_i \]

Here, \(\tilde{\beta}_i\) denotes the effect estimates of heat and cold waves in city \(i\) \((i = 1, \ldots, 31)\); \(\theta_0\) is the average partial coefficient across all cities. \(\theta_i\) is the change in partial coefficient for an inter-quartile change in the \(j\) city-level factor \(x_i\); \(v_i\) and \(\epsilon_i\) represent the random effect of the city-specific deviation and random error of sampling variability, respectively.

### 2.3.3. Statistical test of difference in subgroup analysis

In order to reveal the high-risk diseases and subpopulation to heat and cold waves, the aforementioned two-stage analysis strategies were separately conducted by the causes of death, sex, age group, educational attainments, climatic and geographical zones. Then, the significance test for difference between two strata is as follows:

\[Z = (E_1 - E_2) / \sqrt{SE(E_1)^2 + SE(E_2)^2} \]

where \(Z\) is the Z-test following standard normal distribution; \(E_1\) and \(E_2\) denote the logarithm of (PI + 1) of two subgroups; \(SE(E_1)\) and \(SE(E_2)\) mean the corresponding standard errors (Altman 2003, Chen et al. 2019, Yang et al. 2019).

### 2.3.4. Sensitivity analysis

To check the robustness of the main results, we repeated the statistical analysis procedure to estimate mortality risks of heat and cold waves and their characteristics on cardiovascular mortality using different definitions and parameter settings. In addition, we changed degrees of freedom for relative humidity (4–6), air pressure (4–6), API (4–6), and time variable (4–6).

All data manipulation was conducted using the R software version 3.5.1 (R foundation for Statistical Computing, Vienna, Austria), with packages of ‘dlm’ (Gasparrini 2011) and ‘metafor’ (Viechtbauer 2010). Two-tailed \(P < 0.05\) values were viewed as statistically significant for all statistical tests.

### 3. Results

Table 1 summarizes the meteorological variables and mortality of different causes in days with and without extreme temperature events. Heat wave days had a higher temperature, lower relative humidity and air pressure, worse air quality compared to other days in hot season, with contrary trend for cold wave days. Consistently, heat and cold wave days showed a higher mortality rate than days without cold or heat waves.
Table 1. Mean (range) of meteorological variables and numbers of deaths from various causes in hot and cold seasons and in days with and without heat or cold wave in 31 provincial capitals.

| Variable                  | Hot Season                          | Cold Season                         |
|---------------------------|-------------------------------------|-------------------------------------|
|                           | Total  | Heat Wave Days | Non-Heat Wave Days | Total  | Cold Spell Days | Non-Cold Spell Days |
| **Meteorological Condition** |        |                |                    |        |                |                      |
| Temperature (°C)           | 28.3(3.4, 42.5)                     | 35.1(27.7, 41.9)                    | 28.0(3.4, 42.5) | 4.2(−29.3, 28.3) | −5.5(−29.3, 13.0)   | 4.6(−26.2, 28.3)    |
| Relative humidity (%)      | 68.2(0.0, 100.0)                    | 56.6(16.0, 86.0)                    | 68.7(0.0, 100.0) | 62.3(5.0, 100.0)  | 63.7(11.0, 98.0)    | 62.3(5.0, 100.0)    |
| Air Pressure (hPa)         | 4989(810, 10,201)                   | 4972(813, 10,085)                   | 4989(810, 10,201) | 5050(808, 10,376) | 5078(820, 10,371)   | 5048(808, 10,376)   |
| API                       | 61.6(10.0, 500.0)                   | 66.5(22.0, 148.0)                   | 61.4(10.0, 500.0) | 82.7(0.0, 500.0)  | 77.7(9.0, 500.0)    | 82.9(0.0, 500.0)    |
| **Causes of Death**        |        |                |                    |        |                |                      |
| Cardiovascular disease     | 33(0, 333)                          | 37(0, 224)                          | 33(0, 333) | 44(0, 438)      | 50(0, 403)           | 43(0, 438)          |
| Ischemic heart disease     | 12(0, 119)                          | 13(0, 92)                           | 12(0, 119) | 15(0, 105)      | 18(0, 104)           | 15(0, 105)          |
| Stroke                    | 15(0, 148)                          | 17(0, 106)                          | 15(0, 148) | 20(0, 221)      | 22(0, 197)           | 19(0, 221)          |

Note: hot season: May–September; cold season: November–March.
Figure 2. Heat and cold waves characteristics in 31 cities (2007–2013). (A) Heat wave (B) Cold spell. **Intensity:** Average daily mean temperature of each heat or cold wave within a city (tick marks within blue bars). **Duration:** The number of heat and cold waves according to duration (shading) by city. By definition, all heat waves lasted $\geq 3$ d and cold waves lasted $\geq 2$ d. **Timing in season:** Occurring time of heat and cold waves by city (tick marks indicate the first day of individual heat or cold wave). **Note:** Each horizontal line represents one city, and the length of each line indicates the range of characteristics in that city. Northern (Bottom panel) and southern (Upper panel) cities were distinguished by the solid line in each figure.

Figure 2 shows the characteristics of cold and heat waves intuitively. Generally, the characteristics of heat and cold waves showed significant spatial variations. Longer and more intense heat waves were commonly seen in southern cities, while longer and higher intense cold waves were more common in northern cities (figure 2). The first heat wave in hot season mostly occurred in June–July, while it was December–January for cold waves (figure 2). Extremely early and late heat waves (i.e. in May or September) and cold waves (i.e. in November or March) were infrequent.

Supplemental Table S2 represents the summary statistics of heat and cold waves characteristics across 31 cities, indicating spatial variations across cities. The total number of heat wave days during the whole study period ranged from 7 in Shijiazhuang to 62 in Haikou. The intensity of heat waves was lowest in Guangzhou (0.6 °C), and highest in Xining (2.5 °C). The duration of heat waves showed a range of 1.0–4.7 d. The occurring time of most heat waves was in July or August. Similarly, the average number of cold waves ranged from 12 in Shijiazhuang to 47 in Changsha per year. The temperature during cold waves decreased at a range of 0.7 °C (Nanchang)–3.8 °C (Lanzhou). Cold waves lasted for 0.8–7.4 d on average. Most of the cold waves occurred in January.

Figure 3 shows heat and cold wave impacts by causes of death, sex, age group, education level, climatic and geographical zones. Effect estimates of heat wave were particularly higher for ischemic heart disease, females, the elderly, those with low education levels, residents in the temperate continental and monsoon zones, and northern areas. For the cold wave, death risks were found to be higher in ischemic heart diseases, females, the elderly, those with lower education levels, people in the tropical and subtropical monsoon zones, and southwest and southern areas. The significant negative effect was unexpectedly observed in alpine zone.

Considering substantial heterogeneity among cities (heat wave: $Q = 100.06, I^2 = 70.24\%$, $P < 0.001$; cold wave: $Q = 122.87, I^2 = 84.32\%, P < 0.001$), we further investigated city-level effect modifiers using meta-regression. The mortality risk associated with heat wave increased with city-level longitude, latitude, GDP per capita, levels of PM$_{2.5}$, which cumulatively explained 65.29% of total heterogeneity in the effects of heat waves. While cities with fewer hospital beds per 10,000 populations, larger city population, higher mean temperature, smaller diurnal temperature range suffered from higher effects of cold waves, which accounted for 42.57% of total...
Figure 3. Effects of heat and cold waves on cardiovascular mortality stratified by causes of death and individual characteristic. (A) Heat wave (B) Cold wave. Note: Values are point estimates and corresponding 95% confidence intervals of percentage changes. Abbreviations: CVD: cardiovascular disease, IHD: Ischemic heart disease, Strk: stroke; M: male; F: female; Y, young (aged ≤64 years); O, old people (aged 65 + years); L: lower education level (primary school or lower); H: higher education level (high school or higher). AZ: Alpine Zone, TCZ: Temperate Continental Zone, TMZ: Temperate Monsoon Zone, TSMZ: Tropical and Subtropical Monsoon Zone; SW: Southwest, S: South, NW: Northwest, NE: Northeast, N: North, E: East, CE: Central.

heterogeneity together (available in Supplemental Table S4 and S5).

Table 2 showed the percentage change in mortality risk for each unit increase in heat and cold waves characteristics (intensity, duration, and timing) in different subgroups. Mortality risk was generally increased with the intensity and duration of heat and cold waves, but decreased with the occurring time, although most estimated effects and differences between subgroups were not statistically significant (available in Supplemental Table S3).

For heat waves, 1 °C increase in intensity, 1-d increase in duration and 1-d later in hot season was associated with percentage change of 3.28% (95%CI: −0.06%, 6.73%), 2.84% (95%CI: 0.92%, 4.80%) and −0.07% (95% CI: −0.38%, 0.24%) in cardiovascular mortality, respectively. Notably, consistent with the main effects, the effects of heat waves’ characteristics were stronger among females, those aged ≥65 years, those with the education level of primary school or lower, and people in temperate continental zones.

For cold waves, per unit increase in intensity, duration and timing in cold season was associated with percentage change of 1.82% (95% CI: −0.40%, 3.72%), 1.52% (95%CI: 0.60%, 2.44%) and −0.26% (95% CI: −0.67%, 0.16%) in cardiovascular mortality, respectively. Moreover, we found that females, the youth, those with lower education level, people in tropical and subtropical monsoon, and southern zone were susceptible to the change in cold wave characteristics.

In the sensitivity analysis, we re-estimated the effects of extreme temperature events for cardiovascular mortality using different definitions and parameter settings (available in Supplemental Table S6). The point estimates of effects changed slightly and the trends were similar, suggesting that our statistical analysis was robust.

4. Discussion

To our best knowledge, the study is one of the few multi-city studies to examine the health impact of heat and cold waves and quantify the modifying effects of their characteristics in China. We estimated that cardiovascular mortality risk increased by 19.03% (95%CI: 11.92%, 26.59%) during heat waves and 54.72% (95%CI: 21.20%, 97.51%) during cold waves in China. Furthermore, our study also detected vulnerable populations and the determinants of spatial heterogeneity of the effects. The overall effect estimates of heat and cold waves showed that estimated effects were higher for ischemic heart disease, females, the elderly, those with lower education attainment level, specific climatic zones and geographical zones. These heat and cold waves with higher intensity, longer duration and earlier occurring time in the season were more likely to cause higher health impacts. As expected, changes in characteristics of heat and cold waves had greater mortality risks in susceptible populations.

The significant links between extreme temperature events and cardiovascular mortality were observed, which was consistent with existing epidemiological studies (Basagana et al 2011, Ma et al 2015, Chen et al 2019, Yang et al 2019). Several physiological mechanisms may be associated with the sensitivity of cardiovascular patients to extreme temperature, such
| Intensity | Variables | Heat wave Duration | Heat wave Day in season | Cold wave Duration | Cold wave Day in season |
|-----------|-----------|--------------------|-------------------------|--------------------|-------------------------|
| Causes    | Cardiovascular | 3.28(-0.06, 6.73) | 2.84(0.92, 4.80) | -0.07(-0.38, 0.24) | 1.82(-0.04, 3.72) | 1.52(0.60, 2.44) |
|          | IHD       | 2.83(-0.26, 6.02) | 3.05(0.37, 5.80) | -0.08(-0.63, 0.47) | 6.00(0.96, 11.29) | 1.98(-0.73, 4.77) |
|          | Stroke    | 3.91(-2.46, 10.70) | 4.23(0.54, 8.06) | -0.40(-0.89, 0.09) | 1.51(-1.36, 4.46) | 1.65(0.57, 2.73) |
| Gender    | Male      | 2.62(0.18, 5.12)  | 2.72(0.66, 4.82) | -0.12(-0.56, 0.33) | 1.59(-0.36, 3.57) | 1.17(0.19, 2.16) |
|           | Female    | 5.98(-0.59, 12.99) | 3.17(1.00, 5.39) | -0.01(-0.35, 0.32) | 0.51(-2.35, 3.45) | 3.28(-1.66, 8.46) |
| Age(years)| 0-64      | 0.45(-3.72, 4.80) | 1.83(-1.00, 4.74) | 0.29(-0.07, 0.64) | 3.86(1.02, 6.78) | 1.38(0.07, 2.72) |
|           | 65+       | 5.36(0.80, 10.12) | 3.24(1.08, 5.44) | -0.14(-0.49, 0.21) | 2.33(-0.07, 4.79) | 1.48(0.60, 2.38) |
| Education level | Primary school or lower | 4.54(-0.68, 10.05) | 5.12(1.72, 8.64) | -0.13(-0.73, 0.47) | -1.08(-9.87, 8.55) | 2.98(0.22, 5.84) |
|           | High school or higher | 0.44(-7.02, 8.50) | 3.45(0.32, 6.68) | -0.07(-0.50, 0.37) | 1.08(-1.34, 3.55) | 0.53(-1.87, 2.99) |
| Climatic zone | Alpine Zone | 26.31(6.74, 49.47) | -3.54(-16.94, 12.01) | 1.79(-1.47, 5.16) | 42.01(3.62, 94.63) | -8.25(-21.55, 7.31) |
|           | Temperate Continental Zone | -22.48(-52.04, 25.31) | 10.91(-12.55, 40.67) | -1.53(-4.71, 1.75) | -1.64(-15.38, 14.33) | 5.49(-3.27, 15.05) |
|           | Temperate Monsoon Zone | 2.05(-2.70, 7.04) | 1.27(-4.09, 6.93) | -0.01(-0.65, 0.63) | 1.24(-1.47, 4.02) | -0.27(-5.27, 5.00) |
|           | Tropical and Subtropical Monsoon Zone | -1.89(-14.72, 12.87) | 4.53(0.61, 8.61) | -0.02(-0.66, 0.61) | 1.74(-6.30, 10.48) | 1.40(-0.69, 3.54) |
| Geographical zone | Southwest | -11.00(-29.18, 11.86) | 6.60(2.05, 11.35) | -0.74(-1.37, -0.10) | 10.70(-3.64, 27.16) | -0.46(-6.73, 6.23) |
|           | South | 0.95(-69.26231, 50) | 9.40(-17.10, 44.37) | 0.03(-1.67, 1.76) | 14.20(-11.49, 47.33) | 1.00(-8.79, 11.85) |
|           | Northwest | 5.75(-14.32, 30.52) | 1.17(-9.52, 13.12) | -0.31(-2.05, 1.45) | 1.89(-18.16, 26.86) | -3.36(-14.49, 9.21) |
|           | Northeast | 2.55(-4.62, 10.26) | 6.07(-3.12, 16.12) | -0.90(-2.12, 0.33) | 4.45(-1.74, 11.03) | 3.83(-3.43, 11.64) |
|           | North | 0.81(-5.60, 7.66) | -1.65(-8.51, 5.72) | 0.23(-0.34, 0.80) | -0.44(-4.11, 3.38) | -1.68(-4.77, 1.50) |
|           | East | 4.69(-7.19, 18.10) | 2.23(-6.94, 12.31) | 0.36(-0.54, 1.26) | -3.65(-21.57, 18.36) | 1.48(-8.60, 12.68) |
|           | Central | -6.02(-46.41, 64.82) | 2.49(-4.58, 10.08) | 1.03(-0.44, 2.52) | -3.38(-13.45, 7.87) | -0.99(-20.76, 23.71) |

Note: * indicate p < 0.05
as corresponding physiological changes (e.g. higher blood pressure and blood viscosity and increasing systematic vascular resistance) of impaired autonomic thermoregulatory (Gómez-Acebo et al 2013, Kenny et al 2015, Hajat et al 2017, Yang et al 2019). Furthermore, the ischemic heart disease is identified to be at higher risk of extreme temperature events, which was in accordance with previous studies (Tian et al 2013, Chen et al 2015, 2019, Yang et al 2019). Interestingly, the health impacts of heat waves were detected lower than that of cold waves, which may be due to that health impacts of heat waves were immediate and short-term, while those of cold waves were accumulated for longer days (Song et al 2017, Chen et al 2019, Yang et al 2019). In addition, our estimates of the effects of heat and cold waves were higher than those reported in two previous studies (O’Neill et al 2003, Anderson and Bell 2011), primarily because our study aims to assess the total effect of temperature during heat and cold waves (Chen et al 2019, Yang et al 2019), while these studies only reflected the net effect of heat and cold waves.

We found that the effects of heat and cold waves on mortality differed from different individual characteristics. Females seemed to be more susceptible to heat wave than males, which may be due to the heat intolerance of women (Druyan et al 2012). The sensitivity of female toward cold wave may be due to longer female’s life expectancy and a larger proportion of susceptible women (Zhou et al 2014), although the sex difference was not statistically significant in previous studies (Ryti et al 2016, Chen et al 2019). Nevertheless, another study reported a higher death risk among males than female (O’Neill et al 2003), which underscores the importance of further studies on this inconsistent issue. The disclosed vulnerability of the elderly might be caused by aging-induced degeneration of physiological functions in thermoregulation, increased concomitant chronic diseases and limited thermal perception (Zhou et al 2014). The possible explanation for the difference of sensitivity in education level might be that lower education levels with disadvantaged socioeconomic status are essentially equivalent to be associated with poorer baseline working and living conditions, limited medical service available and less protective awareness (Chen et al 2019, Yang et al 2019).

Furthermore, significant heterogeneity in the effects of heat and cold waves among cities was observed in this study. Specifically, the effects of heat waves were positively associated with latitude, GDP per capita, and PM$_{2.5}$ concentrations, while effects of cold spells were positively associated with city population and mean temperature, but negative associated with the number hospital beds per 10,000 populations and diurnal temperature range. Previous studies have documented that people living in southern regions equivalent to lower latitude but higher annual temperature were particularly vulnerable to the cold spell (Chen et al 2019), with the opposite trend for the heat wave (Wang et al 2016). The discrepancy can be corroborated by the difference in the local population’s physiological adaption (e.g. building structure and dietary intake), individual behaviors and awareness among geographical zones (Wang et al 2016). In addition, we observed the unexpected negative effect of cold wave toward population in alpine zone, which may be partly explained by a sparse population (Yin et al 2018) and the preference to stay indoors during extreme cold on the plateau with the higher altitude. For PM$_{2.5}$, its synergistic effects with high temperature may be explained by the stronger sunlight during days with high temperature, which could increase the production of toxic secondary pollutants such as ultrafine particles during days with heat wave (Li et al 2017). Consistent with the report by Nakaya and Dorling (2005), we found positive modification of heatwave effects by GDP per capita. However, it was contrary to a few previous studies (Soares et al 2013, Lim et al 2015). The role of economic levels is complex and may vary by other factors (i.e. economic structure, population aging rate, air pollution level, urbanization rate) (Nakaya and Dorling 2005, Yao et al 2018, Zhao et al 2018, Yang et al 2019, Baptista et al 2020). It is possible that the linear increasing trend observed from the limited span of GDP per capita in 31 capital cities under study cannot fully capture the exposure-response relationship. Finally, our study found that mortality risk of cold spell was decreased by the number of hospital beds per 10,000 individuals, underscoring the importance of sufficient medical service and preventive preparations preceding the extreme weather events.

We estimated that heat and cold waves’ effects increased by the intensity and duration but decreased with timing in season, which were in accordance with previous findings (Anderson and Bell 2011, Barnett et al 2012, Tian et al 2013, Zeng et al 2014). Physiological evidence indicates when the ambient temperature turns high or low, our body temperature maintains normal through thermoregulation in the cardiovascular system (Havenith 2005, Barnett et al 2012). Hence, the more intense or longer duration of cold and heat waves, the heavier burden of cardiovascular system to perform thermoregulation. Previous documents have found some evidence about effects of timing in season (Anderson and Bell 2011, Barnett et al 2012). When heat and cold waves occur later in the season, the left pool of susceptible units was smaller due to the deaths attributable to risk factors such as air pollution, high and low temperatures other than minimum mortality temperature. The acclimatization of local people may evolve stronger due to antecedent heat and cold waves when the later ones in the season occur. Thus, those heat and cold waves with earlier occurring time in the season were more likely to cause higher health impacts. Additional mechanistic studies are warranted to demonstrate reasons behind the
effect of timing, such as mortality displacement, biological adaption, and behavior modification.

Our estimates of the modification effects of heat wave characteristics were higher than those reported elsewhere (Anderson and Bell 2011, Barnett et al 2012). For example, Anderson and Bell (2011) reported a 2.49% increase in deaths for \(1^\circ\) F higher in mean temperature, 0.38% increase for every extra day the heat wave lasted and \(-0.063\%\) increase for every 1-d late the heat wave occurred in the United States. And Barnett et al (2012) estimated a 0.66% increase in deaths for 5\(^{\circ}\)F increase in intensity, \(-0.52\%\) increase for 5 d increase in duration and \(-0.77\%\) increase for 50 d later in timing of heat waves defined using a threshold of 99th percentile in the United States. A 0.07% increase in deaths for 5\(^{\circ}\)F increase in intensity, \(-0.05\%\) increase for 5 d increase in duration and \(-1.26\%\) increase for 50 d later in timing was also reported using a threshold of 1st percentile (Barnett et al 2012). The potentially influential factors for the different estimates were summarized as follows: (a) demographic characteristics (e.g. proportion of vulnerable population such as the elderly); (b) preparedness and responses to heat and cold waves (e.g. the early warning system); (c) city-level designs and factors that influence exposure levels (e.g. greenness cover) (Davis et al 2016); (d) physiological acclimatization of local residents; (e) individual behavioral habits or behavior modification (e.g. the use of air conditioner and central heating system and dressing habits); (f) other factors including air pollution. As confirmed in our study, the demographic characteristics (e.g. city population), climate (mean temperature, and diurnal temperature range), and other factors (e.g. latitude, GDP per capita and PM\(_{2.5}\) concentration) could modify the associations between heat and cold waves and mortality.

The study has significant public health implications to guide targeted work against the health threats of heat and cold waves. Firstly, we observed substantial effects of heat and cold waves in 31 Chinese major cities. This highlights the government should strengthen public risk perception towards heat and cold waves and appreciate the importance of well-prepared public resources (e.g. public facilities like central heating system) (Yang et al 2019). Secondly, greater harm to heath from earlier and longer heat and cold waves underscores the importance of prompting earlier warning system and response preparations. The substantial attention should be attached to the opportunity to intervene at the start of warm and cold seasons, and prepare public for possible severer or longer heat and cold waves in the aftermath of the short-term and mild ones. Thirdly, due to the variations in subpopulations, we should put emphasis on the targeted work of vulnerable populations, which includes raising their individual self-protection perception measures. Among cardiovascular patients, the female, those with lower education level are recommended to adopt proper behavior self-protect measures against extreme temperature events (e.g. use of air conditioning, electronic fans or central heating, staying indoors and wear extra clothes) (Anderson and Bell 2011).

The current study has some limitations. Firstly, characteristics of heat and cold waves considered in the study (intensity, duration, and timing in season) may not fully account for the variations in heat and cold waves effects (Anderson and Bell 2011). The health risk of heat or cold waves may change over time due to the implementation of intervention and increasing public perception of waves. Secondly, we must face the inevitable misclassification bias classifying the causes of death via ICD-10. Thirdly, the current study only collected information from urban residents. The information of inhabitants from the countryside was unavailable. Fourthly, we used the average values of climatic variables of all monitoring stations in the same city as a proxy of exposure for the whole population in this city, as commonly used in meteorological epidemiological studies (Wang et al 2016, Yin et al 2018). The lack of spatial resolution in the collected meteorological data inevitably induced the measurement bias. Fifthly, there were certain inevitable measurement bias when temperature data from the monitoring system substituted individual exposure (Yin et al 2018). Sixthly, regarding this complex association between GDP per capita and heatwave effect, well-designed studies involving more cities with various economic levels are warranted to help deeply address this issue. Lastly, the health impacts of heat and cold waves might be underestimated due to that people tend to stay indoors during heat or cold waves (Chen et al 2019, Yang et al 2019).

5. Conclusions

The effects of heat and cold waves on cardiovascular mortality was significant in China, with remarkable spatial variations in different climatic zones and geographical zones, and the effects were particularly higher for the waves which were more intense, longer, or started earlier. Patients with ischemic heart diseases, the female, the elderly, those with lower education level were more vulnerable to heat and cold waves. The study has implications for the development of early warning systems and response plans.

Acknowledgments

The study was supported by the Guangdong Basic and Applied Basic Research Foundation (No.
Davis A Y, Jung J, Pijanowski B C and Minor E S 2016 Combined application of anonymous data in this study. Ethical approval was not required for secondary analysis of anonymous data in this study.

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Data availability statement

The data that support the findings of this study are available upon reasonable request from the authors.

Ethical statement

Ethical approval was not required for secondary analysis of anonymous data in this study.
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