LETTER

The impact of cold spells on mortality from a wide spectrum of diseases in Guangzhou, China

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Abstract

Cold spells have been associated with mortality from a few broad categories of diseases or specific diseases. However, there is a lack of data about the health effects of cold spells on mortality from a wide spectrum of plausible diseases which can reveal a more comprehensive contour of the mortality burden of cold spells. We collected daily mortality data in Guangzhou during 2010–2018 from the Guangzhou Center for Disease Control and Prevention. The quasi-Poisson generalized linear regression model mixed with the distributed lag non-linear model (DLNM) was conducted to examine the health impacts of cold spells for 11 broad causes of death groupings and from 35 subcategories in Guangzhou. Then, we examined the effect modification by age group (0–64 and 65+ years) and sex. Effects of cold spells on mortality generally delayed for 3–5 d and persisted up to 27 d. Cold spells were significantly responsible for increased mortality risk for most categories of deaths, with cumulative relative risk (RR) over 0–27 lagged days of 1.57 [95% confidence interval (CI): 1.48–1.67], 1.95 (1.49–2.55), 1.58 (1.39–1.79), 1.54 (1.26–1.88), 1.92 (1.15–3.22), 1.75, (1.14–2.68), 2.02 (0.78–5.22), 1.92 (1.49–2.48), 1.48 (1.18–1.85), and 1.18 (1.06–1.30) for non-accidental causes, cardiovascular diseases, respiratory diseases, digestive diseases, nervous system diseases, genitourinary diseases, mental diseases, endocrine diseases, external cause and neoplasms, respectively. The magnitudes of the effects of cold spells on mortality varied remarkably among the 35 subcategories, with the largest cumulative RR of 2.87 (1.72–4.79) estimated for pulmonary heart diseases. The elderly and females were at a higher risk of mortality for most diseases after being exposed to cold spells. Increased mortality from a wide range of diseases was significantly linked with cold spells. Our findings may have important implications for formulating effective preventive strategies and early warning response plans that mitigate the health burden of cold spells.

1. Introduction

Under the background of climate change, extreme climate events are expected to occur more frequently (e.g. heat waves and floods) (Stocker et al 2013). The associations between extreme temperatures and mortality have been well documented (Anderson and Bell 2009, Barnett et al 2012, Xie et al 2013, Huynen and Martens 2015, Guo et al 2017, Kim et al 2018, Lee et al 2018, Chen et al 2019, Yang et al 2019). Some studies speculated that excessive and consecutive periods of extreme cold or sudden and substantial decreases in temperature could cause significant harmful health effects (Chen et al 2019). Furthermore, cold weather
was reported to account for a higher proportion of health burden than heat, particularly in temperate regions (Gasparrini et al 2015, Yang et al 2016). Thus, the health burden of cold spells is undoubtedly an important public health issue (Wang et al 2016, Chen et al 2019).

A large body of literature has shown that cold spells were distinctly associated with increased mortality (Barnett et al 2012, Xie et al 2013, Wang et al 2016, Chen et al 2019). However, the causes of death considered in previous studies only covered a few broad categories of diseases or specific diseases, such as all causes, cardiorespiratory diseases (e.g. ischemic heart disease, stroke, and chronic obstructive pulmonary disease) and diabetes (Xie et al 2013, Wang et al 2016, Chen et al 2019). Mortality or morbidity from some specific diseases (e.g. endocrine, nervous, renal failure, and infectious gastroenteritis) has been linked to cold weather in a few studies (Manser et al 2017, Kim et al 2018, Ma et al 2020). Based on the same population, assessing the impacts of cold spells on cause-specific mortality from a wide range of diseases (figure 1) can reveal a more comprehensive contour of the mortality burden of cold spells. Nevertheless, it remains uncertain about the disproportionate mortality risk from various diseases for individuals exposed to cold spells and how the potential effects of cold spells on mortality from various diseases vary across different lag time. In addition, whether sex and age group are effect modifiers of the impacts of cold spells needs to be further confirmed, so as to identify the high-risk subgroups and further be conducive to developing targeted prevention strategies for reducing the health burden of cold spells (Wang et al 2016, Chen et al 2019).

Guangzhou is one of the largest metropolises in Southern China, with a longitude of 113.27°E and latitude of 23.13°N. Climatically, the typical subtropical climate brings it mild winter and hot summer (Yang et al 2012). Residents in Guangzhou could be more prone to the threats of cold weather than those living in temperate regions. In this study, we intended to investigate the association between cold spells and mortality from a wide range of diseases in Guangzhou, China during 2010–2018, and also identify the possible effect modifiers (i.e. cause of death or personal characteristics) of such associations.

2. Methods

2.1. Study area

Guangzhou, the capital city of Guangdong province, is located in the center of the province, with an area of about 7434 km² and 14.9 million permanent residents (Guangzhou Statistics Bureau 2018) (figure 2).

2.2. Data collection

The Guangzhou Center for Disease Control and Prevention (www.gzcdc.org.cn/) provided daily mortality data from 1 January 2010 to 31 December 2018. Causes of death were encoded according to the International Statistical Classification of Diseases, Revi-
sion 10 (ICD-10). We considered 11 broad causes of death groupings, including all causes (ICD-10: A00–Z99), non-accidental causes of death (A00–R99), cardiovascular diseases (I00–I99), respiratory diseases (J00–J99), digestive diseases (K00–K93), nervous diseases (G00–G99), genitourinary diseases (N00–N99), mental and behavioural disorders (F00–F99), external causes (V01–Y89), endocrine diseases (D50–D89, E00–E90), and neoplasms (C00–D48). Further, we also examined 35 subcategories within the broad cause of death groupings (details available in supplemental table S1 thereafter (available online at stacks.iop.org/ERL/16/015009/mmedia)).

The China Meteorological Data Center (CMDC; http://data.cma.cn/) provided daily meteorological data (e.g. minimum, mean, and maximum temperature, mean relative humidity, atmospheric pressure, wind speed, and rainfall). Additionally, the daily average concentrations of sulphur dioxide (SO\textsubscript{2}), nitrogen dioxide (NO\textsubscript{2}), and particulate matter \(\leq 10\ \mu\text{g m}^{-3}\) in aerodynamic diameter (PM\textsubscript{10}) were collected from the Environmental Protection Bureau of Guangzhou Municipality (www.gzepb.gov.cn).

2.3. Statistical analysis

In the present study, we determined a weather fluctuation as the cold spell in accordance with our previous study (Chen et al 2019): at least two consecutive days with daily mean temperatures below the 5th percentile of the temperature distribution during 2010–2018. The descriptive information of the distribution of daily mortality was provided in supplemental figures S1 and S2. The mortality data for most categories of diseases was detected to be overdispersed (Böhning 1994) (available in supplemental table S2).

2.3.1. Variable selection and parameter setting

In order to determine the variables to be included in final models, the Spearman correlation relationship, and the significance test of the covariate in the multivariate quasi-Poisson regression model were examined, with all covariates as independent variables and all-cause mortality as dependent variable (available in supplemental tables S3–S5). Air pollutants were included when the Spearman correlation coefficients less than 0.70 to avoid collinearity (Dormann et al 2013, Yang et al 2020). Finally, time trend, day of week, PM\textsubscript{10}, mean temperature, and relative humidity were incorporated into the model (Kim et al 2018).

2.3.2. Model choice

We applied the generalized linear quasi-Poisson regression combined with the distributed lag non-linear model (DLNM) to capture the delayed effects of cold spells on cause-specific mortality (Gasparrini et al 2010, Gasparrini and Armstrong 2013, Gasparrini 2014, Wang et al 2016, Chen et al 2019). The model was as follows:

\[
\text{Log}(\mu_t) = \alpha + \beta T_{i,t}(CS_t) + \text{NS}(\text{Time}_t, 5 \times 9) + \gamma \text{Dow}_t + \text{NS}(\text{Temp}_t, 3) + \text{NS}(\text{Hum}_t, 3) + \text{NS}(\text{PM}_{10}, 3)
\]

Here, \(\mu_t\) is the expected deaths on day \(t\); \(\alpha\) represents the intercept; the dummy variable \(CS_t\) indicates the day \(t\) with or without cold spell (0: non-cold spell day, 1: cold spell day). Considering that the impacts of cold spells on mortality may occur with

Figure 2. The geographical location of Guangzhou in Guangdong province, China.
delay, cross-basis $T_{cl}(·)$ was constructed, with a linear function for $CS$, and a natural cubic spline with two internal knot placed along equally-spaced values on the log scale for the lag (Zhou et al 2014, Kim et al 2018). The largest lag day of cold spells was chosen as 27 d (Chen et al 2019). NS(·) means the natural cubic spline. We used a natural cubic spline with 5 degrees of freedom (dfs) per year for time ($Time_0$) to adjust for the seasonal variation and long-term trend (Yang et al 2012), while a natural cubic spline with 3 dfs was applied for the relative humidity (Hum) and PM$_{10}$ (Gao et al 2019). Day of the week ($Dow_0$) were included in the model as a categorical variable (Guo et al 2017, Chen et al 2019, Gao et al 2019); $\beta$ and $\gamma$ were vectors of regression coefficients. The selection of aforementioned dfs was decided according to the information criterion for quasi-Poisson (Q-AIC) (available in supplemental table S6) (Chen et al 2019). Furthermore, we performed stratified analyses by age group (0–64 and 65+ years) and sex (female and male) for the broad cause of deaths.

2.3.3. Detection of effect modifiers
A significant effect modifier means subjects with this condition are significantly more vulnerable to cold spells compared with those without the same condition. To determine the effect modifiers (i.e. cause of death or personal characteristics) of the association between cold spell and mortality, the case-only approach, which only focuses the cases and tests the association between cold spells and stratum factor of interest, was adopted to examine the statistical significance of effect modification (Yang et al 2012). The case-only approach has been regarded as a prevalent approach to investigate how time-constant factors (e.g. gender or socioeconomic status) modify the impacts of a time-dependent exposure (e.g. extreme temperature) on the health outcome (e.g. death) (Schwartz 2005, Medina-Ramón et al 2006, Yang et al 2012, Madrigano et al 2015). In the case-only design, a logistic regression model served as the main modeling strategy with a categorical variable indicating the subgroups of interest as the dependent variable and the indicator variable of cold spells as the independent variable. To incorporate the typical nonlinear relationship between cold spells and mortality, we combined the logistics regression with the DLNM with the same parameters from the model in section 2.3.2.

Coherent with previous documents (Schwartz 2005, Medina-Ramón et al 2006, Yang et al 2012), sine and cosine functions with a 365.24 d period were included in the model to account for the seasonal trend.

2.3.4. Sensitivity analysis
The aim of sensitivity analyses was to examine the robustness of estimated cumulative relative risks (RRs) of all-cause mortality attributed to cold spells. Firstly, we used other cold spell definitions from previous studies ($CS_1$; at least two consecutive days with daily mean temperature below the 3rd percentile (Wang et al 2016); $CS_2$; at least two consecutive days with daily mean temperature below the 10th percentile (Gao et al 2019); $CS_3$; at least five consecutive days with daily min temperature below the 5th percentile (Xie et al 2013); $CS_4$; at least three consecutive days with daily max temperature below the 3rd percentile (Ma et al 2011)). Additionally, we changed the dfs for the time variable (4–6, and 8), mean relative humidity, PM$_{10}$, and mean temperature (4–6) to observe the consistency of our main results.

All statistical analyses were conducted in the work environment of R software version 3.5.0 (R Foundation for Statistical Computing), with ‘dlnm’ (Gasparrini 2011) and ‘pscl’ (Zeileis et al 2008) packages. The two-tailed $P$-value <0.05 was the criterion to certify statistical significance.

3. Results
Cold spells occurred in Guangzhou every year during the study period and mainly appeared between December and March. The frequency of cold spells showed a declining trend, within the range of 1 (in 2015) to 8 (in 2011). The duration of cold spells varied by year, ranging from 2 d in 2015 to 28 d in 2011 (figure 3).

During 2010–2018, average daily mean temperature and relative humidity were 21.9 °C (range: 3.4 °C–32.2 °C) and 78.9% (30%–100%), respectively. The mean concentrations of SO$_2$, NO$_2$, and PM$_{10}$ were 17.6 µg m$^{-3}$, 46.7 µg m$^{-3}$, and 59.9 µg m$^{-3}$, respectively. Over the course of this study, there were on average 126 residents died every day, among which 49, 20 and 36 residents died from cardiovascular diseases, respiratory diseases and neoplasms. The daily numbers of death for most categories of causes were higher during days with cold spells than those without cold spells, except for neoplasms, while means of meteorological variables and air pollutant concentrations were lower during cold spells (table 1).

Figure 4 shows the effects of cold spells on mortality of 11 broad causes of death over the lags of 0–27 d. In general, the lagged effects of cold spells on different causes of death categories exhibited similar patterns, with the highest mortality risk following the exposure of the first few days and declining risk afterward. However, the effects of cold spells on mortality from mental and behavioural disorders were not statistically significant over the lags of 0–27 d; and the mortality risks of cold spells on digestive disease decreased rapidly over lag 0–10 d but lasted longer.

Figure 5 displays the estimated cumulative RRs of cold spells on cause-specific mortality for lag 0–14 d and lag 0–27 d. Cold spells were associated with elevated mortality risk for all the 11 broad categories of causes, with higher cumulative effects at lag 0–27 d relative to lag 0–14 d. Significant cumulative...
Table 1. Summary statistics for meteorological variables, air pollutants, and cause-specific mortality during 2010–2018 in Guangzhou, China.

| Causes                               | Minimum | Median | Maximum | SD   | Overall | Days with cold spells | Days without cold spells |
|--------------------------------------|---------|--------|---------|------|---------|-----------------------|--------------------------|
| All causes                           | 53      | 124    | 251     | 27.0 | 126     | 149                   | 125                      |
| Non-accidental                       | 47      | 118    | 238     | 25.9 | 120     | 142                   | 119                      |
| Cardiovascular diseases              | 13      | 48     | 115     | 14.1 | 49      | 64                    | 49                       |
| Respiratory diseases                 | 5       | 18     | 51      | 6.6  | 20      | 24                    | 20                       |
| Digestive diseases                   | 0       | 4      | 12      | 2.1  | 4       | 5                     | 4                        |
| Nervous diseases                     | 0       | 1      | 7       | 1.1  | 2       | 2                     | 2                        |
| Genitourinary diseases               | 0       | 1      | 8       | 1.4  | 2       | 3                     | 2                        |
| Mental and behavioural disorders     | 0       | 0      | 4       | 0.6  | 1       | 1                     | 1                        |
| External causes                      | 0       | 6      | 19      | 2.9  | 7       | 8                     | 7                        |
| Endocrine diseases                   | 0       | 4      | 16      | 2.5  | 5       | 6                     | 5                        |
| Neoplasms                            | 12      | 35     | 68      | 7.8  | 36      | 35                    | 36                       |

| Weather variables                    |         |        |         |      |         |                       |                          |
| Mean temperature (°C)                | 3.4     | 23.3   | 32.2    | 6.2  | 21.9    | 8.4                   | 22.6                     |
| Mean relative humidity (%)           | 30.0    | 80.0   | 100.0   | 11.2 | 78.9    | 69.4                  | 79.3                     |

| Air pollutants                       |         |        |         |      |         |                       |                          |
| SO₂ (µg m⁻³)                         | 3.0     | 14.0   | 98.0    | 12.1 | 17.6    | 13.0                  | 17.8                     |
| NO₂ (µg m⁻³)                         | 8.0     | 43.0   | 180.0   | 18.7 | 46.7    | 36.9                  | 47.1                     |
| PM₁₀ (µg m⁻³)                        | 9.0     | 53.0   | 241.0   | 30.3 | 59.9    | 50.4                  | 60.3                     |
RRs of cold spells at lag 0–27 d were estimated for non-accidental mortality (RR = 1.57, 95% confidence interval (CI): 1.48–1.67), cardiovascular diseases (RR = 1.95, 95% CI: 1.49–2.55), respiratory diseases (RR = 1.58, 95% CI: 1.39–1.79), digestive diseases (RR = 1.54, 95% CI: 1.26–1.88), nervous system diseases (RR = 1.92, 95% CI: 1.15–3.22), genitourinary diseases (RR = 1.75, 95% CI: 1.14–2.68), mental diseases (RR = 2.02, 95% CI: 0.78–5.22), endocrine diseases (RR = 1.92, 95% CI: 1.49–2.48), external causes (RR = 1.48, 95% CI: 1.18–1.85) and neoplasms (RR = 1.18, 95% CI: 1.06–1.30). For the specific causes of death, the largest estimated mortality risk was observed for pulmonary heart diseases (RR = 2.87, 95% CI: 1.72–4.79).

In addition, we further explored the modification effects of cold spells on mortality for the broad cause-of-death categories (available in supplemental table S7). Statistically significant effect modifiers were obtained for almost all the broad categories, except for digestive diseases, with the largest odds ratio (OR) of 2.04 (95% CI: 1.31–3.17) for nervous disease than for other causes. However, negative estimates of ORs were observed for mortality from external causes and neoplasms when comparing to their counterparts.

Figure 6 illustrates the estimates of cumulative RRs of cold spells on mortality of all broad causes of death stratified by age groups and sex. It was observed that the RRs of cold spells were stronger in those aged ≥65 years old than those aged <64 years, with statistical significance for effect modification test for most of the cause of death categories, except for respiratory diseases, nervous diseases, genitourinary diseases, mental and behavioural disorders, and external causes (available in supplemental table S8). Females were found to be more vulnerable to cold spells than males for mortality from all-cause, non-accidental, cardiovascular diseases, respiratory diseases, while males were at higher risk among digestive diseases.

Results of sensitivity analysis suggested that point estimates of the effects of cold spells changed a little using other cold spell definitions and the different dfs for time, mean relative humidity, PM$_{10}$, and mean temperature, with the cumulative RRs of all-cause...
mortality ranging from 1.36 to 1.51 for the lag of 0–14 d and from 1.39 to 1.67 for the lag of 0–27 d (available in supplemental table S9).

4. Discussion

To the best of our knowledge, the study is one of few studies to systematically examine the health impact of cold spells on mortality of a wide range of diseases, including 11 broad causes of death groupings and 35 subcategories. The application of a universal modelling framework permits the comparability of the mortality risks from a wide range of diseases. We found that exposure to cold spells was associated with elevated mortality risks from most of the categories of diseases considered, although the effect estimates for some categories were not statistically significant. Moreover, the higher vulnerability was observed in the elderly and females for most of the categories of diseases when exposed to cold spells.

So far, the comprehensive contours of the mortality burden of cold spells have not been well examined in current evidence. Our study observed significant and universal health risk of exposure to cold spells, which was supported by the adamant evidence that the significant increase in mortality for almost all broad causes of death was observed during days with cold spells (Xie et al 2013, Zhou et al 2014, Wang et al 2016, Chen et al 2019). Cold spells were found significantly related to non-accidental, cardiovascular diseases, and respiratory

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Figure 4. The effects of cold spells on mortality for 11 broad causes of deaths across the lags of 0–27 d. The blue solid lines represent RRs of mortality during days with cold spells comparing with days without cold spells, and grey regions are the corresponding 95% CI.

Figure 5. The cumulative effects of cold spells on cause-specific mortality over lag 0–14 and lag 0–27 d in Guangzhou. The diamonds represent RRs for broad categories of causes. The asterisk (*) means the significant effect modifier.

| Broad cause of death category | Causes                          | RR/95% CI          | RR/95% CI          |
|-------------------------------|--------------------------------|--------------------|--------------------|
| All causes                    |                                | 1.47 (1.14–1.53)   | 1.51 (1.48–1.66)   |
| Non-accidental causes         |                                | 1.27 (1.04–1.77)   |                    |
| Cardiovascular diseases       |                                |                    |                    |
| cerebrovascular disease       |                                | 1.63 (1.53–1.74)   | 1.74 (1.60–1.89)   |
| ischemic heart disease        |                                | 1.39 (1.35–1.42)   | 1.48 (1.40–1.58)   |
| stroke                        |                                | 1.65 (1.47–1.84)   | 1.81 (1.69–1.94)   |
| acute ischemic heart disease  |                                | 1.62 (1.43–1.84)   | 1.63 (1.53–1.73)   |
| heart attack                   |                                |                    |                    |
| myocardial infarction         |                                | 1.61 (1.42–1.84)   | 1.60 (1.51–1.71)   |
| chronic ischemic heart disease|                                | 1.56 (1.38–1.78)   | 1.75 (1.62–1.90)   |
| ischemic stroke               |                                | 1.71 (1.42–2.05)   | 1.80 (1.48–2.20)   |
| intra-cranial hemorrhage      |                                | 1.61 (1.44–1.89)   | 1.67 (1.51–1.84)   |
| other forms of heart disease  |                                | 1.42 (1.05–1.92)   | 1.65 (1.12–2.44)   |
| hypertensive disease          |                                | 1.62 (1.35–1.95)   | 1.85 (1.43–2.34)   |
| pulmonary heart disease       |                                | 2.52 (1.68–3.76)   | 2.87 (1.72–4.79)   |
| pulmonary embolism            |                                | 2.41 (1.84–3.53)   | 2.73 (2.07–3.59)   |
| amyotrophines                 |                                | 1.29 (0.84–2.19)   | 1.27 (0.92–1.75)   |
| heart failure                 |                                | 0.65 (0.28–2.10)   | 0.73 (0.35–1.54)   |
| chronic rheumatic heart disease|                                | 1.66 (1.31–2.11)   | 1.72 (1.34–2.25)   |
| arterio-sclerosis and capillaries|                        | 1.37 (0.83–2.27)   | 1.70 (0.93–3.15)   |
| Respiratory diseases          |                                |                    |                    |
| chronic obstructive pulmonary disease|                    | 1.46 (1.32–1.60)   | 1.59 (1.39–1.79)   |
| chronic obstructive pulmonary disease|                    | 1.57 (1.36–1.89)   | 1.57 (1.36–1.89)   |
| chronic lower respiratory disease|                        | 1.29 (1.02–1.64)   | 1.26 (1.00–1.59)   |
| influenzas                    |                                | 1.54 (1.24–1.92)   | 1.54 (1.24–1.92)   |
| other respiratory disease     |                                | 1.53 (1.02–2.27)   | 1.52 (1.01–2.27)   |
| other respiratory disease/affect interstitial lung disease| | 1.50 (1.08–2.09)   | 1.50 (1.08–2.09)   |
| Digestive diseases            |                                |                    |                    |
| liver disease                 |                                | 1.58 (1.29–2.24)   | 1.66 (1.35–2.22)   |
| hemorrhage                    |                                | 1.61 (1.46–1.77)   | 1.71 (1.54–1.90)   |
| gallbladder, bile tract and pancreas|              | 1.40 (1.22–1.60)   | 1.40 (1.22–1.60)   |
| digestive system              |                                | 1.50 (1.30–1.75)   | 1.50 (1.30–1.75)   |
| Gastrointestinal disease      |                                | 1.52 (1.28–1.81)   | 1.52 (1.28–1.81)   |
| respiratory system            |                                | 1.41 (1.18–1.68)   | 1.41 (1.18–1.68)   |
| extrapoluminal and movement disorders|        | 1.53 (1.23–1.89)   | 1.53 (1.23–1.89)   |
| renal failure                 |                                | 1.30 (0.92–1.81)   | 1.30 (0.92–1.81)   |
| Mental and behavioral disorders|                                | 1.83 (1.58–2.11)   | 1.83 (1.58–2.11)   |
| dermatology                   |                                | 1.20 (0.97–1.48)   | 1.20 (0.97–1.48)   |
| digestive tract injury        |                                | 1.09 (0.80–1.48)   | 1.09 (0.80–1.48)   |
| External causes               |                                | 1.42 (1.20–1.68)   | 1.40 (1.18–1.68)   |
| road traffic injury           |                                | 1.00 (0.68–1.51)   | 1.00 (0.68–1.51)   |
| Dementia                      |                                | 1.56 (1.39–1.79)   | 1.56 (1.39–1.79)   |
| Neoplasms                     |                                | 1.10 (1.06–1.28)   | 1.10 (1.06–1.28)   |

Figure 6. The cumulative effects of cold spells on cause-specific mortality stratified by age group and sex in Guangzhou. The asterisk (*) means the significant effect modifier.

| Broad cause of death category | Age(years) | RR (95% CI) | Gender | RR (95% CI) |
|-------------------------------|------------|-------------|--------|-------------|
| All-cause                     | 65 +       | 1.35 (1.54–1.76) | Female | 1.66 (1.33–1.77) |
| Non-accidental causes         | 65 +       | 1.35 (1.54–1.76) | Male   | 1.50 (1.39–1.61)  |
| Cardiovascular disease        | 65 +       | 1.59 (1.31–1.92) | Female | 1.71 (1.51–1.91)  |
| Respiratory disease           | 65 +       | 1.61 (1.61–1.93) | Male   | 1.51 (1.40–1.62)  |
| Digestive disease             | 65 +       | 1.74 (1.52–1.99) | Female | 1.82 (1.68–2.02)  |
| Nervous system                | 65 +       | 2.44 (1.11–5.40) | Male   | 2.00 (1.42–2.83)  |
| Neoplasms                     | 65 +       | 1.10 (0.59–2.15) | Female | 1.56 (0.75–3.29)  |
| Mental and behavioral disorders| 65 +       | 1.69 (0.79–2.31) | Male   | 2.31 (1.16–4.63)  |
| External causes               | 65 +       | 2.22 (0.63–7.85) | Female | 1.44 (0.75–2.74)  |
| Endocrine disease             | 65 +       | 1.30 (0.97–1.73) | Male   | 2.02 (1.35–3.03)  |
| Neoplasms                     | 65 +       | 1.25 (0.75–2.09) | Female | 1.65 (1.17–2.34)  |
| Neoplasms                     | 65 +       | 2.18 (1.63–2.93) | Male   | 1.53 (0.70–2.55)  |

We observed higher mortality risks on cardiovascular diseases (1.95, 95% CI: 1.49–2.55) than a previous multicity study in China (Chen et al. 2019) with an effect estimate of 1.69 (95% CI: 1.48–1.89) for cardiovascular diseases. However, the estimated effect for respiratory diseases in that previous study (1.88; 95% CI: 1.65–2.11) was higher than our result (1.58; 95% CI: 1.39–1.79) (Chen et al. 2019). Interestingly, significant relationships between cold spells and mortality from digestive and genitourinary diseases were...
observed in the present study, which was inconsistent with previous studies (Manser et al 2017, Kim et al 2018, Ma et al 2020). For instance, a recent study by Ma et al (2020) reported no associations between cold spells and mortality due to digestive and genitourinary diseases (Ma et al 2020). Moreover, Kim et al (2018) claimed a nonsignificant association between the cold temperature and hospital admissions of renal diseases (Kim et al 2018). Furthermore, Manser’s team reported that cold days did not present a significant impact on the incidence of either infectious gastroenteritis or inflammatory bowel disease flares (Manser et al 2017). The inconsistent findings might be due to the differences in the mortality rates of these diseases (Ma et al 2020), climatic characteristics, and adaptability to cold weather. Furthermore, the current study suggested an increased mortality risk associated with cold spells for nervous, endocrine diseases, and external causes. This finding is consistent with a previous study that reported heat and cold accounted for the substantial mortality burden of endocrine, nervous, and mental diseases, and external causes (Ma et al 2020). Our findings can help shed light on the pathological mechanisms and pathways of those rare-examined diseases which underlie the health effects.

Many epidemiological studies confirmed that age group and sex were latent effect modifiers of temperature-related mortality risk (Xie et al 2013, Chen et al 2019, Yang et al 2019). Whereas, whether effect modification by factors of interest was statistically significant was less tested in the aftermath of stratified analysis in previous studies. In this study, we found that the elderly were the high-risk group to cold spells rather than those aged <65 years, which was consistent with findings of recent researches (Xie et al 2013, Zhou et al 2014, Chen et al 2019, Yang et al 2019). The vulnerability of the elderly may be partially attributed to the high prevalence of chronic diseases and weakened adaptation, resulting from aging-induced physiological declination in thermoregulation and homeostasis (Wang et al 2016, Chen et al 2019). Moreover, females had higher mortality risks of most of the categories of diseases than males, except for diseases of the digestive system, nervous, genitourinary system, and mental system. The prolonged life expectancy of Chinese females leads to a larger proportion of susceptible women, which may partly explain the higher vulnerability of females (Zhou et al 2014). Besides, the male was thought to have significant physiological differences than the female, including better thermoregulation ability, hormone levels, physical capacity, and different living habits and routines (Marchand et al 2001, Zhou et al 2014). In contrast, males were also found to have higher mortality risks for some categories of diseases (O’Neill et al 2003). The sex difference may be partly due to the disparity in occupational exposure to cold weather (Zhou et al 2014).

Pathophysiologically, the vasomotor response mediated by the sympathetic nervous system induces peripheral vasoconstriction to reduce peripheral blood flow, meanwhile, metabolic heat production is enhanced via thermoregulatory response, thereby increasing the insulation of the body to cold stress (Harinath et al 2005). Epidemiologically, numerous previous studies drew coherent findings, and further proposed and discussed possible disease mechanisms and pathways (Ma et al 2013, Sartini et al 2016, Han et al 2017, Kim et al 2018, Chen et al 2019, Gao et al 2019). The underlying mechanisms navigated the considerable health risk of cold spells on cardiovascular patients may be physiological changes induced by autonomic thermoregulatory and heavier stress on the cardiovascular system out of body’s reactions to cold, such as higher blood pressure and viscosity and increasing systematic vascular resistance (Nayha et al 2002, Mercer et al 2003, Tan et al 2003, Gómez-Acebo et al 2013, Ma et al 2013).

Cold spells were found significantly associated with an increase in respiratory disease mortality, with an RR of 1.58 (95% CI: 1.39–1.79). Previous studies attributed the mortality risk of respiratory disease to the possible mechanism including high prevalence of respiratory infection, hematological changes by cold-induced vasoconstriction including increasing plasma cholesterol and fibrinogen which predispose the individual to hypertension and trigger thrombosis, and fewer medical care services available due to heavier medical needs during cold spells (Fong et al 2000, Chen et al 2019). The paper discovered a significant association (RR = 1.54, 95% CI: 1.26–1.88) between cold spell exposure and diseases of the digestive system, which may be elucidated via the physiological mechanisms. These mechanisms contain decreasing cardiac output flowing to the gastrointestinal tract and stimulated secretion of excessive anabolic hormones, which aim to increase the mobilization of energy sources for use by the shivering muscles to cope with cold stress (Young 2010). The insufficient blood supply of the digestive system induces poor nutrient absorption, while excessive anabolic hormones secretion is wrongly stimulated. These two processes work synergistically to cause heavy burdens to digestive system. Notably, the nonlinear lag pattern of digestive disease indicated the effects of cold spells on mortality were still significant at later days. Regarding the longer course of digestive disease, the stress due to cold spell among patients with this disease may affect the nutrient intake, further influence other body systems and organs, and even cause lethal event. Moreover, previous research has suggested that raised sympathetic tone and enhanced metabolism are the possible disease mechanisms that underpin the cold stress on diseases of nervous system (Westfall et al 2005). During the period of cold spells, consecutive cold exposure elicits urinary tension and frequent urination even aggravates existing urinary
dysfunctions (Harinath et al. 2005, Ishizuka et al. 2012, Imamura et al. 2013).

With respect to mental and behavioural disorders, our study detected the highest mortality risk (2.02, 95% CI: 0.78–5.22) of cold spells among the death causes discussed, which was inconsistent with previous studies (Wang et al. 2014, Chan et al. 2018, Almendra et al. 2019). Although our study did not detect the significant association, extreme temperatures may aggravate mental and behavioural disorders disease for following physiological and behavioral pathways. First, some psychiatric disorders where specific neurotransmitters about thermoregulation are also involved can increase the physiological susceptibility of subjects (Sung et al. 2011). Second, the illness-induced decreases of cognitive ability towards the surrounding environment elicit defective self-maintenance to daily living activities (e.g. taking on clothes when needed, standing inside to keep warm, and drinking warm water). Third, the confirmed disruption to normal thermoregulatory of many psychotropic medications due to their pharmacological properties also accounts for the substantial association between cold stress and psychiatric disorders (Sung et al. 2011, Chan et al. 2018, Almendra et al. 2019).

Those patients with digestive diseases were confirmed to suffer from higher health risks with an RR of 1.54 (95% CI: 1.26–1.88). To withstand the cold stress, increased metabolic heat production proposes the heavy burden towards digestive and endocrine system, which may partly interpret the latent reasons (Harinath et al. 2005). Cold stress can alter cognitive functions to diminish the ability to perform mental and physical activities, such as declined accuracy, impaired executive function, and prolong reaction time, and this may partially demonstrate the mechanism of external cause mortality risk (Makinen and Hassi 2009, Taylor et al. 2016, Orru and Åström 2017). Lastly, the lowest mortality risk of neoplasms (1.18, 95% CI: 1.06–1.30) was detected, which was agreed with other studies (Goggins et al. 2013). There are some wide-accepted mechanisms from previous studies. In cold winter, the lack of sunlight, vitamin D and so on may lead to the declination of host immunity. Besides, some studies suggested the harvesting effect was probably the main mechanism upon cold-related cancer mortality (Gómez-Acebo et al. 2013).

Our study has some strengths. First, this is one of few studies that systematically applies a generalized linear model to quantify the health impact of cold spells on a wide range of diseases, including some well-documented categories of diseases (non-accidental, cardiovascular diseases, and respiratory diseases) and many under-investigated specific diseases (digestive diseases, genitourinary diseases, nervous diseases, and external causes). The pernicious effects of cold spells and various mechanisms of diseases underscore the importance of well-prepared organization and targeted precautionary systems and control measures. The policymakers, health promotion workforce and public health practitioners (e.g. healthcare workers) are highly recommended to comprehend the scientific evidence about the association between cold spell and diseases (Yang et al. 2012). Moreover, infrastructure construction and public medical services supplied by the local government is the primary aspect; in peril of cold spell, the local government is supposed to increase the supply of public heating resources, like the central heating system, and ensure the medical services available. On top of that, reinforcing public awareness is conducive in response to the threat of cold spells. The community health knowledge pervasion plays an essential role in the promotion of public awareness. The other is the detection of high-risk populations from subgroup analysis contribute to targeted policies and measures to well protect the population. The remarkable health threat towards vulnerable population reminds us to carry out targeted tackling scheme. From the individual level, the popularization of important scientific knowledge about diseases is highly welcomed to raise individual risk perception (Chen et al. 2019).

Several limitations of the current study should be claimed here. Firstly, the scientific findings in this paper were derived from a single city. The potential spatial heterogeneity of the effects of cold spells, especially on those under-investigated specific causes of death, needs to be further examined in future multi-city studies. Secondly, the exposure-response relationships between cold spells and mortality were assumed linear. Such an ideal association between cold spells and mortality were likely to overturn due to potential nonlinear relationships. Thirdly, we used a model with the same independent variables and parameter settings to estimate the mortality risks of cold spells on different categories of diseases in order to make the results comparable. However, such a modelling strategy may not be the best choice for all the causes of death considered. Fourthly, we did not adjust P-value for multiple testing. Hence, more attention was focused on presenting the effect sizes rather than statistical test results in our study (Li et al. 2021). Fifthly, we may face the inevitable misclassification bias since the ICD-10 dictionary was applied to register the cause of death (Yang et al. 2015, Chen et al. 2019). Sixthly, the current study investigated the exposure-response relationship between cold spells and various diseases using the data for urban residents and thus it remains uncertain whether the results can be generalized to the rural population. Seventhly, the data on meteorological variables air pollutant concentration were collected from a certain amount of monitoring stations which may not precisely reflect
the exposure level of each individual. Such inevitable measurement bias is likely to underestimate the influences of cold spells (Chen et al. 2019). Lastly, the preference in which people avoid being exposed outdoors during cold spells might result in underestimations of the health threats of cold spells (Chen et al. 2019).

5. Conclusions

Our study found that higher mortality risk of a wide spectrum of diseases was significantly relevant with cold spells in Guangzhou, China, including some under-investigated causes of death, such as those subtypes of digestive diseases, genitourinary diseases, nervous diseases, and external causes. The elderly and females exposed to cold spells were vulnerable populations to death from most of the categories of diseases. Our findings may pave the way to formulating preventive strategies and response plans that mitigate the health burden of cold spells.

Data availability statement

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

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Ethics statement

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

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