REPORT

The modification effect of ozone pollution on the associations between heat wave and cardiovascular mortality

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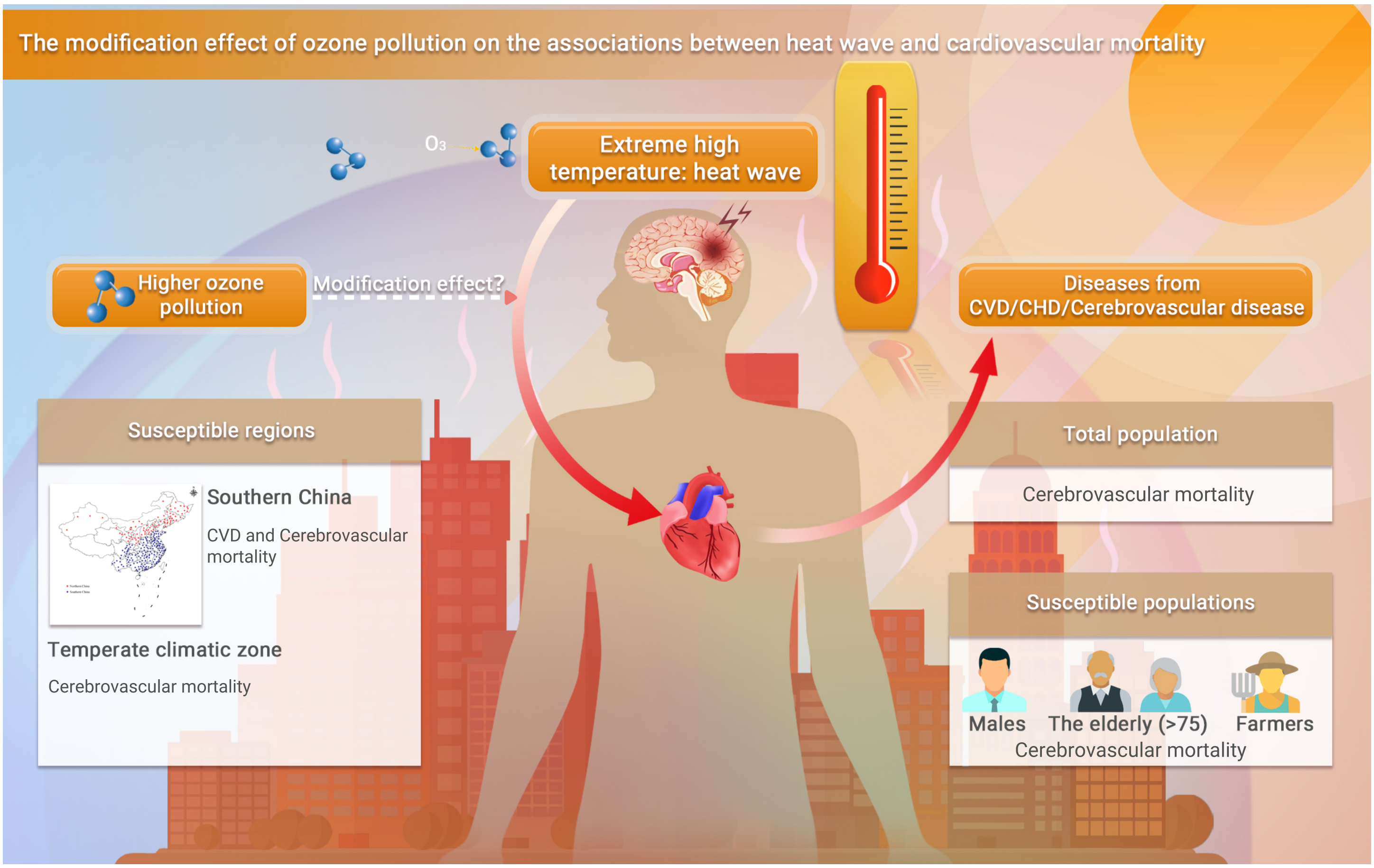
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Heat wave had an adverse health effect on mortality from cardiovascular diseases.
- High concentration of ozone pollution enhanced the associations between heat wave and mortality from cerebrovascular diseases.
- The modification effect of ozone pollution on heat wave was observed in southern China and temperate climatic zone.

The modification effect of ozone pollution on the associations between heat wave and cardiovascular mortality

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Epidemiological evidence concerning whether ozone modifies the impact of heat waves remain unexplored, especially in developing countries. To comprehensively evaluate the potential modification effect of ozone on heat wave impacts in warm seasons, we adopted a dataset (including mortality from overall cardiovascular diseases, chronic heart diseases and cerebrovascular diseases) in 250 Chinese cities from 2015 to 2019. A conditional quasi-Poisson regression model within the framework of the space-time-stratified case-crossover design was applied to obtain province-level associations, and a meta-analysis was adopted to pool province-level associations to national-average associations. Ozone concentration was categorized into low, medium and high levels using the 33rd and 66th percentiles of the location-specific levels as cutoffs, then we calculated the effect of heat waves in various ozone strata. Further stratification analyses on sub-populations (age group, sex and occupation) and regions were carried out. Heat waves were found to be positively associated with mortality from overall cardiovascular diseases (*RR*=1.043, 95% *CI*: 1.027-1.059). Higher concentrations of ozone significantly enhanced the effects of heat waves on cerebrovascular mortality. The mortality risk of heat waves was 1.071 (95% *CI*: 1.036-1.108) and 1.069 (95% *CI*: 1.039-1.100) at the medium and high levels, respectively (*P* for interaction=0.012 and 0.040, compared to the low level). A significant modification effect of ozone on the cerebrovascular mortality impact of heat waves was observed among people over 75, males and farmers, as well as in southern China and temperate climatic zones. Our findings suggest that ozone might potentially modify the mortality effect of heat waves.

INTRODUCTION

China has made substantial progress in reducing the burden of mortality and diseases.[1] However, epidemiological investigations and the Global Burden of Disease Study revealed that cardiovascular disease (CVD) remains the top cause of death in China, and its prevalence has doubled since 1990.[2,3] The attributable fractions were 17.48% for overall cardiovascular disease and 18.76% for coronary heart disease reported in the 272 Chinese cities study,[4] leading to a nonnegligible disease burden. Climate change is causing extreme high-temperature events to occur more frequently and intensely worldwide.[5,6] Notably, China experienced serious heat wave events in the summer of 2022. Heat-related health impacts have also become a particular concern facing global warming.[7] It has been well documented that extreme high temperature can affect cardiovascular health.[8,9]

Exposure to high ambient pollution is widely recognized as a threat to public health and is associated with excess morbidity and mortality.[10-12] To mitigate the serious air pollution situation in China, the State Council of China issued the Air Pollution Prevention and Control Action Plan (APPCAP) in 2013, which has been a milestone of national pollution control strategies.[13] Since then, studies have reported improvements in air quality, while the concentration of ozone has continued to increase.[14-16] Therefore, the adverse health impacts of ozone have attracted scientific and public attention. A large quantity of time-series studies has demonstrated significant positive associations between ozone exposure and CVD morbidity and mortality.[17-19] Prior scholars have pointed out that China is among the highest ozone-related death countries in the world, accounting for 67,000 attributable premature deaths in 2015.[20] Ozone is more likely to reach unhealthy levels in dry and hot weather environments.[21] Questions have arisen regarding whether ozone concentration modifies the health hazards of temperature.

Studies conducted in some developed countries have been carried out on the modification effects of temperature on the air pollutant-mortality relationship,[22-25] while inconsistent results have been reached, especially for ozone.[26] The meta-analysis showed that the ERs for all-cause and nonaccidental mortality were 5.1% (3.9%-6.3%) and 3.6% (0.1%-7.2%) at the low O_3 level and 7.6% (6.3%-9.0%) and 12.5% (4.7%-20.9%) at the high O_3 level, respectively. In conclusion, O_3 modifies heat-related all-cause and nonaccidental mortality. However, significant effect modification by air pollutants was not observed for heatwave or cold effects.[24] A study on two-way effect modifications of air pollution and air temperature on mortality in eight European urban areas found that on days with high air pollution (>50th percentile), both heat- and cold-related mortality risks increased.[22] The pooled cumulative risks (percent increase) were 14.61 (95% *CI*: 8.24-21.36) for total or natural mortality and 14.83 (95% *CI*: 2.35-28.83) at the high ozone pollution level; among them, the total or natural mortality risk was significantly different from that at the low level.[22] Nevertheless, there have been very few studies on the modification effect of ozone on the effect of extreme high temperature based on the latest data. In conclusion, a nationwide analysis in developing countries such as China that pays more attention to the potential modification effect of ambient ozone exposure on the adverse health impact of heat waves is urgently needed.

To quantify the association between heat waves and cardiovascular mortality, we used a space-time-stratified case-crossover design and employed a conditional quasi-Poisson regression model to conduct a time-series study of 250 Chinese cities with the latest reliable data from 2015 to 2019. The mortality effect of heat waves was estimated in low, medium and high ozone strata due to ozone stratification using tertiles as cutoffs, and the significance of modification was evaluated by between-strata differences (medium vs. low; high vs. low). We hypothesized that the mortality impact of heat waves was stronger at higher ozone pollution levels than at the lowest level. We additionally aggregated the daily death counts by age group, sex and occupation to further identify how ozone modifies the heat wave-mortality association in various subgroups. Regional stratification was also performed to observe the interaction between extreme high temperature and ozone from the perspective of climate factors.

MATERIALS AND METHODS

Data collection

The mortality data were obtained from China's Disease Surveillance System (DSPS),administered by the Chinese Center for Disease Control and Prevention. The death data from this database have shown good accuracy and national representativeness in published literature.[27,28] We extracted daily death counts from cardiovascular diseases defined by the International Classification of Diseases, 10th revision (ICD-10), which contained diseases of the circulatory system (ICD-10: I00-I99), coronary heart disease (ICD-10: I20-I25) and cerebrovascular diseases (ICD-10: I60-I69). These data comprised date, sex, age group and occupation. To ensure sufficient statistical power when fitting models, we first screened out the eligible cities with annual changes of

Table 1. Relative risks (*RR*, 95%*CI*) of mortality from cardiovascular diseases associated with heat wave (>97.5th for ≥2d) in the total population, sub-populations and different regions

Population	CVD mortality		CHD mortality		Cerebrovascular disease mortality	
	RR (95%*CI*)	$P_{interaction}$	*RR* (95%*CI*)	$P_{interaction}$	*RR* (95%*CI*)	$P_{interaction}$
Total	1.043 (1.027, 1.059)	<0.001**	1.035 (1.007, 1.064)	0.014*	1.059 (1.035, 1.084)	<0.001***
Age						
<64	1.024 (0.991, 1.059)	0.154	1.042 (0.989, 1.098)	0.119	1.026 (0.979, 1.076)	0.277
65-74	1.074 (1.041, 1.109)	<0.001***	1.064 (1.008, 1.122)	0.024*	1.091 (1.043, 1.141)	<0.001***
>75	1.042 (1.022, 1.062)	<0.001***	1.029 (0.994, 1.065)	0.109	1.061 (1.029, 1.094)	<0.001***
Sex						
Male	1.051 (1.030, 1.073)	<0.001***	1.036 (0.998, 1.074)	0.061	1.063 (1.030, 1.097)	<0.001***
Female	1.041 (1.018, 1.064)	<0.001***	1.039 (0.999, 1.080)	0.054	1.058 (1.023, 1.095)	0.001***
Occupation						
Farmer	1.049 (1.030, 1.068)	<0.001***	1.048 (1.015, 1.082)	0.004**	1.049 (1.021, 1.078)	<0.001***
Non-farmer	1.035 (1.007, 1.062)	0.012*	1.008 (0.963, 1.055)	0.728	1.101 (1.055, 1.149)	<0.001***
Administrative zone						
Northern China	1.046 (1.017, 1.076)	0.002	1.042 (0.994, 1.092)	0.087	1.084 (1.036, 1.135)	<0.001***
Southern China	1.042 (1.023, 1.061)	<0.001**	1.031 (0.997, 1.067)	0.073	1.050 (1.022, 1.079)	<0.001***
Climatic zone						
Tropical or arid zone	1.129 (1.068, 1.193)	<0.001***	1.122 (1.026, 1.228)	0.012*	1.142 (1.049, 1.244)	0.002**
Temperate zone	1.028 (1.008, 1.048)	0.007**	1.015 (0.978, 1.055)	0.429	1.038 (1.008, 1.069)	0.013*
Cold zone	1.045 (1.018, 1.074)	0.001***	1.033 (0.988, 1.081)	0.156	1.074 (1.028, 1.123)	0.001***

Note: ****P*<0.001; **0.001<*P*<0.01; *0.01<*P*<0.05.

Table 2. Relative risks (*RR*, 95%*CI*) of mortality from cardiovascular diseases associated with heat wave (>97.5th for ≥2d) at different ozone levels (4-day moving average ozone) in the total population, and *p*-value for potential modification effect

Mortality cause	Ozone level	*RR* (95%*CI*)	$P_{interaction}$
All CVD	Low	1.020 (0.992, 1.049)	Ref
	Medium	1.044 (1.021, 1.068)	0.214
	High	1.046 (1.027, 1.066)	0.302
CHD	Low	1.038 (0.986, 1.092)	Ref
	Medium	1.027 (0.986, 1.069)	0.310
	High	1.036 (1.002, 1.072)	0.574
Cerebrovascular disease	Low	1.016 (0.972, 1.062)	Ref
	Medium	1.071 (1.036, 1.108)	0.012*
	High	1.069 (1.039, 1.100)	0.040*

Note: *0.01<*P*<0.05.

more than three total deaths (the sum of diseases from various causes included) at the daily level. Therefore, the analysis was based on time-series data including 250 Chinese cities from 2015 to 2019.

Daily air pollution data were collected from the National Urban Air Quality Real-time Publishing Platform covering all cities in China at the prefecture level by 2015 (http://106.37.208.233:20035/). We extracted the 24-h average concentrations of fine particulate matter ($PM_{2.5}$), nitrogen dioxide (NO_2) and maximum of 8-hour mean concentrations for ozone, averaged from all monitoring sites in each city. The platform is administered by China's Ministry of Environmental Protection. By 2015, all Chinese cities at the prefecture level or higher had been covered, indicating reliable national representativeness. To adjust for weather conditions, city-level daily mean temperature and mean relative humidity were also obtained from the China Meteorological Data Sharing Service System (http://data.cma.cn/).

Study design

The case-crossover study could be considered a type of self-matched case–control study. Exposure data were collected for the 'case' day and a series of 'control' days that were not associated with the event of interest. To accommodate the demand for multicenter studies, we applied the space-time-stratified case-crossover design developed from the time-stratifiedcase-crossover design and applied to multi time-series data proposed by Wu.[29] The stratum combining two dimensions of time (the same day of the week within the same month) and space(city) was used as the source of 'control'

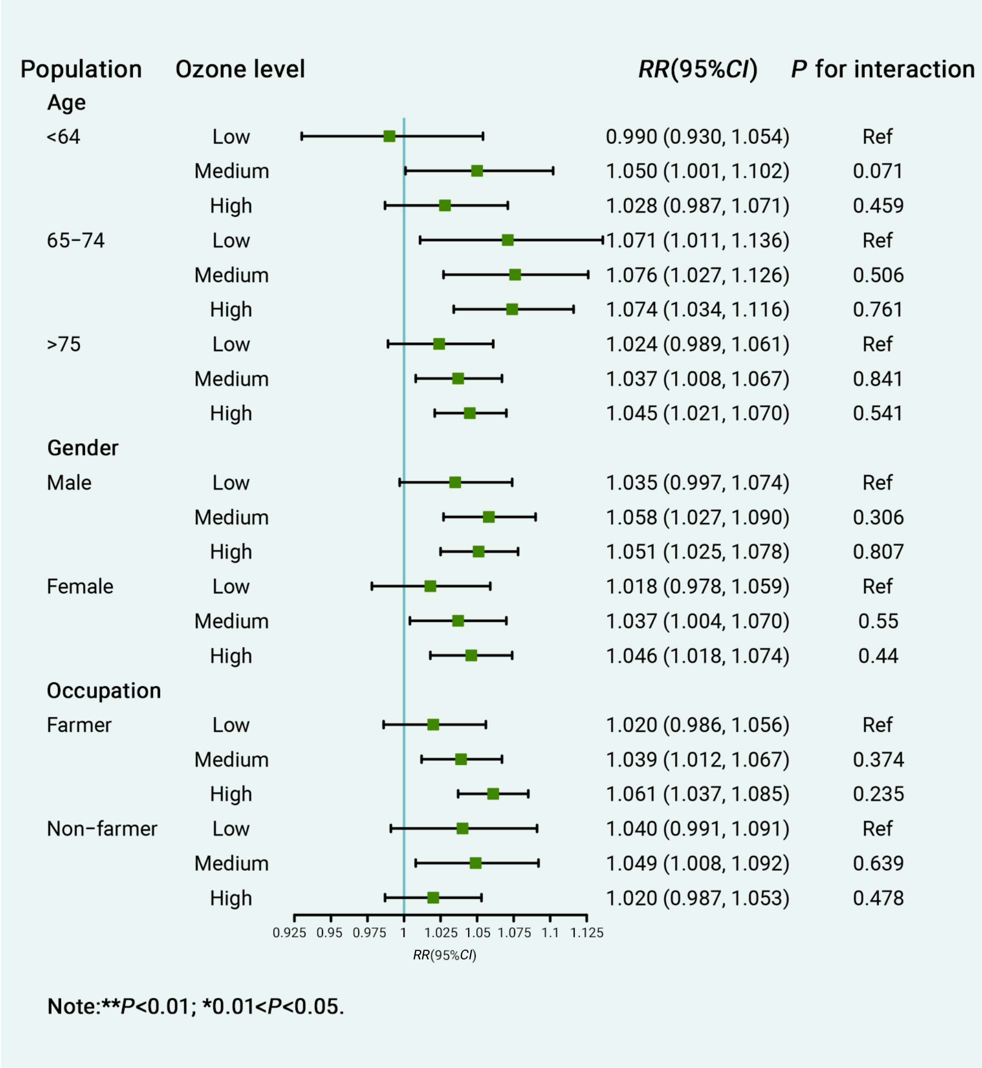

Figure 1. Relative risks (*RR*, 95%*CI*) of mortality from all cardiovascular diseases associated with heat wave (>97.5th for ≥2d) at different ozone levels (4-day moving average ozone) in different sub-populations, and p-value for potential modification effect.

days for each case on one day, allowing researchers to simultaneously control for the impacts of the day of the week, seasonality, long-term trend, and between-city spatial variation. This study design also avoids bias resulting from time trends by removing patterns in the placement of referents.[30,31]

Statistical analysis

The study period was restricted to warm seasons (from May to September) to focus on heat wave events as indicators of extreme high temperatures. Due to the lack of a universally accepted definition of a heatwave, we considered prior scientific evidence; therefore, a heat wave was defined through city-specific relative thresholds (97.5th) with a duration of ≥2 days.[6] In terms of ozone, we referred to published literature and applied a 4-day moving average concentration to make our results comparable.[10]

We fitted a conditional quasi-Poisson regression model to perform the space-time-stratified case-crossover design and estimated the province-level associations in the first stage. The following variables were introduced in the model: 1) a binary variable of heat wave (0 means non-heat wave days and 1 means heat wave days), 2) a continuous variable of 4-day moving average concentration of short-term ozone exposure, 3) a distributed lag nonlinear model (DLNM) for daily mean temperature with a lag period of 7 days to control for the main effect of temperature and 4) a natural cubic B-spline function with 3 df for current day relative humidity to exclude potential confounding effects.[6,10,32] The DLNM for temperature included a quadratic B-spline with 2 internal knots placed at the 50th and 75th percentiles of location-specific temperature contributions and a lag-response curve with a natural cubic B-spline with 3 internal knots (plus an intercept) placed at equally spaced values in the log scale. The added effects of heat waves on CVD mortality, CHD mortality and cerebrovascular disease mortality were reported in the total population. Then, the modification effect of ozone was assessed through stratification analysis. The 4-day moving average concentration of ozone was categorized into low, medium, and high levels using the 33rd and 66th percentiles of the location-specific 4-day moving average ozone data as cutoffs. After defining the basic model to estimate the effect of heat waves on CVD mortality, we developed an interaction model with a multiplicative interaction term for categorical ozone variables (shown as Eq. 1 as follows) and categorical heat wave variables.

*Outcome~HW+Ozone1*HW+Ozone_continuous+cb(meant)+ns(meanrh)* (Eq. 1)

HW means a binary variable indicating a heat wave; *Ozone1* means a categorical variable of ozone based on tertile distribution; *cb(meant)* means the nonlinear cross-basis function of daily average temperature; *ns(meanrh)* means the natural spline function of relative humidity.

We used *Ozone_continuousas* a numerical variable to control for the main effect of ozone to avoid potential residual confounding. The effect estimates of heat waves at a low ozone level were the same as the coefficient of the 'heatwave' variable in Equation 1, and the effect estimates of heat waves at medium and high ozone levels were obtained from the coefficients of the 'heatwave' variable and the interaction term. To test the potential interactive effect between ozone and heatwaves, we adopted a Wald test of the meta-analytic value of the coefficient of interaction between ozone1 and the heat wave statistic (actually 'heatwave1:ozone12' and heatwave1:ozone13') comparing pooled RRs of heat waves at medium or high ozone levelscompared to low ozone levels.

We also conducted a series of further sensitivity analyses: 1) we contained all the cities without screening with daily total death counts, and 291 cities were finally selected; 2) we compared different results under different heat wave definitions based on the Akaike information criterion for quasi-Poisson (Q-AIC) value through our previous study based on 14-year data across 136 Chinese cities;[32] 3) we chose a maximum lag period of 5-10 days to conduct the reanalysis; 4) we defined the ozone categories based on quartiles (low: the 25th percentile and less; medium: 25th~75th percentile; and high: 75th percentile and higher) to divide three strata; 5) we controlled 4-day moving average relative humidity rather than current day humidity as a confounder in the model; and 6) we additionally controlled for the same-day concentrations of $PM_{2.5}$ and NO_2 (lag0) in the above two-stage models in our sensitivity analyses.

Subpopulation-specific and region-specific modification effects

To further identify the modification effect among various subpopulations and regions, we stratified the total population into several subpopulations by age group (<64, 65-74 and >75years), sex (male and female) and occupation (farmers and nonfarmers). The criterion of occupation stratification was based on the distribution of occupations among the total population, as over 70% were farmers, and those directly exposed to an outdoor heat environment might be the potential susceptible subpopulation. The classification categories including retired, unemployed and others were merged as

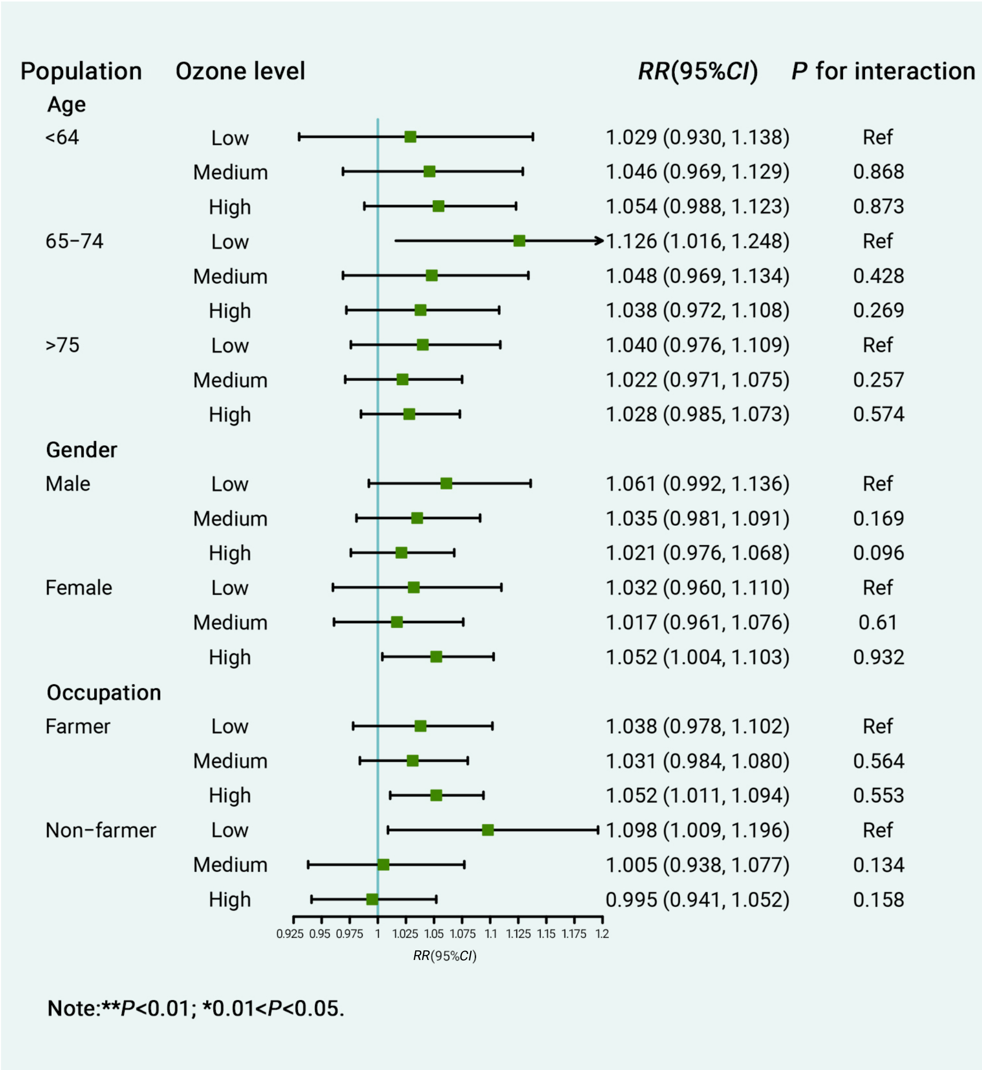

Figure 2. Relative risks (*RR*, 95%*CI*) of mortality from all chronic heart diseases associated with heat wave (>97.5th for ≥2d) at different ozone levels (4-day moving average ozone) in different sub-populations, and p-value for potential modification effect.

nonfarmers. With regard to regional stratification, we concentrated on both administrative divisions and climatic zones. On the one hand, we observed the separate mortality effects of heat waves in each ozone stratum in northern or southern China. Among them, North China, Northwest China and Northeast China were classified as northern China, and South China, Southwest China and East China were classified as southern China.

On the other hand, the 250 studied cities were divided by the Köppen climate classification, a type of climate classification system based on temperature, precipitation and vegetation distribution. We developed an updated global map of climate using the Koppen-Geiger system based on a large global dataset of long-term monthly precipitation and temperature data calculated at each station and interpolated between stations using a two-dimensional (latitude and longitude) thin-plate spline with tension onto a 0.1°×0.1° grid for each continent produced by Peel.[33] In China, 5 climate groups have been defined, described as tropical (A), arid (B), temperate (C), cold (D), and polar (E) zones. Each climatic group contains 2 to 4 secondary subcategories, among which the arid, temperate, and cold zones also contain multilevel subcategories, and a total of 30 climate types have been established globally. In our study, considering the limited number of tropical cites, we merged the tropical and arid zones into one group, the 'tropical or arid zone'. In addition, no city was described as a polar zone, so the 250 cities could be divided into 3 climatic groups: tropical or arid zone, temperate zone and cold zone.

All analyses were performed using the 'gnm' package in R 4.1.3 with an a priori α level of 0.05 to determine statistical significance.

RESULTS

Descriptive Statistics

Figure S1 reveals the geographical locations of 250 Chinese cities included in the main analysis covering three climatic zones. Tables S2-S3 show the summary descriptions of various variables across provinces. The average overall cardiovascular death during warm seasons was 65.8 (17.3 for mortality from CHD and 25.4 for mortality from cerebrovascular diseases). During the study period, the maximum 8-hour mean concentration of O_3 was 113.7 μg/m^3. The average daily mean temperature and relative humidity were 23.3 °C and 71%, respectively. The average concentrations of ozone during days with and without heat waves were 134 μg/m^3 and 112 μg/m^3, respectively. According to the selected definition, during the warm seasons from 2015 to 2019, the number of days with heat waves was 6 942 days.

Effect modification among the total population and sub-populations

Table 1 presents the relative risks (*RR*s, 95% *CI*s) of mortality from cardiovascular diseases associated with heat waves (>97.5th for ≥2 d) in the total population, sub-populations and different regions. Based on the conditional quasi-Poisson regression model, heat waves were found to be significantly positively associated with mortality from the 3 cardiovascular diseases, with *RR*s of 1.043 (95% *CI*: 1.027-1.059), 1.035 (95% *CI*: 1.007-1.064) and 1.059 (95% *CI*: 1.035-1.084).

Table 2 demonstrates the pooled effect of heat waves on cardiovascular mortality at different ozone levels stratified by province-specific ozone concentration tertiles. The associations between heat waves and CVD mortality were stronger at medium and high ozone levels (*RR*=1.044, 95% *CI*: 1.021-1.068; and *RR*=1.046, 95% *CI*: 1.027-1.066, respectively) than at low ozone levels (*RR*=1.020, 95% *CI*: 0.992-1.049), while no significant interaction effect between ozone and heat waves was observed in the total population (*P* for interaction>0.05). However, a higher concentration of ozone pollution (>1st tertile) might significantly enhance the acute mortality effect of heat waves on cerebrovascular diseases, with a relative risk of 1.071 (95% *CI*: 1.036-1.108) for the medium level and 1.069 (95% *CI*: 1.039-1.100) for the high level (*P* for interaction=0.012 and 0.040, respectively).

The results of the populational analyses (shown in Figures 1-3) provided evidence for a modification effect of ozone on the added effect of heat waves among elderly individuals over 75 years old, males and farmers but only for mortality from cerebrovascular diseases. In detail, concerning age, the effect of heat waves on cerebrovascular mortality was more pronounced at higher ozone levels among people aged over 75 years. The *RR*s were 1.063 (95% *CI*: 1.017-1.112, *P* for interaction=0.048) at the medium ozone level and 1.082 (95% *CI*: 1.041-1.123, *P* for interaction=0.017) at the high ozone level. With regard to sex, we also observed a positive interaction effect between ozone and heat waves (*P* for interaction=0.038 and 0.017, respectively). Regarding occupation, heat waves showed a stronger cerebrovascular mortality effect at medium ozone levels (*RR*=1.059, 95% *CI*: 1.017-1.112, *P* for interaction=0.025) than at low ozone levels (*RR*=1.007, 95% *CI*: 0.957-1.059). Among the other sub-populations, no significant modification effect of ozone was discovered. In the sensitivity analysis (shown in Table S1), the results remained relatively stable.

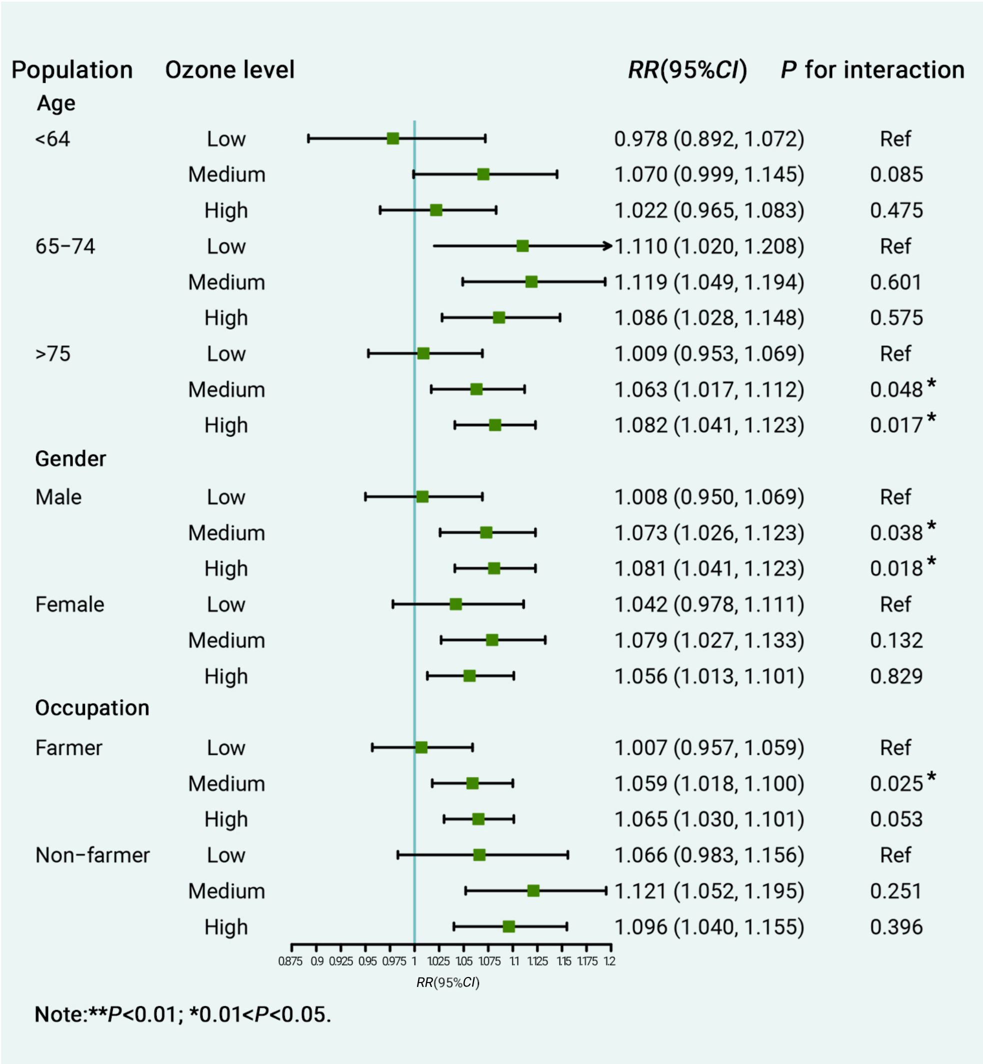

Figure 3. Relative risks (*RR*, 95%*CI*) of mortality from all cerebrovascular diseases associated with heat wave (>97.5th for ≥2d) at different ozone levels (4-day moving average ozone) in different sub-populations, and p-value for potential modification effect.

stratification analyses. Southern China and the temperate climatic zone might be susceptible regions faced with higher mortality risks associated with heat waves when ozone pollution surpasses the 1st or 2nd tertile.

DISCUSSION

The results revealed that heat waves were significantly associated with an excess mortality risk of cardiovascular diseases. A positive interaction effect of higher ozone pollution (>1st tertile) on the acute mortality effect of heat waves was observed among the total population for cerebrovascular diseases. Higher concentrations of ozone pollution might enhance the acute mortality effect of heat waves, especially among people aged over 75, males and farmers recurrently working outdoors for cerebrovascular mortality. The associations between heat waves and CVD and cerebrovascular disease mortality was significantly stronger at medium or high ozone concentration levels than at low ozone levels in southern China for all cardiovascular mortality and cerebrovascular mortality and in the temperate climatic zone for cerebrovascular mortality. In general, ozone may serve as a potential modifier of the acute adverse health effects of heat waves.

Elderly individuals aged 75 years and older, males and farmers were sensitive to the cerebrovascular mortality effect of heat waves on medium and high ozone polluted days, with statistical significance for the modification effect of ozone on heat waves, which may indicate that the modification role of ozone appears among these sub-populations. Previous studies have proven that elderly individuals are more vulnerable to air pollution and temperature variations.[34-36] Multiple chronic diseases and present declines in physiological processes make the elderly vulnerable to the modification effect of ozone on extreme high temperature.[37] Farmers engaged in agricultural work spend much more time outdoors, and their movement patterns may influence the exposure intensity of both ambient ozone and heat waves. On the highly polluted days, the heavier outdoor chores contributed to much more exposure to excess heat in warm seasons compared with those working indoors. Exposure to heat leads to a higher core body temperature, a range of acute and chronic heat-induced diseases, and life-threatening multiple organ dysfunction, contributing to excess mortality risk.[38,39] Our findings highlighted the need for developing regional heatwave warning systems, especially on high ozone pollution days or in cities with high concentrations of ozone, to develop local heatwave prevention plans with flexible times, especially for farmers and people working outside.[40,41]

Trends in cardiovascular mortality across Asia and Europe both demonstrated significant geographical variation, so stratification analysis due to the region was necessary.[2,42] The modification effect of ozone on the acute mortality impact of heat waves was discovered in southern China. It was found in the Yangtze River Delta (YRD) region that chemical reactions play the most important role in ozone formation during heat wave days, which results in 12 ppb ozone enhancement compared to non-heat wave days. During heat waves, more stagnant conditions, controlled by anti-cyclones with sink airflow, led to less water vapor in the YRD from the south and

Effect modification among different regions

The results of the regional analyses are shown in Figure 4. The association between heat waves and CVD mortality was significantly stronger at high ozone levels than at low levels in southern China (*P* for interaction=0.046). When focused on cerebrovascular disease mortality, the results in southern China showed a positive interaction effect of ozone at both medium and high ozone levels and heat waves compared with low levels (*P* for interaction=0.003 and 0.002, respectively). And the mortality risk was 1.054 (95% *CI*: 1.031-1.079) for CVD mortality and 1.071 (95% *CI*: 1.035-1.108).

Similar findings were found in the temperate climatic zone in which the association between heat waves and cerebrovascular mortality increased when the ozone concentration increased from a low to a high level, with a relative risk of 1.048 (95% *CI*: 1.005-1.093) for the medium level and 1.061 (95% *CI*: 1.023-1.100) for the high level, and a positive modification effect was discovered (*P* for interaction=0.005 and 0.005, respectively). In terms of the cold zone, a higher effect was also observed when ozone increased to a medium or high level, although the interaction effect was not significant. Nevertheless, in the tropical or arid climatic zone, we observed a various situation occurring in three outcomes in which the mortality effect of heat waves showed the largest effect estimate at the low ozone level, and the effect estimate attenuated when ozone increased to medium or high levels. Among the three mortality causes, ozone exposure showed a significant negative interaction effect on heat wave-CHD mortality (*P* for interaction=0.026 and 0.055 for medium and high levels, respectively). The mortality risk was 1.475 (95% *CI*: 1.129-1.926) at the low ozone level but decreased to 1.104 (95% *CI*: 0.951-1.282) at the medium ozone level and 1.098 (95% *CI*: 0.995-1.212) at the high ozone level.

In addition, we did not observe any other significant results in the regional

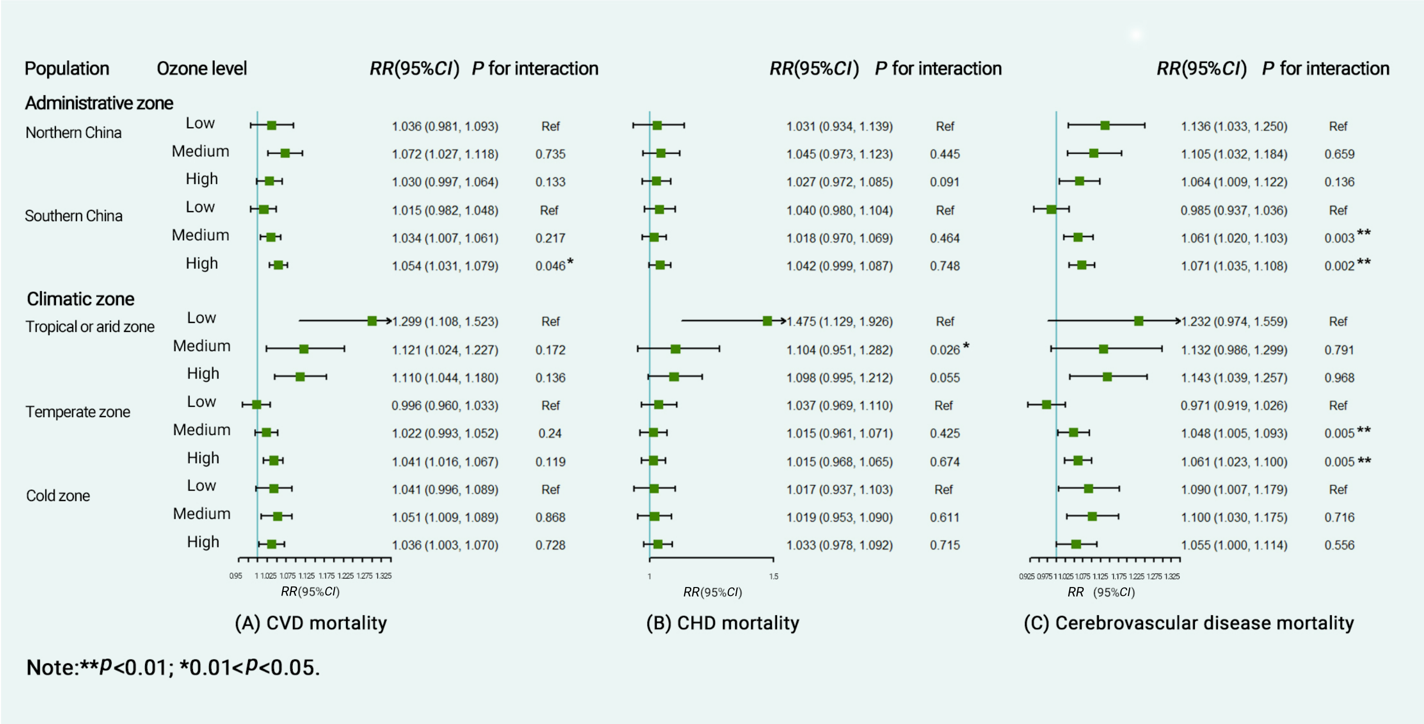

Figure 4. Relative risks (*RR*, 95%*CI*) of mortality from three cardiovascular diseases associated with heat wave (>97.5th for ≥2d) at different ozone levels (4-day moving average ozone) in different regions, and p-value for potential modification effect.

contributed to less cloud cover, which favored a strong solar radiation environment and a significant increase in ozone.[43] Cao and Yin reported that atmospheric circulation variations would benefit ozone pollution control in the Beijing-Tianjin-Hebei region, representative of the northern China region, mainly caused by enhanced convectional precipitation and changes in lower-level wind and the temperature difference between the upper and lower-level troposphere.[44] Additionally, there exists an eightfold difference in the rate of the population at high risk for cardiovascular diseases in China, with the highest rate in northeast China and northern China and the lowest rate in southern China.[45] Risk factors, such as obesity and high blood pressure (northern China) and consumption of unhealthy food (northeast China), pose more adverse effects on cardiovascular disease, which might cover part of the impacts of high-level ozone and heat waves on health.[45,46] The conclusion in the temperate zone was similar to the above, as we observed a distribution of cities from the temperate zone, which was mainly located in southern China.

The impact of heat waves was more obvious in tropical or arid climatic zones than in other climatic zones, which might lie in the behavior patterns. On the one hand, we observed the strongest effect of heat waves in tropical or arid zones compared with the other two climatic zones on all mortality outcomes, suggesting that residents from tropical or arid zones are the most vulnerable to extreme high temperature. On the other hand, the province-average number of days with heat waves at the low ozone level was 2.44, and the number of days increased threefold at the medium ozone level (7.52). The situation at low and medium ozone levels was 5.40 days and 8.76 days in the temperate zone (increased by 1.62 times) and 4.57 days and 7.93 days in the cold zone (increased by 1.74 times). Furthermore, the average number of days with heat waves at the high ozone level reached 17.64, which was 7 times higher than that at the low level. In the most vulnerable climatic zone, the evident increasing occurrence of heat wave on highly ozone polluted days might alert residents to consciously change behaviors to avoid outdoor activities to reduce the combined exposure to ozone pollution and heat waves so that the corresponding health risk decreases. The economic development level and industrial structure of different regions are significantly different, so there are certain differences in the spatiotemporal characteristics of such situations with persistent hot days and high ozone exposure levels.[47] Notably, the limited city numbers and death counts in tropical or arid climatic zones restricted the statistical power of our analysis; therefore, the results should be interpreted with caution.

The biological mechanisms underlying the interaction effect came from the mutual impact between temperature and ozone. Physiology studies once reported that marked changes in temperature could influence individuals' responses to ambient toxicants, including ozone pollution.[48] From the independent effects of ozone and heat, under high temperature, the human body may lead to dehydration and a reduction in central blood volume, leading to increased blood viscosity and altered serum osmolality, which may increase the risk of microvascular thrombosis and subsequent ischemic stroke.[49] Besides, heat may damage the endothelial cells of blood vessels and lead to coagulation dysfunction and consequently to consumptive coagulation, which may result in multiple organ dysfunction syndrome, including cerebral hemorrhages.[50] High ambient temperature could also lead to a systemic inflammatory response.[50,51] Meanwhile, ozone is involved in the process of systemic inflammation, and ozone exposure can cause an increase in systemic inflammation, as evidenced by increased interleukin (IL)-1β and CRP (C-reactive protein).[49] The association between ozone and markers of coagulation has been examined.[52] Cerza et al. found an association between ozone exposure and hospitalization for Alzheimer's disease (AD).[53] In animal models, O_3 exposure has also been found to induce increased IL-17 expression, primarily in hippocampal neurons, similar to that observed in human AD.[54] From the interaction effect of ozone and heat, at elevated temperature, an increase in PAI-1 (plasminogen activator inhibitor-1) and a concomitant increase in plasminogen and decrease in D-dimer were observed, which indicates the impairment of the fibrinolytic pathway, in favor of thrombosis and ischemic stroke.[21] The effect of the combined stimulation of the fibrinolytic pathway by both ozone and heat results in the triggering of this compensatory mechanism and the overproduction of PAI-1. The fibrinolytic pathway is complex and may result in clinically significant outcomes.[21]

Our study has some strengths. First, to our knowledge, this study is the largest multi-city study to date to investigate the modification effect of ozone on the mortality effect of heat waves by using mortality data with both national and regional reliability. DSPs were based on surveillance points covering 73 million people, approximately 6% of the total Chinese population since 2004. Second, we assessed the modification effect among sub-populations and regions and observed novel conclusions in specific sub-populations and zones, which provided a hint for the exploration of the mutual effect between ozone and heat waves.

Some limitations exist in the present study. First, the ambient ozone data from monitor stations were directly used to match the death ministry database, which may contribute to individual exposure measurement errors.[55] However, as recent findings from China found pollution concentrations only attenuated drastically with 100 m alongside the main roads, the intracity variations due to traffic were limited. As the monitoring sites and the residence address were not located in the areas within 100 m alongside the main roads, individual exposure measurement errors derived from monitor station data would contribute to a few substantial errors in observational studies.[56] Second, we did not control for the prevalence of other diseases and socioeconomic development information because we mainly focused on the short-term effect of heat waves and the model was established from time-series data and the case-crossover design controlled for long-term time trends. The distribution of the above factors did not vary from day to day, and thus, at the population level, they would not substantially bias the association between short-term exposure to extreme high temperature and mortality.[57] Third, the city-level data did not include individual covariates, such as time-activity patterns spending outdoors and indoors, housing conditions, and air conditioner installment. These factors may modify an individual's vulnerability to heat effects. To enhance the prediction accuracy of the model and reduce residual confounding, elaborate individual studies with individual-time-stratified case-crossover designs are recommended.[29] Fourth, as with many previous studies, the ecological study could not capture a causal relationship.[58]

CONCLUSION

In summary, this study found positive associations between short-term exposure to heat waves and increased mortality risk from cardiovascular diseases. The modification effect of ozone on such association was observed among the total population, people aged over 75, males and farmers recurrently working outdoors for mortality from cerebrovascular diseases, in southern China and temperate climatic zones for mortality from overall cardiovascular diseases or cerebrovascular diseases, concretely expressed as an enhanced acute mortality effect under higher concentrations of ozone pollution. These findings imply that ozone may be an effect modifier in the associations between extreme high temperature and mortality. We appeal for counterpart measures against heat waves and heavy ozone pollution for susceptible populations and areas.

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AUTHOR CONTRIBUTIONS

J.Q. and G.L. conceived the research idea. J.Q., G.L. and R.C. designed the study. J.Q. and Y.W. conducted the main analysis. Y.W. wrote the manuscript. Y.W., L.W., J.H. and P.Y. reviewed and edited the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

ETHICAL STATEMENT AND PATIENT CONSENT

This study was conducted using publicly available de-identified data; therefore, it did not require additional ethical approval or patient consent.

DATA AND MATERIALS AVAILABILITY

Daily air pollution data were collected from the National Urban Air Quality Real-time Publishing Platform covering all cities in China at the prefecture level by 2015 (http://106.37.208.233:20035/). City-level daily mean temperature and mean relative humidity were obtained from the China Meteorological Data Sharing Service System (http://data.cma.cn/).

SUPPLEMENTAL INFORMATION

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