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Exposure to Concurrent Heatwaves and Ozone Pollution and Associations with Mortality Risk: A Nationwide Study in China

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BACKGROUND: Concurrent extreme events are projected to occur more frequently under a changing climate. Understanding the mortality risk and burden of the concurrent heatwaves and ozone (O_3) pollution may support the formulation of adaptation strategies and early warning systems for concurrent events in the context of climate change.

OBJECTIVES: We aimed to estimate the mortality risk and excess deaths of concurrent heatwaves and O_3 pollution across 250 counties in China.

METHODS: We collected daily mortality, meteorological, and air pollution data for the summer (1 June to 30 September) during 2013–2018. We defined heatwaves and high O_3 pollution days, then we divided the identified days into three categories: *a*) days with only heatwaves (heatwave-only event), *b*) days with only high O_3 pollution (high O_3 pollution-only event), and *c*) days with concurrent heatwaves and high O_3 pollution (concurrent event). A generalized linear model with a quasi-Poisson regression was used to estimate the risk of mortality associated with extreme events for each county. Then we conducted a random-effects meta-analysis to pool the county-specific estimates to derive the overall effect estimates. We used mixed-effects meta-regression to identify the drivers of the heterogeneity. Finally, we estimated the excess death attributable to extreme events (heatwave-only, high O_3 pollution-only, and concurrent events) from 2013 to 2020.

RESULTS: A higher all-cause mortality risk was associated with exposure to the concurrent heatwaves and high O_3 pollution than exposure to a heatwave-only or a high O_3 pollution-only event. The effects of a concurrent event on circulatory and respiratory mortality were higher than all-cause and nonaccidental mortality. Sex and age significantly impacted the association of concurrent events and heatwave-only events with all-cause mortality. We estimated that annual average excess deaths attributed to the concurrent events were 6,249 in China from 2017 to 2020, 5.7 times higher than the annual average excess deaths attributed to the concurrent events from 2013 to 2016. The annual average proportion of excess deaths attributed to the concurrent events in the total excess deaths caused by three types of events (heatwave-only events, high O_3 pollution-only events, and concurrent events) increased significantly in 2017–2020 (31.50%; 95% CI: 26.73%, 35.53%) compared with 2013–2016 (9.65%; 95% CI: 5.67%, 10.81%). Relative excess risk due to interaction revealed positive additive interaction considering the concurrent effect of heatwaves and high O_3 pollution.

DISCUSSION: Our findings may provide scientific basis for establishing a concurrent event early warning system to reduce the adverse health impact of the concurrent heatwaves and high O_3 pollution. https://doi.org/10.1289/EHP13790

Introduction

The *Sixth Assessment Report of the Intergovernmental Panel on Climate Change* (IPCC AR6) reported that the frequency of concurrent extreme events will increase under global warming.[1,2] The frequency and intensity of extreme heat are projected to increase significantly.[1] At the same time, the frequent high temperature will accelerate the atmospheric photochemical reaction and increase ambient ozone (O_3) concentration,[3–5] leading to co-occurring heatwaves and high O_3 pollution. Given that high temperature and O_3 pollution are major global public health concerns, exposure to co-occurring heatwaves and O_3 pollution may have a concurrent health impact. Therefore, it is crucial to quantify the effect of the concurrent heatwaves and O_3 pollution.

According to the Global Burden of Disease study, high temperature and O_3 pollution have respectively accounted for >307,846 and 365,222 premature deaths worldwide in 2019.[6] Epidemiological studies have demonstrated that heatwaves and O_3 pollution are associated with increased risk for many health outcomes.[7–11] However, little is known regarding the health impacts of the combination of both heatwaves and O_3 pollution. A few studies have investigated the interactive health effect of ambient O_3 and temperature.[12–15] A recent review on the synergistic health effects of air pollution and temperature reported an interactive effect between heat and O_3 pollution exposure, showing that high temperature could enhance the adverse health effects of O_3.[15] These findings suggest that exposure to concurrent heatwaves and O_3 pollution events poses a more significant threat to human health than heatwaves or O_3 pollution-only events.

Although several studies have examined the concurrent effects of temperature and air pollution,[16–18] few have been conducted in China.[14] A study conducted in California reported that certain areas observed strong joint effects between O_3 and heat exposure.[18] Another study, also conducted in California, found that the effect of coexposure to extreme heat and particulate matter ≤ 2.5 μm in aerodynamic diameter ($PM_{2.5}$) was larger than the sum of their individual effects.[16] However, these studies were conducted in developed countries with low pollution levels. Few studies, to our knowledge, have explored the concurrent effect of heatwaves and O_3 pollution in developing countries where ambient air pollution is typically higher.

Some countries have implement ed early warning systems for high temperature[19–21] and air pollution.[22] In the 1990s, the United States took the lead in the early warning system of high temperature based on the population-based excess death assessment

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attributable to high temperature, which was based on synoptic climatological procedure and uses model output statistics guidance forecast data, enabling prediction of high-temperature weather occurrence 48 h in advance.[19] After experiencing a severe heatwave in the summer of 2003, European countries established a relatively complete health early warning system for heatwaves.[20,21] By contrast, the health risk warning system started relatively late in China, with an early warning system for heat applied in Shanghai in 2007.[22] In 2013, the National Environmental Air Monitoring Network of China was officially put into operation, releasing real-time air pollution monitoring data, an environmental air quality index, and other information for early warning (National Air Quality Forecast Information Release System; https://air.cnemc.cn:18014/). Although individual early warning systems exist for high temperature and air pollution, an early warning system for the combination of heatwaves and air pollution events has not been implemented, making it impossible to alarm the population to the occurrence of the concurrent events in time.

In the present study, we conducted a time-series analysis to explore the mortality risk of the combination of heatwaves and O_3 pollution. We first estimated the associations of mortality with concurrent exposure events, heatwave-only, and O_3 pollution-only events using daily data for 250 Chinese counties in the summer (from 1 June to 30 September for each year) from 2013 to 2018, we then assessed the excess death of concurrent events, heatwave-only, and O_3 pollution-only events from 2013 to 2020 in China.

Materials and Methods

Study Area

Our study areas included 250 Chinese counties (Figure 1; accounting for 8.79% of all the 2,843 counties in China), with residential population sizes varying from 500,000 to 10 million. These counties were included because *a*) each county's annual crude mortality rate, which was calculated based on the number of deaths of people and the residential population in each year from 2013 to 2018, as determined by the Disease Surveillance Points System (DSPS) of the Chinese Center for Disease Control and Prevention (China CDC), was higher than 4.5‰, and *b*) the fluctuation in each county's annual mortality rates from 2013 to 2018 was <20%. County-level socioeconomic (SES) characteristics data were obtained from the Sixth National Population Census in 2010, including gross domestic product (GDP; ×10,000), the agricultural population of this county (in percentage), the low-income population (population with a monthly income of <2,000 CNY; in percentage), the low–normalized difference vegetation index (NDVI) areas (proportion of areas with an NDVI of <0.4; in percentage), population living alone (in percentage), the population >65 years of age (in percentage), the illiterate population (in percentage), the minority population (proportion of people ≥15 years of age who do not recognize characters; in percentage), and population density (persons per square kilometer).

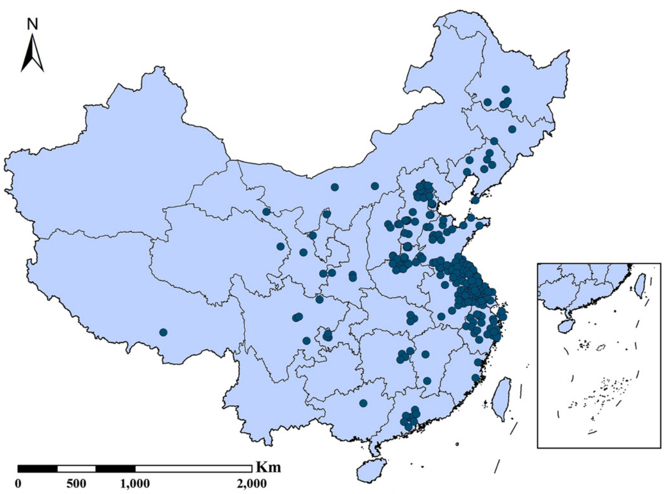

Figure 1. Map of the locations of the 250 study counties in China. The dots represent the sites of the 250 counties, and the zoomed-in panel represents the South China Sea archipelago and boundary lines. The map data was obtained from the Ministry of Natural Resources of the People's Republic of China [GS (2019) 1822] and created using ArcGIS (version 10.7; ESRI).

Mortality Data

Daily mortality data for the study counties were obtained from the DSPS of the China CDC for the summer season (from 1 June to 30 September) from 2013 to 2018. Mortality data were classified according to the *International Statistical Classification of Disease, Tenth Revision* (ICD-10), including all-cause (ICD-10 codes A00–Z99), nonaccidental (codes A00–R99), circulatory disease (codes I00–I99), cardiovascular disease (codes I00–I59), cerebrovascular disease (codes I60–I69), and respiratory disease (codes J00–J99). We further considered nine cardiopulmonary mortality categories: hypertensive heart disease (codes I10–I15), acute myocardial infarction (codes I21–I22), myocardial infarction (codes I21–I23), chronic ischemic heart disease (code I25), hemorrhagic stroke (codes I60–I61), cerebral stroke (codes I60–I64), ischemic stroke (code I63), lower respiratory tract infection (codes J12–J18 and J20–J22), and chronic obstructive pulmonary disease (codes J41–J44). County-level daily mortality data for these causes were also classified by sex (male and female) and age (<65, 65–74, and >74 y).

Environmental Data

Hourly $PM_{2.5}$ and O_3 concentration data from 2013 to 2018 were obtained from the National Urban Air Quality Real-Time Release Platform. This platform, which includes 1,436 air pollutant monitoring stations nationwide, is established and maintained by the China National Environmental Monitoring Centre. If a county had more than one monitoring station, we calculated average air pollution concentrations for all the stations of the county. If a county had no station, we used air pollutant monitoring data from the station closest to the centroid of the county. We calculated the daily average 24-h concentration of $PM_{2.5}$ and the daily maximum 8-h concentration for O_3. $PM_{2.5}$ was considered as a confounder in estimating the associations between extreme events and mortality. In assessing the nationwide mortality burden from 2013 to 2020, we obtained O_3 daily maximum 8-h average concentration data from 2013 to 2020 based on a multivariable random forest model at a spatial resolution of 1×1 km.[23]

Daily temperature and relative humidity data from 2013 to 2020 were obtained from the European Centre for Medium-Range Weather Forecasts,[24] with a resolution of $0.1^{\circ} \times 0.1^{\circ}$. We extracted meteorological data based on the longitude and latitude of each county's centroid.

Definition of Extreme Events

We set the primary heatwaves definition as 2 consecutive days exceeding the 98th percentiles of the county-specific daily mean temperature for the summer season from 2013 to 2018. Similarly, we primarily defined a high O_3 pollution event as 2 consecutive days with a daily maximum 8-h O_3 concentration exceeding $160\,\mu g/m^3$, which is the secondary concentration limit of O_3 based on the Ambient Air Quality Standard of China (CAAQS; GB3095-2012). Then, we divided the identified heatwave days and high O_3 pollution days into three categories: *a*) days with only heatwaves (heatwave-only event), *b*) days with only high O_3 pollution (high O_3 pollution-only event), and *c*) days with both heatwaves and high O_3 pollution (concurrent event); similar classification strategy has been used in one previous study.[16] Days when neither heatwaves nor high O_3 pollution occurred were defined as referent days.

Statistical Analysis

We estimated the association between extreme events (i.e., heatwave-only, high O_3 pollution-only, and concurrent events) and mortality via a two-stage approach, which has been widely used in multicenter environmental epidemiological studies.[11,25] In the first stage, we estimated mortality risk associated with extreme events exposure for each county using a generalized linear model (GLM) with a quasi-Poisson regression, controlling for the confounding effects of relative humidity, $PM_{2.5}$, long-term trends, and day of week. To investigate potential lagged effects, we analyzed the mortality effect of an extreme event at a single-day lag (i.e., lag 0, 1, 2, and 3). The model equation is as follows:

$$\begin{aligned} log\,[E(Y_t)] = \beta_0 + \beta X_t + ns(RH, df) + ns(PM_{2.5}, df) \\ + ns(Time, df) + Dow, \end{aligned} \tag{1}$$

where $E(Y_t)$ represents the expected number of deaths at day t; β_0 is the model intercept; and X_t is a categorical variable denoting event exposure on day t (X_t is "0" for referent days, "1" for days with a heatwave-only event, "2" for days with a high O_3 pollution-only event, and "3" for days with a concurrent event). β is the coefficient vector with a length of three; *ns* is a natural cubic spline function; *df* is the degrees of freedom of the natural spline function; and *RH* is the mean relative humidity on day t, included using natural cubic spline functions with three df per year. $PM_{2.5}$ is the daily average concentration of $PM_{2.5}$ on day t, included using natural cubic spline functions with three df per year; *Time* is the long-term trends of mortality, with non-summer days excluded, included using natural cubic spline functions with three df per year; and *Dow* is a dummy variable indicating the day of the week.

In the second stage, we conducted a random-effects meta-analysis to estimate the overall mortality risk by pooling county-specific results from the first stage for each lag effect. We calculated relative risks (RRs) and 95% confidence intervals (CIs). Heterogeneity in county-specific results was evaluated as an I^2 statistic. Using the pooled results from the meta-analysis, we calculated relative excess risk due to interaction (RERI) to evaluate whether the combined effect of the heatwaves and high O_3 pollution is more or less than additive, which can provide scientific evidence for public health management.[18,26] RERI was estimated only for the lag of overall mortality effect estimates for extreme events, which was both the largest and statistically significant.[16]

We also conducted stratified analysis by sex (male and female) and age (<65, 65–74, and >74 y) for the overall mortality risk of all-cause. We used the one-sided z-test (Equation 2) to evaluate whether the difference in effect estimates between subgroups was statistically significant.[16,27]

$$z = \frac{\beta_1 - \beta_2}{\sqrt{SE_1^2 + SE_2^2}}, \tag{2}$$

where β_1 and β_2 represent effect estimates for two subgroups (e.g., male vs. female), and SE_1 and SE_2 represent the corresponding standard errors. The z-test was used to compare the pooled mortality risk associated with three extreme events.

We also performed a mixed-effects meta-regression to identify possible drivers of the heterogeneity in the pooled RR between extreme events and all-cause mortality. We considered county-level GDP ($\times 10{,}000$), agricultural population (in percentage), low-income population (in percentage), proportion of low-NDVI area (in percentage), proportion of population living alone (in percentage), population >65 years of age (in percentage), illiterate population (in percentage), minority population (in percentage), and population density (persons/km^2).

With the pooled all-cause mortality risk from the meta-analysis, we separately calculated the excess deaths attributable to extreme events (i.e., heatwave-only, high O_3 pollution-only, and concurrent events) for each county from 2013 to 2020. In addition, daily all-cause mortality counts for the whole year and that on referent days (days of nonextreme events) were very close (Figure S1); we used the annual daily mortality from the census year 2010 to calculate excess death, given that daily mortality data was unavailable for 2019 and 2020. The equation is as follows[27,28]:

$$ED_{i,j} = P_i \times I_i \times (RR - 1) \times D_{i,j}, \tag{3}$$

where $ED_{i,j}$ is the excess deaths attributable to extreme events for county i in year j (i.e., $j = 2013, \ldots 2020$); P_i is the population for county i, which is from the Sixth National Population Census in 2010; I_i is the expected daily mortality count on referent days, estimated using the annual daily mortality count in 2010 for county i, which is from the Sixth National Population Census; *RR* is the pooled all-cause mortality risk associated with extreme events (heatwave-only, high O_3 pollution-only, and concurrent events) estimated from the meta-analysis; and $D_{i,j}$ is the number of days of extreme events (i.e., heatwave-only, high O_3 pollution-only, and concurrent events) for county i in year j.

Finally, we performed a series of sensitivity analyses to examine the robustness of the associations between extreme events and all-cause mortality. First, we used different definitions for the heatwaves and high O_3 pollution days to estimate the overall mortality risk of extreme events. Alternative thresholds based on different percentiles (i.e., 95th, 97th, and 99th percentiles) were considered in heatwaves definitions,[10,11] and we also considered four alternative definitions of daily maximum 8-h O_3 concentration: 1 d exceeding 160 $\mu g/m^3$ and 2 consecutive days exceeding 100, 180, and 200 $\mu g/m^3$, respectively. Second, we changed the df in the natural splines functions for time ($df = 2$, 3, 4), relative humidity ($df = 2$, 3, 5), and $PM_{2.5}$ ($df = 2$, 3, 5) to estimate the mortality risk of extreme events.

The map data was obtained from the Ministry of Natural Resources of the People's Republic of China [GS (2019) 1822] and created using ArcGIS (version 10.7; ESRI). All analyses were performed in R (version 3.6.3; R Development Core Team). A $p < 0.05$ was considered statistically significant in this study.

Results

During the summer periods from 2013 to 2018 in 250 Chinese counties, the total death counts were 1,603,633, 1,484,975, 652,923, 325,012, 317,125, and 163,307 for all-cause, nonaccidental, circulatory, cardiovascular, cerebrovascular, and respiratory mortality, respectively (Table 1). The average daily maximum 8-h concentrations of O_3 and daily mean concentration of $PM_{2.5}$ were 119.94 $\mu g/m^3$ and 39.43 $\mu g/m^3$, respectively, across all the study counties in the summer from 2013 to 2018 (Table S1). The average of daily mean summer temperatures across the study counties from 2013 to 2018 was 25.05°C. The average daily summer relative humidity from 2013 to 2018 was 75%. In the summer periods of 250 counties from 2013 to 2018, the high O_3 pollution-only event

Table 1. Mortality in 250 Chinese counties in the summer from 2013 to 2018.

Cause	ICD-10 codes	Total (*N*)	Mean	SD	Min	Median	Max
All-cause	A00–Z99	1,603,633	11	7	0	9	139
Nonaccidental cause	A00–R99	1,484,975	10	7	0	8	134
Circulatory disease	I00–I99	652,923	5	4	0	4	83
Cardiovascular disease	I00–I59	325,012	2	2	0	2	60
Cerebrovascular disease	I60–I69	317,125	2	2	0	2	65
Respiratory disease	J00–J99	163,307	1	1	0	1	33
Hypertensive heart disease	I10–I15	44,881	0	1	0	0	16
Acute myocardial infarction	I21–I22	139,303	1	1	0	1	18
Myocardial infarction	I21–I23	139,358	1	1	0	1	18
Chronic ischemic heart disease	I25	113,446	1	1	0	1	52
Hemorrhagic stroke	I60–I61	103,587	1	1	0	1	45
Cerebral stroke	I60–I64	95,630	1	1	0	1	45
Ischemic stroke	I63	108,009	1	1	0	1	19
Lower respiratory tract infection	J12–J18 and J20–J22	39,651	0	1	0	0	12
Chronic obstructive pulmonary disease	J41–J44	105,041	1	1	0	0	32

Note: Numbers shown in the table are total death counts in all counties (total), and summary statistics of daily death counts across all the counties, including the mean, standard deviation (SD), minimum (min), median, and maximum (max) of daily death counts. ICD-10, *International Statistical Classification of Disease Version 10*.

occurred in 26,601 d, the heatwave-only event in 5,191 d, and concurrent events in 3,252 d. Table S2 shows the descriptive statistics for the county-level SES characteristics from the Sixth National Population Census in 2010: The average GDP was 2,496,064.42 $\times$10,000, the average proportion of the agricultural population in the total population of this county was 0.34%, the average proportion of the population with a monthly income of $<2,000$ CNY was 0.03%, the average proportion of areas with NDVI <0.4 was 12.52%, the average proportion of the population living alone was 5.43%, the average proportion of the population >65 years of age was 9.95%, the average proportion of the illiterate population was 3.87%, and the average proportion of the minority population was 1.92%. The details of total death counts for mortality due to all-cause, nonaccidental, circulatory disease, cardiovascular disease, cerebrovascular disease, and respiratory disease in extreme event days for 250 counties from 2013 to 2018 are shown in Excel Table S1.

We estimated the pooled mortality risk at lag 0–3 d associated with heatwave-only, high O_3 pollution-only, and concurrent events (Figure S2 and Table S3). Effects estimates were generally the strongest at lag 1 (Table S3); we used the lag-1 estimates to calculate the RERI, as discussed below. Figure 2 shows the pooled mortality risk of the three extreme events at lag 1 d compared with referent days. The concurrent events are consistently associated with higher risk than the heatwave-only and high O_3 pollution-only events. The concurrent event was associated with elevated risk for all-cause mortality (RR = 1.29; 95% CI: 1.25, 1.33), nonaccidental mortality (1.27; 95% CI: 1.23, 1.30), circulatory mortality (1.39; 95% CI: 1.34, 1.45), cardiovascular mortality (1.43; 95% CI: 1.36, 1.51), cerebrovascular mortality (1.36; 95% CI: 1.30, 1.43), and respiratory mortality (1.35; 95% CI: 1.27, 1.44). Concurrent events were also associated with higher risk than heatwave-only and high O_3 pollution-only events for mortality due to some specific cardiopulmonary causes, including hypertensive heart disease, myocardial infarction, acute myocardial infarction, chronic ischemic heart disease, ischemic stroke, and chronic obstructive pulmonary disease. For example, the pooled RRs for ischemic stroke mortality were 1.29 (95% CI: 1.23, 1.36), 1.20 (95% CI: 1.15, 1.25), and 1.02 (95% CI: 1.00, 1.04) associated with concurrent, heatwave-only, and high O_3 pollution-only events, respectively. Exposure to the heatwave-only event was associated with increases in all-cause mortality (1.22; 95% CI: 1.19, 1.25), nonaccidental mortality (1.21; 95% CI: 1.18, 1.24), circulatory mortality (1.32; 95% CI: 1.27, 1.36), cardiovascular mortality (1.35; 95% CI: 1.29, 1.41), cerebrovascular mortality (1.29; 95% CI: 1.24, 1.34), and respiratory mortality (1.30; 95% CI: 1.23, 1.37). We also found that exposure to the high O_3 pollution-only event was significantly associated with increases in all-cause mortality (1.02; 95% CI: 1.01, 1.03), nonaccidental mortality (1.02; 95% CI: 1.01, 1.03), circulatory mortality (1.03; 95% CI: 1.01, 1.04), cardiovascular mortality (1.03; 95% CI: 1.01, 1.04), cerebrovascular mortality (1.02; 95% CI: 1.01, 1.04), and respiratory mortality (1.02; 95% CI: 1.00, 1.04) at lag 1 d.

RERIs revealed additive effects under the primary definitions for heatwaves (98th percentile) and high O_3 pollution ($>160\ \mu g/m^3$) for all the mortality outcomes; for example, the calculated RERIs were 1.05 (95% CI: 1.01, 1.08), 1.05 (95% CI: 0.99, 1.11), and 1.03 (95% CI: 0.96, 1.11) for all-cause, circulatory, and respiratory mortality, respectively (Excel Table S2). Using these alternative definitions of extreme events, RERIs varied depending on the extreme event definition. For example, when the heatwave was defined as 2 consecutive days exceeding the 97th or 98th percentiles, the RERI was higher with more extreme O_3 pollution events for the two lenient thresholds (i.e., 100 and $160\ \mu g/m^3$), but lower with more extreme exposures for the other two strict thresholds (i.e., 180 and $200\ \mu g/m^3$). This pattern remained consistent for all-cause, nonaccidental, and circulatory mortality. Counterintuitively, we observed smaller RERI with more extreme O_3 pollution events, and negative RERIs when defining heatwaves using the 99th percentile of the mean temperature.

Table 2 shows the pooled all-cause mortality effect associated with the three exposure events (concurrent events, heatwave-only events, and high O_3 pollution-only events) for sex and age groups. According to the result of the z-tests, the estimated all-cause mortality risk associated with the concurrent and heatwave-only events was statistically significant higher for males than females; for example, concurrent event-associated pooled RRs were 1.36 (95% CI: 1.31, 1.42) and 1.24 (95% CI: 1.20, 1.27) for males and females, respectively. The elderly group >74 years of age [RR = 1.37 (95% CI: 1.32, 1.43) for concurrent events, and RR = 1.28 (95% CI: 1.24, 1.32) for heatwave-only events] had a higher risk for all-cause mortality than the younger age group <65 years of age [RR = 1.16 (95% CI: 1.13, 1.20) for concurrent events, and RR = 1.14 (95% CI: 1.12, 1.17) for heatwave-only events] for the concurrent and heatwave-only events. All-cause mortality risk associated with high O_3 pollution-only event did not differ statistically significant by age or sex.

Results of the meta-regression analysis are shown in Table 3. County-level characteristics, including the agricultural population (1.095; 95% CI: 1.074, 1.117), low-income population (0.989; 95% CI: 0.979, 0.998), proportion of low-NDVI area (0.983; 95% CI: 0.977, 0.989), illiterate population (1.107; 95% CI: 1.089, 1.125), minority population (0.985; 95% CI: 0.980, 0.991), and

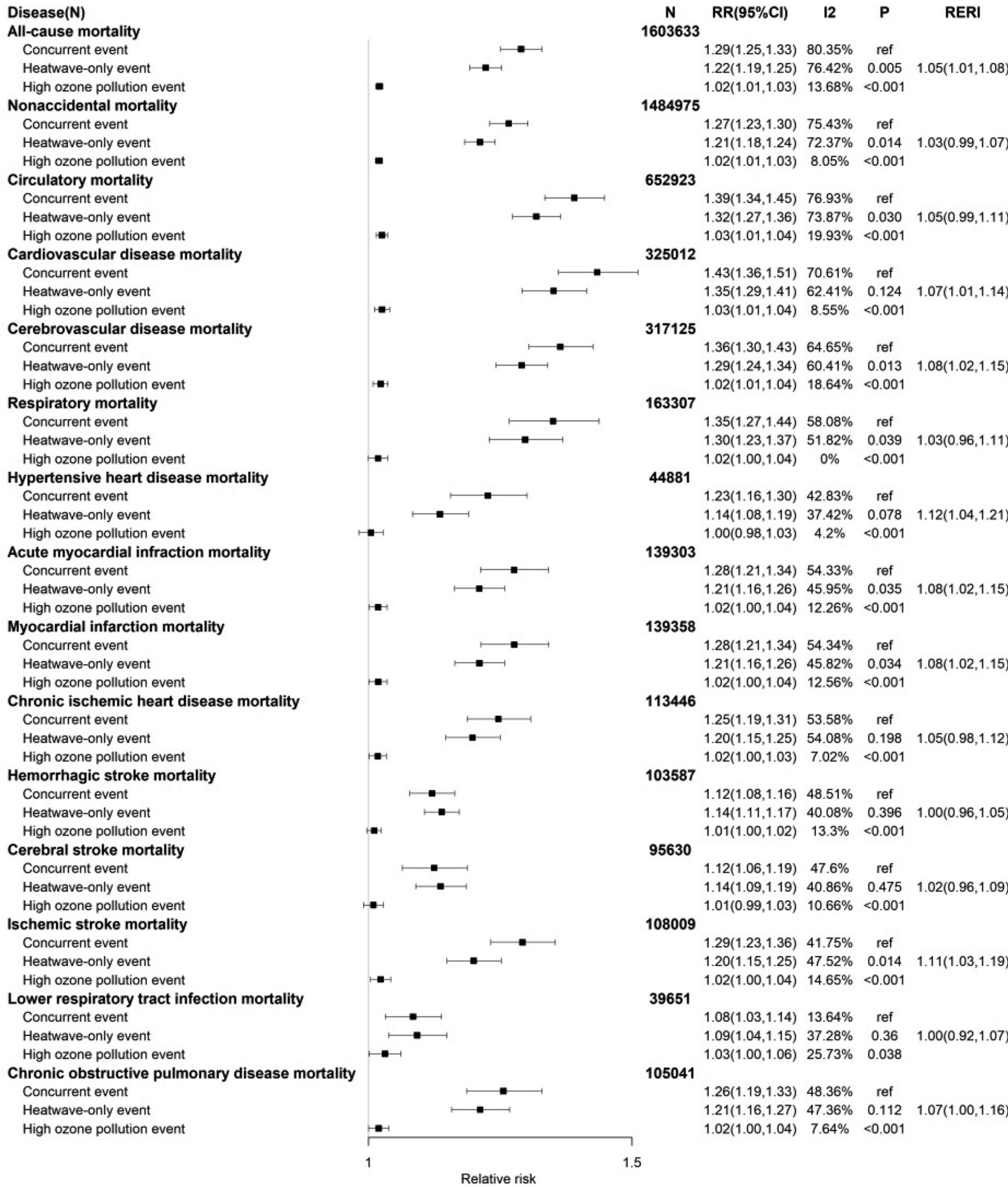

Figure 2. Pooled mortality risk at lag 1 for the concurrent, heatwave-only, and high O_3 pollution-only events, compared with referent days of 250 Chinese counties in the summer from 2013 to 2018. Pooled mortality risk was estimated by meta-analysis, and mortality risk for each county was estimated using a GLM model, controlling for the confounding effects of relative humidity, $PM_{2.5}$, long-term trends, and day of week. I^2 shows heterogeneity in the pooled effect estimates for each extreme event. p-Values show statistical significance of the z-test comparing the pooled RRs for heatwave-only and high O_3 pollution-only events with the concurrent events (referent event). Note: GLM, generalized linear model; O_3, ozone; $PM_{2.5}$, particulate matter ≤ 2.5 μm in aerodynamic diameter; ref, reference; RERI, relative excess risk due to interaction.

proportion of population >65 years of age (1.123; 95% CI: 1.112, 1.134), significantly impacted the association between concurrent events and all-cause mortality. The agricultural population (1.106; 95% CI: 1.088, 1.125), low-income population (1.014; 95% CI: 1.004, 1.024), proportion of low-NDVI area (0.979; 95% CI: 0.974, 0.984), proportion of population living alone (0.911; 95% CI: 0.900, 0.922), illiterate population (1.090; 95% CI: 1.075, 1.104), minority population (0.988; 95% CI: 0.983, 0.993), and proportion of population >65 years of age (1.072; 95% CI: 1.061, 1.083), significantly impacted the association between a heatwave-only event exposure and all-cause mortality ($p < 0.05$). The proportion of the population

Table 2. Pooled all-cause mortality risk associated with extreme events exposure in 250 Chinese counties for sex and age groups in the summer from 2013 to 2018.

Sub group	N	Pooled RR (95% CI)	I^2 (%)	z-Test p-value
Sex				
Concurrent event				
Male	21,326	1.36 (1.31, 1.42)	75.53	Ref
Female	18,485	1.24 (1.20, 1.27)	62.45	<0.001
Heatwave-only event				
Male	29,078	1.29 (1.25, 1.33)	69.69	Ref
Female	24,229	1.18 (1.16, 1.21)	59.43	<0.001
High O_3 pollution-only event				
Male	148,080	1.03 (1.02, 1.04)	17.74	Ref
Female	112,804	1.02 (1.01, 1.03)	10.34	0.116
Age (y)				
Concurrent event				
<65	8,638	1.16 (1.13, 1.20)	18.51	Ref
65–74	7,479	1.22 (1.18, 1.26)	36.02	0.024
>74	23,694	1.37 (1.32, 1.43)	80.64	<0.001
Heatwave-only event				
<65	13,113	1.14 (1.12, 1.17)	26.92	Ref
65–74	10,180	1.17 (1.14, 1.21)	28.77	0.103
>74	30,013	1.28 (1.24, 1.32)	76.00	<0.001
High O_3 pollution-only event				
<65	65,377	1.02 (1.00, 1.03)	2.40	Ref
65–74	52,537	1.02 (1.01, 1.03)	0.02	0.214
>74	142,971	1.03 (1.02, 1.04)	27.52	0.084

Note: N represents the all-cause mortality of each subgroup for each extreme event. The pooled RRs are all-cause mortality risk associated with heatwave-only, high O_3 pollution-only, and concurrent events at lag 1 d, compared with referent days of 250 counties in the summer from 2013 to 2018, by GLM and meta-analysis, adjusting for relative humidity, $PM_{2.5}$, long-term trends, and day of week. The I^2 shows heterogeneity in the pooled estimates for each extreme event in sex and age groups. The z-test p-value shows statistical significance when comparing the pooled RR in sex and age groups. CI, confidence interval; GLM, generalized linear model; O_3, ozone; Ref, reference; RR, relative risk.

>65 years of age (1.006; 95% CI: 1.003, 1.008) significantly impacted the association between a high O_3 pollution-only event and all-cause mortality.

The annual average days of the concurrent events from 2017 to 2020 were more than those from 2013 to 2016. For 1,028 Chinese counties, the concurrent events occurred in 3,718 d in 2017 and 3,450 d in 2019 (Figure S3). From 2013 to 2020, the proportion of the days of each extreme event to the total days of the three events varied greatly (Figure 3; Table S4). The heatwave-only event (9,006 d, the proportion was 80.35%) accounted for most of the total days (11,208 d) of extreme events in 2013; by contrast, the high O_3 pollution event (20,341 d, 90.51%) accounted for most of the total days (22,475 d) in 2020. The concurrent events (3,718 d, 14.36%) accounted for <20% of the total days (25,886 d) of extreme events, with the highest observed in 2017.

Based on the estimation of excess deaths using the exposure–response relationship coefficient from 2013 to 2018, we obtained the annual excess deaths from 2013 to 2020 for heatwave-only, high O_3 pollution-only, and concurrent events (Figure S4 and Table S5). Because there was a noticeable increase in excess deaths attributable to concurrent events in 2017, we divided the entire study period into two periods (i.e., 2013–2016 and 2017–2020). From 2017 to 2020, the estimated annual average excess deaths attributed to concurrent events in China was 6,249 (8,966, 5,176, 8,668, and 2,185 excess deaths in 2017, 2018, 2019, and 2020, respectively), 5.7 times higher than the annual average excess deaths (934 deaths) attributed to concurrent events from 2013 to 2016 (872, 384, 1,449, and 1,029 excess deaths in 2013, 2014, 2015, and 2016, respectively). In 2013, the excess deaths attributed to heatwave-only events (20,999 deaths) accounted for 94.25% of the total excess deaths (22,279 deaths) attributable to the three extreme events, whereas excess deaths attributed to concurrent events (872 deaths) accounted for 3.91% (Figure 4; Table S5). However, the numbers of excess deaths attributed to the concurrent, heatwave-only, and high O_3 pollution-only events were nearly identical in 2020. Furthermore, from 2017 to 2020, the annual average proportion of the concurrent event

Table 3. Estimates from meta-regression for the associations between pooled all-cause mortality risk and county-level socioeconomic (SES) characteristics for per IQR of 250 Chinese counties in the summer from 2013 to 2018.

SES variables	IQR	RR (95% CI)	I^2 (%)	p-Value
Concurrent event (3,252 d)				
GDP ($\times$10,000)	2,199,106	1.030 (1.020, 1.039)	76.92	<0.001
Agricultural population (%)	0.44	1.095 (1.074, 1.117)	75.87	<0.001
Low-income population (%)	0.03	0.989 (0.979, 0.998)	77.22	0.024
Low-NDVI areas (%)	13.96	0.983 (0.977, 0.989)	76.65	<0.001
Population living alone (%)	3.33	0.987 (0.973, 1.001)	77.17	0.076
Illiterate population (%)	3.96	1.107 (1.089, 1.125)	74.73	<0.001
Minority population (%)	1.84	0.985 (0.980, 0.991)	76.81	<0.001
Population >65 years of age (%)	2.84	1.123 (1.112, 1.134)	68.97	<0.001
Heatwave-only event (5,765 d)				
GDP ($\times$10,000)	2,199,106	0.996 (0.987, 1.005)	77.09	0.353
Agricultural population (%)	0.44	1.106 (1.088, 1.125)	75.02	<0.001
Low-income population (%)	0.03	1.014 (1.004, 1.024)	76.91	0.004
Low-NDVI areas (%)	13.96	0.979 (0.974, 0.984)	76.14	<0.001
Population living alone (%)	3.33	0.911 (0.900, 0.922)	74.07	<0.001
Illiterate population (%)	3.96	1.090 (1.075, 1.104)	74.85	<0.001
Minority population (%)	1.84	0.988 (0.983, 0.993)	76.76	<0.001
Population >65 years of age (%)	2.84	1.072 (1.061, 1.083)	74.68	<0.001
High O_3 pollution-only event (26,601 d)				
GDP ($\times$10,000)	2,199,106	1.000 (0.999, 1.001)	10.83	0.049
Agricultural population (%)	0.44	1.002 (0.998, 1.007)	10.55	0.299
Low-income population (%)	0.03	1.000 (0.997, 1.003)	10.54	0.922
Low-NDVI areas (%)	13.96	0.999 (0.998, 1.001)	10.49	0.306
Population living alone (%)	3.33	1.001 (0.998, 1.004)	10.64	0.528
Illiterate population (%)	3.96	1.001 (0.997, 1.005)	10.51	0.643
Minority population (%)	1.84	1.000 (0.998, 1.002)	10.54	0.906
Population >65 years of age (%)	2.84	1.006 (1.003, 1.008)	10.32	<0.001

Note: Estimates were calculated per IQR change in county-level SES characteristics. All these data were from the Sixth National Population Census in 2010. CI, confidence interval; GDP, counties' gross domestic product; low-income population, proportion of population with monthly income of <2,000 CNY; IQR, interquartile range; low-NDVI area, the proportion of the area with an NDVI of <0.4; NDVI, normalized difference vegetation index; O_3, ozone; RR, relative risk; SES, socioeconomic status.

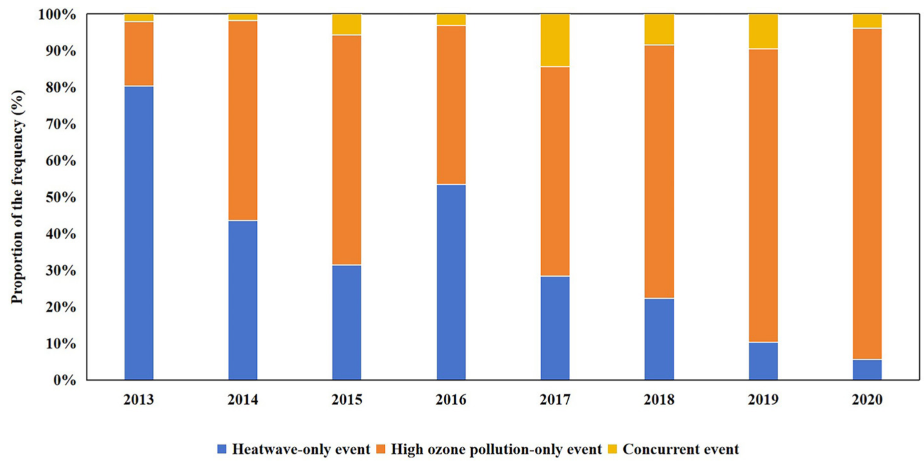

Figure 3. The proportion of frequency (number of days) of each event to the total days of heatwave-only, high O_3 pollution-only, and concurrent events in summer from 2013 to 2020 in China. The details for the frequency (number of days and proportion) are shown in Table S4. Note: O_3, ozone.

attributable excess deaths to the total excess deaths attributed to three events was 31.50% (95% CI: 26.73%, 35.53%), whereas this proportion was 9.65% (95% CI: 5.67%, 10.81%) from 2013 to 2016.

Under the alternative definition of the concurrent events as mean temperature exceeding the 98th percentile and O_3 exceeding $160\,\mu g/m^3$ for 1 d, the estimated mortality risk was lower than the estimates under our primary definition of the concurrent events (Excel Table S2). In addition, the results of other alternative definitions are shown in Table S4. Under our primary definition of the high O_3 pollution event (2 consecutive days exceeding $160\,\mu g/m^3$), concurrent events-associated all-cause mortality risk increased with more extreme heatwave exposures. Under our primary definition of the heatwaves events (2 consecutive days exceeding the 98th percentile of average temperature), the concurrent events-associated mortality risk was highest when the high O_3 pollution event was defined using the threshold of $160\,\mu g/m^3$. Sensitivity analysis results using different degrees of freedom in spline functions were generally consistent with our primary findings (Table S6).

Discussion

This study explored the mortality risk associated with the concurrent heatwaves and high O_3 pollution events, and it estimated the excess deaths by nationwide temperature and O_3 exposure and mortality data in China. The results indicated a higher risk of mortality across China in association with exposure to the concurrent, heatwave-only, and high O_3 pollution-only events. Mortality risk associated with the concurrent event was more pronounced than the risk of heatwave-only and high O_3 pollution-only events for circulatory, cardiovascular, cerebrovascular, and respiratory mortality. RERI revealed additive interaction for combining heatwaves and high O_3 pollution events under certain definitions of extreme events. We estimated that the annual average excess deaths attributed to a concurrent event was 6,249 in China from 2017 to 2020, 5.7 times higher than the annual average excess deaths attributed to a concurrent event from 2013 to 2016. The mortality risks of a concurrent event in males and elderly people >74 years of age were higher. Our results imply that more attention should be paid to the adaptability to respond to concurrent extreme events in the context of climate change, especially for vulnerable populations.

Although it is well established that heatwaves and high O_3 pollution individually have acute effects on mortality,[7–11] little is known regarding the effects of the concurrent events on mortality. We found that the mortality risk was much higher with the concurrent events than for the heatwave-only and high O_3 pollution-only events. Similarly, one study reported joint exposure effects of O_3

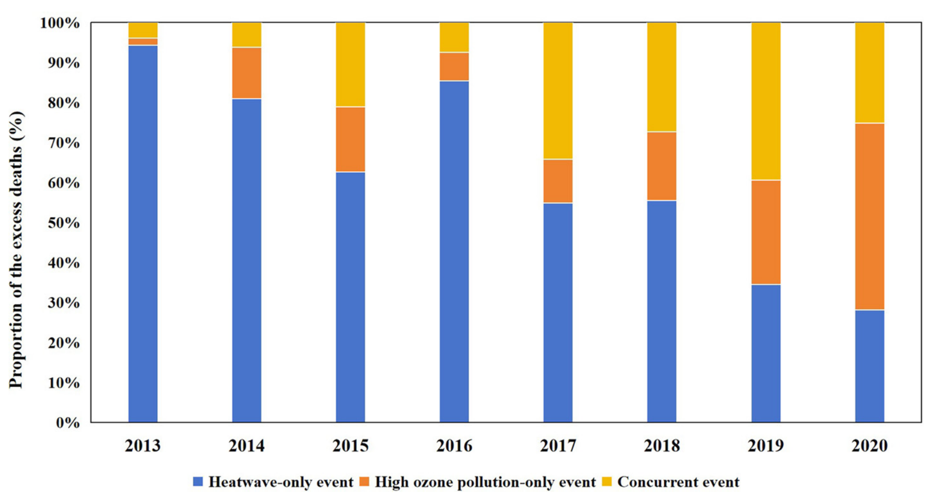

Figure 4. The proportion of attributable excess deaths attributed to each event to the total excess deaths attributed to three extreme events in summer from 2013 to 2020 in China. The details for the attributable excess deaths (number of days and proportion) are shown in Table S5.

and heatwaves in California.[18] However, evidence has yet to be derived from developing countries, where O_3 pollution is typically more severe than in developed countries. Furthermore, recent epidemiological studies have reported an interaction effect of temperature and O_3 on mortality.[12–14,29,30] For example, a European study showed that the mortality risk of O_3 differed depending on temperature, with a per-10 $\mu g/m^3$ increase of O_3 associated with an increased mortality risk of 0.17% (95 CI%: −0.14%, 0.49%), 0.24% (95 CI%: −0.08%, 0.57%), and 0.67% (95 CI%: 0.36%, 0.98%) at low (<25th percentile), medium (25th–75th percentile), and high (>75th percentile) temperatures, respectively.[29] Another study consistently found that the mortality risk of O_3 was enhanced at higher temperatures in 128 Chinese counties.[14] Our findings align with those results to some extent, with concurrent events associated with a greater mortality risk than heatwave-only and high O_3 pollution-only events.

Previous studies have reported that heatwaves and O_3 exposures are associated with increased mortality risk.[10,11,31–34] For example, heatwaves were associated with a 15.7% (95% CI: 12.5%, 18.9%) increase in the risk of nonaccidental mortality in 130 Chinese counties.[11] Our study found a similar effect of heatwave-only events on nonaccidental mortality, with an estimated RR of 1.21 (95% CI: 1.19%, 1.24%) at lag 1 d. Consistent with previous findings,[35–37] our results indicated that heatwave-only events substantially impacted circulatory mortality more than all-cause mortality. The pronounced impact of heatwaves on circulatory mortality is possibly due to increased blood flow and blood pressure caused by high temperatures, leading to a decreased oxygen supply and an increased risk of mortality from cardiovascular diseases.[37] In addition, high O_3 pollution-only events were significantly associated with increased mortality risk in this study, which aligns with previous relevant findings.[9,33,38,39] A study of 95 US urban communities found that mortality risk increased by 0.52% (95% CI: 0.27%, 0.77%) per 10-ppb increase in O_3 concentration.[38] A study of 272 Chinese cities reported that a per-10 $\mu g/m^3$ increase in O_3 was associated with a 0.24% (95% CI: 0.13%, 0.35%) increase in daily all-cause mortality.[9] We also found the association of high O_3 pollution-only events with circulatory was higher than all-cause mortality, consistent with previous studies.[9,34]

We also observed that concurrent events were associated with a higher risk for the cardiopulmonary mortality than all-cause mortality, suggesting that individuals with cardiopulmonary disease might be particularly susceptible to concurrent events. A study conducted in California also observed the associations between all-cause, cardiovascular, and respiratory diseases and co-occurring extreme heat and particulate air pollution, which is consistent with our findings.[16] Individuals with cardiopulmonary diseases may be more susceptible to the concurrent events as a result of the increased load on the circulation system required to maintain a typical body temperature.[40] O_3 may directly affect the respiratory tract through inhalation and affect the autonomic nervous system regulation, thus increasing people's susceptibility to temperature variability.[41]

The RERI results for different definitions of O_3 and heat extreme events highlight the importance of heatwave limits within the additive effect for concurrent events. However, the estimated RERIs varied depending on the extreme event definitions, with negative values in some cases. The varying RERIs may suggest potential spatial heterogeneity,[18] given that we also found that county-level characteristics significantly impact the pooled mortality risk of extreme events. Thus, further studies can be conducted to explore the spatial variation of RERIs in China. In addition, the estimated RERIs were negative under the strictest definition of the heatwaves (99th percentile), which seems inconsistent with a previous study in California examining the additive effects of exposure to heatwaves and $PM_{2.5}$.[16] Using different definitions for the extreme events may help to account for the inconsistency; although the study in California used percentile-based relative definitions for both the heatwaves and the air pollution events, we used the absolute definition for air pollution events. We speculate that we should focus more on extreme concurrent event exposures under certain thresholds (i.e., 98th percentile and 160 $\mu g/m^3$). When more extreme temperature or O_3 pollution events occur, the impact of concurrent events may be weakened and the health impact of a single event is extremely strong.

In this study, we observed a higher mortality risk associated with the concurrent event for males than for females. Few studies have explored the sex and age differences in the mortality risk for a concurrent event; however, previous studies of heatwaves in China generally reported the opposite results, with females more vulnerable than males.[42,43] Sex differences in the mortality risk associated with extreme events may be due to differences in social and living conditions and occupational exposures.[44–46] For example, men are more likely to engage in occupational work and outdoor activities under high-temperature conditions, which may explain why the RR for males is higher than that for females in concurrent events and heatwave-only events.[45] Moreover, we found that elderly people >74 years of age were more vulnerable to the heatwave-only and concurrent events than younger people <65 years of age, which is consistent with previous findings in China, Europe, and the United States.[14,29–31,37] Elderly people >65 years of age often have chronic cardiopulmonary diseases and poor immune function, making them more vulnerable to extreme events.[47–49] Through the meta-regression analysis, we found that county-level characteristics (e.g., GDP and the proportion of the agricultural population may impact the association between extreme events and all-cause mortality). As a result of the urban heat island effect, areas with a higher GDP may also have a higher heat vulnerability.[49,50] Farmworkers are often occupationally exposed to heat stress and are, therefore, more susceptible to heat stress than the general public.[51–53]

This study has several limitations. First, there may be exposure measurement errors. We used ambient air pollution and temperature to define exposure, which may have introduced measurement errors because we could not determine the indoor air pollution level; however, people spend $\sim 90\%$ of the time indoors.[53,54] However, concurrent events are usually affected by outdoor exposure. Second, adaptive behaviors are different among populations from different regions. Residents living in hot areas may be more adaptable to heat and less likely to exhibit adverse symptoms of health effects, which might have led to the underestimation of the effects thereof.[54] Third, residual confounding is possible in the estimated results because we did not control for other potential confounders, such as the air-conditioning utilization rate. Finally, uncertainty may exist in assessing excess deaths attributable to extreme events for 2013–2020, given that the influence of the COVID-19 pandemic (which started in 2019) was not considered,[55,56] and the mortality risk was estimated using data from 2013 to 2018.

One strength of this study is its large sample size. This nationwide analysis included >1.1 million deaths and multiple specific causes of diseases, providing a comprehensive assessment exploring the mortality risk associated with the concurrent heatwaves and high O_3 pollution event.

In summary, our study provided novel evidence on the increasing mortality risk and burden of concurrent heatwaves and high O_3 pollution events. We speculate that the frequency and excess deaths attributed to concurrent events have increased slightly over time. Our findings contribute to scientific evidence supporting the necessity and importance of establishing an early warning system for concurrent events, more attention should be paid to the early warning classification of high O_3 pollution when continuous heatwaves are expected.

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