

Ozone, Heat Wave, and Cardiovascular Disease Mortality: A Population-Based Case-Crossover Study

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Cite This: *Environ. Sci. Technol.* 2024, 58, 171–181



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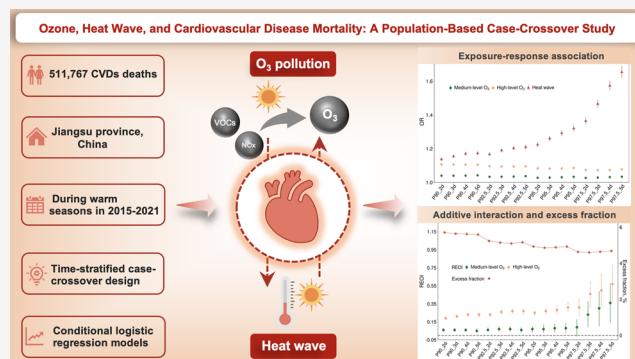
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ABSTRACT: A case-crossover study among 511,767 cardiovascular disease (CVD) deaths in Jiangsu province, China, during 2015–2021 was conducted to assess the association of exposure to ambient ozone (O_3) and heat wave with CVD mortality and explore their possible interactions. Heat wave was defined as extreme high temperature for at least two consecutive days. Grid-level heat waves were defined by multiple combinations of apparent temperature thresholds and durations. Residential O_3 and heat wave exposures were assessed using grid data sets (spatial resolution: 1 km × 1 km for O_3 ; $0.0625^\circ \times 0.0625^\circ$ for heat wave). Conditional logistic regression models were applied for exposure–response analyses and evaluation of additive interactions. Under different heat wave definitions, the odds ratios (ORs) of CVD mortality associated with medium-level and high-level O_3 exposures ranged from 1.029 to 1.107 compared with low-level O_3 , while the ORs for heat wave exposure ranged from 1.14 to 1.65. Significant synergistic effects on CVD mortality were observed for the O_3 and heat wave exposures, which were generally greater with higher levels of the O_3 exposure, higher temperature thresholds, and longer durations of heat wave exposure. Up to 5.8% of the CVD deaths were attributable to O_3 and heat wave. Women and older adults were more vulnerable to the exposure to O_3 and heat wave exposure. Exposure to both O_3 and heat wave was significantly associated with an increased odds of CVD mortality, and O_3 and heat wave can interact synergistically to trigger CVD deaths.

KEYWORDS: ozone, heat wave, apparent temperature, cardiovascular mortality, interaction



1. INTRODUCTION

Ambient ozone (O_3) is a typical secondary air pollutant that is formed through sunlight-driven reactions between volatile organic compounds and nitrogen oxides. As a growing public health issue globally, O_3 has become one of the main pollutants in summer and is expected to rise with increasing climate warming.¹ According to findings of the Global Burden of Disease 2019, approximately 0.4 million deaths could be attributed to ambient O_3 pollution worldwide.² Heat wave, a period of extreme high temperature that typically lasts two or more days, is commonly defined as a combination of different temperature thresholds and durations. As another critical public health challenge in summertime under the context of climate change, heat wave is projected to be more frequent, more intense, and longer in the future, and its adverse health impacts have drawn much concern globally. Accumulating epidemiological studies have separately linked O_3 and heat wave to a variety of health outcomes, especially cardiovascular diseases (CVDs).^{3,4} In 2019, CVDs were responsible for 18.6 million deaths worldwide, with an estimated 4.6 million deaths in China. Despite there being evidence on the association of

short-term exposure to both O_3 and heat wave with an increased risk of CVD mortality, the ability of these two exposures to elicit cardiovascular effects still remained unclear. In addition, given that the co-occurrence of O_3 pollution and heat wave in a warming climate is becoming more frequent, it has drawn much attention if O_3 and heat wave interact synergistically to trigger CVD deaths.

O_3 pollution and heat wave share common underlying meteorological drivers or conditions (i.e., abundant solar insolation, high air temperatures, low wind speeds, and precipitation) that can accumulate pollutants and heat in warm seasons. Therefore, the O_3 pollution and heat wave often coincide, making it possible to synergistically worsen health

Received: August 22, 2023

Revised: November 27, 2023

Accepted: November 27, 2023

Published: December 15, 2023



impacts beyond the sum of their individual effects.⁵ However, the potential interactive effects of O₃ and heat wave exposures on CVD mortality are yet to be evaluated. To date, only two time-series studies in multiple European cities in 2014 and 2018 quantified the associations between heat wave exposure and CVD mortality under different O₃ levels.^{6,7} Interestingly, the study in 2014 reported that the association of exposure to heat wave with CVD mortality was stronger during high-level O₃ days,⁷ while the study in 2018 identified stronger associations during low-level O₃ days.⁶ Note that these two studies did not detect any significant interaction of O₃ and heat wave on CVD mortality. These inconsistent and inconclusive results hindered the public from fully understanding the potential impacts of coexposure to O₃ and heat wave on CVD mortality and taking targeted adaptation strategies in the context of global climate change.

Therefore, we conducted a population-based case-crossover study in Jiangsu province, China, during 2015–2021, and aimed to (1) evaluate the association of exposure to O₃ and heat wave with CVD mortality, (2) examine synergistic effects for O₃ and heat wave exposures, and (3) quantify corresponding excess mortality with consideration of possible interactive effects.

2. METHODS

2.1. Study Population. In this study, mortality data were obtained from the Jiangsu provincial mortality surveillance system. From this system, we identified residents who died from CVDs in Jiangsu province, China, during 2015–2021, and extracted individual data on race, sex, marital status, dates of birth and death, and residential address for each subject. This study has received approval by the Ethics Committee of the School of Public Health, Sun Yat-sen University with an exemption from informed consent.

2.2. Outcomes. Mortality from CVDs as the underlying cause of death was the study outcome of interest. Based on codes in the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10), we defined CVD deaths with I00–I99.

2.3. Study Design. The association of short-term exposure to ambient O₃ and heat wave with CVD mortality was investigated with the use of a time-stratified case-crossover design. By design, each subject was considered as a case on the date of death and as his/her own matched control during the dates before (and/or after) the date of death within the month of death (i.e., a time stratum).^{8,9} Specifically, for each case, the date of death was the case day, and 3 or 4 control days were matched to the case day on the same weekday within the time stratum to control the effects of day of week, seasonality, and long-term time trend.¹⁰ For example, if a subject died on June 16, 2019 (Sunday), June 2019 was defined as the time stratum, June 16, 2019 (Sunday) was defined as the case day, and all other Sundays in June 2019 (June 2, 9, 23, and 30) were defined as the corresponding control days. In this design, individual factors (e.g., sex, age, race, or marital status) that were time-invariant or unlikely to change materially in the time stratum could be adequately controlled.¹¹

2.4. Exposure Assessment. We obtained daily grid data on ambient O₃ and fine particulate matter (PM_{2.5}) from the ChinaHighAirPollutants (CHAP, which is available at <https://weijing-rs.github.io/product.html>) data set (spatial resolution: 1 km × 1 km), which has been validated with good agreements between predicted values and monitoring values (cross-

validated coefficient of determination [R^2] for O₃ and PM_{2.5}: 0.89 and 0.92; root-mean-square error [RMSE] for O₃ and PM_{2.5}: 15.77 and 10.76 $\mu\text{g}/\text{m}^3$) in previous studies.^{12,13,14} For each subject, the daily maximum 8 h O₃ and 24 h mean PM_{2.5} concentrations during the case day and control days were assessed by extracting pollutant concentrations at the geocoded residential address from the CHAP data set using a bilinear interpolation method.¹⁵ As proposed in previous studies, mean exposure of the same day of death and 1 day prior, denoted as lag 0–1 day, was used as the main exposure metric in this study.^{9,16,17}

From the China Meteorological Administration Land Data Assimilation System (CLDAS version 2.0), we extracted grid data (spatial resolution of $0.0625^\circ \times 0.0625^\circ$) on daily 24 h mean air temperature ($^\circ\text{C}$), specific humidity (kg/kg), surface pressure (mb), and wind speed (m/s), and retrieved daily 24 h mean relative humidity (%) in Jiangsu province, China during 2015–2021.¹⁸ For each day in 2015–2021, we used daily 24 h mean air temperature (T), specific humidity (q), wind speed (w), and surface pressure (p) to calculate daily 24 h mean apparent temperature ($^\circ\text{C}$; AT) by the following formula,^{19,20} and built a corresponding grid data set.

$$\text{AT} = T + 0.33 \times \frac{q \times p}{0.378 \times q + 0.622} - 0.7 \times w - 4$$

Because there is no standard heat wave definition worldwide, we applied a combination of intensity (temperature threshold) and duration (number of consecutive day) proposed in previous studies to define heat wave.²¹ In each grid of the apparent temperature data set, temperature thresholds of heat wave were defined as the 90th, 92.5th, 95th, and 97.5th percentile of daily mean apparent temperature during 2015–2021. Different numbers of consecutive days (i.e., ≥ 2 , 3, 4, and 5 days) were considered as the duration of heat wave. By combining different temperature thresholds and consecutive days, heat wave was defined as a daily mean apparent temperature equal to or higher than temperature thresholds of P90, P92.5, P95, and P97.5 for at least 2, 3, 4, and 5 consecutive days for each grid. Based on this method, we built 16 heat wave definitions (Table S1) and generated 16 corresponding heat wave grid data sets in Jiangsu province during 2015–2021 with a spatial resolution of $0.0625^\circ \times 0.0625^\circ$. For each grid of each heat wave data set, we assigned heat wave days and non-heat wave days as 1 and 0, respectively. For each subject, we assessed heat wave exposure during each of the case day and control days by extracting exposure information at the geocoded residential address from the 16 heat wave data sets using a simple interpolation method.

2.5. Statistical Analysis. We used conditional logistic regression models to quantify the association of short-term exposure to O₃ and heat wave with CVD mortality. Our analyses were restricted to warm seasons (i.e., from May to September) and were conducted for each heat wave definition. We included the O₃ as a natural cubic spline with 3 degrees of freedom (df), the heat wave as a binary variable (1 = yes, 0 = no), and the public holiday as a binary variable (1 = yes, 0 = no) in the models. The association for exposure to O₃ and heat wave was quantified by the odds ratio (OR) and its 95% confidence interval (CI). To compare with estimates in previous studies, we also included O₃ exposure as a continuous variable to calculate ORs associated with each 10 $\mu\text{g}/\text{m}^3$ increase in exposure to O₃ at lag 0–1 day. We applied likelihood ratio tests to detect potential nonlinear associations

by comparing the model including O₃ exposure as a natural cubic spline function and that including it as a continuous variable.

To investigate the possible additive interaction of O₃ and heat wave exposures on CVD mortality, which may provide more information when translating results into public health actions than departures from multiplicative risks,²² we classified O₃ exposure into low, medium, and high levels according to the tertiles of O₃ exposure. The conditional logistic regression model was employed to quantify the association of a combination of O₃ and heat wave exposures (6 levels) with CVD mortality: (1) low-level O₃ and non-heat wave (level 1; reference group), (2) medium-level O₃ and non-heat wave (level 2), (3) high-level O₃ and non-heat wave (level 3), (4) low-level O₃ and heat wave (level 4), (5) medium-level O₃ and heat wave (level 5), and (6) high-level O₃ and heat wave (level 6). We calculated relative excess odds due to interaction (REOI), proportion attributable to interaction (AP), and synergy index (S) to examine additive interactions.²³

$$\text{REOI} = \text{OR}_{11} - \text{OR}_{10} - \text{OR}_{01} + 1$$

$$\text{AP} = \frac{\text{REOI}}{\text{OR}_{11}}$$

$$S = \frac{\text{OR}_{11} - 1}{(\text{OR}_{10} - 1) + (\text{OR}_{01} - 1)}$$

where OR₁₀, OR₀₁, and OR₁₁ indicate the OR in exposure to medium-level O₃ and non-heat wave (or high-level O₃ and non-heat wave), low-level O₃ and heat wave, and medium-level O₃ and heat wave (or high-level O₃ and heat wave) relative to the OR in exposure to low-level O₃ and non-heat wave (OR₀₀ = 1), respectively. REOI > 0, AP > 0, and S > 1 represent the effects of coexposure to O₃ and heat wave on CVD mortality beyond the sum of their individual effects, suggesting a synergistic effect; otherwise, no additive interaction was detected. A delta method was applied to calculate the corresponding 95% CIs for REOI, AP, and S.²⁴

Using the estimated associations, we then calculated excess fraction and number of excess deaths to quantify excess mortality, which has been detailedly described in our previous studies (Supporting Methods).²⁵ Besides, we calculated the proportion of excess deaths among cases of death on heat wave days to further quantify the excess mortality during heat wave days.

Stratified analyses were conducted to explore potentially vulnerable populations by sex (male, female) and age (≤ 80 years, >80 years). A two-sample *z* test was implemented to assess statistical differences in the effects for exposure to O₃ and heat wave between categories for each stratification variable.²⁶

To examine the robustness of our results, several sensitivity analyses were performed with respect to (1) adjusting for PM_{2.5} in the main models as a natural cubic spline with 3 df, (2) using daily minimum apparent temperature and maximum apparent temperature to define heat wave, (3) defining heat wave using daily mean air temperature and adjusting for relative humidity exposure at lag 0–3 day in the main models as a natural cubic spline with 3 df, (4) defining heat wave based on temperature thresholds during warm seasons, and (5) restricting analysis in subjects died before 2020 to avoid the possible impact of the COVID-19 pandemic. R version 4.3.0

was applied to conduct all analyses. A two-sided test with *P*-value < 0.05 was considered statistically significant.

3. RESULTS

During 2015–2021, a total of 511,767 CVD deaths and 1,754,390 control days during warm seasons were identified. Of these subjects, 56.4% died after 80 years, 50.4% were female, 98.6% were Han race, and 57.9% were married (Table 1 and Figure S1). Mean exposure to O₃, PM_{2.5}, mean apparent

Table 1. Characteristic of Study Population^a

characteristic	N (%)
no. of CVD deaths (case days)	511,767
no. of control days	1,754,390
age, years	
mean (SD)	79.1 (11.9)
median (IQR)	81.7 (14.0)
≤80, n (%)	223,360 (43.6)
>80, n (%)	288,407 (56.4)
sex, n (%)	
male	253,816 (49.6)
female	257,951 (50.4)
race, n (%)	
han	504,395 (98.6)
other	1072 (0.2)
unknown	6300 (1.2)
marital status, n (%)	
married	296,459 (57.9)
unmarried	12,648 (2.5)
widowed	190,019 (37.1)
divorced	4734 (0.9)
unknown	7907 (1.5)
year at death, n (%)	
2015	68,747 (13.4)
2016	72,004 (14.1)
2017	73,832 (14.4)
2018	68,234 (13.3)
2019	69,354 (13.6)
2020	79,104 (15.5)
2021	80,492 (15.7)

^aCVD, cardiovascular disease; IQR, interquartile range; and SD, standard deviation.

temperature, minimum apparent temperature, and maximum apparent temperature was 135.1, 31.5 µg/m³, 28.9, 24.8, and 33.3 °C, respectively. The first and second tertile of O₃ exposure was 116.1 and 148.0 µg/m³, respectively. The mean temperature threshold of each grid across Jiangsu province was 32.8, 34.2, 35.7, and 37.4 °C for P90, P92.5, P95, and P97.5, respectively (Table S2).

During the study period, the average O₃ concentrations in Jiangsu province slightly increased across calendar years (Figure 1). With the heat wave definition of P95_3d, temperature thresholds and number of heat wave days ranged from 32.6 to 37.6 °C and 91 to 120, respectively. In general, the number of heat wave days decreased with increasing temperature thresholds and durations (Figures 2, 3, and S2–S4).

Under the heat wave definition of P95_3d, 31.0% (158,675), 30.4% (155,504), 29.9% (152,905), 1.0% (5034), 3.0% (15,163), and 4.8% (24,486) of subjects died during low-level O₃ and non-heat wave days, medium-level O₃ and non-

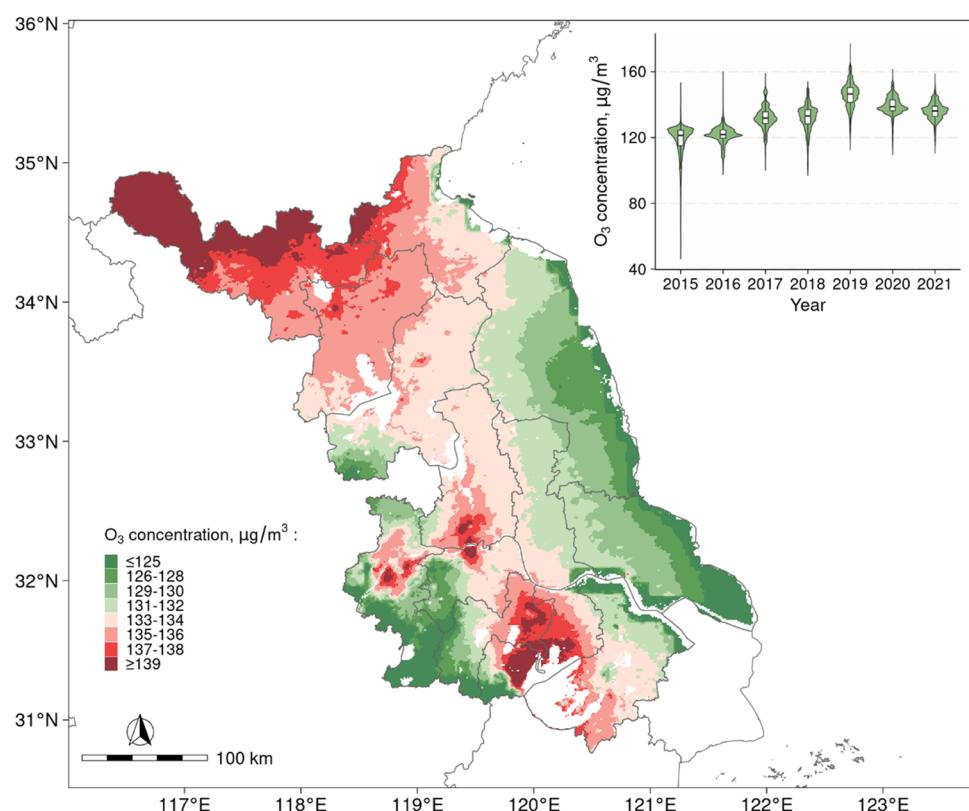


Figure 1. Distribution of ambient O₃ concentrations in Jiangsu province, China, during warm seasons between 2015 and 2021. The spatial resolution of each grid was 1 km × 1 km. O₃, ozone.

heat wave days, high-level O₃ and non-heat wave days, low-level O₃ and heat wave days, medium-level O₃ and heat wave days, and high-level O₃ and heat wave days, respectively. Under different O₃ exposure levels, the number of subjects died during heat wave days generally decreased with increasing temperature thresholds and number of consecutive days, ranging from 15,444 (3.0%) with the definition of P97.5_5d to 107,840 (21.1%) with the definition of P90_2d (Table S3).

We observed that lag 0–1 day exposure to O₃ was significantly associated with an increased odds of CVD mortality with adjustment for different heat wave definitions (Figure S5). These associations were generally linear (*P* for nonlinear >0.05), except that the associations under heat wave definitions of P90_2d, P92.5_2d, P92.5_3d, and P95_2d were detected with nonlinearities (all *P* for nonlinear <0.05). With adjustment for heat wave under different definitions, the ORs of CVD mortality for each 10 $\mu\text{g}/\text{m}^3$ increment of exposure to O₃ at lag 0–1 day ranged from 1.009 to 1.012, which slightly decreased with higher temperature thresholds and longer consecutive days of heat wave (Table S4). In comparison with exposure to low-level O₃, the ORs of CVD mortality associated with medium-level and high-level O₃ exposures were 1.03 (95% CI: 1.02, 1.04) and 1.08 (1.07, 1.09), respectively, while the OR associated with heat wave exposure was 1.26 (1.24, 1.28) under the definition of P95_3d. Generally, the ORs for medium-level and high-level O₃ exposures did not change markedly across different heat wave definitions, while the ORs for heat wave exposure increased with higher temperature thresholds and longer consecutive days of heat wave (ranging from 1.14 with the definition of P90_2d to 1.65 with the definition of P97.5_5d) (Figure 4 and Table S4).

With the heat wave definition of P95_3d, the ORs of CVD mortality were 1.03 (95% CI: 1.02, 1.04), 1.11 (1.08, 1.15), and 1.22 (1.13, 1.32) for exposure to medium-level O₃ and non-heat wave, low-level O₃ and heat wave, and medium-level O₃ and heat wave, respectively, while the ORs were 1.07 (1.06, 1.08), 1.11 (1.08, 1.15), and 1.45 (1.34, 1.57) for exposure to high-level O₃ and non-heat wave, low-level O₃ and heat wave, and high-level O₃ and heat wave, respectively (Table S5). The REOI, AP, and S for exposure to medium-level O₃ and heat wave was 0.07 (95% CI: 0.03, 0.12), 0.06 (0.03, 0.10), and 1.51 (1.15, 2.00), respectively, and was 0.27 (0.23, 0.31), 0.19 (0.16, 0.22), and 2.52 (2.03, 3.13) for exposure to high-level O₃ and heat wave, respectively (Table S6). The additive interaction of exposure to high-level O₃ and heat wave on CVD mortality was generally higher than that of exposure to medium-level O₃ and heat wave, both of which consistently increased with higher temperature thresholds and longer consecutive days of heat wave, with the REOI ranging from 0.05 with the definition of P90_5d to 0.57 with the definition of P97.5_5d (Figure 5 and Table S6).

With the heat wave definition of P95_3d, an estimated 4.9% (24,860) of CVD mortality was attributable to exposure to medium-level O₃, high-level O₃, and heat wave. Of them, 18.5% (excess fraction: 0.90%), 37.9% (1.84%), 2.0% (0.10%), 10.9% (0.53%), and 30.7% (1.49%) were due to exposure to medium-level O₃ and non-heat wave, high-level O₃ and non-heat wave, low-level O₃ and heat wave, medium-level O₃ and heat wave, and high-level O₃ and heat wave, respectively (Figure 6B and Table S7). In general, under different heat wave definitions, the excess fraction of CVD mortality attributed to O₃ and heat wave exposures during warm seasons ranged from 4.6 to 5.7%, corresponding to 23,542 to 29,204

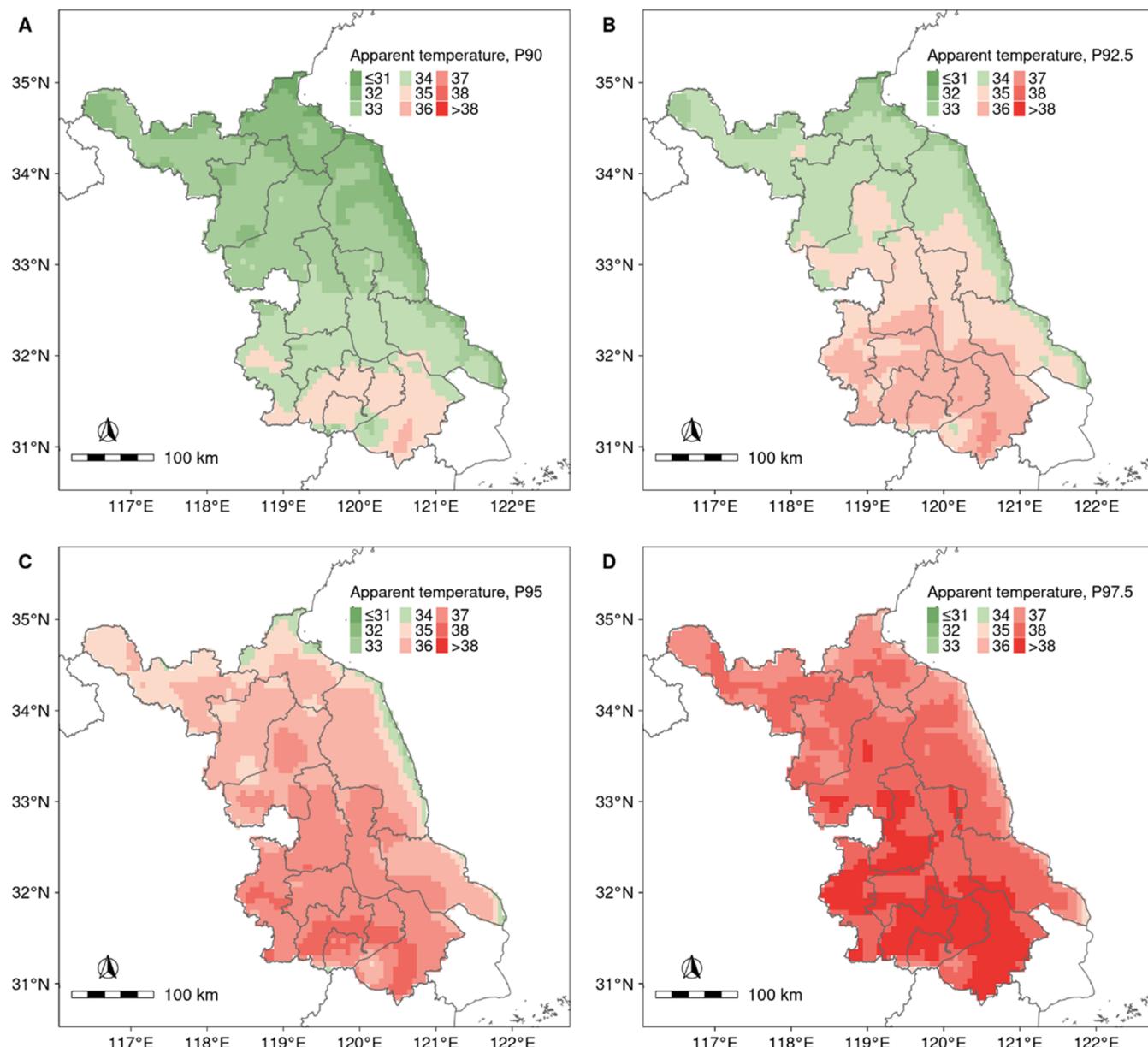


Figure 2. Spatial distribution of different temperature thresholds in Jiangsu province, China, during warm seasons between 2015 and 2021. The unit of daily mean apparent temperature was degrees Celsius (°C). The spatial resolution of each grid was $0.0625^\circ \times 0.0625^\circ$. P90 (A), P92.5 (B), P95 (C), and P97.5 (D).

excess deaths, which decreased with higher temperature thresholds and longer consecutive days of heat wave exposure owing to the corresponding decreased proportions of CVD deaths (Figure 6 and Tables S7–S8).

Under the definition of P95_3d, the proportions of excess deaths during heat wave days attributable to exposure to low-level O₃ and heat wave, medium-level O₃ and heat wave, and high-level O₃ and heat wave were 1.15% (95% CI: 0.81%, 1.48%), 6.07% (3.78%, 8.18%), and 17.03% (13.96%, 19.87%), respectively. Overall, the proportions of excess deaths due to O₃ and heat wave exposures generally increased with higher temperature thresholds and longer consecutive days of heat wave exposure and higher exposure levels of O₃, which ranged from 0.14 to 34.63% under different exposure levels and were much higher than that of during warm seasons (Tables S7 and S9).

In stratified analysis, significantly higher independent association of exposure to high-level O₃ and heat wave with CVD mortality was observed in women and older adults, while significantly higher REOI of O₃ and heat wave exposures on CVD mortality was observed in women than that in men (all *P* for difference <0.05; Table 2). No significant difference in REOI of O₃ and heat wave exposures on CVD mortality was identified across age (*P* for difference >0.05; Table 2). Sensitivity analyses showed that the independent and interactive effects for O₃ and heat wave exposures remained stable or became slightly stronger when adjusting for PM_{2.5} in the models (Table S10), using daily minimum apparent temperature (Table S11), maximum apparent temperature (Table S12), mean air temperature (Table S13), and temperature thresholds during warm seasons (Table S14) to define heat wave, and restricting analysis in subjects died during 2015–2019 (Table S15), except that the associations

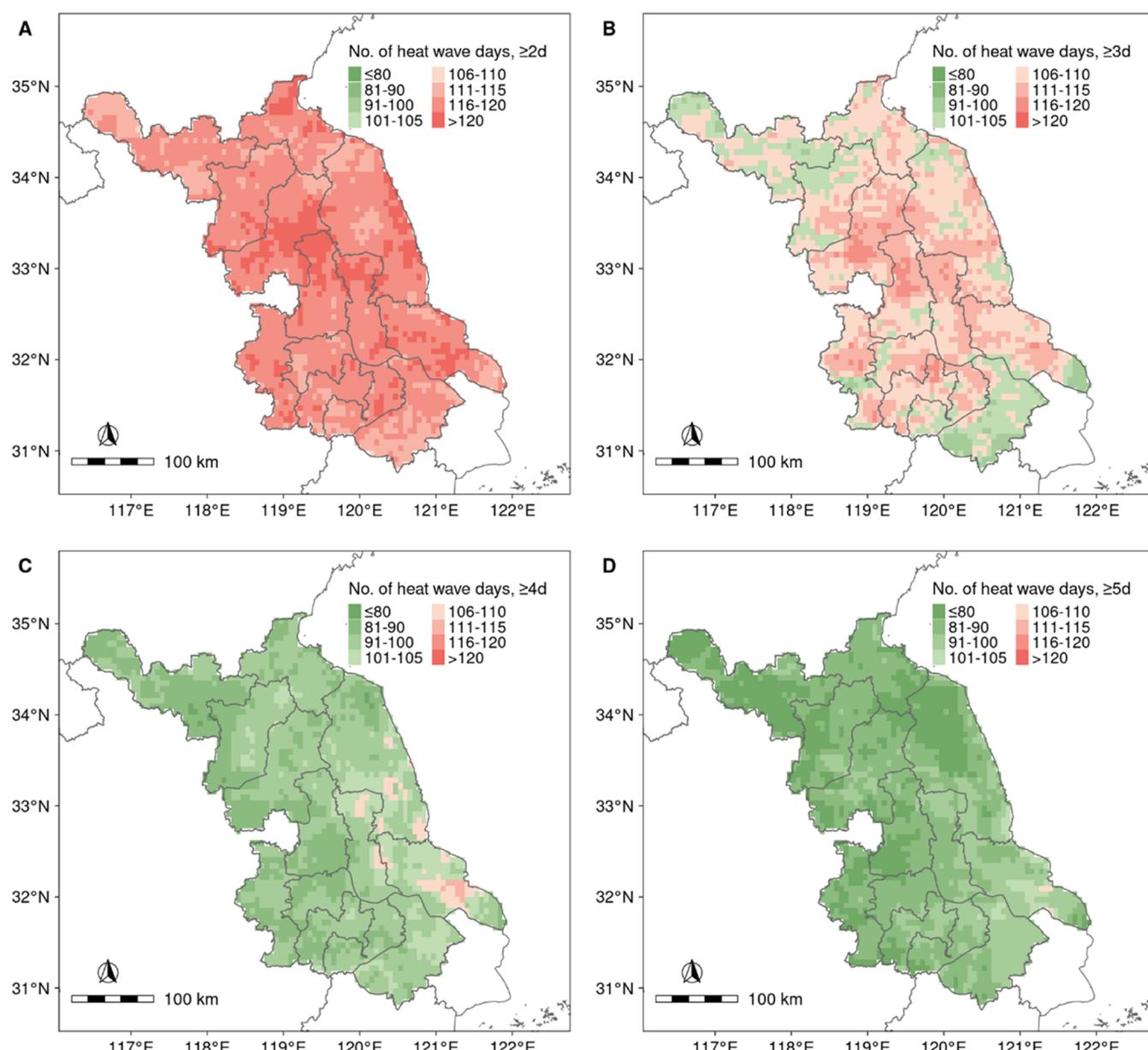


Figure 3. Spatial distribution of number of heat wave days in Jiangsu province, China, during warm seasons between 2015 and 2021. Heat wave was defined as the daily mean apparent temperature ($^{\circ}\text{C}$) equal to or higher than the 95th percentile of temperature for at least 2 (A), 3 (B), 4 (C), and 5 (D) consecutive days. The spatial resolution of each grid was $0.0625^{\circ} \times 0.0625^{\circ}$.

for exposure to medium-level and high-level O_3 slightly decreased when using daily mean air temperature to define heat wave (Table S13).

4. DISCUSSION

In this large study in Jiangsu province, China, between 2015 and 2021, we found consistent evidence that independent exposure to O_3 and heat wave was significantly associated with an increased odds of mortality from CVDs. In addition, O_3 and heat wave could interact synergistically to trigger CVD deaths, with the synergistic effects increasing with higher levels of O_3 exposure as well as increased intensities and longer durations of heat wave exposure. It was estimated that up to 5.7% of CVD deaths can be attributed to O_3 and heat wave exposures. Women and older adults were more vulnerable to exposure to

O_3 and the heat wave, while the synergistic effects for exposure to O_3 and the heat wave did not vary across age.

The positive association of exposure to O_3 with CVD mortality was generally in line with findings from previous studies.^{3,4,27} In 2018, a meta-analysis included 10 investigations in low- and middle-income countries, which investigated the acute effects of O_3 on CVD mortality and reported that with each $10 \mu\text{g}/\text{m}^3$ increase in exposure to O_3 at lag 0–1 day, the relative risk (RR) of mortality from CVDs was 1.0039,²⁷ which was lower than ours (ORs ranging from 1.009 to 1.012). Similarly, our findings of significant associations between heat wave exposure and CVD mortality have been documented in previous studies.³ A recent meta-analysis summarized 60 effect estimates from 37 studies worldwide before 2021 and concluded that the pooled RR of CVD mortality associated with exposure to heat wave was 1.117, which was also lower than our corresponding estimates (ORs ranging from 1.14 to

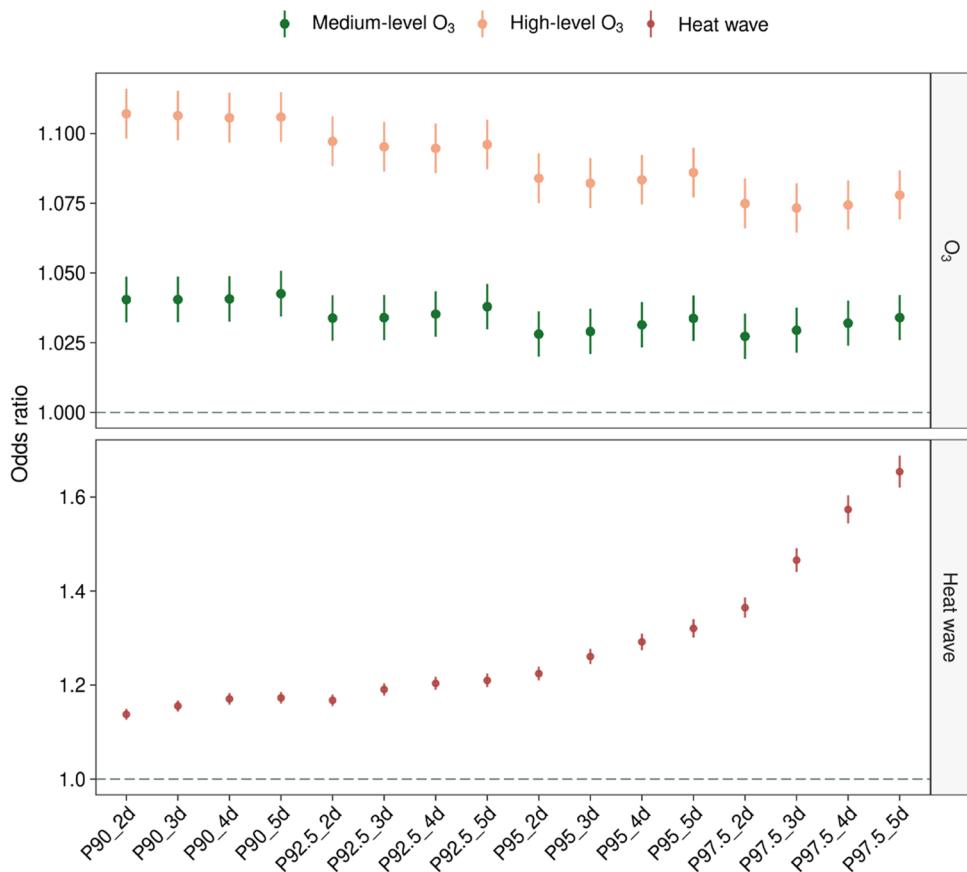


Figure 4. Independent association of exposure to ambient O₃ and heat wave with CVD mortality. For example, P95_3d represents a heat wave defined as the daily mean apparent temperature equal to or higher than the 95th percentile of temperature for at least 3 consecutive days. CVD, cardiovascular disease and O₃, ozone.

1.65).³ In addition, this meta-analysis further estimated the associations under different intensities of heat wave and revealed that the pooled risk effects increased as the heat wave intensity increased, which was consistent with our findings. Nonetheless, future investigations are warranted to further evaluate the ability of O₃ and heat wave to elicit cardiovascular effects.

Under the context of global warming, the concurrence of O₃ pollution and heat wave is becoming more frequent in summer. Although there has been an increasing awareness of possible health effects of coexposure to O₃ and heat wave, their possible combined effects on CVD mortality remain largely unknown. In 2014, a time-series study in 9 European cities from 1990 to 2004 explored potential effect modifications of O₃ on the association between heat wave exposure and CVD mortality and found that the effect of heat wave exposure on CVD mortality was larger during high-level O₃ days (percent change in the daily number of CVD deaths associated with exposure to low-level O₃ vs high-level O₃: 16.6 vs 19.9%); however, in 2018, another time-series study in Europe reported that the association of heat wave exposure with CVD mortality was stronger during low-level O₃ days (12.33 vs 9.18%).⁶ Note that these two studies detected the interactive effect of the O₃ and heat wave on CVD mortality by introducing a product interaction term in the models, and both failed to observe any significant interaction. The difference of interactions among these two studies and our study can be possibly explained by the heterogeneity in subject characteristic, exposure assessment (e.g., heat wave definition), statistical strategy, and study

design. Notably, our study is the first to quantitatively explore the potential synergistic effects of O₃ and heat wave exposures on CVD mortality. In addition to contributing to a systematic understanding of interactive effects of O₃ and heat wave on CVD mortality with quantitative estimates, our results revealed that the synergistic effect of O₃ and heat wave increased with higher O₃ levels and more severe heat waves, which were responsible for considerable CVD deaths. Overall, our findings highlight the important public health significance of reducing O₃ concentrations and developing an early warning system for health protection during heat wave days; moreover, combating O₃ pollution and heat wave events with the consideration of synergistic effects of these two exposures may create larger health benefits for individuals and the society.

In this study, we found that women and older adults had higher odds of CVD mortality associated with O₃ and heat wave exposures than other groups. According to evidence of previous epidemiological studies, women have shorter respiratory tract, greater airway reactivity, and higher expression of lung inflammatory mediators and signaling and are more susceptible to air pollutants in comparison with men, which has been also observed in animal studies.^{28–30} Meanwhile, the possible sex difference in fitness conditions, vascular characteristics, percentage of body fat, and hormone levels may be responsible for the greater difficulty in dissipating heat for women.³¹ With regard to older adults, the degeneration in cardiovascular function that occurs with aging can compromise the body's adaptation ability during

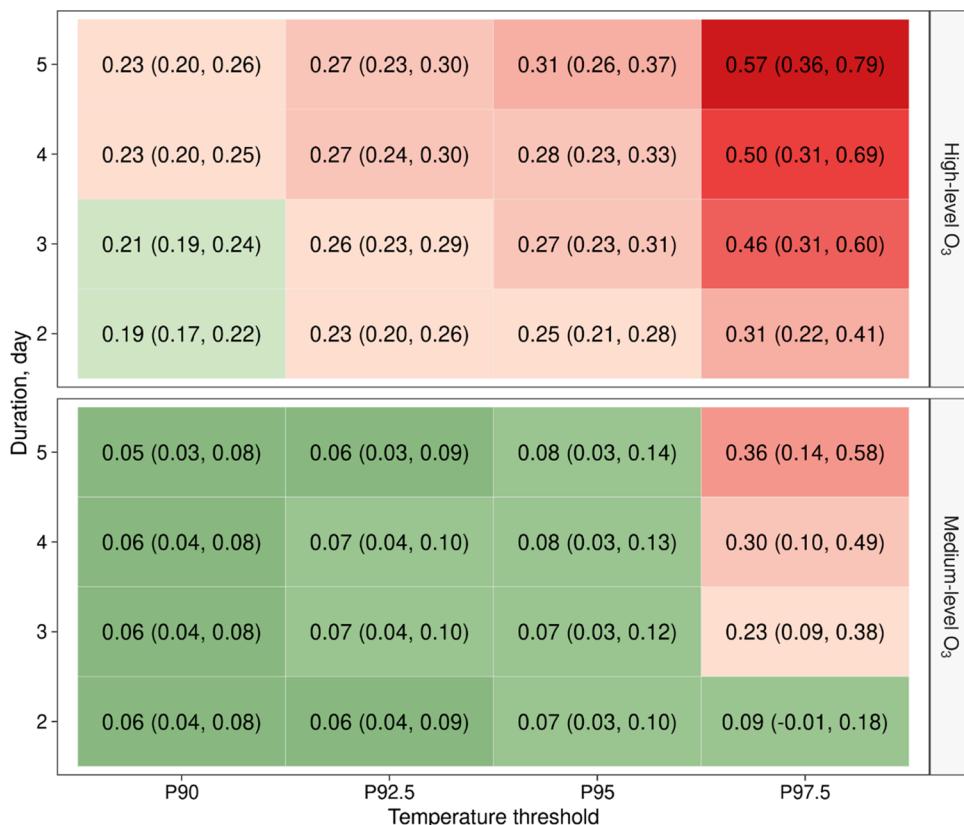


Figure 5. Relative excess odds due to interaction of exposure to ambient O₃ and heat wave on CVD mortality in Jiangsu province, China, during warm seasons between 2015 and 2021. The cutoff value of medium- and high-level O₃ exposure was 116.1 and 148.0 μg/m³, respectively. CVD, cardiovascular disease and O₃, ozone.

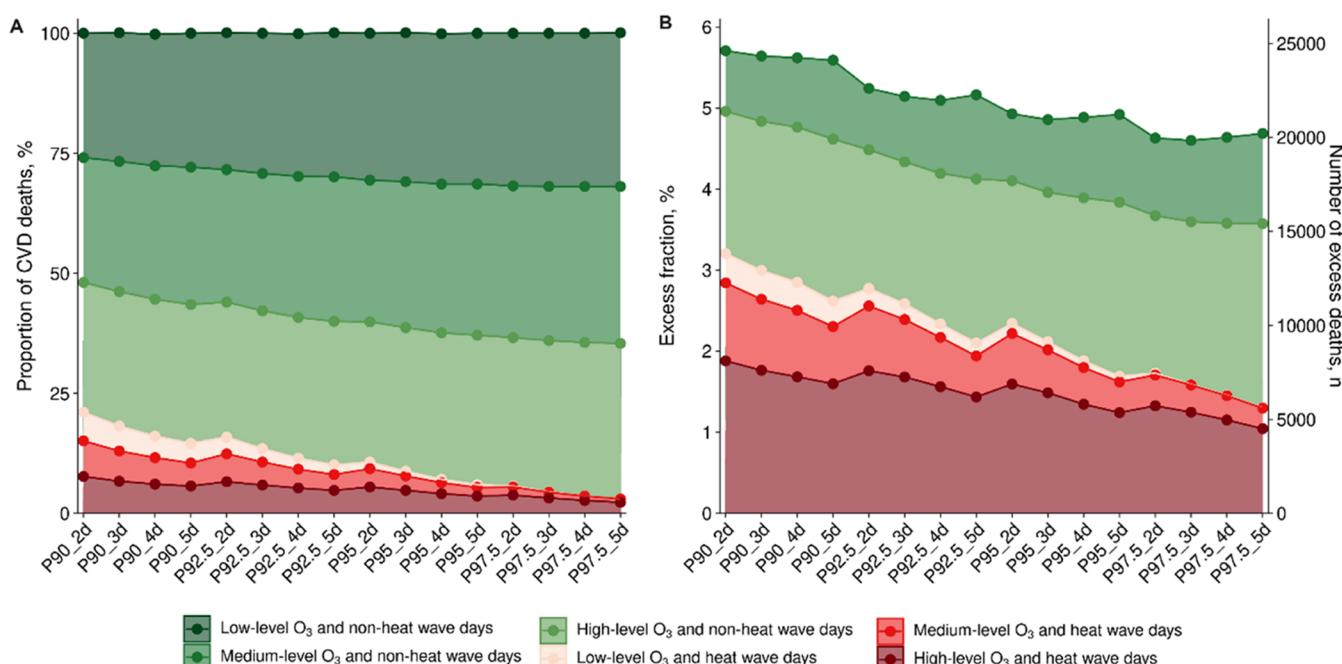


Figure 6. (A) Proportion of CVD deaths under different exposure levels and (B) excess fraction and number of excess deaths due to exposure to ambient O₃ and heat wave in Jiangsu province, China, during warm seasons between 2015 and 2021. CVD, cardiovascular disease and O₃, ozone.

pollution events or thermoregulation when exposed to heat wave.³²

Although previous studies have revealed significant associations of short-term exposure to O₃ and heat wave with

increased odds of CVD mortality, the underlying pathophysiological mechanisms are still uncertain. Evidence of previous experimental and animal studies indicates that exposure to O₃ can cause systemic inflammation, oxidative stress, and averse

Table 2. OR and REOI of Exposure to Ambient O₃ and Heat Wave on CVD Mortality, Stratified by the Sex and Age^{a,b}

stratification variable	OR (95% CI)			REOI (95% CI)		
	low-level O ₃	medium-level O ₃	high-level O ₃	heat wave	medium-level O ₃ and heat wave	high-level O ₃ and heat wave
sex						
male	reference	1.03 (1.01, 1.04)	1.07 (1.06, 1.08)	1.22 (1.19, 1.24)	0.04 (-0.02, 0.10)	0.21 (0.15, 0.27)
female	reference	1.03 (1.01, 1.04)	1.09 (1.08, 1.11)	1.30 (1.28, 1.33)	0.11 (0.04, 0.17)	0.34 (0.27, 0.40)
P-value ^c		0.51	0.02	<0.001	0.15	0.003
age						
≤80	reference	1.02 (1.01, 1.03)	1.07 (1.05, 1.08)	1.21 (1.19, 1.24)	0.06 (-0.002, 0.12)	0.26 (0.20, 0.32)
>80	reference	1.03 (1.01, 1.04)	1.09 (1.08, 1.11)	1.30 (1.27, 1.32)	0.09 (0.03, 0.14)	0.28 (0.22, 0.34)
P-value ^c		0.17	0.003	<0.001	0.56	0.64

^aCI, confidence interval; CVD, cardiovascular disease; O₃, ozone; OR, odds ratio; and REOI, relative excess odds due to interaction. ^bThe definition of heat wave was P95_3d. ^cEstimated by the 2-sample z test.

cardiac autonomic effects, which may contribute to the cardiovascular mortality due to short-term O₃ exposure.^{33,34} Additionally, when individuals are exposed to heat temperatures, body core temperature rises, and the thermoregulatory system is accelerated to help transfer heat to the environment. The thermoregulatory progress could induce increased sweating and skin blood flow, dehydration, increased cardiac output, as well as hemoconcentration.³⁵ With the extension of heat exposure, the above thermoregulatory progress depletes, which may trigger systemic inflammation, oxidative stress, endothelial dysfunction, and eventually lead to adverse cardiovascular outcomes.³⁶ Of note, the increase in overall O₃ concentrations during heat wave days and the common mechanisms of O₃ and heat exposures on physiology (including systemic inflammation and oxidative stress) can be possible reasons for their synergistic effects on CVD mortality. Nonetheless, the exact mechanism is worth illustrating in future investigations.

Several strengths of this study should be noted. First, this study included over 0.5 million CVD deaths with a based population of more than 85 million. The large sample size with individual subject information (e.g., personal data on residential address, sex, and age) enabled us to conduct a comprehensive analysis to maximize the validity of our results. Second, different from studies in western developed counties, the wide range of O₃ concentrations provided us a unique opportunity to systematically investigate the independent as well as interactive effects of O₃ and heat wave exposures on CVD mortality, the evidence from which can be considered generalizable when interpreting our results to other regions with low or high O₃ concentrations. Third, we applied apparent temperature to define heat wave at a grid level and performed exposure assessment at an individual level for each subject by extracting exposure information from a series of validated grid data sets with relatively high resolutions. As an indicator that combines multiple meteorological conditions, apparent temperature is a more comprehensive meteorological metric in characterizing heat wave exposure than air temperature.³⁷ Besides, exposure assessment at the individual level based on a relative high-resolution grid data set can aid in achieving more accurate exposure estimations. Finally, the time-stratified case-crossover design of this study can provide more accurate estimates of the associations as individual-level time-invariant confounders can be autonomically controlled by the design.

This study has certain limitations. First, we used exposure data from validated grid data sets to perform exposure

assessment as the proxy of personal exposure for each subject, which has been widely accepted in environmental epidemiological studies; however, because we did not have data on each subject's direct exposure measurement, personal activity, or change in residential address (people may not always stay in the same grid cell during the case and control days, especially at a high spatial resolution), exposure misclassification is inevitable. Nonetheless, the misclassification is generally nondifferential and thus may bias our estimates toward null.³⁸ Second, although time-invariant confounders can be sufficiently controlled by the case-crossover design, residual confounders that may vary for an individual within the case and control days could not be fully excluded and might bias our estimates. Third, given the large sample size of our study, misclassifications of the identified CVD deaths were still possible, though the determination of causes of death was under strict quality control. Finally, our study was conducted in one province in China, and therefore, one should be cautious when interpreting our results.

In conclusion, this population-based case-crossover study among over 0.5 million CVD deaths from Jiangsu province, China, provides essential evidence that independent exposure to O₃ and heat wave is significantly associated with an increased odds of CVD mortality and that O₃ and heat wave can interact synergistically to trigger more CVD deaths, especially at exposures to higher O₃ levels and more severe heat waves. Given more frequent O₃ pollution and heat wave under climate change, the findings of this study highlight urgent actions to reduce coexposure to O₃ and heat wave and implement joint early warning systems to combat their dual CVD mortality burdens.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.est.3c06889>.

Additional information on the calculation of three additive interaction measures and sensitivity analyses ([PDF](#))

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Notes

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ACKNOWLEDGMENTS

This work was supported by the National Science and Technology Major Project (grant 2022YFC3700105) and the Key Project of Medical Science Research of Jiangsu Provincial Health Commission (grant ZD2023045).

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