Circulation

ORIGINAL RESEARCH ARTICLE

Extreme Temperature Events, Fine Particulate Matter, and Myocardial Infarction Mortality

Ruijun Xu, MD*; Suli Huang, MD, PhD*; Chunxiang Shi, PhD; Rui Wang, MD; Tingting Liu, MS; Yingxin Li, MD; Yi Zheng, MD; Ziquan Lv, MD, PhD; Jing Wei, PhD; Hong Sun, MD, PhD; Yuewei Liu, MD, PhD

BACKGROUND: Extreme temperature events (ETEs), including heat wave and cold spell, have been linked to myocardial infarction (MI) morbidity; however, their effects on MI mortality are less clear. Although ambient fine particulate matter ($PM_{2.5}$) is suggested to act synergistically with extreme temperatures on cardiovascular mortality, it remains unknown if and how ETEs and $PM_{2.5}$ interact to trigger MI deaths.

METHODS: A time-stratified case-crossover study of 202 678 MI deaths in Jiangsu province, China, from 2015 to 2020, was conducted to investigate the association of exposure to ETEs and $PM_{2.5}$ with MI mortality and evaluate their interactive effects. On the basis of ambient apparent temperature, multiple temperature thresholds and durations were used to build 12 ETE definitions. Daily ETEs and $PM_{2.5}$ exposures were assessed by extracting values from validated grid datasets at each subject's geocoded residential address. Conditional logistic regression models were applied to perform exposure-response analyses and estimate relative excess odds due to interaction, proportion attributable to interaction, and synergy index.

RESULTS: Under different ETE definitions, the odds ratio of MI mortality associated with heat wave and cold spell ranged from 1.18 (95% CI, 1.14–1.21) to 1.74 (1.66–1.83), and 1.04 (1.02–1.06) to 1.12 (1.07–1.18), respectively. Lag 01-day exposure to $PM_{2.5}$ was significantly associated with an increased odds of MI mortality, which attenuated at higher exposures. We observed a significant synergistic interaction of heat wave and $PM_{2.5}$ on MI mortality (relative excess odds due to interaction >0, proportion attributable to interaction >0, and synergy index >1), which was higher, in general, for heat wave with greater intensities and longer durations. We estimated that up to 2.8% of the MI deaths were attributable to exposure to ETEs and $PM_{2.5}$ at levels exceeding the interim target 3 value (37.5 μg/m^3) of World Health Organization air quality guidelines. Women and older adults were more vulnerable to ETEs and $PM_{2.5}$. The interactive effects of ETEs or $PM_{2.5}$ on MI mortality did not vary across sex, age, or socioeconomic status.

CONCLUSIONS: This study provides consistent evidence that exposure to both ETEs and $PM_{2.5}$ is significantly associated with an increased odds of MI mortality, especially for women and older adults, and that heat wave interacts synergistically with $PM_{2.5}$ to trigger MI deaths but cold spell does not. Our findings suggest that mitigating both ETE and $PM_{2.5}$ exposures may bring health cobenefits in preventing premature deaths from MI.

Key Words: cold temperature ■ death ■ hot temperature ■ mortality ■ myocardial infarction ■ particulate matter

Editorial, see p 324

In the context of global climate change, extreme temperature events (ETEs), including heat wave and cold spell, are expected to be more frequent, longer, and more intense in the near future, which has drawn growing concern due to their potential adverse effects on human health.[1,2] Emerging epidemiological studies suggest that ETEs can trigger acute cardiovascular events, especially myocardial infarction (MI).[3–5] Exposure to ETEs has been

Correspondence to: Yuewei Liu, MD, PhD, Department of Epidemiology, School of Public Health, Sun Yat-sen University, 74 Zhongshan Second Road, Guangzhou, Guangdong 510080, China, Email liuyuewei@mail.sysu.edu.cn; Hong Sun, MD, PhD, Institute of Environment and Health, Jiangsu Provincial Center for Disease Control and Prevention, 172 Jiangsu Rd, Nanjing, Jiangsu 210009, China, Email hongsun@jscdc.cn; or Jing Wei, PhD, Department of Atmospheric and Oceanic Science, Earth System Science Interdisciplinary Center, University of Maryland, 7901 Regents Drive, College Park, MD 20740, Email weijing_rs@163.com

*R. Xu and S. Huang contributed equally.

Supplemental Material is available at: https://www.ahajournals.org/doi/suppl/10.1161/CIRCULATIONAHA.122.063504.

Continuing medical education (CME) credit is available for this article. Go to http://cme.ahajournals.org to take the quiz.

For Sources of Funding and Disclosures, see page 322.

Circulation is available at www.ahajournals.org/journal/circ

Clinical Perspective

What Is New?

- Exposure to both extreme temperature events and fine particulate matter is significantly associated with an increased odds of myocardial infarction mortality especially among women and older adults.
- Heat wave exposure interacts synergistically with fine particulate matter to trigger myocardial infarction deaths, but cold spell exposure does not.
- Under different extreme temperature event definitions, up to 2.8% of myocardial infarction deaths were attributable to exposure to extreme temperature events and fine particulate matter at levels exceeding the interim target 3 value (37.5 μg/m³) of World Health Organization air quality guidelines in Jiangsu province, China, from 2015 to 2020.

What Are the Clinical Implications?

- The findings of this study provide useful clues for clinical practitioners to improve the treatment and management of myocardial infarction by taking into consideration the independent and interactive effects of extreme temperature events and fine particulate matter.
- Reducing exposure to both extreme temperature events and fine particulate matter may bring health cobenefits in preventing premature deaths from myocardial infarction.

Nonstandard Abbreviations and Acronyms

AP	proportion attributable to interaction
CO	carbon monoxide
ETE	extreme temperature event
ICD-10	*International Statistical Classification of Diseases and Related Health Problems, 10th Revision*
MI	myocardial infarction
OR	odds ratio
$PM_{2.5}$	fine particulate matter
REOI	relative excess odds due to interaction
S	synergy index
SES	socioeconomic status

linked to a higher risk of MI emergency department visits and hospitalizations.[5–8] Although some previous evidence indicates that exposure to nonoptimum temperatures is significantly associated with an increased risk of MI mortality,[9–11] the association between ETEs and MI mortality remains poorly understood.

To date, only a limited number of single-city studies in Beijing, Shanghai, and Jinan, China, specifically explored the adverse effects of heat wave or cold spell on MI mortality, and the results are mixed.[12–16] The studies in Beijing[13] and Jinan[14,15] concluded that heat wave was significantly associated with an increased odds of MI mortality, whereas the study in Shanghai[12] reported null results. One possible reason for the inconsistent results is that these studies applied an identical heat wave definition (daily maximum air temperature ≥35 °C for at least 3 consecutive days) but did not account for intercity variation of exposure and adaptation to ambient temperatures, which can lead to imprecise and incomparable estimates.[17] Likewise, the study in Beijing defined a cold spell as daily minimum air temperature dropping by >8 °C within 48 hours with the minimum air temperature <4 °C simultaneously, and found that exposure to cold spell was significantly associated with a higher odds of MI mortality.[16] Note that all these studies used a univariate indicator for ETEs without considering various intensities and durations, which fails to characterize ETEs in a comprehensive manner.[17,18]

Ambient fine particulate matter ($PM_{2.5}$) pollution continues to be a critical public health issue worldwide.[19] Epidemiological studies have reported that exposure to extreme temperatures and $PM_{2.5}$ can act synergistically to trigger cardiovascular deaths.[20] In our previous study in 2021, we provided convincing evidence that exposure to $PM_{2.5}$ was significantly associated with an increased odds of MI mortality.[21,22] Given that the current evidence suggests a link between ETEs and MI mortality, it remains unknown, but is of great interest and importance, to understand if ETEs and $PM_{2.5}$ interact synergistically to trigger MI deaths.

To fill these gaps, we conducted a population-based case-crossover study of >0.2 million MI deaths in Jiangsu province, China, from 2015 to 2020. This study aimed to comprehensively assess the association of exposure to ETEs and ambient $PM_{2.5}$ with MI mortality, quantitatively evaluate their interactive effects on MI mortality, and estimate the corresponding excess mortality. We also performed stratified analyses to explore potentially vulnerable populations.

METHODS

Data Availability

Air pollution data are available from https://weijing-rs.github.io/product.html. Data on MI mortality and meteorological conditions are not publicly available.

Study Population

We obtained mortality data from the Jiangsu provincial mortality surveillance system, which was developed and administrated by the Chinese Center for Disease Control and Prevention since 2008 and covered the entire population of Jiangsu province since 2011.[23] Jiangsu is an eastern central province of China (116°21′–121°56′ E, 30°45′–35°08′ N) and covers an area of 107 200 km². With 4 distinct seasons, most of Jiangsu has a humid subtropical climate, which begins to transit into a humid continental climate in the far north. In 2021, Jiangsu province had a population of 85.1 million, accounting for 6.0% of the total population in China. As a national economic and commercial center, Jiangsu had the highest gross domestic product per capita among all provinces of China in 2021. After excluding subjects without detailed demographic information (n=970, 0.48%), we identified a total of 202 678 subjects who lived in Jiangsu province and died from MI between 2015 and 2020. For each subject, we extracted data on date of birth, sex, marital status, residential address, date of death, and diagnostic basis from the surveillance system, and collected data on gross domestic product per capita of the subject's residential county in the year of death from the Jiangsu Statistical Yearbooks (2016–2021). This study was approved by the Ethics Committee of School of Public Health, Sun Yat-sen University, with a waiver of informed consent.

Outcomes

The study outcome of interest was mortality from MI as the underlying cause of death. According to the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (*ICD-10*), we used the *ICD-10* codes of I21 and I22 to define MI mortality. In the Jiangsu provincial mortality surveillance system, diagnosis of the underlying cause of death for each case was made on the basis of symptoms/signs, physiobiochemistry, pathology, autopsy, surgery, or inference. The diagnostic basis was divided into 4 classes (class I, autopsy, pathology, or surgery; class II, symptoms/signs and physiobiochemistry; class III, symptoms/signs; and class IV, inference), and the diagnosis reliability was highest in class I and lowest in class IV.

Study Design

We investigated the association of exposure to ETEs and ambient $PM_{2.5}$ with MI mortality and quantified their interactive effects using a time-stratified case-crossover design that has been widely used to evaluate the transient effects of environmental exposures on a variety of health outcomes.[21,24] In this design, each subject serves as his or her own reference by comparing exposures on the date of death with referent exposures before and after the date of death within a time stratum (ie, the month of death). For each subject, the date of death was defined as the case day, whereas all other dates sharing the same year, month, and day of week with the case day were chosen as the corresponding control days. For example, if a subject died on June 12, 2019 (Wednesday), June 2019 was defined as the time stratum, June 12, 2019, was defined as the case day, and all other Wednesdays in the time stratum (ie, June 5, 19, and 26) were defined as the corresponding control days. With this design, factors that were less likely to change within the time stratum (eg, age, sex, socioeconomic status [SES], lifestyle, or chronic comorbidities) and the effects of long-term time trend, seasonality, and day of week could be adequately controlled.[25,26] Because a case day can be matched with 3 or 4 control days, 202 678 case days and 687 972 control days were finally included in the analysis.

Exposure Assessment

We retrieved daily grid data on meteorological conditions including air temperature (°C) and relative humidity (%) from the China Meteorological Administration Land Data Assimilation System (CLDAS version 2.0; spatial resolution: 0.0625°×0.0625°).[27–29] Each day from 2015 to 2020, we used daily 24-hour average air temperature and relative humidity to calculate daily 24-hour average apparent temperature (or heat index, °C) with the *weathermetrics* package in R software (version 4.1.2) and generated a grid dataset for daily apparent temperature. Because there is no standard definition for either heat wave or cold spell, we defined ETEs with a combination of ETE intensity and duration as proposed in previous studies.[17,30] In each grid, we first calculated the 90th, 92.5th, 95th, and 97.5th percentile of daily apparent temperature from 2015 to 2020 as temperature thresholds for heat wave and the 10th, 7.5th, 5th, and 2.5th percentile as temperature thresholds for cold spell. Heat waves were then identified as daily apparent temperature equal to or higher than a threshold (ie, P90, P92.5, P95, or P97.5) for at least 2, 3, or 4 consecutive days, whereas cold spells were identified as daily apparent temperature equal to or lower than a threshold (ie, P10, P7.5, P5, or P2.5) for at least 2, 3, or 4 consecutive days. For example, P95_3d represents a heat wave defined as daily apparent temperature equal to or higher than the 95th percentile of temperature for at least 3 consecutive days, whereas P5_3d represents a cold spell defined as daily apparent temperature lower than or equal to the 5th percentile of temperature for at least 3 consecutive days. According to this approach, we built 12 definitions for both heat wave and cold spell (Table S1) and generated 12 corresponding ETE grid datasets with a spatial resolution of 0.0625°×0.0625° from 2015 to 2020. For each grid of 12 ETE grid datasets, heat wave and cold spell days were assigned 1 and 2, respectively, whereas the remaining days were assigned 0 (non-ETE days). From the ETE grid datasets, exposure to ETEs on each of the case day and control days was assessed by extracting ETE information (0=non-ETE days, 1=heat wave days, or 2=cold spell days) at each subject's geocoded residential address.

Daily ambient air pollution data on $PM_{2.5}$, sulfur dioxide (SO_2), nitrogen dioxide (NO_2), carbon monoxide (CO), and ozone (O_3) were obtained from the ChinaHighAirPollutants dataset (available at https://weijing-rs.github.io/product.html), which was generated from our proposed artificial intelligence models combined with ground measurements, satellite remote sensing products, and atmospheric reanalysis. The ChinaHighAirPollutants dataset had a full spatiotemporal coverage in China during the study period with a spatial resolution of 1 × 1 km for $PM_{2.5}$ and O_3, and 10 × 10 km for SO_2, NO_2, and CO. The cross-validated coefficient of determination (R^2) for $PM_{2.5}$, SO_2, NO_2, CO, and O_3 was 0.92, 0.84, 0.84, 0.80, and 0.89, respectively, whereas the corresponding root-mean-square error was 10.76 μg/m^3, 10.07 μg/m^3, 7.99 μg/m^3, 0.29 mg/m^3, and 15.77 μg/m^3, respectively.[31–34] For each subject, we extracted daily 24-hour average $PM_{2.5}$, SO_2, NO_2, CO, and daily maximum 8-hour average O_3 concentrations at his or her geocoded residential address during the case day and control days. As proposed in most previous studies, we used the mean of exposure on the same day of death and 1 day before (lag 01-day exposure) as the air pollution exposure metric in the main analysis.[19,21]

Statistical Analysis

Conditional logistic regression models were used to assess the association of exposure to ETEs and ambient $PM_{2.5}$ with MI mortality by including ETEs as a categorical variable and $PM_{2.5}$ as a natural cubic spline with 3 *df*. Odds ratio (OR) with its

95% CI was used to quantify the associations. We visualized exposure-response curves of the association between $PM_{2.5}$ and MI mortality, and examined their nonlinearity using a likelihood ratio test, which was conducted by constructing a nested model with the $PM_{2.5}$ exposure as a continuous variable. When a departure from linearity was detected, piecewise conditional logistic regression models were applied to explore potential breakpoint of $PM_{2.5}$ exposure.

To further evaluate the interactive effects of exposure to ETEs and $PM_{2.5}$ on MI mortality, we classified $PM_{2.5}$ exposure as a binary variable according to the interim target 3 in World Health Organization air quality guidelines 2021 for $PM_{2.5}$ (low-level: ≤37.5 μg/m^3, high-level: >37.5 μg/m^3),[35] and generated a new variable with 4 levels to represent the combination of exposure to ETEs (heat wave or cold spell) and $PM_{2.5}$, including (1) non-ETEs and low-level $PM_{2.5}$ (level 1); (2) ETEs and low-level $PM_{2.5}$ (level 2); (3) non-ETEs and high-level $PM_{2.5}$ (level 3); and (4) ETEs and high-level $PM_{2.5}$ (level 4). The level 1 served as the reference group. By including this variable in the conditional logistic regression model, additive interactive effects, which is more informative than departures from multiplicativity when translating epidemiological results into public health actions,[36] were assessed using 3 measures including relative excess odds due to interaction (REOI), proportion attributable to interaction (AP), and synergy index (S), which represent part of the effect that is due to interaction, proportion of the combined effect that is due to interaction, and ratio between combined effect and individual effects, respectively. These 3 measures were calculated with the following formulas[37,38]:

$$\begin{aligned} REOI &= (OR_{11}-1)-(OR_{10}-1)-(OR_{01}-1) \\ &= OR_{11}-OR_{10}-OR_{01}+1 \end{aligned}$$

$$AP = \frac{REOI}{OR_{11}}$$

$$S = \frac{OR_{11}-1}{(OR_{10}-1)+(OR_{01}-1)}$$

where OR_{10}, OR_{01}, and OR_{11} refer to the OR in level 2, level 3, and level 4 in comparison with level 1 (OR_{00}=1), respectively. REOI=0, AP=0, and S=1 indicate no interactive effects of ETEs and $PM_{2.5}$ on MI mortality; REOI >0, AP >0, and S >1 indicate that the combined effects of ETEs and $PM_{2.5}$ on MI mortality are greater than the sum of the effects of each exposure alone (ie, synergistic effects); whereas REOI <0, AP <0, and S <1 indicate that the combined effects are smaller than the sum of individual effects of ETEs and $PM_{2.5}$. The corresponding 95% CIs for the 3 measures were calculated using the delta method.[39]

To quantify excess mortality due to exposure to ETEs and $PM_{2.5}$, we further estimated excess fraction and number of excess deaths according to exposure to level 2, level 3, and level 4, separately.

$$\text{Excess fraction} = \frac{\sum_{i=1}^{N} 1-\frac{1}{e^{\beta\times C}}}{N}$$

$$\text{Number of excess deaths} = \text{Excess fraction} \times N$$

where β indicates the point estimate of exposure in level 2, level 3, or level 4 in the conditional logistic regression model; C indicates if the exposure on the day of deaths was level 2, level 3, or level 4 (1=yes, 0=no); N indicates the total number of MI deaths.

To identify potential vulnerable populations, we conducted stratified analyses by fitting separate models by sex (male, female), age (≤80 years, >80 years), and SES (low, ≤the median gross domestic product per capita; high, >the median gross domestic product per capita) to assess the independent effects of exposure to ETEs and $PM_{2.5}$ on MI mortality and their interactive effects. Two-sample *z* tests were used to examine the difference of strata-specific effect estimates for each stratification variable (eg, sex)[40]:

$$z = \frac{\beta_{male}-\beta_{female}}{\sqrt{SE_{male}^2+SE_{female}^2}}$$

where β indicates the strata-specific point estimate (ie, ln OR) in the conditional logistic regression model; SE indicates the corresponding standard error for each β.

Several sensitivity analyses were performed to test the robustness of our results. First, we separately added each of the other gaseous pollutants (ie, SO_2, NO_2, CO, and O_3) in the same model to fit a 2-pollutant model and applied the likelihood ratio test to compare the nested models. For O_3, we further constructed a 2-pollutant model by restricting the analysis in summer season (June to August). Second, we used air temperature instead of apparent temperature to define ETEs and adjusted for mean relative humidity in the past 3 days as a natural cubic spline with 3 *df* in the model to examine the independent and interactive effects of exposure to ETEs and $PM_{2.5}$ on MI mortality. Third, we used the median value of $PM_{2.5}$ exposure to classify $PM_{2.5}$ as a binary variable in exploring the interactive effects of exposure to ETEs and $PM_{2.5}$ on MI mortality. Fourth, we used the same day (lag 0-day), the previous 1 day (lag 1-day), lag 02-day, and lag 03-day exposure as the exposure metric for $PM_{2.5}$ exposure and used the minimized Akaike

Table 1. Characteristics of the Study Subjects in Jiangsu Province, China, From 2015 to 2020

Characteristic	n (%)
All myocardial infarction deaths (case days)	202 678
Control days	687 972
Age, mean±SD	77.6±13.3
≤80 y	97 158 (47.9)
>80 y	105 520 (52.1)
Sex	
Male	105 466 (52.0)
Female	97 212 (48.0)
Marital status	
Married	130 603 (64.4)
Unmarried	5040 (2.5)
Widowed	65 359 (32.2)
Divorced	1676 (0.8)
Season at death	
Spring (March to May)	49 197 (24.3)
Summer (June to August)	42 813 (21.1)
Autumn (September to November)	46 447 (22.9)
Winter (December to February)	64 221 (31.7)

information criterion to compare models with different lag periods. Last, given that the diagnosis was considered reliable if it was made on the basis of symptoms/signs, physiobiochemistry, pathology, autopsy, or surgery, we restricted the analysis to MI deaths determined on the basis of classes I and II, and classes I, II, and III, as well, respectively. All analyses were performed using R (version 4.1.2), and a 2-sided *P* value <0.05 was considered statistically significant.

RESULTS

During the study period, there were 202 678 case days with 687 972 control days. Among the subjects, the mean age was 77.6 years, 52.1% died at >80 years, 52.0% were male, 64.4% were married, and 31.7% died in winter (Table 1, Figure 1D). The MI deaths determined on the basis of class I, II, and III diagnostic basis accounted for 1.5%, 60.2%, and 24.6% of all MI deaths, respectively. From 2015 to 2020, the mean value of P2.5, P5, P7.5, P10, P90, P92.5, P95, and P97.5 of daily apparent temperature in each gird was 0.3 °C, 1.7 °C, 2.6 °C, 3.2 °C, 31.9 °C, 34.7 °C, 37.4 °C, and 40.3 °C, respectively; mean exposure to ambient $PM_{2.5}$, SO_2, NO_2, CO, and O_3 was 54.0 μg/m³, 17.4 μg/m³, 35.6 μg/m³, 0.93 mg/m³, and 102.5 μg/m³, respectively, whereas mean exposure to O_3 in summer season was 134.4 μg/m³ (Table S2). The exposure to $PM_{2.5}$, SO_2, NO_2, and CO was positively correlated, whereas exposure to O_3 was negatively correlated with other air pollutants (all $P<0.05$; Table S3).

The spatial distribution of temperature thresholds and number of ETE days in each grid under different ETE definitions in Jiangsu province, China, from 2015 to 2020 are provided in Figure 1B and 1C, 1E and 1F, and Figures S1 to S5. Under the definition of P95_3d, the temperature thresholds and number of heat wave days ranged from 32.9 °C to 40.4 °C and 82 to 104, respectively, whereas the temperature thresholds and number of cold spell days in the definition of P5_3d ranged from −0.02 °C to 4.1 °C and 57 to 90, respectively. Overall, the number of ETE days decreased with higher temperature thresholds and longer durations for heat wave and with lower temperature thresholds and longer durations for cold spell. The annual average number of ETE days from 2015 to 2020 in Jiangsu province, China, is shown in Table S4.

The number of MI deaths under different exposure levels in Jiangsu province, China, from 2015 to 2020

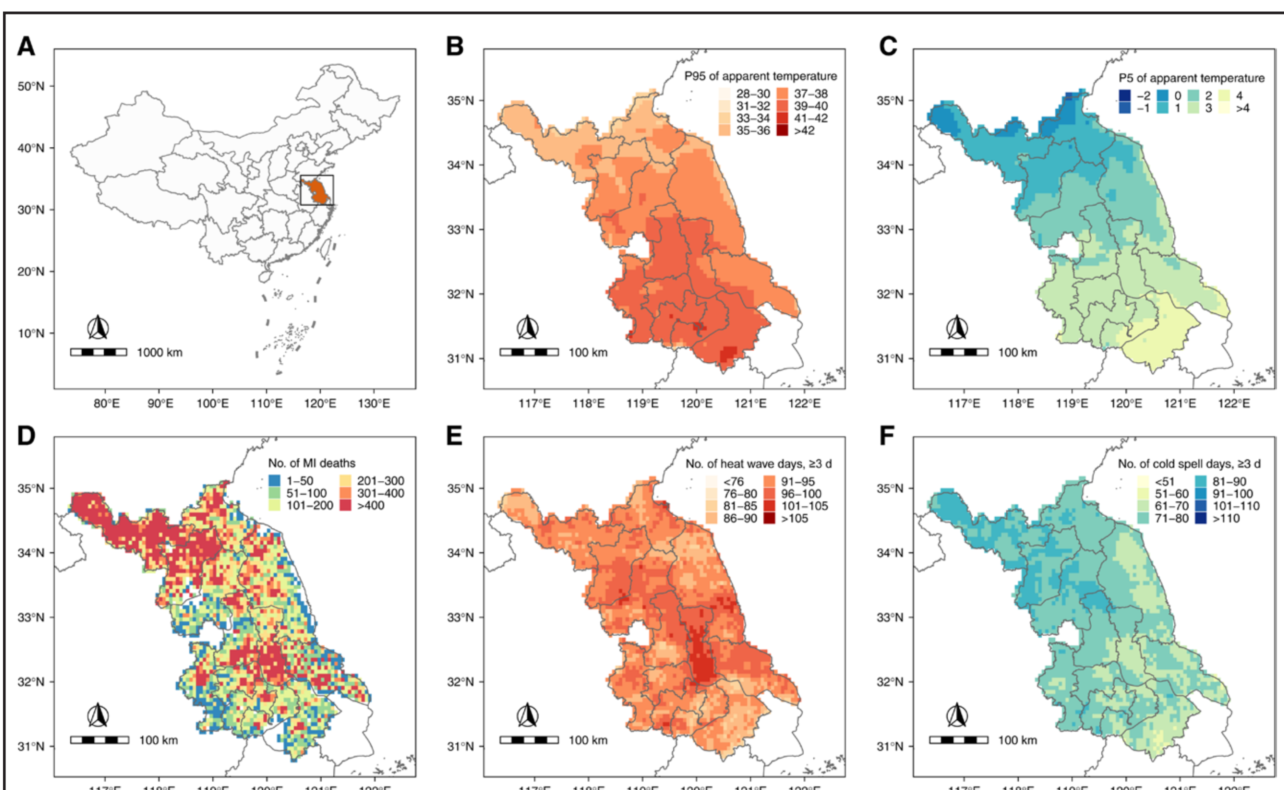

Figure 1. Location of Jiangsu province in China, spatial distribution of the study population, temperature thresholds, and number of extreme temperature event days in Jiangsu province, China, from 2015 to 2020.
Location of Jiangsu province in China (**A**) and spatial distribution of temperature thresholds of the 95th percentile (**B**), temperature thresholds of the 5th percentile (**C**), study population (**D**), number of heat wave days under the definition of P95_3d (**E**), and number of cold spell days under the definition of P5_3d (**F**). P95_3d represents a heat wave defined as daily apparent temperature (°C) equal to or higher than the 95th percentile of temperature for at least 3 consecutive days, whereas P5_3d represents a cold spell defined as daily apparent temperature lower than or equal to the 5th percentile of temperature for at least 3 consecutive days.

is presented in Table 2 and Figure 4D. Under the definition of P95/P5_3d, 6417 (3.2%) subjects died during heat wave days, 6331 (3.1%) subjects died during cold spell days, and most subjects (189 930, 93.7%) died during non-ETE days. Among these, 34.7% (2227) of MI deaths during heat wave days, 83.2% (5269) of MI deaths during cold spell days, and 64.4% (122 311) of MI deaths during non-ETE days were identified with high-level $PM_{2.5}$. Overall, the number of MI deaths during heat wave days decreased with higher temperature thresholds and longer durations, whereas the number of deaths during cold spell days decreased with lower temperature thresholds and longer durations.

Figure 2A shows the association between exposure to ETEs and MI mortality. We observed that exposure to heat wave and cold spell was significantly associated with an increased odds of MI morality. The OR of exposure to heat wave ranged from 1.18 (95% CI, 1.14–1.21) for the P90_2d definition to 1.74 (1.66–1.83) for the P97.5_4d definition, whereas the OR of exposure to cold spell ranged from 1.04 (1.02–1.06) for the P10_2d definition to 1.12 (1.07–1.18) for the P2.5_3d definition (all $P<0.05$). Overall, the odds of MI mortality increased with a higher temperature threshold and longer duration for heat wave, and with a lower temperature threshold and longer duration for cold spell (Table S5).

The association between lag 01-day exposure to ambient $PM_{2.5}$ and MI mortality is presented in Figure 2B. With adjustment for heat wave with the definition of P95_3d and cold spell with the definition of P5_3d in the model, the exposure-response curve shows that the OR of MI mortality increased monotonically with increasing $PM_{2.5}$ exposures but attenuated after an estimated breakpoint of 39.5 μg/m³ ($P_{nonlinearity}<0.05$). Similar trends and breakpoints of the exposure-response curves of associations between $PM_{2.5}$ and MI mortality were observed with adjustment for ETEs with other definitions in the model.

The additive interactive effects of exposure to ETEs and $PM_{2.5}$ on MI mortality are shown in Figure 3, Table S6, and Table 3. Under the P95_3d definition, the OR_{10}, OR_{01}, and OR_{11} of MI mortality was 1.19 (95% CI, 1.14–1.23), 1.02 (1.004–1.03), and 1.72 (1.54–1.93), respectively; the REOI, AP, and S was 0.52 (95% CI, 0.42–0.62), 0.30 (0.26–0.35), and 3.57 (2.77–4.60), respectively, indicating significant synergistic effects of exposure to heat wave and $PM_{2.5}$ on MI mortality. Similar significant synergistic effects were observed under different heat wave definitions (indicated by REOI >0, AP >0, and S >1; all $P<0.05$), which, in general, increased with more stringent temperature thresholds and prolonged durations of heat wave. No significant synergistic effect was observed for exposure to cold spell and $PM_{2.5}$.

The excess mortality due to exposure to ETEs and high-level $PM_{2.5}$ are presented in Figure 4A through 4C and Tables S7 to S8. The excess fraction under different ETE definitions ranged from 1.8% to 2.8%, corresponding to 3699 to 5668 excess deaths, respectively. Under the definition of P95/P5_3d, the estimated excess fraction was 2.1%, corresponding to 4186 MI deaths; among them, 15.7% (excess fraction, 0.3%; number of excess deaths, 656), 2.6% (0.05%, 108), 49.7% (1.0%, 2079), 22.3% (0.5%, 935), and 9.7% (0.2%, 408) were attributable to exposure to heat wave and low-level $PM_{2.5}$, cold spell and low-level $PM_{2.5}$, non-ETEs and high-level $PM_{2.5}$, heat wave and high-level $PM_{2.5}$, and cold spell and high-level $PM_{2.5}$, respectively. Overall, the excess mortality decreased with a higher temperature threshold and longer duration for heat wave, and with a lower temperature threshold and longer duration for cold spell.

Table 2. Number of Myocardial Infarction Deaths During Extreme Temperature Event Days in Jiangsu Province, China, From 2015 to 2020

	No. of myocardial infarction deaths (%)		
Definition*	Overall	With high-level fine particulate matter	With low-level fine particulate matter
Heat wave			
P90_2d	15 198	3606 (23.7)	11 592 (76.3)
P90_3d	13 284	3047 (22.9)	10 237 (77.1)
P90_4d	11 949	2811 (23.5)	9138 (76.5)
P92.5_2d	11 699	2911 (24.9)	8788 (75.1)
P92.5_3d	10 055	2659 (26.4)	7396 (73.6)
P92.5_4d	8728	2485 (28.5)	6243 (71.5)
P95_2d	7919	2450 (30.9)	5469 (69.1)
P95_3d	6417	2227 (34.7)	4190 (65.3)
P95_4d	5274	2009 (38.1)	3265 (61.9)
P97.5_2d	4229	1899 (44.9)	2330 (55.1)
P97.5_3d	3405	1732 (50.9)	1673 (49.1)
P97.5_4d	2811	1557 (55.4)	1254 (44.6)
Cold spell			
P10_2d	19 192	15 960 (83.2)	3232 (16.8)
P10_3d	13 956	12 121 (86.9)	1835 (13.1)
P10_4d	10 343	9387 (90.8)	956 (9.2)
P7.5_2d	14 175	11 574 (81.7)	2601 (18.3)
P7.5_3d	9863	8473 (85.9)	1390 (14.1)
P7.5_4d	7073	6301 (89.1)	772 (10.9)
P5_2d	9319	7334 (78.7)	1985 (21.3)
P5_3d	6331	5269 (83.2)	1062 (16.8)
P5_4d	4460	3838 (86.1)	622 (13.9)
P2.5_2d	4249	3052 (71.8)	1197 (28.2)
P2.5_3d	2597	1969 (75.8)	628 (24.2)
P2.5_4d	1531	1242 (81.1)	289 (18.9)

*For example, P95_3d represents a heat wave defined as daily apparent temperature equal to or higher than the 95th percentile of temperature for at least 3 consecutive days, whereas P5_3d represents a cold spell defined as daily apparent temperature lower than or equal to the 5th percentile of temperature for at least 3 consecutive days.

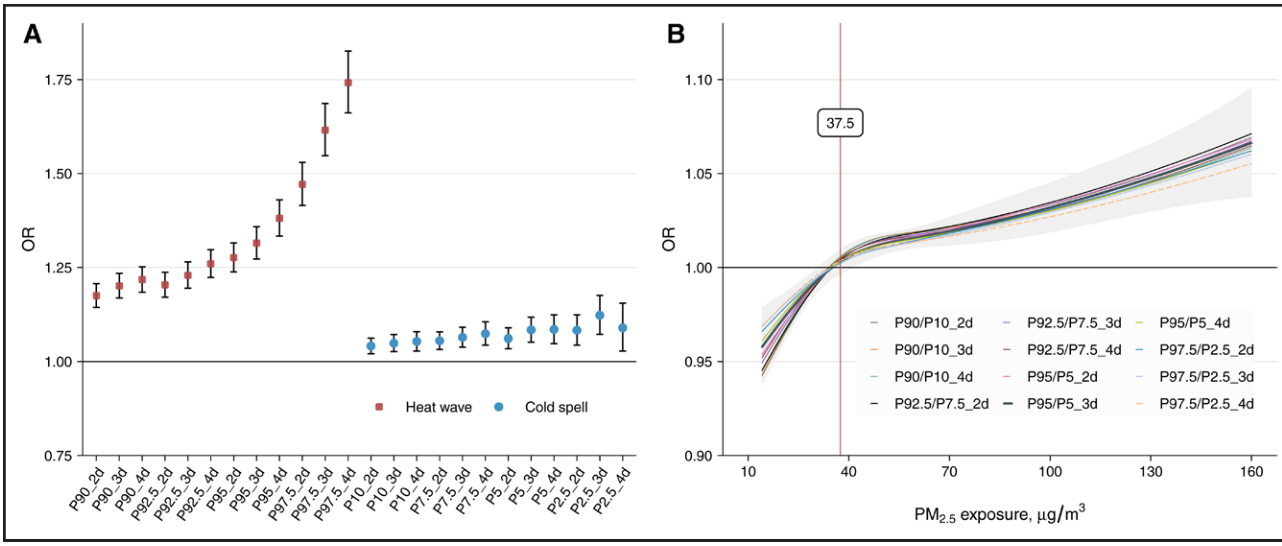

Figure 2. Association of exposure to extreme temperature events and $PM_{2.5}$ with myocardial infarction mortality.
A, OR (95% CI) of myocardial infarction mortality associated with exposure to extreme temperature events. The horizontal black line represents the OR of 1. **B**, Exposure-response curves of the association between lag 01-day exposure to ambient $PM_{2.5}$ and myocardial infarction mortality. The solid dark blue line with shaded region represents the OR of myocardial infarction mortality associated with exposure to $PM_{2.5}$ with adjustment for extreme temperature events defined as daily apparent temperature equal to or higher than the 95th percentile temperature (P95_3d) or equal to or lower than the 5th percentile of temperature (P5_3d) for at least 3 consecutive days and the corresponding 95% CI, respectively. The horizontal black line represents the OR of 1, whereas the vertical red line refers to the cutoff value of high-level $PM_{2.5}$ (>37.5 µg/m³). OR indicates odds ratio; and $PM_{2.5}$, fine particulate matter.

In stratified analyses, we observed that the independent effects of exposure to heat wave on MI mortality were significantly higher in women than that in men, whereas the independent effects of exposure to ETEs and $PM_{2.5}$ were significantly higher in adults >80 years than that in adults ≤80 years ($P_{difference}$<0.05; Table 4). No significant difference in independent effects of exposure to ETEs or $PM_{2.5}$ on MI mortality was detected across SES (all $P_{difference}$>0.05; Table 4). For interactive effects of exposure to ETEs and $PM_{2.5}$ on MI mortality, we did not observe any significant difference in the synergistic effects across sex, age, or SES (all $P_{difference}$>0.05; Table 4).

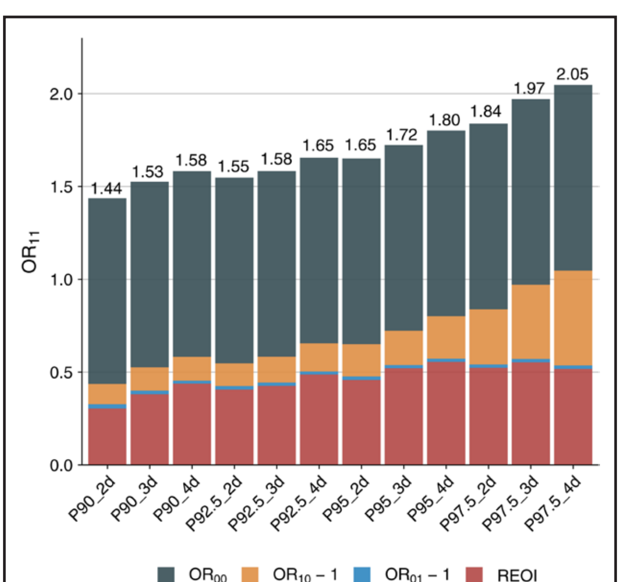

Figure 3. OR of myocardial infarction mortality associated with exposure to heat wave and $PM_{2.5}$.
OR_{00}, OR_{10}, OR_{01}, and OR_{11} represent the OR of myocardial infarction mortality due to exposure to non-extreme temperature events and low-level $PM_{2.5}$, heat wave and low-level $PM_{2.5}$, non-heat wave and high-level $PM_{2.5}$, and heat wave and high-level $PM_{2.5}$, respectively. For example, P95_3d represents a heat wave defined as daily apparent temperature equal to or higher than the 95th percentile of temperature for at least 3 consecutive days. OR indicates odds ratio; $PM_{2.5}$, fine particulate matter; and REOI, relative excess odds due to interaction.

Sensitivity analyses by adjusting for each of the gaseous pollutants in the models (Tables S9 to S13), using air temperature to define ETEs (Table S14), classifying $PM_{2.5}$ with the median value of 45.9 µg/m³ (Table S15), and using lag 0-day, lag 02-day, and lag 03-day exposure as the exposure metric for $PM_{2.5}$ (Tables S16, S18, and S19) gave similar results, whereas the association between $PM_{2.5}$ exposure and MI mortality became slightly weaker when using lag 1-day as the exposure metric (Table S17). The Akaike information criterion value of the association for exposure to $PM_{2.5}$ with different lag periods was minimal for lag 01-day (Table S20). Restricting the analysis to MI deaths determined by classes I, II, or III diagnostic basis showed similar estimates for the independent and interactive effects of exposure to ETEs and $PM_{2.5}$ on MI mortality (Tables S21 and S22).

DISCUSSION

In this population-based case-crossover study of >0.2 million MI deaths in Jiangsu province, China, from 2015 to 2020, we comprehensively investigated the association of exposure to ETEs and ambient $PM_{2.5}$ with

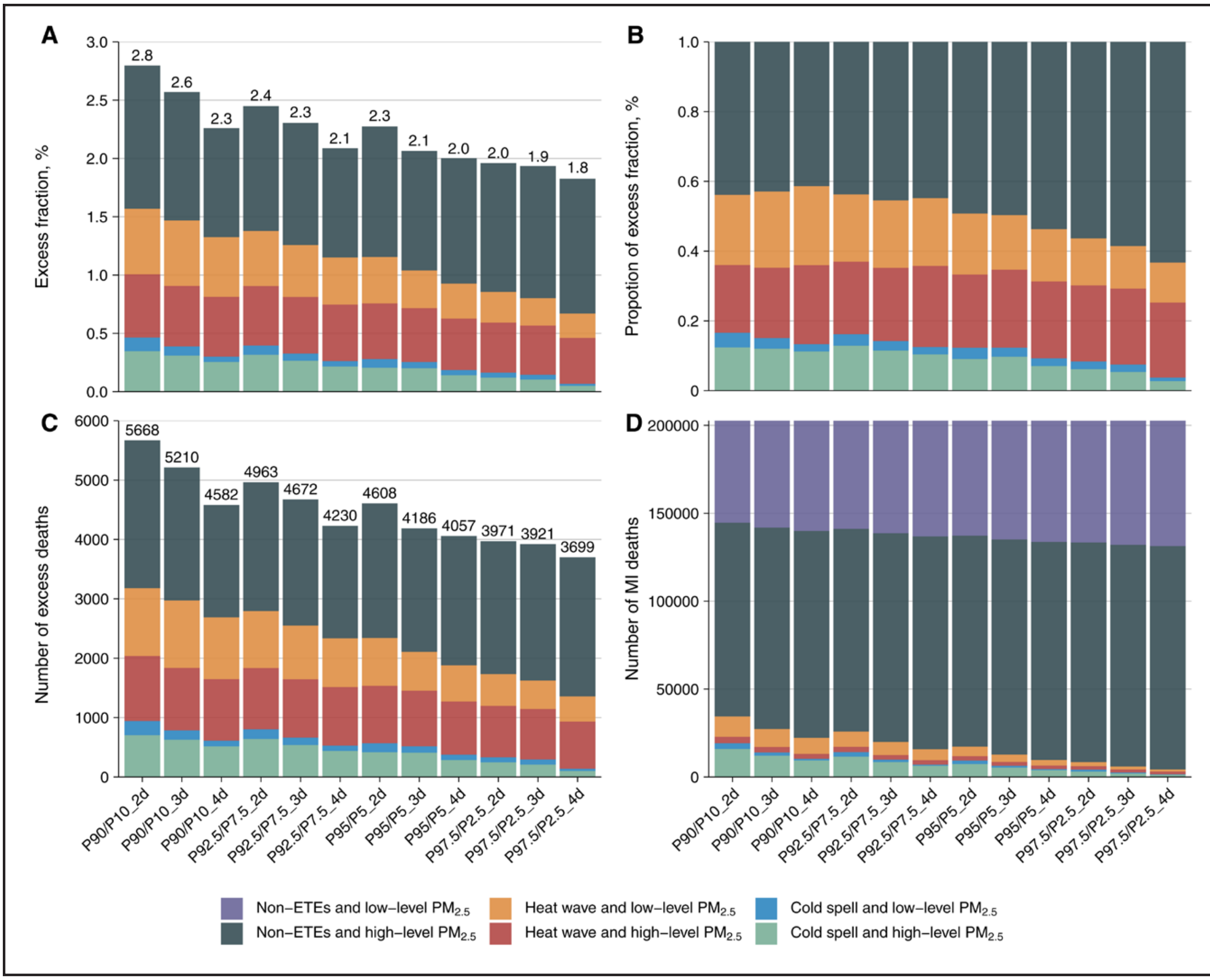

Figure 4. Excess fraction and number of excess deaths due to exposure to ETEs and $PM_{2.5}$, and distribution of MI deaths under different exposure levels.

A, Excess fraction of MI deaths due to exposure to ETEs and high-level $PM_{2.5}$. **B**, Proportion of excess fraction. **C**, Number of excess deaths due to exposure to ETEs and high-level $PM_{2.5}$. **D**, Distribution of MI deaths under different exposure levels. For example, P95/P5_3d represents a heat wave defined as daily apparent temperature equal to or higher than the 95th percentile of temperature for at least 3 consecutive days and a cold spell defined as daily apparent temperature lower than or equal to the 5th percentile of temperature for at least 3 consecutive days. ETE indicates extreme temperature event; MI, myocardial infarction; and $PM_{2.5}$, fine particulate matter.

MI mortality and quantified their interactive effects. We found that exposure to heat wave, cold spell, and $PM_{2.5}$ was significantly associated with an increased odds of MI mortality, and heat wave can interact synergistically with $PM_{2.5}$ to trigger MI deaths. The independent effects of ETEs and interactive effects of heat wave and $PM_{2.5}$ on MI mortality increased with greater intensities and longer durations of ETEs. We estimated that exposure to ETEs and high-level $PM_{2.5}$ was responsible for up to 2.8% of MI deaths. Women were more vulnerable to heat wave, whereas older adults were more vulnerable to heat wave, cold spell, and $PM_{2.5}$. The interactive effects of ETEs and $PM_{2.5}$ on MI mortality did not vary across sex, age, or SES.

There were limited studies examining the association of exposure to heat wave or cold spell with MI mortality, and the results were inconsistent.[12–16] A case-crossover study in Beijing and 2 case-crossover studies in Jinan, China, reported that exposure to heat wave was significantly associated with an increased odds of MI mortality (OR in Beijing, 2.857; ORs in Jinan, 1.60 and 1.38)[13–15]; in contrast, a time-series study in Shanghai, China, did not observe any significant association between heat wave and daily MI deaths.[12] For cold spell, only 1 case-crossover study in Beijing, China, investigated its association with MI mortality and found that cold spell was significantly associated with a 67.9% increase in odds of MI mortality.[16] Except for the null association for heat wave in the Shanghai study,[12] the other 4 studies reported positive associations between ETEs and MI mortality, with effect estimates close to or higher than ours. Possible reasons for the inconsistent estimates may be heterogeneities in the characteristics of subjects, exposure pattern, and exposure assessment (eg, definition of

ORIGINAL RESEARCH ARTICLE

Table 3. Additive Interactive Effects of Exposure to Extreme Temperature Events and $PM_{2.5}$ on Myocardial Infarction Mortality

Definition*	Additive interaction		
	REOI (95% CI)	AP (95% CI)	S (95% CI)
Heat wave			
P90_2d	0.30 (0.24 to 0.37)	0.21 (0.17 to 0.25)	3.29 (2.49 to 4.34)
P90_3d	0.38 (0.31 to 0.45)	0.25 (0.21 to 0.29)	3.61 (2.78 to 4.70)
P90_4d	0.44 (0.36 to 0.51)	0.28 (0.24 to 0.31)	4.02 (3.07 to 5.26)
P92.5_2d	0.41 (0.33 to 0.48)	0.26 (0.22 to 0.30)	3.85 (2.93 to 5.07)
P92.5_3d	0.43 (0.35 to 0.51)	0.27 (0.23 to 0.31)	3.69 (2.84 to 4.80)
P92.5_4d	0.49 (0.40 to 0.57)	0.29 (0.25 to 0.33)	3.92 (3.02 to 5.10)
P95_2d	0.46 (0.37 to 0.55)	0.28 (0.24 to 0.32)	3.37 (2.64 to 4.30)
P95_3d	0.52 (0.42 to 0.62)	0.30 (0.26 to 0.35)	3.57 (2.77 to 4.60)
P95_4d	0.55 (0.45 to 0.66)	0.31 (0.26 to 0.35)	3.25 (2.55 to 4.14)
P97.5_2d	0.52 (0.40 to 0.64)	0.28 (0.23 to 0.34)	2.66 (2.10 to 3.36)
P97.5_3d	0.55 (0.41 to 0.69)	0.28 (0.22 to 0.34)	2.32 (1.85 to 2.91)
P97.5_4d	0.52 (0.35 to 0.68)	0.25 (0.18 to 0.32)	1.98 (1.58 to 2.48)
Cold spell			
P10_2d	−0.06 (−0.11 to −0.01)	−0.06 (−0.10 to −0.01)	0.45 (0.25 to 0.81)
P10_3d	−0.06 (−0.12 to 0.003)	−0.06 (−0.12 to 0.003)	0.48 (0.25 to 0.91)
P10_4d	−0.07 (−0.16 to 0.01)	−0.07 (−0.15 to 0.01)	0.45 (0.21 to 0.96)
P7.5_2d	−0.03 (−0.08 to 0.03)	−0.03 (−0.08 to 0.02)	0.67 (0.35 to 1.31)
P7.5_3d	−0.05 (−0.13 to 0.02)	−0.05 (−0.12 to 0.02)	0.56 (0.28 to 1.09)
P7.5_4d	−0.08 (−0.18 to 0.02)	−0.08 (−0.17 to 0.02)	0.48 (0.23 to 0.99)
P5_2d	−0.04 (−0.11 to 0.02)	−0.04 (−0.10 to 0.02)	0.59 (0.29 to 1.20)
P5_3d	−0.05 (−0.13 to 0.04)	−0.05 (−0.12 to 0.03)	0.63 (0.31 to 1.28)
P5_4d	−0.11 (−0.23 to 0.004)	−0.11 (−0.21 to 0.003)	0.42 (0.20 to 0.87)
P2.5_2d	−0.01 (−0.10 to 0.07)	−0.01 (−0.09 to 0.07)	0.88 (0.37 to 2.23)
P2.5_3d	−0.06 (−0.18 to 0.06)	−0.05 (−0.16 to 0.06)	0.68 (0.32 to 1.45)
P2.5_4d	−0.09 (−0.26 to 0.08)	−0.08 (−0.24 to 0.08)	0.51 (0.16 to 1.65)

AP indicates proportion attributable to interaction; $PM_{2.5}$, fine particulate matter; REOI, relative excess odds due to interaction; and S, synergy index.

*For example, P95_3d represents a heat wave defined as daily apparent temperature equal to or higher than the 95th percentile of temperature for at least 3 consecutive days, whereas P5_3d represents a cold spell defined as daily apparent temperature lower than or equal to the 5th percentile of temperature for at least 3 consecutive days.

ETEs, source of exposure data). In addition, it should be noted that all of these studies used a univariate indicator for heat wave or cold spell without considering the variation of temperature distributions and personal adaptive capacities in different climate zones and did not capture characteristics of ETEs under various intensities and durations. In comparison, our study applied a series of grid-specific relative temperature thresholds and durations to comprehensively characterize the exposure to ETEs. In addition to confirming the adverse effects of ETEs on MI mortality in a comprehensive manner, our results revealed that these adverse effects increased with greater intensities and longer durations of ETEs. Overall, our findings provide crucial information for public health policy that developing ETE early warning systems may be useful to help prevent premature deaths from MI and highlight that the intensity and duration of ETEs should be considered simultaneously to help provide comprehensive warning services.

As the climate crisis progresses, the co-occurrence of ETEs and $PM_{2.5}$ pollution continues to be more frequent in recent years. Although research interests in the interactive effects of extreme temperatures and $PM_{2.5}$ on cardiovascular mortality are increasing,[20] the possible synergistic effects of ETEs and $PM_{2.5}$ on MI mortality are yet to be evaluated. To our knowledge, this is the first study to systematically investigate the interactive effects of ETEs and $PM_{2.5}$ on MI mortality under various intensities and durations of ETEs. Our study provides novel evidence that heat wave and $PM_{2.5}$ can interact synergistically to trigger MI deaths, and these interactive effects increase with greater intensities and longer durations of heat wave, highlighting the importance and potential benefits of mitigating co-exposure to heat wave and $PM_{2.5}$. In addition, we estimated that reducing exposure to ETEs and high-level $PM_{2.5}$ would avoid up to 2.8% of MI deaths. Therefore, mitigating $PM_{2.5}$ exposure when providing ETE warning services, particularly for heat wave, can bring great public health cobenefits.

Previous studies have reported that exposure to extremely high temperatures can accelerate the thermoregulatory progress (eg, increasing sweating and skin blood flow), induce water loss and dehydration, as well, and increase cardiac output.[41] When the thermoregulatory system fails, the core body temperature will rise, which may lead to a series of responses, including systemic inflammation, oxidative stress, endothelial dysfunction, and direct cytotoxic effects, and potentially trigger myocardial ischemia.[42] In addition, it has been reported that exposure to extremely low temperatures can activate the sympathetic nervous system and the renin-angiotensin system, induce multiple physiological changes (eg, blood vessels contracting and blood pressure elevation), and finally provoke cardiovascular impairments.[43] Moreover, our study suggests significant synergistic interactions of heat wave and $PM_{2.5}$ on MI mortality. It is biologically plausible that high temperatures may accelerate the uptake of $PM_{2.5}$ by sweating, elevating skin blood flow, and minute ventilation.[44] In addition, the common biological pathways of heat wave and $PM_{2.5}$ exposures, including increased systemic inflammation and oxidative stress, can make synergistic health effects plausible.[42,45] Nonetheless, the exact mechanisms underlying the independent effects of ETEs and the interactive effects of heat wave and $PM_{2.5}$ on MI mortality need to be clarified in future investigations.

Our stratified analyses suggest that the associations between ETEs and MI mortality were stronger in women and older adults. From a physiological point of view, women appear to have poor thermoregulation, lower sweating capacity, and greater airway reactivity

Table 4. OR and REOI of Exposure to Extreme Temperature Events and Fine Particulate Matter on Myocardial Infarction Mortality by Sex, Age, and Socioeconomic Status

	Sex		Age		Socioeconomic status	
Definition*	Male	Female	≤80 y	>80 y	Low	High
OR						
Heat wave						
P95_2d	1.22 (1.17 to 1.28)	1.35 (1.29 to 1.41)†	1.17 (1.12 to 1.22)	1.39 (1.34 to 1.45)†	1.29 (1.24 to 1.34)	1.27 (1.20 to 1.33)
P95_3d	1.22 (1.17 to 1.28)	1.43 (1.36 to 1.50)†	1.18 (1.13 to 1.24)	1.46 (1.40 to 1.53)†	1.33 (1.28 to 1.39)	1.29 (1.22 to 1.36)
P95_4d	1.27 (1.21 to 1.33)	1.51 (1.44 to 1.59)†	1.23 (1.17 to 1.30)	1.54 (1.47 to 1.61)†	1.39 (1.33 to 1.45)	1.38 (1.30 to 1.46)
Cold spell						
P5_2d	1.05 (1.02 to 1.09)	1.05 (1.01 to 1.09)	1.04 (0.999 to 1.08)	1.06 (1.03 to 1.10)	1.04 (1.01 to 1.07)	1.07 (1.03 to 1.12)
P5_3d	1.08 (1.04 to 1.13)	1.07 (1.02 to 1.11)	1.05 (1.002 to 1.10)	1.10 (1.05 to 1.14)	1.07 (1.03 to 1.11)	1.09 (1.03 to 1.15)
P5_4d	1.10 (1.04 to 1.15)	1.06 (1.01 to 1.11)	1.03 (0.98 to 1.09)	1.11 (1.06 to 1.16)†	1.06 (1.02 to 1.11)	1.11 (1.05 to 1.18)
$PM_{2.5}$	1.03 (1.01 to 1.04)	1.04 (1.02 to 1.06)	1.02 (0.998 to 1.04)	1.05 (1.03 to 1.07)†	1.03 (1.02 to 1.05)	1.03 (1.01 to 1.06)
REOI						
Heat wave						
P95_2d	0.31 (0.19 to 0.42)	0.62 (0.48 to 0.76)	0.36 (0.24 to 0.47)	0.56 (0.42 to 0.69)	0.40 (0.29 to 0.50)	0.57 (0.42 to 0.73)
P95_3d	0.38 (0.26 to 0.51)	0.67 (0.51 to 0.82)	0.42 (0.29 to 0.55)	0.62 (0.47 to 0.77)	0.47 (0.34 to 0.59)	0.62 (0.45 to 0.78)
P95_4d	0.38 (0.24 to 0.52)	0.74 (0.57 to 0.91)	0.47 (0.33 to 0.61)	0.63 (0.47 to 0.80)	0.49 (0.36 to 0.63)	0.66 (0.47 to 0.84)
Cold spell						
P5_2d	−0.04 (−0.13 to 0.05)	−0.04 (−0.13 to 0.05)	−0.05 (−0.14 to 0.04)	−0.04 (−0.13 to 0.05)	−0.09 (−0.17 to −0.003)	0.03 (−0.07 to 0.13)
P5_3d	−0.05 (−0.17 to 0.07)	−0.05 (−0.17 to 0.07)	0.002 (−0.12 to 0.12)	−0.10 (−0.22 to 0.02)	−0.12 (−0.24 to 0.01)	0.04 (−0.09 to 0.16)
P5_4d	−0.13 (−0.29 to 0.04)	−0.10 (−0.26 to 0.07)	−0.01 (−0.17 to 0.15)	−0.21 (−0.38 to −0.04)	−0.21 (−0.38 to −0.04)	0.002 (−0.16 to 0.16)

OR indicates odds ratio; $PM_{2.5}$, fine particulate matter; and REOI, relative excess odds due to interaction.

*For example, P95_3d represents a heat wave defined as daily apparent temperature equal to or higher than the 95th percentile of temperature for at least 3 consecutive days, whereas P5_3d represents a cold spell defined as daily apparent temperature lower than or equal to the 5th percentile of temperature for at least 3 consecutive days.

†$P_{difference}$<0.05, estimated using the 2-sample *z* test.

than men that can weaken their adaptive capacities for extreme environmental factors.[46,47] These biological characteristics may also be a part of underlying reasons for their reasonably higher vulnerability when simultaneously exposed to $PM_{2.5}$, although the difference in the interactive effects did not reach statistical significance. In addition, it is known that older adults tend to have degradation of physiological processes that occurs as an individual ages, which can lead to a higher rate of preexisting conditions and therefore increase the risks of MI events when exposed to extreme temperatures.[48]

Our study has several strengths. First, this case-crossover study of >0.2 million MI deaths was designed on the basis of a population of 85.1 million in Jiangsu province from 2015 to 2020. The large sample size enabled us to systematically investigate the association of exposure to ETEs and $PM_{2.5}$ with MI mortality and quantify their interactive effects with a sufficient statistical power. Second, we performed individual-level exposure assessments by extracting ETE information from a series of relatively high spatial resolution grid datasets. Multiple grid-specific ETE definitions allowed us to account for the variation of exposure and adaptation to ambient temperatures in different regions on exposure assessments and to comprehensively explore the associations of ETEs with MI mortality under different intensities and durations. Furthermore, we used apparent temperature as an indicator of human perceived temperature to define ETEs, which combines multiple meteorological conditions (including air temperature and relative humidity) and has been proposed as a reasonably comprehensive weather metric to better characterize ETE exposures.[49] In comparison with using air temperature as a single indicator to define ETEs, the application of apparent temperature can help provide more accurate exposure assessments. Third, the time-stratified case-crossover design provided us with unique opportunities to control time-invariant personal confounding factors (eg, age, sex, SES, lifestyle, or chronic comorbidities), long-term time trend, and seasonality in the analysis.

Some limitations in our study should also be discussed. First, as in most previous studies, we used ambient meteorological data (the spatial resolution was relatively coarse) and air pollution data from grid datasets rather than individual direct measurements, and we were unable to account for personal adaptive behaviors (eg, the use of an air conditioner, staying indoors in extreme temperature days) due to lack of data, which might introduce certain inevitable exposure misclassifications. In addition, because we did not have data on the specific time and exact location at MI onset or death for each subject, misclassifications were also possible in assessing the exposure to both ETEs and $PM_{2.5}$ on the date of death on the basis of each subject's residential address. Note that these exposure misclassifications tended to be nondifferential and can lead to an underestimation of associations.[50] Second, because ETE definitions used in this study were directly relevant to personal exposure characteristics and adaption capacities, researchers should be cautious when generalizing our results to other regions or populations. Third, although we used the time-stratified case-crossover design to control for some time-variant confounders, certain unmeasured confounders (eg, medication use) were possible and might introduce inaccurate risk estimates. Last, although strict quality control measurements were implemented to determine the causes of death, there may still be potential misclassifications on the identified MI deaths in this study with a large sample size. However, our sensitivity analyses, restricting to MI deaths determined using more reliable diagnostic basis, demonstrated that the findings were robust.

In conclusion, we found that exposure to heat wave, cold spell, and ambient $PM_{2.5}$ was significantly associated with an increased odds of MI mortality especially among women and older adults, and that heat wave could interact synergistically with $PM_{2.5}$ to trigger MI deaths. The independent effects of ETEs and interactive effects of heat wave and $PM_{2.5}$ on MI mortality increased with greater intensities and longer durations of ETEs. Our findings provide crucial evidence that mitigating exposure to ETEs and $PM_{2.5}$ may be useful to prevent premature deaths from MI and highlight great public health significance to take particulate pollution into consideration when providing ETE warning services to the public.

ARTICLE INFORMATION

Received December 3, 2022; accepted May 8, 2023.

Affiliations

Department of Epidemiology, School of Public Health, Sun Yat-sen University, Guangzhou, Guangdong, China (R.X., T.L., Y. Li, Y.Z., Y. Liu). Department of Environment and Health, Shenzhen Center for Disease Control and Prevention, Shenzhen, Guangdong, China (S.H.). Meteorological Data Laboratory, National Meteorological Information Center, Beijing, China (C.S.). Luohu District Chronic Disease Hospital, Shenzhen, Guangdong, China (R.W.). Central Laboratory of Shenzhen Center for Disease Control and Prevention, Shenzhen, Guangdong, China (Z.L.). Department of Atmospheric and Oceanic Science, Earth System Science Interdisciplinary Center, University of Maryland, College Park (J.W.). Institute of Environment and Health, Jiangsu Provincial Center for Disease Control and Prevention, Nanjing, Jiangsu, China (H.S.).

Sources of Funding

This work was supported by the National Science and Technology Major Project (grant number: 2022YFC3700105).

Disclosures

None.

Supplemental Material

Tables S1–S22
Figures S1–S5

REFERENCES

1. Pörtner H, Roberts DC, Tignor M, Poloczanska E, Mintenbeck K, Alegría A, Craig M, Langsdorf S, Löschke S, Möller V, et al, eds. *IPCC 2022: Climate Change 2022: Impacts, Adaptation, and Vulnerability.* Cambridge: Cambridge University Press; 2022. doi:10.1017/9781009325844
2. Bergquist M, Nilsson A, Schultz PW. Experiencing a severe weather event increases concern about climate change. *Front Psychol.* 2019;10:220. doi: 10.3389/fpsyg.2019.00220
3. Liu J, Varghese BM, Hansen A, Zhang Y, Driscoll T, Morgan G, Dear K, Gourley M, Capon A, Bi P. Heat exposure and cardiovascular health outcomes: a systematic review and meta-analysis. *Lancet Planet Health.* 2022;6:e484–e495. doi: 10.1016/S2542-5196(22)00117-6
4. Ryti NR, Guo Y, Jaakkola JJ. Global association of cold spells and adverse health effects: a systematic review and meta-analysis. *Environ Health Perspect.* 2016;124:12–22. doi: 10.1289/ehp.1408104
5. Cicci KR, Maltby A, Clemens KK, Vicedo-Cabrera AM, Gunz AC, Lavigne E, Wilk P. High temperatures and cardiovascular-related morbidity: a scoping review. *Int J Environ Res Public Health.* 2022;19:11243. doi: 10.3390/ijerph191811243
6. Vaičiulis V, Jaakkola JJK, Radišauskas R, Tamošiūnas A, Lukšienė D, Ryti NRI. Association between winter cold spells and acute myocardial infarction in Lithuania 2000–2015. *Sci Rep.* 2021;11:17062. doi: 10.1038/s41598-021-96366-9
7. García-Lledó A, Rodríguez-Martín S, Tobías A, Alonso-Martín J, Ansede-Cascudo JC, de Abajo FJ. Heat waves, ambient temperature, and risk of myocardial infarction: an ecological study in the community of Madrid. *Rev Esp Cardiol.* 2020;73:300–306. doi: 10.1016/j.rec.2019.05.016
8. Sohail H, Kollanus V, Tiittanen P, Schneider A, Lanki T. Heat, heatwaves and cardiorespiratory hospital admissions in Helsinki, Finland. *Int J Environ Res Public Health.* 2020;17:7892. doi: 10.3390/ijerph17217892
9. Xu R, Shi C, Wei J, Lu W, Li Y, Liu T, Wang Y, Zhou Y, Chen G, Sun H, et al. Cause-specific cardiovascular disease mortality attributable to ambient temperature: a time-stratified case-crossover study in Jiangsu province, China. *Ecotoxicol Environ Saf.* 2022;236:113498. doi: 10.1016/j.ecoenv.2022.113498
10. Ban J, Xu D, He MZ, Sun Q, Chen C, Wang W, Zhu P, Li T. The effect of high temperature on cause-specific mortality: a multi-county analysis in China. *Environ Int.* 2017;106:19–26. doi: 10.1016/j.envint.2017.05.019
11. Basu R. High ambient temperature and mortality: a review of epidemiologic studies from 2001 to 2008. *Environ Health.* 2009;8:40. doi: 10.1186/1476-069X-8-40
12. Xu D, Ban J, Chen C, Zhang Y, Wang W, Li T. Effects of heat waves on risk of non-accidental mortality during 2013 to 2015 in Shanghai. *J Environ Health.* 2017;34:991–995. doi: 10.16241/j.cnki.1001-5914.2017.11.012
13. Zhang J, Liu L, Chai F. A case-crossover study on the association between heat waves and daily deaths caused by acute myocardial infarction. *Zhonghua Liu Xing Bing Xue Za Zhi.* 2012;33:710–716. doi: 10.3760/cmaj.issn.0254-6450.2012.07.015
14. Zhang J, Liu S, Zhou L, Yang L, Han J, Zhang Y, Zhang J. An ecological study on impact of heat waves on non-accidental and cause-specific deaths in Ji'nan, China. *J Environ Health.* 2015;32:813–815. doi: 10.16241/j.cnki.1001-5914.2015.09.016
15. Zhang X, Zhou M, Huang J, Lin H, Liu Q. Impact of heat wave on non-accidental mortality of local residents in Jinan. *South China J Prev Med.* 2014;40:327–332. doi: 10.13217/j.scjpm.2014.0327
16. Zhong K, Liu L, Zhang J. Impact of cold wave on mortality of cerebra-cardiovascular diseases in Beijing: a case-crossover study. *J Environ Health.* 2010;27:100–105. doi: 10.16241/j.cnki.1001-5914.2010.02.011

17. Chen J, Yang J, Zhou M, Yin P, Wang B, Liu J, Chen Z, Song X, Ou CQ, Liu Q. Cold spell and mortality in 31 Chinese capital cities: definitions, vulnerability and implications. *Environ Int*. 2019;128:271–278. doi: 10.1016/j.envint.2019.04.049
18. Guo Y, Gasparrini A, Armstrong BG, Tawatsupa B, Tobias A, Lavigne E, Coelho M, Pan X, Kim H, Hashizume M, et al. Heat wave and mortality: a multicountry, multicommunity study. *Environ Health Perspect*. 2017;125:087006. doi: 10.1289/ehp1026
19. Liu C, Chen R, Sera F, Vicedo-Cabrera AM, Guo Y, Tong S, Coelho M, Saldiva PHN, Lavigne E, Matus P, et al. Ambient particulate air pollution and daily mortality in 652 cities. *N Engl J Med*. 2019;381:705–715. doi: 10.1056/NEJMoa1817364
20. Rahman MM, McConnell R, Schlaerth H, Ko J, Silva S, Lurmann FW, Palinkas L, Johnston J, Hurlburt M, Yin H, et al. The effects of coexposure to extremes of heat and particulate air pollution on mortality in California: implications for climate change. *Am J Respir Crit Care Med*. 2022;206:1117–1127. doi: 10.1164/rccm.202204-0657OC
21. Liu Y, Pan J, Fan C, Xu R, Wang Y, Xu C, Xie S, Zhang H, Cui X, Peng Z, et al. Short-term exposure to ambient air pollution and mortality from myocardial infarction. *J Am Coll Cardiol*. 2021;77:271–281. doi: 10.1016/j.jacc.2020.11.033
22. Rajagopalan S, Narula J. Guilt by emissions. *J Am Coll Cardiol*. 2021;77:282–284. doi: 10.1016/j.jacc.2020.11.032
23. Liu S, Wu X, Lopez AD, Wang L, Cai Y, Page A, Yin P, Liu Y, Li Y, Liu J, et al. An integrated national mortality surveillance system for death registration and mortality surveillance, China. *Bull World Health Organ*. 2016;94:46–57. doi: 10.2471/BLT.15.153148
24. Di Q, Dai L, Wang Y, Zanobetti A, Choirat C, Schwartz JD, Dominici F. Association of short-term exposure to air pollution with mortality in older adults. *JAMA*. 2017;318:2446–2456. doi: 10.1001/jama.2017.17923
25. Bateson TF, Schwartz J. Control for seasonal variation and time trend in case-crossover studies of acute effects of environmental exposures. *Epidemiology*. 1999;10:539–544.
26. Carracedo-Martínez E, Taracido M, Tobias A, Saez M, Figueiras A. Case-crossover analysis of air pollution health effects: a systematic review of methodology and application. *Environ Health Perspect*. 2010;118:1173–1182. doi: 10.1289/ehp.0901485
27. Liu J, Shi C, Sun S, Liang J, Yang ZL. Improving land surface hydrological simulations in China using CLDAS meteorological forcing data. *J Meteor Res*. 2019;33:1194–1206. doi: 10.1007/s13351-019-9067-0
28. Han S, Liu B, Shi C, Liu Y, Qiu M, Sun S. Evaluation of CLDAS and GLDAS datasets for near-surface air temperature over major land areas of China. *Sustainability*. 2020;12:4311. doi: 10.3390/su12104311
29. Tie R, Shi C, Wan G, Hu X, Kang L, Ge L. CLDASSD: reconstructing fine textures of the temperature field using super-resolution technology. *Adv Atmos Sci*. 2022;39:117–130. doi: 10.1007/s00376-021-0438-y
30. Robinson PJ. On the definition of a heat wave. *J Applied Meteor*. 2001;40:762–775. doi: 10.1175/1520-0450(2001)040<0762:Otdoah>2.0.Co;2
31. Wei J, Li Z, Lyapustin A, Sun L, Peng Y, Xue W, Su T, Cribb M. Reconstructing 1-km-resolution high-quality $PM_{2.5}$ data records from 2000 to 2018 in China: spatiotemporal variations and policy implications. *Remote Sens Environ*. 2021;252:112136. doi: 10.1016/j.rse.2020.112136
32. Wei J, Liu S, Li Z, Liu C, Qin K, Liu X, Pinker RT, Dickerson RR, Lin J, Boersma KF, et al. Ground-level NO_2 surveillance from space across China for high resolution using interpretable spatiotemporally weighted artificial intelligence. *Environ Sci Technol*. 2022;56:9988–9998. doi: 10.1021/acs.est.2c03834
33. Wei J, Li Z, Li K, Dickerson RR, Pinker RT, Wang J, Liu X, Sun L, Xue W, Cribb M. Full-coverage mapping and spatiotemporal variations of ground-level ozone (O_3) pollution from 2013 to 2020 across China. *Remote Sens Environ*. 2022;270:112775. doi: 10.1016/j.rse.2021.112775
34. Wei J, Li Z, Wang J, Li C, Gupta P, Cribb M. Ground-level gaseous pollutants (NO_2, SO_2, and CO) in China: daily seamless mapping and spatiotemporal variations. *Atmos Chem Phys*. 2023;23:1511–1532. doi: 10.5194/acp-23-1511-2023
35. Kan H. World Health Organization air quality guidelines 2021: implication for air pollution control and climate goal in China. *Chin Med J*. 2022;135:513–515. doi: 10.1097/cm9.0000000000002014
36. Rothman KJ. *Epidemiology: An Introduction*. New York: Oxford University Press; 2002.
37. Correia K, Williams PL. Estimating the relative excess risk due to interaction in clustered-data settings. *Am J Epidemiol*. 2018;187:2470–2480. doi: 10.1093/aje/kwy154
38. Knol MJ, VanderWeele TJ, Groenwold RH, Klungel OH, Rovers MM, Grobbee DE. Estimating measures of interaction on an additive scale for preventive exposures. *Eur J Epidemiol*. 2011;26:433–438. doi: 10.1007/s10654-011-9554-9
39. Knol MJ, VanderWeele TJ. Recommendations for presenting analyses of effect modification and interaction. *Int J Epidemiol*. 2012;41:514–520. doi: 10.1093/ije/dyr218
40. Altman DG, Bland JM. Interaction revisited: the difference between two estimates. *BMJ*. 2003;326:219. doi: 10.1136/bmj.326.7382.219
41. Liu C, Yavar Z, Sun Q. Cardiovascular response to thermoregulatory challenges. *Am J Physiol Heart Circ Physiol*. 2015;309:H1793–H1812. doi: 10.1152/ajpheart.00199.2015
42. Alahmad B, Khraishah H, Shakarchi AF, Albaghdadi M, Rajagopalan S, Koutrakis P, Jaffer FA. Cardiovascular mortality and exposure to heat in an inherently hot region: implications for climate change. *Circulation*. 2020;141:1271–1273. doi: 10.1161/CIRCULATIONAHA.119.044860
43. Sun Z. Cardiovascular responses to cold exposure. *Front Biosci*. 2010;2:495–503. doi: 10.2741/e108
44. Gordon CJ, Johnstone AF, Aydin C. Thermal stress and toxicity. *Compr Physiol*. 2014;4:995–1016. doi: 10.1002/cphy.c130046
45. Kelly FJ, Fussell JC. Linking ambient particulate matter pollution effects with oxidative biology and immune responses. *Ann N Y Acad Sci*. 2015;1340:84–94. doi: 10.1111/nyas.12720
46. Kim CS, Hu SC. Regional deposition of inhaled particles in human lungs: comparison between men and women. *J Appl Physiol*. 1998;84:1834–1844. doi: 10.1152/jappl.1998.84.6.1834
47. Marchand I, Johnson D, Montgomery D, Brisson GR, Perrault H. Gender differences in temperature and vascular characteristics during exercise recovery. *Can J Appl Physiol*. 2001;26:425–441. doi: 10.1139/h01-026
48. Shumake KL, Sacks JD, Lee JS, Johns DO. Susceptibility of older adults to health effects induced by ambient air pollutants regulated by the European Union and the United States. *Aging Clin Exp Res*. 2013;25:3–8. doi: 10.1007/s40520-013-0001-5
49. Zhang K, Li Y, Schwartz JD, O'Neill MS. What weather variables are important in predicting heat-related mortality? a new application of statistical learning methods. *Environ Res*. 2014;132:350–359. doi: 10.1016/j.envres.2014.04.004
50. Zeger SL, Thomas D, Dominici F, Samet JM, Schwartz J, Dockery D, Cohen A. Exposure measurement error in time-series studies of air pollution: concepts and consequences. *Environ Health Perspect*. 2000;108:419–426. doi: 10.1289/ehp.00108419