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# Short-Term Exposure to Ambient Air Pollution and Mortality From Myocardial Infarction

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## ABSTRACT

**BACKGROUND** Short-term exposure to ambient air pollution has been linked to occurrence of myocardial infarction (MI); however, only a limited number of studies investigated its association with death from MI, and the results remain inconsistent.

**OBJECTIVES** This study sought to investigate the association of short-term exposure to air pollution across a wide range of concentrations with MI mortality.

**METHODS** A time-stratified case-crossover study was conducted to investigate 151,608 MI death cases in Hubei province (China) from 2013 to 2018. Based on each case's home address, exposure to particulate matter with an aerodynamic diameter ≤2.5 μm ($PM_{2.5}$), particulate matter with an aerodynamic diameter ≤10 μm ($PM_{10}$), sulfur dioxide, nitrogen dioxide ($NO_2$), carbon monoxide, and ozone on each of the case and control days was assessed as the inverse distance-weighted average concentration at neighboring air quality monitoring stations. Conditional logistic regression models were implemented to quantify exposure-response associations.

**RESULTS** Exposure to $PM_{2.5}$, $PM_{10}$, and $NO_2$ (mean exposure on the same day of death and 1 day prior) was significantly associated with increased odds of MI mortality. The odds associated with $PM_{2.5}$ and $PM_{10}$ exposures increased steeply before a breakpoint ($PM_{2.5}$, 33.3 μg/m$^3$; $PM_{10}$, 57.3 μg/m$^3$) and flattened out at higher exposure levels, while the association for $NO_2$ exposure was almost linear. Each 10-μg/m$^3$ increase in exposure to $PM_{2.5}$ (<33.3 μg/m$^3$), $PM_{10}$ (<57.3 μg/m$^3$), and $NO_2$ was significantly associated with a 4.14% (95% confidence interval [CI]: 1.25% to 7.12%), 2.67% (95% CI: 0.80% to 4.57%), and 1.46% (95% CI: 0.76% to 2.17%) increase in odds of MI mortality, respectively. The association between $NO_2$ exposure and MI mortality was significantly stronger in older adults.

**CONCLUSIONS** Short-term exposure to $PM_{2.5}$, $PM_{10}$, and $NO_2$ was associated with increased risk of MI mortality. (J Am Coll Cardiol 2021;77:271–81) © 2021 by the American College of Cardiology Foundation.

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**ABBREVIATIONS AND ACRONYMS**

**CI** = confidence interval

**CO** = carbon monoxide

**ICD-10** = International Classification of Diseases-10th Revision

**IDW** = inverse distance weighting

**MI** = myocardial infarction

**$NO_2$** = nitrogen dioxide

**$O_3$** = ozone

**$PM_{2.5}$** = particulate matter with an aerodynamic diameter ≤2.5 μm

**$PM_{10}$** = particulate matter with an aerodynamic diameter ≤10 μm

**$SO_2$** = sulfur dioxide

Exposure to ambient air pollutants has been linked to increased cardiovascular morbidity and mortality, and continues to be a public health concern worldwide (1,2). Accumulating evidence suggests that short-term exposure to particulate matter with an aerodynamic diameter ≤2.5 μm ($PM_{2.5}$), particulate matter with an aerodynamic diameter ≤10 μm ($PM_{10}$), sulfur dioxide ($SO_2$), nitrogen dioxide ($NO_2$), carbon monoxide (CO), and ozone ($O_3$) contributes to the occurrence of myocardial infarction (MI) (3–6). Because MI is a leading cause of death that accounts for over 30% of all deaths from ischemic heart diseases (7), it is of great importance to understand whether air pollutant exposures also trigger deaths from MI.

To date, several studies have proposed potential biological mechanisms how air pollution contributes to the occurrence of MI including oxidative stress and inflammation (8–10); only a limited number of studies have explored the association of short-term exposure to $PM_{2.5}$ (11–19), $PM_{10}$ (15,20,21), $SO_2$ (11,15,20,22), $NO_2$ (11,15,22), CO (15,20), or $O_3$ (11,15,23) with MI mortality, and the results remain largely inconsistent and inconclusive. In 2012, Mustafic et al. (10) conducted a systematic review and meta-analysis, and concluded that short-term exposures to $PM_{2.5}$, $PM_{10}$, $SO_2$, $NO_2$, and CO, but not $O_3$, were significantly associated with a near-term increase in MI risk; however, this study included both the occurrence of MI and its death as the outcome of interest, and did not investigate MI mortality separately. In 2016, another meta-analysis reported significant associations of MI mortality with $PM_{2.5}$ and $PM_{10}$ exposures, but major

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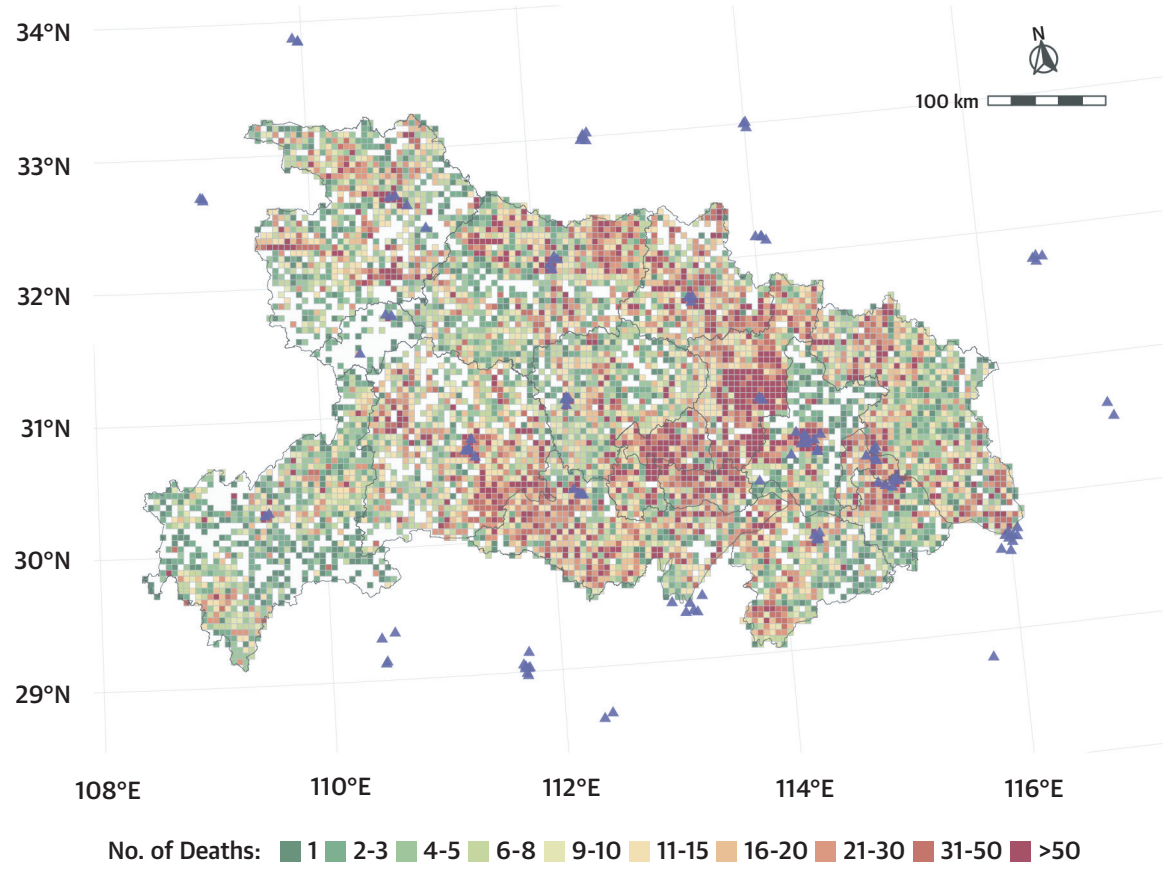
**FIGURE 1** Spatial Distribution of the Study Population and Air Quality Monitoring Stations in Hubei Province, China, 2013 to 2018




The grids with different colors indicate the number of myocardial infarction deaths at a 5 km × 5 km spatial resolution. The **blue triangles** indicate locations of the air quality monitoring stations.

concerns were raised by the limited number of included studies (24).

Here, we conducted a large case-crossover study in Hubei province (China) to quantitatively assess the association of short-term exposure to air pollution across a wide range of concentrations with MI mortality. Our hypothesis was that exposure to some of the main air pollutants was significantly associated with increased risk of MI mortality.

## METHODS

**STUDY POPULATION.** By extracting data from the national mortality surveillance system in Hubei province, we investigated 151,608 individuals who lived in Hubei province and died from MI between January 18, 2013, and December 31, 2018 (Figure 1). Data on sex, age at death, race, marital status, home address, and date of death were collected for each death case. This study was approved by the Ethical Committee of Hubei Provincial Center for Disease Control and Prevention with a waiver of informed consent.

**OUTCOME.** The study outcome was mortality from MI as an underlying cause of death, which was coded based on the International Classification of Diseases-10th Revision (ICD-10). In this study, we investigated 2 types of MI including acute MI (ICD-10 code: I21) and subsequent MI (ICD-10 code: I22), in which acute MI included myocardial infarction specified as acute or with a stated duration of 4 weeks (28 days) or less from onset, while subsequent MI included infarction of any myocardial site, occurring within 4 weeks (28 days) from onset of a previous infarction.

**STUDY DESIGN.** We investigated the association between short-term exposure to air pollution and MI mortality using a time-stratified case-crossover design, which has been widely used to assess acute effects of air pollution on various health outcomes (25–27). This design features that each case serves as his or her own control by assessing referent exposures on the days before or after the case day, and can therefore account for the influence of potential confounding factors that remain constant on the case and control days. For each death case, we defined the day of death as the case day; the control days were defined as days sharing the same year, month, and day of week with the case day to control the effects of long-term trend, seasonality, and day of week (28). According to this method, each case day was assigned 3 to 4 control days. For example, if a subject died on the first Friday of January 2015 (January 2, 2015), January 2, 2015 was assigned as the case day and all other Fridays (January 9, 16, 23, and 30, 2015) in January 2015 were assigned as the control days; if a subject died on the second Monday of January 2015 (January 12, 2015), January 12, 2015 was assigned as the case day, and all other Mondays in January 2015 (January 5, 19, and 26, 2015) were assigned as the control days. In this study, 514,855 control days were selected for the 151,608 MI death cases.

**TABLE 1 Baseline Characteristics of the Study Population, 2013 to 2018**

| | |
|---|---|
| MI deaths | 151,608 |
| Acute MI (ICD-10 code: I21) | 148,864 (98.2) |
| Subsequent MI (ICD-10 code: I22) | 2,744 (1.8) |
| Case days | 151,608 |
| Control days | 514,855 |
| Sex | |
| Male | 81,859 (54.0) |
| Female | 69,749 (46.0) |
| Age at death, yrs | 75.2 ± 12.9 |
| <70 yrs | 43,645 (28.8) |
| 70–74 yrs | 18,470 (12.2) |
| 75–79 yrs | 24,577 (16.2) |
| 80–84 yrs | 30,373 (20.0) |
| ≥85 yrs | 34,543 (22.8) |
| Race | |
| Han | 147,006 (97.0) |
| Other | 4,602 (3.0) |
| Marital status | |
| Married | 97,651 (64.4) |
| Widowed | 47,751 (31.5) |
| Unmarried | 3,212 (2.1) |
| Divorced | 1,197 (0.8) |
| Unknown | 1,797 (1.2) |
| Season at death | |
| Cool (January to March, October to December) | 84,613 (55.8) |
| Warm (April to September) | 66,995 (44.2) |

Values are n, n (%), or mean ± SD.
ICD-10 = International Classification of Diseases-10th Revision; MI = myocardial infarction.

**EXPOSURE ASSESSMENT.** From the National Urban Air Quality Real-Time Publishing Platform in China and the Bureau of Ecology and Environment of Shennongjia Forestry District, we collected daily 24-h average concentrations of $PM_{2.5}$, $PM_{10}$, $SO_2$, $NO_2$, CO, and daily maximum 8-h average concentrations of $O_3$ from 109 air quality monitoring stations located in Hubei province with a 100-km buffer (Figure 1). These stations were added to the publishing platforms in a staged manner from 2013 to 2018.

**TABLE 2 Distribution of Exposure to Ambient Air Pollutants and Meteorological Conditions on Case Days and Control Days**

| | Mean | SD | Percentile | | | | |
|---|---|---|---|---|---|---|---|
| | | | 5th | 25th | 50th | 75th | 95th |
| On case days (n = 151,608) | | | | | | | |
| Air pollutant* | | | | | | | |
| $PM_{2.5}$, μg/m³ | 63.4 | 40.5 | 20.1 | 34.9 | 53.2 | 80.8 | 141.3 |
| $PM_{10}$, μg/m³ | 100.4 | 53.1 | 37.4 | 61.9 | 89.0 | 125.9 | 202.8 |
| $SO_2$, μg/m³ | 21.2 | 15.6 | 6.6 | 10.7 | 16.3 | 26.2 | 52.8 |
| $NO_2$, μg/m³ | 35.4 | 17.2 | 15.1 | 23.1 | 31.9 | 43.6 | 67.5 |
| CO, mg/m³ | 1.14 | 0.37 | 0.69 | 0.89 | 1.07 | 1.31 | 1.84 |
| $O_3$, μg/m³ | 88.5 | 39.7 | 33.2 | 57.3 | 84.5 | 114.5 | 159.8 |
| Meteorological condition† | | | | | | | |
| Temperature, °C | 15.8 | 9.0 | 2.1 | 8.1 | 15.7 | 23.5 | 30.1 |
| Dew point temperature, °C | 10.6 | 9.6 | -4.7 | 2.7 | 10.7 | 18.9 | 25.4 |
| On control days (n = 514,855) | | | | | | | |
| Air pollutant* | | | | | | | |
| $PM_{2.5}$, μg/m³ | 62.1 | 40.5 | 18.5 | 34.0 | 52.3 | 78.6 | 142.3 |
| $PM_{10}$, μg/m³ | 99.5 | 53.7 | 35.3 | 61.1 | 88.6 | 124.8 | 203.8 |
| $SO_2$, μg/m³ | 21.4 | 16.1 | 6.4 | 10.5 | 16.5 | 26.6 | 52.2 |
| $NO_2$, μg/m³ | 35.3 | 17.8 | 15.0 | 22.5 | 31.4 | 43.7 | 67.5 |
| CO, mg/m³ | 1.15 | 0.39 | 0.69 | 0.88 | 1.07 | 1.31 | 1.92 |
| $O_3$, μg/m³ | 88.5 | 40.9 | 32.7 | 56.0 | 83.5 | 115.7 | 163.9 |
| Meteorological condition† | | | | | | | |
| Temperature, °C | 15.8 | 8.8 | 2.1 | 8.2 | 15.8 | 23.2 | 29.5 |
| Dew point temperature, °C | 10.6 | 9.5 | -4.3 | 2.9 | 10.5 | 18.9 | 25.1 |

*24-h average concentration for $PM_{2.5}$, $PM_{10}$, $SO_2$, $NO_2$, and CO; maximum 8-h average concentration for $O_3$.
†24-h average value for temperature and dew point temperature.

CO = carbon monoxide; MI = myocardial infarction; $NO_2$ = nitrogen dioxide; $O_3$ = ozone; $PM_{2.5}$ = particulate matter with an aerodynamic diameter ≤2.5 μm; $PM_{10}$ = particulate matter with an aerodynamic diameter ≤10 μm; $SO_2$ = sulfur dioxide.

We assessed air pollutant exposures using the inverse distance weighting (IDW) method. For each death case, we computed predicted concentrations at his/her home address as an inverse distance weighted average of concentrations at all neighboring monitoring stations on each of the case and control days. The weights were defined as 1/distance², in which distance refers to distance between the home address and each neighboring station. A 10-fold cross-validation technique was applied to evaluate performance of the IDW method in exposure assessment. We randomly split the monitoring stations into 10 subsets and employed the IDW method to predict air pollutant concentrations at stations in each subset using data from the remaining 9 subsets, until all subsets were predicted. We calculated coefficient of determination ($R^2$) and root mean square error according to the measured and predicted concentrations during the study period. As used in extensive studies, we used the mean of daily exposure on the same day of death and 1 day prior (lag 01-day) as the exposure metric in the main analysis (29,30).

**COVARIATES.** Gridded data on daily 24-h average air temperature (°C) and 24-h average dew point temperature (°C) in Hubei province from January 17, 2013, to December 31, 2018, were estimated using meteorological data from the National Meteorological Information Center in China (Supplemental Methods) (29,31). The spatial and temporal resolutions were 0.0625° × 0.0625° and 1 day, respectively. We retrieved daily air temperature and dew point temperature at each death case's home address on each of the corresponding case and control days. We did not consider other individual-level covariates including sex, age, race, and marital status, because they remain constant in comparing case day with the corresponding control days.

**STATISTICAL ANALYSIS.** The correlation between air pollutant exposures was estimated by Spearman's correlation coefficients. Conditional logistic regression models were implemented to quantify the exposure-response associations between short-term $PM_{2.5}$, $PM_{10}$, $SO_2$, $NO_2$, CO, and $O_3$ exposures and MI mortality. Using data on case days and their matched control days, we first included exposure to each pollutant as a natural cubic spline function (degrees of freedom = 3) in the model to plot exposure-response curves and examine possible nonlinear associations using likelihood ratio tests. When a departure from linearity was detected, piecewise conditional logistic regression models were used to explore potential breakpoints of exposure and estimate percent changes (defined as [odds ratio − 1] * 100%) in odds of MI mortality and their 95% confidence intervals (CIs) for different levels of exposure; otherwise, the percent change in odds of MI mortality associated with each 10-μg/m³ increase of exposure was estimated. All models were adjusted for daily air temperature and dew point temperature by including each of them as a natural cubic spline function (degrees of freedom = 3).

We conducted stratified analysis by sex (male, female), age (<75 years, ≥75 years) and season (warm, cool), and examined their potential effect modifications by 2-sample z-tests using the stratification-specific point estimates (β = ln odds ratio) and their SEs (32):

$$z = (\beta\_\text{male} - \beta\_\text{female}) \Big/ \sqrt{([\text{SE\_male}]^2 + [\text{SE\_female}]^2)}$$

The robustness of our results was evaluated by several sensitivity analyses. We conducted 2-pollutant models for each of the 6 air pollutants by including another pollutant in the same model. For each pollutant, the likelihood ratio test was used to

examine the heterogeneity between the nested single-pollutant (e.g., $PM_{2.5}$) and 2-pollutant (e.g., $PM_{2.5}$ + $SO_2$) models, with the null hypothesis that there was no difference between the 2 nested models. Because $PM_{2.5}$ and $PM_{10}$ exposures were strongly correlated (Spearman's correlation coefficient >0.9), we did not include them in the same model to avoid potential collinearity. In addition, we restricted the analysis to acute MI deaths (ICD-10 code: I21). All data analyses were performed using R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria). All p values were 2-sided, and a p value <0.05 was considered as statistically significant. The 95% CIs and p values presented in this report have not been adjusted for multiplicity, and therefore inferences drawn from these statistics may not be reproducible.

## RESULTS

Among the identified 151,608 MI death cases from 2013 to 2018, 98.2% died from acute MI, 54.0% were male, 41.0% died before 75 years of age, and 55.8% died in cool season (Table 1). The age at death ranged from 12.7 to 114.9 years (mean 75.2 years). Married and nonmarried (including widowed, unmarried, divorced) accounted for 64.4% and 34.4% of all death cases, respectively.

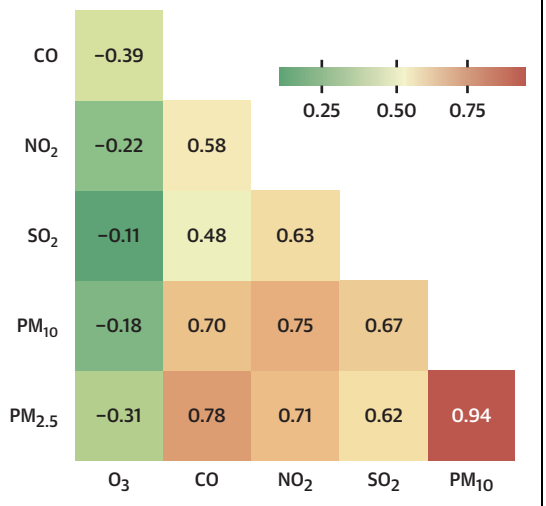
The IDW method performance was shown in Supplemental Table 1. The $R^2$ for $PM_{2.5}$, $PM_{10}$, $SO_2$, $NO_2$, CO, and $O_3$ was 0.76, 0.89, 0.58, 0.69, 0.44, and 0.76, respectively, indicating relatively low performance for CO exposure. The mean exposures to $PM_{2.5}$, $PM_{10}$, $SO_2$, $NO_2$, CO, and $O_3$ on the day of MI death were 63.4 μg/m³, 100.4 μg/m³, 21.2 μg/m³, 35.4 μg/m³, 1.14 mg/m³, and 88.5 μg/m³, respectively (Table 2). $PM_{2.5}$, $PM_{10}$, $SO_2$, and $NO_2$ exposures were positively correlated with pairwise correlation coefficients higher than 0.60 except for that between $NO_2$ and CO exposures, $SO_2$ and CO (all p < 0.05) (Figure 2), while $O_3$ exposure was negatively and weakly correlated with all other air pollutant exposures (all p < 0.05).

In single-pollutant models, lag 01-day exposure to $PM_{2.5}$ and $PM_{10}$ was significantly associated with MI mortality, and departures from linearity were detected ($PM_{2.5}$: p for nonlinear trend < 0.001; $PM_{10}$: p for nonlinear trend = 0.006) (Figure 3). The mortality risk increased monotonically with increasing exposure but attenuated after an estimated breakpoint of 33.3 μg/m³ and 57.3 μg/m³ for $PM_{2.5}$ and $PM_{10}$, respectively (Table 3). When the exposure was lower than the breakpoint, each 10-μg/m³ increase of $PM_{2.5}$ and $PM_{10}$ exposures was significantly associated with a 4.14% (95% CI: 1.25% to 7.12%) and 2.67% (95% CI: 0.80% to 4.57%) increase in odds of MI mortality. No significant associations were observed when the exposure was higher than the breakpoint. In 2-pollutant models, we obtained very similar results for both $PM_{2.5}$ and $PM_{10}$ exposures, though the estimates were higher with the inclusion of $NO_2$ in the model (both p for heterogeneity < 0.05).

No departures from linearity were observed for $SO_2$, $NO_2$, CO, and $O_3$ (Figure 3). In single-pollutant models, each 10-μg/m³ increase of lag 01-day exposure to $SO_2$ and $NO_2$ was significantly associated with a 1.30% (95% CI: 0.27% to 2.35%) and 1.46% (95% CI: 0.76% to 2.17%) increase in odds of MI mortality, respectively (Table 4). The association between $SO_2$ and MI mortality became insignificant when exposure to other pollutant was adjusted. In contrast, the association between $NO_2$ exposure and MI mortality remained significant and stable in all 2-pollutant models. We did not observe any significant association of CO and $O_3$ exposures with MI mortality.

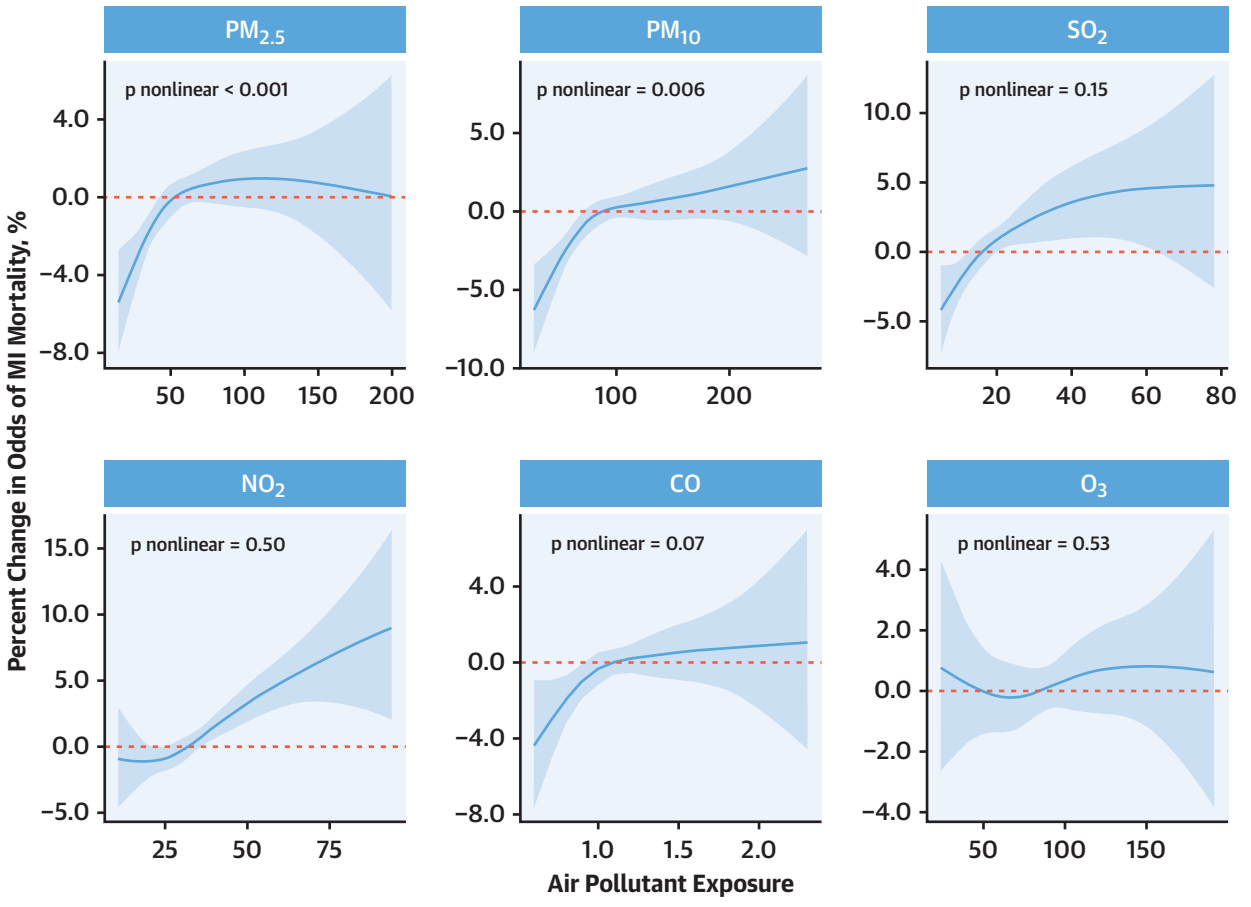
In the stratified analysis, we observed significantly higher odds of MI mortality associated with $NO_2$ exposure among cases ≥75 years of age (percent change in odds: 2.24%; 95% CI: 1.39% to 3.10%) compared with those <75 years of age (percent change in odds: 0.36%; 95% CI: -0.64% to 1.38%; p for effect modification = 0.006). No significant effect

**FIGURE 2** Spearman's Correlation Coefficients Between Air Pollutant Exposures on the Day of Myocardial Infarction Death




p for all pairwise correlations < 0.05. CO = carbon monoxide; $NO_2$ = nitrogen dioxide; $O_3$ = ozone; $PM_{2.5}$ = particulate matter ≤2.5 μm in aerodynamic diameter; $PM_{10}$ = particulate matter ≤10 μm in aerodynamic diameter; $SO_2$ = sulfur dioxide.

**FIGURE 3** Exposure-Response Association of Short-Term Exposure to $PM_{2.5}$, $PM_{10}$, $SO_2$, $NO_2$, CO, and $O_3$ With MI Mortality




The **solid blue lines with shaded regions** indicate percent changes in odds of myocardial infarction (MI) mortality and their corresponding 95% confidence intervals, respectively. The **red dotted lines** represent the referent percent change of 0. The percent changes were estimated relative to the median exposure for each pollutant. Abbreviations as in Figure 2.

modifications were observed for sex or season (all p for effect modification >0.05). Restricting our analyses to acute MI yielded very similar results (Supplemental Figure 1).

## DISCUSSION

In this large case-crossover study in China from 2013 to 2018, we found consistent evidence that short-term exposure to $PM_{2.5}$, $PM_{10}$, and $NO_2$ was associated with increased risk of MI mortality (**Central Illustration**). The odds associated with $PM_{2.5}$ and $PM_{10}$ exposures increased steeply at relatively low levels and flattened out above 33.3 and 57.3 μg/m$^3$, respectively, while the association between $NO_2$ exposure and MI mortality was almost linear and stronger in older adults. We did not observe consistent associations for exposure to $SO_2$, CO, and $O_3$.

Two large time-series studies in the United States (mean $PM_{2.5}$ concentration 13.3 μg/m$^3$; range, 6.7 to 24.9 μg/m$^3$) and a time-series study in Hong Kong (mean $PM_{2.5}$ concentration 29.1 μg/m$^3$) found linear associations and estimated that each 10-μg/m$^3$ increase of $PM_{2.5}$ exposure (lag 01-day) was significantly associated with a 1.22%, 1.18%, and 2.35% increase in MI deaths, respectively (11,16,17). In comparison, we observed significant nonlinear association for $PM_{2.5}$ exposure (lag 01-day) in which the mortality risk increased monotonically with increasing exposure before 33.3 μg/m$^3$ and flattened out afterward. Each

**TABLE 3** Estimated Percent Change in Odds of MI Mortality Associated With Exposure to Each 10-μg/m³ Increase in $PM_{2.5}$ and $PM_{10}$ Using Single- and 2-Pollutant Models

| Pollutant | Model* | Percent Change (95% CI) | | | p Value for Heterogeneity† |
|---|---|---|---|---|---|
| | | Estimated Breakpoint (SE), μg/m³ | < Breakpoint | > Breakpoint | |
| $PM_{2.5}$ | | | | | |
| | Single | 33.3 (3.6) | 4.14 (1.25 to 7.12) | 0.14 (-0.15 to 0.44) | |
| | 2-pollutant | | | | |
| | + $SO_2$ | 33.1 (3.0) | 4.11 (1.58 to 6.70) | 0.02 (-0.30 to 0.35) | 0.38 |
| | + $NO_2$ | 33.3 (3.6) | 4.55 (1.07 to 8.15) | -0.16 (-0.48 to 0.17) | 0.001 |
| | + CO | 33.7 (4.0) | 3.93 (0.88 to 7.07) | 0.07 (-0.31 to 0.44) | 0.95 |
| | + $O_3$ | 33.2 (2.9) | 4.66 (1.95 to 7.44) | 0.18 (-0.12 to 0.48) | 0.38 |
| $PM_{10}$ | | | | | |
| | Single | 57.3 (5.7) | 2.67 (0.80 to 4.57) | 0.18 (-0.03 to 0.40) | |
| | 2-pollutant | | | | |
| | + $SO_2$ | 56.8 (5.5) | 2.67 (0.74 to 4.64) | 0.09 (-0.15 to 0.33) | 0.58 |
| | + $NO_2$ | 57.8 (4.7) | 2.95 (1.06 to 4.88) | -0.07 (-0.32 to 0.19) | 0.003 |
| | + CO | 56.8 (5.9) | 2.59 (0.67 to 4.55) | 0.17 (-0.09 to 0.43) | 0.76 |
| | + $O_3$ | 57.8 (5.1) | 2.97 (1.11 to 4.86) | 0.21 (-0.02 to 0.43) | 0.32 |

*Exposure to co-pollutant was included as a natural cubic spline function (degrees of freedom = 3) in all 2-pollutant models. Break points and percent changes were estimated using piecewise conditional logistic regression models. †p for heterogeneity was estimated with the use of likelihood ratio test by comparing 2 nested models: a single model including the main pollutant as a natural cubic spline function (degrees of freedom = 3) and a 2-pollutant model further including a co-pollutant.

CI = confidence interval; other abbreviations as in Table 2.

10-μg/m³ increase of $PM_{2.5}$ exposure (lag 01-day; mean $PM_{2.5}$ exposure 25.2 μg/m³) lower than 33.3 μg/m³ was associated with a 4.14% increased odds of MI mortality, which was relatively higher (11). Note that the mean $PM_{2.5}$ exposure in our study was also close to that in the Hong Kong study but higher than the 2 U.S. studies if we truncated the exposure at 33.3 μg/m³ (11,16,17). A multicounty time-series study in China reported that each 10-μg/m³ increase of $PM_{2.5}$ exposure (lag 0-day; mean $PM_{2.5}$ exposure 71.7 μg/m³) was significantly associated with a 0.42% increase in MI mortality; however, this study did not examine nonlinearity of the association, which may have underestimated the association at low exposures (12). Possible explanations on the steep exposure-response association for MI mortality risk at low levels of $PM_{2.5}$ exposure and flattening out at high exposures may include: 1) $PM_{2.5}$ constituent variation across areas; and 2) a possible saturation phenomenon that relatively low $PM_{2.5}$ exposure can activate relevant biological pathways (33). We found similar exposure-response associations for $PM_{10}$ exposure, which was comparable with the results from a time-series study in the United States (21). In contrast, another 5 studies in the United Kingdom, United States, Brazil, Japan, and China did not find any significant association of MI with short-term exposures to $PM_{2.5}$ or $PM_{10}$ (13–15,18,20).

The nonlinear association of $PM_{2.5}$ and $PM_{10}$ exposures with increased odds of MI mortality are of particular public health concern. In 2012, the Chinese government released the Ambient Air Quality Standards (GB 3095-2012). The Grade II standards that were applied to general areas set 24-h average concentration limits to 75 and 150 μg/m³ for $PM_{2.5}$ and $PM_{10}$, respectively. According to our findings, if the breakpoints of $PM_{2.5}$ (33.3 μg/m³) and $PM_{10}$ (57.3 μg/m³) exposures in the associations hold, the Grade II standards are more than twice the breakpoints and are unlikely to help reduce MI deaths related to $PM_{2.5}$ or $PM_{10}$ exposures.

The association between gaseous air pollutant exposure and MI mortality was rarely studied. We found that only $NO_2$ exposure was consistently associated with increased risk of MI mortality. Significant association between $SO_2$ exposure and MI mortality was observed in the Brazil study (20) and the study in Hong Kong, China (11). Note that the median $SO_2$ exposure in the UK study was 3.1 μg/m³ (15), which was much lower compared with that in our study (median exposure 16.3 μg/m³), the Brazil study (mean concentration 18.9 μg/m³) and the Hong Kong study (median $SO_2$ concentration 10.4 μg/m³) (11,20). No significant associations were observed for $SO_2$, $NO_2$, CO, and $O_3$ in the UK study (15); $NO_2$ and $O_3$ in the Hong Kong study (11); CO in the Brazil study (20); $O_3$ in a case-crossover study in the United States (23); and $SO_2$ and $NO_2$ in a time-series study in Italy (22). For $O_3$, the Hong Kong study used daily 24-h average concentration for exposure assessment (11).

Several potential mechanisms have been proposed for the association between air pollution and MI,

**TABLE 4** Estimated Percent Change in Odds of MI Mortality Associated With Exposure to Each 10-μg/m³ Increase in $SO_2$, $NO_2$, CO, and $O_3$ Using Singe- and 2-Pollutant Models

| Pollutant | Model* | Percent Change (95% CI) | p for Heterogeneity† |
|---|---|---|---|
| $SO_2$ | Single | 1.30 (0.27 to 2.35) | |
| | 2-pollutant | | |
| | + $PM_{2.5}$ | 0.82 (−0.19 to 1.83) | 0.001 |
| | + $PM_{10}$ | 0.63 (−0.39 to 1.66) | 0.003 |
| | + $NO_2$ | −0.43 (−1.61 to 0.75) | <0.001 |
| | + CO | 0.90 (−0.09 to 1.89) | 0.12 |
| | + $O_3$ | 0.92 (−0.02 to 1.88) | 0.55 |
| $NO_2$ | Single | 1.46 (0.76 to 2.17) | |
| | 2-pollutant | | |
| | + $PM_{2.5}$ | 1.36 (0.61 to 2.10) | 0.01 |
| | + $PM_{10}$ | 1.28 (0.51 to 2.06) | 0.05 |
| | + $SO_2$ | 1.58 (0.70 to 2.47) | 0.78 |
| | + CO | 1.55 (0.80 to 2.30) | 0.26 |
| | + $O_3$ | 1.44 (0.77 to 2.11) | 0.71 |
| CO | Single | 0.027 (−0.004 to 0.059) | |
| | 2-pollutant | | |
| | + $PM_{2.5}$ | 0.006 (−0.032 to 0.044) | 0.001 |
| | + $PM_{10}$ | −0.0003 (−0.035 to 0.035) | 0.002 |
| | + $SO_2$ | 0.009 (−0.022 to 0.040) | 0.08 |
| | + $NO_2$ | −0.013 (−0.047 to 0.200) | <0.001 |
| | + $O_3$ | 0.019 (−0.010 to 0.049) | 0.44 |
| $O_3$ | Single | 0.07 (−0.25 to 0.39) | |
| | 2-pollutant | | |
| | + $PM_{2.5}$ | −0.07 (−0.40 to 0.26) | 0.001 |
| | + $PM_{10}$ | −0.08 (−0.41 to 0.26) | 0.002 |
| | + $SO_2$ | 0.08 (−0.23 to 0.40) | 0.07 |
| | + $NO_2$ | 0.07 (−0.24 to 0.38) | <0.001 |
| | + CO | 0.13 (−0.18 to 0.44) | 0.10 |

*Exposure to co-pollutant was included as a natural cubic spline function (degrees of freedom = 3) in all 2-pollutant models. †p for heterogeneity was estimated with the use of likelihood ratio test by comparing 2 nested models: a single model including the main pollutant as a continuous variable and a 2-pollutant model further including a co-pollutant.

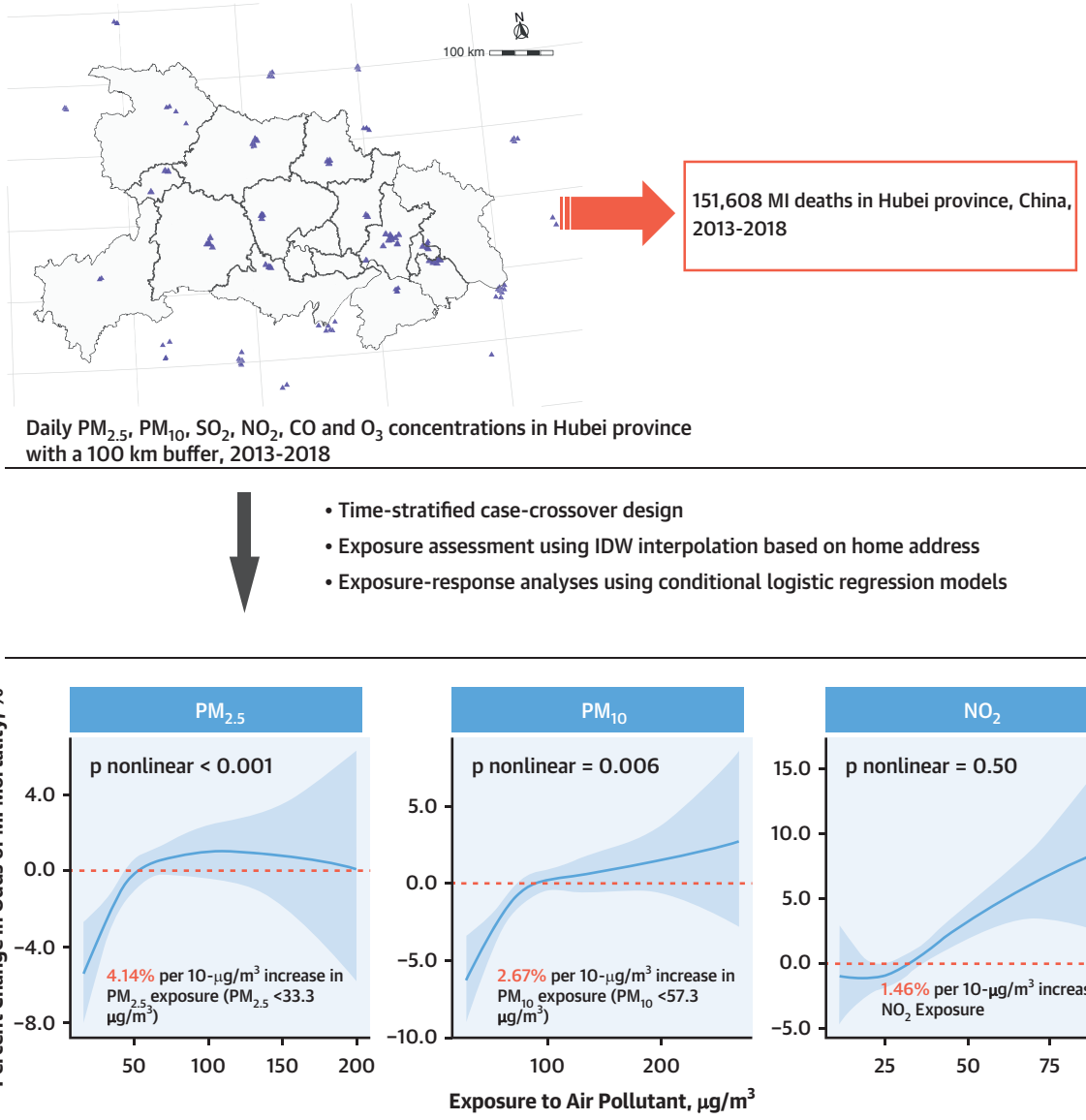
Abbreviations as in Tables 2 and 3.

including oxidative stress, inflammation, abnormal regulation of the cardiac autonomic system, vascular dysfunction, thrombosis, and atherosclerosis (8-10). Previous epidemiological studies reported that exposure to air pollutants (especially $PM_{2.5}$) was associated with elevated circulating proinflammatory biomarkers, increased platelet and fibrinogen activities, and plaque formation, which lead to binding of circulating platelets to each other, vessel wall damage, thrombosis, and finally trigger MI (8,9,34). It has been reported that inhaling PM was associated with the activation of platelets and coagulation enzymes and might decrease the total myocardial flow significantly and increase the resistance of coronary vascular in animal studies (35,36). Clinical studies have suggested that $NO_2$ and the produced nitrogen dioxide ion ($NO_2^-$) were involved in oxidative stress and adversely increased blood coagulability (37,38).

**STUDY STRENGTHS.** First, China was experiencing severe air pollution issues during the study period, which provided unique possibilities to study detailed exposure-response association of MI with a wide range of air pollutant concentrations. The exposure levels in most previous studies were much lower, especially in developed countries. This may have in part contributed to the null results in previous studies. Second, we used a case-crossover design with a considerably large sample size, which controlled for long-term trends, known or unknown time-invariant covariates (e.g., socioeconomic status, genetics), and time-varying meteorological conditions. In addition, this design allowed us to use the IDW method to implement individual-level exposure assessment based on the death case's home address that was more accurate in comparison with that in time-series studies. Most previous studies on this topic were time-series studies in which a city-level air pollution concentration was typically used for exposure assessment. To date, there have been only 3 case-crossover studies that have investigated the association between short-term air pollution exposure and MI mortality, and only 2 of them assessed individual-level air pollutant exposures (14,15,23). Third, we investigated 6 main air pollutants concerned worldwide in the same population, and used 2-pollutant models to confirm the robustness of our results.

**STUDY LIMITATIONS.** First, we did not and were unable to measure personal air pollutant concentrations directly (e.g., using personal air quality monitoring equipment), but rather used estimated air pollutant concentration at the death case's home address as a proxy of air pollutant exposure. This may lead to exposure misclassifications due to lack of data on indoor air pollution or the cases' time-activity patterns. Besides, the air quality monitoring stations were not evenly distributed in the study area, which might reduce the accuracy of exposure assessment using the IDW method. It should be noted that the performance of exposure assessment for some air pollutants, especially CO, was relatively low. The differences in associations of different air pollutants may be in part a function of the accuracy of exposure estimation. Second, exposures to some of the studied air pollutants were highly correlated, limiting our ability to conduct multipollutant models and making it difficult to distinguish their respective effects on MI mortality. Third, the study outcome was mortality from MI as the underlying cause of death. Because we did not have sufficient information on MI onset, it was difficult to distinguish mortality from MI and death due to its comorbidities; however, the underlying cause of death has been widely used to investigate the association between exposure to air pollution and a variety of

**CENTRAL ILLUSTRATION** **Short-Term Exposure to $PM_{2.5}$, $PM_{10}$, and $NO_2$ Is Significantly Associated With Increased Odds of Myocardial Infarction Mortality**




Overview and main findings of this study on the association of short-term exposure to air pollution with myocardial infarction (MI) mortality. The **blue triangles** indicate locations of the air quality monitoring stations. The **solid blue lines with shaded regions** indicate percent changes in odds of MI mortality and their corresponding 95% confidence intervals (CIs), respectively. The **red dotted lines** represent the referent percent change of 0. CO = carbon monoxide; IDW = inverse distance weighting; $NO_2$ = nitrogen dioxide; $O_3$ = ozone; $PM_{2.5}$ = particulate matter with aerodynamic diameter ≤2.5 μm; $PM_{10}$ = with aerodynamic diameter ≤10 μm; $SO_2$ = sulfur dioxide.

diseases. Fourth, as in any observational study, although the case-crossover design accounted for time-invariant confounding factors and we further adjusted for meteorological conditions, residual or unmeasured confounding is still possible. Fifth, although the death registration data used in our study was under strict quality control, diagnosis or coding errors for MI were still possible given the large sample size. Last, because our findings were obtained from a single province in China, cautions should be made when generalizing our findings to populations in other regions or countries.

## CONCLUSIONS

We found that short-term exposure to air pollution was significantly associated with increased risk of MI mortality. For $PM_{2.5}$ and $PM_{10}$, the exposure-response association was nonlinear, with risk increasing steeply at relatively low exposures and flattening out at higher exposures, while the association for $NO_2$ exposure was linear. These findings add to the understanding of acute adverse effects of air pollution on cardiovascular mortality and highlight the needs for either general population or policy practitioners to take effective measures in reducing air pollution exposures, especially for older adults and those with higher risk of MI occurrence.

## AUTHOR DISCLOSURES

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** Short-term exposure to $PM_{2.5}$, $PM_{10}$, and $NO_2$ is associated with an increased risk of myocardial infarction mortality.

**TRANSLATIONAL OUTLOOK:** Further investigations are needed to explore the biological mechanisms underlying the association of short-term exposure to air pollution with adverse cardiovascular events.

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**KEY WORDS** air pollution, mortality, myocardial infarction, nitrogen dioxide, particulate matter

**APPENDIX** For an expanded Methods section, a supplemental table, and a supplemental figure, please see the online version of this paper.