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Reductions in acute myocardial infarction burden linked to short-term $PM_{2.5}$ exposure: Evidence from the Chinese CCA Registry

Yilin Li,[1,2,3,5] Guanhao He,[1,2,3,5] Qijiong Zhu,[1,2] Xinjie Xiao,[1,2] Yayi Li,[1,2] Yixiang Huang,[1,2] Siwen Yu,[1,2] Zhiqing Chen,[1,2] Ying Zhu,[1,2] Wan Peng,[1,2] Shangfeng Yang,[1,2] Jianxiong Hu,[1,2] Ziqiang Lin,[1,2] Kai Huang,[4,*] Tao Liu,[1,2,3,*] and Wenjun Ma[1,2,3]

*Correspondence: gztt_2002@163.com (T.L.); huangkai1@hust.edu.cn (K.H.)

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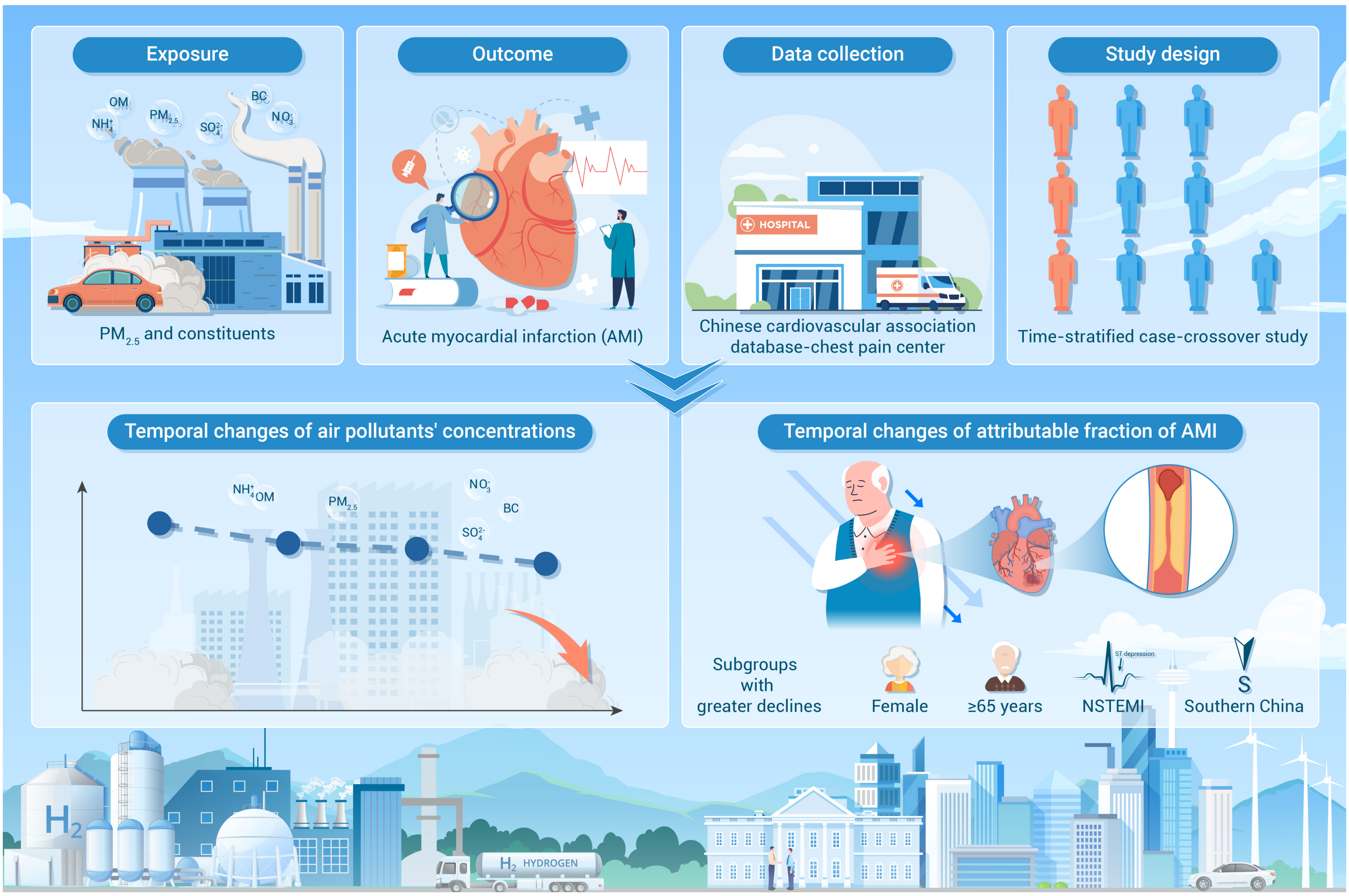
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Concentrations of fine particulate matter ($PM_{2.5}$) and its constituents pronouncedly declined during 2017-2020.
- The burden of acute myocardial infarction (AMI) by $PM_{2.5}$ mass and its constituents substantially declined.
- The declines of AMI morbidity burden were greater for organic matter and sulfate than other constituents.
- The AMI morbidity burden by $PM_{2.5}$ declined more in females, people aged ≥65 years, and in Southern China.
- Our study could assist in establishing targeted policies and driving actions in prevention strategies for AMI.

Reductions in acute myocardial infarction burden linked to short-term $PM_{2.5}$ exposure: Evidence from the Chinese CCA Registry

Yilin Li,[1,2,3,5] Guanhao He,[1,2,3,5] Qijiong Zhu,[1,2] Xinjie Xiao,[1,2] Yayi Li,[1,2] Yixiang Huang,[1,2] Siwen Yu,[1,2] Zhiqing Chen,[1,2] Ying Zhu,[1,2] Wan Peng,[1,2] Shangfeng Yang,[1,2] Jianxiong Hu,[1,2] Ziqiang Lin,[1,2] Kai Huang,[4,*] Tao Liu,[1,2,3,*] and Wenjun Ma[1,2,3]

[1]Department of Public Health and Preventive Medicine, School of Medicine, Jinan University, Guangzhou 510632, China

[2]China Greater Bay Area Research Center of Environmental Health, School of Medicine, Jinan University, Guangzhou 510632, China

[3]Key Laboratory of Viral Pathogenesis & Infection Prevention and Control (Jinan University), Ministry of Education, Guangzhou 510632, China

[4]Department of Cardiology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China

[5]These authors contributed equally

*Correspondence: gztt_2002@163.com (T.L.); huangkai1@hust.edu.cn (K.H.)

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Background:$PM_{2.5}$ (fine particulate matter with aerodynamic diameter ≤ 2.5μm) concentrations have substantially declined in the past decade across China, but temporal changes of morbidity burden of acute myocardial infarction (AMI) attributable to short-term exposures to $PM_{2.5}$ and its various chemical constituents, including black carbon (BC), organic matter (OM), ammonium (NH_4^+), nitrate (NO_3^-) and sulfate (SO_4^{2-}) in China remain unknown. Methods:A time-stratified case-crossover design was applied in 785,052 AMI cases across China during 2017-2020. We utilized conditional logistic regression models to estimate the excess risks (ERs) and attributable fractions (AFs) from AMI onset attributable to short-term exposures (lag01 day) to $PM_{2.5}$ and constituents, and used linear regression models to estimate temporal changes of AFs of AMI morbidity. Results:The annual average reductions in concentrations of $PM_{2.5}$ mass, BC, OM, NH_4^+, NO_3^- and SO_4^{2-} during 2017-2020 were respectively 3.05μg/m^3/year, 0.15μg/m^3/year, 0.70μg/m^3/year, 0.31μg/m^3/year, 0.44μg/m^3/year, and 0.51μg/m^3/year. Correspondingly, the annual average reductions in AFs were recorded as -0.53% (95%CI: -0.92%, -0.15%), -0.29% (95%CI: -0.43%, -0.15%), -0.45% (95%CI: -0.78%, -0.12%), -0.33% (95%CI: -0.51%, -0.16%), -0.36% (95%CI: -0.59%, -0.13%), and -0.48% (95%CI: -0.86%, -0.10%), respectively. The temporal reduction of $PM_{2.5}$-attributed and chemical constituents-attributed AFs were greater in females, people aged ≥65 years, non-ST-segment-elevation myocardial infarction (NSTEMI) cases, and people resided in Southern China. Conclusions:As the concentration of $PM_{2.5}$ mass and chemical constituents decreased over the years, the decline was observed in the morbidity burden of AMI attributable to $PM_{2.5}$ and its constituents across China from 2017 to 2020.

INTRODUCTION

Ischemic heart disease (IHD) remains a leading global cause of mortality, with deaths rising from 5.37 million in 1990 to 8.99 million in 2021.[1] Acute myocardial infarction (AMI) is a major category of IHD, contributing substantially to the global disease burden.[2] AMI can be classified into two principal categories: ST-segment-elevation myocardial infarction (STEMI) and non-ST-segment-elevation myocardial infarction (NSTEMI). In the United States from 2005 to 2014, approximately 605,000 incident and 200,000 recurrent AMI events occurred annually.[3] In China, the National Center for Cardiovascular Diseases in China reported that the AMI mortality rate in urban areas surged from 43.19 to 78.65 deaths per 100,000 population between 2010 and 2020, imposing severe burdens on families and society.[4-6] According to the projections by the World Bank, the estimated number of myocardial infarction (MI) cases in China is expected to 23 million by 2030.[7]

Air pollution is one of the major risk factors for AMI morbidity and mortality, with ambient fine particular matter ($PM_{2.5}$) serving as the primary contributor to disease burden caused by air pollution.[4,8,9] $PM_{2.5}$ is a complex mixture comprising multiple chemical species, including black carbon (BC), organic matter (OM), ammonium (NH_4^+), nitrate (NO_3^-), sulfate (SO_4^{2-}) and other components.[10-14] Previous research has suggested that both short- and long-term exposures to $PM_{2.5}$ mass concentration and chemical constituents play crucial roles in triggering AMI and other cardiovascular diseases.[5,11-16] In a meta-analysis, Mustafić and colleagues revealed that each 10μg/m^3 increment in ambient $PM_{2.5}$ at lag0 day was associated with 2.50% excess risk for MI.[17] Madrigano et al. documented a positive association between long-term exposure to $PM_{2.5}$ and occurrence of AMI.[12] A large-scale time-series study illustrated that short-term exposures to ammonium and organic carbon notably increased the risk of MI mortality in China.[18] Additionally, a study conducted in five southern provinces of China uncovered a connection between short-term elemental carbon and organic carbon exposures and an elevated risk of MI.[9] As a dominant environmental risk factor affecting global public health, $PM_{2.5}$ with its chemical constituents will persist as a focal point for policymakers and the public, given their universality and adverse health impacts.[19,20]

It is becoming increasingly evident that ambient $PM_{2.5}$ contributes to a significant extent to the global burden of AMI.[21] Owing to environmental protection efforts, ambient $PM_{2.5}$ concentrations have declined significantly in the United States, Western Europe and China over the past decades.[22-26] Conversely, in most developing countries, especially in South America and sub-Saharan Africa, $PM_{2.5}$ concentrations have stayed high or even risen.[26] Consequently, $PM_{2.5}$-related disease burden have diverged between developed and developing countries in recent years.[27-29] For example, Cohen et al. noted that the all-age proportion of cardiovascular disease deaths attributed to $PM_{2.5}$ dropped from 10.0% to 8.1% in World Bank high-income countries.[27] Li et al. also observed a downward trend in mortality rates (including IHD) in the United States and some European countries, while a significant net increase in mortality rates was observed in several developing countries, including India, North Africa and Malaysia.[28]

To tackle the severe air pollution crisis, Chinese governments have implemented a series of policies initiatives over the past decade, including the Air Pollution Prevention and Control Action Plan (APPCAP)[30-32] in 2013 and Three-Year Action Plan for Winning the Blue Sky Defense Battle[33-35] in 2018. These unprecedented measures have drastically improved the air quality nationwide, leading to substantial reductions in $PM_{2.5}$ mass and chemical constituents.[22,34] Previous studies have demonstrated that the morbidity and mortality burden of cardiovascular diseases attributable to ambient $PM_{2.5}$ has decreased in synchrony with $PM_{2.5}$ levels in China.[29,36,37] For instance, between 2013 and 2017, $PM_{2.5}$ mass concentrations dropped by 39.5% in 13 priority areas and 5 non-priority areas in China, resulting in a 12.6% reduction in $PM_{2.5}$-attributable premature deaths.[36] However, there is limited evidence on how the morbidity burden of AMI linked to $PM_{2.5}$ chemical constituents has changed over time in China.

In this study, we utilized data from a nationwide registry dataset of China to quantify the risk of AMI onset and temporal changes in morbidity burden attributable to short-term exposures to $PM_{2.5}$ mass and its five major chemical constituents during 2017 to 2020, employing a time-stratified case-crossover design. Findings of this study could provide novel insights into the health impacts of ambient $PM_{2.5}$ pollution, informing guiding updates to air pollution control policies.

MATERIALS AND METHODS

Study design

We estimated the associations between $PM_{2.5}$ exposure and AMI incidence using a time-stratified case-crossover design, a common approach for assessing short-term associations of pollutants on various health outcomes.[38,39] To control for mid-term and long-term seasonality and variations, we compared exposures to $PM_{2.5}$ and its constituents on the AMI symptom onset day (case day) with those on the same day of the week (control day) within the same calendar month for each case. Each case day was matched with three or four control days. For instance, if an AMI event occurred on Saturday, February 11th, 2017, we would define February 11th, 2017 as the case day, and remaining Saturdays in February 2017 (February 4th, 18th, 25th) would be designated as control days.

Data source and study population

The current study extracted de-identified patients with AMI symptomatic onset from the Chinese Cardiovascular Association (CCA) Database-Chest Pain Centers, a nationwide and multicenter registry for monitoring the quality of patients experiencing acute chest pain or discomfort.[40] Patients presenting with acute chest pain and subsequently visiting the Chest Pain Centers would be recorded. Collected information includes demographic characteristics (e.g. age, sex), disease diagnosis (e.g. admission and discharge diagnosis), symptom onset dates, treatment procedures, etc. Besides, the Expert Committee and the Executive Committee of CCA performs quality control of these recorded data routinely. Further details of the CCA Database-Chest Pain Center have been described elsewhere.[41-45]

In our analysis, we collected data on AMI cases between January 1st, 2017 and December 31th, 2020 from the CCA Database-Chest Pain Center. An AMI case was defined as a hospitalized patient with either STEMI and NSTEMI. All diagnoses of AMI onset were ascertained by specialized cardiologists and clinicians based on clinical symptoms, electrocardiography and biochemical test results, following the standard guidelines published by Chinese Society of Cardiology.[46-48] Cases with incomplete symptom onset dates, missing diagnostic information, or key variables were excluded from our analysis. Ultimately, a total of 785,052 AMI cases from 2,962 hospitals across 1,870 counties/districts in China were included in this study (Figures 1 & S1).

Variables and outcomes

The data of $PM_{2.5}$ mass and its five main constituents, including BC, OM, NH_4^+, SO_4^{2-}, NO_3^- for 2017-2020 were obtained from Tracking Air Pollution in China (TAP). The concentrations of $PM_{2.5}$ mass with a spatial resolution of 10 km × 10 km across China were predicted by a two-staged machine learning algorithm, incorporating the synthetic minority oversampling technique and a tree-based gap-filling method. The accuracy of the two-stage machine learning model in $PM_{2.5}$ mass was estimated using out-of-bag cross-validation coefficient of determination (CV-R^2) of 0.80 to 0.88 and root-mean-square error (RMSE) of 13.9 to 22.1μg/m^3.[49-51] In this stage, including a series of multi-domain data sources, such as ground-based observations, meteorological information, elevation, operational Weather Research and Forecasting/Community Multiscale Air Quality Modeling System (WRF/CMAQ), satellite aerosol optical depth (AOD), land use data, etc., the TAP dataset utilized a random forest model to predict high pollution events. In the second stage, based on a spatial resolution of 10 km×10 km in $PM_{2.5}$ mass concentration, daily $PM_{2.5}$ chemical components were developed with same resolution. The TAP data has an out-of-bag cross-validation CV-R^2 of 0.72, 0.64, 0.75, 0.75, 0.70 for OM, BC, NO_3^-, NH_4^+, and SO_4^{2-}, respectively, showing good performance in modelling.[50]

We also gathered daily concentration data of other air pollutants from National Earth System Science Data Center, National Science & Technology Infrastructure of China, including nitrogen dioxide (NO_2), sulfur dioxide (SO_2), carbon dioxide (CO) and daily maximum 8-hour average ozone (MDA8 O_3). Ground-based observations, atmospheric reanalysis, and remote sensing products were employed in this dataset in the assessment process. The daily concentrations of these four air pollutants were modeled using satellite imagery with a resolution of 10 km × 10 km, demonstrating a good fit (NO_2: CV-R^2=0.84, RMSE=7.99μg/m^3; SO_2: CV-R^2=0.84, RMSE=10.07μg/m^3; CO: CV-R^2=0.80, RMSE=0.29mg/m^3; MDA8 O_3: CV-R^2=0.87, RMSE=11.70μg/m^3).[52,53]

Daily average air temperature and relative humidity data from 2017 to 2020 were obtained from the fifth generation of European Reanalysis (ERA5) produced by the European Centre for Medium-Range Weather Forecasts (ECMWF), with a 0.25°×0.25° spatial and hourly temporal resolution.[54] Comparison with data from 698 climate stations in China showed ERA5 data were reliable (temperature: CV-R^2=0.93, RMSE=3.22°C; relative humidity: CV-R^2=0.84, RMSE=7.71%) (Figure S2). Detailed validation methodology is descripted in Section 1.1 in Supplemental materials.

For each AMI case, we calculated the daily averages of air pollutants concentrations and meteorological data for all grids covering counties/districts where the hospitals were located.

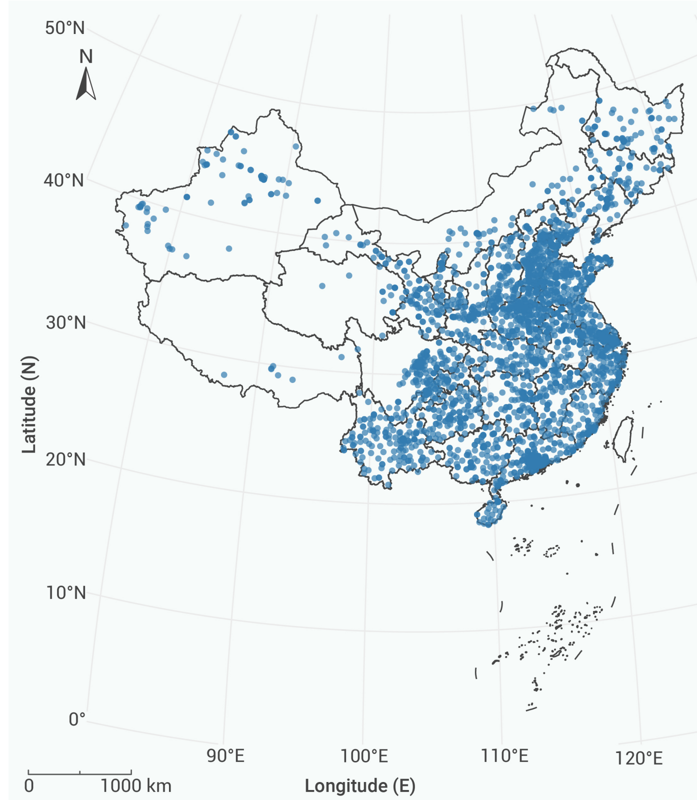

Figure 1. Geographic distribution of chest pain centers across China from 2017 to 2020.

Statistical methods

We employed conditional logistic regression models to estimate the relationships between $PM_{2.5}$ mass concentration with its constituents and the AMI onset. When assessing the associations of specific $PM_{2.5}$ constituents on AMI, a two-stage model was applied to avoid the effect of potential multi-collinearity among various constituents. In the first step, we regressed $PM_{2.5}$ mass concentration on each chemical constituent individually, and then extracted the residuals that represented $PM_{2.5}$ mass variability unexplained by that specific constituent.[55] The residual served as a rough measure of each constituent's independent contribution.[56,57] Subsequently, these $PM_{2.5}$-residuals were fitted in the conditional logistic regression models in the second stage. This two-stage model could reduce overlap in associations among different $PM_{2.5}$ constituents caused by multi-collinearity, enhancing parameter estimate accuracy. The two-stage models were described below:

Stage I:

$$\text{Res}_i = \text{PM}_{2.5} - \alpha_0 - \alpha_1 P_i \quad (1)$$

In equation (1), Res_i indicates the residuals between observed $PM_{2.5}$ and predicted constituent P_i concentrations from a linear regression. α_0 and α_1 are the estimates of intercept and slope of constituent i, respectively.

Stage II:

$$Logit(p\ in\ stratum_a) = \beta_0 + \beta_{1i}P_i + \beta_{2i}\text{Res}_i + ns(TM_{0-3}, df=3) + ns(RH_0, df=3) \quad (2)$$

In the equation (2), p represents the conditional probability of AMI onset in stratum *α*. P_i denotes the concentration of i^{th} air pollutant ($PM_{2.5}$ mass and its constituents). $β_0$ represents an intercept. $β_{1i}$ and $β_{2i}$ indicate the regression coefficient and the residual of constituent P_i, respectively. When estimating the association of $PM_{2.5}$ mass and AMI, the residuals from $PM_{2.5}$-constituent regressions do not need to be considered in the regression model.

Previous studies have indicated that the lag effects of $PM_{2.5}$ on cardiovascular diseases could last up to a week.[5,58] We observed that the associations of $PM_{2.5}$ mass concentration exhibited a downward trend from 2-day moving average (lag01 day) to 5-day moving average (lag04 day), with the strongest associations observed at lag01 day (Table S15). Therefore, we estimated nonlinear associations of AMI onset with $PM_{2.5}$ and its constituents using the moving average of two days (lag01), applying a natural cubic spline (*ns*) with three degrees of freedom (*df*s) to capture potential nonlinear associations. Following previous studies,[59,60] we controlled for the temperature using a 4-day moving average (lag03) and relative humidity at the current day (lag0) applying a function with three *df*s. To mitigate the impacts of outliers on model fitting, we removed concentrations of $PM_{2.5}$ and its constituents below the 1st and above the 99th percentile from the analysis models. We reported main results using excess risk (ER) along with the corresponding 95% confidence intervals (CI) per interquartile range (IQR) increase for associations between $PM_{2.5}$ mass and its chemical components with AMI mortality. The ER is calculated as below:

$$ER = [\exp(\beta) - 1] \times 100\% \tag{3}$$

where β indicates the regression coefficient of $PM_{2.5}$ and its constituents from conditional logistic model. Furthermore, the corresponding attributable fractions (AFs) of the onset of AMI attributable to $PM_{2.5}$ and its constituents were calculated based on the nonlinear exposure-response relationships. The formula of AF can be expressed as:[61]

$$AF_i = \frac{\sum pop_{i,c} \times \exp(\beta_i \times c) - 1}{\sum pop_{i,c} \times \exp(\beta_i \times c)} \times 100\% \tag{4}$$

where $pop_{i,c}$ is the proportion of AMI cases exposed to the level *c* of air pollutant *i* ($PM_{2.5}$ mass and constituents); $β_i$ indicates the slopes of air pollutant *i* from the equation (2).

To explore the potential effect modifications, stratified analyses were conducted by sex (male *vs* female), age (<65 *vs* ≥65 years), region (Southern *vs* Northern) and subtypes of AMI (STEMI *vs* NSTEMI). Statistical differences were tested by a 2-sample *Z*-test, and *P* values calculated from 2-by-2 comparisons between different groups were corrected utilizing the Bonferroni method.[62] The formula for the between-group variability test is described as follows:

$$Z = \frac{b_1 - b_2}{\sqrt{SE_1^2 + SE_2^2}} \tag{5}$$

where b_1 and b_2 are the regression coefficients of two different groups, SE_1 and SE_2 are the corresponding standard errors.

Finally, to estimate the temporal trends in burden of $PM_{2.5}$ mass concentration and its constituents on AMI onset during 2017 to 2020, we constructed a linear regression model with AFs as the dependent variable and year as independent variable. Regression coefficients and corresponding 95% CI from the linear models were extracted to represent annual changes (%) of AFs for each air pollutant.

Sensitivity analyses

A series of sensitivity analyses were performed to assess the robustness of our results. First, we evaluated different lag days (lag01 to lag04) to examine the linear associations of $PM_{2.5}$ and its components with the onset of AMI. Second, we utilized two-pollutant models incorporating other air pollutants (i.e. MDA8 O_3, SO_2, CO and NO_2). Third, given the influences of the medical practice in COVID-19 (Coronavirus disease-2019) pandemic, we excluded 2020 data and analyzed the associations between $PM_{2.5}$ mass and its chemical constituents with AMI onset during 2017 to 2019. All analyses mentioned above were conducted using R software (version 4.3.1), and we used "survival" package to conduct conditional logistic regression models. A 2-tailed *P* value < 0.05 was considered statistically significant.

Table 1. Characteristics of AMI onset population, air pollutants and meteorological conditions in this study.

Group	n (%)
Total AMI onset	785 052 (100.00)
Type of AMI	
STEMI	532 123 (67.78)
NSTEMI	252 929 (32.22)
Sex	
Male	580 351 (73.93)
Female	204 701 (26.07)
Age (years)	
<65	400 082 (50.96)
≥65	384 970 (49.04)
Region	
Southern	416 542 (53.06)
Northern	368 510 (46.94)
	Mean ± SD
Air pollutants	
$PM_{2.5}$ (μg/m^3)	37.03 ± 25.29
BC (μg/m^3)	1.73 ± 1.11
OM (μg/m^3)	9.00 ± 6.19
NH_4^+ (μg/m^3)	5.30 ± 4.51
NO_3^- (μg/m^3)	8.00 ± 7.43
SO_4^{2-} (μg/m^3)	6.75 ± 4.50
Meteorological condition	
Temperature (°C)	16.36 ± 9.03
Relative humidity (%)	66.70 ± 18.66

Abbreviations: AMI: acute myocardial infarction, STEMI: ST-segment-elevation myocardial infarction, NSTEMI: non-ST-segment-elevation myocardial infarction, SD: standard deviation, $PM_{2.5}$: fine particulate matter with aerodynamic diameters ≤ 2.5μm, BC: black carbon, OM: organic matter, NH_4^+: ammonium, NO_3^-: nitrate, SO_4^{2-}: sulfate.

RESULTS

Descriptive results

A total of 785,052 AMI cases from 2,962 hospitals across 1,870 counties/districts were derived from the CCA Database-Chest Pain Center from January 1st, 2017 to December 31th, 2020. Among them, 532,123 (67.78%) were STEMI cases, 580,351 (73.93%) were males, 400,082 (50.96%) were aged <65 years, and 416,542 (53.06%) resided in Southern China (Table 1). Compared with the control days, case days showed higher concentrations of ambient MDA8 O_3, SO_2, NO_2, and $PM_{2.5}$ mass concentrations and its specific constituents, higher daily temperature, along with lower CO concentrations and lower relative humidity in all participants (Table 2). $PM_{2.5}$ mass concentration positively correlated with CO (r = 0.59, P < 0.001), NO_2 (r = 0.53, P < 0.001), MDA8 O_3 (r = 0.03, P < 0.001) and SO_2 (r = 0.38, respectively, P < 0.001), and negatively correlated with temperature (r = -0.29, P < 0.001) and relatively humidity (r = -0.10 P < 0.001) (Figure S3).

Temporal changes in concentrations of $PM_{2.5}$ mass and its chemical components

Figures 2A-B & S4-S8 and Table S1 show the spatiotemporal changes of concentrations of $PM_{2.5}$ mass and its chemical constituents from 2017 to

Table 2. Statistical description (Mean ± SD) of study variables on control and case days in all study participants.

Variables	Control days (n=2 662 782)	Case days (n=785 052)	*t* value	*P* value
$PM_{2.5}$ (μg/m^3)	37.032 ± 20.007	37.327 ± 25.503	12.290	<0.001
BC (μg/m^3)	1.726 ± 0.860	1.741 ± 1.125	13.364	<0.001
OM (μg/m^3)	8.999 ± 4.816	9.079 ± 6.250	13.300	<0.001
NH_4^+ (μg/m^3)	5.302 ± 3.527	5.343 ± 4.548	9.434	<0.001
NO_3^- (μg/m^3)	8.010 ± 5.931	8.076 ± 7.499	9.540	<0.001
SO_4^{2-} (μg/m^3)	6.750 ± 3.349	6.794 ± 4.529	9.557	<0.001
CO (mg/m^3)	0.869 ± 0.296	0.867 ± 0.250	8.980	<0.001
NO_2 (μg/m^3)	30.669 ± 11.701	30.830 ± 13.660	15.061	<0.001
MDA8 O_3 (μg/m^3)	103.843 ± 34.914	104.339 ± 42.727	13.317	<0.001
SO_2 (μg/m^3)	12.544 ± 7.304	12.600 ± 8.154	10.405	<0.001
Temperature (°C)	16.293 ± 8.618	16.351 ± 9.058	13.267	<0.001
Relative humidity (%)	66.727 ± 15.235	66.589 ± 18.642	8.319	<0.001

Abbreviations: SD: standard deviation, $PM_{2.5}$: fine particulate matter with aerodynamic diameters ≤ 2.5 μm, BC: black carbon, OM: organic matter, NH_4^+: ammonium, NO_3^-: nitrate, SO_4^{2-}: sulfate, CO, carbon monoxide, NO_2, nitrogen dioxide, MDA8 O_3, daily maximum 8-hour average ozone, SO_2, sulfur dioxide.

2020. Considerable declines in the concentrations of these air pollutants were observed across China. For instance, annual average $PM_{2.5}$ mass concentrations decreased from 42.35μg/m^3 in 2017 to 32.66μg/m^3 in 2020, with a reduction of 22.88%, or 3.05μg/m^3/year (Figure 2A). Similarly, annual declines in BC, OM, NH_4^+, NO_3^- and SO_4^{2-} across China were 0.15μg/m^3/year, 0.70μg/m^3/year, 0.31μg/m^3/year, 0.44μg/m^3/year, and 0.51μg/m^3/year, respectively. (Figure 2B and Table S1).

Associations of $PM_{2.5}$ and its chemical constituents with AMI morbidity

Figure 3 displays the nonlinear exposure-response curves of short-term exposure to $PM_{2.5}$ mass and constituents (lag01) with the overall AMI onset from 2017 to 2020. $PM_{2.5}$ mass and all constituents were positively associated with the AMI onset during the entire study period. The nonlinear exposure-response curves of $PM_{2.5}$ mass and chemical constituents showed a monotonic increase, with no significant departures from linearity (all *P* for nonlinearity > 0.05). Each IQR increment in $PM_{2.5}$ mass was associated the increased risk on AMI onset (ER = 2.21%, 95% CI: 1.76%, 2.67%). In addition, five major chemical components were also positively linked to AMI morbidity, with OM and SO_4^{2-} showing stronger associations with AMI morbidity than the other compositions (Figure S9).

Burden of AMI morbidity attributed to $PM_{2.5}$ and its chemical constituents

Based on the results of nonlinear associations, we estimated the $PM_{2.5}$- and chemical constituents-attributed AF on overall AMI morbidity. As illustrated in Table S2, 3.70% (95%CI: 3.21%, 4.18%) could be attributed to the exposure of $PM_{2.5}$ mass. Additionally, the results showed the AFs from AMI onset were higher for OM and SO_4^{2-} compared to other components (Tables S3-S7).

Our analysis further revealed a declining trend in AFs attributable to $PM_{2.5}$ during the period from 2017 to 2020. Specifically, in the overall participants, the annual average reductions in AFs associated with $PM_{2.5}$ mass, as well as its components were as follows: -0.53% (95%CI: -0.92%, -0.15%) for $PM_{2.5}$ mass, -0.29% (95%CI: -0.43%, -0.15%) for BC, -0.45% (95%CI: -0.78%, -0.12%) for OM, -0.33% (95%CI: -0.51%, -0.16%) for NH_4^+, -0.36% (95%CI: -0.59%, -0.13%) for NO_3^-, and -0.48% (95%CI: -0.86%, -0.10%) for SO_4^{2-} (Figure 4 and Table S8). Therefore, among $PM_{2.5}$ chemical constituents, SO_4^{2-} and OM could play an important role on potential effects of AMI morbidity, and reducing concentrations of SO_4^{2-} and OM may effectively reduce the burden of AMI onset.

Stratified analysis by sex, age, subtypes of AMI, and region

Stratified analysis revealed significant variations in annual changes of AFs across different subgroups, with more pronounced reductions observed in females, individuals aged ≥65 years, NSTEMI cases, and population in Southern China. Specifically, annual changes of $PM_{2.5}$-related AFs were -0.60% (95%CI: -0.98%, -0.23%) in females and -0.51% (95%CI: -0.91%, -0.12%) in males, -0.59% (95%CI: -1.01%,-0.17%) in people ≥65 years and -0.48% (95%CI: -0.85%, -0.12%) in people aged <65 years, -0.65% (95%CI: -1.06%, -0.23%) in NSTEMI cases and -0.48% (95%CI: -0.86%, -0.10%) in STEMI cases, as well as -0.76% (95%CI: -1.69%, 0.17%) in Southern residents and -0.33% (95%CI: -0.43%, -0.22%) in Northern residents (Figure 5 and Table S9). Detailed results of stratified analyses for annual changes of chemical constituents-attributed AFs are provided in Tables S10-S14.

Sensitivity analyses

The results from sensitivity analyses showed the robustness in our findings (Table S15). Altering the $PM_{2.5}$ mass exposure windows (lag02, lag03 and lag04 days) did not substantially change the associations between $PM_{2.5}$ mass with AMI morbidity. Two-pollutants models adjusting for MDA8 O_3, SO_2, CO, and NO_2 also showed similar results with that from the main models. Moreover, the results indicated that the associations of $PM_{2.5}$ mass and chemical constituents with AMI onset did not change substantially between 2017-2020 and 2017-2019.

DISCUSSION

This nationwide study is the first to investigate the temporal trends in burden of AMI morbidity attributable to $PM_{2.5}$ and its chemical constituents. This study revealed several notable discoveries: First, we found that $PM_{2.5}$ mass and chemical constituents were associated with the risk of AMI onset. Second, the AMI burden from $PM_{2.5}$ mass and its constituents significantly decreased during 2017 to 2020, with steeper reductions among females, elderly people, NSTEMI cases, and residents of Southern China. Our findings highlight the substantial health benefits of Chinese air pollution prevention and offer valuable insights for other developing countries, underscoring the advantages of reducing air pollution levels.

This study first reported that short-term exposure to $PM_{2.5}$ and chemical constituents were positively associated with AMI onset, consistent with previous studies.[9,63-65] The toxicity of $PM_{2.5}$ mass largely depend on its chemical constituents, with OM and SO_4^{2-} demonstrating greater associations than other chemical components (Figure S9). OM is a marker of the particles from combustion of fossil fuels, biomass and secondary production from oxidation of organic gases.[66,67] Besides, OM composition in $PM_{2.5}$ mass is a complicated mixture comprised of a multitude of trace chemicals, incorporating polycyclic aromatic hydrocarbons (PAHs), hopanes, methoxyphenols,

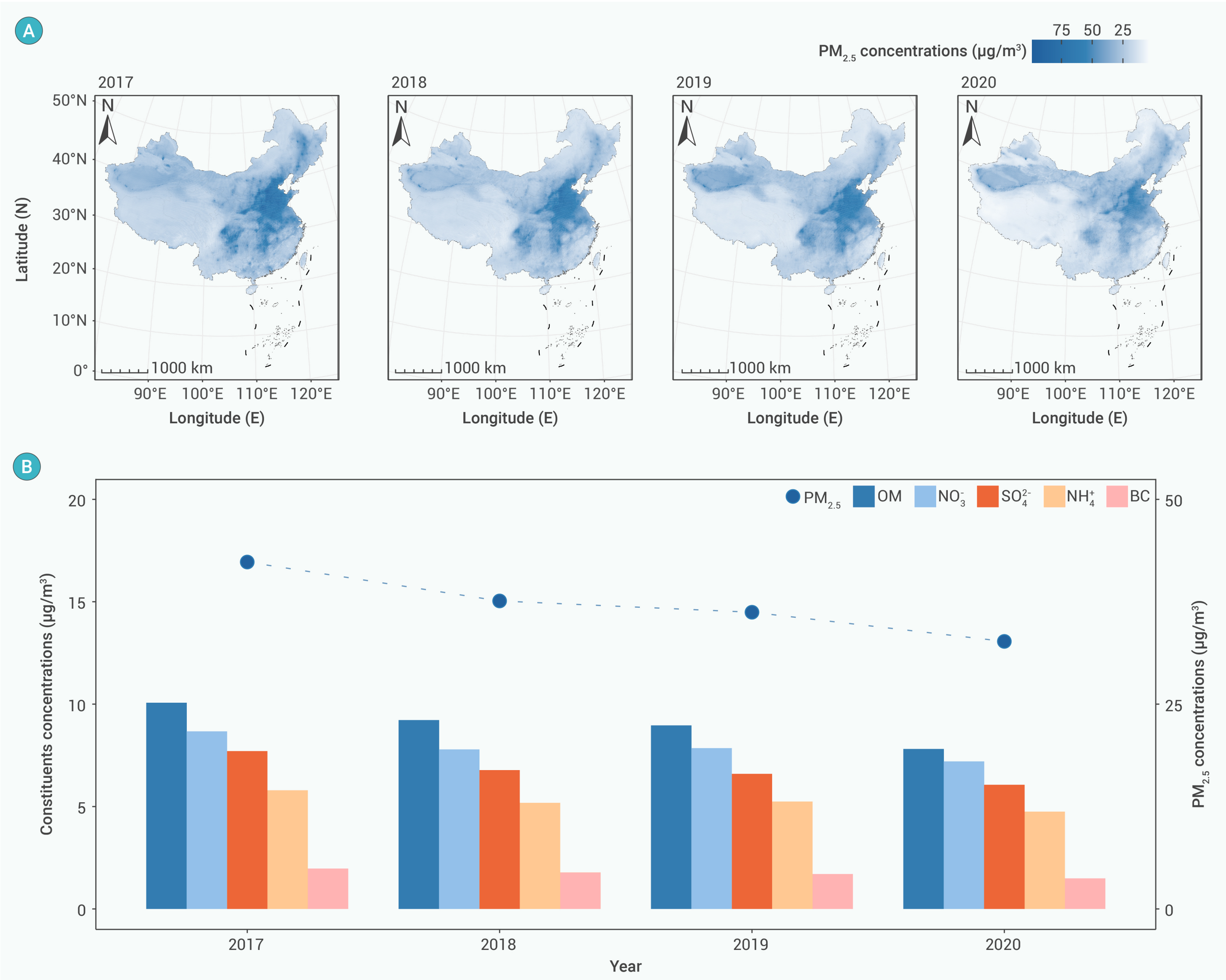

Figure 2. Spatial distribution of $PM_{2.5}$ concentrations (A) and the changes in concentrations of $PM_{2.5}$ mass and its chemical constituents (B) during 2017 to 2020 in China.

and so forth.[68] The exposure to OM would lead to a considerable risk to human health by multiple pathological pathways, including oxidative stress, systemic inflammation, and atherosclerosis development.[69,70] SO_4^{2-}, a water-soluble ion, is a secondary inorganic aerosol generated in the atmosphere from precursor substances.[66,71] SO_4^{2-} fraction of $PM_{2.5}$ mass could induce platelet aggregation and stimulate vascular proliferation, consequently augmenting the risk of cardiovascular disease.[72] In view of these associations between $PM_{2.5}$ chemical constituents and AMI onset, further comprehensive analyses are required to elucidate the mechanisms of how $PM_{2.5}$ chemical components trigger the AMI onset.

We further observed substantial declines of $PM_{2.5}$ related morbidity burden of AMI as indicated by AF during the study periods. AF serves as a quantitative metric that assesses the combined impact of alterations in $PM_{2.5}$ concentration and the associated exposure-response relationship between $PM_{2.5}$ with AMI risk. Consistent with prior studies, our study revealed that both $PM_{2.5}$ levels and its associations on AMI declined substantially, contributing to the reduction of AMI morbidity burden.[24,73,74] However, it is noteworthy that some studies have reported a paradoxical impact, indicating the cardiovascular burden associated with $PM_{2.5}$ may increase over time, even as $PM_{2.5}$ concentrations themselves are being reduced.[25,75] There are several possible explanations for these inconsistences. First, changes in the chemical compositions of $PM_{2.5}$ may influence the observed temporal trends in AFs. Our research indicated that several $PM_{2.5}$ constituents with stronger associations on human health, such as OM and SO_4^{2-}, exhibited greater reductions (Table S8). As a result, the AMI burden largely decreased after the $PM_{2.5}$ concentration was substantially controlled across China. In contrast, the proportion of more toxic components was larger and even increased in the developed countries,[76] amplifying detrimental effects. For example, Li et al. uncovered an increase in the fraction of organic matter (OM) within particulate matter in the United States from 1998 to 2019. This observation was attributed to the growing prevalence of volatile organic compounds (VOCs) emanating from volatile chemical products, which have surpassed VOC emissions from vehicles.[76] Second, disparities in population characteristics, geographical factors, socioeconomic status, air quality standards and implemented policies may contribute to the variations of morbidity burden in the temporal trend.[25,28,75,77] For instance, the rapid ageing process of population in developed countries may enhance susceptibility to air pollution.[28]

Our findings robustly highlight the substantial health benefits from air pollution control efforts. Over the past decade, Chinese governments have implemented a series of rigorous policies to control air pollution nationwide.[30-32] In addition, it might be attributed to the increasing public health awareness and the implementation of targeted behavioral interventions aiming at reducing air pollution exposure (e.g., mask-wearing, staying at home and the use of air purifiers), leading to relatively lower disease burden of AMI.[59] The significant health benefits in China serve as a valuable example for other countries facing high levels of air pollution, inspiring them to tackle environmental chal-

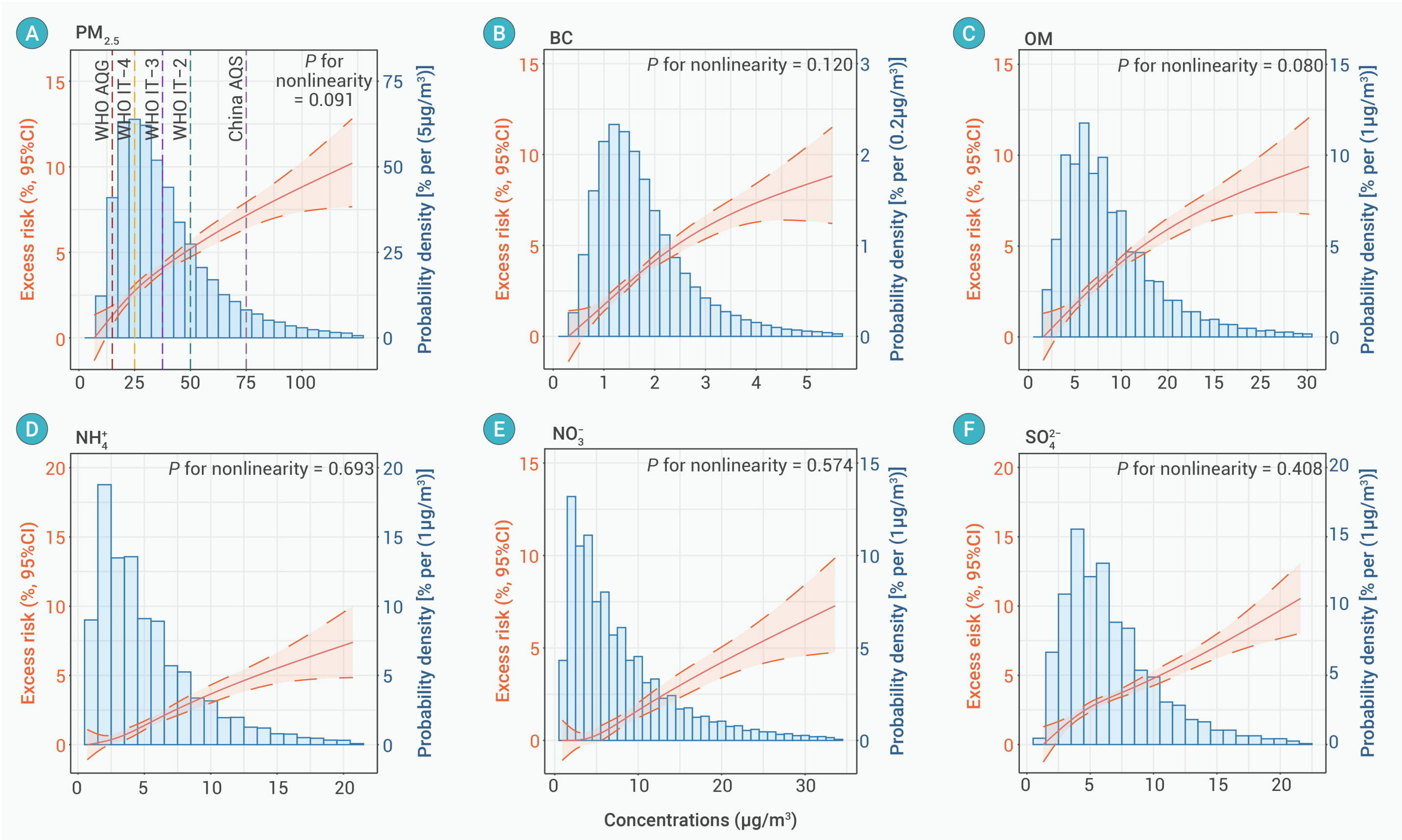

Figure 3. Nonlinear exposure-response associations of short-term exposure to ambient $PM_{2.5}$ and its chemical constituents with overall AMI onset from 2017 to 2020.

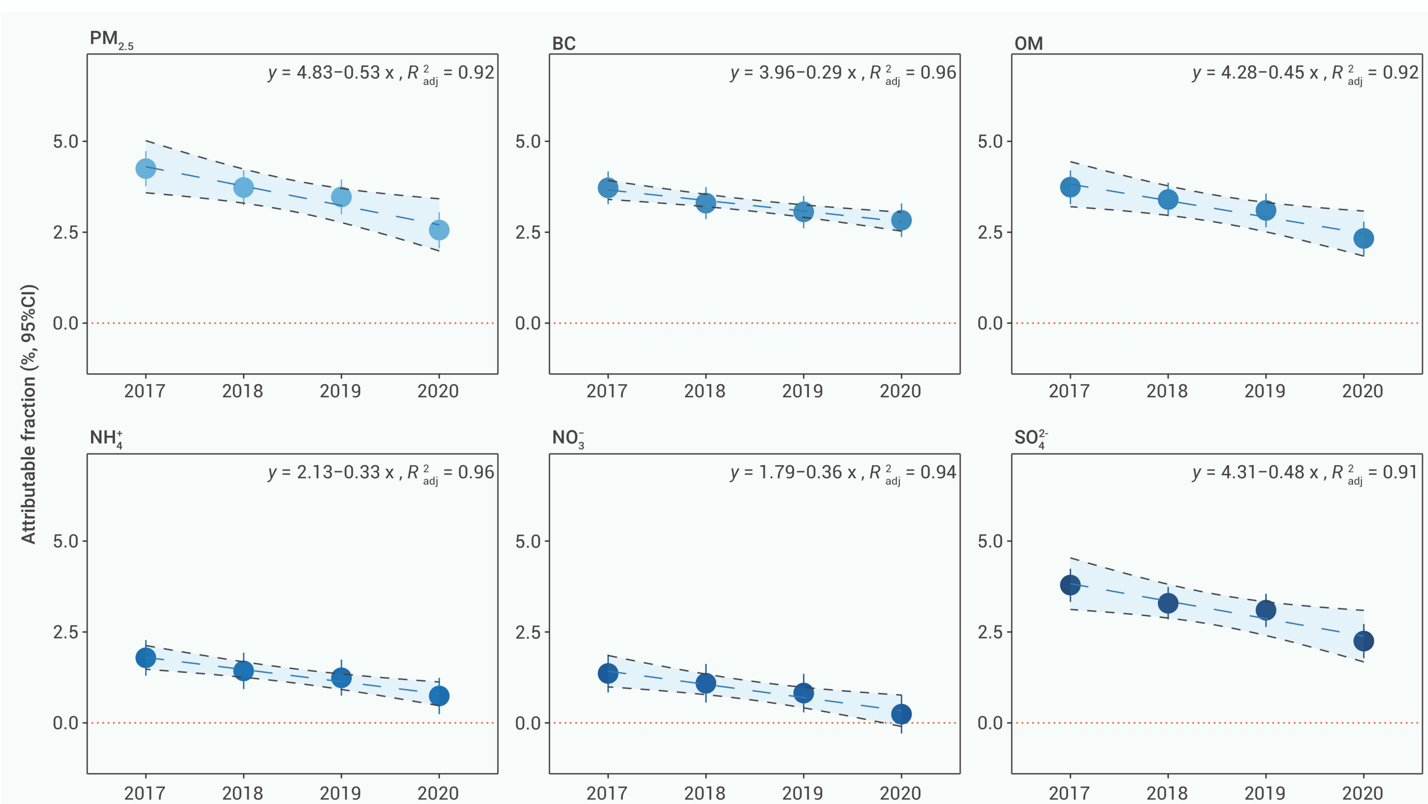

Figure 4. The attributable fraction (AF, %) of AMI onset attributable to short-term exposure to $PM_{2.5}$ and its chemical constituents during 2017 to 2020.

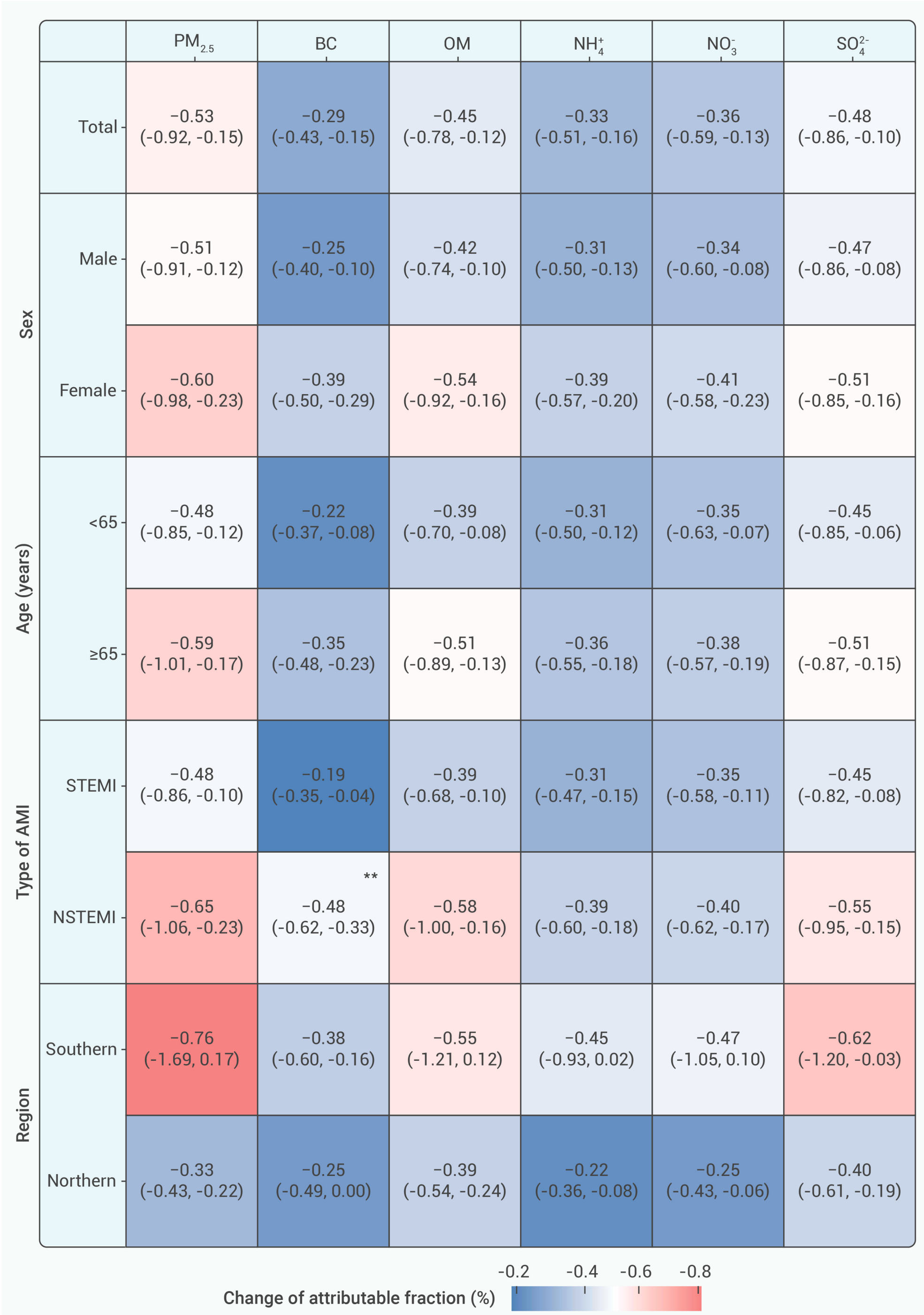

Figure 5. The average change of attributable fraction (AF, %) of AMI onset caused by $PM_{2.5}$ with its chemical constituents' exposure during 2017 to 2020 in different subgroups.

lenges. However, it is important to note that the $PM_{2.5}$-related AMI burden still remain considerably higher in China than in developed countries. Thus, in the long term, urgent multisector actions at government and individual levels are needed to sustainably and persistently improve China's air quality.

Stratified analyses can assist in identifying the sensitive groups. We observed that the greater reduction of AFs caused by $PM_{2.5}$ and chemical constituents per year was observed among females than males. These differences might be ascribed to several reasons. First, compared to males, females tended to exhibit higher particle deposition, and were more susceptible to the oxidative and inflammatory effects of air pollution.[5,78-80] Second, females with AMI usually have more multi-morbidities and traditional risk factors, such as metabolic syndrome, hypertensive disease and chronic kidney disease,[81] which makes them more susceptible to air pollutants exposure.[82,83] As a result, the current decline in $PM_{2.5}$ concentration may be more adequate to mitigate AMI morbidity burden in females than in males.

Results of stratified analyses also revealed steeper declines in the $PM_{2.5}$-attributed burdens of AMI in people aged ≥65 cases compared to those aged <65 years. This age-related difference may partly result from the heightened susceptibility to air pollution in the elderly.[38,84-86] Compared with younger individuals, older people are more vulnerable to adverse environmental conditions due to their weakened metabolic and physiological processes.[87] Worse compensatory capacity would lead to the accumulation of atmospheric particles within the human body, thereby imposing an additional health burden in older population.[88] Additionally, older population is predisposed to developing comorbidities, intensifying the deleterious effects caused by adverse ambient air conditions.[89] Thus, it is evident that enhancing air quality can mitigate $PM_{2.5}$-attributed AMI burden across various age groups, particularly among the elderly, which achieved more substantial reductions in $PM_{2.5}$-attributed AF.

Our analysis also revealed a more significant decline in $PM_{2.5}$-related AMI morbidity burden among NSTEMI patients compared to STEMI patients. The mechanisms underlying the disparity between chemical constituents with AMI subtypes still remains limited. However, several findings provided supports for our findings. Some studies found that stronger associations between $PM_{2.5}$ and NSTEMI than STEMI.[64,87] Therefore, as $PM_{2.5}$ and chemical compositions decreased, the AMI morbidity burden decreased greater in NSTEMI cases than in STEMI cases. We also found a larger reduction in AMI morbidity burden in Southern China compared to Northern China, primarily attributed to more pronounced reductions in $PM_{2.5}$ concentrations in Southern China. For example, the annual average reductions in $PM_{2.5}$ mass concentrations in Southern regions was 3.52μg/m^3/year and the percentage of reductions was 29.47%, while those in Northern regions were respectively 2.30μg/m^3/year and 15.52% (Table S1).

This research presents several notable strengths. First, we provided novel and comprehensive evidence on the trends in AMI morbidity burden attributable to $PM_{2.5}$ with constituents across China. It is beneficial for the public and policymakers to gain a more comprehensive understanding in the health impacts of air pollution. Second, we utilized a nationally representative registry dataset of AMI cases covering major cities and hospitals across mainland China. The large sample size and extensive coverage ensures robust statistical power for analysis to maximize the validity of results. Third, time-stratified case-crossover design could enhance causal inference by controlling for time-invariant confounders at the individual level.

However, several limitations in this study need to be concerned. First, the exposure assessments were based on the county where the included hospital was located rather than individual residential addresses due to the privacy concerns, potentially introducing nondifferential misclassification bias in exposure assessment.[46] Bergen et al. reported that such measurement error would potentially underestimate pollutant-related health risk.[90] Nevertheless, such misclassification bias may be mitigated because AMI cases are usually sent to the nearest hospital for prompt care.[91,92] A study conducted in 21 provinces in China showed that the median time to the hospital for AMI cases arrival was 4 hours, clarifying that the actual distance from the patient's residence to the hospital is generally not very far.[93] Moreover, this measurement error will not influence the linear exposure-response relationships.[94] Therefore, the exposure measurement error is unlikely to significantly affect our findings. Second, only hospitalized AMI cases were included, while patients who died before admission were excluded, which may overlook the most vulnerable AMI cases. Third, although time-stratified case-crossover design can control for time-invariant confounders, several time-varying confounders could not be entirely excluded, such as physical training, alcohol drinking and diets. Fourth, it is worth noting that self-reported time of the AMI onset may be subjected to reporting errors, but they are likely to be random in nature and do not significantly bias our findings.[91] Fifth, exposure assessment was limited to ambient $PM_{2.5}$ measurements and did not account for indoor pollution levels. Given that people spend approximately 80%-90% of their time indoors, and the indoor air quality would significantly influence health outcomes, this limitations could potentially confound the associations between ambient air pollution with AMI morbidity or introduce misclassification bias.[95]

CONCLUSION

This study revealed that the exposure of short-term $PM_{2.5}$ and chemical constituents were significantly associated with AMI onset. In addition, as the concentration of ambient $PM_{2.5}$ and its components declined, the morbidity burden had decreased collectively during 2017 to 2020. The downward trend of burden from AMI onset were greater in females, elderly people, NSTEMI cases, and Southern China. Our findings provide references which could assist governments in establishing targeted policies and driving actions in prevention strategies for AMI and management for air quality across the world.

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AUTHOR CONTRIBUTIONS

TL and KH contributed equally as correspondence authors. TL and KH designed the study. YL and GH are joint first authors with equal contribution. YL and GH coordinated the work, conducted the statistical analysis, and took the lead in drafting the manuscript and interpreting the results. QZ, XX, YL, YH, SY, ZC, YZ, WP, SY, JH, ZL and WM provided substantial scientific input in interpreting the results and drafting the manuscript. KH provided the data and contributed to the revision of the submitted version of the manuscript. TL and WM are the guarantors. All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

ETHICAL STATEMENT AND PATIENT CONSENT

Our study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline, and waived the requirement for informed consent because the study involved analysis of deidentified data.

DATA AND MATERIALS AVAILABILITY

The data of $PM_{2.5}$ and the constituents can be obtained from Tracking Air Pollution in China (TAP, https://tapdata.org.cn/). The data of NO_2, SO_2, CO and MDA8 O_3 have been collected from National Earth System Science Data Center, National Science & Technology Infrastructure of China (http://www.geodata.cn). Meteorological data can be accessed from the fifth generation of European Reanalysis (ERA5, https://www.ecmwf.int/en/forecasts/dataset/ecmwf-reanalysis-v5). The raw AMI case data in this study were obtained from Chinese Cardiovascular Association Database-Chest Pain Center and could not be required because of confidentiality agreement. Code are available from the corresponding author upon reasonable request (send requests to gztt_2002@163.com).

SUPPLEMENTAL INFORMATION

It can be found online at https://doi.org/10.59717/j.xinn-med.2025.100148.