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Article

Cardiovascular Emergency Hospitalization Risks of $PM_{2.5}$ Transition Metals: A Time-Stratified Case-Crossover Study

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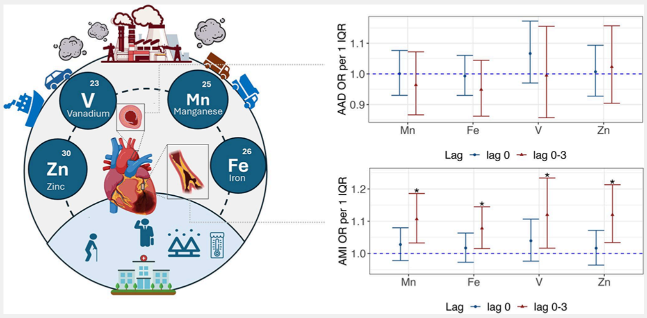
ABSTRACT: $PM_{2.5}$ pollution poses significant health risks in urban areas, yet the specific cardiovascular impacts of its hazardous components, especially transition metals, remain insufficiently understood. This study evaluated the associations of $PM_{2.5}$ components on acute myocardial infarction (AMI) and acute aortic dissections (AAD) emergency hospitalizations (n = 9985) using a time-stratified case-crossover between 2017 and 2023 in Xiamen, China. We collected comprehensive data on daily air pollutants, $PM_{2.5}$ components (water-soluble ions, carbon components, metals, and other elements), and meteorological variables. Conditional logistic regressions were used to estimate odds ratios (OR) per the interquartile range (IQR) of exposures. Our finding reveals significant short-term associations of exposures to air pollutants and $PM_{2.5}$ components with increased cardiovascular emergency hospitalizations. The strongest associations were observed between cumulative 3-day lagged (lag 0−3) $PM_{2.5}$ transition metals including Mn [odds ratio, OR = 1.106 (95% CI: 1.032−1.186)], Fe [OR = 1.078, (95% CI: 1.015−1.145)], V [OR = 1.117 (95% CI: 1.024−1.219)], and Zn [OR = 1.08, (95% CI: 1.005−1.161)] exposure with AMI. These associations were stronger among older (age >65 years), male patients, and during colder seasons. Our study highlights the underexplored subacute cardiovascular risks of $PM_{2.5}$ transition metals, underscoring the need to integrate them into urban air quality management to promote environmental sustainability.



KEYWORDS: *$PM_{2.5}$, transition metals, subacute effects, acute myocardial infarction, acute aortic dissections, environmental sustainability*

1. INTRODUCTION

Cardiovascular diseases (CVDs) remain the foremost drivers of morbidity and mortality across the globe, imposing a substantial public health burden and economic costs, profoundly influenced by environmental factors.[1] According to the World Health Organization, CVD has claimed nearly 17.9 million lives, making up 32% of all deaths worldwide.[2] In China, CVDs stand as the leading contributor to morbidity and mortality, responsible for over 5 million deaths per year.[3,4] Understanding the environmental determinants of these CVD events is crucial to crafting effective public health measures for disease prevention.

Urbanization and industrialization have increased air pollutant emissions in many cities, exacerbating public health issues, particularly cardiovascular diseases.[5,6] Ambient $PM_{2.5}$ (particulate matter measuring under 2.5 μm in aerodynamic diameter) is shown to cause respiratory and cardiovascular events.[7−11] Numerous studies have demonstrated that both short-term (one to a few days) and long-term (a few months to years) exposure to $PM_{2.5}$ can elevate the risks of CVD-related morbidity and mortality,[12−16] with possible mechanisms including increased systemic inflammation, oxidative stress, and translocation of harmful $PM_{2.5}$ components throughout the human body.[17−19] Furthermore, in cities with multiple pollution sources, $PM_{2.5}$ comprises a diverse mixture of solid and liquid particles,[20,21] leading to heterogeneous effects on CVD morbidity and mortality.[22]

While the adverse impacts of $PM_{2.5}$ on cardiovascular health are well-documented, understanding the specific constituents of $PM_{2.5}$ that contribute to these outcomes has gained growing interest. Recent research has emphasized the importance of identifying the toxic components within $PM_{2.5}$, including metals, organic compounds, as well as elemental carbon, each exhibiting distinct cardiovascular health impacts.[23−25] Controlled exposure studies in humans show that elemental carbon can impair peak forearm blood flow response to ischemia.[26,27] Toxicological research reported that various transition metals

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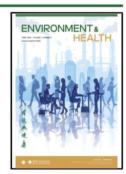

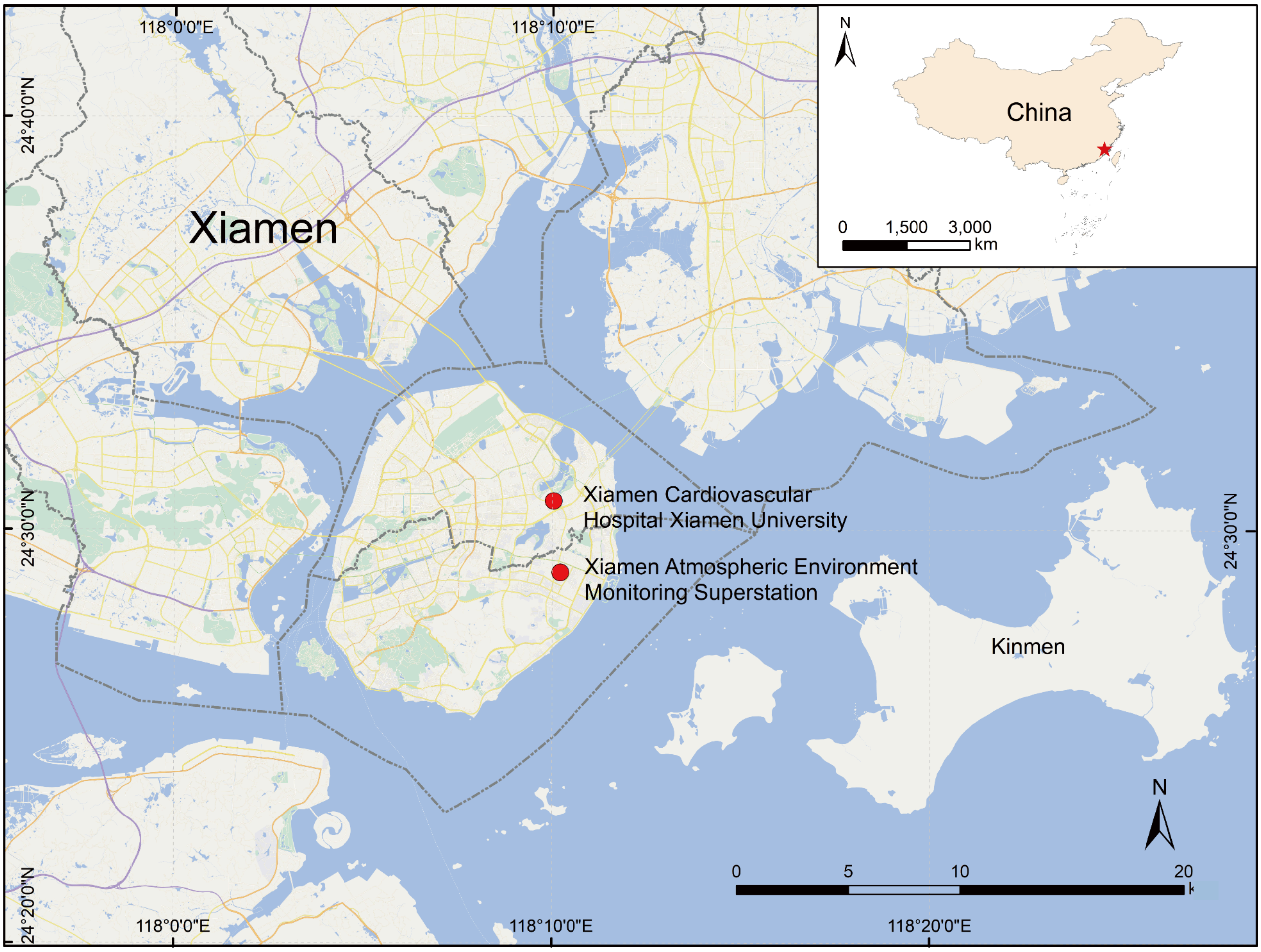

Figure 1. Locations of the monitoring site for air pollution and cardiovascular hospital.

(e.g., iron (Fe), vanadium(V), copper (Cu), nickel (Ni), and zinc (Zn)) and organic carbon compounds can induce oxidative stress and inflammation, thereby potentially causing biological harm.[27,28] To promote effective emission controls targeting harmful $PM_{2.5}$ components, it is crucial to provide epidemiological evidence on which $PM_{2.5}$ constituents pose the most significant cardiovascular health risks, independent of total $PM_{2.5}$ mass. Previous epidemiological research provided evidence showing links between short-term exposure to components of $PM_{2.5}$ and cardiovascular morbidity. They found that elemental carbon, nitrate, ammonia, and sulfate components are closely tied to adverse cardiovascular outcomes.[24,29,30] Recent emerging population studies suggested that transition metal components are also significant determinants of cardiovascular risks from short-term exposure.[31,32] However, these limited studies did not assess specific population group effects or examine the critical exposure window. To date, limited epidemiological evidence is available for the short-term adverse health effects induced by $PM_{2.5}$ components, including metal exposures to CVD morbidity, as well as investigation of critical lag periods.

To address this knowledge gap, we conducted a comprehensive case-crossover study in Xiamen, China, a coastal region with diverse emission sources, using a relatively large sample size and a long-time span. We investigated the associations between a wide range of daily monitored pollutants (including SO_2, NO_2, PM_{10}, $PM_{2.5}$, O_3, PM_1) and $PM_{2.5}$ components, including water-soluble ions (Ca^{2+}, K^+, Mg^{2+}, NH^{4+}, SO_4^{2-}, NO^{3-}, Na^+), carbon components (OC, EC, BC), metals, and other elements (Ca, Cl, Fe, K, Ni, S, Mn, Si, V, Zn), with the two most common cardiovascular emergency hospitalizations (myocardial infarction (AMI) and acute aortic dissections (AAD)) in Xiamen, China. To facilitate public health intervention strategies and identify vulnerable groups, we also aimed to investigate the lag patterns of associations and determine whether associations were stronger by season, age, sex, and hospitalization times.

2. MATERIALS AND METHODS

2.1. Study Area

Xiamen (coordinates: 24°38′ to 24°90′ N, 117°88′ to 117°37′ E) covers an area of approximately 1700.61 km^2 and a population of about 5.33 million in 2023 (http://www.xm.gov.cn/). Xiamen Cardiovascular Hospital Xiamen University (Xiamen Heart Center, XMHC) is located in the central Huli District, as depicted in Figure 1. The fine particles used for $PM_{2.5}$ component analysis were collected from a fixed monitoring site on the rooftop (65 m above ground) of the Xiamen Atmospheric Environment Monitoring Superstation (24.48°N, 118.17°E), situated approximately 3.80 km south of XMHC. Surrounded by roads with heavy traffic, residential apartments, and office buildings, and influenced by shipping emissions, the rooftop sampling presumably reflects ground-level pollution due to vertical mixing within the atmospheric boundary layer, providing a representative measure of overall air pollution levels and $PM_{2.5}$ components across Xiamen. Xiamen features a subtropical maritime monsoon climate and has comparatively lower levels of ambient particulate pollution than other major Chinese cities. However, one of

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the primary air pollutants in Xiamen, $PM_{2.5}$, still exceeds the levels of WHO Global Air Quality Guidelines (5 $\mu g/m^3$),[33] with components originating from multiple sources.

2.2. Data Collection

2.2.1. Cardiovascular Emergency Hospitalization. The AMI and AAD emergency hospitalizations were collected from XMHC from November 17th, 2017−December 29th, 2023. For each emergency hospitalization, we extracted the admission date and demographics, including sex, age, and times of hospitalization. Following the 10th Revision of the International Classification of Diseases (ICD-10),[34] AMI emergency hospitalizations were identified through ICD-10 codes, including I21.0, I21.1, I21.2, I21.3, and I21.9, and AAD emergency hospitalizations were identified using ICD-10 code I71. Hospitalization dates were classified into cold (November to April) and warm (May−October) seasons. This study received approval from the XMHC ethics committee (IRB# 20200110).

2.2.2. Exposure Definition and Measurement. Ambient meteorological factors, concentrations of criteria air pollutants, and the components of $PM_{2.5}$ were monitored at the Xiamen Atmospheric Environment Monitoring Superstation from November 17th, 2017 to December 29th, 2023. Temperature (T), relative humidity (RH), and pressure (P) were recorded using the Lufft WS500 Smart Weather Sensor. $PM_{2.5}$ and PM_{10} were measured using a Thermo 5014i (Thermo Scientific, USA), while PM_1 was measured by a Thermo TEOM-1405 (Thermo Scientific, USA). Sulfur dioxide (SO_2), nitrogen dioxide (NO_2), carbon monoxide (CO), and ozone (O_3) levels were tracked using Thermo 42i, 43i, 48i, and 49i (Thermo Scientific, USA), respectively. For PM measurements, the flow rate was inspected monthly and multipoint calibration was performed biannually. Trace gas analyzers underwent weekly zero and span calibrations, and multipoint calibration was conducted biannually following the Chinese NAAQS GB 3095−2012. Organic carbon (OC) and elemental carbon (EC) levels were tracked using a thermal-optical carbon analyzer (EC/OC-1000, WUXI CAS Photonics, China), while BC concentration was determined by an aethalometer (Model AE33, Aerosol Magee Scientific, Slovenia). Water-soluble ions of $PM_{2.5}$, including calcium ion (Ca^{2+}), magnesium ion (Mg^{2+}), sodium ion (Na^+), potassium ion (K^+), ammonium (NH_4^+), nitrate (NO_3^-), and sulfate (SO_4^{2-}) levels, were assessed daily using an ambient Ion Monitor-Ion Chromatograph (URG9000D, Thermo Scientific, USA). Metals and other elements, as listed in the Supporting Information (SI) text, were extracted from the daily $PM_{2.5}$ filters and measured using X-ray fluorescence techniques (EHM-X200, Skyray Instrument, China). All of the data were collected at an hourly resolution and averaged daily.

The limit of detection (LOD) of criteria air pollutants and particulate matters was provided by the instruments' manufacturer, and the LOD of water-soluble ions, carbon components, metals, and other elements of the $PM_{2.5}$ was determined by the three times the standard deviation of the seven repeated measurements of the same sample.[35] Table S1 lists the LOD of daily air pollutants and $PM_{2.5}$ component concentrations. For measurements below the daily LOD, we used the LOD/2 to replace that value.[31,35] Daily $PM_{2.5}$ component concentrations exceeding six-times the geometric standard deviation of all daily values were considered outliers and excluded. We calculated the percentage of sampling days that were below the LOD or identified as extreme outliers during the study period. We included only those $PM_{2.5}$ components with concentrations above the LOD and components not classified as outliers for at least 85% of the sampling period. Finally, criteria air pollutants and particulate matter (NO_2, O_3, CO, PM_{10}, $PM_{2.5}$, and PM_1), water-soluble ions (K^+, Mg^{2+}, NO_3^-, SO_4^{2-}, Na^+, NH_4^+, and Ca^{2+}), carbon components (EC, OC, and BC), metals, and other elements (Fe, K, Ca, Cl, Mn, Si, S, V, Zn, and Ni) were included in the analysis.

2.3. Statistical Analysis

In this study, a time-stratified case-crossover design was applied to examine the associations between AMI and AAD emergency hospitalizations. This method was widely used for investigating the short-term impact of environmental exposure on health outcomes.[32,36−39] In the case crossover study, each case (patient) will act as the case's own control by comparing exposures on the date (or short lags before) on cardiovascular emergency hospitalizations with the reference exposures in the same month as well as the day of the week before and after the emergency hospitalization date. The case date was defined as the emergency hospitalization date. Control dates included all other dates with the same day of the week (DOW), month, and year. For example, if an emergency department visit occurred on Friday, May 10th, 2019, the control dates will be selected on the same day of the week (DOW) in that month, including May third, May 17th, May 24th, and May 31st, 2019. This design enables us to adjust seasonality, DOW, long-term trends, and individual socioeconomic characteristics (such as age, sex, and socioeconomic status), which were unlikely to change between case dates and control dates.[40] After excluding participants without covariates, meteorological variable, $PM_{2.5}$ air pollution exposure, our study included 9,985 case dates and 33,848 control dates in total.

We employed conditional logistic regression models to investigate the associations of air pollutants (including PM_{10}, SO_2, NO_2, CO, and O_3) and a wide range of $PM_{2.5}$ components with cardiovascular emergency hospitalizations due to AMI and AAD. We estimated the odds ratio (OR) per one interquartile range (IQR) increase of concentrations and the 95% confidence interval of the point estimate. We assessed different lag patterns of exposure to air pollutants and $PM_{2.5}$ components on cardiovascular emergency hospitalizations, including exposure on the same day (lag 0), and the first day to the fourth day before the case or control date (referred to as lag 1 to lag 4), as well as cumulative one-day averaged to four-day averaged before the case or control date (referred to as lag 0−1 to lag 0−4). We conduct single-day and cumulative-day lagged analyses to understand both the acute and subacute effects of air pollutants and $PM_{2.5}$ components and the critical time period of exposure. Each lag of the air pollutant or $PM_{2.5}$ components was included in the model separately. The model also adjusted for natural cubic spline functions with a degree of freedom (*df*) of three of temperature, pressure, and relative humidity as well as a holiday indicator for the case or control date. Lastly, to understand the susceptible subpopulation, subgroup analysis was conducted by sex (female and male), age group (less than 65 years and equal or older than 65 years), number of emergency hospitalizations (first and second or above), and seasons (cold season: between November and April, and warm season: between May and October). All analyses were conducted based on R software (v4.2.3).

3. RESULTS

3.1. Descriptive Results

Table 1 and Figure S1 outline the statistical characteristics of hospital admission cases for AMI and AAD included in the analysis between 2017 and 2023. A total of 9985 cardiovascular emergency hospitalizations were included. The study participants had a mean (standard deviation, SD) age of 62.1 (13.5) years. Among them, 2023 (20.3%) were younger than 50 years, 3758 (37.6%) were between 51 and 65 years, and 4204 (42.1%) were older than 65 years. Most of the participants with cardiovascular emergency hospitalizations were male (7358, 80.2%), with 1980 (19.8%) being female. A vast majority of patients (8762, 87.6%) were hospitalized for the first time, while a smaller fraction (1236, 12.4%) were emergency hospitalized for the second or above times. Most patients were admitted to the hospital due to AMI (7358, 73.7%), and 2627 patients (26.3%) were admitted for AAD. The distribution of case years from 2018 to 2023 shows an increasing trend in patient numbers, with a peak in 2023 accounting for 20.1% (n = 2004) of the cases. The proportion of emergency hospitalizations was slightly higher in the cold season between November and April (n = 5387, 53.9%) than

Table 1. Basic Characteristics of Participants with Acute Cardiovascular Emergency Hospitalizations in Xiamen Cardiovascular Hospital from 2017−2023 (n = 9985)

Characteristics of Study Participants	Mean (SD) or n (%) n = 9985
Age, year	62.1 (13.5)
Age category	
Age ≤50	2023 (20.3%)
50 < Age ≤65	3758 (37.6%)
Age >65	4204 (42.1%)
Times of Emergency Hospitalization from the Same Disease	
1	8762 (87.6%)
2 or above	1236 (12.4%)
Sex	
Female	1980 (19.8%)
Male	8005 (80.2%)
Disease Type	
Acute Myocardial Infarction (AMI)	7358 (73.7%)
Acute Aortic Dissection (AAD)	2627 (26.3%)
Case Year	
2018	1358 (13.6%)
2019	1607 (16.1%)
2020	1342 (13.4%)
2021	1725 (17.3%)
2022	1951 (19.5%)
2023	2004 (20.1%)
Season	
Cold (November−April)	5387 (53.9%)
Warm (May−October)	4598 (46.1%)

that in the warm period between May and October (n = 4598, 46.1%).

Table 2 shows the descriptive statistics of the pollutants over all seasons, and Table S2 shows these separately in the warm and cold seasons. OC, EC, NH_4^+, SO_4^{2-}, and NO_3^- together contributed about 86.43% of the $PM_{2.5}$ mass, whereas the contributions of metals and other elements were much lower. Among the metals and other elements, S and Si were the most abundant. Except for O_3, Cl, and V, the concentrations of most pollutants were higher during the cold season compared to the warm season. Due to some sampling discontinuity and values below LOD, not all case and control days were matched with exposure, but over 60% of case days were matched with valid air pollution exposure levels.

We calculated the Pearson correlations of the pollutants across all the case days (Figure S2 and Table S3). PM_{10} and $PM_{2.5}$ exhibited strong positive correlations (r = 0.748). NO_2 showed moderate positive correlations with both $PM_{2.5}$ (r = 0.439) and PM_{10} (r = 0.340). Additionally, a moderate positive correlation was found between O_3 and PM_{10} (r = 0.375). Among $PM_{2.5}$ components, BC showed the highest correlation with $PM_{2.5}$ (r = 0.679), followed by S (r = 0.651), Mn (r = 0.650), and Fe (r = 0.592). Notably, BC exhibited strong correlations with Mn (r = 0.708), Fe (r = 0.620), and Zn (r = 0.587) and showed significant correlation with air pollutants such as NO_2 (r = 0.714), PM_{10} (r = 0.564), and $PM_{2.5}$ (r = 0.679). OC and EC had a moderate correlation with each other (r = 0.421), while only OC showed a moderate correlation with $PM_{2.5}$ (r = 0.431). Other $PM_{2.5}$ components show moderate to high correlations with each other. Details of $PM_{2.5}$ components correlations were provided in the SI. The moderate to strong correlations among air pollutants and $PM_{2.5}$ components indicated multicollinearity and supported our primary analysis using single pollutant models.

3.2. Regression Results

The relationships among various $PM_{2.5}$ components and the incidence of AMI and AAD were analyzed across different lag periods, including individual days (lag 0 (the same day), lag 1, lag 2, lag 3, and lag 4) and cumulative days (lag 0−1, lag 0−2, lag 0−3, and lag 0−4) (Figure 2, Table S4, Table S5). For AMI, each IQR increase in NO_2 concentration at cumulative lag 0−3, the highest observed lag, was associated with an 8.1% (95% CI: 2.1−14.4%) higher risk of AMI emergency hospitalizations. The highest effects for particulate matters were observed for PM_1 at lag 2 with a 6.4% (95% CI: 0.3−13.0%) increase, $PM_{2.5}$ at cumulative lag 0−3 with a 5.6% (95% CI: 1.0−11.4%) increase, and PM_{10} at cumulative lag 0−3 with a 10.8% (95% CI: 2.5−19.8%) increase in AMI risk. Among water-soluble ions, the most significant association was observed with each IQR increase in NO_3^- at cumulative lag 0−3, leading to a 5.2% (95% CI: 0.0−10.5%) higher risk. Carbon components such as EC, BC, and OC also exhibited the strongest positive effects at lag 0−3, with each IQR increase in the concentrations of EC, BC, and OC associated with a 17.0% (95% CI: 4.5−31.1%), 7.8% (95% CI: 1.2−14.8%), and 10.0% (95% CI: 2.2−18.3%) higher risk of AMI, respectively. Metals and other elements, including Ca, Si, S, Fe, V, Zn, and Mn, exhibited the strongest positive associations at lag 0−3 and gradually attenuated to null at longer lag times, with Ca, Fe, V, Zn, and Mn being the most significant. Each IQR increase in the concentrations of Ca, Fe, V, Zn, and Mn at lag 0−3 showed an increase of 7.7% (95% CI: 2.2−13.5%), 7.8% (95% CI: 1.5−14.5%), 12.0% (95% CI: 1.6−23.4%), 12.0% (95% CI: 3.4−21.3%), and 10.6% (95% CI: 2−15.8%) risk of AMI, respectively. Additionally, V components were significant at lag 1 (7.3% (95% CI:9−14.2%), Fe was significant at lag 2 (4.8% (95% CI: 4−9.4%)) and Zn was significant at lag 3 (7.5% (95% CI: 1.8−13.5%)), respectively, while Mn and Ca both showed significant effects at lag 2 and lag 3. K^+, Mg^{2+}, Ca^{2+}, and K were not significantly associated with AMI emergency hospitalizations. These findings highlight the cumulative exposure's role in increasing AMI risk and the consistent impact of multiple pollutants across different categories. The most pronounced effects were observed within the first few days (lag 0−3) and gradually attenuated with longer lag periods, although most components such as EC, OC, Ca, Fe, V, Zn, and Mn remained significant at lag 0−4.

For AAD emergency hospitalizations, significant associations were found with fewer pollutants compared with AMI, at shorter lag periods. Each IQR increase in SO_2 at lag 1 showed an increase of 7.8% (95% CI: 2.9−12.8%) risk, and cumulative lag 0−1 with an 8.2% (95% CI: 1.2−15.7%) increase. EC showed a significant effect at lag 0, with each IQR increase linked to a 20.1% (95% CI: 2.1−41.3%) higher risk. OC was significant at lag 3, with each IQR increase associated with a 13.2% (95% CI: 2.8−24.6%) higher risk.

In the subgroup analysis, stronger associations between various air pollutants and AMI were observed among those aged >65 years, males, and during the cold season at lag 0−3 (Figure 3, Table S6). Specifically, air pollutants, including NO_2, $PM_{2.5}$, and PM_{10}, as well as EC, BC, OC, and transition metals such as Ca, Mn, Fe, and Zn, along with NO_3^-, were more strongly associated with AMI hospitalization in cold

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Table 2. Air Pollution, $PM_{2.5}$ Component Exposure, and Weather Variables on the Case Day of Acute Cardiovascular Emergency Hospitalizations

		Unit	*n*	Mean	SD	Median	IQR	Q1	Q3
Air Pollutant and Particulate Matters	SO_2	$\mu g/m^3$	9640	9.243	11.773	6.41	6.254	4.24	10.495
	NO_2	$\mu g/m^3$	9985	20.321	11.082	17.87	12.471	12.696	25.167
	O_3	$\mu g/m^3$	9985	95.821	35.829	92.873	51.5	69.25	120.75
	PM_{10}	$\mu g/m^3$	9985	38.026	17.55	35.636	23.304	24.946	48.25
	$PM_{2.5}$	$\mu g/m^3$	9985	18.143	9.155	16.66	10.967	11.879	22.845
	CO	ppm	9985	0.666	0.276	0.637	0.291	0.499	0.79
	PM_1	$\mu g/m^3$	4700	10.679	5.323	9.708	6.917	6.625	13.542
Water-Soluble Ions	NO_3^-	$\mu g/m^3$	9323	2.573	3.034	1.534	2.898	0.555	3.453
	SO_4^{2-}	$\mu g/m^3$	9811	3.278	2.938	2.862	2.482	1.756	4.238
	Na^+	$\mu g/m^3$	9917	0.691	2.519	0.413	0.592	0.12	0.713
	NH_4^+	$\mu g/m^3$	9717	2.238	2.137	1.771	2.019	0.95	2.969
	K^+	$\mu g/m^3$	9794	0.461	2.375	0.125	0.193	0.066	0.258
	Mg^{2+}	$\mu g/m^3$	9841	0.045	0.158	0.021	0.023	0.013	0.036
	Ca^{2+}	$\mu g/m^3$	9898	0.141	0.671	0.078	0.085	0.047	0.132
Carbon Components	OC	$\mu g/m^3$	9421	3.364	1.755	3.388	2.299	2.125	4.424
	EC	$\mu g/m^3$	9461	1.036	0.781	0.931	1.144	0.387	1.531
	BC	$\mu g/m^3$	6058	1.244	0.716	1.092	0.81	0.753	1.563
Metals and Other Elements	Fe	ng/m^3	7006	163.41	123.74	137.04	128.04	81.22	209.26
	K	ng/m^3	6849	220.46	400.21	163.32	170.71	91.33	262.04
	Ca	ng/m^3	7005	111.37	75.78	95.13	70.52	64.3	134.83
	Cl	ng/m^3	7002	233.11	209.39	190.53	149.43	129.62	279.04
	Mn	ng/m^3	7012	14.3	9.55	12.35	10.95	7.57	18.52
	Si	ng/m^3	6999	338.69	286.35	286.26	289.36	159.39	448.75
	S	ng/m^3	7012	1004.45	582.99	916.76	668.65	599.22	1267.87
	V	ng/m^3	6950	3.3	1.9	3.21	3.14	1.1	4.24
	Zn	ng/m^3	6827	51.67	41.91	42.09	50.74	20.77	71.51
	Ni	ng/m^3	6853	5.99	7.42	5	4.7	2.33	7.03
Weather Variables	Temp	°C	9985	21.87	5.81	21.97	10.58	17	27.58
	RH	%	9985	79.7	12.36	81.4	17.27	71.64	88.91
	Pressure	kPa	9985	100.79	0.7	100.82	1.07	100.25	101.32

seasons than in warm seasons. For subgroup analysis by age, slightly stronger associations were observed in the equal or older than 65 years group than the group younger than 65 years. Ca, Mn, Fe, and V showed higher associations among the older population, while OC, EC, and Zn showed stronger associations among the younger population. By sex group, the associations exhibited different patterns, while stronger associations were among males. We found that NO_2, EC, BC, and OC, as well as transition metals Ca, Mn, Fe, and Zn, showed significant associations among males than females. Lastly, we found stronger associations of $PM_{2.5}$ components such as V, Zn, Fe, and Mn on AMI hospitalization among patients who are in the first hospitalization than patients who are in the second or more hospitalizations, even though no statistically significant differences were identified. The subgroup analysis for AAD emergency hospitalization is shown in Figure S3 and Table S6. Similar patterns were observed, indicating that males showed stronger associations between air pollutants and AAD, while the times of hospitalization, age, and season did not show clear differences in these associations. In the multipollutant models, the risks of AMI emergency hospitalizations associated with pollutants remained relatively stable after adjusting for total $PM_{2.5}$ mass and other copollutants (Figure S4, Table S7). This stability was particularly pronounced for EC, Ca, Zn, V, and Mn, although the associations with BC, OC, and Fe were reduced after adjustment.

4. DISCUSSION

This study examined the short-term impacts of various $PM_{2.5}$ components, including water-soluble ions, carbon elements, metals, and other elements, on cardiovascular morbidity across different lag periods. Our results highlight significant associations between exposure to $PM_{2.5}$ components, including carbon elements (BC, EC, and OC), nitrate (NO_3^-), and transition metals (Ca, Fe, V, Zn, and Mn) and the emergency hospitalizations of AMI. Weaker associations were observed for AAD hospitalization. To the best of our knowledge, our study provides the first comprehensive evaluation of the short-term health effects of wide range of $PM_{2.5}$ components, and fills the knowledge gap of subacute effects of $PM_{2.5}$ components, especially transition metals on CVD health.

Among single-day and cumulative lag patterns, we found the cumulative three-day lagged exposure (lag 0−3) to transition metals showed the strongest associations with cardiovascular events. Previous studies, such as Weichenthal et al. (2021),[32] Liu et al. (2016),[41] and Sarnat et al. (2015),[42] only assessed the same day effect of (lag 0) metals within $PM_{2.5}$ on all CVD emergency visits or hospitalizations. Only Basagaña et al. (2015)[43] and Lu et al. (2019)[24] analyzed effects at single lags but without cumulative lags. In contrast, our study investigated lag patterns and found the highest effects of Fe, Zn, Mn, and V at lags of 0−3 for associations with AMI, a specific cause of CVD hospitalizations. Another significant advancement of our study over previous research is the implementation of a time-stratified case-crossover approach in China. This design, with

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Figure 2. Estimated odds ratio (OR) of AMI and AAD emergency hospitalizations per 1 interquartile range (IQR) increase of air pollutant and $PM_{2.5}$ components exposure at different lag patterns. *p-value < 0.05.

its self-control nature, provides a more precise elucidation of the subacute health effects of $PM_{2.5}$ transition metal components on AMI hospitalization. Previous studies predominantly employed a time-series design to explore the relationships among $PM_{2.5}$ components and CVDs. However, these studies often faced challenges related to residual time-varying confounders, such as seasonality, since exposure and health outcomes both show seasonal patterns. Currently, the number of studies regarding metal components in PM pollutants is quite limited, and most of the existing studies were conducted in West Europe or North America,[44] while our study offers robust and convincing evidence of the increased morbidity of cause-specific CVD associated with $PM_{2.5}$ transition metal exposures and provides insights into the critical exposure window and vulnerable population.

Among all components of $PM_{2.5}$, we found that these transition metal components exhibit the most robust associations, implying that these components are essential determinants of the health impacts of $PM_{2.5}$. Our findings of significantly increased AMI emergency hospitalizations associated with exposure to Fe and Mn align with findings by Weichenthal et al. (2021)[32] and Lu et al. (2019),[24] while we also found a subacute effect. Though our findings for Fe, Zn, and Mn align with Weichenthal et al. (2021),[32] we did not observe significant effects from S, possibly due to higher S concentrations in our study. However, some other studies reported smaller or nonsignificant effects on all-cause CVD hospitalizations, such as those by Liu et al. (2016)[41] and Basagaña et al. (2015),[43] which found limited or nonsignificant associations for Fe, Zn, Mn, and V. Similarly, Sarnat et al. (2015)[42] and Bell et al. (2014)[45] reported marginal or no

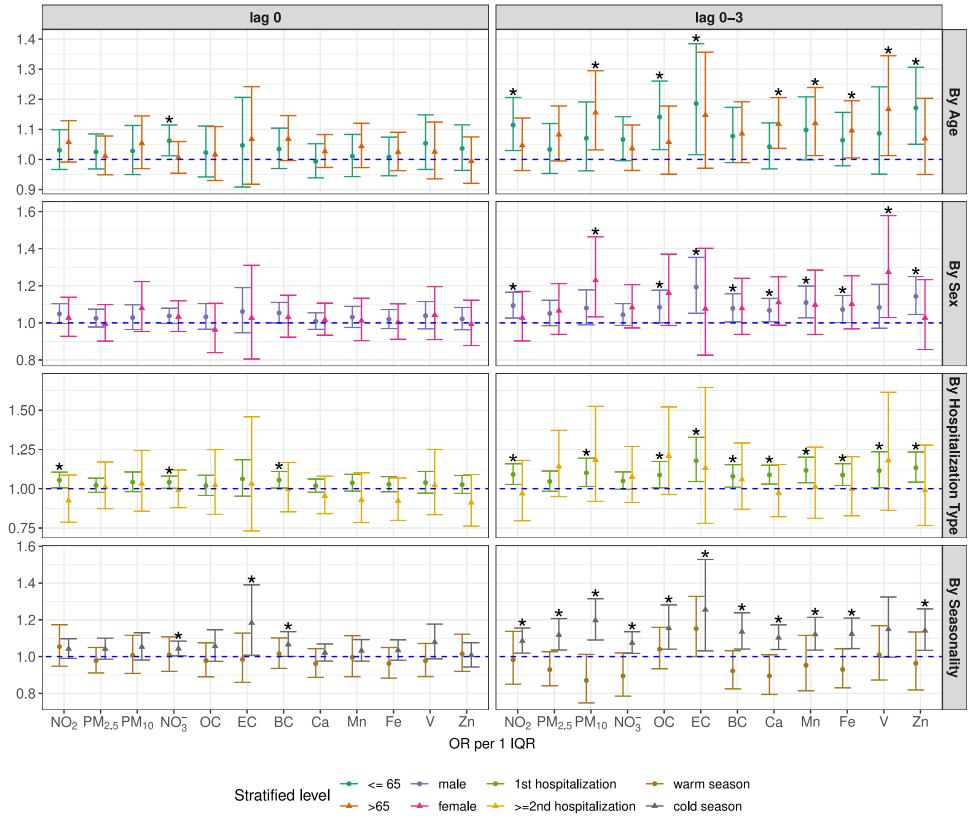

Figure 3. Estimated odds ratios (OR) of AMI emergency hospitalization per interquartile range (IQR) increase of air pollutant and $PM_{2.5}$ components by age, sex, times of hospitalizations, and season. *p-value < 0.05.

significant effects for Zn and V. The main cause of the inconsistencies may be that those studies often focus on all-cause CVD, whereas our research analyzed cause-specific CVD emergency hospitalizations and assessed the cumulative lag effects. Our study's associations between daily mean outdoor NO_2 and PM with CVDs align with previous analyses.[46−48] The findings for OC and EC match Sarnat et al. (2015)[42] but are higher than Ye et al. (2018),[31] while the associations for BC and NO_3^- are consistent with Ma et al. (2023)[47] and also higher than those found by Ye et al. (2018),[31] Zhang et al. (2022),[50] and Tian et al. (2024).[49] Our AAD results for PM, NO_2, CO, and SO_2 are also comparable with previous studies.[13] While further confirmation is warranted, our study provided novel evidence of the independent impacts of $PM_{2.5}$ transition metals on cardiovascular health.

When analyzing results by subgroups, exposure to $PM_{2.5}$ transition metals, including Mn, Fe, and V, was significantly associated with AMI hospitalization in individuals over 65 years, while carbon components like OC, EC, and Zn show stronger effects for those equal to or under 65 years. Similar to our findings, the research of Bell et al. (2014)[45] and Lu et al. (2019)[24] also reported higher effects on groups aged over 65. Among males, the associations with $PM_{2.5}$ components, including EC, BC, and transition metals, were more pronounced than in females, which aligns with studies by Weichenthal et al. (2021)[32] and Huang et al. (2012).[51] However, Lu et al. (2019)[24] found stronger effects among women, and Bell et al. (2013)[52] noted a slightly higher risk in women compared to men. The impact of $PM_{2.5}$ components on AMI was more pronounced during the cold season, consistent with numerous prior findings.[31,51] This may be due to the fact that $PM_{2.5}$ component concentrations were higher in cold months. Inconsistent with us, Liu et al. (2016)[41] reported higher effect estimates for most $PM_{2.5}$ components during the warm seasons in Texas, United States.

Transition metals serve as catalysts and could generate reactive oxygen species (ROS) *in vivo* and within the living systems, resulting in increased oxidative stress levels,[53,54] a major mechanism of cardiovascular health impacts of particulate matter.[27,55] Particle-bound metals and other toxic components can be dissolved in blood and enter circulatory systems. Dissolved zinc ions can induce inflammations, damage mitochondria, increase ROS levels, and induce oxidative stress.[56,57] Other transition metals, including Fe, V, and Mn, could act as catalysts to promote the production of active free radicals and ROS. These elevated ROS and oxidative stress will impair vascular function,[58] promote systemic endothelial damage,[59] and increase systemic inflammations,[60,61] leading to plaque ruptures and the onset of acute cardiovascular events.[13,62] However, transition metals need to be dissolved as metal ions to manifest their biological effects to induce ROS, which takes at least 10−20 h to reach plateaus.[55,63] This process could partially explain our observation regarding the subacute effects of $PM_{2.5}$ transition metals and EC on AMI hospitalizations with the strongest effects observed for cumulative 3-day lags. In addition, other studies on altered biomarkers of oxidative stress and vascular dysfunction from $PM_{2.5}$ and its metal components exposure also support that more robust effects occurred up to exposure periods of 3−6 days.[60,64] These lagged patterns of AMI hospitalizations associated with $PM_{2.5}$ transition metals could imply specific roles of transition metals in the adverse health effects induced by $PM_{2.5}$ exposure.

The identified lagged cardiovascular impacts of $PM_{2.5}$ metals also have important public health implications. For example, relying on 24 h concentrations only could underestimate cardiovascular health risks posed by $PM_{2.5}$ transition metals. In our study area Xiamen, transition metals, including Fe, Zn, Mn, and V, were primarily emitted from dust, traffic, industrial manufacturing, and shipping emissions.[65] While China has implemented stringent measures to reduce overall particulate matter and other pollutants such as NO_x and SO_2, specific controls targeting transition metals such as Mn, Fe, V, and Zn are less clearly defined and require further enhancement. Yan et al. (2022)[66] reported that transition metals such as Fe, Zn, and Mn, which are major components of $PM_{2.5}$, have shown a rebound in mass concentration and an increase in percentage within $PM_{2.5}$ after 2018, despite overall reductions in particulate matter concentrations. The trend of Mn, Fe, V, and Zn during the study period is shown in Figure S5. Hence, regulatory efforts should be strengthened to control $PM_{2.5}$ transition metals to protect the vulnerable groups for AMI hospitalizations we identified in this study, such as males older than 65 years in the colder seasons. To reduce urban exposure to transition metals, specific strategies include strengthening vehicle emission controls with a focus on electric and hybrid vehicles with regenerative braking systems to minimize metal emissions,[67] enforcing stricter regulations and cleaner production technologies in industrial manufacturing,[68] improving port emissions management through measures such as cleaner fuels and port electrification,[69] and promoting green infrastructure to capture particulate matter.[70]

This study has several strengths. First, we leveraged the data extracted from standardized and validated emergency hospitalizations of cardiovascular patients from a major cardiovascular hospital in Xiamen over a long period (6 years) with a relatively large sample size. Second, we included a wide range of $PM_{2.5}$ components in the analysis such as water-soluble ions, carbon elements, metals, and other elements, extending the coverage of components of $PM_{2.5}$ in previous studies. Finally, we utilized a time-stratified case-crossover methodology, investigated various lag effects of individual $PM_{2.5}$ components, independent of total $PM_{2.5}$ mass, and conducted the subgroup analysis to identify vulnerable subpopulations.

Our study also has some limitations. First, we include hospitalization data only from Xiamen, which may affect the generalizability of the findings. Second, we encountered some missing data on certain $PM_{2.5}$ components due to different monitoring start times for these components. Third, we did not have the medical history of patients and their chronic comorbidity information. Lastly, a limitation of this study is the reliance on only one air pollution station in Xiamen to represent exposure for all participants in this city, which may not capture fine-scale variability in individual exposures, potentially leading to exposure misclassification and bias in the associations. Future studies could benefit from incorporating individual-level air pollution predictors, such as residential traffic density and green space metrics, to improve exposure estimates and reduce potential misclassification bias.

5. CONCLUSION

In closing, our time-stratified case-crossover study offers new evidence of the subacute impacts of $PM_{2.5}$ transition metals on severe CVD occurrence. Particularly, elemental carbon (EC) and transition metals (including Fe, Mn, Zn, and V) are found to be related to a higher risk of AMI hospitalizations, with the strongest associations of the cumulative 3 day lagged exposure (lag 0−3). The estimated subacute effects were independent of total $PM_{2.5}$ mass, and stronger associations were observed among older adults and male patients and during colder seasons. The findings of this study imply that transition metals may play essential roles in $PM_{2.5}$-related cardiovascular events and support the inclusion of $PM_{2.5}$ transition metals as regularly monitored pollutants. Our study provides valuable insights for informing targeted interventions and policies to reduce emissions from key sources and improve sustainable urban living environments.

■ ASSOCIATED CONTENT

Data Availability Statement

The code is available upon request to the corresponding author (liaojiaw@usc.edu).

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/envhealth.4c00204.

Correlation matrices, time-series plots of cardiovascular hospitalizations, odds ratios for pollutant exposure, limit of detection, correlations of air pollutants and $PM_{2.5}$ components, results of the sensitivity analysis (PDF)

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Author Contributions

[¶]Lin Wang and Bin Wang are co-first authors and contributed equally. Jiawen Liao and Lina Tang are joint corresponding authors and contributed equally to this work. Lin Wang and Lina Tang conducted the statistical analysis. Jiawen Liao, Lin Wang, Lina Tang, Bin Wang, and Jinshan Yan led the interpretation of the results and were responsible for writing the initial and subsequent drafts of the manuscript. Jieru Zhang, Bin Wang, Jiyi Lin, Xin Su, Wei Xu, Lunche Wang, and Guangfeng Sun provided the data, contributed to interpreting the results, and assisted in preparing the final version of the manuscript. Lin Wang, Jiawen Liao, and Lina Tang conceived and planned the study and meticulously reviewed and edited the manuscript.

Notes

The authors declare no competing financial interest.

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