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Ambient $PM_{2.5}$ Chemical Composition and Cardiovascular Disease Hospitalizations in China

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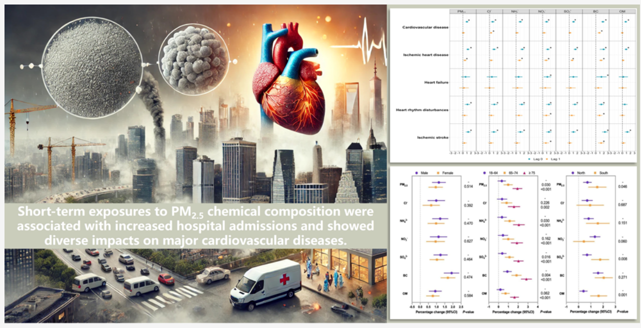
ABSTRACT: Little is known about the impacts of specific chemical components on cardiovascular hospitalizations. We examined the relationships of $PM_{2.5}$ chemical composition and daily hospitalizations for cardiovascular disease in 184 Chinese cities. Acute $PM_{2.5}$ chemical composition exposures were linked to higher cardiovascular disease hospitalizations on the same day and the percentage change of cardiovascular admission was the highest at 1.76% (95% CI, 1.36−2.16%) per interquartile range increase in BC, followed by 1.07% (0.72−1.43%) for SO_4^{2-}, 1.04% (0.63−1.46%) for NH_4^+, 0.99% (0.55−1.43%) for NO_3^-, 0.83% (0.50−1.17%) for OM, and 0.80% (0.34%−1.26%) for Cl^-. Similar findings were observed for all cause-specific major cardiovascular diseases, except for heart rhythm disturbances. Short-term exposures to $PM_{2.5}$ chemical composition were related to higher admissions and showed diverse impacts on major cardiovascular diseases.



KEYWORDS: *$PM_{2.5}$ chemical composition, black carbon, short-term exposure, hospital admission, cardiovascular disease*

■ INTRODUCTION

Cardiovascular disease is a major threat to global public health. Globally, there were 55.45 million incident cases of cardiovascular disease and 18.56 million deaths in 2019.[1] China suffers a huge public health burden from cardiovascular disease. Approximately 330 million people in China suffer from cardiovascular disease, and the rural and urban mortality rates of cardiovascular disease are 323.29 and 277.92 per 100 000, respectively.[2]

Ambient particulate matter pollution emerged as the foremost cause of the global health burden in 2021.[3] Prior studies have indicated that ambient particulate matter, particularly $PM_{2.5}$, was related to morbidity and mortality of cardiovascular diseases.[4] Hospital admission is a pivotal end point in epidemiologic studies, crucial for assessing the wide-ranging health impacts of air pollution on the general population. It provides a means to explore the temporal delay between air pollution and clinical manifestation of diseases.[5,6] Our previous study reported that acute $PM_{2.5}$ exposure was related to increased cardiovascular disease admissions in China.[7]

Previous studies and regulations aimed at safeguarding public health from airborne particles have predominantly focused on the risks associated with the total particle mass, neglecting other particle characteristics aside from size.[7] In reality, $PM_{2.5}$ consists of a diverse mixture of components. For example, $PM_{2.5}$ composition comes from various sources, e.g., sulfate (SO_4^{2-}) is generally from fossil fuel burning, and nitrate (NO_3^-) is mainly from vehicles. While toxicological studies have demonstrated associations between PM constituents and different health outcomes, only a limited number of these findings have been corroborated in epidemiological research.[8] The limited understanding of the varying toxicity of different PM components poses a challenge to control programs aimed at reducing the public health impact caused by airborne PM. Establishing more focused air quality guidelines that incorporate PM chemical composition requires a scientific basis that is more comprehensive than that currently available. Several agencies have suggested that pinpointing the most harmful chemical components of particles could assist in mitigating or preventing exposure to those specific sources.[9]

Temporal patterns of $PM_{2.5}$ composition may offer fresh insights into the health impacts of $PM_{2.5}$.[10] Varied lag patterns in the $PM_{2.5}$ composition might indicate the effects of different sources. For instance, Kim et al.[10] revealed that elemental and organic carbon typically exhibited more immediate patterns, while SO_4^{2-} and NO_3^- exhibited delayed patterns. China is facing serious air pollution challenges for the rapid urbanization and industrialization.[11] Thus, it is particularly important

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to explore the links of $PM_{2.5}$ composition and cardiovascular hospitalization and identify which components may pose a potential toxicity. While some studies from China have examined the impact of specific $PM_{2.5}$ chemical composition on cardiovascular risk, they were limited to small study area and finite number of chemical composition, and the results were mixed.[12−14] A time-series study conducted in Guangzhou found relationships between organic matter (OM), black carbon (BC), SO_4^{2-}, NO_3^-, and ammonium (NH_4^+), but not chloride (Cl^-), with cardiovascular mortality.[14] Zhang et al.[13] reported increased cardiovascular admissions associated with EC, SO_4^{2-}, NO_3^-, and NH_4^+, but not OM. Another investigation revealed that NH_4^+, SO_4^{2-}, NO_3^-, and Cl^- were correlated with cardiovascular hospitalizations. However, the study did not examine the associations of BC and OM.[12] Furthermore, the impacts of various $PM_{2.5}$ constituents on subtypes of cardiovascular disease are expected to be diverse, but such evidence is scarce. As China has a vast territory, the origins and composition of $PM_{2.5}$ vary widely depending on location, necessitating nationwide studies.[15]

For this study, we performed a national time-series analysis to estimate relationships between $PM_{2.5}$ chemical composition and hospitalizations related to all cardiovascular diseases and cause-specific major cardiovascular disease.

■ METHODS

Study Area. 184 representative cities were included as our study sites based on the availability of hospitalization data. The 184 cities are located throughout the length of China and the specific geographical locations are shown in Figure 1.

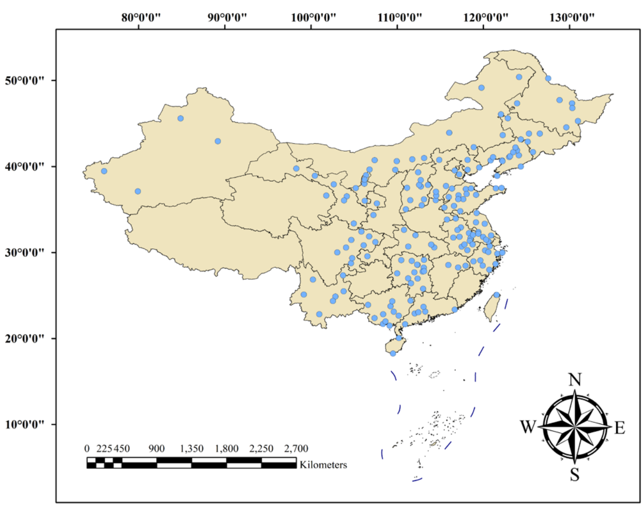

Figure 1. Locations of 184 cities analyzed in this study.

Health Data. China has attained nationwide coverage for health insurance, supported by three primary programs: New Rural Cooperative Medical Scheme, Urban Resident Basic Medical Insurance, and Urban Employee Basic Medical Insurance (UEBMI). Private medical insurance offers minimal coverage and usually serves as a supplement to basic insurance plans. At the end of 2011, these three programs covered 92% of the entire Chinese population.[16]

The daily hospital admission records used in this analysis were sourced from the UEBMI database for the period from 2014 to 2017. The UEBMI provides coverage for urban employees and retirees aged 18 years and above.[17] In 2016, the UEBMI database included 282.93 million beneficiaries in 31 provincial administrative regions. We retrieved anonymized patient data such as age, gender, home address, admission date, and primary diagnosis from each record. Hospitalizations for cardiovascular diseases were identified using primary diagnosis as defined by the International Classification of Diseases, 10th Revision (ICD-10) and included ischemic heart disease (I20−I25), heart failure (I50), heart rhythm disturbances (I47−I49), and ischemic stroke (I63).[7] The outcome in this study was a city-specific daily count of hospitalizations for CVD and its subtypes.

Air Pollutant and Meteorological Data. The daily ambient $PM_{2.5}$ chemical composition data were gathered from the ChinaHighAirPollutants (CHAP) data set, which was compiled by integrating big data from the ground, satellites, and models to provide high-spatial-resolution (1 km) ground-level $PM_{2.5}$ chemical components, including SO_4^{2-}, NO_3^-, NH_4^+, Cl^-, BC, and OM. More details can be found elsewhere.[18,19] To briefly summarize, our satellite-derived 1 km ChinaHigh$PM_{2.5}$ product was adopted as the main constraint data together with auxiliary inputs including modeled mass concentrations of $PM_{2.5}$ components, anthropogenic emissions, meteorological characteristics, land-use and populated variables (e.g., vegetation index, elevation, and population density), and the spatiotemporal terms.[20,21] A more powerful spatiotemporal deep forest model was applied to apportion components from total $PM_{2.5}$.[18] The daily estimates were assessed with 10-fold cross-validation approaches, by randomly generating independent training (i.e., 9-fold) and validation (remained 1-fold) samples. Details can be found in our previous paper.[21] Chemical components show strong coefficients of determination (CV-R^2) with ground-based measurements ranging from 0.66 to 0.82 and root-mean-square errors (RMSE) ranging from 1.6 to 6.6 $\mu g/m^3$. Here, we obtained daily population-weighted averages of six $PM_{2.5}$ chemical components within each city for the period 2014−2017.

The meteorological data were derived from the China Meteorological Data Sharing Service System, including daily 24 h average temperature and relative humidity. The city-specific daily environmental data were matched with the city-specific daily count of hospitalizations by date.

Statistical Analysis. Descriptive statistics were performed to outline the overall epidemiological characteristics of reported daily hospitalizations for cardiovascular diseases, $PM_{2.5}$ chemical composition, and meteorological factors.

A common two-stage method was applied to quantify the relation between $PM_{2.5}$ composition and cardiovascular disease. In the first stage, the quantitative city-specific estimates of hospitalizations associated with $PM_{2.5}$ chemical composition exposure were analyzed using a generalized additive model (GAM) employing quasi-Poisson regression, which accommodates overdispersed counts of admissions.[22] Natural cubic splines were employed to control for the confounding effects of meteorological factors and long-term and seasonal trends. The model adjusted for confounding covariates, including day of the week, relative humidity, temperature, and public holidays, as predefined in accordance with prior studies.[7,23] Here is the model as presented

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Table 1. Demographic Characteristics of Individuals Enrolled in the UEBMI Programme in 184 Cities in China in 2017

variable	overall	Southern China[a]	Northern China[a]
number of cities	184	94	90
total	197 230 556	127 263 223	69 967 333
age (years)			
18−64 (%)	172 616 807 (87.5)	113 036 386 (88.8)	59 580 421 (85.2)
65−74 (%)	14 553 516 (7.4)	8 376 202 (6.6)	6 177 314 (8.8)
≥75 (%)	9 645 159 (4.9)	5 448 893 (4.3)	4 196 266 (6.0)
sex			
male (%)	107 209 773 (54.4)	68 600 413 (53.9)	38 609 360 (55.2)
female (%)	90 020 783 (45.6)	58 662 810 (46.1)	31 357 973 (44.8)

[a]Southern and northern regions are separated by the Huai River-Qinling Mountains line.

$$\begin{aligned}\mathrm{Log}[E(Y_t)] = \alpha + \beta(\mathrm{PM}_{2.5}\ \text{chemical composition}) \\ + \text{day of the week} + \text{public holiday} \\ + ns(\text{calendar time}, df = 7/\text{year}) \\ + ns(\text{relative humidity}, df = 3) \\ + ns(\text{temperature}, df = 6)\end{aligned}$$

where: $E(Y_t)$ indicates the expected count of admissions on day t; β represents the log-relative risk of hospitalization associated with a unit increment in $PM_{2.5}$ chemical composition; $ns(\ )$ denotes natural cubic spline function: a natural spline of calendar time with 7 degrees of freedom (df) per year to control for seasonality and long-term trends, and natural splines with 6 df for 6-day moving average temperature and 3 df for 3-day moving average relative humidity to adjust for lagged and nonlinear impacts of meteorology; indicators of day of the week and public holiday to allow for potential variations of admission in a week. This model was in line with prior studies.[7,23−26] To account for the delayed effects of $PM_{2.5}$ chemical composition, we prespecified various lag patterns, including a lag of 0 days (lag 0) indicating a relation between $PM_{2.5}$ chemical composition and hospitalization on the same day and lag 1 denoted the risk associated with $PM_{2.5}$ chemical composition 1 day before the event.

At the second stage, first-stage effect estimates were pooled using multivariate random-effects models at national and regional levels.[7,27] This method is commonly employed to integrate risk estimates across multiple sampling sites, effectively handling within-city statistical error and between-city variability of the true risks.[7,27]

Furthermore, we conducted stratification analyses by sex (male and female), age, and geographical region (north and south regions, defined following the Huai River-Qinling Mountains line) to investigate potential effect modifiers. Two-sample Z-test was utilized to determine whether differences in estimates between subgroups were significant.[28] For example, to test effect differences between sex subgroups, the formula used would be

$$z = \frac{\mathrm{PE}_{\mathrm{male}} - \mathrm{PE}_{\mathrm{female}}}{\sqrt{\mathrm{SE}(E_{\mathrm{male}})^2 - \mathrm{SE}(E_{\mathrm{female}})^2}}$$

We conducted three sensitivity analyses. First, we simultaneously incorporated $PM_{2.5}$ components to derive regression coefficients for each component while accounting for the other components. We excluded NH_4^+ from models containing SO_4^{2-} and NO_3^- due to their high correlation. Instead, NH_4^+ was included in a separate multipollutant model that included SO_4^{2-} or NO_3^- but incorporated the other constituents. Additionally, we made further adjustments for the $PM_{2.5}$ mass in single-constituent models. Third, we examined the associations using case-crossover analysis.

The findings were presented as percentage changes and 95% confidence intervals (CIs) in cardiovascular hospitalizations per interquartile range (IQR) increment of $PM_{2.5}$ chemical composition concentrations. We conducted the first-stage analyses using R version 3.2.2 and the second-stage analyses using Stata 12.

RESULTS

Table 1 depicts the demographic profile of individuals enrolled in the UEBMI program across 184 cities in 2017. Table 2 describes the distribution characteristics of cardiovascular disease admissions, $PM_{2.5}$ chemical composition levels, and meteorological conditions. The annual-average concentration of $PM_{2.5}$ was 46.3 $\mu g/m^3$ (standard deviation, (SD) 14.8 $\mu g/m^3$) across all cities. The annual-average concentrations (SD) of SO_4^{2-}, NO_3^-, NH_4^+, Cl^-, BC, and OM across all cities were 9.8 (3.2), 8.1 (3.5), 6.1 (2.2), 2.0 (0.9), 3.0 (0.9), and 17.4 (6.2) $\mu g/m^3$, respectively. Cities in northern China have higher levels of $PM_{2.5}$, Cl^-, NH_4^+, NO_3^-, and OM and have lower levels of SO_4^{2-} and BC. The temperatures and relative humidity in northern China were much lower than those in southern China. Over the study period, 47 (74) admissions per day per city occurred for cardiovascular disease (Table 2).

The total $PM_{2.5}$ concentration showed highly positive correlations with its six chemical composition, with all Spearman's correlation coefficients >0.78 ($p < 0.001$) (Table 3), while $PM_{2.5}$ main chemical composition showed moderate to high correlations with each other (correlation = 0.51 to 0.92, $p < 0.001$) (Table 3).

Figure 2 presents the relationships of $PM_{2.5}$ chemical compositions with hospitalizations for cardiovascular diseases on lag 0 and lag 1. For the lag day 0, total $PM_{2.5}$ was significantly related to admissions for all cardiovascular diseases (percentage change: 1.00%, 95% CI: 0.65−1.35%, $p < 0.001$), for ischemic heart disease (1.25%, 95% CI: 0.86%−1.63%, $p < 0.001$), for heart rhythm disturbances (1.13%, 95% CI: 0.48%−1.78%, $p = 0.001$), and for ischemic stroke (1.31%, 95% CI: 0.72−1.90%, $p < 0.001$), but not for heart failure (0.66%, 95% CI: −0.44 to 1.75%, $p = 0.236$). Percentage change of the hospital admission on lag 1 $PM_{2.5}$ concentrations was lower than the estimate on the lag 0 for all outcomes, and this similar effects were also observed for all $PM_{2.5}$ chemical composition.

For $PM_{2.5}$ chemical composition on lag 0, acute $PM_{2.5}$ chemical composition exposures were associated with higher

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Table 2. Summary Statistics on Daily Hospital Admissions for All Cardiovascular Diseases, Cause-Specific Major Cardiovascular Diseases, $PM_{2.5}$ Levels, $PM_{2.5}$ Chemical Composition Levels, and Meteorological Conditions in 184 Chinese Cities from 2014 to 2017 by Geographical Region[a,b]

variable	nationwide	South	North
number of cities, *n*	184	94	90
Pollutants			
annual-average $PM_{2.5}$, $\mu g/m^3$ (mean ± SD)	46.3 ± 14.8	43.3 ± 10.9	49.6 ± 17.5
annual-average Cl^-, $\mu g/m^3$ (mean ± SD)	2.0 ± 0.9	1.5 ± 0.5	2.6 ± 0.9
annual-average NH_4^+, $\mu g/m^3$ (mean ± SD)	6.1 ± 2.2	6.0 ± 1.7	6.2 ± 2.6
annual-average NO_3^-, $\mu g/m^3$ (mean ± SD)	8.1 ± 3.5	7.9 ± 3.4	8.2 ± 3.6
annual-average SO_4^{2-}, $\mu g/m^3$ (mean ± SD)	9.8 ± 3.2	9.9 ± 1.8	9.7 ± 4.3
annual-average BC, $\mu g/m^3$ (mean ± SD)	3.0 ± 0.9	3.0 ± 0.8	2.9 ± 1.0
annual-average OM, $\mu g/m^3$ (mean ± SD)	17.4 ± 6.2	15.0 ± 3.8	20.0 ± 7.2
Meteorological Factors			
Annual-average temperature, °C (mean ± SD)	14 ± 5	18 ± 3	10 ± 4
Annual-average relative humidity, % (mean ± SD)	68 ± 12	77 ± 5	57 ± 8
Daily Hospital Admissions (mean ± SD)			
all cardiovascular disease	47 ± 74	33 ± 56	51 ± 87
ischemic heart disease	26 ± 53	20 ± 35	33 ± 66
heart failure	1 ± 5	1 ± 1	1 ± 7
heart rhythm disturbances	2 ± 4	1 ± 1	2 ± 6
ischemic stroke	14 ± 28	12 ± 26	17 ± 29

[a]Abbreviations: SD, standard deviation; PM2.5, fine particulate matter with diameter ≤2.5 μm; SO_4^{2-}, sulfate; NO_3^-, nitrate; NH_4^+, ammonium; Cl^-, chloride; BC, black carbon; OM, organic matter. [b]Southern and northern regions separated by the Huai River-Qinling Mountains line.

Table 3. Spearman's Correlation Coefficients among Daily Concentrations for $PM_{2.5}$ and $PM_{2.5}$ Chemical Composition in 184 Chinese Cities from 2014 to 2017[a,b]

variables	$PM_{2.5}$	Cl^-	NH_4^+	SO_4^{2-}	NO_3^-	BC	OM
$PM_{2.5}$	1.00						
Cl^-	0.78[c]	1.00					
NH_4^+	0.90[c]	0.70[c]	1.00				
SO_4^{2-}	0.84[c]	0.51[c]	0.87[c]	1.00			
NO_3^-	0.89[c]	0.77[c]	0.92[c]	0.77[c]	1.00		
BC	0.79[c]	0.59[c]	0.75[c]	0.70[c]	0.70[c]	1.00	
OM	0.89[c]	0.69[c]	0.65[c]	0.60[c]	0.67[c]	0.66[c]	1.00

[a]Abbreviations: $PM_{2.5}$, fine particulate matter with diameter ≤2.5 μm; SO_4^{2-}, sulfate; NO_3^-, nitrate; NH_4^+, ammonium; Cl^-, chloride; BC, black carbon; OM, organic matter. [b]Number indicates Spearman's correlation coefficients. [c]Indicates $p < 0.01$.

admissions for cardiovascular disease. BC showed the highest percentage change of all cardiovascular disease admissions, followed by SO_4^{2-}, NH_4^+, NO_3^-, OM, and Cl^- (Figure 2). Increases of IQR in the same-day concentrations of Cl^-, NH_4^+, NO_3^-, SO_4^{2-}, BC, and OM exposure were associated with 0.80% (95% CI, 0.34−1.26%), 1.04% (95% CI, 0.63−1.46%), 0.99% (95% CI, 0.55−1.43%), 1.07% (95% CI, 0.72−1.43%), 1.76% (95% CI, 1.36−2.16%), and 0.83% (95% CI, 0.50−1.17%) increases in all cardiovascular disease admissions, respectively. BC also showed the highest hospital admission risk for all major cardiovascular diseases, except for heart rhythm disturbances. For example, percentage change of the ischemic heart disease admission on lag 0 was highest at 1.92% (95% CI: 1.00−2.36%) for BC. This is followed by 1.54% (95% CI: 1.06%−2.01%) for NH_4^+, 1.53% (95% CI: 1.12%−1.94%) for SO_4^{2-}, 1.28% (95% CI: 0.82−1.75%) for NO_3^-, 1.13% (95% CI: 0.64−1.63%) for Cl^-, and 0.93% (95% CI: 0.58−1.29%) for OM, respectively. However, for heart rhythm disturbances, average percentage increases in hospital admissions from high to low were NO_3^- (1.55%, 0.88−2.22%), NH_4^+ (1.43%, 0.73−2.14%), SO_4^{2-} (1.42%, 0.81−2.03%), BC (1.37%, 0.72−2.03%), Cl^- (1.21%, 0.42−2.00%), and OM (0.59%, −0.08 to 1.27%) on lag 0 (Figure 2). BC continued to yield the most significant increases in the sensitivity analyses (Table S1). The case-crossover analysis yielded similar results (Table S2).

Figure 3 lists subgroup-specific associations stratified by sex, age, and geographical region. No evidence for the effect modification by sex was found ($p > 0.05$). Significant age differences, especially in patients aged ≥75 years, were identified for all cardiovascular causes (*p*-values <0.01). The associations between $PM_{2.5}$, SO_4^{2-}, and OM concentrations and cardiovascular disease hospitalizations were stronger in the south region (*p*-values for $PM_{2.5}$, SO_4^{2-}, and OM concentrations were 0.046, 0.008, and 0.001, respectively).

■ DISCUSSION

Based on the nationwide comprehensive data, we examined the relationships between ambient $PM_{2.5}$ composition and hospitalizations of cardiovascular disease in 184 Chinese cities. Short-term $PM_{2.5}$ chemical composition exposures were related to higher cardiovascular disease hospitalizations. For subtypes of cardiovascular disease, most of the $PM_{2.5}$ chemical composition examined similarly yielded significant or nearly significant associations at lag 0 day. We also found that exposure to BC brought the highest percentage change of cardiovascular disease hospital admissions among the six main $PM_{2.5}$ chemical components. We also observed that the greatest increases in cardiovascular disease admissions linked with $PM_{2.5}$ chemical composition were typically among the elderly (especially at ≥75 years). The SO_4^{2-} and OM-related effects were generally stronger among the southern cities of China.

Epidemiological research has explored the potential toxicity of $PM_{2.5}$ composition on cardiovascular admissions at local or regional scales. However, the epidemiologic evidence was mixed. For instance, Peng et al.[29] found that cardiovascular disease hospital admission increased by 0.46% (95% CI, 0.17−0.75%) and 0.68% (95% CI, 0.31−1.06%) per IQR increase in NO_3^- and NH_4^+ in 119 U.S. urban communities, respectively. Similarly, a study including five Southern-Europe cities reported that 1.28% (0.01−2.56%) increase in cardiovascular admission was associated with an IQR increase in SO_4^{2-}.[30] In addition, Zhang et al. found that NH_4^+, SO_4^{2-}, and NO_3^- were associated with cardiovascular admissions in 18 cities in China, but BC and OM were not studied.[12] Meanwhile, some other studies have also reported a lack of relation between the $PM_{2.5}$ constituent and cardiovascular admissions. Liu et al.[31] conducted a time-series study and found that SO_4^{2-}, NO_3^-, NH_4^+, and organic carbon were not statistically significantly

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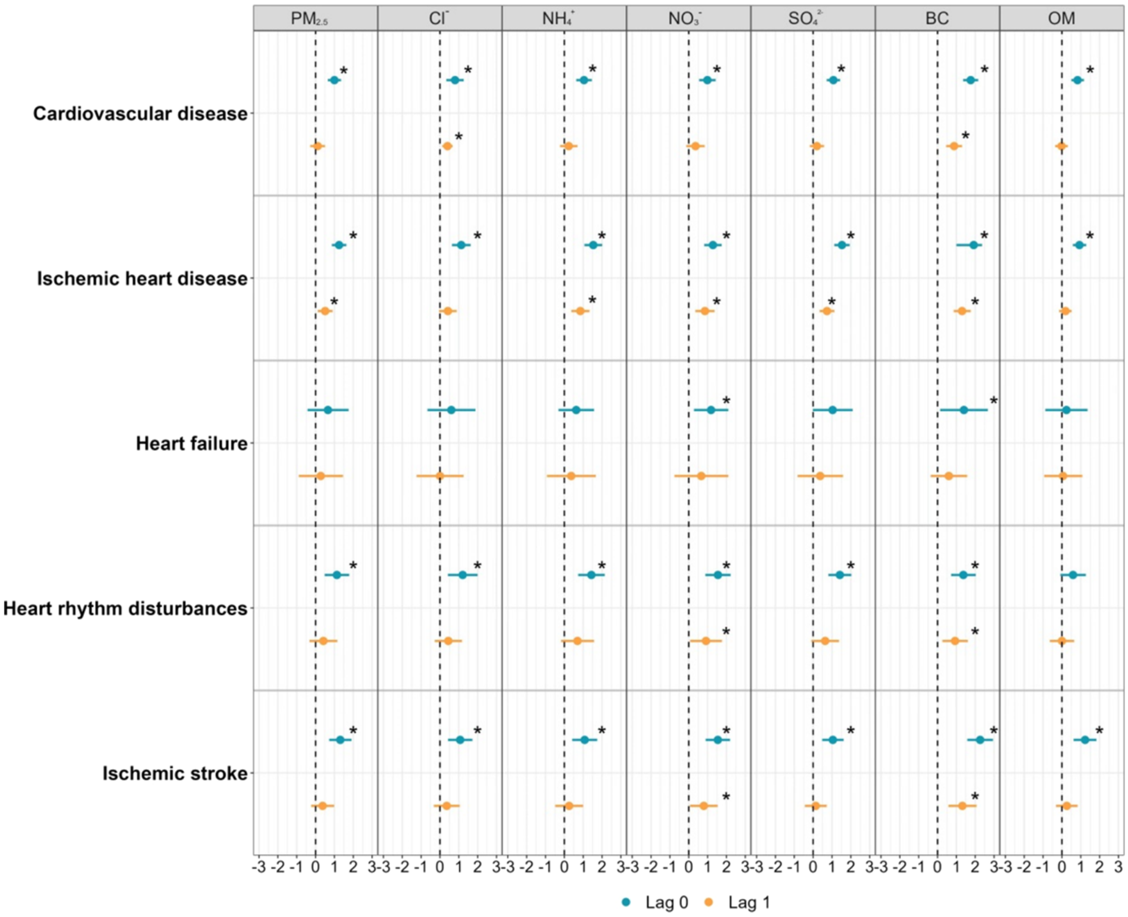

Figure 2. National average estimates and 95% CIs for the percent increase in hospital admissions for all cardiovascular diseases as well as cause-specific major cardiovascular diseases on lag 0 and lag 1 per IQR increase in each of $PM_{2.5}$ and $PM_{2.5}$ chemical composition in 184 Chinese cities during 2014−2017.

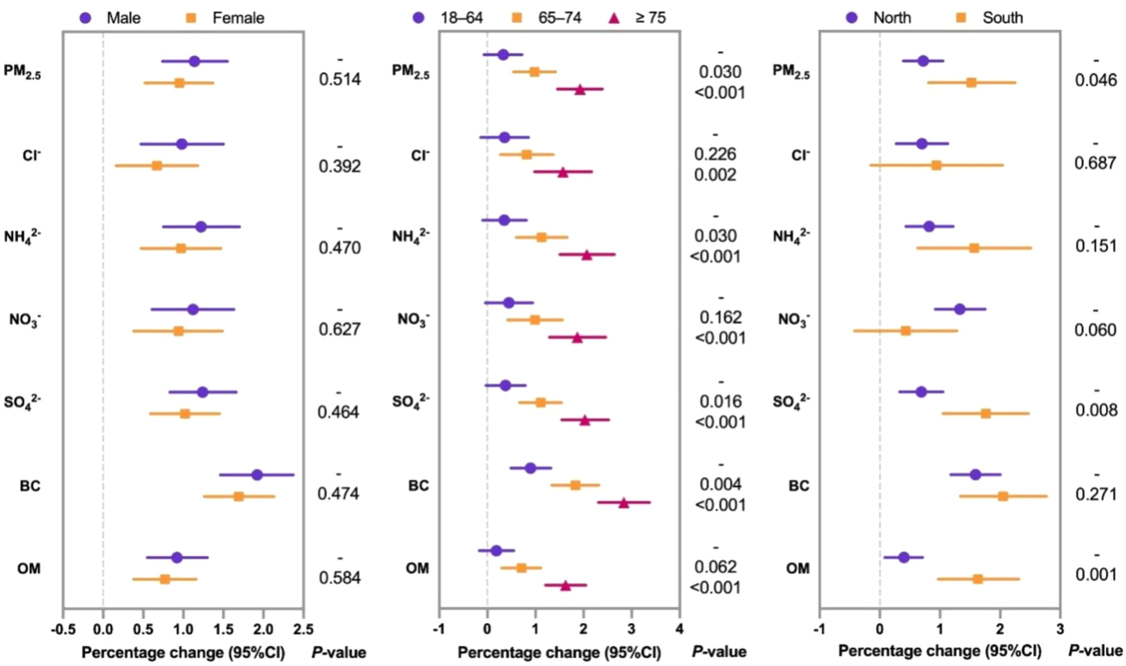

Figure 3. National average percentage change in daily hospital admissions for all cardiovascular diseases per IQR increase in concurrent day concentrations of $PM_{2.5}$ chemical composition (lag 0) stratified by sex, age, and geographical region. *p*-value was calculated based on the two-sample z-test to examine whether between-subgroup differences in the estimated effects.

related to cardiovascular disease hospitalizations in nine counties of Texas. Furthermore, SO_4^{2-} and NO_3^- did not demonstrate an association with an elevated risk in total emergency department visits for cardiovascular causes in Denver.[10] The heterogeneity in effects of $PM_{2.5}$ chemical components on cardiovascular health might be explained by different statistical methods used, exposure assessment methods, and the difference in population and pollution patterns in different regions. It is noteworthy that our results suggest that $PM_{2.5}$ composition was related to cardiovascular disease hospital visits at lag 0. These results imply that acute exposure to $PM_{2.5}$ chemical composition may contribute to increased cardiovascular hospitalizations.

In addition, various subtypes of cardiovascular outcomes showed sensitivity to distinct $PM_{2.5}$ components. For instance, we found no significant link of SO_4^{2-}, NH_4^+, Cl^-, or OM with heart failure hospitalizations. However, these components were significantly associated with other subtypes of cardiovascular disease. Existing evidence suggested significant heterogeneity on the effect of different $PM_{2.5}$ chemical compositions across different subtypes of cardiovascular disease. For example, Zhang et al. found NH_4^+ and NO_3^- were related to ischemic heart disease hospitalization; however, these two constituents had no significant effects on stroke admission in five Chinese cities.[13] In addition to the different biological mechanisms of toxicity caused by $PM_{2.5}$ chemical composition,[32] pathophysiological differences in subtypes of cardiovascular disease also contribute to the heterogeneity of the results.[33] Various cardiovascular diseases have different underlying pathophysiological mechanisms. Air pollution can affect these mechanisms in diverse ways. For instance, it may contribute to inflammation, oxidative stress, endothelial dysfunction, and thrombosis, which can exacerbate certain cardiovascular diseases more than others.[7] Notably, given the smaller number of heart failure admissions in our study, the findings may have been accidental.

In our study, we found immediate estimated impacts on cardiovascular admissions at day lag 0. These immediate effects may stem from rapid cardiac responses triggered by activation of the autonomic nervous system,[34,35] given that individuals tend to seek hospital care promptly upon experiencing cardiovascular symptoms.[7] There is also no evident lag pattern for cause-specific major cardiovascular diseases. Moreover, we found that BC posed the highest risk in terms of hospitalizations for cardiovascular disease. BC is a traffic-related particle produced as a combustion byproduct, which exerts stronger adverse health impacts than $PM_{2.5}$.[36,37] A meta-analysis concluded that the estimate of a 1 $\mu g/m^3$ increase in exposure was larger for black carbon particles compared to $PM_{2.5}$ or PM_{10}.[37] Roger et al.[29] discovered that elemental carbon and organic carbon matter were linked to the highest risks of emergency cardiovascular hospitalization in America. The evidence for BC indicates that transportation sources play a role in causing hazardous impacts.

Individual variations in the relations between $PM_{2.5}$ constituents and cardiovascular hospitalization are of significant interest. Our analyses revealed that old individuals have obviously stronger components-admission associations for cardiovascular causes. This finding is similar to the trend found in previous studies.[13] This age difference may be related to degradation of immune defense systems and biological function, as well as prevalence of morbidity in the elderly. For example, adrenergic dysfunction for old people might contribute significantly to the age-related deterioration in health and responsiveness of the cardiovascular system.[38] Furthermore, the immune system is weakened by advancing age, which can increase vulnerability to and severity of multiple diseases.[39] Our study also suggested that there was notable geographical variability. In our subgroup analyses, point estimates of SO_4^{2-} and OM were significantly higher for the south than for the north. Geographical location differences may be related to various factors, including lifestyle, socioeconomic structure, population susceptibility, geographical conditions, and climate conditions.[40] For instance, the time for outdoor activities at different geographical regions may cause different exposure levels between north and south. Generally, people in warmer areas spend more time outdoors.

Biological responses to $PM_{2.5}$ can vary, depending on its components. However, the impacts of $PM_{2.5}$ chemical components on various cardiovascular diseases remain unclear. There are some underlying mechanisms that could shed light on these associations. For example, SO_4^{2-} and NH_4^+ might induce systematic inflammation and coagulation.[41] NO_3^- can impact endocrine homeostasis by transforming into nitric oxide, altering crucial proteins, and directly disrupting the movement of chloride ions and iodide.[42] The biological mechanisms underlying the cardiopulmonary risks associated with BC and OM likely involve mediation of DNA methylation,[43] promotion of oxidative stress,[44] vasoconstriction, systemic inflammation, and elevation of blood pressure.[45,46] However, some animal studies have noted the effects of carbon particles on heart rate, heart rate variability, and blood pressure, but not on the inflammatory response.[30]

This is the first nationwide research in China that has thoroughly explored the relationship between multiple $PM_{2.5}$ chemical composition and cardiovascular admissions. Our research helps bridge the knowledge gap on this topic on a national scale (in particular in the 184 cities which located throughout the length of China). In addition, we used the largest database on $PM_{2.5}$ components with high-resolution (1 km spatial resolution) available. This study utilized a substantial sample size and conducted an analysis of national data within a consistent framework. This approach provided a distinct opportunity to evaluate correlations with various cardiovascular disease subtypes while minimizing the influence of selection and publication bias. Therefore, our research can offer more reliable assessments of relationships between $PM_{2.5}$ chemical composition and cause-specific cardiovascular disease. Our findings regarding BC indicate that implementing control strategies aimed at its sources could effectively alleviate the public health burden associated with $PM_{2.5}$. Understanding the health impacts of different components is vital for elucidating how $PM_{2.5}$ affects health and will also enhance the development of effective regulations and policymaking regarding $PM_{2.5}$.

Nevertheless, some limitations exist. First, we used the average of measurements in each city to estimate population exposure, perhaps resulting in errors in the exposure estimation. Nevertheless, such nondifferential exposure misclassification typically biases estimates downward.[47] Second, this study included only urban-employed and retired individuals. Given the variations in sociodemographic characteristics and PM levels between rural and urban areas, the applicability of our findings should be approached cautiously. Third, we lacked data on several individual-level attributes, such as weight, height, and comorbidities, which restricted our

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ability to identify potentially vulnerable populations. Fourth, we did not distinguish the source of $PM_{2.5}$ chemical components; the collinearity among the pollutants introduced ambiguity in interpreting the results and constrained our ability to distinguish the independent effects of $PM_{2.5}$ chemical components on cardiovascular hospitalizations. Fifth, only four CVD subtypes were analyzed in this study. More disease definitions should be considered in future research. Sixth, we associated $PM_{2.5}$ chemical composition exposures with CVD events based on hospitalization dates rather than symptom onset dates, potentially leading to nondifferential measurement errors and underestimation of the effect estimates.[17] However, since CVD events typically necessitate urgent care and hospitalization, the measurement error is likely to have a minimal impact on the estimates. This partly supported the acute association (lag 0) observed in the study. Finally, because of the nature of time-series design, we were unable to establish a causal relation of ambient $PM_{2.5}$ chemical composition with cardiovascular admissions. Future studies are required to determine the mechanisms underlying the relationship.

In summary, acute exposures to $PM_{2.5}$ chemical composition, including SO_4^{2-}, NO_3^-, NH_4^+, Cl^-, BC, and OM, were associated with higher cardiovascular admissions. Exposed to BC brought the largest increases in cardiovascular disease hospital visits among the six main $PM_{2.5}$ chemical composition. Relatively larger increases in cardiovascular hospitalizations associated with $PM_{2.5}$ chemical composition were found among the elderly and southern China.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.est.4c05718.

> Sensitivity analysis between $PM_{2.5}$ constituents and hospital admissions for all cardiovascular diseases on lag 0; and analysis using case-crossover analysis (PDF)

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