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Association of ambient particulate matter with hospital admissions, length of hospital stay, and hospital costs due to cardiovascular disease: time-series analysis based on data from the Shanghai Medical Insurance System from 2016 to 2019

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Abstract

Background There is limited evidence supporting a relationship of ambient particulate matter (PM), especially PM_1, with hospital admissions, hospital costs, and length of hospital stay (LOS) due to cardiovascular disease (CVD). We used a generalized additive model (GAM) to estimate the associations of these indicators due to CVD for each 10 μg/m^3 increase in the level of PM_1, $PM_{2.5}$, and PM_{10}, and the attributable risk caused by PM on CVD was determined using the WHO air quality guidelines from 2005 and 2021.

Results For each 10 μg/m^3 increase in the level of each PM and for a 0-day lag time, there were significant increases in daily hospital admissions for CVD (PM_1: 1.006% [95% CI 0.859, 1.153]; $PM_{2.5}$: 0.454% [95% CI 0.377, 0.530]; PM_{10}: 0.263% [95% CI 0.206, 0.320]) and greater daily hospital costs for CVD (PM_1: 523.135 thousand CNY [95% CI 253.111, 793.158]; $PM_{2.5}$: 247.051 thousand CNY [95% CI 106.766, 387.336]; PM_{10}: 141.284 thousand CNY [95% CI 36.195, 246.373]). There were no significant associations between PM and daily LOS. Stratified analyses demonstrated stronger effects in young people and males for daily hospital admissions, and stronger effects in the elderly and males for daily hospital costs. Daily hospital admissions increased linearly with PM concentration up to about 30 μg/m^3 (PM_1), 60 μg/m^3 ($PM_{2.5}$), and 90 μg/m^3 (PM_{10}), with slower increases at higher concentrations. Daily hospital costs had an approximately linear increase with PM concentration at all tested concentrations. In general, hospital admissions, hospital costs, and LOS due to CVD were greater for $PM_{2.5}$ than PM_{10}, and the more stringent 2021 WHO guidelines indicated greater admissions, costs, and LOS due to CVD.

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Conclusions Short-term elevation of PM of different sizes was associated with an increased risk of hospital admissions and hospital costs due to CVD. The relationship with hospital admissions was strongest for men and young individuals, and the relationship with hospital costs was strongest for men and the elderly. Smaller PM is associated with greater risk.

Keywords Ambient particulate matter, Cardiovascular disease, Hospital admissions, Length of hospital stay, Hospital costs, Attributable risk

Introduction

There is increasing concern about the effects of air pollution on public health, and China is one of the most polluted countries in the world due to its rapid industrialization and urbanization [1]. The 2019 Global Burden of Disease Study (GBD2019) showed that air pollution was the fourth-leading risk factor for disability adjusted life years (DALYs) worldwide, and that particulate matter (PM) was responsible for 4.14 million deaths and 118 million DALYs globally during 2019, with 1.42 million (34.30%) of these deaths and 32.9 million (27.88%) of these DALYs in China [2].

Cardiovascular disease (CVD) is the leading cause of mortality and a major contributor to disability worldwide [2, 3]. From 1990 to 2019, the number of CVD cases worldwide increased from 271 million (95% uncertainty interval [UI]: 257 to 285 million) to 523 million (95% UI: 497 to 550 million), and the number of CVD deaths increased from 12.1 million (95% UI: 11.4 to 12.6 million) to 18.6 million (95% UI: 17.1 to 19.7 million). Several measures of the global burden of disease related to CVD (DALYs, years of life lost [YLL], and years lived with disability [YLDs]) have also increased greatly. In particular, from 1990 to 2019 the YLDs related to CVD increased from 17.7 million (95% confidence interval [CI]: 12.9 to 22.5 million) to 34.4 million (95% CI 24.9 to 43.6 million) [3].

Ambient air pollutants are recognized as modifiable risk factors for CVD [4, 5], and many epidemiological studies have shown that PM is associated with CVD [6, 7]. Similarly, many basic medical studies have provided mechanism-level evidence for a relationship between air pollution and CVD. In particular, air pollution can lead to increased oxidative stress, and the direct translocation of PM or secondary mediators produced in response to PM can lead to systemic effects, such as the induction of inflammatory factors [8–10].

Many studies have reported associations of hospital admissions for CVD with short-term increased levels of PM that has an aerodynamic diameter of 10 μm or less (PM_{10}) and 2.5 μm or less ($PM_{2.5}$) [6, 11–14]. However, these reported effects depend on the geographic region, the epidemiological model, and the specific type of PM. Thus, the results of many of these previous studies have limited relevance for Shanghai, which has a permanent population of 24.8 million (according to the seventh national census) and is one of the most polluted cities in China. Although some studies have reported associations of short-term elevations of PM with hospital admissions, length of hospital stay (LOS), and hospital costs [6, 11–13, 15, 16], no study has yet examined the association of PM_1 with all of these indicators of CVD simultaneously, however, these indicators are very important for the formulation of medical policies, the allocation of medical resources and the prevention and control of air pollution [17].

Given this background, we assessed the impact of elevated levels of PM_1, $PM_{2.5}$, and PM_{10} on hospital admissions, LOS, and hospital costs due to CVD in Shanghai.

Materials and methods

Data collection

Patient data

Data on daily hospital admissions, LOS, and hospital costs were from the Shanghai Medical Insurance System for the period of January 1, 2016 to December 31, 2019. The Shanghai Medical Insurance System includes basic medical insurance data for employees and basic medical insurance data for urban and rural residents. By the end of 2019, the number of employees and urban and rural residents covered by basic medical insurance in Shanghai had reached 15.41 million and 3.50 million, respectively, with a total number of 18.91million, accounting for 76% of total permanent population (http://ybj.sh.gov.cn/tjsj).

The original database includes personal data containing patient ID, gender, age, date of hospital admission, LOS, hospital costs, and clinical diagnosis. We then reconstructed the original database into time series data including daily admissions, LOS, and hospital costs for CVD patients with basic demographic information.

Additionally, these data were from all tier 1, tier 2, and tier 3 hospitals in the entire city of Shanghai, and from a period before the imposition of COVID-19-related restrictions. The clinical diagnostic criteria for CVD were disease codes I00 to I99 (Diseases of the Circulatory System) from *International Classification of Diseases, Tenth Revision* (ICD-10) and all patients diagnosed within this disease codes range were enrolled in the study. Basic demographic information included gender and age group (<45 years, 45–64 years, 65–74 years, and ≥75 years). Before data collection, this study was approved by the Ethics Committee of the School of Public Health of Fudan University.

Air pollution data

Data were collected for the seven most common air pollutants: PM_1, $PM_{2.5}$, PM_{10}, nitrogen dioxide (NO_2), sulfur dioxide (SO_2), ozone (O_3), and carbon monoxide (CO). Daily PM_1, $PM_{2.5}$, and PM_{10} concentrations were from the ChinaHighAirPollutants (CHAP) dataset, which has a high resolution (1 km^2) and high quality (https://weijing-rs.github.io/product.html). The PM_{10}, $PM_{2.5}$, and PM_1 dataset was from the latest version of open-source products, and were estimated using the Space-Time-Extra-Trees (STET) model from satellite remote sensing data. Previous research showed that these datasets had good predictability, and the cross-validation coefficients of determination were 0.90 (PM_{10}), 0.92 ($PM_{2.5}$), and 0.83 (PM_1) [18–20]. The daily concentrations of NO_2, O_3, CO, and SO_2 were from the Shanghai Municipal Bureau of Ecological Environment (https://sthj.sh.gov.cn/) from December 28, 2015 to December 31, 2019.

To improve the accuracy of recorded levels, aggregated daily concentrations of PM_1, $PM_{2.5}$, and PM_{10} in Shanghai from December 25, 2015 to December 31, 2019 were calculated [21]. The specific steps used for these calculations were as follows: first, the administrative boundaries of each district of Shanghai were obtained, utilizing Easy-Poi (Baidu version), a simple and free Baidu map poi data acquisition tool. Second, using the "rgdal", "raster" and "sf" packages in R software, daily PM_1, $PM_{2.5}$ and PM_{10} concentrations of 16 districts in Shanghai from December 25, 2015 to December 31 were extracted from the raster data. Third, the weights of the population of 16 districts to the total population of Shanghai were calculated using seventh national census of China (Additional file 1: Table S15). Fourth, the air pollutant concentration of each district was multiplied by the weights obtained in the previous step. Finally, the population-weighted air pollution of the study area was obtained by summing the districts' obtained in the fourth step. Relatively simply, the daily concentrations of NO_2, O_3, CO, and SO_2 were expressed as arithmetic means of all monitoring stations, as in most previous time-series studies [6, 12, 22].

Meteorological data

To control for the potential confounding effects of meteorological factors in the models, daily mean temperature and relative humidity in Shanghai were collected from the National Meteorological Information Center (http://data.cma.cn/) for the period from December 25, 2015 to December 31, 2019. There are 11 ground meteorological stations in Shanghai to collect relevant meteorological data, including temperature, atmospheric pressure, relative humidity, wind speed, precipitation and other factors.

CPI for medical care

Consumer Price Index (CPI) is a relative number that measures the price level of consumer goods and services over time, and comprehensively reflects the changes in the price level of consumer goods and services purchased by residents [23]. Previous research suggested that the Consumer Price Index (CPI) was related to hospital costs in a population [12, 24]. Thus, the monthly CPI for medical care in Shanghai from January, 2016 to December, 2019 were downloaded from the official website of the Shanghai Statistics Bureau (https://tjj.sh.gov.cn/ydsj61/index_2.html). We set the CPI of medical care in January 2016 as the baseline, then the follow-up monthly fixed base CPI was calculated one by one (Additional file 1: Table S16), and finally, the subsequent monthly hospital costs were adjusted with the monthly fixed base CPI (i.e., the hospital costs data we finally included in the study were equivalent to the price level of January, 2016).

Statistical analysis

Means, standard deviations (SDs), and percentiles (P_5, P_{25}, P_{50}, P_{75}, and P_{95}) were used to describe the distributions of air pollutants, meteorological factors, hospital admissions, LOS, and hospital costs due to CVD. A calendar heat map was used to present daily variations of hospital admissions, LOS, and hospital costs due to CVD.

Spearman correlation coefficients were calculated to characterize the relationships of the seven atmospheric pollutants (PM_1, $PM_{2.5}$, PM_{10}, NO_2, SO_2, CO, and O_3) with meteorological factors (daily average temperature, daily average relative humidity).

A generalized additive model (GAM) was used to assess the relationship of PM with daily hospital admissions, LOS, and hospital costs due to CVD. The GAM model, an extension of a generalized linear model, allows analysis of complex nonlinear relationships of variables using a smooth function, as proposed by Hastie and Tibshirani [25], and has been widely used in time series analysis [26–28]. The percentage change of daily admissions and the absolute increases of daily LOS and hospital costs were the dependent variables in the GAM model [6, 12, 16, 22].

The percentage change of daily admissions and the absolute increase of daily LOS and hospital costs as was calculated using the following formulas [6, 13, 22]:

$$\text{Percentage Change} = [\exp(\beta * 10) - 1] * 100,$$

$$\text{Absolute increase} = \beta * 10,$$

where β is the regression coefficient of PM from the GAM model.

The effect of different time lag(t) was examined including five individual lag days: (i) lag 0, the present day, that is, the day patients were admitted; (ii) lag 1, the previous day; (iii) lag 2, the day before lag 1; (iv) lag 3, the day before lag 2; (v) lag 4, the day before lag 3; and four cumulative lag days: (i) lag 01, the 2-day moving average of the present and previous day; (ii) lag 02, the 3-day moving average of the present and previous 2 days; (iii) lag 03, the 4-day moving average of the present and previous 3 days; (iii) lag 04, the 5-day moving average of the present and previous 4 days.

And then, based on preceding studies [22, 29], some covariates were selected, and the degree of freedom (*df*) for the time trends and other meteorological variables were used: 7 *df* per year for the time trends and seasonality, 6 *df* for the daily mean temperature (temp) and 3 *df* for the relative humidity (rh). Additionally, we also adjusted for the day of the week (dow) and public holidays (ph) in the GAM model. Therefore, the main model is shown as follows:

$$\log(E(Yt)) \text{ or } Y't = \alpha + \beta Zt + \text{ns}(\text{time}, 7) + \text{ns}(\text{temp}, 6) + \text{ns}(\text{rh}, 3) + \text{factor}(\text{dow}) + \text{factor}(\text{ph}),$$

where $E(Yt)$ is the estimated daily hospital admissions due to CVD, $Y't$ is the estimated daily LOS or hospital costs due to CVD, Zt is the PM concentration on lag(t) as mentioned above, β is the regression coefficient for Zt, α is the intercept and ns() means natural spline.

The effect of individual characteristics on outcome was investigated using stratified analyses. The subgroup variables included gender and age group (< 45, 45–64, 65–74, and ≥ 75 years). The effect of subgroup variables and PM was tested using a Z statistic [30]:

$$Z = \frac{(\beta_1 - \beta_2)}{\sqrt{\text{SE}_1^2 + \text{SE}_2^2}},$$

where $\beta1$ and $\beta2$ are the effect estimates of the two groups, and SE_1 and SE_2 are their corresponding standard errors.

To better evaluate the burden of CVD due to PM, two different standards were used as reference concentrations: the WHO 2005 Air Quality Guidelines (AQG; https://www.who.int/publications/i/item/WHO-SDE-PHE-OEH-06.02) and the WHO 2021 AQG (https://www.who.int/publications/i/item/9789240034228). The formulas of calculating the attributable number (AN) and population attributable fraction (PAF) of hospital admissions, LOS, and hospital costs due to PM elevation based on previous studies are as follows [6, 13, 16, 22, 31]:

$$\text{AF for admissions} = 1/[\exp(\beta * \Delta\text{Ci}) - 1],$$

$$\text{AN for admissions} = \sum_{i=1}^{n} \text{AF} * \text{daily admissions},$$

$$\text{AN for LOS or costs} = \sum_{i=1}^{n} \beta * \Delta\text{Ci},$$

$$\text{PAF} = \frac{\text{Attributable number}}{\text{Total number}} * 100\%,$$

where AF denotes daily attributable fraction, β denotes the coefficients extracted from the previous GAM model, ΔCi is the difference between actual pollutant concentration and reference pollutant concentration. Total number is the total value of CVD patient admissions, LOS or hospital costs in study period. The difference in calculating *AN* is because different link function is used in GAM model for hospital admissions, LOS and hospital costs.

We characterized the dose–response relationship of PM_1, $PM_{2.5}$, and PM_{10} concentrations with the percentage change of daily hospital admissions, absolute increase of daily LOS, and hospital costs due to CVD, as described previously [22].

Finally, four sensitivity analyses were performed to check whether there were any interactions between pollutants or possible multicollinearity problems and confirm the robustness of the results. First, the results were fit to a two-pollutant model (PM_1, $PM_{2.5}$, PM_{10} with O_3, SO_2, NO_2, CO). Second, the degrees of freedom for calendar time were changed from 5 to 9 per year. Third, the degrees of freedom for temperature were changed from 4 to 8. Finally, the degrees of freedom for relative humidity were changed from 1 to 5.

All statistical analyses were conducted using R software version 4.2.1 with the following packages: splines, MGCV, ggplot2, raster, sf, rgdal, as indicated. EasyPoi (Baidu version) software was used to define the administrative boundaries of all districts in Shanghai. All statistical tests were two-sided, and a P-value less than 0.05 was considered significant.

Results

Descriptive results

We identified 1,896,741 hospital admissions due to CVD (I00–I99 in ICD-10) for the entire city of Shanghai from January 1, 2016 to December 31, 2019. These admissions were associated with 14,829,931 LOS days and hospital costs of 39,981,403 thousand Chinese Yuan (CNY). Among these patients, 51.02% were males and 50.42% were older than 75 years (Table 1). We also presented

Table 1 Mean, SD, and distributions of hospital admissions, LOS, and hospital costs due to cardiovascular disease during the study period, and characteristics of different patient subgroups

Variable	Total	Mean[a]	SD[a]	P_5	P_{25}	P_{50}	P_{75}	P_{95}
Hospital admissions	1,896,741	1298.25	485.83	429	947	1469	1634	1873
LOS (days)	14,829,931	10,150.53	4301.60	3033	6484	11,580	13,013	14,869
Hospital costs[b] (1000 CNY)	39,981,403	27,366	10,402	8104	21,974	29,875	34,715	41,099
Gender								
Male	967,736 (51.02%)	662.38	251.96	210	486	741	838	976
Female	929,005 (48.98%)	635.87	235.76	215	457	726	799	909
Age group, years								
≤45	84,373 (4.45%)	57.75	23.01	18	43	59	73	93
45–64	337,039 (17.77%)	230.69	97.00	62	169	245	302	370
65–75	519,085 (27.37%)	355.29	142.37	103	265	386	457	552
≥75	956,244 (50.42%)	654.51	240.96	229	443	754	817	914

LOS length of hospital stay

[a] Here and below: mean and SD refer to average per day and corresponding standard deviation

[b] Hospital costs were calculated according to CNY in January 2016

these data using a calendar heat map that describes the daily variations in the number of hospital admissions, LOS, and hospital costs due to CVD (Additional file 1: Fig. S1). Analysis of the seven air pollutants indicated the mean daily levels were as follows: PM_1 (21.38 μg/m^3), $PM_{2.5}$ (37.73 μg/m^3), PM_{10} (60.47 μg/m^3), O_3 (97.47 μg/m^3), NO_2 (40.09 μg/m^3), SO_2 (10.01 μg/m^3), and CO (0.67 mg/m^3). The mean daily temperature was 17.66 °C and the mean relative humidity was 73.33% (Table 2).

Correlations of air pollutants and meteorological variables

We calculated Spearman correlation coefficients to examine the relationships of air pollution and meteorological variables (Additional file 1: Table S1 and Fig. S2). The results indicated that daily levels of PM_1, $PM_{2.5}$, and PM_{10} had positive correlations with O_3, NO_2, SO_2, and CO, and negative correlations with temperature and relative humidity.

Effects of different particulate matter and lag times

We then used a GAM model with different lag times to examine the effects of PM_1, $PM_{2.5}$, and PM_{10} on daily hospital admissions, LOS, and hospital costs due to CVD (Fig. 1, Additional file 1: Table S2). Each of the three PMs had a significant positive association with daily hospital admissions and hospital costs, but not with daily LOS. Additionally, as the diameter of PM decreased, the effect was greater, although the increases were not always statistically significant. The number of lag days with the greatest effect differed among the different PMs.

Analysis of the percentage of increased daily hospital admissions indicated the increase for PM_1 was 1.089% (95% CI 0.927, 1.251) for a cumulative 1-day lag (lag 01), the increase for $PM_{2.5}$ was 0.454% (95% CI 0.377, 0.530) for a lag of 0 days (lag 0), and the increase for PM_{10} was 0.263% (95% CI 0.206, 0.320) for a lag of 0 days (lag 0).

For daily hospital costs in thousands of CNY, the increase for PM_1 was 649.703 (95% CI 322.490, 976.916)

Table 2 Mean, SD, and distributions of daily levels of seven air pollutants, temperature, and relative humidity (CHAP dataset)

Variables	Mean	SD	P_5	P_{25}	P_{50}	P_{75}	P_{95}
PM_1, μg/m^3	21.38	11.16	7.69	13.34	18.93	27.01	43.28
$PM_{2.5}$, μg/m^3	37.73	21.39	13.82	22.24	32.35	47.34	78.61
PM_{10}, μg/m^3	60.47	29.25	26.36	38.79	53.18	76.23	115.22
O_3, μg/m^3	97.47	41.6	43	68	90	120	182
NO_2, μg/m^3	40.09	18.12	16	27	37	50	75
SO_2, μg/m^3	10.01	4.75	5	7	9	12	19
CO, mg/m^3	0.67	0.22	0.4	0.5	0.6	0.8	1.1
Temp, °C	17.66	8.72	3.8	10.1	18.5	24.7	30.7
Relative humidity, %	73.33	12.37	51	65	74	83	92

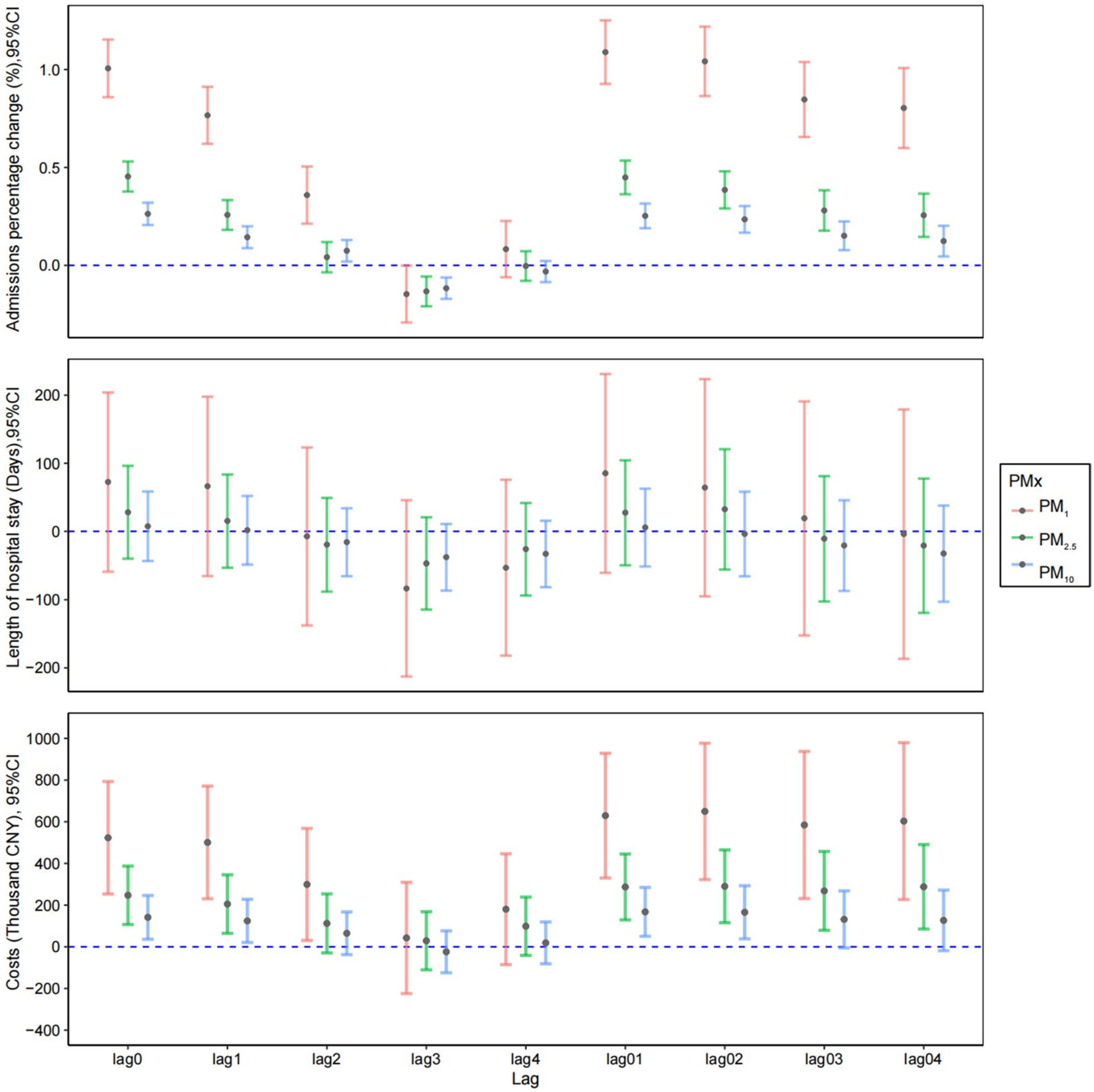

Fig. 1 Effect of different PM and lag time on percentage change in daily hospital admissions, absolute LOS, and absolute hospital costs due to CVD. PM_1, $PM_{2.5}$, and PM_{10} are per 10 μg/m^3 and CNY is Chinese Yuan

for lag 01, the increase for $PM_{2.5}$ was 290.178 (95% CI 115.641, 464.714) for lag 02, and the increase for PM_{10} was 167.635 (95% CI 50.379, 284.890) for lag 02.

Stratified analyses

Subgroup analysis with stratification by gender indicated the effect of PM on daily hospital admissions, LOS, and hospital costs due to CVD were consistently greater in males than females, although most of these differences were not significant for different PM and lag days (Fig. 2, Additional file 1: Tables S3–S5). In general, stratification by age indicated that the associations of PM with daily hospital admissions were greater in patients less than 45 years old (Fig. 3, Additional file 1: Table S6); the associations of PM with daily LOS were greater in patients more than 75 years old, although these associations were not significant (Fig. 3, Additional file 1: Table S7); and the associations of PM with daily hospital costs were greater

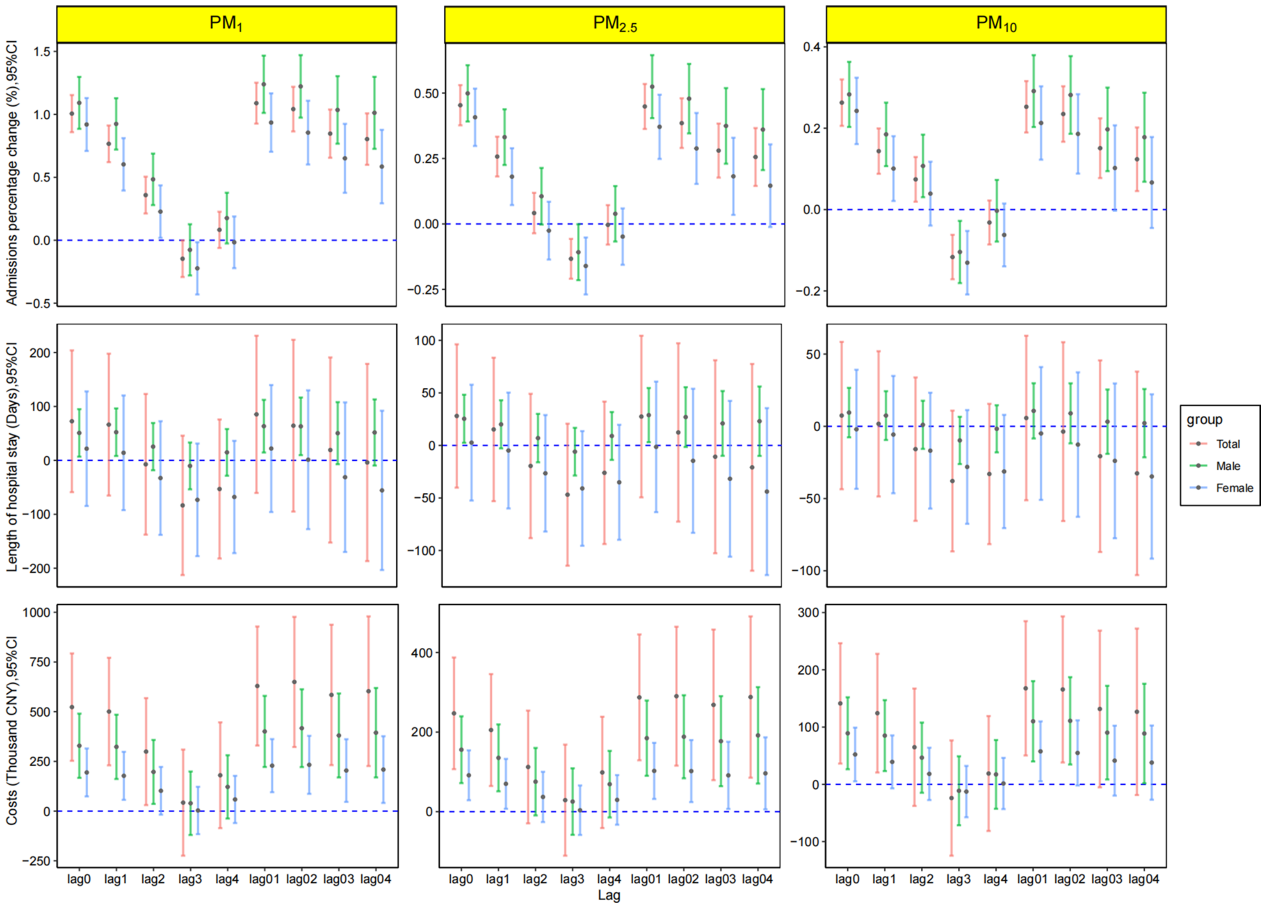

Fig. 2 Effect of PM and lag time on percentage change in daily hospital admissions, LOS, and hospital costs due to CVD for all patients, males, and females. PM_1, $PM_{2.5}$ and PM_{10} are per 10 μg/m^3 and CNY is Chinese Yuan

in patients more than 75 years old (Fig. 3, Additional file 1: Table S8). Additionally, there were significant associations between PM and daily LOS in patients less than 45 years old on some lag days, in contrast to the results from analysis of all patients (Fig. 3, Additional file 1: Table S7).

Attributable risk from particulate matter

We then assessed the attributable risk (i.e., attributable number [AN] and population attributable fraction [PAF]), of air pollutants on hospital admissions, LOS, and hospital costs due to CVD using the WHO 2005 AQG and the WHO 2021 AQG (Table 3). The lower target values in the 2021 AQG were proposed to address concerns related to the high hospital admissions and costs when higher target values were used. In general, hospital admissions, costs, and LOS due to CVD were greater for $PM_{2.5}$ than for PM_{10}, and the more stringent 2021 WHO AQG guidelines indicated greater admissions, costs, and LOS due to CVD. For example, based on the WHO 2021 AQG, from January 1, 2016 to December 31, 2019, the overall total excess hospital admissions were 19,419 (95% CI 16,160, 22,666) due to $PM_{2.5}$ and 7716 (95% CI 6053, 9374) due to PM_{10}; the overall total excess hospital costs in thousands of CNY were 82,0255 (95% CI 354,482, 1,286,027) due to $PM_{2.5}$ and 319,302 (95% CI 81,800, 556,804) due to PM_{10}. The results were similar after stratification by sex and age (Additional file 1: Tables S9, S10).

Effect of different levels of particulate matter

We then analyzed the relationship of different levels of PM_1, $PM_{2.5}$, and PM_{10} with daily hospital admissions, LOS, and hospital costs due to CVD (Fig. 4). The relationships of each PM level with daily hospital admissions were approximately linear at low concentrations (PM_1: 0–30 μg/m^3; $PM_{2.5}$: 0–60 μg/m^3; PM_{10}: 0–90 μg/m^3), but there was a saturation or decrease at high PM concentrations ($PM_1 > 30$ μg/m^3; $PM_{2.5} > 60$ μg/m^3; $PM_{10} > 90$ μg/m^3). There were no significant associations of PM with daily LOS. The relationships of PM_1 and $PM_{2.5}$ with daily hospital costs were approximately linear, but there was a nonlinear relationship for PM_{10}.

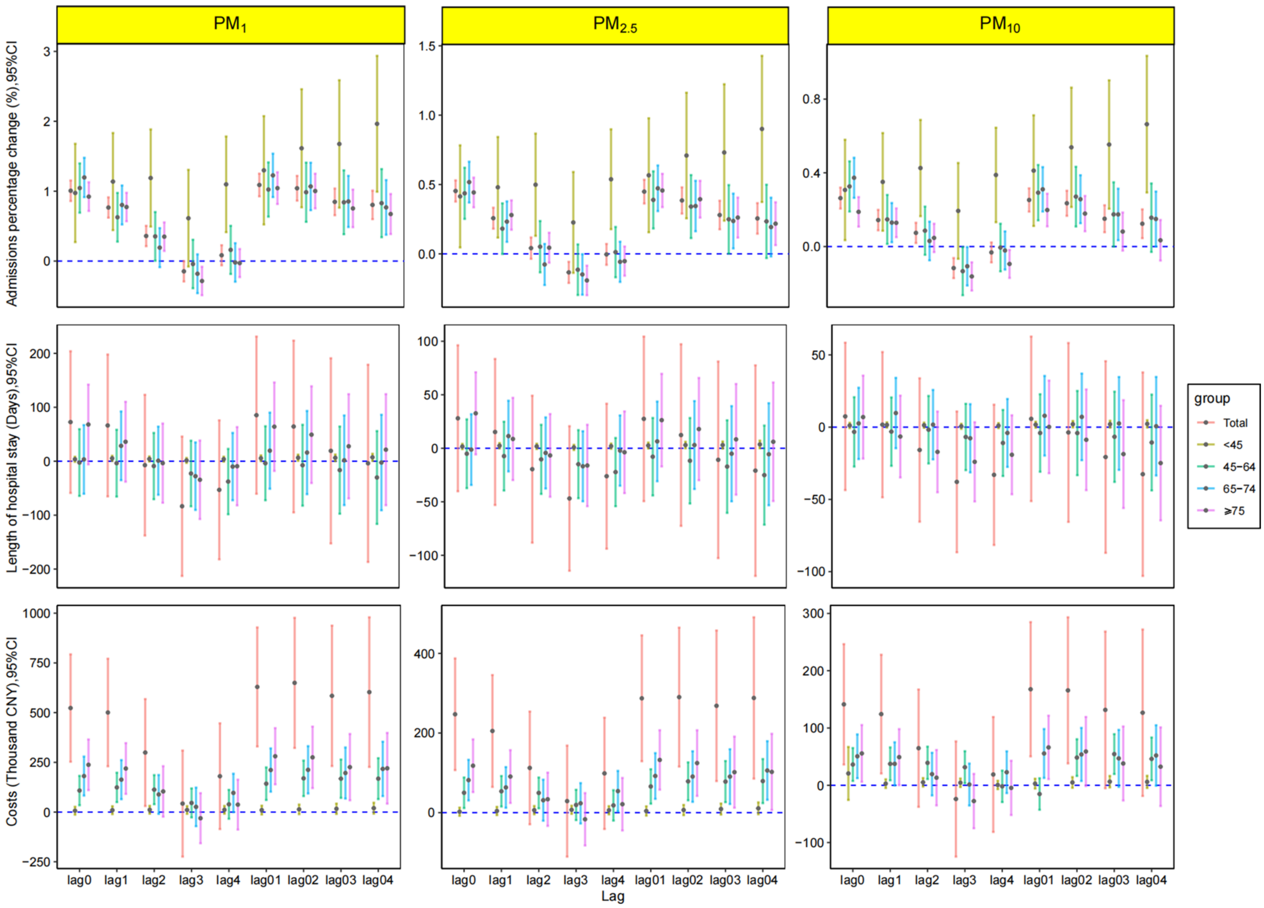

Fig. 3 Effect of PM and lag time on percentage change in daily hospital admissions, LOS, and hospital costs due to CVD in different age groups. PM_1, $PM_{2.5}$ and PM_{10} are per 10 μg/m^3 and CNY is Chinese Yuan

Table 3 Hospital admissions, LOS, and hospital costs due to CVD according to the 2005 and 2021 WHO air quality guidelines

	Guideline	**WHO 2005**		**WHO 2021**	
	PM	**$PM_{2.5}$**	**PM_{10}**	**$PM_{2.5}$**	**PM_{10}**
	Target (μg/m^3)	**25 (24 h)**	**50 (24 h)**	**15 (24 h)**	**45 (24 h)**
Hospital admissions	AN, 95% CI	10,886 (9062, 12,704)	5233 (4107, 6353)	19,419 (16,160, 22,666)	7716 (6053, 9374)
	PAF (%), 95% CI	0.574 (0.478, 0.700)	0.276 (0.217, 0.335)	1.024 (0.852, 1.195)	0.407 (0.319, 0.494)
LOS (days)	AN, 95% CI	52,127 (−74,698, 178,953)	11,407 (−66,634, 89,448)	93,090 (−133,398, 319,578)	16,855 (−98,459, 132,169)
	PAF (%), 95% CI	0.352 (−0.504, 1.207)	0.077 (−0.449, 0.603)	0.628 (−0.009,0.0215)	0.114 (−0.664, 0.891)
Hospital cost (1000 CNY)	AN, 95% CI	459,313 (198,497, 720,129)	216,094 (55,360, 376,829)	820,255 (354,482, 1,286,027)	319,302 (81,800, 556,804)
	PAF (%), 95% CI	1.149 (0.496, 1.801)	0.581 (0.127, 1.035)	2.052 (0.887, 3.217)	0.799 (0.205, 1.393)

Particulate matter concentration is lag 0 for admissions, LOS and hospital cost

AN attributable number, *LOS* length of hospital stay, *PM* particulate matter, *PAF* population attributable fraction, *CNY* Chinese Yuan

Sensitivity analysis

We performed two sensitivity analyses to assess the robustness of our results. The results of the first analysis showed that fitting using a two-pollutant model (Additional file 1: Table S11) generally led to similar results regarding the effects of PM on daily hospital admissions, LOS, and hospital costs after adjusting for other pollutants. However, the effect estimates were not

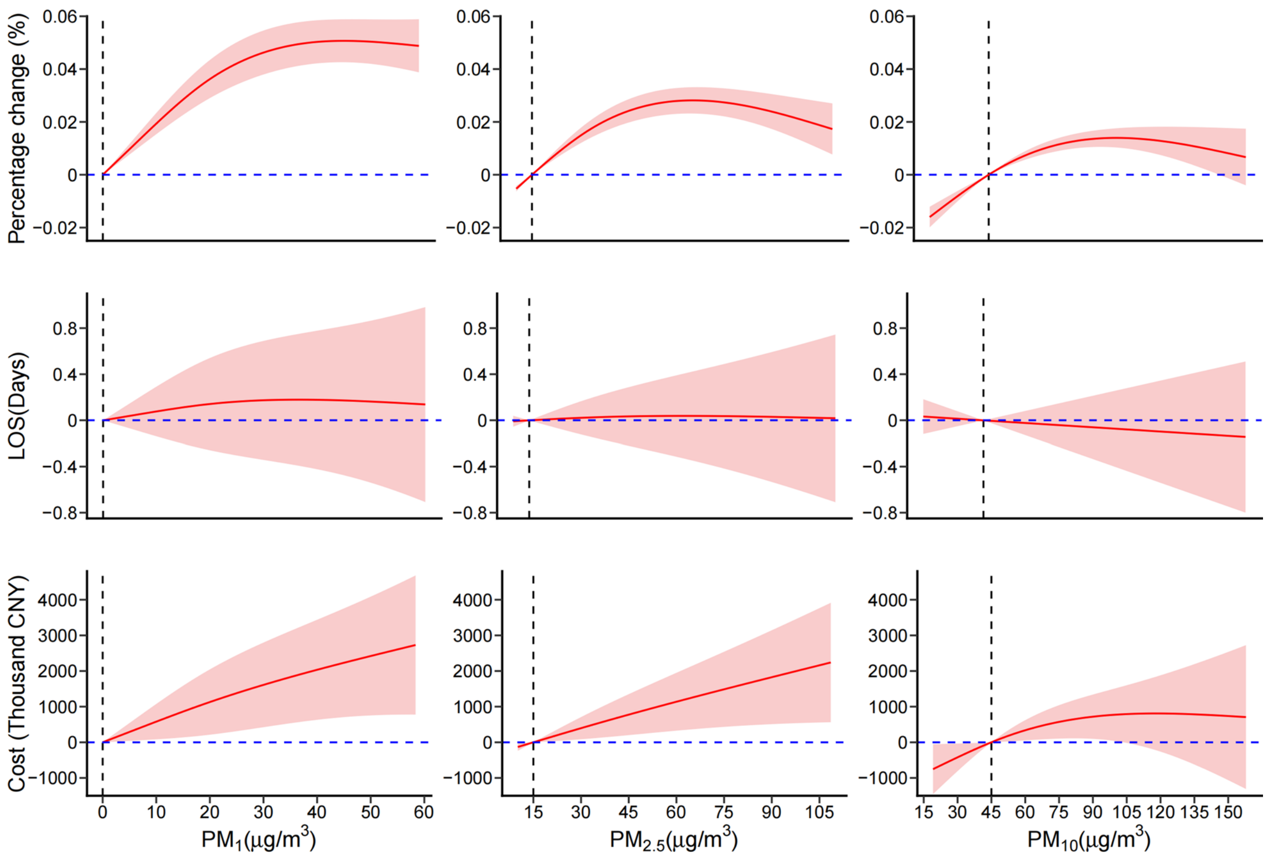

Fig. 4 Relationship of PM levels at lag0 with daily hospital admissions, LOS, and hospital costs due to CVD. The dashed vertical lines (0 μg/m^3 for PM$_1$, 15 μg/m^3 for PM$_{2.5}$ and 45 μg/m^3 for PM$_{10}$) are the target values. *LOS* length of hospital stay, *PM* particulate matter, *CNY* Chinese Yuan

significant for the associations of some PM sizes and partial outcomes after adjusting for NO_2 and CO. The rest sensitivity analyses indicated that there were almost no changes of the effect estimates after changing the degrees of freedom for calendar time, temperature and relative humidity (Additional file 1: Tables S12–S14).

Discussion

Main findings and comparisons with previous studies

The major finding of this ecological time-series study is that an elevated level of PM was significantly associated with a rapid increase in the risk of hospital admissions and hospital costs due to CVD and smaller PM had a greater effect. Previous studies also reported associations of PM with hospital admissions and hospital costs for CVD [11–13, 32]. For instance, a recent study reported that short-term elevation of PM$_{2.5}$ and PM$_{10}$ increased hospital admissions and hospital costs for CVD and diabetes mellitus [6], and other studies reported that long-term elevation of PM$_1$ and PM$_{2.5}$ increased the risk of CVD and smaller PM had a greater effect than larger [7, 33–35]. However, some studies reported the possibility of relationship between PM and daily LOS due to CVD [6, 36]. Therefore, our contrary findings regarding the relationship of PM and daily LOS due to CVD require an explanation. We suggest that the unique characteristics of our population and heterogeneity of PM may explain our findings.

Previous studies of the effect of lag time on the association of PM$_{2.5}$ and PM$_{10}$ with CVD reported maximal effects for longer lag days than in the present study [32, 37]. We found maximal effects for lag days of lag0, lag01, and lag02, depending on the PM. This difference in lag times among studies may be because individual geographic regions have PM that differ in chemical composition [38], and also have populations that differ in the proportions of different CVD subtypes. Consistent with this interpretation, a recent study reported an association between PM and acute coronary syndrome (a subtype of CVD) with lag times measured in hours [39].

In line with previous studies [22, 40, 41], we found that males tended to be more vulnerable to PM based on daily hospital admissions, LOS, and hospital costs due to CVD. However, gender was not a statistically significant modifier in our study, consistent with several previous studies [40, 41]. Our age-stratified analysis indicated that patients less than 45 years old were more vulnerable to PM based on daily hospital admissions due to CVD, in line with previous studies [6, 42]. This may be because younger people engage in more outdoor activities, making them more likely to inhale air pollutants [42]. However, the elderly were more vulnerable to PM based on daily hospital costs due to CVD, in line with a previous study [6]. This may be because CVD in the elderly is a more serious threat because of their weaker immune responses [43], and hospital costs are closely related to disease severity [44].

We used the 2005 AQG and 2021 AQG from the WHO to calculate the attributable risk, and our results were consistent with several previous studies [6, 13, 32]. Importantly, our results showed that there would be significant public health and economic benefits if the air quality standards in Shanghai met the most recent guidelines of the WHO. For example, if Shanghai followed the WHO's 2021 AQG on $PM_{2.5}$ during the 4-year study period, there would have been nearly 20,000 fewer hospitalizations and the total hospital costs would have been more than 800 million CNY lower. Thus, if policy makers and the government can meet these targets in the future, it will have profound public health and economic implications.

Our analysis of dose–response relationships of PM and CVD indicated a linear association between at low PM concentrations, and a progressively weaker effect at higher PM concentrations. There was a nearly linear association between PM and hospital costs in the concentration range we analyzed. Previous studies also reported a nonlinear relationship between PM and hospital admissions [22, 45], although these studies focused on respiratory diseases. A possible explanation for this saturation effect may simply be that people avoid the outdoors or wear dust masks when outside when the level of air pollution is very high. The nearly linear relationship of PM level with hospital costs was unsurprising because hospital costs have a closer relationship with disease severity than hospital admissions [44].

Our sensitivity analysis using a two-pollutant model showed the associations between PM and CVD remained positive, except after adjusting for NO_2 and CO in partial outcomes. Previous studies reported similar results. For example, Tsai et al. found that the adverse effect of $PM_{2.5}$ was not statistically significant after adjusting for NO_2 or CO [46]. A detailed analysis in a recent review proposed that the higher CVD mortality from $PM_{2.5}$ alone and NO_2 alone than from NO_2 and $PM_{2.5}$ together may be because these two pollutants have antagonistic effects or multicollinearity between them [47, 48].

Potential biological mechanism

At present, the biological mechanism responsible for the increased risk of CVD due to PM is not completely clear, but there are several possible explanations. Firstly, PM can cause oxidative stress [8–10, 49]. Oxidative stress following PM exposure is the first response in humans, followed by more delayed responses in other variables, suggesting that oxidative stress may be the primary cause of CVD [50]. Secondly, PM can directly damage the cardiovascular system by translocation throughout the body, and cause tissue damage [51]; after this damage, secondary mediators play a key role in damage of the cardiovascular system damage [8]. For example, air pollution can lead to an increase in coagulation factors and platelet activation, thus favoring thrombus formation [49]. A meta-analysis showed that PM exposure increased the level of TNF-α [10], and the presence of PM in the lungs led to the release of inflammatory factors and other mediators, which then moved to various parts of the body through the systemic circulation [52]. These many mediators may enhance oxidative stress in the vasculature via activation of TLR4 pathways [53].

The possible reason for smaller PM had a greater effect than larger for all lag times is that PM_1 tends to have a larger relative surface area and more readily absorbs toxic substances and heavy metals, remains airborne and near ground level for a longer period of time, and can more easily enter the alveoli and systemic circulation [54]

Strengths and limitations

Our study had several major strengths. First, to the best of our knowledge, this is the first study that simultaneously examined the relationship of PM of three different sizes (PM_1, $PM_{2.5}$, and PM_{10}) with hospital admissions, LOS, and hospital costs due to CVD; to analyze the dose–response relationships of different PM with CVD; and to assess the burden of CVD attributable to air pollutants using different two different sets of criteria (AQG) from the WHO. Our results thus provide a comprehensive overview of the relationship between air pollutants and CVD in terms of acute effects and disease burden, which was also not done in other previous studies. Second, our study had a large sample size, in that there were nearly 2 million CVD patients, and we included almost all CVD patients in Shanghai during the 4-year study period, making our estimates highly representative and reliable. Third, to improve the accuracy of the recorded levels of PM, we calculated aggregated daily PM_1, $PM_{2.5}$ and PM_{10} concentrations in Shanghai from December 25, 2015 to December 31, 2019 and used statistical weighting that was based on populations in different regions of Shanghai. Finally, we used the monthly CPI for medical care to adjust our estimates of hospital costs.

However, some limitations should be considered. Firstly, this was an ecological study and therefore could have been affected by the ecological fallacy. Thus, we cannot make definitive conclusions regarding the association of air pollution with an individual's risk of CVD, and cannot make inferences regarding causality, even though we used several methods to reduce confounding bias. Second, we had no data on the exact residential locations of patients, and merely calculated average air pollutant concentrations using fixed monitoring stations and PM raster data, a method that could result in measurement errors. Thus, we had no data on the actual exposures of individual residents. Third, hospitals of all three tiers in Shanghai performed the diagnoses of CVD, so some classification bias is inevitable. Additionally, potential confounding factors, including occupation, education level, medication history, socioeconomic status, and individual behaviors (e.g., drinking and smoking status), were not available from the Medical Insurance System, making it impossible to perform adjustment in our models. Finally, although all of our analyses were prespecified based on clear hypotheses and biological plausibility, we acknowledge that our use of multiple comparisons increased the risk of type I error.

Implications for policy makers

Our findings suggest that the government should implement aggressive and prompt strategies that aim to improve air quality because this could yield significant public health benefits and reduce the disease burden and economic burden. Additionally, PM_1 was responsible for a considerable part of the risk for CVD. Therefore, a more effective policy should focus more on PM_1, rather than $PM_{2.5}$ and PM_{10}.

Conclusion

Our results suggest that an elevation of PM may lead to a rapid increase in the risk of hospital admissions and hospital costs due to CVD. The effect on hospital admissions was especially strong for men and younger individuals, and the effect on hospital costs was especially strong for men and elderly individuals. These findings suggest that governments should improve air quality by implementing aggressive strategies to reduce the burden of disease and economic burden. Notably, smaller PM was associated with greater risk. Thus, to reduce the burden of air pollution on human health and hospital costs, we suggest that PM_1 should be considered a priority in future air quality standards and guidelines. However, considering the limitations of our study, we also recommend performing additional large and well-designed studies to confirm our results.

Abbreviations

AF	Attributable fraction
AN	Attributable number
AQG	Air quality guideline
CHAP	China High Air Pollutants Dataset
CI	Confidence interval
CNY	Chinese yuan
CO	Carbon monoxide
CVD	Cardiovascular disease
DALYs	Disability adjusted life years
df	Degree of freedom
GAM	Generalize additive model
GBD2019	Global Burden of Disease Study 2019
ICD-10	International Classification of Diseases 10th Revision
LOS	Length of hospital stay
NO_2	Nitrogen dioxide
ns	Natural Spline Function
O3	Ozone
PAF	Population attributable fraction
PM	Particulate matter
PM_1	Particulate matter with an aerodynamic diameter < 1 μm
PM_{10}	Particulate matter with an aerodynamic diameter < 10 μm
$PM_{2.5}$	Particulate matter with an aerodynamic diameter < 2.5 μm
Rh	Relative humidity
SD	Standard deviations
SO_2	Sulfur dioxide
UI	Uncertain interval
WHO	World health organization
YLDs	Years lived with disability
YLLs	Years of life lost

Supplementary Information

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Additional file 1: Table S1. Spearman correlation coefficients among air pollutants and meteorological factors. **Table S2.** Effect of different PM and lag time on percentage change in daily hospital admissions, absolute LOS, and absolute hospital costs due to CVD. **Table S3.** Effect of PM_1 and lag time on percentage change in daily hospital admissions, LOS, and hospital costs due to CVD for males and females. **Table S4.** Effect of $PM_{2.5}$ and lag time on percentage change in daily hospital admissions, LOS, and hospital costs due to CVD for males and females. **Table S5.** Effect of PM_{10} and lag time on percentage change in daily hospital admissions, LOS, and hospital costs due to CVD for males and females. **Table S6.** Effect of PM and lag time on percentage change (%) in daily hospital admissions due to CVD in different age groups. **Table S7.** Effect of PM and lag time on LOS (days) due to CVD in different age groups. **Table S8.** Effect of PM and lag time on hospital costs (Thousand CNY) due to CVD in different age groups. **Table S9.** Hospital admissions, LOS, and hospital costs due to CVD for males and females according to the 2005 and 2021 WHO air quality guidelines. **Table S10.** The Hospital admission, LOS and Hospital costs attributable risk of for CVD on age group with different air quality guideline. **Table S11.** The effect of PMs with 95% confidence interval of hospital admissions, LOS and hospital costs for cardiovascular diseases per 10 μg/m^3 increase in concentrations of PM_1, $PM_{2.5}$ and PM_{10} using two-pollutant models. **Table S12.** Hospital admissions percentage change, LOS and hospital costs with 95% confidence interval in hospital admissions for cardiovascular diseases associated with a 10 μg/m^3 increase in concentrations of PM1, PM2.5 and PM10 through changing degrees of freedom for the calendar time. **Table S13.** Hospital admissions percentage change, LOS and hospital costs with 95% confidence interval in hospital admissions for cardiovascular diseases associated with a 10 μg/m^3 increase in concentrations of PM_1, $PM_{2.5}$ and PM_{10} through changing degrees of freedom for temperature. **Table S14.** Hospital admissions percentage change, LOS and hospital costs with 95% confidence interval in hospital admissions for cardiovascular diseases associated with a 10 μg/m^3 increase in concentrations of PM_1, $PM_{2.5}$ and PM_{10} through changing degrees of freedom for relative humidity. **Table S15.** Population size and weight of each district in Shanghai from China's 2020 census data.

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Author contributions
WZ: conceptualization, data curation, software, formal analysis, writing—original draft. ZW: conceptualization, data curation, software, formal analysis, writing—original draft. WP: data curation, resources, formal analysis. XW: formal analysis. MY: formal analysis. WW: conceptualization, resources, methodology, writing—review and editing, project administration, funding acquisition. JW: data curation, resources writing review and editing. HX: conceptualization, resources, methodology, writing—review and editing, project administration, funding acquisition. The author(s) read and approved the final manuscript.

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Availability of data and materials
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Competing interests
The authors declare they have nothing to disclose.

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