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Effects of short-term ambient particulate matter exposure on the risk of severe COVID-19

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SUMMARY

Objectives: Previous studies have suggested a relationship between outdoor air pollution and the risk of coronavirus disease 2019 (COVID-19). However, there is a lack of data related to the severity of disease, especially in China. This study aimed to explore the association between short-term exposure to outdoor particulate matter (PM) and the risk of severe COVID-19.
Methods: We recruited patients diagnosed with COVID-19 during a recent large-scale outbreak in eastern China caused by the Delta variant. We collected data on meteorological factors and ambient air pollution during the same time period and in the same region where the cases occurred and applied a generalized additive model (GAM) to analyze the effects of short-term ambient PM exposure on the risk of severe COVID-19.
Results: A total of 476 adult patients with confirmed COVID-19 were recruited, of which 42 (8.82%) had severe disease. With a unit increase in PM_{10}, the risk of severe COVID-19 increased by 81.70% (95% confidence interval [CI]: 35.45, 143.76) at a lag of 0–7 days, 86.04% (95% CI: 38.71, 149.53) at a lag of 0–14 days, 76.26% (95% CI: 33.68, 132.42) at a lag of 0–21 days, and 72.15% (95% CI: 21.02, 144.88) at a lag of 0–28 days. The associations remained significant at lags of 0–7 days, 0–14 days, and 0–28 days in the multipollutant models. With a unit increase in $PM_{2.5}$, the risk of severe COVID-19 increased by 299.08% (95% CI: 92.94, 725.46) at a lag of 0–7 days, 289.23% (95% CI: 85.62, 716.20) at a lag of 0–14 days, 234.34% (95% CI: 63.81, 582.40) at a lag of 0–21 days, and 204.04% (95% CI: 39.28, 563.71) at a lag of 0–28 days. The associations were still significant at lags of 0–7 days, 0–14 days, and 0–28 days in the multipollutant models.
Conclusions: Our results indicated that short-term exposure to outdoor PM was positively related to the risk of severe COVID-19, and that reducing air pollution may contribute to the control of COVID-19.

Introduction

In December 2019, coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, was first reported in Wuhan and escalated into a global pandemic.[17,32] There is no doubt that COVID-19 poses a severe threat to global health. Patients with COVID-19 can be categorized as mild, moderate, severe, or critical based on their condition. The prognosis of severe and critical patients is poor,[29] and the risk factors for these categories include older age and hypertension.[10]

Levels of particulate matter (PM), which are produced by the combustion of biomass, diesel and spark-ignited vehicle emissions, is highly correlated with environmental pollution.[3] In particular, PM with an aerodynamic diameter of ≤ 10 μm (PM_{10}) or ≤ 2.5 μm ($PM_{2.5}$) has attracted widespread public attention, as particles of this size are inhalable.[19,23] PM was found to be positively associated with the risk of communicable and noncommunicable diseases.[8,13,26] A global time-series study showed that short-term PM exposure contributed to increased mortality due to cardiovascular and respiratory disease.[11] Recently, several studies have revealed the possible links between PM exposure and the risk of developing COVID-19.[21,35] For example, a multicity study in China found that for each 10 $\mu g/m^3$ increase in PM_{10} and $PM_{2.5}$, the risk of COVID-19 increased by 5% and 6%, respectively.[22] Another study in Germany showed that every 1 $\mu g/m^3$ increase in PM_{10} and $PM_{2.5}$ was associated with 52.38 and 199.46 more confirmed COVID-19 cases per 100,000 inhabitants, respectively.[20] The associations

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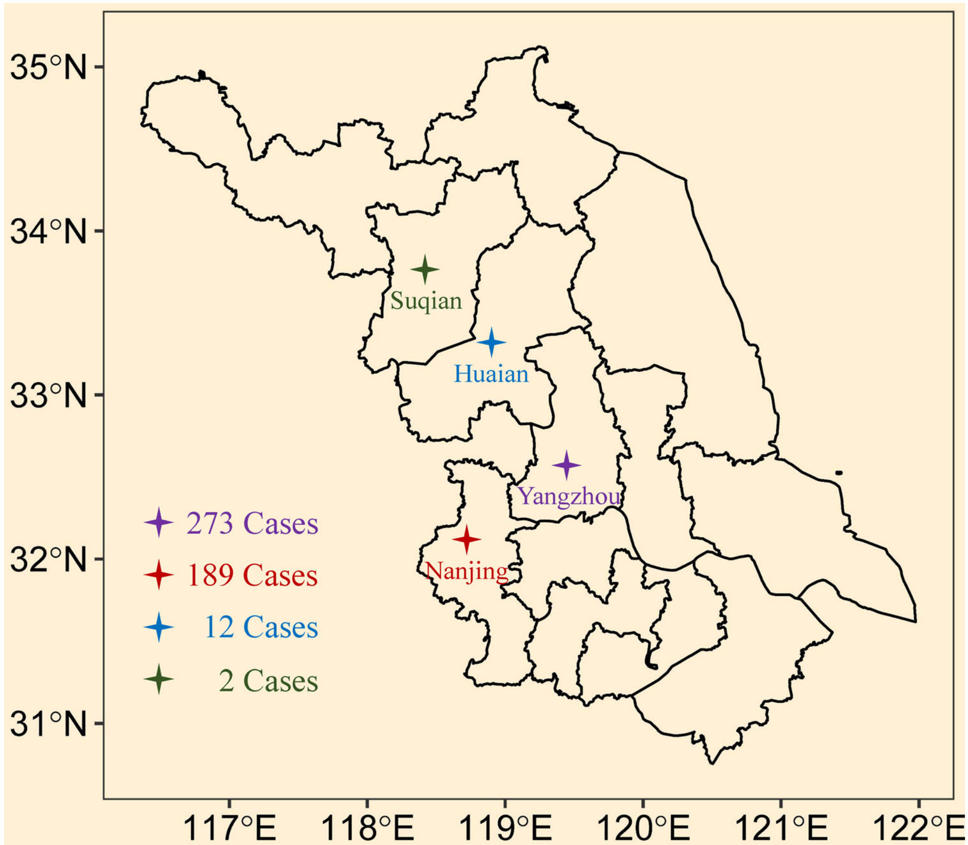

Fig. 1. The geographic locations of the four cities in Jiangsu Province.

between ambient PM exposure and the risk of COVID-19 have been ardently discussed. In Italy, COVID-19 cases in the most polluted areas had higher rates of intensive care unit (ICU) admissions and mortality rates, indicating a possible link between air pollution and severe COVID-19.[5] Nevertheless, studies on the effects of outdoor PM exposure on the severity of COVID-19 are insufficient, notably in China.

On July 20, 2021, Nanjing Lukou International Airport identified nine domestic COVID-19 cases through regular screening. Subsequently, the disease spread rapidly to surrounding cities, resulting in hundreds of confirmed cases in four cities in Jiangsu Province, including Nanjing, Yangzhou, Huaian, and Suqian. The scale of this epidemic in China was second only to the Wuhan epidemic in 2020. Genome sequencing confirmed that the pathogen causing this epidemic was the SARS-CoV-2 B1.617.2 (Delta) variant, which initially appeared in India.[2] Thus, we collected data from COVID-19 patients identified in this outbreak and data on meteorological factors and air pollutant concentrations during the same time period and in the same region where the cases occurred, aiming to evaluate the relationships between short-term ambient PM exposure and COVID-19 severity.

Materials and methods

Study population

We collected data from COVID-19 patients admitted to Nanjing Public Health Medical Center from July 20, 2021 to August 17, 2021. All of the cases came from Nanjing, Yangzhou, Huaian, or Suqian and were related to the recent outbreak of COVID-19 that originated in Nanjing Lukou International Airport. The locations of the four cities are shown in Fig. 1. The inclusion criteria were as follows: (1) patients aged $\geq$18 years and (2) patients infected with the Delta variant. We collected data on the general characteristics of patients, including city, sex, age, current or past hypertension (yes or no), current or past diabetes (yes or no), current or past heart disease (yes or no), current or past carcinoma (yes or no), current or past COPD (yes or no), current or past asthma (yes or no), current or past autoimmune disease (yes or no), vaccination status (unvaccinated, partially vaccinated, or fully vaccinated), and number of days between onset and hospitalization. Patients were defined as fully vaccinated if they had received two doses of a vaccine with an interval between the two doses of $\geq$21 days and a disease onset date of $\geq$14 days from the second dose.[7]

The diagnosis and classification of COVID-19 was based on the "Guidelines for Diagnosis and Treatment of COVID-19 (Trial Eighth Edition)" issued by the National Health Commission (http://www.nhc.gov.cn/). Patients were categorized as mild, moderate, severe, and critical based on their symptoms. In the current study, we combined the severe and critical categories, referred to as "severe".[6]

Data on meteorological factors and air pollutant concentrations

We extracted data on meteorological factors, including daily average temperature (°C) and daily average wind speed (m/s) in four cities between June 15, 2021 and August 15, 2021 from the China Meteorological Data Sharing Center (http://data.cma.cn/), as well as daily average concentrations of six ambient air pollutants, including PM_{10}, $PM_{2.5}$, SO_2, NO_2, CO, and O_3 (the concentration of O_3 was the maximum 8-hour moving average) in four cities during the same period from the National urban air quality real-time release platform (http://106.37.208.233:20035/). Except for the unit of CO concentration, which was mg/m^3, the concentration of other pollutants was measured in μg/m^3.

Statistical analysis

We applied the generalized additive model (GAM) with the logit link function to estimate the effects of short-term PM exposure on the severity of COVID-19. The GAM has been widely used in exploring the associations between air pollutants and health outcomes.[11,24] Covariates adjusted for in the model included city, sex, age, current or past hypertension, current or past diabetes, current or past heart disease, current or past carcinoma, current or past COPD, current or past asthma, current or past autoimmune disease, vaccination status, days between disease onset and hospitalization, daily average ambient temperature, and daily average wind speed. The thin plate spline function was applied to control for the nonlinear effects of meteorological factors on COVID-19.[24] Previous studies have shown that PM exposure might have lag effects on health.[1,27] Thus, we calculated the moving average concentration of PM to describe personal PM exposure levels according to the onset date of COVID-19 and city of residence.[1,34] For instance, if the onset date was August 1, we extracted the daily average concentration of PM in the same city from July 4 to August 1. Then, we calculated the average concentration from July 25 to August 1 as the 8-day moving average, from July 18 to August 1 as the 15-day moving average, and from July 4 to August 1 as the 29-day moving average. We used four different lag times, including lags of 0–7 days (8-day moving average), 0–14 days (15-day moving average), 0–21 days (22-day moving average), and 0–28 days (29-day moving average).[24,34] The strength of associated evidence was expressed as the change in the risk of severe COVID-19 and its corresponding 95% confidence interval (CIs) for a unit increase in PM concentration.

We conducted two sensitivity analyses to examine the robustness of the relationships between PM exposure and severe COVID-19. First, as mentioned above, we estimated the association at different lag times. Second, we included data for other air pollutants to construct multipollutant models. We used the Spearman rank correlation test to evaluate the correlation among air pollutants. Only pollutants with an |r| of <0.7 were entered in the multipollutant models to address the problem of multiple collinearity.[33] Moreover, to ensure the comparability of the models, only pollutants with an |r| of <0.7 at each of the four lag times were entered in the multipollutant models. For example, if the |r| between SO_2 and PM_{10} was <0.7 at all four lag times, while the |r| between NO_2 and PM_{10} were <0.7 at only three of the lag times, then SO_2 was included in the multipollutant models, while NO_2 was not.

Additionally, we performed subgroup analyses to explore whether the effects of PM exposure on the risk of severe COVID-19 were modified by sex or age. The difference in effects between subgroups was examined by the following formula: $|\beta_1 - \beta_2|/\sqrt{SE_1{}^2 + SE_2{}^2}$, where β_1 and β_2 are the estimated effects, and SE_1 and SE_2 are the standard errors of the estimates. The difference was considered to be statistically significant if the value was >1.96.[30]

Moreover, we plotted the exposure-response curve between average wind speed and the risk of severe COVID-19 based on the single-pollutant models of PM_{10} and $PM_{2.5}$. If the curve was linear or approximately linear, then we used a linear function to estimate the effects of wind speed on severe COVID-19. Otherwise, we used a piecewise linear function to assess the effects of wind speed on severe COVID-19. All analyses were performed using R software version 4.0.4 (https://www.r-project.org/). The significance level for testing was 0.05.

Results

Patient characteristics

A total of 533 COVID-19 patients were screened, and 476 patients who met the inclusion criteria were included in the current study, of which 273 (57.35%) came from Yangzhou, 189 (39.71%) came from Nanjing, 12 (2.52%) came from Huaian, and 2 (0.42%) came from Suqian (Fig. 1). Among them, 42 (8.82%) were classified as severe, 289 (60.71%) were females, 298 (62.61%) were 18–59 years old, 109 (22.90%) had hypertension, 43 (9.03%) had diabetes, 21 (4.41%) had heart disease, 11 (2.31%) had carcinoma, 3 (0.63%) had COPD, 9 (1.89%) had asthma, 5 (1.05%) had autoimmune disease, and 151 (31.72%) patients were fully vaccinated (Table 1).

Concentrations of PM10 and PM2.5 in four cities

Descriptive statistics of meteorological factors and air pollutant concentrations in four cities between June 15, 2021 and August 15, 2021 are shown in Table 2. During this period, the median (interquartile range) concentration of PM_{10} was 34.00 (20.25) μg/m^3 in Yangzhou, 31.50 (17.25) μg/m^3 in Nanjing, 28.00 (19.75) μg/m^3 in Huaian, and 34.00 (20.50) μg/m^3 in Suqian (Table 2). The median (interquartile range) concentration of $PM_{2.5}$ was 17.50 (13.25) μg/m^3 in Yangzhou, 15.50 (12.00) μg/m^3 in Nanjing, 16.00 (11.25) μg/m^3 in Huaian, and 17.50 (12.25) μg/m^3 in Suqian (Table 2).

PM10 and severe COVID-19

In the single-pollutant models, PM_{10} was positively associated with the risk of severe COVID-19 at lags of 0–7 days, 0–14 days, 0–21 days, and 0–28 days. The maximum effect was at lag 0–14 days. For a unit increase in PM_{10}, the risk of severe COVID-19 increased by 86.04% (95% CI: 38.71, 149.53). In the multipollutant models, the associations remained significant at lags of 0–7 days, 0–14 days, and 0–28 days (Table 3).

PM2.5 and severe COVID-19

In the single-pollutant models, $PM_{2.5}$ was positively associated with the risk of severe COVID-19 at lags of 0–7 days, 0–14 days, 0–21 days, and 0–28 days. The maximum effect was at a lag of 0–7 days. For a unit increase in $PM_{2.5}$, the risk of severe COVID-19 increased by 299.08% (95% CI: 92.94, 725.46). In the multi-pollutant models, the associations remained significant at lags of 0–7 days, 0–14 days, and 0–28 days (Table 3).

Subgroup analysis

The associations between PM_{10} and the risk of severe COVID-19 remained significant in different sex or age groups at lags of 0–14 days and 0–21 days. For a unit increase in PM_{10} at lag 0–14 days, the risk of severe COVID-19 increased by 108.55% (95% CI: 29.10, 236.90) in males, 84.65% (95% CI: 22.80, 177.65) in females, 77.59% (95% CI: 7.31, 193.89) in patients aged 18–59 years, and 81.41% (95% CI: 18.61, 177.47) in patients over 60 years of age. The effects of PM_{10} on the risk of severe COVID-19 were not significantly modified by sex or age (P >0.05) (Table 4).

The associations between $PM_{2.5}$ and the risk of severe COVID-19 remained significant in different sex or age groups at lags of 0–21 days and 0–28 days. For a unit increase in $PM_{2.5}$ at a lag of 0–28 days, the risk of severe COVID-19 increased by 648.57% (95% CI: 93.94, 2789.41) in males, 153.17% (95% CI: 6.10, 504.09) in females, 520.90% (95% CI: 1.29, 3706.12) in patients aged 18–59 years, and 177.60% (95% CI: 17.00, 558.61) in patients over 60 years of age. The effects of $PM_{2.5}$ on the risk of severe COVID-19 were significantly

Table 1
Characteristics of 476 COVID-19 patients with or without severe illness.

Characteristics	Non-severe illness n (%) or median (interquartile range)	Severe illness n (%) or median (interquartile range)	P[a]
Sex			0.247
Male	167 (89.30)	20 (10.70)	
Female	267 (92.39)	22 (7.61)	
Age group (years)			<0.001
18–59	286 (95.97)	12 (4.03)	
≥60	148 (83.15)	30 (16.85)	
Medical conditions			
Hypertension	94 (86.24)	15 (13.76)	0.038
Diabetes	35 (81.40)	8 (18.60)	0.037
Heart disease	16 (76.19)	5 (23.81)	0.037
Carcinoma	9 (81.82)	2 (18.18)	0.252
COPD	1 (33.33)	2 (66.67)	0.022
Asthma	8 (88.89)	1 (11.11)	0.568
Autoimmune disease	4 (80.00)	1 (20.00)	0.371
Vaccination status			<0.001
Unvaccinated	114 (84.44)	21 (15.56)	
Partially vaccinated	170 (89.47)	20 (10.53)	
Fully vaccinated	150 (99.34)	1 (0.66)	
Days between onset and hospitalization	3.00 (4.00)	3.00 (3.00)	0.152

[a] : As appropriate, a comparison between groups was made using the Chi-square test, Fisher's exact test, or Mann-Whitney U test.

Table 2
Daily average of meteorological factors and air pollutant concentrations in four cities in Jiangsu between June 15, 2021 and August 15, 2021.

City	Variable	Minimum	Q_{25}	Median	Mean	Q_{75}	Maximum
Yangzhou	Temperature (°C)	23.20	26.48	28.10	27.94	29.50	33.70
	Wind speed (m/s)	0.80	1.48	1.85	1.92	2.40	3.50
	PM_{10} ($\mu g/m^3$)	8.00	27.50	34.00	37.35	47.75	82.00
	$PM_{2.5}$ ($\mu g/m^3$)	5.00	13.00	17.50	19.39	26.25	38.00
	SO_2 ($\mu g/m^3$)	7.00	9.00	9.00	9.89	11.00	14.00
	NO_2 ($\mu g/m^3$)	4.00	10.00	18.00	18.03	24.25	38.00
	CO (mg/m^3)	0.30	0.40	0.50	0.51	0.60	0.90
	O_3 ($\mu g/m^3$)	51.00	81.75	107.00	120.55	161.25	268.00
Nanjing	Temperature (°C)	22.60	25.95	27.65	27.59	29.30	32.80
	Wind speed (m/s)	1.10	1.90	2.35	2.63	3.23	5.40
	PM_{10} ($\mu g/m^3$)	6.00	24.75	31.50	33.63	42.00	71.00
	$PM_{2.5}$ ($\mu g/m^3$)	3.00	11.00	15.50	17.68	23.00	47.00
	SO_2 ($\mu g/m^3$)	3.00	5.00	5.00	5.16	6.00	7.00
	NO_2 ($\mu g/m^3$)	6.00	14.75	18.50	18.92	24.25	32.00
	CO (mg/m^3)	0.30	0.48	0.50	0.56	0.70	0.90
	O_3 ($\mu g/m^3$)	48.00	84.25	105.50	116.77	146.75	207.00
Huaian	Temperature (°C)	22.40	25.88	27.30	27.03	28.23	31.20
	Wind speed (m/s)	0.60	1.50	2.15	2.29	2.83	6.00
	PM_{10} ($\mu g/m^3$)	8.00	20.75	28.00	30.44	40.50	68.00
	$PM_{2.5}$ ($\mu g/m^3$)	6.00	12.00	16.00	18.34	23.25	40.00
	SO_2 ($\mu g/m^3$)	3.00	4.00	4.00	4.37	5.00	8.00
	NO_2 ($\mu g/m^3$)	4.00	8.00	10.00	12.00	13.25	35.00
	CO (mg/m^3)	0.20	0.20	0.40	0.36	0.43	1.00
	O_3 ($\mu g/m^3$)	42.00	72.75	103.50	108.76	133.00	231.00
Suqian	Temperature (°C)	22.70	25.88	27.65	27.27	28.50	31.50
	Wind speed (m/s)	0.30	1.40	2.05	2.10	2.80	4.90
	PM_{10} ($\mu g/m^3$)	9.00	26.00	34.00	36.63	46.50	78.00
	$PM_{2.5}$ ($\mu g/m^3$)	5.00	13.00	17.50	18.65	25.25	40.00
	SO_2 ($\mu g/m^3$)	2.00	4.00	5.00	5.16	6.00	9.00
	NO_2 ($\mu g/m^3$)	2.00	6.00	9.00	10.26	13.25	25.00
	CO (mg/m^3)	0.30	0.40	0.40	0.47	0.60	0.90
	O_3 ($\mu g/m^3$)	44.00	84.75	108.50	116.85	145.25	259.00

Table 3
Changes in the risk of severe COVID-19 and their 95% CIs for a unit increase in the concentration of particulate matter.

Lag time	PM_{10}		$PM_{2.5}$	
	Single-pollutant model[a]	Multi-pollutant model[b]	Single-pollutant model[a]	Multi-pollutant model[b]
Lag 0–7 days	81.70 (35.45, 143.76)	59.25 (7.82, 135.22)	299.08 (92.94, 725.46)	235.01 (68.68, 565.39)
Lag 0–14 days	86.04 (38.71, 149.53)	98.67 (7.58, 266.92)	289.23 (85.62, 716.20)	131.34 (6.20, 403.90)
Lag 0–21 days	76.26 (33.68, 132.42)	−16.22 (−55.36, 57.23)	234.34 (63.81, 582.40)	32.59 (−47.09, 232.26)
Lag 0–28 days	72.15 (21.02, 144.88)	195.35 (28.83, 577.11)	204.04 (39.28, 563.71)	464.63 (0.50, 3072.09)

[a] : Adjusted for the city, sex, age, current or past hypertension, current or past diabetes, current or past heart disease, current or past carcinoma, current or past COPD, current or past asthma, current or past autoimmune disease, vaccination status, days between onset and hospitalization, and average temperature and average wind speed at the same lag time.
[b] : Based on single-pollutant models, additionally adjusted for other air pollutants at the same lag time.

Table 4
Changes in the risk of severe COVID-19 and their 95% CIs for a unit increase in PM_{10} concentration in subgroups, based on the single-pollutant models.

Lag time	Sex		Age	
	Male	Female	18–59 years	≥60 years
Lag 0–7 days	143.85 (38.15, 330.43)	61.90 (10.67, 136.85)[a]	118.32 (−33.52, 617.02)	120.10 (40.97, 243.63)[a]
Lag 0–14 days	108.55 (29.10, 236.90)	84.65 (22.80, 177.65)[a]	77.59 (7.31, 193.89)	81.41 (18.61, 177.47)[a]
Lag 0–21 days	115.07 (28.57, 259.77)	55.58 (9.78, 120.49)[a]	116.89 (10.84, 324.40)	67.30 (19.58, 134.05)[a]
Lag 0–28 days	186.05 (44.08, 467.92)	55.72 (4.91, 131.14)[a]	163.14 (7.51, 544.07)	48.08 (−1.44, 122.49)[a]

[a] : There was no significant difference in the effects between the subgroups (P >0.05).

Table 5
Changes in the risk of severe COVID-19 and their 95% CIs for a unit increase in $PM_{2.5}$ concentration in subgroups, based on the single-pollutant models.

Lag time	Sex		Age	
	Male	Female	18–59 years	≥60 years
Lag 0–7 days	242.12 (38.39, 745.81)	341.50 (35.86, 1334.71)[a]	46.95 (−49.62, 328.64)	740.65 (171.79, 2500.15)[b]
Lag 0–14 days	367.39 (48.24, 1373.70)	427.51 (64.80, 1588.55)[a]	121.60 (−14.65, 475.36)	781.10 (96.79, 3844.90)[a]
Lag 0–21 days	398.28 (49.83, 1557.14)	179.83 (9.39, 615.80)[a]	454.00 (15.31, 2561.75)	141.14 (6.82, 444.33)[a]
Lag 0–28 days	648.57 (93.94, 2789.41)	153.17 (6.10, 504.09)[a]	520.90 (1.29, 3706.12)	177.60 (17.00, 558.61)[a]

[a] : There was no significant difference in the effects between the subgroups (P >0.05).
[b] : The effects between the subgroups were significantly different (P <0.05).

Table 6
Changes in the risk of severe COVID-19 and their 95% CIs for a unit increase in average wind speed.

Lag time	Model[a]	Model[b]
Lag 0–7 days	−62.44 (−85.09, −5.37)	−89.89 (−96.92, −66.82)
Lag 0–14 days	−62.01 (−87.54, 15.81)	−58.02 (−85.92, 25.10)
Lag 0–21 days	−56.10 (−88.07, 61.50)	−77.31 (−93.46, −21.26)
Lag 0–28 days	−45.44 (−85.80, 109.74)	−82.39 (−95.18, −35.72)

[a] Based on single-pollutant models of PM_{10}.
[b] Based on single-pollutant models of $PM_{2.5}$.

different among different age groups at a lag of 0–7 days (P <0.05) (Table 5).

Wind speed and severe COVID-19

As shown in Fig. 2, the exposure-response curves between average wind speed and the risk of severe COVID-19 were approximately linear at different lag times. Based on the single-pollutant models of PM_{10}, the wind speed was negatively associated with severe COVID-19 at all lag times but was only significant at a lag of 0–7 days. For a unit increase in wind speed at a lag of 0–7 days, the risk of severe COVID-19 decreased by 62.44% (95% CI: −85.09, −5.37). Based on the single-pollutant models of $PM_{2.5}$, the wind speed was negatively associated with severe COVID-19 at all lag times and was significant at lags of 0–7 days, 0–21 days, and 0–28 days. For a unit increase in wind speed at lags of 0–7 days, 0–21 days, and 0–28 days, the risk of severe COVID-19 decreased by 89.89% (95% CI: −96.92, −66.82), 77.31% (95% CI: −93.46, −21.26), and 82.39% (95% CI: −95.18, −35.72), respectively (Table 6).

Discussion

In this study, we conducted a time-series analysis of 476 patients with COVID-19 caused by the Delta SARS-CoV-2 variant to explore the effects of short-term PM exposure on the risk of severe COVID-19. We observed that short-term exposure to PM was positively associated with the risk of severe COVID-19. To our knowledge, this is the first individual-level study to evaluate the relationship between short-term PM exposure and the risk of severe COVID-19 in China.

A multicenter study in 33 European countries found that $PM_{2.5}$ was positively related to the number of COVID-19 deaths.[9] Although this study was qualitative and did not consider potential confounding factors, it provided evidence of PM exposure contributing to a poor prognosis of COVID-19. Global research based on satellite data showed that approximately 15% of the global COVID-19 mortality (27% in East Asia, 19% in Europe, and 17% in North America) was attributed to long-term $PM_{2.5}$ exposure.[18] A study in California reported that a wildfire increased the $PM_{2.5}$ concentration in ten counties by 220.71%, and subsequently, the number of deaths from COVID-19 in these areas increased by 148.2%.[15] Another study in London showed that environmental $PM_{2.5}$ was positively correlated with mortality due to COVID-19. For a unit increase in $PM_{2.5}$, the number of deaths due to COVID-19 increased by 2.3%.[16] Another study explored the relationships between long-term exposure to $PM_{2.5}$ and COVID-19 hospitalization rates in Cincinnati and found that a unit increase in 10-year average $PM_{2.5}$ concentration was correlated with an 18% higher hospitalization rate.[14] Although most of the previous studies were epidemiological and focused on COVID-19 mortality or hospitalization rates, their findings implied that PM exposure was related to the severity of COVID-19. Moreover, our results showed that the effect of $PM_{2.5}$ seemed to be stronger than that of PM_{10}. This may be attributed to the smaller particle size of $PM_{2.5}$, which can penetrate more deeply into the alveoli and bronchioles and thus has more potent biological toxicity.[11] We also found an inverse relationship between average wind speed and severe COVID-19, although this association was only significant at some lag times. One possible explanation is that higher wind speeds can dilute the concentration of PM in the environment, thereby indirectly reducing the risk of severe COVID-19.

The following reasons may explain the potential links between PM and severe COVID-19. First, PM suspended in the air, especially $PM_{2.5}$, may not only carry SARS-CoV-2 but also enhance the attachment and replication of the virus in the bronchus by damaging the integrity of bronchial epithelial cells.[14] Second, as pointed out by Domingo et al., SARS-CoV-2 attached to PM may survive longer and have a stronger effect on the immune system, which is triggered by exposure to high concentrations of air pollutants.[4,28] Third, as mentioned before, $PM_{2.5}$ can reach the alveoli, thereby delivering SARS-CoV-2 to target type II alveolar cells.[14] Previous studies have shown that PM, especially $PM_{2.5}$, can stimulate activated alveo-

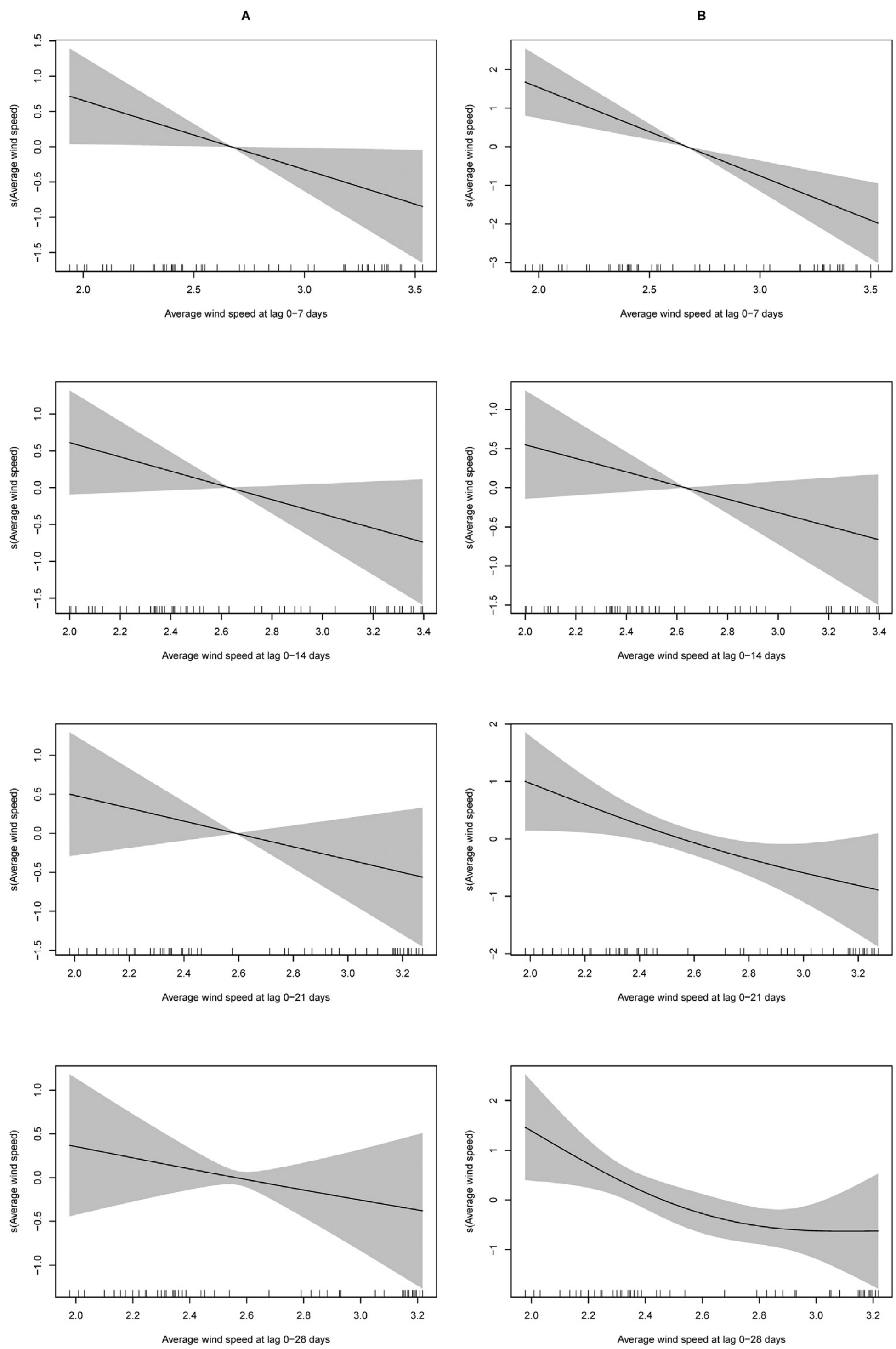

Fig. 2. The exposure-response curve between average wind speed and the risk of severe COVID-19. The x-axis represents the average wind speed, while the y-axis represents the contribution of the smooth term to the fitted values.A: based on the single-pollutant models of PM_{10}; B: based on the single-pollutant models of $PM_{2.5}$.

lar macrophages and then induce proinflammatory cytokine production and release, thus triggering allergic inflammation in the lungs.[12] Fourth, the metals and polycyclic aromatic hydrocarbons that make up $PM_{2.5}$ facilitate the production of free radicals, which may oxidize alveolar cells. Excessive free radicals weaken the cellular antioxidant capacity, leading to lipid peroxidation and increased intracellular calcium concentrations, further inducing cellular damage.[25] Finally, SARS-CoV-2 enters the cell through binding to the angiotensin-converting enzyme 2 (ACE2) receptor, and this process can be enhanced by PM exposure.[21] The binding of SARS-CoV-2 and the ACE2 receptor resulted in the downregulation of the latter. ACE2 mediated the transformation of angiotensin II to angiotensin 1–7 through the G protein-coupled receptor pathway and worked with angiotensin 1–7 by anti-inflammatory and antioxidant activities to protect the body. Downregulation of ACE2 decreased its protective effect and lessened the effect of angiotensin II.[31] Frontera et al. also postulated that long-term exposure to $PM_{2.5}$ resulted in overexpression of alveolar ACE2 receptors. This may increase the viral load in PM-exposed patients, weakening the defenses of the host.[5]

Our study had several limitations. First, we estimated the PM exposure level of each patient based on the monitoring data from the fixed sites, which may not accurately reflect individual exposure. Second, other factors related to the severity of COVID-19, which were not considered in the analysis, may affect the results. Third, since the epidemic was under control for a short time, the sample size of this study was relatively small, especially in terms of the number of severe patients. The association between PM and severe COVID-19 needs to be further confirmed in future studies.

Conclusion

Our results showed that short-term PM exposure was positively correlated with the risk of severe COVID-19. Curbing outdoor PM pollution will help decrease the burden of COVID-19 and improve patient prognosis.

Authors contributions

Zhongqi Li: Conceptualization, Data Curation, Methodology, Software, Formal analysis, Writing - Original Draft, Visualization. **Bilin Tao:** Conceptualization, Data Curation, Methodology, Writing - Original Draft, Visualization. **Zhiliang Hu:** Conceptualization, Resources, Supervision. **Yongxiang Yi:** Conceptualization, Resources, Supervision. **Jianming Wang:** Conceptualization, Resources, Writing - Review & Editing, Visualization, Supervision, Project administration, Funding acquisition.

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Data sharing statement

All data generated or analyzed during this study are included in this published article.

Ethical approval

This study was approved by the Ethics Committee of Nanjing Public Health Medical Center.

Patient consent for publication

Not required.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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