

Short-term association between particular matter air pollution and pediatric clinical visits for wheezing in a subarea of Shanghai

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Abstract To assess the association between the concentration of ambient particulate matter (PM) and the pediatric clinical visits for wheezing among children under 3 years old, data of daily air pollutants (PM_{2.5}, PM₁₀, NO₂, SO₂, CO), meteorological reports, along with the number of daily clinical visits of the children with wheezing at the Pediatric Department of Shanghai Renji Hospital (South Campus) were collected from January through December 2014. Correlation between the levels of air pollutants and the number of clinical patients for wheezing were analyzed by a time series analysis with a generalized additive model (GAM). During the study period, the daily average concentrations of PM_{2.5}, PM₁₀, NO₂, SO₂, and CO were 51.84 ± 32.51 , 72.69 ± 41.15 , 43.25 ± 18.07 , 17.45 ± 10.42 , and 0.82 ± 0.26 $\mu\text{g}/\text{m}^3$, respectively, which were abnormally higher compared to the standard defined by the Chinese Ministry of Environment Protection. The average number of daily clinical patients with wheezing was 23 ± 14 persons/day. The number of clinical visit by children with wheezing was significantly correlated with concentration of PM_{2.5} or PM₁₀ when the effect of SO₂ and NO₂ was

adjusted ($P < 0.05$). It was also found that exposure-response relationship was a linear non-threshold mode when it was analyzed by the GAM, and the percent of the clinical visits of children with wheezing increased from 0 to nearly 20 % with every interquartile increase of PM_{2.5}. The visiting number of children at a pediatric outpatient clinic increased due to the increase of PM_{2.5} in Pujiang, Shanghai, China.

Keywords Particulate matter (PM) · Air pollution · Wheezing · Pediatric · GAM model

Introduction

Ambient particulate matter 2.5 (PM_{2.5}) and PM₁₀ refer to particles less than 2.5 or 10 μm in diameter (Nel 2005). It is mostly made up of inorganic salt, carbonaceous matter, other inorganic elements, and organics. In China, the main sources of PM_{2.5} are vehicle exhausts and industrial pollution (Li et al. 2015; Wang et al. 2015). As is widely known, urbanization, with its high level of automobile and industrial emissions, is always accompanied by an increase in pollution, and air pollution has been worsening with constant advancement of urbanization process in China. According to the data published by the Chinese Ministry of Environmental Protection (CMEP), most of the cities in China currently fail to meet the standard level of annual PM_{2.5} concentration (35 $\mu\text{g}/\text{m}^3$). In this regard, Shanghai is internationally known as a rapidly urbanized city, and the PM_{2.5} has been increased recently, that is, it was 52.2 $\mu\text{g}/\text{m}^3$ in 2014 and was 67.9 $\mu\text{g}/\text{m}^3$ in 2015.

Prevalence of wheezing in children has been increasing worldwide (Azad et al. 2016; Urrutia-Pereira et al. 2016).

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Air pollution, especially particulate matter pollution, has been considered as one of the main risk factors for pediatric wheezing. In this regard, studies have indicated that PM_{10} has an adverse effect on the rates of pediatric asthma exacerbation and hospital admission (Beard et al. 2012; Nastos et al. 2010). Wheezing is a common symptom in children under 3 years old and it has been reported that the incidence rate of wheezing is higher in children of younger age (Asthma 2013; Cano-Garcinuno et al. 2014). In China, it has been reported that 70 % of wheezing occurred in children 3 years old or younger (Chen 2003). However, to our knowledge, the association between PM and wheezing in children under 3 years old has not been studied, especially in China.

Pujiang locates at the southern urban area of Shanghai, China, and covers 78.51 km² with a population of 336,300 in 2013. The air quality of Pujiang has become worse in recent years with concentrations of $PM_{2.5}$, PM_{10} , and NO_2 being higher than the China National Air Quality Index ($PM_{2.5} < 35 \mu g/m^3$, $PM_{10} < 70 \mu g/m^3$, and $NO_2 < 40 \mu g/m^3$). Thus, the current study was designed to assess the correlation between the concentration of $PM_{2.5}$ or PM_{10} and the number of clinical patients with wheezing and to explore the negative impact of ambient particulate matter pollution on wheezing episodes among children under 3 years old from Pujiang, Shanghai.

Methods

Study population

The current study was carried out in Pujiang Town, Shanghai, China. The number of daily clinical children under 3 years old with wheezing who visited The Pediatric Department of Shanghai Renji Hospital (South Campus) was collected from Jan. 1, 2014 to Dec. 31, 2014. Wheezing was defined as a continuous high-pitched sound with musical quality emitting from the chest during expiration (Brand et al. 2008).

Air quality monitoring

The quality of ambient air in the Pujiang area and the daily average concentration of $PM_{2.5}$, PM_{10} , NO_2 , SO_2 , and CO were provided by The Air Quality Monitoring and Controlling Agency, located at Minhang, Shanghai. The following equipment were used to measure the components and concentration of air pollutants: Q-TOF liquid chromatography-mass spectrometry, gas chromatography-mass spectrometry double, gas chromatography/mass spectrometer, multidimensional gas chromatograph, HPLC triple quadrupole mass spectrometer, and inductively coupled plasma atomic emission spectroscopy. An aerosol scattering instrument was used to measure PM_{10} concentration. OC/EC

analyzer and $PM_{2.5}$ Hyperspectral Analyzer were used to measure $PM_{2.5}$ concentration. Local meteorological data, including daily average temperature, relative humidity, and barometric pressure, were obtained from The Database of China Meteorological Administration. All of the aforementioned data were collected at the same time throughout 2014.

Statistical analysis

Poisson distribution was used to analyze the prevalence of wheezing in the selected population. Specifically, a time series analysis with generalized additive model (Poisson regression) was applied to estimate the correlation between the ambient $PM_{2.5}$ or PM_{10} concentration and the number of outpatient clinical visit for children with wheezing on the day of PM measurement (day 0) through lag 7 days (day 7).

A generalized additive model (GAM) was used to create a generalized linear model and to establish a more flexible way of estimating the linear relationship between the predictor variable and the response variable (Hastie and RJ 1990). Specifically, we predicted a simple linear relationship between the predictor variable and response variable in the model linear regression. In contrast, in the GAM model, we hypothesized that each predictor variable affects response variable by unknown smooth functions of the predictor variables. As shown by the formula below, the univariate response variable Y_i (number of visitors on day i) depends on some predictor variables such as day of week, temperature, humidity, etc.

By the sequentially and generalized additive Poisson regression model, the dependent variables were fitted through adding different functions by non-linear as well as linear fitting. The association of $PM_{2.5}$ and children health was primarily investigated in the current study. PM_{10} was also analyzed as a second contributor to the air pollution by the GAM model. Other air pollutants were also examined by the GAM model in that they showed better fitting results. In this regard, weather factors (average temperature and humidity), day of the week, and time were treated as “controlling factors” and analyzed by non-parametric and smoothing spline function in order to examine the “factors of control, weekday effect, long-term effect, and seasonal effect.” Of the controlling factors, 1~365 days and 1~4 (spring = 1, summer = 2, fall = 3, winter = 4) seasons were used to calculate the day and season factors, respectively. The model formula was as follows:

$$\begin{aligned} \text{Log}[E(y_i)] = & \beta X + s(\text{time, df}) + \text{as Factor (DOW)} \\ & + s(\text{temperature, df}) + s(\text{humidity, df}) + a. \end{aligned}$$

Y_i is the number of the visitors with wheezing on “ i ” day; $E(Y_i)$ is the expected number of the visitors with wheezing on “ i ” day; β are the linear regression coefficients calculated from the regression model; DOW is day of week, as subvariable; s

(time, df) is spline smoothing function of time; s (temperature, df) is spline smoothing function of daily average temperature; s (humidity, df) is spline smoothing function of daily average humidity; and a is the intercept.

Exposure-response relationship curve was created to study the correlation between the level of PM_{2.5} or PM₁₀ exposure and the percent of increase in the number of visiting children with wheezing.

SPSS 19.0 software (IBM, Armonk, NY, USA) was used for both the performance of descriptive statistical analysis and calculation of correlation coefficients. A generalized additive model was built by the GAM module using S plus 8.0 (Insightful, Tempe, AZ, USA).

Results

Descriptive statistical analysis

From Jan.1, 2014 to Dec. 31, 2014 (total of 365 days), the number of children under 3 years old who visited the outpatient clinic due to wheezing was 8266, and the average number of daily visit was 23 persons/day. As shown in Table 1, during the study period of January through December, 2014, the daily average ambient concentration of PM_{2.5}, PM₁₀, NO₂, SO₂, and CO in Shanghai were 51.84 ± 32.51 , 72.69 ± 41.15 , 43.25 ± 18.07 , 17.45 ± 10.42 , and 0.82 ± 0.26 $\mu\text{g}/\text{m}^3$, respectively, and the daily average number of children who visited the outpatient clinic with wheezing symptom was 23 ± 14 persons/day.

Correlation between air pollutants and meteorological factors

As shown in Table 2, the daily concentration of the PM_{2.5} was significantly correlated with concentration of CO ($r = 0.66$, $P < 0.01$), NO₂ ($r = 0.54$, $P < 0.01$), SO₂ ($r = 0.60$, $P < 0.01$),

degree of temperature ($r = 0.28$, $P = 0.02$), or humidity ($r = 0.15$, $P < 0.01$), but not with ambient air pressure ($r = 0.14$, $P = 0.11$).

Similarly, Table 3 showed that the daily concentration of PM₁₀ was significantly correlated with meteorological parameters including CO ($r = 0.63$, $P < 0.01$), NO₂ ($r = 0.55$, $P < 0.01$), SO₂ ($r = 0.64$, $P < 0.01$), temperature ($r = 0.32$, $P < 0.01$), humidity ($r = 0.31$, $P < 0.01$), and ambient air pressure ($r = 0.23$, $P < 0.01$).

Time-dependent variation of the air pollution and clinical visit for children with wheezing

The concentrations of the PM_{2.5} and PM₁₀ peaked in January, March through May, and November through December, respectively. The variation of NO₂ and SO₂ concentration was mild in the whole year. NO₂ level was relatively low from May through September, while SO₂ was slightly higher in December (Fig 1). Consistent with the change of ambient pollutants, the number of daily outpatient clinical visit dramatically increased in January, October through December, and the peak appeared on January 1 and October 25 (Fig 2).

Since particular matters are the most critical factors contributing to the development of airway symptoms, the correlation between PM_{2.5} or PM₁₀ and the number of clinical visit for children with wheezing was analyzed. As shown in Tables 4 and 5, when univariate analysis was conducted on the number of clinical visit from day 0 through day 7 and PM concentrations on day 0 without adjusting the effect of NO₂ and SO₂, PM_{2.5} concentration was not significantly correlated with the number of clinical visit ($P > 0.05$); however, PM₁₀ concentration on day 0 was significantly correlated with the number of clinical visit from day 0 through day 6 ($P < 0.05$, Table 5). Furthermore, when the influence of NO₂ and SO₂ was adjusted, both PM_{2.5} and PM₁₀ concentration on day 0 were significantly correlated with the number of clinical visits from day 0 through day 7 ($P < 0.01$, Tables 4 and 5), except on

Table 1 Data of meteorological parameters and air pollutants in 2014

Parameters	Days	Mean $\pm$ SD	Percentile					IQR
			0	25	50	75	100	
Temperature ($^{\circ}\text{C}$)	365	17.5 ± 8.3	0.5	10	18	24.5	32	14.5
Humidity (%)	365	73.7 ± 12.5	35	67	75	82	98	15
Pressure (hPa)	365	1016 ± 9	995	1009	1016	1023	1034	136
		8.52						
PM _{2.5} ($\mu\text{g}/\text{m}^3$)	365	51.8 ± 32.5	7	28	44	65	188	37
PM ₁₀ ($\mu\text{g}/\text{m}^3$)	365	72.7 ± 41.2	7	45	62	90	242	45
SO ₂ ($\mu\text{g}/\text{m}^3$)	365	17.5 ± 10.4	5	10	14	21	62	11
NO ₂ ($\mu\text{g}/\text{m}^3$)	365	43.3 ± 18.1	10	29	41	53	108	24
CO ($\mu\text{g}/\text{m}^3$)	365	0.8 ± 0.3	0.4	0.6	0.7	0.9	1.8	0.3

Table 2 Correlation of PM_{2.5} concentration and CO, NO₂, SO₂, and meteorological factors

Factors	Grade	PM _{2.5} concentration, <i>N</i> (%)				Coefficient	<i>P</i> value
		<30 µg/m ³	30–50 µg/m ³	45–65 µg/m ³	>65 µg/m ³		
CO (µg/m ³)	<0.65	70 (69.3)	22 (26.8)	9 (10.2)	0 (0.0)	0.66	<0.01
	0.65–0.75	23 (22.8)	37 (45.1)	20 (22.7)	4 (4.3)		
	0.75–0.95	8 (7.9)	18 (21.9)	40 (45.5)	23 (24.5)		
	>0.95	0 (0.0)	5 (6.1)	19 (21.6)	67 (71.3)		
NO ₂ (µg/m ³)	<30	57 (56.4)	25 (30.5)	9 (10.2)	1 (1.1)	0.54	<0.01
	30–40	25 (24.8)	21 (25.6)	25 (28.4)	8 (8.5)		
	40–55	18 (17.8)	25 (30.5)	32 (36.4)	36 (38.3)		
	>55	1 (1.0)	11 (13.4)	22 (25.0)	49 (52.1)		
SO ₂ (µg/m ³)	<10	40 (39.6)	11 (13.4)	5 (5.7)	0 (0.0)	0.60	<0.01
	10–15	51 (50.50)	47 (57.3)	27 (30.7)	13 (13.8)		
	15–20	9 (8.9)	18 (21.9)	31 (35.2)	15 (15.9)		
	>20	1 (1.0)	6 (7.3)	25 (28.4)	66 (70.2)		
Temper. (°C)	<10	24 (23.8)	10 (12.2)	21 (23.9)	32 (34.0)	0.28	0.02
	10–15	11 (10.9)	28 (34.2)	25 (28.4)	26 (27.7)		
	15–20	36 (35.6)	26 (31.7)	22 (25.0)	14 (14.9)		
	>20	30 (29.7)	18 (21.9)	20 (22.7)	22 (23.4)		
Humidity (%)	<65	18 (17.8)	17 (20.7)	18 (20.5)	29 (30.9)	0.15	<0.01
	65–75	24 (23.8)	19 (23.2)	20 (22.7)	22 (23.4)		
	75–85	35 (34.7)	27 (32.9)	36 (40.9)	29 (30.9)		
	>85	24 (23.8)	19 (23.2)	14 (15.9)	14 (14.9)		
Pressure (hPa)	<1010	35 (34.7)	24 (29.3)	26 (29.6)	25 (26.6)	0.14	0.11
	1010–1015	16 (15.8)	12 (14.6)	12 (13.6)	11 (11.7)		
	1015–1020	17 (16.8)	13 (15.9)	22 (25.0)	16 (17.0)		
	>1020	33 (32.7)	33 (40.2)	28 (31.8)	42 (44.7)		

day 3 and day 4 for PM₁₀ concentration ($P > 0.05$, Table 5). The interaction of SO₂ or NO₂ and particular matters was adjusted in that the concentration of SO₂ or NO₂ was significantly correlated with the number of clinical visit ($r = 0.32$, $P < 0.01$ for SO₂ and $r = 0.34$, $P < 0.01$ for NO₂, respectively), while the correlation of CO concentration and the number of clinical visit was not statistically significant ($r = 0.18$, $P = 0.07$, Table 6).

Exposure-response relationship

The interquartile of PM_{2.5} and PM₁₀ was substituted into the model to calculate the number of outpatient clinical visit on the corresponding day, and by which formula, the percentage of increased outpatient clinical visit was obtained. A scatter plot was drawn and from which, a smooth curve was obtained (Figs. 3 and 4). As shown in Fig 3, the correlation between PM_{2.5} and wheezing attack, i.e., exposure-response correlation, was nearly linear without threshold; specifically, for

every interquartile increase of PM_{2.5}, the percent of outpatient clinical visits increased from 0 to nearly 20 % (Fig 3). Similarly, as shown in Fig 4, when PM₁₀ concentration increased to 45 µg/m³, the percent of outpatient clinical visits increased nearly 7 %, then dropped to 1 % at 62 µg/m³ and increased again to 12 % at 90 µg/m³ (Fig 4).

Discussion

The current study demonstrated that ambient concentrations of PM_{2.5}, PM₁₀, SO₂, NO₂, and CO in Pujiang, Shanghai, were abnormally higher during the study period compared to the air quality index defined by the Chinese Environment Protection Agency, and that the number of clinical visits for the children with wheezing increased when the concentrations of the aforementioned pollutants increased. With the justification of the effect of SO₂ and NO₂, the concentration of PM_{2.5} or PM₁₀ was significantly correlated with the number of

Table 3 Correlation of PM₁₀ concentration and CO, NO₂, SO₂, and meteorological factors

Factors	Grade	PM ₁₀ concentration				Coefficient	P value
		<45 µg/m ³	45–65 µg/m ³	65–90 µg/m ³	>90 µg/m ³		
CO (µg/m ³)	<0.65	59 (66.3)	30 (28.3)	11 (14.1)	1 (1.1)	0.63	<0.01
	0.65–0.75	21 (23.6)	44 (41.5)	15 (19.2)	4 (4.4)		
	0.75–0.95	8 (9.0)	23 (21.7)	35 (44.9)	23 (25.0)		
	>0.95	1 (1.1)	9 (8.5)	17 (21.8)	64 (69.6)		
NO ₂ (µg/m ³)	<30	49 (55.1)	34 (32.1)	8 (10.3)	1 (1.1)	0.55	<0.01
	30–40	24 (27.0)	29 (27.4)	18 (23.1)	8 (8.7)		
	40–55	16 (18.0)	31 (29.3)	35 (44.9)	29 (31.5)		
	>55	0 (0.0)	12 (11.3)	17 (21.8)	54 (58.7)		
SO ₂ (µg/m ³)	<10	39 (43.8)	16 (15.1)	1 (1.3)	0 (0.0)	0.64	<0.01
	10–15	41 (46.1)	63 (59.4)	29 (37.2)	5 (5.4)		
	15–20	9 (10.1)	22 (20.8)	27 (34.6)	15 (16.3)		
	>20	0 (0.0)	5 (4.7)	21 (26.9)	72 (78.3)		
Temper. (°C)	<10	24 (27.0)	17 (16.0)	10 (12.8)	36 (39.1)	0.32	<0.01
	10–15	10 (11.2)	24 (22.6)	32 (41.0)	24 (26.1)		
	15–20	30 (33.7)	37 (34.9)	18 (23.1)	13 (14.1)		
	>20	25 (28.1)	28 (26.4)	18 (23.1)	19 (20.7)		
Humidity (%)	<65	11 (12.4)	14 (13.2)	20 (25.6)	37 (40.2)	0.31	<0.01
	65–75	18 (20.2)	26 (24.5)	19 (24.4)	22 (23.9)		
	75–85	32 (35.9)	45 (42.5)	29 (37.2)	21 (22.8)		
	>85	28 (31.5)	21 (19.8)	10 (12.8)	12 (13.0)		
Pressure (hPa)	<1010	35 (39.3)	36 (33.9)	18 (23.1)	21 (22.)	0.23	<0.01
	1010–1015	15 (16.9)	11 (10.4)	13 (16.7)	12 (13.0)		
	1015–1020	11 (12.4)	29 (27.4)	13 (16.7)	15 (16.3)		
	>1020	28 (31.5)	30 (28.3)	34 (43.6)	44 (47.8)		

clinical visit for children with wheezing for a whole 1-week period. In addition, the daily concentration of the PM_{2.5} was significantly correlated with concentration of CO, NO₂, SO₂, degree of temperature, or humidity, but not with ambient air pressure. Similarly, daily concentration of the PM₁₀ was significantly correlated with meteorological parameters including CO, NO₂, SO₂, temperature, humidity, and ambient air pressure. It was also found that exposure-response relationship of PM_{2.5} and the percent of number of visit increase was a linear non-threshold mode when it was analyzed by the GAM.

Several longitudinal cohort studies have demonstrated that children with asthma experienced short-term increase in symptoms as well as decrements in lung function following exposure to outdoor particulate matter with aerodynamic diameter of 2.5 µm or less (PM_{2.5}) (Cai et al. 2014; Jacquemin et al. 2015; Stoner et al. 2013). While this association has been well described in the developed countries, it remains largely unexplored in China where heavy air pollution has been

noticed in recent years. In this regard, PM_{2.5} is the major contributor to the air pollution in Shanghai, China. Therefore, the association of PM_{2.5} and children health was primarily investigated in the current study in order to provide scientific evidence as regards the occurrence of respiratory symptoms for children under 3 years old in response to ambient air pollution. It was found that both PM_{2.5} and PM₁₀ were high risk factors for children's symptom of wheezing in the Shanghai area. Specifically, daily concentration of the PM_{2.5} or PM₁₀ was significantly correlated with the number of clinical visit for children with wheezing, and that concentration of CO, NO₂, SO₂, degree of temperature, or relative humidity also affect the contribution of PM to respiratory disease prevalence.

By the definition of the World Health Organization (WHO), air pollution associated morbidity and mortality will dramatically increase when the PM_{2.5} concentration reaches 35 µg/m³ (http://www.who.int/phe/health_topics/outdoorair/outdoorair_aqg/en/). The current study

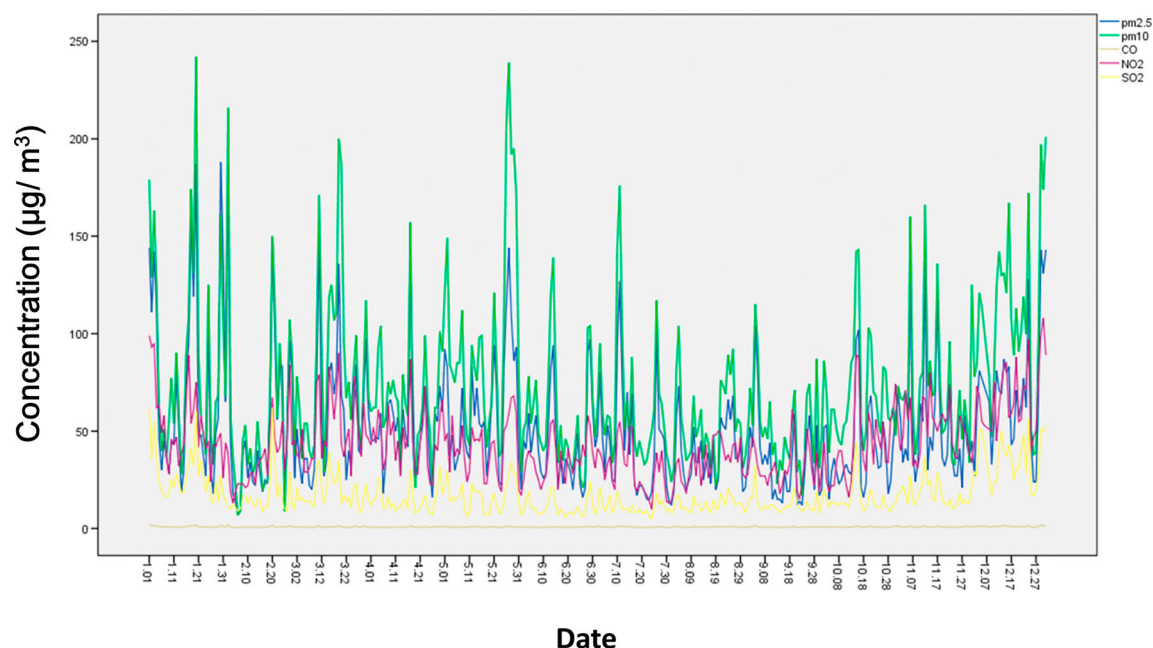


Fig. 1 Variation of the air pollutants during the study period. *Vertical axis:* concentration of indicated pollutants ($\mu\text{g}/\text{m}^3$); *horizontal axis:* time (date)

demonstrated that average daily concentration of $\text{PM}_{2.5}$ was $51.84 \mu\text{g}/\text{m}^3$, which was lower than the standard of China ($75 \mu\text{g}/\text{m}^3$) but much higher than the standard of WHO ($10 \mu\text{g}/\text{m}^3$). Consistent with the WHO definition, the finding of the current study suggested that PM concentration contributes to the increased incidence of respiratory symptoms, especially in winter and spring.

Particulate matter contains lots of toxic substances, which can enter the body through breathing, even directly into the alveolar and blood circulation, because the physical structure

of the human body does not have any filtering or blocking capability to protect itself against PM invasion. Studies have proved that $\text{PM}_{2.5}$ or PM_{10} can lead to the damage of the pulmonary tissues and the biomembrane, interfering the humoral immune response and local mucosal immunity, which can cause acute respiratory tract injury (Mukherjee et al. 2013; Santini et al. 2004). The current study demonstrated that PM_{10} concentration on day 0 was significantly correlated with the number of clinical visits from day 0 through day 6, and that when the influence of NO_2 and SO_2 was adjusted, both $\text{PM}_{2.5}$

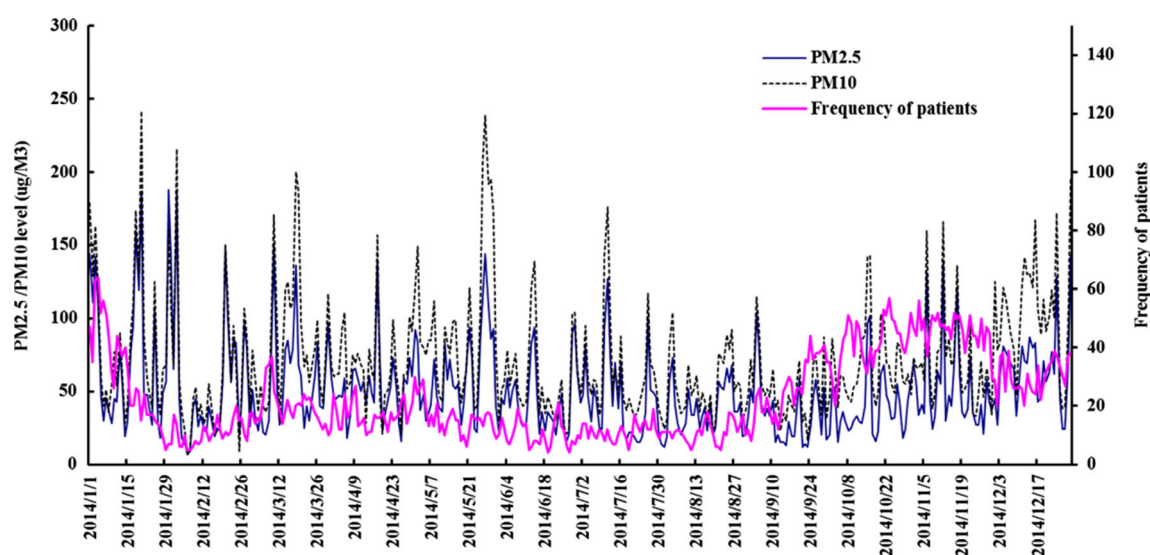


Fig. 2 Variation of $\text{PM}_{2.5}$, PM_{10} , and the number of clinical visits during the study period. *Left vertical axis:* concentration of $\text{PM}_{2.5}$ and PM_{10} ($\mu\text{g}/\text{m}^3$); *right vertical axis:* number of children that visited the outpatient clinic (frequency of patients). *Horizontal axis:* time (date)

Table 4 Correlation of PM_{2.5} concentration and the number of clinical visit

Day	No. of clinical visit	PM _{2.5} concentration, <i>N</i> (%)				Coefficient	<i>P</i> value ^a	<i>P</i> value ^b
		<30 µg/m ³	30–50 µg/m ³	45–65 µg/m ³	>65 µg/m ³			
Day 0	<12	31 (30.7)	14 (17.1)	20 (22.7)	26 (27.7)	0.15	0.515	<0.01
	12–17	24 (23.8)	16 (19.5)	20 (22.7)	16 (17.0)			
	17–33	24 (23.8)	27 (32.9)	25 (28.4)	29 (30.9)			
	>33	22 (21.8)	25 (30.5)	23 (26.1)	23 (24.5)			
Day 1	<12	29 (28.7)	20 (24.4)	22 (25.0)	20 (21.5)	0.15	0.33	<0.01
	12–17	25 (24.8)	13 (15.9)	21 (23.9)	17 (18.3)			
	17–33	24 (23.8)	22 (26.8)	25 (28.4)	34 (36.6)			
	>33	23 (22.8)	27 (32.9)	20 (22.7)	22 (23.7)			
Day 2	<12	29 (28.7)	18 (21.9)	24 (27.3)	20 (21.7)	0.17	0.52	<0.01
	12–17	22 (21.8)	19 (23.2)	18 (20.5)	17 (18.5)			
	17–33	27 (26.7)	17 (20.7)	26 (29.6)	35 (38.0)			
	>33	23 (22.8)	28 (34.2)	20 (22.7)	20 (21.7)			
Day 3	<12	34 (34.0)	17 (20.7)	21 (23.9)	19 (21.1)	0.19	0.24	<0.01
	12–17	20 (20.0)	19 (23.2)	21 (23.9)	16 (17.8)			
	17–33	21 (21.0)	22 (26.8)	25 (28.4)	37 (41.1)			
	>33	25 (25.0)	24 (29.3)	21 (23.9)	18 (20.0)			
Day 4	<12	37 (36.6)	14 (17.1)	24 (27.3)	16 (17.8)	0.24	0.16	<0.01
	12–17	18 (17.8)	21 (25.6)	20 (22.7)	17 (18.9)			
	17–33	20 (19.8)	22 (26.8)	24 (27.3)	39 (43.3)			
	>33	26 (25.7)	25 (30.5)	20 (22.7)	18 (20.0)			
Day 5	<12	36 (36.0)	14 (17.1)	23 (26.1)	18 (20.0)	0.22	0.40	<0.01
	12–17	17 (17.0)	18 (21.9)	20 (22.7)	21 (23.3)			
	17–33	25 (25.0)	22 (26.8)	23 (26.1)	35 (38.9)			
	>33	22 (22.0)	28 (34.2)	22 (25.0)	16 (17.8)			
Day 6	<12	36 (36.4)	14 (17.1)	17 (19.3)	24 (26.7)	0.24	0.79	<0.01
	12–17	13 (13.1)	23 (28.1)	23 (26.1)	17 (18.9)			
	17–33	26 (26.3)	18 (21.9)	28 (31.8)	33 (36.7)			
	>33	24 (24.2)	27 (32.9)	20 (22.7)	16 (17.8)			
Day 7	<12	30 (30.3)	18 (21.9)	22 (25.3)	21 (23.3)	0.14	0.99	<0.01
	12–17	20 (20.2)	17 (20.7)	17 (19.5)	22 (24.4)			
	17–33	25 (25.3)	21 (25.6)	28 (32.2)	31 (34.4)			
	>33	24 (24.2)	26 (31.7)	20 (23.0)	16 (17.8)			

^a *P* values by Cochran-Mantel-Haenszel (CMH) nonzero correlation analysis^b *P* values by CMH nonzero correlation analysis after adjusted with SO₂ and NO₂

and PM₁₀ concentration on day 0 were significantly correlated with the number of clinical visits from day 0 through day 7, except on day 3 and day 4, for PM₁₀ concentration. These findings indicated that PM_{2.5} and PM₁₀ may contribute to the development of children wheezing.

Consistent with our findings, Loftus et al. 2015 reported that exposure to ambient PM_{2.5} could lead to acute episodes of asthma, and when the concentration of PM_{2.5} increased by 10 µg/m³, the relative risk of asthmatic symptoms rose up to 1.1. Similarly, a study conducted in Canada which investigated a city with

heavy traffic concluded that an increasing exposure to PM_{2.5} by each IQR (=6 µg/m³) in the past 24 h would lead to a decrease in bedtime FEV₁ by 0.5 % (Dales et al. 2009). A recent multicenter study of 10 years across 81 centers in the USA indicated that continued exposure to PM_{2.5} would even reduce the survival rate of children, and the relative risk was up to a factor of 1.11 (Kioumourtoglou et al. 2015). These findings suggested that airway inflammation following PM exposure leads to heightened permeability of airway epithelia, which in turn may enhance the allergenic potential of

Table 5 Correlation of PM₁₀ concentration and the number of clinical visit

Day	No. of clinical visit	PM ₁₀ concentration, <i>N</i> (%)				Coefficient	<i>P</i> value ^a	<i>P</i> value ^b
		<45 µg/m ³	45–65 µg/m ³	65–90 µg/m ³	>90 µg/m ³			
Day 0	<12	30 (33.7)	25 (23.6)	18 (23.1)	18 (19.6)	0.20	<0.01	<0.01
	12–17	24 (26.9)	23 (21.7)	12 (15.4)	17 (18.5)			
	17–33	20 (22.5)	31 (29.3)	21 (26.9)	33 (35.9)			
	>33	15 (16.9)	27 (25.5)	27 (34.6)	24 (26.1)			
Day 1	<12	29 (32.6)	29 (27.4)	20 (25.6)	13 (14.3)	0.25	<0.01	0.02
	12–17	24 (26.9)	24 (22.6)	13 (16.7)	15 (16.5)			
	17–33	20 (22.5)	24 (22.6)	20 (25.6)	41 (45.1)			
	>33	16 (17.9)	29 (27.4)	25 (32.1)	22 (24.2)			
Day 2	<12	30 (33.7)	27 (25.5)	18 (23.1)	16 (17.8)	0.22	<0.01	<0.01
	12–17	20 (22.5)	28 (26.4)	12 (15.4)	16 (17.8)			
	17–33	24 (26.9)	21 (19.8)	24 (30.8)	36 (40.0)			
	>33	15 (16.9)	30 (28.3)	24 (30.8)	22 (24.4)			
Day 3	<12	32 (36.4)	26 (24.5)	18 (23.1)	15 (17.1)	0.25	<0.01	0.06
	12–17	22 (25.0)	28 (26.4)	11 (14.1)	15 (17.1)			
	17–33	18 (20.5)	25 (23.9)	24 (30.8)	38 (43.2)			
	>33	16 (18.2)	27 (25.5)	25 (32.1)	20 (22.7)			
Day 4	<12	35 (39.3)	28 (26.4)	13 (16.7)	15 (17.1)	0.27	<0.01	0.1
	12–17	21 (23.6)	23 (21.7)	19 (24.4)	13 (14.8)			
	17–33	17 (19.1)	28 (26.4)	21 (26.9)	39 (44.3)			
	>33	16 (17.9)	27 (25.5)	25 (32.1)	21 (23.9)			
Day 5	<12	36 (40.9)	24 (22.6)	16 (20.5)	15 (17.1)	0.28	<0.01	0.03
	12–17	14 (15.9)	28 (26.4)	19 (24.4)	15 (17.1)			
	17–33	23 (26.1)	25 (23.6)	17 (21.8)	40 (45.5)			
	>33	15 (17.1)	29 (27.4)	26 (33.3)	18 (20.5)			
Day 6	<12	35 (40.2)	21 (19.8)	16 (20.5)	19 (21.6)	0.27	0.02	0.03
	12–17	13 (14.9)	29 (27.4)	20 (25.6)	14 (15.9)			
	17–33	25 (28.7)	27 (25.5)	16 (20.5)	37 (42.1)			
	>33	14 (16.1)	29 (27.4)	26 (33.3)	18 (20.5)			
Day 7	<12	30 (34.5)	24 (22.9)	18 (23.1)	19 (21.6)	0.16	0.07	<0.01
	12–17	19 (21.8)	24 (22.9)	14 (17.9)	19 (21.6)			
	17–33	22 (25.3)	31 (29.5)	21 (26.9)	31 (35.2)			
	>33	16 (18.4)	26 (24.8)	25 (32.1)	19 (21.6)			

^a *P* values by Cochran-Mantel-Haenszel (CMH) nonzero correlation analysis^b *P* values by CMH nonzero correlation analysis after adjusted with SO₂ and NO₂

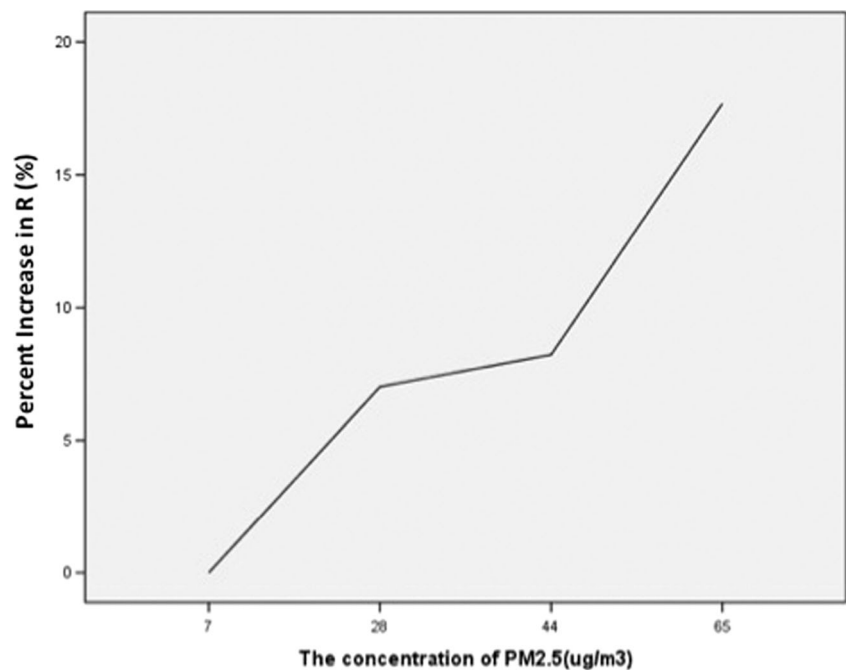
aeroallergens for sensitized individuals (D'Amato et al. 2005).

Exposure-response relationship is the correlation between the level of environmental exposure and the occurrence of

Table 6 Correlation of CO, NO₂, and SO₂ concentration and the number of clinical visit

Pollutant	Grade	The number of clinical visit, <i>N</i> (%)				Coefficient	<i>P</i> value
		<12	12–17	17–33	>33		
SO ₂ (µg/m ³)	<10	22 (24.2)	19 (25.0)	11 (10.5)	4 (4.3)	0.32	<0.01
	10–15	37 (40.7)	31 (40.8)	37 (35.2)	33 (35.5)		
	15–20	21 (23.1)	14 (18.4)	16 (15.3)	22 (23.7)		
	>20	11 (12.1)	12 (15.8)	41 (39.1)	34 (36.6)		
NO ₂ (µg/m ³)	<30	35 (38.5)	23 (30.3)	26 (24.8)	8 (8.6)	0.34	<0.01
	30–40	23 (25.3)	18 (23.9)	15 (14.3)	23 (24.7)		
	40–55	27 (29.7)	25 (32.9)	33 (31.4)	26 (27.9)		
	>55	6 (6.6)	10 (13.2)	31 (29.5)	36 (38.7)		
CO (µg/m ³)	<0.65	26 (28.6)	25 (32.9)	33 (31.4)	17 (18.3)	0.18	0.07
	0.65–0.75	24 (26.4)	14 (18.4)	23 (21.9)	23 (24.7)		
	0.75–0.95	20 (21.9)	24 (31.6)	21 (20.0)	24 (25.8)		
	>0.95	21 (23.1)	13 (17.1)	28 (26.7)	29 (31.2)		

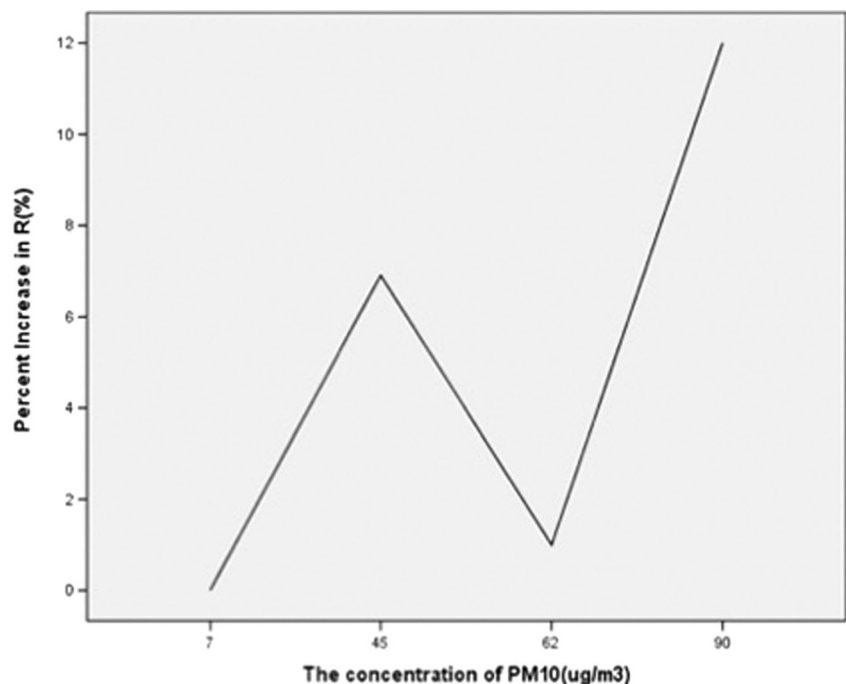
Fig. 3 Exposure-response relationship curve of $PM_{2.5}$ and percent of increase in visit number for children with wheezing. An exposure-response relationship curve was created by the analysis as described in the “Methods” section. *Vertical axis:* percentage increase in visit number (R/%); *horizontal axis:* interquartile of $PM_{2.5}$ concentration ($\mu g/m^3$)



certain negative reactions in the human body. In the epidemiologic study of atmospheric pollution, it is usually defined as the change of the concentration of atmospheric pollutants and the corresponding changes in the proportion of individuals in the population. With the wide adoption of the time series analysis and other related models, these methods have gained popularity in the quantitative research of the relationship between air pollution and population health in recent years.

Considering the fact that clinical visit is related to lots of factors besides the $PM_{2.5}$, PM_{10} , and other air pollutants, we introduced the time, daily average temperature, daily relative humidity, and “day of the week (DOW); DOW = 1–7” as spline smoothing functions into the model to control the effect of long-term trend, meteorological factor, and effects of day of the week. Using the GAM model, we got an exposure-response relationship of air pollution and clinical wheezing,

Fig. 4 Exposure-response relationship curve of PM_{10} and percent of increase in visit number for children with wheezing. An exposure-response relationship curve was created by the analysis as described in the “Methods” section. *Vertical axis:* percentage increase in visit number (R/%); *horizontal axis:* interquartile of PM_{10} concentration ($\mu g/m^3$)



which was a linear non-threshold mode. Similar results in studies of the exposure-response relationship between fine particulate matter and population health were found in most of the published studies (Kan et al. 2005; Riojas-Rodriguez et al. 2014; Zeng et al. 2015). The linear non-threshold model indicated that an increase in PM_{2.5} at any level leads to a rising number of wheezing children.

The main sources of PM_{2.5} in China are vehicle exhausts and industrial emissions in most regions (Li et al. 2015; Wang et al. 2015). The relationship between particulate matter (PM) exposure and respiratory health observed for children in Shanghai may not be generalizable to other regions because the PM composition may vary in different regions. However, the current study found that daily concentration of the ambient PM_{2.5} during the study period in Pujiang Town, Shanghai was 51.84 µg/m³, which was dramatically higher than the Chinese national standard (35 µg/m³) and the WHO standard (<10 µg/m³). The number of pediatric patients in the outpatient clinic with wheezing in Pujiang, Shanghai significantly went up during the winter and spring seasons when the ambient air quality was worst, suggesting air pollution may contribute to the rise of patients' visit to an outpatient clinic with wheezing. Although the mechanisms are not well understood, it seems that particulate matter increases susceptibility to respiratory illnesses by impairing host defense mechanisms and by weakening immunologic and mucociliary response, causing a strong component of oxidative stress and proinflammatory response (MacNee and Donaldson 2000; Sigaud et al. 2007), which may be similar to the effect of tobacco smoke (Milnerowicz et al. 2015).

There are limitations in the current study. Firstly, the study population only comes from one single center, which might be insufficient to represent the exposure-response relationship for the whole population in Shanghai, China. Secondly, assessment of air particulate matters was obtained from a single monitoring site, which might not reflect the exact PM_{2.5} concentration exposed by each individual in the study. Thirdly, this study was carried out in a single medical center, and thus, it was plausible to miss some cases of children with wheezing in the Pujiang area. Fourthly, the environmental difference for each infant was not taken into account, and as a result, bias might exist.

In conclusion, the current study investigated the relationship of the concentration of particulate matters in the ambient air and the number of children who visited the clinic due to respiratory symptom of wheezing in Pujiang, Shanghai, China, from January through December 2014. It was found that ambient concentrations of PM_{2.5}, PM₁₀, SO₂, NO₂, and CO were abnormally higher than the standard of China Environment Protection Agency during the study period. SO₂ or NO₂ contributes to the increase of the number of clinical visits for children with wheezing, and the number of clinical visits for children with wheezing was significantly

correlated with the concentration of PM_{2.5} or PM₁₀ after justification of the SO₂ and NO₂ effect. In addition, exposure-response relationship of PM_{2.5} and percent of visit number increase was a linear non-threshold mode when it was analyzed by the GAM. Findings of this study indicate that increase of PM_{2.5} and PM₁₀ in the Pujiang area led to increase of the visit number for children with wheezing.

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Compliance with ethical standards

Conflict of interest statements The authors declare that they have no conflict of interest.

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