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# The relationship between air quality and respiratory pathogens among children in Suzhou City

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## Abstract

**Objective:** We studied the short-term effects of air pollutant concentrations in Suzhou City on respiratory infections in children of different age groups.

**Methods:** We employed clinical data from children hospitalized with respiratory infections at the Children's Hospital of Soochow University during 2014–2016, and air quality for Suzhou City covering the same period. We investigated the relationships between the air pollutant concentrations and respiratory tract infections in children by causative pathogen using time series models with lagged effects.

**Results:** The results of single-pollutant models showed that PM<sub>2.5</sub>, PM<sub>10</sub>, NO<sub>2</sub>, SO<sub>2</sub> and CO had statistically significant associations with respiratory tract infections in children under 3 years, with the largest effect sizes at a lag of 3 weeks. Notably, the multi-pollutant model found PM<sub>2.5</sub> was significantly associated with viral respiratory in children under 7 months, and bacterial respiratory infections in other age groups, while PM<sub>10</sub> concentrations were associated with viral infections in preschool children.

**Conclusion:** PM<sub>2.5</sub>, PM<sub>10</sub> and NO<sub>2</sub> are the main atmospheric pollutants in Suzhou. The associations between pollutant concentrations and viral and bacterial respiratory infections were stronger among children under 3 years than for older age groups. PM<sub>2.5</sub> had the strongest influence on viral and *Mycoplasma pneumoniae* respiratory infections when multiple pollutants were tested together.

**Keywords:** Air quality, Respiratory tract infection, Pathogens, Children, Model selection

## Introduction

The impact of air pollution on respiratory health in China has recently received significant attention. Air pollutants have been associated with multiple adverse effects on human health; in particular respiratory and cardiovascular health [1]. Residents of different regions have variable sensitivity to potential health effects of air pollutants [2]. Acute respiratory tract infection (ARI) is a common infectious disease to which children are particularly susceptible. Viruses account for over 80% of respiratory infections in infants and young children,

although *Mycoplasma pneumoniae* and chlamydia are also implicated [3]. Secondary bacterial infection can follow viral infection. Bacteria of the genus *Mycoplasma* are among the most common causative pathogens of respiratory infection in children, and incidence of such infections has increased in China in recent years [4]. The developmental, structural and physiological characteristics of a child's respiratory system determine sensitivity to effects of atmospheric pollution [5]. Previous work has found a positive correlation between air pollutant concentrations and incidence of respiratory diseases in children [6–8]. Furthermore, inhalation of air pollutants can change the micro-ecology of the respiratory tract and increase the susceptibility of children to respiratory infections [9].

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This study sought to establish the most appropriate statistical model to assess short-term associations between air pollutant concentrations and respiratory tract infections in children, and to test the susceptibility of different age groups to inform health risk assessments and development of public health policy responses.

## Materials and methods

### Materials

We employed hospitalization data collected from the Children's Hospital of Soochow University during 2014–2016 meeting diagnostic criteria for ARI [4], and extracted variables including age, gender, disease diagnosis, date of visit, medical record number, residential address, and pathogens detected. Our analytic sample included 5487 children with ARI aged 1 month to 15 years registered as being resident in Suzhou. It comprised 3373 boys (61.5%) and 2114 girls (38.5%) (male-to-female ratio: 1.6:1). This study was conducted with the approval of the Institutional Human Ethical Committee of Children's Hospital of Soochow University. An informed consent was obtained from all the subjects or guardians who participated in this study.

We also used air quality data from the same period provided by the Suzhou Environmental Protection Agency. Readings included fine particulate matter (PM<sub>2.5</sub>), inhalable particulate matter (PM<sub>10</sub>), nitrogen dioxide (NO<sub>2</sub>), sulfur dioxide (SO<sub>2</sub>), carbon monoxide (CO) and ozone (O<sub>3</sub>). Daily air pollutant concentrations were calculated as the mean per 24-h period, except for O<sub>3</sub> which was calculated flow-weighted mean concentration per eight-hour period. Concentrations of air pollutants were expressed in µg/m<sup>3</sup>, except CO for which mg/m<sup>3</sup> was used.

### Methods

Descriptive statistics were carried out with SPSS 21.0 statistical software, including mean, standard deviation, the 25th, 50th (median) and 75th percentiles, minimum and maximum. The correlation between air pollutants was analyzed by Spearman correlation analysis.

First, the basic model was constructed, without an air pollutant and with other covariates, including time, day of the week and public holidays. While meteorological factors were not controlled. Bayesian Information Criterion (BIC) was used to measure how well the model fitted the data. The smallest BIC value indicates the preferred model. Air pollutants were included step by step into the model. If the BIC value was smaller when a new variable was introduced, the variable remained in the model. This was the Model Selection mode.

Next, Single-pollutant models were established, each model contained one type of air pollutant. The associations between air pollution and health effects can be described as exhibiting a hysteresis effect, in which risk of a given

outcome is dependent on both current and past pollutant concentrations, and where exposure to air pollutants may demonstrate a lagged effect after one or more days [10]. Lag<sub>0</sub> to lag<sub>4</sub> were used to analyze the associations between single pollutant and incidence of different types of respiratory tract infections (viral, Mycoplasma or other bacteria) among children of different age groups (1 month ≤ age<sub>1</sub> ≤ 6 months, 6 months < age<sub>2</sub> ≤ 1 year, 1 year < age<sub>3</sub> ≤ 3 years, 3 years < age<sub>4</sub> ≤ 6 years, age<sub>5</sub> > 6 years). Here, lag<sub>0</sub> corresponded to the current-day air pollutant concentration and lag<sub>1</sub> referred to the average concentration of air pollutants in the week before admission and so on.

There is also the potential for interaction effects between various pollutants, however, and models fitting exposure to a single pollutant may underestimate the impact of atmospheric pollution on human health [11]. Studies have shown differential susceptibility of children to different respiratory pathogens by age group [12, 13]. Considering the maximum effect of each air pollutant in the single-pollutant models, the air pollutant concentrations corresponding to the lag day were used to develop the multi-pollutant models. Based on the principle of BIC minimum value, the optimal model was selected to determine the main pollutants and sensitive period of different pathogens affecting children's respiratory tract infection.

SPSS version 21.0 and SAS version 9.4 were used for data handling. All time series analyses were performed using R version 3.3.1. Results were expressed in terms of odd ratios (OR) for each additional 10 µg/m<sup>3</sup> in atmospheric concentration with 95% confidence interval (95% CI), and *p*-values of < 0.05 were considered to indicate statistically significant associations.

## Results

### Characteristics of the air quality indicators

Mean annual concentrations of PM<sub>2.5</sub> in Suzhou were 66.38 µg/m<sup>3</sup> in 2014, 57.51 µg/m<sup>3</sup> in 2015 and 45.41 µg/m<sup>3</sup> in 2016. Annual mean PM<sub>10</sub> concentrations were 89.94 µg/m<sup>3</sup>, 80.51 µg/m<sup>3</sup> and 71.27 µg/m<sup>3</sup> respectively. For NO<sub>2</sub> these were 51.72 µg/m<sup>3</sup>, 50.85 µg/m<sup>3</sup>, and 48.71 µg/m<sup>3</sup>. Concentration of each of these pollutants exceeded the annual average secondary concentration limits established by the GB3095–2012 Ambient Air Quality Standard (PM<sub>2.5</sub>: 35 µg/m<sup>3</sup>, PM<sub>10</sub>: 70 µg/m<sup>3</sup>, NO<sub>2</sub>: 40 µg/m<sup>3</sup>). Mean concentrations of NO<sub>2</sub>, PM<sub>2.5</sub> and PM<sub>10</sub> were highest in winter (December, January and February) and decreased during the summer (June, July and August). The mean primary concentration limits for SO<sub>2</sub>, CO and O<sub>3</sub> indicated by the GB3095–2012 standard are 20 µg/m<sup>3</sup>, 4 mg/m<sup>3</sup> and 100 µg/m<sup>3</sup>. Atmospheric concentrations of SO<sub>2</sub> in Suzhou exceeded the limit in 2014 and 2015 but not in 2016. Annual mean concentrations of CO and O<sub>3</sub> remained within the limit for the duration of the period studied. While

concentrations of O<sub>3</sub> are elevated in summer compared with winter, there was no significant monthly fluctuation in CO concentrations. These readings indicate that poor air quality in Suzhou City during 2014–2016 posed a risk to human health, and that concentrations of particulates were of notable concern (Table 1).

There were statistically significant differences in mean concentrations of PM<sub>2.5</sub>, PM<sub>10</sub>, NO<sub>2</sub> and SO<sub>2</sub> by year ( $p < 0.05$ ), with higher concentrations of PM<sub>2.5</sub>, PM<sub>10</sub>, NO<sub>2</sub> and SO<sub>2</sub> in 2014 than in 2015 and 2016. (Table 2).

We also found positive and statistically significant correlations between concentrations of PM<sub>2.5</sub>, PM<sub>10</sub>, NO<sub>2</sub>, SO<sub>2</sub> and CO. There was a significant negative correlation between O<sub>3</sub>, PM<sub>2.5</sub>, NO<sub>2</sub>, SO<sub>2</sub> and CO. (Table 3).

**Characteristics of respiratory infections**

During the period 2014–2016, nasopharyngeal peripheral blood samples were collected from 5487 children with ARI. Viral pathogens were detected in 1827 (33.3%) of these cases. The proportion of cases with a viral infection was higher in 2014 than in 2015 and 2016. These annual differences were statistically significant ( $\chi^2 = 43.80$ ,  $p < 0.001$ ). *M. pneumoniae* was detected in 1581 cases (28.8%) overall, including 542 (27.6%), 537 (29.6%), and 502 (29.2%) in 2014, 2015 and 2016 while 1657 other bacterial infections (30.2%) were detected with 629 (32.1%), 539 (29.7%), and 502 (29.2%) in each year (Table 4).

In the same period, our sample children aged 1 month to 15 years hospitalized for ARI included 2079 cases

(37.9%) aged less than or equal to 6 months old, 753 (13.7%) aged 6 months to 1 year, 1262 (23%) aged 1 year to 3 years, 937 (17.1%) aged 3 years to 6 years, and 456 (8.3%) aged greater than 6 years (Table 5).

**Lagged associations between air quality and respiratory tract infections attributable to different pathogens in children by age group in single-pollutant model**

**Relationship between air quality and viral respiratory tract infections**

We found significant associations between concentrations of PM<sub>2.5</sub>, PM<sub>10</sub>, NO<sub>2</sub>, SO<sub>2</sub> and CO at lag 0–lag 4 and incidence of viral respiratory tract infections in children under 3 years of age in Suzhou City during 2014–2016 ( $p < 0.05$ ), with the largest effect size found for lag 3. The association between NO<sub>2</sub> and incidence of viral respiratory infections in preschool children was statistically significant ( $p < 0.05$ ), with the largest effect size found at lag 2. No such associations were found for PM<sub>2.5</sub>, PM<sub>10</sub>, SO<sub>2</sub> and CO, however ( $p > 0.05$ ). There was also a significant association between SO<sub>2</sub> concentrations and viral respiratory infections in school-age children ( $< 0.05$ ), with the largest effect size at lag 4. There was no significant association found for PM<sub>2.5</sub>, PM<sub>10</sub>, NO<sub>2</sub> or CO ( $p > 0.05$ ). We also found a negative association between O<sub>3</sub> concentrations at lag 0–lag 4 and viral respiratory infections in children under 3 years ( $p < 0.05$ ) (Table 6).

**Relationship between air quality and bacterial respiratory tract infections**

We found significant associations between PM<sub>2.5</sub>, PM<sub>10</sub>, NO<sub>2</sub> and SO<sub>2</sub> concentrations at lag 0–lag 4 and bacterial respiratory tract infections among children less than or equal to 6 months of age during 2014–2016 ( $p < 0.05$ ). The largest effect sizes were found for lag 4. Associations between concentrations of PM<sub>2.5</sub>, PM<sub>10</sub> and SO<sub>2</sub> at lag 0–lag 4 and respiratory tract infections in children aged 6 months to 3 years were also statistically significant ( $p < 0.05$ ), with the largest effect size at lag 4. We found PM<sub>10</sub> and SO<sub>2</sub> concentrations were significantly associated with infections in preschool children ( $p < 0.05$ ). The largest effect sizes for PM<sub>10</sub> and SO<sub>2</sub> were at lag 4 and lag 1. No significant associations were found in school-age children, however ( $p > 0.05$ ). While there was a significant association between O<sub>3</sub> concentration at any lag and incidence of bacterial respiratory infection in children less than or equal to 6 months ( $p < 0.05$ ), no significant associations were found for children in other age groups ( $p > 0.05$ ). (Table 7).

**Relationship between air quality and respiratory tract infections caused by *mycoplasma pneumoniae***

PM<sub>2.5</sub>, NO<sub>2</sub>, and SO<sub>2</sub> concentrations were negatively associated with respiratory infections attributable to *M.*

**Table 1** Descriptive analysis air pollutants in Suzhou City, 2014–2016

	Pollutants	Mean	Sd	Min	P <sub>25</sub>	P <sub>50</sub>	P <sub>75</sub>	Max
2014	PM <sub>2.5</sub> (µg/m <sup>3</sup> )	66.38	22.22	12	53	64	74	230
	PM <sub>10</sub> (µg/m <sup>3</sup> )	89.94	26.25	14	72	87	102	283
	NO <sub>2</sub> (µg/m <sup>3</sup> )	51.72	13.74	14	41	48	59	125
	SO <sub>2</sub> (µg/m <sup>3</sup> )	23.06	7.68	5	16	19	24	60
	CO(mg/m <sup>3</sup> )	0.93	0.18	0.48	0.82	0.9	1.0	2.32
	O <sub>3</sub> (µg/m <sup>3</sup> )	55.98	22.03	5	39	39	69	157
2015	PM <sub>2.5</sub> (µg/m <sup>3</sup> )	57.51	23.40	7	41	53	69	230
	PM <sub>10</sub> (µg/m <sup>3</sup> )	80.51	26.77	16	62	74	95	283
	NO <sub>2</sub> (µg/m <sup>3</sup> )	50.58	14.37	13	40	50	62	125
	SO <sub>2</sub> (µg/m <sup>3</sup> )	21.23	7.65	5	15	18	23	62
	CO(mg/m <sup>3</sup> )	0.93	0.21	0.43	0.77	0.88	1.05	2.32
	O <sub>3</sub> (µg/m <sup>3</sup> )	57.44	23.63	5	36	62	75	157
2016	PM <sub>2.5</sub> (µg/m <sup>3</sup> )	45.41	22.04	6	28	40	58	157
	PM <sub>10</sub> (µg/m <sup>3</sup> )	71.27	24.96	10	53	67	86	281
	NO <sub>2</sub> (µg/m <sup>3</sup> )	48.71	13.91	17	40	47	56	123
	SO <sub>2</sub> (µg/m <sup>3</sup> )	16.84	5.30	5	12	14	18	39
	CO(mg/m <sup>3</sup> )	0.94	0.19	0.51	0.82	0.92	1.04	1.81
	O <sub>3</sub> (µg/m <sup>3</sup> )	60.07	22.86	4	40	57	78	151

**Table 2** Annual average concentration of air pollutants in Suzhou City in 2014–2016

Index	2014	2015	2016	F	P
PM2.5	66.38 ± 22.22	57.51 ± 23.40 <sup>ab</sup>	45.41 ± 22.04 <sup>a</sup>	97.54	< 0.001
PM10	89.94 ± 26.25	80.51 ± 26.77 <sup>ab</sup>	71.27 ± 24.96 <sup>a</sup>	51.4	< 0.001
NO <sub>2</sub>	51.72 ± 13.74	50.58 ± 14.37 <sup>b</sup>	48.71 ± 13.91 <sup>a</sup>	7.40	0.025
SO <sub>2</sub>	23.06 ± 7.68	21.23 ± 7.65 <sup>ab</sup>	16.84 ± 5.30 <sup>a</sup>	72.69	< 0.001
CO	0.93 ± 0.18	0.93 ± 0.21	0.94 ± 0.19	3.03	0.220
O <sub>3</sub>	55.98 ± 22.03	57.44 ± 23.63	60.07 ± 22.86	4.07	0.131
Number of patients	1959	1812 <sup>a</sup>	1716 <sup>a</sup>	16.56	< 0.001

Note: Compared with 2014, <sup>a</sup> $p < 0.05$ ; compared with 2016, <sup>b</sup> $p < 0.05$

*pneumoniae* in children under 3 years. PM2.5 was also negatively associated with *M. pneumoniae* infections among children of pre-school age, while negative associations were found for both PM2.5 and PM10 in school-age children. There was a positive and statistically significant association between O<sub>3</sub> concentrations at lag 0–lag 4 and *M. pneumoniae* respiratory tract infections in children under 6 years old ( $p < 0.05$ ), with the largest effect size found for lag 4 (Table 8).

#### Analysis of multi-pollutant effects on the risk of respiratory infections in children by age subgroups and model selection

The multi-pollutant model showed that after mutual adjustment for effects of other air pollutants, there were significant associations between both PM2.5 and O<sub>3</sub> concentrations and viral respiratory infections in children less than or equal to 6 months ( $p < 0.05$ ) with ORs of 1.019 (95% CI: 1.012–1.026) and 1.025 (95% CI: 1.018–1.033) for each additional 10 µg/m<sup>3</sup>. The associations between O<sub>3</sub> and viral respiratory infections in children aged 6 months to 3 years was also statistically significant (OR: 1.025, 95% CI: 1.016–1.033,  $p < 0.05$ ), and PM10 and viral respiratory infections virus in pre-school children (OR: 1.025, 95% CI: 1.008–1.042,  $p < 0.05$ ) were both statistically significant but had similar effect sizes to the single pollutant model. When included in the same multi-pollutant model, negative associations were found between SO<sub>2</sub> and NO<sub>2</sub> concentrations and viral infections across all age groups (Table 9).

We found a significant relationship between NO<sub>2</sub> and bacterial respiratory tract infections in children less than

or equal to 6 months (OR: 1.050, 95% CI: 1.029–1.072,  $p < 0.05$ ) with a larger effect size than in the single-contaminant model. The results of the same model show inverse associations for PM2.5, PM10, and SO<sub>2</sub>. Meanwhile, the association between O<sub>3</sub> and infections in children aged 6 months to 6 years was also statistically significant (OR: 1.005, 95% CI: 1.001–1.010,  $p < 0.05$ ). Similar associations and effect sizes were found for other age groups (Table 10).

Except for O<sub>3</sub>, which was negatively associated with *M. pneumoniae* respiratory infections in children less than or equal to 6 months of age, there were no statistically significant associations found for the remaining pollutants. We found a significant association between PM2.5 and *M. pneumoniae* infections in children in all four age groups over 6 months ( $p < 0.05$ ), with ORs of 1.021 (95% CI: 1.007–1.034), 1.048 (95% CI: 1.029–1.067), 1.067 (95% CI: 1.042–1.094) and 1.025 (95% CI: 1.010–1.041). The mutually-adjusted association between PM10 and *M. pneumoniae* infections was statistically significant for children in aged 6 months to 1 year and greater than 6 years ( $p < 0.05$ ), with ORs of 1.029 (95% CI: 1.013–1.046) and 1.015 (95% CI: 1.002–1.019). The effect of NO<sub>2</sub> on the incidence of respiratory infection with *M. pneumoniae* was statistically significant ( $p < 0.05$ ), and the corresponding OR value was 1.048 (95% CI: 1.025–1.071). The mutually-adjusted association between SO<sub>2</sub> and *M. pneumoniae* infection in school-age children (Age 5) was also statistically significant (OR: 1.016, 95% CI: 1.001–1.031,  $p < 0.05$ ) (Table 11).

**Table 3** Correlation between air pollutants

	PM2.5	PM10	NO <sub>2</sub>	SO <sub>2</sub>	CO	O <sub>3</sub>
PM2.5	1					
PM10	0.894**	1				
NO <sub>2</sub>	0.616**	0.600**	1			
SO <sub>2</sub>	0.690**	0.740**	0.643**	1		
CO	0.723**	0.643**	0.616**	0.544**	1	
O <sub>3</sub>	-0.137**	0.001	-0.470**	-0.183**	-0.343**	1

Note: \* $p < 0.05$ ; \*\* $p < 0.01$

## Discussion

This study investigated the relationship between different air pollutants and respiratory infections in children of different age groups over a three-year period, and used model selection to identify optimal models with mutual adjustment for multiple pollutants based on the BIC.

Air pollution, which not only has adverse ecological effects but also results in direct and indirect harm to human health, has become an increasingly prominent



**Table 4** Detection of pathogens of respiratory infections in 2014–2016

Pathogens	2014 <i>n</i> = 1959	2015 <i>n</i> = 1812	2016 <i>n</i> = 1716	Total <i>n</i> = 5487	$\chi^2$	<i>P</i> -value
virus	780(39.8%)	535(29.5%) <sup>a</sup>	512(29.8%) <sup>a</sup>	182(33.3%)	43.80	< 0.001
bacteria	629(32.1%)	539(29.7%)	502(29.2%)	165(30.2%)	2.45	0.121
Mycoplasma	542(27.6%)	537(29.6%)	502(29.2%)	158(28.8%)	3.74	0.058

Note: Compared with 2014, <sup>a</sup>*p* < 0.05

public health issue as China's economy has developed. At present, most Chinese research on atmospheric pollution and its public health effects has concentrated on populations of megacities or heavily polluted areas. Contexts where pollution exposure is moderate, however, have received less attention. The air quality and environment of Suzhou City have gradually deteriorated in recent years due to accelerating development.

While viral infections are most common in infants and young children, respiratory infections in preschool and school-age children are often bacterial [14]. The reported annual incident of bacterial respiratory infections in Chinese children is 10.90–56.82% [15], while incidence of *M. pneumoniae* infections has increased in recent years to reach 15–20% [16, 17]. This study retrospectively analyzed the pathogens found in nasopharyngeal samples and *M. pneumoniae* antibodies detected in peripheral blood in hospitalized children with ARIs. Among them, 1827 specimens, or 33.3% of our sample, tested positive for viral infections. This is lower than in analytic samples in Tianjin, 74.8% [18] and Vietnam 69.0% [19], but higher than in a study in Zhejiang 22.0% [20]. Furthermore, 1657 (30.2%) cases tested positive for bacterial infections (excluding *M. pneumoniae*). This proportion is higher than in another study in Suzhou (26.3%) [21] but lower than reported in central and southern Sichuan (34.6%) [22]. We found 28.8% of cases tested positive for *M. pneumoniae*. This proportion was lower than that reported in Shenyang [23] but higher than in another study based in Suzhou (19.0%) [24].

The atmosphere represents a medium through which microbes proliferate and transmit infection. One study found that air pollution can change the balance of respiratory flora in children, in particular a reduction in commensal *a-hemolytic streptococcus*, which can lead to an increase in other abnormal flora and increase the susceptibility to respiratory diseases [25]. This may represent a mechanism through which the air pollutants tested in our study may have influenced the incidence of respiratory infections in our study population.

#### Effects of air pollutants on viral and bacterial respiratory tract infections in children of different ages

The results of the single-contaminant models showed that PM<sub>2.5</sub>, PM<sub>10</sub>, NO<sub>2</sub>, SO<sub>2</sub>, and CO had stronger associations with viral and bacterial respiratory infections in children

under 3 years of age than in older children. This may be due to the faster respiratory rate of infants and young children, immune system immaturity, and lower capacity to synthesize antibodies; all of which may lead to greater susceptibility to air pollutants. More advanced development of immune system function in preschool and school-age children may reduce the probability of respiratory infections. A study of the short-term association between ambient air pollution and daily hospitalization for respiratory infections in children aged 0–17 years in Hanoi, Vietnam found that all ambient air pollutants tested were positively associated with hospitalization for pneumonia and nearly all were positively associated with bronchitis and hospitalization for asthma [26]. These associations were stronger for infants and young children than for those aged 3–5 years. Another study based in the United States tested the effects of short-term changes in air pollutant concentrations on the number of hospital visits attributed to respiratory infections in children aged 0–4 years. The results showed that O<sub>3</sub> had the strongest association, and that the rate of hospital visits was higher in the preschool group than in infants [27]. Similar to the results of the single-contaminant models in this study, air pollutants are more strongly associated with viral and bacterial respiratory infections in children under 3 years of age than in older children. We also found that concentrations of air pollutants at lags of three and 4 weeks had the greatest effect sizes. Toxicological studies have shown that the effects of air pollutants on human health have a physiological lag period [28]. A large population-based study found an association between the number of emergency room visits by children under 5 years of age for respiratory infections and short-term increases in O<sub>3</sub> and NO<sub>2</sub> concentrations with a lag of 3 days. Other literature suggests that the length of this lag period may be greater for children under 5 years of age than for older children [29]. These lag periods have been found to differ in length between studies, and this variability may be related to differences in the characteristics of their study populations, research designs,

**Table 5** Age stratification of children with respiratory infection

Year	Age 1	Age 2	Age 3	Age 4	Age 5
2014	763	281	474	289	152
2015	693	284	385	309	141
2016	623	188	403	339	163
Total	2,079(37.9%)	753(13.7%)	1,262(23%)	937(17.1%)	456(8.3%)

**Table 6** Hysteresis effect of air quality on respiratory tract infection virus in children in age group

Age	Pollutants	Lag 0		Lag 1		Lag 2		Lag 3		Lag 4	
		OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Age 1	PM2.5	1.005	1.002–1.008	1.009	1.005–1.014	1.012	1.008–1.018	1.013	1.008–1.018	1.011	1.006–1.016
	PM10	1.003	1.001–1.006	1.006	1.002–1.010	1.009	1.005–1.014	1.010	1.006–1.015	1.009	1.005–1.014
	NO <sub>2</sub>	1.020	1.015–1.026	1.033	1.025–1.040	1.039	1.031–1.047	1.045	1.036–1.053	1.044	1.035–1.053
	SO <sub>2</sub>	1.039	1.028–1.049	1.059	1.045–1.072	1.068	1.054–1.083	1.070	1.055–1.085	1.066	1.051–1.081
	CO	2.598	1.857–3.634	11.307	6.535–19.563	28.952	15.453–44.244	40.146	20.978–59.315	35.576	16.467–54.686
	O <sub>3</sub>	0.979	0.974–0.983	0.968	0.963–0.973	0.967	0.962–0.973	0.967	0.962–0.972	0.968	0.963–0.973
Age 2	PM2.5	1.004	0.999–1.009	1.010	1.004–1.018	1.010	1.003–1.018	1.011	1.003–1.019	1.011	1.003–1.019
	PM10	1.002	0.998–1.006	1.007	1.001–1.012	1.007	1.000–1.014	1.009	1.002–1.017	1.009	1.000–1.015
	NO <sub>2</sub>	1.012	1.004–1.020	1.030	1.020–1.044	1.031	1.019–1.045	1.032	1.017–1.043	1.029	1.015–1.042
	SO <sub>2</sub>	1.022	1.005–1.039	1.049	1.027–1.070	1.051	1.029–1.075	1.052	1.027–1.077	1.052	1.027–1.076
	CO	2.060	1.008–3.111	5.385	1.698–9.020	6.076	2.411–9.712	12.140	2.936–21.273	11.715	3.254–20.177
	O <sub>3</sub>	0.985	0.979–0.991	0.978	0.971–0.986	0.976	0.968–0.984	0.978	0.971–0.986	0.979	0.971–0.987
Age 3	PM2.5	1.006	1.002–1.011	1.012	1.005–1.019	1.012	1.005–1.021	1.013	1.005–1.021	1.012	1.004–1.020
	PM10	1.005	1.001–1.009	1.010	1.004–1.016	1.011	1.004–1.019	1.012	1.004–1.020	1.011	1.004–1.020
	NO <sub>2</sub>	1.016	1.008–1.024	1.025	1.013–1.037	1.027	1.015–1.041	1.031	1.015–1.047	1.029	1.015–1.045
	SO <sub>2</sub>	1.042	1.026–1.058	1.056	1.034–1.078	1.056	1.034–1.080	1.059	1.035–1.083	1.058	1.035–1.082
	CO	2.717	1.356–4.078	9.770	2.949–16.590	13.575	3.479–23.671	19.182	4.414–33.950	17.478	4.038–30.917
	O <sub>3</sub>	0.989	0.983–0.995	0.983	0.976–0.991	0.981	0.973–0.989	0.980	0.972–0.988	0.979	0.971–0.987
Age 4	PM2.5	1.004	0.996–1.011	1.000	0.991–1.011	1.001	0.991–1.012	1.001	0.988–1.011	0.999	0.988–1.011
	PM10	1.002	0.996–1.008	0.999	0.990–1.009	0.999	0.989–1.009	0.999	0.986–1.008	0.995	0.984–1.007
	NO <sub>2</sub>	1.016	1.004–1.028	1.024	1.008–1.041	1.025	1.007–1.043	1.024	0.999–1.038	1.015	0.995–1.036
	SO <sub>2</sub>	1.018	0.994–1.043	1.023	0.990–1.056	1.018	0.984–1.053	1.018	0.977–1.052	1.007	0.968–1.047
	CO	1.823	0.810–4.101	1.257	0.361–4.381	1.478	0.380–5.752	1.478	0.421–8.195	2.032	0.454–9.092
	O <sub>3</sub>	0.989	0.980–0.998	0.992	0.982–1.003	0.993	0.982–1.004	0.993	0.980–1.003	0.989	0.978–1.001
Age 5	PM2.5	1.008	0.997–1.019	1.012	0.994–1.032	1.016	0.996–1.039	1.021	0.999–1.043	1.021	0.999–1.042
	PM10	1.002	0.992–1.013	1.010	0.994–1.026	1.011	0.992–1.031	1.016	0.995–1.036	1.018	0.998–1.039
	NO <sub>2</sub>	1.000	0.975–1.025	1.028	0.999–1.058	1.031	0.998–1.066	1.033	0.998–1.070	1.035	0.999–1.073
	SO <sub>2</sub>	1.039	0.997–1.083	1.052	0.999–1.108	1.062	1.005–1.123	1.072	1.014–1.133	1.085	1.024–1.146
	CO	2.863	0.751–10.915	9.244	0.951–89.866	10.963	0.812–147.987	10.893	0.701–169.223	12.177	0.764–194.023
	O <sub>3</sub>	0.986	0.969–1.003	0.981	0.961–1.001	0.981	0.961–1.002	0.976	0.955–0.998	0.985	0.954–0.997

modeling strategies, pollutant measurement standards, and whether they investigated potential confounding factors. After all air pollutants were considered for inclusion in the multi-pollutant model as part of our model selection procedure, negative associations were found between SO<sub>2</sub> and NO<sub>2</sub> and respiratory tract infections while there was a positive association for O<sub>3</sub>. PM2.5, PM10 and SO<sub>2</sub> concentrations were negatively associated with respiratory tract infections in children while a positive association was found for O<sub>3</sub>. The strength of the association between NO<sub>2</sub> concentrations and infections increased with age. This may be due correlation in concentrations of different air pollutants, SO<sub>2</sub> attaching to PM2.5, the fact that toxicity of pollutants is greater when they penetrate into the lower respiratory

tract, and the negative correlation between the concentration of O<sub>3</sub> and polycyclic aromatic hydrocarbons. As a result, when different pollutants interact, their potential effects on incidence of respiratory tract infections may be strengthened or weakened. This may have explained the inconsistencies between the results of our single pollutant and multi-pollutant models.

A study in Shenzhen [30] found that short-term exposure to ambient air pollution was significantly associated with hospitalization for ARIs. Children under 14 years of age were identified as most susceptible population to infections attributed to PM2.5, PM10 and NO<sub>2</sub> pollution. An Iranian study has concluded that atmospheric particulate matter, NO<sub>2</sub> and O<sub>3</sub> are significantly

**Table 7** Hysteresis effect of air quality on bacteria in respiratory tract infection in children in age group

Age	Pollutants	Lag 0		Lag 1		Lag 2		Lag 3		Lag 4	
		OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Age1	PM2.5	1.004	1.002–1.007	1.010	1.006–1.014	1.012	1.007–1.016	1.013	1.009–1.018	1.014	1.010–1.019
	PM10	1.004	1.002–1.006	1.010	1.006–1.013	1.011	1.007–1.016	1.015	1.010–1.019	1.016	1.011–1.020
	NO <sub>2</sub>	1.004	1.004–1.014	1.008	1.002–1.015	1.007	1.000–1.014	1.008	1.002–1.017	1.009	1.001–1.017
	SO <sub>2</sub>	1.028	1.018–1.038	1.050	1.037–1.063	1.049	1.035–1.063	1.050	1.035–1.065	1.051	1.036–1.065
	CO	1.110	0.815–1.510	1.130	0.697–1.833	0.988	0.575–1.698	1.278	0.633–2.009	0.937	0.514–1.708
	O <sub>3</sub>	0.995	0.992–0.999	0.994	0.990–0.998	0.995	0.991–1.000	0.995	0.991–1.000	0.996	0.991–1.000
Age2	PM2.5	0.999	0.995–1.003	1.007	1.001–1.013	1.008	1.002–1.015	1.008	1.002–1.015	1.009	1.002–1.015
	PM10	0.999	0.996–1.002	1.006	1.001–1.011	1.009	1.003–1.015	1.009	1.003–1.016	1.010	1.004–1.016
	NO <sub>2</sub>	1.002	0.995–1.009	1.008	0.998–1.017	1.005	0.995–1.016	1.005	0.994–1.016	1.005	0.993–1.016
	SO <sub>2</sub>	1.007	0.992–1.021	1.029	1.010–1.049	1.028	1.008–1.050	1.028	1.006–1.050	1.030	1.007–1.052
	CO	0.854	0.530–1.375	1.547	0.760–3.149	1.469	0.662–3.257	1.263	0.540–2.955	1.071	0.448–2.559
	O <sub>3</sub>	0.995	0.990–0.999	0.996	0.990–1.001	0.997	0.991–1.003	0.997	0.991–1.004	0.997	0.991–1.004
Age3	PM2.5	1.001	0.998–1.004	1.005	1.000–1.010	1.006	1.001–1.012	1.007	1.002–1.013	1.008	1.002–1.014
	PM10	1.001	0.998–1.004	1.004	0.999–1.008	1.006	1.001–1.011	1.008	1.003–1.014	1.009	1.003–1.015
	NO <sub>2</sub>	1.003	0.998–1.009	1.003	0.995–1.011	1.000	0.992–1.010	1.001	0.992–1.011	1.000	0.991–1.010
	SO <sub>2</sub>	1.009	0.997–1.022	1.017	1.001–1.033	1.020	1.003–1.038	1.022	1.004–1.041	1.024	1.006–1.042
	CO	1.025	0.685–1.532	0.789	0.427–1.456	0.564	0.281–1.130	0.597	0.285–1.250	0.586	0.276–1.241
	O <sub>3</sub>	0.995	0.992–0.999	1.000	0.995–1.005	1.003	0.998–1.008	1.004	0.998–1.009	1.004	0.998–1.009
Age4	PM2.5	1.001	0.999–1.007	1.001	0.998–1.010	1.006	1.000–1.012	1.006	1.000–1.013	1.006	1.000–1.013
	PM10	1.003	0.998–1.005	1.003	1.000–1.010	1.006	1.001–1.012	1.006	1.002–1.014	1.007	1.001–1.014
	NO <sub>2</sub>	1.007	0.995–1.010	1.007	0.998–1.017	1.006	0.995–1.017	1.006	0.991–1.013	0.999	0.988–1.011
	SO <sub>2</sub>	0.978	0.992–1.022	1.033	1.012–1.053	1.032	1.011–1.053	1.028	1.006–1.050	1.021	0.998–1.044
	CO	0.995	0.607–1.577	0.995	0.323–1.329	0.717	0.328–1.567	0.717	0.228–1.285	0.538	0.222–1.301
	O <sub>3</sub>	1.000	0.990–1.000	1.000	0.990–1.002	0.998	0.991–1.004	0.998	0.993–1.005	0.999	0.992–1.005
Age5	PM2.5	1.000	0.994–1.006	1.004	0.996–1.013	1.008	0.999–1.018	1.009	0.999–1.019	1.009	0.999–1.019
	PM10	0.999	0.994–1.004	1.004	0.996–1.012	1.009	1.000–1.018	1.010	1.000–1.019	1.009	1.000–1.019
	NO <sub>2</sub>	0.995	0.984–1.006	0.991	0.977–1.005	0.992	0.976–1.008	0.990	0.974–1.006	0.987	0.971–1.005
	SO <sub>2</sub>	1.001	0.979–1.023	1.010	0.983–1.038	1.017	0.987–1.047	1.016	0.986–1.047	1.015	0.985–1.047
	CO	0.633	0.307–1.306	0.422	0.132–1.350	0.483	0.128–1.829	0.447	0.112–1.789	0.345	0.080–1.480
	O <sub>3</sub>	0.994	0.987–1.001	1.002	0.993–1.010	1.005	0.996–1.014	1.006	0.996–1.016	1.006	0.996–1.017

associated with death by respiratory causes, and that these associations are subject to long lag times [31]. Although the findings of these studies may not be fully consistent to our own, this may be due to differences in pollutant monitoring, air pollutant composition and statistical methods employed.

#### Effects of air pollutants on respiratory tract infections in children of different ages in our study

The results of single-pollutant models showed significant associations between O<sub>3</sub> concentrations and respiratory tract infections with *M. pneumoniae* in children under 6 years old, with exposure at a lag of 4 weeks having the greatest effect size. In contrast to the single-contaminant

model, the results of the multi-pollutant model show that O<sub>3</sub> was negatively associated with *M. pneumoniae* infection in children with aged 6 months and older; although this association was not significant for the remaining age groups. *M. pneumoniae* is a common cause of respiratory infection in children, and its incidence has increased in recent years. Although incidence of Mycoplasma infection tends to peak among school-age children, its mean age of first occurrence has risen in China. Animal experiments show that the pathological changes appear in tissues 1–2 weeks after initial infection with *M. pneumoniae*. When reinfection occurs, these changes usually appear within 3 days after infection. This suggests that the immune response has strengthened following the first infection.

**Table 8** Hysteresis effect of air quality on the respiratory tract infection of *Mycoplasma pneumoniae* in children in the subgroup of children

Age	Pollutants	Lag0		Lag1		Lag2		Lag3		Lag4	
		OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Age1	PM2.5	0.999	0.997–1.002	0.995	0.991–0.998	0.993	0.989–0.997	0.992	0.988–0.997	0.991	0.986–0.995
	PM10	1.001	0.999–1.003	1.000	0.996–1.003	0.999	0.995–1.003	0.998	0.994–1.002	0.996	0.992–1.001
	NO <sub>2</sub>	1.000	0.995–1.005	0.991	0.985–0.998	0.989	0.982–0.996	0.987	0.980–0.994	0.983	0.976–0.991
	SO <sub>2</sub>	1.004	0.995–1.013	0.992	0.981–1.003	0.985	0.973–0.998	0.979	0.967–0.992	0.974	0.961–0.987
	CO	1.017	0.750–1.380	0.740	0.458–1.196	0.644	0.376–1.104	0.533	0.300–0.946	0.622	0.232–0.770
	O <sub>3</sub>	1.003	1.000–1.006	1.007	1.003–1.011	1.008	1.004–1.012	1.009	1.005–1.014	1.010	1.005–1.014
Age2	PM2.5	0.995	0.991–1.000	0.992	0.986–0.998	0.991	0.984–0.997	0.989	0.982–0.996	0.988	0.981–0.995
	PM10	0.998	0.995–1.002	0.996	0.991–1.001	0.996	0.990–1.002	0.995	0.988–1.001	0.993	0.987–1.000
	NO <sub>2</sub>	0.991	0.984–0.998	0.987	0.977–0.997	0.988	0.977–0.998	0.986	0.975–0.997	0.983	0.971–0.994
	SO <sub>2</sub>	0.991	0.977–1.007	0.984	0.966–1.002	0.982	0.963–1.002	0.974	0.954–0.995	0.971	0.951–0.992
	CO	0.797	0.485–1.311	0.683	0.327–1.426	0.627	0.275–1.429	0.472	0.196–1.139	0.387	0.158–0.952
	O <sub>3</sub>	1.004	0.999–1.009	1.007	1.001–1.013	1.008	1.002–1.015	1.009	1.003–1.016	1.011	1.004–1.019
Age3	PM2.5	0.999	0.995–1.003	0.991	0.986–0.997	0.989	0.983–0.995	0.986	0.980–0.993	0.986	0.980–0.993
	PM10	1.000	0.997–1.003	0.995	0.990–1.000	0.993	0.987–0.999	0.997	0.985–0.997	0.996	0.985–0.997
	NO <sub>2</sub>	0.998	0.991–1.004	0.989	0.980–0.998	0.983	0.973–0.993	0.980	0.970–0.990	0.978	0.967–0.988
	SO <sub>2</sub>	0.998	0.985–1.012	0.986	0.968–1.003	0.978	0.960–0.996	0.970	0.952–0.989	0.967	0.948–0.985
	CO	1.092	0.687–1.736	0.924	0.460–1.854	0.810	0.370–1.773	0.560	0.245–1.284	0.452	0.197–1.041
	O <sub>3</sub>	1.004	1.000–1.009	1.007	1.002–1.013	1.009	1.004–1.015	1.011	1.004–1.017	1.012	1.006–1.018
Age4	PM2.5	0.996	0.991–1.001	0.991	0.985–0.998	0.989	0.982–0.996	0.989	0.978–0.994	0.985	0.978–0.993
	PM10	1.000	0.996–1.004	0.997	0.991–1.003	0.994	0.988–1.001	0.994	0.984–0.999	0.991	0.984–0.998
	NO <sub>2</sub>	1.000	0.991–1.010	0.996	0.984–1.008	0.992	0.979–1.004	0.992	0.975–1.002	0.985	0.972–1.000
	SO <sub>2</sub>	0.999	0.981–1.018	0.990	0.967–1.013	0.984	0.960–1.008	0.984	0.951–1.001	0.970	0.945–0.996
	CO	1.338	0.728–2.460	1.110	0.462–2.671	0.717	0.278–1.850	0.717	0.230–1.851	0.601	0.209–1.732
	O <sub>3</sub>	1.003	0.997–1.009	1.007	1.001–1.013	1.010	1.003–1.018	1.010	1.003–1.019	1.012	1.003–1.020
Age5	PM2.5	0.995	0.988–1.001	0.987	0.976–0.997	0.985	0.973–0.997	0.984	0.972–0.996	0.985	0.973–0.997
	PM10	0.997	0.991–1.003	0.988	0.979–0.998	0.988	0.978–0.999	0.985	0.974–0.997	0.985	0.974–0.997
	NO <sub>2</sub>	1.001	0.988–1.015	0.984	0.967–1.000	0.982	0.964–1.001	0.982	0.963–1.002	0.983	0.963–1.004
	SO <sub>2</sub>	1.003	0.975–1.033	0.985	0.953–1.018	0.982	0.947–1.018	0.977	0.942–1.013	0.973	0.938–1.009
	CO	0.750	0.322–1.747	0.575	0.144–2.291	0.538	0.110–2.646	0.589	0.112–3.105	0.646	0.115–3.620
	O <sub>3</sub>	1.000	0.991–1.009	0.999	0.988–1.009	0.998	0.986–1.009	0.996	0.984–1.009	0.997	0.984–1.010

Following infection, B lymphocytes can be activated to produce specific antibodies including IgM, IgG and IgA. IgM, which is considered a marker of acute infection, appears more than 1 week after infection, and peaks at 3–4 weeks. While concentrations of IgA and IgM fall shortly afterwards, IgG production peaks later, and concentrations remain elevated for several months [32]. The associations between O<sub>3</sub> and *M. pneumoniae* infections in children found by both the single contaminant and multi-contaminant models differ from those found in other countries. Bono et al. [33] have concluded that, based on the results of a single-contaminant model, O<sub>3</sub> concentrations were associated with higher numbers of emergency

room visits by children for respiratory problems. A study in Hefei City on the relationship between air pollution and upper respiratory tract infection in children aged 0–14 years during 2014–2015 found that O<sub>3</sub> was significantly associated with incidence of infection when tested using a single pollutant model, while only NO<sub>2</sub> was associated with infections when tested using a multi-pollutant model [29]. This difference may be due to the fact that O<sub>3</sub> concentrations in this study did not exceed levels associated with harm to human health. O<sub>3</sub> is considered a secondary pollutant, and, as such, its effect may be masked when present alongside other primary pollutants. Inconsistencies may also appear when comparing results based



**Table 9** Effect of multiple pollutants on the risk of viral respiratory infection in the Model Selection

Age	Pollutants	OR	95%CI	P
Age1	PM2.5	1.019	1.012–1.026	< 0.001
	SO <sub>2</sub>	0.950	0.929–0.972	< 0.001
	O <sub>3</sub>	1.025	1.018–1.033	< 0.001
Age2	NO <sub>2</sub>	0.970	0.953–0.988	0.001
	O <sub>3</sub>	1.025	1.016–1.033	< 0.001
Age3	SO <sub>2</sub>	0.966	0.950–0.981	< 0.001
	O <sub>3</sub>	1.007	1.001–1.014	0.021
Age4	PM10	1.025	1.008–1.042	0.003
	NO <sub>2</sub>	0.940	0.912–0.970	< 0.001
Age5	SO <sub>2</sub>	0.923	0.873–0.977	0.006

on tests of nasopharyngeal samples and serum antibody tests. In addition, most *M. pneumoniae* infections in infants and young children may be due to contact infected family members; particularly older family members who may have more frequent contacts with infected people outside the household. In addition, air pollutants are more strongly associated with *M. pneumoniae* infections in older people than young children. Further consideration of the susceptibility of the wider population, the individual characteristics of the children included in the analytic sample and the composition of air pollution at a regional level would be needed to gain a fuller picture of the determinants of respiratory infections in our study population.

Controlling air pollution remains a significant public health challenge in China. Our results highlight the need for interventions to reduce air pollution at the same time as strengthening the prevention, diagnosis and treatment of respiratory infections in children.

#### Future research directions

The objective of this study was to identify the most appropriate statistical model for testing the relationship between

**Table 10** Effect of multiple pollutants on the risk of bacterial respiratory infections in the Model Selection

Age	Pollutants	OR	95%CI	P
Age1	PM2.5	0.899	0.866–0.933	< 0.001
	PM10	0.969	0.953–0.986	< 0.001
	NO <sub>2</sub>	1.050	1.029–1.072	< 0.001
	SO <sub>2</sub>	0.865	0.832–0.900	< 0.001
Age2	O <sub>3</sub>	1.005	1.001–1.010	0.020
	PM10	0.980	0.971–0.989	< 0.001
Age3	O <sub>3</sub>	1.005	1.001–1.010	0.020
	PM10	0.980	0.971–0.989	< 0.001
Age4	PM10	0.980	0.971–0.988	< 0.001
	O <sub>3</sub>	1.016	1.005–1.027	0.004

**Table 11** Effect of multiple pollutants on the risk of respiratory infections of *Mycoplasma pneumoniae* in the Model Selection

Age	Pollutants	OR	95% CI	P
Age1	O <sub>3</sub>	0.991	0.987–0.995	< 0.001
Age2	PM2.5	1.021	1.007–1.034	0.003
	PM10	1.029	1.013–1.046	< 0.001
Age3	PM2.5	1.048	1.029–1.067	< 0.001
	PM10	0.964	0.947–0.982	< 0.001
Age4	NO <sub>2</sub>	1.048	1.025–1.071	< 0.001
	PM2.5	1.067	1.042–1.094	< 0.001
Age5	PM10	0.961	0.939–0.983	< 0.001
	PM2.5	1.025	1.010–1.041	0.001
Age5	PM10	1.015	1.002–1.029	0.027
	SO <sub>2</sub>	1.016	1.001–1.031	0.036

air quality and respiratory tract infections in children of different ages. We did not adjust for individual factors (such as physical fitness, immune function, and health behaviors) or factors relating to the home environment (such as exposure to passive smoking). Future work on the associations between environmental pollutants and childhood respiratory infections should consider individual family factors to adjust for potential confounding.

#### Conclusions

Our key finding from the single-pollutant models was that air pollutant concentrations had stronger associations with viral and bacterial respiratory infections in children under 3 years than in children older than 3 years. Concentrations of air pollutants at three- and four-week lags showed the strongest effects on respiratory tract infections in infants. When we tested multiple pollutants simultaneously, PM2.5 had the strongest influence on viral and *M. pneumoniae* respiratory tract infections.

Finally, the single-contaminant model showed that O<sub>3</sub> was positively associated with respiratory infections in children under 6 years of age with the greatest effect size at a lag of 4 weeks. The multi-pollutant model showed a positive association between O<sub>3</sub> and respiratory infections after mutual adjustment for other pollutants.

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#### Authors' contributions

DZ analyzed and interpreted the data, drafted the manuscript; YL conceived and designed the study, performed the statistical analysis; QC established the statistical model; YJ participated in the design of the study and performed the statistical analysis; CC participated in the design of the study and performed the statistical analysis; YD participated in the design of the study and performed the statistical analysis; YY collected clinical and laboratory data; YF collected clinical and laboratory data; JS collected clinical and laboratory data; YL conceived and designed the study; WZ conceived of

the study, participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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#### Availability of data and materials

All data is available.

#### Ethics approval and consent to participate

This study was conducted with the approval of the Institutional Human Ethical Committee of Children's Hospital of Soochow University. An informed consent was obtained from all the subjects or guardians who participated in this study.

#### Consent for publication

All authors have read and approved the content, and they agree to submit it for consideration for publication in the journal.

#### Competing interests

The authors declare that they have no competing interests.

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