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## Ambient PM<sub>2.5</sub> and its chemical constituents on lifetime-ever pneumonia in Chinese children: A multi-center study

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### ABSTRACT

The long-term effects of ambient PM<sub>2.5</sub> and chemical constituents on childhood pneumonia were still unknown. A cross-sectional study was conducted in 30,315 children in the China Children, Homes, Health (CCHH) project, involving 205 preschools in six cities in China, to investigate the long-term effects of PM<sub>2.5</sub> constituents on lifetime-ever diagnosed pneumonia. Information on the lifetime-ever pneumonia and demographics were collected by validated questionnaires. The lifetime annual average ambient PM<sub>2.5</sub>, ozone and five main PM<sub>2.5</sub> constituents, including SO<sub>4</sub><sup>2-</sup>, NO<sub>3</sub><sup>-</sup>, NH<sub>4</sub><sup>+</sup>, organic matter (OM) and black carbon (BC), were estimated according to preschool addresses by a combination of satellite remote sensing, chemical transport modeling and ground-based monitors. The prevalence of lifetime-ever diagnosed pneumonia was 34.5% across six cities and differed significantly among cities ( $p = 0.004$ ). The two-level logistic regression models showed that the adjusted odds ratio for PM<sub>2.5</sub> (per 10  $\mu\text{g}/\text{m}^3$ ) and its constituents (per 1  $\mu\text{g}/\text{m}^3$ )-SO<sub>4</sub><sup>2-</sup>, NO<sub>3</sub><sup>-</sup>, NH<sub>4</sub><sup>+</sup>, and OM were 1.12 (95% CI: 1.07–1.18), 1.02 (1.00–1.04), 1.06 (1.04–1.09), 1.05 (1.03–1.07) and 1.09 (1.06–1.12), respectively. Children in urban area, aged < 5 years and breastfeeding time < 6 months enhanced the risks of pneumonia. Our study provided robust results that long-term levels of ambient PM<sub>2.5</sub> and its constituents increased the risk of childhood pneumonia, especially NH<sub>4</sub><sup>+</sup>, NO<sub>3</sub><sup>-</sup> and OM.

### 1. Introduction

Acute lower respiratory infection is the leading cause of death in

children, with most fatal cases occurring as pneumonia in children under 5 years old (Smith et al., 2011). According to a recent WHO estimate, pneumonia accounts for 16% of all deaths of children under 5 years old,

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killing 920,136 children in 2015 in spite of the widespread use of vaccination. And approximately 99% of the pneumonia deaths occur in low- and middle-income countries (Liu et al., 2015; Walker et al., 2013; Zar et al., 2013). The incidence of pneumonia in Chinese children (0.08 episodes/child-year in 0–4 years old, 2010) was significantly higher than that in developed countries (0.01–0.03 episodes/child-year, 2010) (Rudan et al., 2013).

The etiology of pneumonia included multiple pathogens of microorganisms such as bacteria, viruses, and fungi et al. (Kennedy et al., 2018; Shah et al., 2017). Air pollution has been identified as potential risk factors or triggers for childhood pneumonia in prior research (Smith et al., 2011; Darrow et al., 2014; Jary et al., 2015). Among others, fine particulate matter (PM<sub>2.5</sub>) is the most consistent and robust indicator of air pollution. As the largest developing country in the world, China is facing air pollution problems due to the rapid urbanization and industrialization. For example, the annual average of PM<sub>2.5</sub> was 47 µg/m<sup>3</sup> (range 12–158 µg/m<sup>3</sup>) in 2016 in 338 cities in China (Ministry of Environmental Protection. Report on the State of the Environment in China, 2016), close to 5 times of the WHO Air Quality Guidelines for PM<sub>2.5</sub> (10 µg/m<sup>3</sup>).

Certain time-series studies have examined the associations between short-term PM<sub>2.5</sub> levels and hospitalization or emergency visits of childhood pneumonia (Cheng et al., 2019; Nhung et al., 2017). However, investigations on the long-term effects of PM<sub>2.5</sub> on childhood pneumonia were scarce. Some studies indicated that long-term exposure to ambient PM<sub>2.5</sub> was significantly associated with the increased risk of lower respiratory tract infection, including pneumonia mortality (Pun et al., 2017) and chronic bronchitis symptoms (Abbey et al., 1995). Part of previously published studies mainly focused on the effects of PM<sub>2.5</sub> mass concentration on childhood pneumonia. As a complex mixture of more than 50 chemical constituents (Bell et al., 2010), PM<sub>2.5</sub> are supposed to play different roles in the adverse effects on pulmonary health due to different chemical constituents, and the evidence is still not yet found (Brook et al., 2010). Therefore it is crucial to differentiate the toxic constituents of PM<sub>2.5</sub> by analyzing the associations between PM<sub>2.5</sub> components and childhood pneumonia.

In the present study, we aimed to estimate the effects of long-term levels of ambient PM<sub>2.5</sub> on lifetime-ever doctor-diagnosed pneumonia in preschool children in China, as well as PM<sub>2.5</sub> chemical constituents in a multi-center study.

## 2. Methods

### 2.1. Study subjects

This study was based on the China, Children, Homes, Health (CCHH) project, a nationwide questionnaire survey covering 10 cities during 2010–2012 (N = 48,219). The introduction on the subject recruitment and study design was described in previous publications (Chen et al., 2018; Zhang et al., 2013). Because the information on preschool addresses was not collected in 4 cities in CCHH project, subjects (n = 30,759) in other 6 cities who provided complete preschool addresses were enrolled in this study. The involved cities consisted of 2 northern cities (Urumqi, latitude 43°50' N, longitude 87°37'E and Taiyuan, latitude 37°52'N, longitude 112°33'E) and 4 southern cities (Shanghai, latitude 31°53'N longitude 121°43', Nanjing, latitude 32°37'N longitude 118°22'E, Chongqing, latitude 29°35'N longitude 106°3'E and Changsha, latitude 28°41'N longitude 114°15'E). Further, those who had missing information on diagnosed pneumonia, who were aged younger than 3 years or older than 7 years, and those who did not have complete information on demographics or related confounding respiratory factors were also excluded. Finally, a total of 30,315 subjects aged 3–7 years were recruited and analyzed (mean age 4.6 years ± standard deviation 1.1; male, n[%] = 15,694[51.8]). The flowchart of the participants enrollment in this study was showed in Fig. 1.

The 30,315 children were distributed in 205 preschools located in 23 urban and 11 non-urban (suburban or rural) districts. They were analyzed by a hierarchical multivariate logistic regression, with the aim to explore the associations between lifetime-ever diagnosed pneumonia and lifetime annual averages of PM<sub>2.5</sub> levels and chemical components. Data on the geographic, meteorological and social-economic characteristics in each city were obtained from China Statistical Yearbook (<http://www.stats.gov.cn/>)

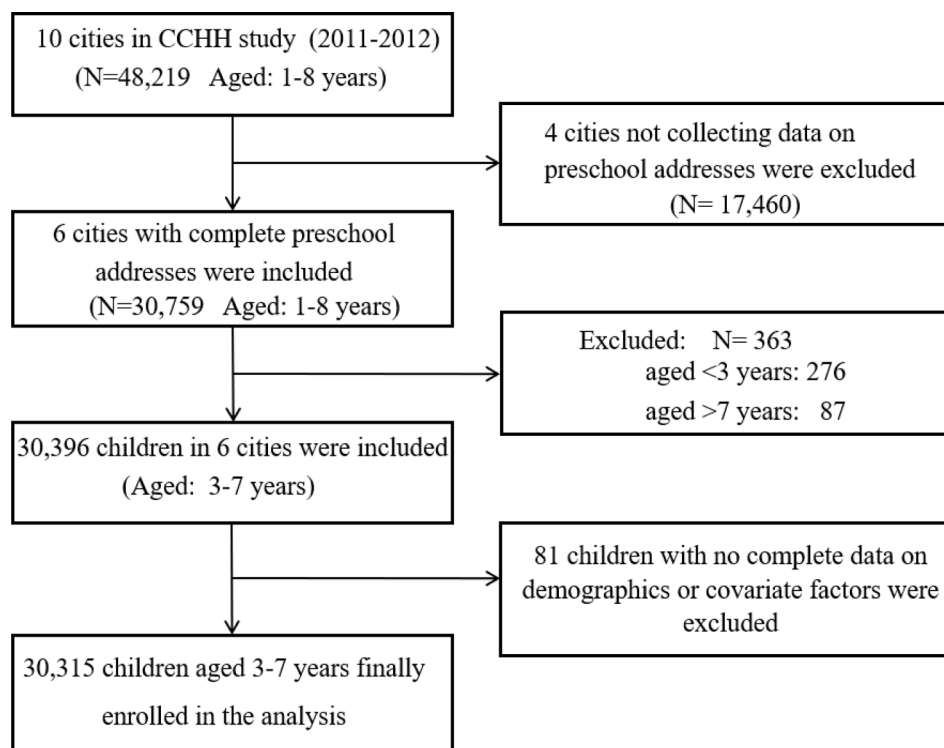


Fig. 1. The flow chart of the subject enrollment in this study.

[p://www.stats.gov.cn/tjsj/ndsj/](http://www.stats.gov.cn/tjsj/ndsj/)).

## 2.2. Ethics

This study was approved by the ethical committee of School of Public Health, Fudan University, Shanghai, China (International Registered Number: IRB00002408 & FWA00002399). Written informed consents were obtained from parents or guardians.

## 2.3. Questionnaire and health outcomes

The information on respiratory diseases was collected by validated CCHH questionnaire which was modified based on the International Study of Asthma and Allergies in Childhood (ISAAC) (Norback et al., 2018; Asher et al., 2006). The classification of diseases or symptoms was based on the 10th Edition encoding of the “International Classification of Diseases” (ICD-10) by the WHO in 2016 (Dunea et al., 2016). The prevalence of lifetime-ever diagnosed pneumonia was evaluated by a yes/no question ‘Has your child ever been diagnosed as pneumonia by a professional physician?’ (Zhuge et al., 2018). Additional information on age, gender, birthweight were collected, as well as the personal life and family factors including breastfeeding time, maternal smoking during pregnancy, passive smoking, family history of allergy (FHA, defined as parents/grandparents’ allergic rhinitis or asthma) (Norback et al., 2018), and home environmental factors including home indoor dampness, home interior decoration (renovated wall/floor material or new furniture during their lifetime) and residential locations. The questions on home indoor environment were modified to fit for the Chinese residential characteristics as reported previously (Zhang et al., 2013).

## 2.4. Long-term ambient air pollution assessment and meteorological data

Ambient PM<sub>2.5</sub> and its 5 main constituents including black carbon (BC), organic matter (OM), sulfate (SO<sub>4</sub><sup>2-</sup>), nitrate (NO<sub>3</sub><sup>-</sup>) and ammonia (NH<sub>4</sub><sup>+</sup>) were obtained from the V4.CH.02 product of the Dalhousie University Atmospheric Composition Analysis Group for 2005–2011. This product extends the V4.NA.02 (North America) methodology over China (van Donkelaar et al., 2019). The detailed methodology has been described previously (van Donkelaar et al., 2016; van Donkelaar et al., 2015; Philip et al., 2014). In brief, this dataset combines satellite retrievals and simulation of aerosol optical depth (AOD) from multiple sources (MISR, MODIS Dark Target, MODIS, and SeaWiFS Deep Blue, MODIS MAIAC, and GEOS-Chem), with the geophysically-based simulated relationship between AOD and near-surface PM<sub>2.5</sub> concentrations. For China, approximately 1000 ground-based observations were then incorporated at a monthly timescale between 2014 and 2016, using a geographically weighted regression to produce a final PM<sub>2.5</sub> dataset at approximately 0.01° × 0.01° resolution. Estimates were extended to the earlier years used in our study based on the inter-annual changes of a global geophysical satellite-derived PM<sub>2.5</sub> dataset (van Donkelaar et al., 2015). For all years, a GEOS-Chem simulation was used to partition this satellite-derived PM<sub>2.5</sub> mass into various constituents, but no further calibration was performed for each chemical constituent owing to the lack of available composition measurements over China. While compositional uncertainties would be reduced if ground-based observations could be included, this approach was found to be effective even without calibration over North America in van Donkelaar et al. (2019); as well as globally in Philip et al. (2014). The resultant annual-mean all-composition PM<sub>2.5</sub> concentrations were consistent with available out of sample, cross-validation annual mean observations over China (R<sup>2</sup> = 0.75–0.83; slope = 1.00–1.04).

In this study, geocoding was performed at each preschool address to evaluate the monthly data of air pollutants at a spatial resolution of 0.01° × 0.01° (approximately 1 km × 1 km). The geocoding and air pollution assignments were performed by the ArcMap software (ESRI, Version 10.2). The lifetime cumulative annual averages of ambient air

pollutants were assessed, which were defined as the temporal moving annual averages of ambient PM<sub>2.5</sub>, O<sub>3</sub> and constituents from children’s birth year to the year of the questionnaire survey.

As a co-pollutant, the annual average concentrations of ozone (O<sub>3</sub>) were obtained from the Global Burden of Disease (GBD) 2013 exposure datasets, with a spatial resolution of 0.1° × 0.1° over the study period. Briefly, O<sub>3</sub> concentrations were estimated by a combination of satellite remote sensing, global chemical transport models, and surface calibrations from ground measurements with increased coverage in recent years (Brauer et al., 2012). Model calibrations were evaluated by randomly excluding 10% of monitoring sites for prediction, the process of which was repeated for a total of three separate sets, with a final adjusted R<sup>2</sup> = 0.64. The overall cross-validation R<sup>2</sup> was obtained at the global level. The lifetime annual average concentration of O<sub>3</sub> for each child was matched with gridded O<sub>3</sub> concentrations based on geocoded preschool addresses. Meteorological factors including annual average temperature, relative humidity (RH) and precipitation in each selected city during 2005–2011 were obtained from the China Meteorological Data website (data.cma.cn). However, only the cumulative annual average temperature was added as an indicator of climate factors in the regression analysis, due to the high inter-correlations between temperature, RH and precipitation (correlation coefficient 0.94, 0.87 and 0.81, respectively).

## 3. Statistical analysis

The prevalence of lifetime-ever doctor-diagnosed pneumonia, demographic characteristics and home environmental factors were summarized in total subjects and in each of the 6 cities. The summaries of lifetime annual averages of ambient PM<sub>2.5</sub>, O<sub>3</sub> and five main constituents of PM<sub>2.5</sub> were described subsequently. The partial correlation analysis was applied to analyze the correlations between any two of air pollutants and PM<sub>2.5</sub> constituents controlling for city variable.

A hierarchical multivariate logistic regression model was constructed to investigate the associations between lifetime-ever diagnosed childhood pneumonia and lifetime annual averages of ambient PM<sub>2.5</sub> and its constituents. The adjusted odds ratio (aOR) and 95% confidence intervals (CI) were used to evaluate the effects of ambient air pollutants on pneumonia. Considering the hierarchical structures of variable levels (subjects- preschools-cities), we first calculated the variance partition coefficients (VPC) to quantify the proportion of observed variation in the outcome that was attributable to the effect of clustering (Austin and Merlo, 2017). In the current study, this was performed in the null model to measure the proportion of the total observed individual variation of the health outcome that was attributable to between-preschool and between-city variation. The VPC was calculated by the formula as follow:

$$VPC = \frac{\tau^2}{\tau^2 + \frac{\pi^2}{3}}$$

where  $\tau^2$  was the random effect variance (Austin and Merlo, 2017; Weinmayr et al., 2017). According to the VPC and the significance of the intercept variance on city-level and preschool-level, the final hierarchical logistic regression model would be determined as 2-level or 3-level (Weinmayr et al., 2017).

After determining the 2- or 3-level hierarchical model, covariates were tested and selected to construct the final regression model, together with the main predictors of air pollutants. We used two criteria to select the covariates: 1) variables that were the known as potential risk factors of childhood pneumonia based on current knowledge; 2) variables with a change of 10% of the main effect after included in the model (Lin et al., 2018). By the first criteria, covariates of age, gender, birthweight, maternal smoking during pregnancy and passive smoking were selected. By the second criteria, covariates of family history of allergy, breastfeeding time, home indoor dampness, residential

locations, annual household income per capita, home interior decoration and cumulative annual average temperature were included. Thus, the final set of covariates consisted of all variables selected and mentioned as above.

To test the effect robustness of ambient PM<sub>2.5</sub> and its constituents on childhood pneumonia, both single-pollutant and two-pollutant models with additional adjustment for O<sub>3</sub> were performed. The aOR and 95% CI on lifetime-ever diagnosed pneumonia were estimated per 10 µg/m<sup>3</sup> increase of PM<sub>2.5</sub> and per 1 µg/m<sup>3</sup> of PM<sub>2.5</sub> constituents, respectively. In addition, we built PM<sub>2.5</sub>-constituent joint models to test the effect robustness of PM<sub>2.5</sub> constituents, in which PM<sub>2.5</sub> mass was introduced as a surrogate of the total PM<sub>2.5</sub> level in the single-constituent model to adjust for potential confounding effects by PM<sub>2.5</sub> itself.

To examine the modification effects of several significant variables, stratified analyses were performed: gender (males vs. females), age (<5 years vs. ≥ 5 years), family history of allergy (yes vs. no), breastfeeding time (<6 months vs. ≥ 6 months), current passive smoking (yes vs. no), residential locations (urban vs. non-urban, which was defined by China's administrative naming system), home indoor dampness (yes vs. no) and home interior decoration (yes vs. no), respectively. We statistically tested the differences of effects between the paired strata as follows:

$$\hat{Q}_1 - \hat{Q}_2 \pm 1.96\sqrt{SE_1^2 + SE_2^2}$$

where  $\hat{Q}_1$  and  $\hat{Q}_2$  were the adjusted estimates in each stratum, and  $s\hat{E}_1$  and  $s\hat{E}_2$  were the corresponding standard errors (Chen et al., 2012).

### 3.1. Sensitivity analysis

We conducted several sensitivity analyses: 1) We examined the city effect by removing one city a time in the multi-level logistic regression model, and repeated 6 times for all 6 cities; 2) We replaced the 1 km × 1 km ambient air pollution and constituents levels based on preschool addresses by those estimated within a 3 km range of preschools, and rerun the association analyses between lifetime annual averages of PM<sub>2.5</sub> and constituents and lifetime-ever diagnosed pneumonia; 3) We examined and compared the associations of PM<sub>2.5</sub> constituents and pneumonia between those who lived in the home addresses all the time and the whole subjects, to investigate the potential bias due to migrant children.

All multi-level logistic regression analyses were performed by MLwin statistical software (version 2.2.3, University of Bristol, England). The statistical tests were two-sided, and  $p < 0.05$  was considered as statistically significant.

## 4. Results

The descriptive statistics of the 30,315 participants were presented

**Table 1**  
Summaries (n, %) on lifetime-ever pneumonia, demographic characteristics and home environmental factors in the total subjects and in each of the 6 cities.†

	Total	Shanghai	Nanjing	Urumqi	Taiyuan	Changsha	Chongqing
<b>Preschools Nr.</b>	205	71	23	15	10	33	53
<b>Prevalence of lifetime-ever pneumonia (%)</b>	34.5	35.4	27.2	41.4	31.1	36.0	34.2
<b>Gender</b>							
Male	15694(51.8)	5762(50.9)	1992(51.1)	1589(53.8)	1980(52.5)	1798(53.5)	2573(51.2)
Female	14621(48.2)	5613(49.1)	1912(48.9)	1364(46.2)	1654(47.5)	1573(46.5)	2505(48.8)
<b>Age</b>							
<5 years	14922(49.2)	5078(45.6)	2444(63.9)	1236(43.9)	1515(40.2)	1994(60.7)	2655(53.5)
≥5 years	15393(50.8)	6247(54.4)	1460(36.1)	1717(56.1)	2119(59.8)	1377(39.3)	2423(46.5)
<b>Birthweight (kg)</b>							
<2.5	763(2.5)	306(2.7)	81(2.1)	57(1.9)	74(2.0)	97(2.9)	148(2.9)
≥2.5	28541(94.1)	10598(93.6)	3722(95.3)	2785(94.3)	3544(97.5)	3170(94.0)	4722(93.0)
<b>Breastfeeding time</b>							
<6 months	14340(47.3)	6535(57.7)	1609(41.2)	1366(46.3)	1146(31.5)	1431(42.5)	2253(44.4)
≥6 months	15162(50.0)	4570(40.4)	2246(57.7)	1445(48.9)	2396(65.9)	1865(55.3)	2640(51.9)
<b>Family history of allergy</b>							
Yes	5261(17.4)	2636 (23.3)	615(15.8)	496 (16.8)	476 (13.1)	505 (15.0)	533 (10.5)
No	23968(79.1)	8384 (74.0)	3264 (83.6)	2226 (75.4)	3040 (83.7)	2796 (82.9)	4258 (83.9)
<b>Moving Home</b>							
Yes	2941(9.7)	1256(11.0)	401(10.2)	281(9.5)	310 (8.4)	321(9.5)	372(7.3)
No	27358(90.2)	10118(88.9)	3500(89.7)	2670(90.4)	3328(91.5)	3036(90.1)	4706(92.7)
<b>Maternal smoking during pregnancy</b>							
Yes	12704 (41.9)	4372 (38.4)	1642 (42.1)	1418 (48.0)	1351 (37.2)	1645 (48.8)	2276 (44.8)
No	16,886 (55.7)	6824 (60.0)	2197 (56.3)	1395 (47.2)	2276 (62.6)	1679 (49.8)	2515 (49.5)
<b>Current passive smoking</b>							
Yes	13769(45.4)	4495(39.5)	1892(48.5)	1426(48.3)	1773(48.8)	1770(52.5)	2413(47.5)
No	15554(51.3)	6517(57.3)	1957(50.1)	1369(46.4)	1781(49.0)	1557(46.2)	2373(46.7)
<b>Residential locations</b>							
Urban	22503(74.2)	8167(71.8)	2431(62.3)	2546(86.2)	2974(81.8)	3025(89.7)	3360(66.2)
Non-urban	6890 (22.7)	2982 (26.2)	1397(35.8)	287(9.7)	567(15.6)	239(7.1)	1418(27.9)
<b>Indoor dampness</b>							
Yes	19425(64.1)	7915(69.6)	2550(65.3)	1728(58.5)	2346(64.6)	2144(63.6)	2742(54.0)
No	6063(20.0)	1756(15.4)	680(17.4)	763(25.8)	846(23.3)	640(19.0)	1378(27.1)
<b>Home interior decoration</b>							
Yes	10096(33.3)	3860(33.9)	1373(35.2)	840(32.4)	1146(31.5)	1172(34.8)	1705(33.6)
No	15013(49.5)	5322(46.8)	2015(51.6)	1503(50.9)	2084(57.3)	1699(50.4)	2390(47.1)
<b>Annual average of family income per capita (1000 RMB, Mean ± SD)</b>	22.0 ± 9.9	30.8 ± 8.9	0.4 ± 7.3	14.5 ± 3.0	16.1 ± 4.6	17.9 ± 3.2	14.2 ± 5.7

† The sum of the numbers and percentages (%) in the paired groups might not be equal to the total number or 100% due to the missing values.



in Table 1. Generally, the subjects had a balanced gender and age distribution (mean age 4.6 years  $\pm$  standard deviation 1.1; male, n[%] = 15,694[51.8]) (Table 1). Nearly half of the children had less than 6 months of breastfeeding and had positive reports on current passive smoking and maternal smoking during pregnancy. More than 60% of children reported home dampness.

The average prevalence of lifetime-ever pneumonia at preschool-level was 34.5% across 6 cities. The highest prevalence of childhood pneumonia was observed in Urumqi (41.1%), followed by Changsha (36.0%), Shanghai (35.4%), Chongqing (34.2%), Taiyuan (31.3%) and Nanjing (27.2%) (Table 1).

The lifetime annual average concentrations of ambient air pollutants, as well as meteorological factors were estimated and summarized in Table 2. The cumulative annual average concentrations of ambient PM<sub>2.5</sub> and O<sub>3</sub> was 62.0  $\pm$  9.8 and 56.8  $\pm$  3.2  $\mu\text{g}/\text{m}^3$  across 6 cities, respectively. And the cumulative annual averages of ambient PM<sub>2.5</sub> in urban area was higher than that in non-urban areas across 6 cities (62.1  $\pm$  9.9  $\mu\text{g}/\text{m}^3$  compared with 59.8  $\pm$  9.4  $\mu\text{g}/\text{m}^3$ ). Moderate and high correlations were observed between PM<sub>2.5</sub> and SO<sub>4</sub><sup>2-</sup>, and between NO<sub>3</sub><sup>-</sup>, NH<sub>4</sub><sup>+</sup> and OM after controlling for cities (correlation coefficient ranged from 0.381 to 0.892) (S1 Table). Temporally, no large variation of PM<sub>2.5</sub>, BC and NH<sub>4</sub><sup>+</sup> levels was observed year by year except for a slight decreasing trend of SO<sub>4</sub><sup>2-</sup> and an increasing trend of NO<sub>3</sub><sup>-</sup> (S1 Figure).

An assumed three-level (children, preschool and city) random intercept null model was firstly performed, and the intercept variances at the preschool and city level were 0.093 (0.014) and 0.028 (0.019), respectively. The intercept variances of health outcomes were significant between preschools (VPC = 2.75%,  $p < 0.001$ ) but not between cities (VPC = 0.84%,  $p$  greater than 0.05). Accordingly, we adopted a two-level binary logistic hierarchical model consisting of the individuals (the 1st level) and preschools (the 2nd level) levels. In S2 Table, 4 two-level regression models were constructed by adding no variables (null model) and variables at personal, urban/rural and city levels, respectively. Compared with other models, the model 4 showed the lowest VPC (2.1%) and highest PCV (37.4%) including all the variables under the two selective criteria (S2 Table), for which it was determined as the primary regression model.

By the determined two-level binary logistic model with PM<sub>2.5</sub> as the > air pollutant (single-pollutant model), each 10  $\mu\text{g}/\text{m}^3$  increase of the cumulative annual averages of PM<sub>2.5</sub> was positively associated with an increased risk of doctor-diagnosed pneumonia by aOR (95%CI) of 1.12 (1.07–1.18) (Model I, Table 3). For the chemical components, each 1  $\mu\text{g}/$

$\text{m}^3$  increase of NO<sub>3</sub><sup>-</sup>, NH<sub>4</sub><sup>+</sup>, and OM was positively associated with an increased risk of doctor-diagnosed pneumonia by aOR (95% CI) of 1.06 (1.04–1.09), 1.05 (1.03–1.07) and 1.09 (1.06–1.12), respectively (Model I, Table 3). All the above significant associations remained consistent in the two-pollutant model (Model II, Table 3). The significant associations of NO<sub>3</sub><sup>-</sup>, NH<sub>4</sub><sup>+</sup> and OM remained consistent with additional adjusting for PM<sub>2.5</sub> mass concentration in the PM<sub>2.5</sub>-constituent joint models (Model III, Table 3). No significant positive effects were observed for ambient SO<sub>4</sub><sup>2-</sup> except in the single-pollutant model (aOR = 1.02, 95% CI 1.00–1.03,  $p = 0.024$ ) (Model I, Table 3).

Stratified analyses showed that age < 5 years, urban areas and breastfeeding time < 6 months might be important effect modifiers on the associations between PM<sub>2.5</sub> constituents and childhood pneumonia (Figs. 2 and 3). We observed younger children aged < 5 years had a higher risk of pneumonia than those aged  $\geq 5$  years in association with SO<sub>4</sub><sup>2-</sup> ( $p = 0.046$ ) and OM ( $p = 0.048$ ) (Fig. 2). We also observed that PM<sub>2.5</sub> and water-soluble ion constituents, particularly the NO<sub>3</sub><sup>-</sup>, NH<sub>4</sub><sup>+</sup> and OM were significantly associated with childhood pneumonia in urban areas by aOR (95%CI) of 1.13 (1.06–1.20), 1.07 (1.04–1.10), 1.05 (1.03–1.07) and 1.10 (1.06–1.13), respectively (Fig. 3). Children who had less than 6 months of breastfeeding had a significantly higher risk of pneumonia with ambient levels of PM<sub>2.5</sub> and NO<sub>3</sub><sup>-</sup> (Fig. 3). No significant differences were observed on the associations of PM<sub>2.5</sub>, NO<sub>3</sub><sup>-</sup>, NH<sub>4</sub><sup>+</sup>, OM with childhood pneumonia, stratified by other factors including passive smoking, indoor dampness and home interior decoration (S2 Figure).

Finally, we performed the sensitivity analyses. First, we tested the associations of PM<sub>2.5</sub> and its constituent and childhood pneumonia by removing one city each time in the multivariate models (S3 Table). The significant associations for ambient PM<sub>2.5</sub> and its constituents (NO<sub>3</sub><sup>-</sup>, NH<sub>4</sub><sup>+</sup> and OM) remained unchanged. Second, by using the air pollution levels in a 3 km range of preschools, instead of the 1 km  $\times$  1 km estimated levels, the significant associations remained almost the same (S4 Table). Last, by comparing the associations in children who had not moved homes ( $n = 27,358$ , 90.2%) during their whole life and the whole participants, no significant changes were observed (S5 Table.)

## 5. Discussion

In this study, the lifetime annual averages of ambient PM<sub>2.5</sub> were significantly associated with lifetime-ever doctor-diagnosed childhood pneumonia across six cities of China. The PM<sub>2.5</sub> constituents, in particular NO<sub>3</sub><sup>-</sup>, NH<sub>4</sub><sup>+</sup>, and OM, showed significant associations with childhood

**Table 2**

Descriptive statistics of the estimated lifetime annual averages of ambient PM<sub>2.5</sub>, constituents, O<sub>3</sub> and meteorology data in each city during the entire period.

Factors		Total	Shanghai	Nanjing	Urumqi	Taiyuan	Changsha	Chongqing
<b>Air pollutants (<math>\mu\text{g}/\text{m}^3</math>)</b>								
PM <sub>2.5</sub>	Mean $\pm$ SD	62.0 $\pm$ 9.8	51.4 $\pm$ 1.2	57.8 $\pm$ 1.1	64.3 $\pm$ 4.1	70.6 $\pm$ 1.5	72.7 $\pm$ 1.0	73.8 $\pm$ 5.1
	IQR	19.9	1.5	0.2	0.5	0.2	0.2	0.2
O <sub>3</sub>	Mean $\pm$ SD	56.8 $\pm$ 3.2	54.3 $\pm$ 1.5	55.5 $\pm$ 0.2	60.4 $\pm$ 0.1	63.3 $\pm$ 0.2	60.0 $\pm$ 0.2	55.8 $\pm$ 0.9
	IQR	6.5	2.6	0.3	0.2	0.2	0.2	1.8
<b>PM<sub>2.5</sub> constituents</b>								
SO <sub>4</sub> <sup>2-</sup>	Mean $\pm$ SD	11.2 $\pm$ 4.1	8.4 $\pm$ 0.2	12.2 $\pm$ 0.3	3.8 $\pm$ 0.2	12.9 $\pm$ 0.4	16.1 $\pm$ 0.4	12.2 $\pm$ 0.3
	IQR	7.3	0.7	0.1	0.3	0.1	0.1	0.2
NO <sub>3</sub> <sup>-</sup>	Mean $\pm$ SD	16.4 $\pm$ 2.3	16.2 $\pm$ 0.6	12.9 $\pm$ 0.4	16.7 $\pm$ 1.2	14.7 $\pm$ 0.4	17.4 $\pm$ 0.5	12.9 $\pm$ 0.4
	IQR	2.4	0.2	0.2	0.2	0.1	0.1	0.2
NH <sub>4</sub> <sup>+</sup>	Mean $\pm$ SD	14.2 $\pm$ 2.8	11.1 $\pm$ 0.4	15.3 $\pm$ 0.4	16.5 $\pm$ 1.3	12.7 $\pm$ 0.3	18.6 $\pm$ 0.4	15.3 $\pm$ 0.4
	IQR	5.5	0.1	0.1	0.3	0.1	0.1	0.2
OM	Mean $\pm$ SD	9.9 $\pm$ 1.6	8.5 $\pm$ 0.2	9.2 $\pm$ 0.2	11.0 $\pm$ 0.8	9.1 $\pm$ 0.2	11.9 $\pm$ 0.2	11.9 $\pm$ 0.2
	IQR	3.2	0.3	0.3	0.1	0.3	0.1	0.2
BC	Mean $\pm$ SD	3.9 $\pm$ 0.7	3.3 $\pm$ 0.1	4.1 $\pm$ 0.1	4.2 $\pm$ 0.3	5.5 $\pm$ 0.2	4.3 $\pm$ 0.1	4.3 $\pm$ 0.1
	IQR	0.9	0.1	0.2	0.4	0.3	0.2	0.2
<b>Meteorology Data</b>								
Average annual T <sup>†</sup> (°C)	Mean	16.0	17.3	16.4	7.9	11.1	18.3	18.8
R.H. (%)	Mean	68.3	69.4	70.6	55.2	53.2	72.5	77.4
Precipitation (dm)	Mean	89.2	116.9	112.6	28.8	41.1	131.0	104.9

T refers to temperature; R.H refers to relative humidity.

**Table 3**

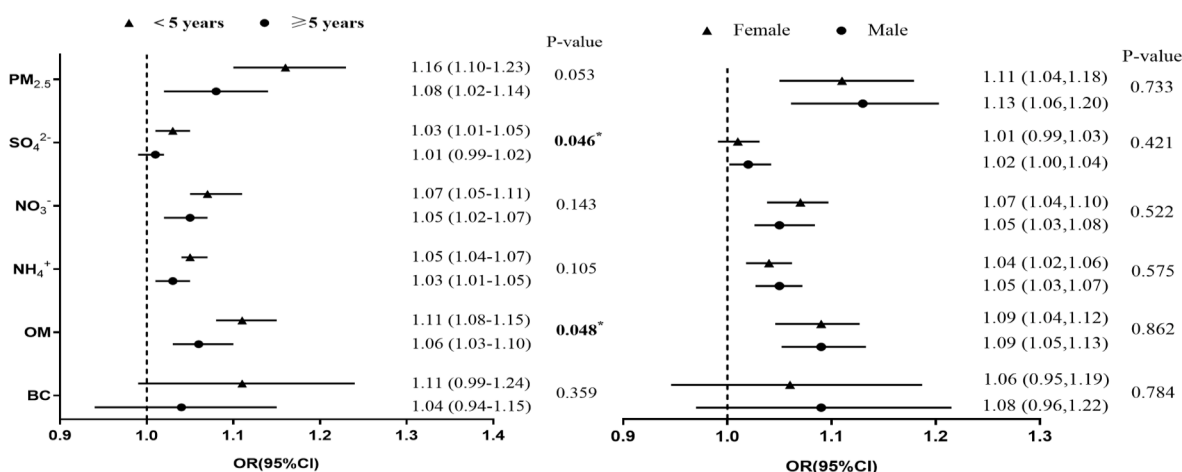
Associations of lifetime-ever doctor-diagnosed pneumonia and lifetime annual averages of ambient PM<sub>2.5</sub> and its components across six cities in China (two-level hierarchical regression model).

Pollutants	Single-pollutant model (Model I) aOR (95% CI)	p-value	Two-pollutant model (Model II) aOR (95%CI)	p-value	PM <sub>2.5</sub> -Constituent joint model (Model III) aOR (95% CI)	p-value
PM <sub>2.5</sub>	1.12(1.07–1.18)	<b>&lt;0.001</b>	1.13(1.05–1.21)	<b>0.001</b>	–	–
SO <sub>4</sub> <sup>2-</sup>	1.02(1.00–1.04)	<b>0.017</b>	1.00(0.98–1.03)	0.179	0.92(0.85–1.01)	0.859
NO <sub>3</sub> <sup>-</sup>	1.06(1.04–1.09)	<b>&lt;0.001</b>	<b>1.05(1.03–1.08)</b>	<b>&lt;0.001</b>	1.04(1.01–1.08)	<b>0.009</b>
NH <sub>4</sub> <sup>+</sup>	1.05(1.03–1.07)	<b>&lt;0.001</b>	<b>1.04(1.02–1.07)</b>	<b>&lt;0.001</b>	1.03(1.00–1.06)	<b>0.039</b>
OM	1.09(1.06–1.12)	<b>0.001</b>	<b>1.09(1.05–1.13)</b>	<b>&lt;0.001</b>	1.15(1.06–1.24)	<b>0.001</b>
BC	1.09(0.98–1.20)	0.099	0.95(0.82–1.09)	0.353	0.82(0.67–1.01)	0.873

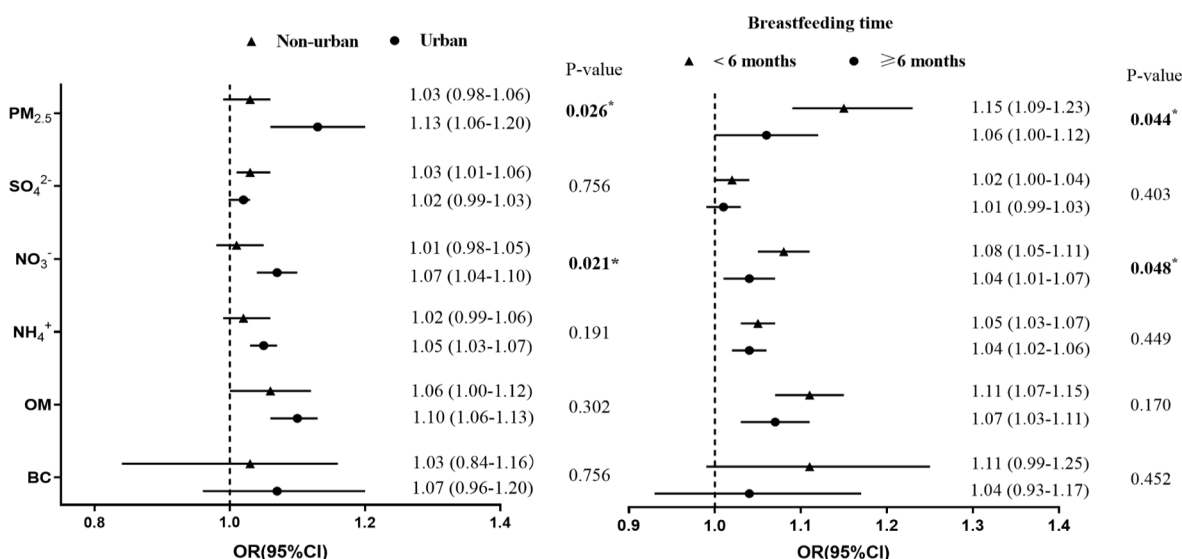
Abbreviations: CI: Confidence interval, aOR: adjusted odds ratio for each increase of 10 µg/m<sup>3</sup> PM<sub>2.5</sub> and 1 µg/m<sup>3</sup> of PM<sub>2.5</sub> chemical components. P < 0.05 in bold text. Model I: A single-pollutant regression model adjusting for gender, age, family history of allergy, birthweight, breastfeeding time, maternal smoking during pregnancy, current passive smoke, home indoor dampness, home interior decoration, annual household income per capita, residential locations and cumulative annual average temperature.

Model II: A two-pollutant regression model with additional adjustment for O<sub>3</sub> based on Model I.

Model III: PM<sub>2.5</sub>-constituent regression model joint models with additional adjustment for the mass concentration of PM<sub>2.5</sub> based on Model I.



**Fig. 2.** The associations (aOR and 95% CI) between lifetime annual averages of ambient PM<sub>2.5</sub> and its components with lifetime-ever childhood pneumonia stratified by age and gender. \*The aOR were statistically different between two groups (p < 0.05).



**Fig. 3.** The associations (aOR and 95%CI) between lifetime annual averages of ambient PM<sub>2.5</sub> and its components and childhood pneumonia stratified by residential locations and breastfeeding time. \*The aOR were statistically different between two groups (p < 0.05).

pneumonia. The health estimates were more pronounced in children who lived in urban areas and those who had less than 6 months' of breastfeeding. Children aged younger than 5 years old were more susceptible to OM levels. This is one of few studies investigating the effects of long-term levels of ambient PM<sub>2.5</sub> on childhood pneumonia in China.

A heavy burden of childhood pneumonia was observed in this study (34.5%) which was consistent with a previous study in 8 cities in China (32.3%) (Zhuge et al., 2018). The prevalence of lifetime-ever pneumonia in our study was higher than that reported in Beijing (26.9%) (Qu et al., 2017) and in Shandong (25.9%) (Chang et al., 2018), China.

The cumulative annual averages of ambient PM<sub>2.5</sub> across 6 cities was 6 times higher than the annual WHO guideline (10 µg/m<sup>3</sup>). The fuel combustion, traffic gas and industry emissions were the common major resources of pollution in six cities, and biofuel combustion in Changsha and Chongqing additionally influenced the PM<sub>2.5</sub> chemical constituents (Zhai et al., 2014; Li et al., 2008; Meng et al., 2007). As reported by Jimenez and colleagues, sulfate, nitrate and ammonium (SNA) were the predominant constituents of water-soluble inorganic ions (WSI) in PM<sub>2.5</sub>, where China has serious SNA polluted areas in the world (Jimenez et al., 2009). A study conducted in Shanghai also implicated that SNA contributed 86% and 77% of total WSI in PM<sub>2.5</sub> during haze and non-haze days, respectively (Behera et al., 2015). Consistent with the prior studies, the sum of water-soluble ions, SO<sub>4</sub><sup>2-</sup>, NO<sub>3</sub><sup>-</sup> and NH<sub>4</sub><sup>+</sup>, accounted for 67.4% (range 51.7%–69.6%) across 6 cities in our study. These constituents were mainly produced as “secondary” compounds from the acidification and oxidation of sulfate dioxide (SO<sub>2</sub>) or nitrogen oxides (NO<sub>x</sub>) (Huang et al., 2014). Typically, SO<sub>4</sub><sup>2-</sup>, NO<sub>3</sub><sup>-</sup> and NH<sub>4</sub><sup>+</sup> in PM<sub>2.5</sub> are largely presented in the atmosphere as sulfate ammonium (NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub>, ammonium nitrate, NH<sub>4</sub>NO<sub>3</sub> (Wang et al., 2018). For carbon components (OM and BC), the pollution sources were mainly from the exhaust gas of gasoline vehicles, biomass or coal combustion in China (Peng et al., 2018).

In our study, we found that lifetime annual averages of ambient PM<sub>2.5</sub> were significantly associated with childhood pneumonia across 6 cities. Generally, consistent results on the association between PM<sub>2.5</sub> exposure and childhood pneumonia have been reported in previous literature. A two-year analysis conducted in Ningbo, China found a significant association between PM<sub>2.5</sub> and increased hospital visits for childhood pneumonia (Peng et al., 2018). Glick et al. found that a high level of PM<sub>2.5</sub> was significantly associated with serious pneumonia hospitalization in children (Glick et al., 2019). A retrospective cohort study conducted in USA showed modest but positive association between PM<sub>2.5</sub> exposure and pediatric pneumonia during early childhood (Kennedy et al., 2018). On the other hand, a combined study consisting of 10 European birth cohorts by meta-analysis, no positive associations were found on ambient PM<sub>2.5</sub> and parents' reports of physician-diagnosed pneumonia in early childhood (up to 3 years old) (MacIntyre et al., 2014). For PM<sub>2.5</sub> constituents, a multi-center study performed in six California counties showed that 3-lag day levels of PM<sub>2.5</sub>, OC, NO<sub>3</sub><sup>-</sup> and sulfate were positively associated with increased risk of respiratory admissions, including childhood pneumonia, acute bronchitis and asthma (Ostro et al., 2009), which were consistent with our study.

The strong associations between water-soluble nitrates and ammonium and childhood pneumonia were observed in the total subjects and in those living in urban areas. The rapid urbanization in China has resulted in a sharp increase in traffic and vehicle ownership (Zhao and Yu, 2017), of which urban areas have a much higher level. The NO<sub>x</sub> in the air also promotes the conversion of SO<sub>2</sub> to sulfate, observed in heavy pollution days in Chinese urban areas (He et al., 2014). A prior study indicated the number concentration of particles near busy freeway was 3 times higher than the background value in urban environment (Boogaard et al., 2010), and decreased rapidly along with the increasing distance from the roadside (Durant et al., 2010). The fuel burning in urban areas could emit large amounts of both trace gases and ultra-fine particles into the atmosphere (Wu et al., 2017), which resulted in pulmonary inflammation and even lung destruction (Chang et al., 2011).

NO<sub>3</sub><sup>-</sup> and OM played important roles in particle formation in urban areas due to traffic mobility and emissions (Liu et al., 2017; Wang et al., 2016). A prior study showed that primary traffic pollutants exacerbate the lower respiratory infections during early life in Children (Darrow et al., 2014). All the above data indicated the nitrates and ammonium related pollution, more commonly in urban areas, had adverse pulmonary effects. In perspective of toxicological studies, since nitrates are acidic in nature, it showed that acidic aerosols lowered the PH values within the airways by depositing hydrogen ions, thereby triggering adverse reactions (Reiss et al., 2007). On the other hand, other components that were not able to quantify in our study, such as heavy metals in PM<sub>2.5</sub>, might have strong adverse effects on airway health as well. It has been postulated that PM<sub>2.5</sub>-associated metal complex could interact with Mycoplasma pneumonia (*M. pneumonia*) by ways of oxidative stress induction, modulation of the host immune system, inflammatory responses via Toll-like receptors (TLRs) and the nuclear factor-kappa B (NF-κB) pathway (Hou et al., 2016), respectively.

The biological mechanisms underlying the associations between ambient PM<sub>2.5</sub> exposure and childhood pneumonia are not fully elucidated. The reasons might be that particulates, especially nanometer- to micrometer-sized particulates, such as PM<sub>2.5</sub>, diesel particles, and sand fine dust, stimulate the immune system to induce pulmonary inflammatory responses as adjuvants, and enhance the occurrence of pathogen-induced pneumonia (eg. bacteria or virus) (Clifford et al., 2018; Kuroda et al., 2013). Also, PM themselves might simultaneously act as vectors for pathogenic bacteria, fungi or virus, in which the synergistic inflammatory effects of particles and mycotoxin have been reported (Capasso et al., 2015). Recently, Liu et al. found the ambient PM<sub>2.5</sub> induced apoptosis in lung epithelial cells through a ROS-DRP1-mitochondrial fission axis-mediated mitochondrial apoptotic pathway which contribute the onset of pulmonary diseases (Liu et al., 2020). More research on the associations and potential mechanisms of childhood pneumonia is needed, particularly in lower or middle-income countries where there are higher air pollution levels.

Children with less breastfeeding were more susceptible to NO<sub>3</sub><sup>-</sup> in PM<sub>2.5</sub> and showed higher risks of pneumonia. The study by Huang C, et al found that children having more than 6 months' of breastfeeding were significantly associated with the reduced risk of childhood pneumonia (Huang et al., 2017), which was consistent with our study. Longer breastfeeding was related to better protection by immune systems toward food or aero-antigens (Belderbos et al., 2012). On the other hand, inadequate breastfeeding was specifically associated with severe pneumonia in children aged < 5 years old (aOR = 2.3; 95%CI:1.4–3.9) (Jackson et al., 2013). In 2015, the WHO estimated that the percentage of infants exclusively breastfed for the first 6 months of life globally was only 36% (Marques et al., 2015). In the past years, minimal change happened and even decreasing rates of breastfeeding were observed in the 10 most populous countries in the world, including China (Roberts et al., 2013).

Consistent with the prior study (Roberts et al., 2013), there was a significant association between organic matter and pneumonia in children aged < 5 years old. OM was an indicator of the related organic components in PM<sub>2.5</sub> and had high correlations with NO<sub>3</sub><sup>-</sup> and NH<sub>4</sub><sup>+</sup> (S2 Table). Younger children or infants represent a population at increased risk of air pollution related respiratory conditions, because of their immature lungs, high breathing rates and immature immune system. A time-series conducted in Beijing reported that exposure to PM<sub>2.5</sub> might increase the incidence of death among children under 5 years (Wang et al., 2019). Further, PM<sub>2.5</sub> can act as vectors for pathogenic bacteria, fungi or virus, in which they irritate the inflammatory effects and arise the occurrence of childhood pneumonia (Marangu and Zar, 2019).

To our knowledge, this is the one of few multi-center studies to investigate the associations between long-term levels of ambient PM<sub>2.5</sub> and chemical constituents with diagnosed pneumonia in preschool children in China. It contributes in filling the knowledge gap of long-term PM<sub>2.5</sub> levels and their chemical constituents, which are likely to



further increase the exposure levels, could exert adverse effects on childhood pneumonia in China. Furthermore, the temporally-adjusted cumulative air pollution estimation, the large sample size, and the application of multi-level logistic regression models presented more convincing results with adequate statistical power.

This study has several limitations. First, the diagnosed pneumonia was collected by parents' reports and the information about the severity and diagnosis age of pneumonia was not available, which might have potential information bias compare with clinical diagnosis. However, the pneumonia prevalence level in our survey was reasonable by comparing to the data calculated from the incidence rate in China by Rudan et al. (2013). Second, we estimated air pollution levels (1 km × 1 km) based on preschools' addresses, which might introduce potential exposure misclassification. However, preschools are usually close to homes in China (within 3 km), and the sensitivity analysis, by using the air pollution levels estimated within 3 km range of preschool addresses, showed no significant changes on the associations between ambient air pollution and pneumonia (Jiang et al., 2018). Third, the estimation on the lifetime accumulated air pollution levels might not be appropriate in migrant children who ever moved from other places since birth. However, we found these subjects only accounted for a small proportion (<10%) and by comparing the non-migrant subjects and the whole subjects, there was almost no differences. Fourth, the information on indoor burning of solid/gas fuel in participants' homes were not available, which did not allow us to adjust for potential confounding in the model. So we must be particularly cautious in explaining the potential effects of indoor air pollution (Accinelli et al., 2017). Finally, the same as all other cross-sectional studies, we cannot identify the chronological sequence between exposure and outcome, which limits the power to establish a causal relationship between air exposure and health assessment. For all these limitations mentioned above, the findings should be interpreted with caution before extension to other population and research.

## 6. Conclusions

This multi-center study suggested the adverse health effects of long-term levels of ambient PM<sub>2.5</sub> and its chemical components on childhood pneumonia in China. The traffic-related constituents, in particular NO<sub>3</sub><sup>-</sup>, NH<sub>4</sub><sup>+</sup>, and OM, could dominate the health effects of ambient PM<sub>2.5</sub> on childhood pneumonia. Living in the urban areas, breastfeeding time < 6 months and age < 5 years could increase the risks of pneumonia by ambient air pollutants. The findings strengthened the rationale to further reduce air pollution and limit the emission of sources, in particular the traffic related air pollutants.

## Author contributions

WS did the statistical analysis, drafted and revised the article, CL provided air pollution data from modelling predictions and revised the article. WS, HK and ZZ contributed the concept and the design of the study. IAM, DN, QD, CH, HQ, XZ, YS, TW, RVM, AVD, YZ, BL, HK and ZZ participated the field work and edited the article. All authors contributed in giving the comments and revised the article.

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## Declaration of Competing Interest

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

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## Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2020.106176>.

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