

# Prenatal and Postnatal Exposure to Ambient Air Pollution and Preschool Asthma in Neonatal Jaundice Infants

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**Purpose:** Both air pollutant exposure and neonatal jaundice (NJ) have known effects on childhood asthma, but a higher total serum bilirubin (TSB) level has been associated with lung protection. This study aimed to assess whether prenatal/postnatal exposure to ambient air pollutants is related to the development of asthma in infants with NJ.

**Patients and Methods:** A nested case-control retrospective study was performed using the data of infants with NJ in the Kaohsiung Medical University Hospital Research Database. Data on average ambient air pollution concentrations within six months, the first year and second year after birth, and in the first, second and third prenatal trimesters were collected. NJ was defined as TSB levels  $\geq 2$  mg/dl with the diagnosis less than one-month-old. Asthma was defined as a diagnosis with medication use. We constructed conditional logistic regression models to estimate adjusted odds ratios (aORs) and 95% confidence intervals (CIs).

**Results:** Exposure to NO and SO<sub>2</sub> at all six time points in the study was significantly associated with an increased risk of preschool asthma in infants with NJ. The overall peak OR (95% CI) of SO<sub>2</sub>, PM<sub>2.5</sub>, PM<sub>10</sub>, NO, NO<sub>2</sub>, and NO<sub>x</sub> were 1.277 (1.129–1.444), 1.057 (1.023–1.092), 1.035 (1.011–1.059), 1.272 (1.111–1.455), 1.168 (1.083–1.259) and 1.104 (1.051–1.161), respectively. Fetuses in the first and second trimester were most vulnerable to ambient air pollutant exposure such as SO<sub>2</sub>, PM<sub>2.5</sub>, NO, NO<sub>2</sub> and NO<sub>x</sub> during the prenatal period. Exposure to all six ambient air pollutants during the first and second years after birth significantly affected preschool asthma in NJ infants.

**Conclusion:** In different time windows, prenatal and postnatal exposure to SO<sub>2</sub>, PM<sub>2.5</sub>, PM<sub>10</sub>, NO, NO<sub>2</sub>, and NO<sub>x</sub> were associated with preschool asthma in NJ infants. The relatively high impact of NO and SO<sub>2</sub> exposure in infants with NJ requires further studies and prevention measures.

**Keywords:** 1000 days, air pollution, SO<sub>2</sub>, neonatal hyperbilirubinemia, asthma

## Introduction

Since 1990, air pollution exposure has been one of the leading health risks influencing the global burdens of disease and injury, and the trend has been increasing.<sup>1</sup> Globally, only 7% of children live in environments with air pollution levels under the

World Health Organization (WHO) guidelines, indicating a lifelong impact of air pollution exposure in most children.<sup>2</sup> Additionally, the increasing prevalence of allergic diseases in recent decades represents a major challenge to children's health and imposes a global economic burden.<sup>3</sup> Emerging evidence indicates that specific forms of ambient air pollution, such as particulate matter 2.5 or 10 mm in diameter (PM<sub>2.5</sub>, PM<sub>10</sub>), sulfur dioxide (SO<sub>2</sub>), nitrogen oxide (NO), nitrogen dioxide (NO<sub>2</sub>), and nitrogen oxides (NO<sub>x</sub>) are associated with asthma onset in the pediatric population.<sup>4–6</sup> Notably, great concern about the direct negative effects of air pollution on the development of pediatric asthma due to the larger air volume inhaled by children than adults has been reported.<sup>7</sup> In addition to exposure via direct inhalation during childhood, prenatal ambient air pollution exposure during the fetal stage could increase the risk of childhood asthma.<sup>8</sup>

Asthma is recognized as a chronic inflammatory disease and multifactor disease that interacts with genetics, drugs, infections, and the environment.<sup>9,10</sup> Neonatal jaundice (NJ) and phototherapy have been associated with the development of childhood asthma.<sup>11,12</sup> Jaundice affects approximately 60% of neonates in the first week of life, and 18% of neonates develop clinically significant jaundice.<sup>13</sup> In the development of allergies, the role of bilirubin is controversial. On the one hand, serum bilirubin is a powerful circulating antioxidant, but on the other hand, it has an immunomodulatory effect on the T helper-1 and T helper-2 cell balance.<sup>14,15</sup> Although a meta-analysis that synthesized fourteen current studies showed that NJ (odds ratio [OR]=1.46; 95% confidence interval [CI], 1.39–1.53) and phototherapy (OR, 1.24; 95% CI, 1.11–1.38) were both associated with an increased risk of childhood-onset asthma,<sup>16</sup> there was no dose–response relationship between asthma incidence and the highest total serum bilirubin (TSB) level in infants with NJ in a large retrospective study in California, USA.<sup>17</sup> In another study, the Asian population had a higher bilirubin level at birth and higher risk of fulfilling the criteria for nonphysiologic jaundice than the white population.<sup>18</sup> A worse pollutant environment but lower asthma prevalence in Asia than in Western countries has been reported, and the role of ambient air pollutants in the development of asthma has been questioned.<sup>19</sup> However, higher unconjugated bilirubin levels in adults showed a lung-protective effect against toxic environmental exposure-induced inflammation.<sup>20</sup> Therefore, we speculated that the oxidative stress caused by ambient air pollutant exposure might play a different role in the development of asthma in infants with different severities of NJ. The aim of this study was to assess the relationship of prenatal and postnatal exposure to different ambient air pollutants with new-onset asthma in infants with NJ to further develop primary prevention strategies targeting these high-risk infants.

## Materials and Methods

### Study Design and Data Source

We conducted a retrospective nested case–control study to examine air pollution exposure and the risk of asthma in children with NJ. This study analyzed data from electronic medical records (EMRs) in the Kaohsiung Medical University Hospital Database (KMUHRD). The KMUHRD consists of 3 million EMRs with patient identifiers from multiple hospitals within the KMU health system (one tertiary medical center, two regional hospitals and one local hospital) in Kaohsiung city, southern Taiwan. According to the 1964 Declaration of Helsinki and the Personal Information Protection Act, the authorized investigators obtained anonymized data from KMUHRD without any personal identification information; the data were used for only research purposes. The data were analyzed from 2020–2021. The Institutional Review Board of the KMUH (IRB number: KMUHIRB-E(1)-20200002) approved this study and waived the requirement for written informed consent because of the retrospective design and use of deidentified data.

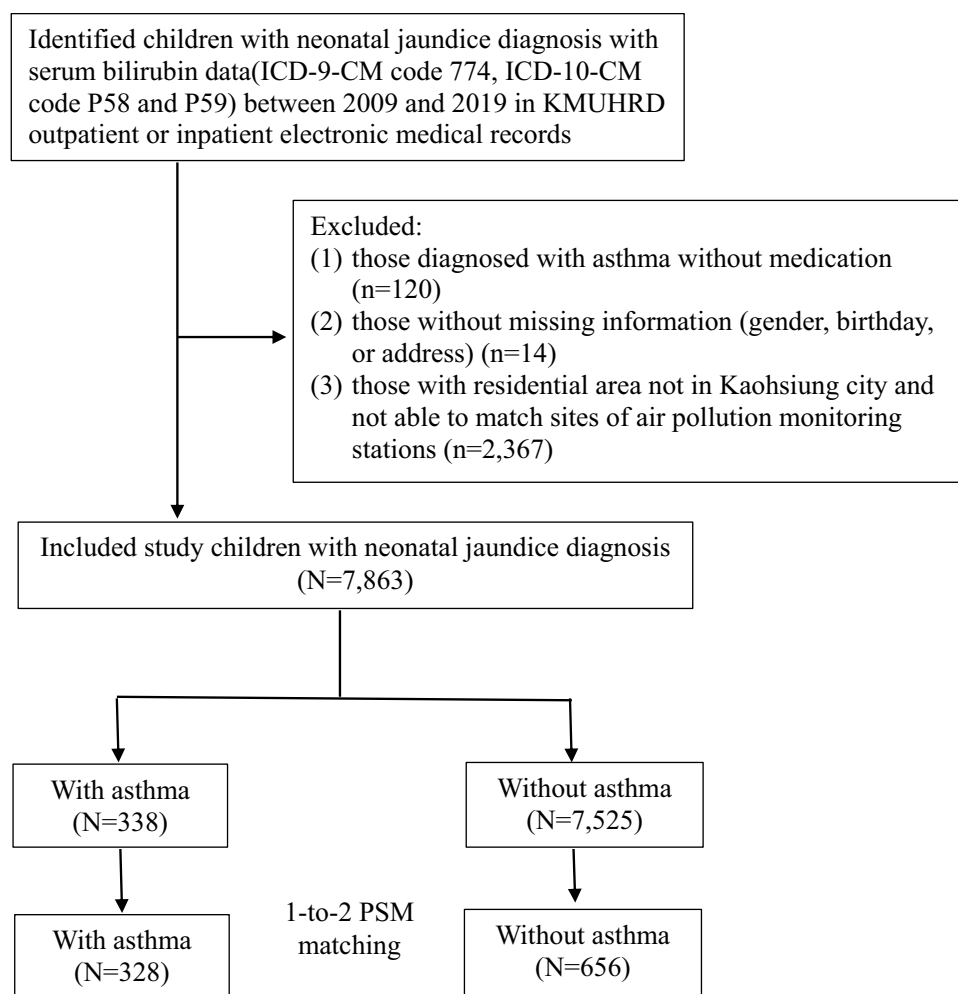
### Study Population

Using KMUHRD EMR record data from 2009 to 2019, we first identified patients with a diagnosis of NJ (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code: 774 or ICD-10-CM code: P59) with TSB level data at the outpatient visit or inpatient admission who were followed for at least 5 years in the KMUH system. All infants with NJ were diagnosed within one month after birth and remained in our health system at least 5 years after the diagnosis of NJ. Phototherapy was administered according to the American Academy of Pediatrics guidelines<sup>21</sup> and defined by procedure code. The case group included children who had NJ and developed asthma, and the control group included children who had NJ without any medical history of asthma. Childhood asthma was defined as a diagnosis on the basis of ICD-9 CM code 493 or ICD-10 CM code J45 and at least two prescriptions for antiasthma drugs at different

times within a 2-year period.<sup>22</sup> Antiasthma drugs included inhaled selective b2-agonists (ATC code R03AC), inhaled corticosteroids (ATC code R03BA), combined inhaled salbutamol/sodium cromoglycate (ATC code R03AK04), and combined inhaled selective b2-agonists/corticosteroids (ATC code R03AK06, R03AK07). The index date for individuals in the case group was defined as the date of the first asthma diagnosis, and the same index date was assigned to the matched control child without asthma. Given that the baseline characteristics between the case and control groups were significantly different, which may lead to selection bias, we used a 1-to-2 propensity score matching approach to match cases with comparable controls.<sup>23,24</sup> The propensity score was generated by logistic regression with covariates, including sex, index age group, and comorbidities. This approach essentially finds the nearest distance of probabilities regarding the estimated propensity score to determine the best matches with the smallest standard deviations between the intervention and comparison groups. The flowchart of the inclusion and exclusion criteria is shown in [Figure 1](#).

## Prenatal and Postnatal Air Pollution Exposure Periods

We analyzed daily (24-hour) average concentrations of longitudinal air quality, including PM<sub>2.5</sub>, PM<sub>10</sub>, SO<sub>2</sub>, NO, NO<sub>2</sub>, and NO<sub>x</sub> levels, collected from thirteen air quality monitoring stations around Kaohsiung city. Each patient's address at the district level was used to confirm the location of the nearest air quality monitoring station within 10 kilometers. We measured average cumulative air pollution exposure in the first, second, and third trimesters before birth and at six months, one year and two years after birth. To compare cumulative air pollution exposure levels across different time



**Figure 1** The flowchart of the inclusion and exclusion criteria.

periods in each individual child, the cumulative air pollution per interquartile range (IQR) was used to adjust the mean variability among multiple datasets.<sup>25</sup>

## Potential Confounders

In addition to the covariates of age and sex, potential baseline confounders known to be associated with asthma were controlled for in the analysis; these confounders included residential area in Kaohsiung city (north, central, and south Kaohsiung), phototherapy treatment (no/yes), TSB level, and comorbidities (eg, perinatal infection [ICD-9-CM code 7602, ICD-10-CM code P399], allergic rhinitis [ICD9-CM code 477, ICD10-CM code J30], acute sinusitis [ICD9-CM code 4619, ICD-10-CM code J01], chronic sinusitis [ICD9-CM code 4739, ICD10-CM code J32], acute bronchitis [ICD9-CM code 466, ICD10-CM code J20, J21], and atopic dermatitis [ICD-9-CM code 691.8, ICD10-CM code L2089, L209]). Significant neonatal jaundice (SNJ) was defined as a TSB level  $\geq 12$  mg/dL, and if the TSB level was  $< 12$  mg/dL, mild neonatal jaundice (MNJ) was confirmed.<sup>13</sup>

## Statistical Analysis

Chi-square tests were used to evaluate the significance of differences in categorical variables between children with and without asthma. Pearson correlation coefficients between exposure to air pollutants and each prenatal and postnatal period in children with NJ were estimated. The association between major air pollution exposure and the risk of asthma was analyzed by conditional logistic regression while controlling for baseline demographic characteristics (age, sex), allergic rhinitis, acute bronchiolitis, and atopic dermatitis. ORs,<sup>1</sup> adjusted ORs (aORs) and 95% CIs<sup>1</sup> were calculated to assess the risk of asthma development in different cumulative air pollution exposure periods. Forest plots were constructed to summarize the aOR results by TSB level (TSB  $< 12$ , or  $\geq 12$ ) and air pollution exposure during the prenatal (1st, 2nd, and 3rd trimesters before birth) and postnatal (6 months, 1 year, and 2 years after birth) periods. Data analysis was performed using SAS<sup>®</sup> software, version 9.4 of the SAS System for Windows (Copyright©2020. SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA). A *p* value  $< 0.05$  was considered statistically significant.

## Results

Table 1 summarizes the demographic and clinical characteristics before and after propensity score matching between children with NJ with and without asthma. After 1-to-2 propensity score matching, 984 children with NJ were included in this study; of these children, 328 had asthma, and 656 did not have asthma. There were no differences in the matched variables, including index age, sex, and comorbidities. Additional baseline routine and asthma-related test results are presented and were controlled for in the following regression models.

The distributions of the common air pollutants that the children with NJ were exposed to in the first, second, and third trimesters before birth and at six months, one year, and second years after birth are in Table 2. The average cumulative distribution of major air pollutants did not vary greatly across different exposure periods.

Tables 3 and 4 summarizes the results from multiple conditional logistic regression models for the association between prenatal and postnatal exposure to air pollutants and the risk of asthma in children with NJ, respectively. Specifically, in the prenatal period, the aORs for asthma attributable to SO<sub>2</sub> and NO exposure were significant in the three prenatal periods (aOR 95% CI, *p* value; SO<sub>2</sub>: 1.133 (1.031–1.245), *p*=0.01; 1.128 (1.035–1.229), *p*=0.006; 1.181 (1.079–1.293), *p*<0.001; NO: 1.123 (1.019–1.238), *p*=0.019; 1.149 (1.047–1.261), *p*=0.003; 1.107 (1.014–1.209), *p*=0.024). The aORs for asthma attributable to PM<sub>2.5</sub>, NO<sub>x</sub>, and NO<sub>2</sub> exposure were significant in first and second trimesters (aOR 95% CI, *p* value; PM<sub>2.5</sub>: 1.021 (1.003–1.039), *p*=0.007; 1.017 (1.002–1.033), *p*=0.022; NO<sub>x</sub>: 1.034 (1.005–1.064), *p*=0.022; 1.033 (1.008–1.059), *p*=0.011; NO<sub>2</sub>: 1.041 (1.003–1.081), *p*=0.034; 1.038 (1.005–1.072), *p*=0.023). Regarding the postnatal period, the aORs for asthma attributable to SO<sub>2</sub>, PM<sub>2.5</sub>, NO, and NO<sub>x</sub> exposure were significant in half years of life after birth (aOR 95% CI, *p* value; SO<sub>2</sub>: 1.201 (1.081–1.335), *p*<0.001; PM<sub>2.5</sub>: 1.028 (1.005–1.051), *p*=0.018; NO: 1.163 (1.044–1.297), *p*=0.006; NO<sub>x</sub>: 1.036 (1.004–1.070), *p*=0.030). In the first and second years after birth, the exposure to all analyzed ambient air pollution in this study significantly increased the risk. Figure 2 shows the effects in different subgroups of children with different TSB levels ( $< 12$  and  $\geq 12$ ) The result of exposure effect on different TSB levels and phototherapy treatment history was in Tables S1–S4. Significant effects of

**Table I** Demographic and Clinical Characteristics Before and After Propensity Score Matching in Neonatal Jaundice Children with/Without Asthma

	Before PSM Matching		p-value	After PSM Matching		p-value
	Without Asthma	Asthma		Without Asthma	Asthma	
<b>N</b>	7525	338		656	328	
<b>Gender (N, %)*</b>						
Female	6075(80.73%)	157(46.45%)	<0.001	339(51.68%)	156(47.56%)	0.224
Male	1450(19.27%)	181(53.55%)		317(48.32%)	172(52.44%)	
<b>Age of asthma diagnosis (N, %)*</b>	1.83±1.59	2.94±1.99	<0.001	2.82±2.12	2.94±2.00	0.369
<b>Birth body weight (N, %)</b>						
< 2500 g	865(11.50%)	76(22.48%)	<0.001	137(20.88%)	75(22.87%)	0.476
≥ 2500 g	86,660(88.50%)	262(77.52%)		519(79.12%)	253(77.13%)	
<b>Gestational age (N, %)</b>						
35–36 weeks	351(4.67%)	8(2.36%)	<0.001	22(3.35%)	6(1.83%)	0.175
≥ 37 weeks	7174(95.34%)	330(97.63%)		634(96.65%)	322(98.17%)	
<b>Resident in Kaohsiung Area (N, %)</b>						
North Kaohsiung	3331(44.27%)	146(43.20%)	0.521	312(47.56%)	142(43.29%)	0.082
Central Kaohsiung	830(11.03%)	32(9.47%)		80(12.20%)	31(9.45%)	
South Kaohsiung	3364(44.70%)	160(47.34%)		264(40.24%)	155(47.26%)	
<b>Phototherapy (N, %)</b>						
No	3996(53.10%)	217(64.20%)	<0.001	365(55.64%)	209(63.72%)	0.015
Yes	3529(46.90%)	121(35.80%)		291(44.36%)	119(36.28%)	
<b>Max TSB level (Mean±SD)</b>	9.47±7.15	12.03±5.75	<0.001	10.92±6.50	12.02±5.81	0.042
<12 mg/dL	6333(84.16%)	215(63.61%)	<0.001	563(85.82%)	260(79.27%)	0.009
≥ 12 mg/dL	1192(15.84%)	123(36.39%)		93(14.18%)	68(20.73%)	
<b>Min TSB level (Mean±SD)(mg/dL)</b>	4.21±3.44	4.70±3.30	0.038	4.45±3.31	4.71±3.31	0.365
<b>Comorbidity (N, %)*</b>						
Perinatal infection	279(3.71%)	11(3.25%)	0.665	21(3.20%)	11(3.35%)	0.899
Allergic rhinitis	187(2.49%)	89(26.33%)	<0.001	128(19.51%)	80(24.39%)	0.077
Acute sinusitis	113(1.50%)	68(20.12%)	<0.001	84(12.80%)	60(18.29%)	0.022
Chronic sinusitis	13(0.17%)	8(2.37%)	<0.001	9(1.37%)	5(1.52%)	0.849
Acute bronchiolitis	105(1.40%)	65(19.23%)	<0.001	90(13.72%)	60(18.29%)	0.060
Atopic dermatitis	194(2.58%)	44(13.02%)	<0.001	71(10.89%)	41(12.58%)	0.435

**Notes:** Chi-square test was used to test binary or category variables and t-test was used to test continuous variables between children diagnosed jaundice with or without asthma. A p-value below 0.05 was considered statistically significant. \*Variables used for propensity score matching.

**Abbreviations:** SD, standard deviation; PSM, propensity score matching; TSB, total serum bilirubin.

air pollution exposure on the risk of asthma tended to occur in infants with MNJ, while no significant or consistent results were found regarding the effect of pollutant exposure on the risk of asthma among children with SNJ or those who received phototherapy treatment.

## Discussion

This study found that prenatal and postnatal exposure to ambient SO<sub>2</sub>, PM<sub>2.5</sub>, PM<sub>10</sub>, NO, NO<sub>2</sub>, and NO<sub>x</sub> were associated with preschool asthma in NJ infants. The critical windows for the development of childhood asthma associated with prenatal air pollution exposure were in the entire pregnancy for SO<sub>2</sub> and NO, in the first and second trimesters for PM<sub>2.5</sub>, NO<sub>x</sub>, and NO<sub>2</sub>. An exposure effect on asthma due to postnatal air pollution exposure was observed at six months, the first year, and the second year after birth for SO<sub>2</sub>, NO, NO<sub>x</sub>, and PM<sub>2.5</sub>, and at the first and second year after birth for NO<sub>2</sub> and PM<sub>10</sub>.

The effect of ambient air pollution exposure in infants with NJ was in accordance with those reported in previous studies in the general pediatric population. There is no consensus regarding the critical window of maternal exposure to air pollution that leads to the development of childhood asthma. A multicity pregnancy cohort study in the United States

**Table 2** Mean Concentration of Ambient Air Pollutants in Different Periods in All Neonatal Jaundice Infants

Pollutants	Mean ± SD	Min	Percentile			Max	IQR
			25%	50%	75%		
The first trimester							
SO <sub>2</sub> (ppb)	6.80 ± 2.61	2.43	4.70	6.37	8.63	13.70	3.93
PM <sub>2.5</sub> (µg/m <sup>3</sup> )	35.08 ± 15.61	7.00	23.00	33.67	47.00	70.67	24.00
PM <sub>10</sub> (µg/m <sup>3</sup> )	67.52 ± 24.33	22.33	47.00	66.00	87.33	129.00	40.33
NO (ppb)	5.52 ± 2.79	0.99	3.72	4.97	6.40	16.55	2.68
NO <sub>2</sub> (ppb)	20.35 ± 7.08	5.19	14.81	19.59	25.21	37.95	10.40
NO <sub>x</sub> (ppb)	25.87 ± 9.41	6.44	19.35	24.34	31.09	51.92	11.74
The second trimester							
SO <sub>2</sub> (ppb)	7.16 ± 2.93	2.40	4.93	6.77	8.87	34.00	3.93
PM <sub>2.5</sub> (µg/m <sup>3</sup> )	36.77 ± 15.96	5.00	24.33	36.33	49.67	73.00	25.33
PM <sub>10</sub> (µg/m <sup>3</sup> )	69.95 ± 24.91	22.33	48.33	71.33	90.00	129.00	41.67
NO (ppb)	5.65 ± 2.62	0.67	3.82	5.33	6.72	15.82	2.90
NO <sub>2</sub> (ppb)	21.01 ± 7.04	0.44	14.94	20.91	26.57	36.34	11.63
NO <sub>x</sub> (ppb)	26.66 ± 9.18	5.99	19.75	25.97	32.83	51.26	13.08
The third trimester							
SO <sub>2</sub> (ppb)	7.22 ± 2.62	2.60	5.18	6.73	8.87	14.83	3.68
PM <sub>2.5</sub> (µg/m <sup>3</sup> )	38.05 ± 15.34	5.00	25.67	37.00	50.50	74.67	24.83
PM <sub>10</sub> (µg/m <sup>3</sup> )	71.08 ± 23.92	22.33	49.67	71.67	90.17	130.00	40.50
NO (ppb)	5.94 ± 2.93	1.18	4.08	5.34	7.08	21.25	3.00
NO <sub>2</sub> (ppb)	21.60 ± 6.89	5.41	15.82	20.86	26.83	41.15	11.01
NO <sub>x</sub> (ppb)	27.54 ± 9.32	6.85	20.54	25.72	33.86	62.40	13.32
The half year of life after birth							
SO <sub>2</sub> (ppb)	6.72 ± 2.41	2.64	4.77	6.42	8.28	14.21	3.52
PM <sub>2.5</sub> (µg/m <sup>3</sup> )	36.14 ± 12.00	11.00	27.92	35.67	45.00	61.83	17.08
PM <sub>10</sub> (µg/m <sup>3</sup> )	68.96 ± 18.33	29.83	55.67	68.28	81.75	116.00	26.08
NO(ppb)	5.55 ± 2.38	1.00	3.84	5.19	6.77	12.53	2.93
NO <sub>2</sub> (ppb)	21.00 ± 5.46	6.35	17.10	20.33	24.83	33.37	7.72
NO <sub>x</sub> (ppb)	26.55 ± 7.53	7.35	21.27	25.41	31.12	45.29	9.85
The first year of life after birth							
SO <sub>2</sub> (ppb)	6.59 ± 2.28	2.45	4.71	6.38	8.22	12.72	3.51
PM <sub>2.5</sub> (µg/m <sup>3</sup> )	35.11 ± 9.02	19.47	27.00	34.83	43.17	59.80	16.17
PM <sub>10</sub> (µg/m <sup>3</sup> )	67.34 ± 12.45	37.42	58.27	69.17	75.67	108.80	17.39
NO (ppb)	5.48 ± 2.10	1.32	3.87	5.24	6.65	11.69	2.78
NO <sub>2</sub> (ppb)	20.60 ± 3.60	11.21	18.08	21.07	23.74	30.83	5.67
NO <sub>x</sub> (ppb)	26.08 ± 5.56	12.54	22.06	25.93	30.71	42.55	8.66
The second year of life after birth							
SO <sub>2</sub> (ppb)	6.31 ± 2.24	2.27	4.55	6.08	7.94	12.34	3.39
PM <sub>2.5</sub> (µg/m <sup>3</sup> )	33.77 ± 8.99	17.89	26.50	33.08	42.42	51.63	15.92
PM <sub>10</sub> (µg/m <sup>3</sup> )	65.44 ± 12.55	38.04	57.41	68.08	73.46	93.00	16.05
NO (ppb)	5.27 ± 1.98	1.26	3.93	5.09	6.41	10.51	2.49
NO <sub>2</sub> (ppb)	20.23 ± 3.65	10.51	17.55	20.86	23.40	27.46	5.85
NO <sub>x</sub> (ppb)	25.50 ± 5.51	11.77	21.31	25.46	29.77	37.96	8.46

**Abbreviations:** SD, standard deviation; IQR, interquartile range; SO<sub>2</sub>, sulphur dioxide; PM<sub>2.5</sub>, particulate matters with diameters at 2.5 micrometers and smaller; PM<sub>10</sub>, particulate matters with diameters at 10 micrometers and smaller; NO, nitrogen oxide (NO); NO<sub>2</sub>, nitrogen dioxide; NO<sub>x</sub>, nitrogen oxides; OR, crude odds ratio; aOR, adjusted odds ratio.

reported that the risk of severe asthma in children increased 1.29 times [95% CI: 1.06, 1.58] per 2 µg/m<sup>3</sup> increase in PM<sub>2.5</sub> during the period of 24 to 36 weeks gestational age.<sup>26</sup> The aORs for childhood asthma associated with exposure to NO<sub>2</sub> and SO<sub>2</sub> during the 1st and 2nd trimesters in a retrospective study in China were both increased (1st trimester: NO<sub>2</sub>: aOR: 1.50, 95% CI: 1.15–1.96; SO<sub>2</sub>: aOR: 1.29, 95% CI: 1.08–1.55, 2nd trimester: NO<sub>2</sub>: aOR: 1.70, 95% CI: 1.26–2.30;

**Table 3** Associations Between Prenatal Exposure to Ambient Air Pollutants and Childhood Asthma in Neonatal Jaundice Infants in Terms of Odds Ratio (OR) and 95% CI (n=978)

Major Air Pollutions (per IQR)	OR	95% CI	p-value	aOR*	95% CI	p-value
The first trimester						
SO <sub>2</sub> (ppb)	1.149	1.050–1.257	0.002	1.133	1.031–1.245	0.010
PM <sub>2.5</sub> (µg/m <sup>3</sup> )	1.025	1.009–1.042	0.002	1.021	1.003–1.039	0.007
PM <sub>10</sub> (µg/m <sup>3</sup> )	1.012	1.002–1.023	0.017	1.009	0.998–1.020	0.093
NO (ppb)	1.147	1.046–1.258	0.004	1.123	1.019–1.238	0.019
NO <sub>2</sub> (ppb)	1.050	1.013–1.088	0.008	1.041	1.003–1.081	0.034
NOx(ppb)	1.040	1.012–1.069	0.004	1.034	1.005–1.064	0.022
The second trimester						
SO <sub>2</sub> (ppb)	1.140	1.050–1.238	0.002	1.128	1.035–1.229	0.006
PM <sub>2.5</sub> (µg/m <sup>3</sup> )	1.020	1.006–1.035	0.005	1.017	1.002–1.033	0.022
PM <sub>10</sub> (µg/m <sup>3</sup> )	1.009	1.000–1.018	0.045	1.007	0.998–1.016	0.122
NO (ppb)	1.164	1.063–1.274	0.001	1.149	1.047–1.261	0.003
NO <sub>2</sub> (ppb)	1.042	1.010–1.075	0.010	1.038	1.005–1.072	0.023
NO (ppb)	1.164	1.063–1.274	0.001	1.149	1.047–1.261	0.003
NOx(ppb)	1.036	1.011–1.062	0.004	1.033	1.008–1.059	0.011
The third trimester						
SO <sub>2</sub> (ppb)	1.194	1.093–1.304	<0.0001	1.181	1.079–1.293	<0.0001
PM <sub>2.5</sub> (µg/m <sup>3</sup> )	1.015	0.999–1.031	0.075	1.012	0.996–1.029	0.138
PM <sub>10</sub> (µg/m <sup>3</sup> )	1.004	0.995–1.014	0.373	1.004	0.994–1.015	0.388
NO (ppb)	1.112	1.020–1.213	0.016	1.107	1.014–1.209	0.024
NO <sub>2</sub> (ppb)	1.022	0.988–1.057	0.200	1.025	0.990–1.061	0.158
NOx(ppb)	1.022	0.997–1.049	0.089	1.023	0.997–1.050	0.081

**Notes:** \*Conditional logistic regressions were conducted controlling baseline demographic characteristics (age, gender), allergic rhinitis, acute bronchiolitis, and atopic dermatitis. ORs (95% CIs) were estimated for per IQR increase in SO<sub>2</sub>, PM<sub>2.5</sub>, PM<sub>10</sub>, NO, NO<sub>2</sub>, and NO<sub>x</sub>.

**Abbreviations:** SO<sub>2</sub>, sulphur dioxide; PM<sub>2.5</sub>, particulate matters with diameters at 2.5 micrometers and smaller; PM<sub>10</sub>, particulate matters with diameters at 10 micrometers and smaller; NO, nitrogen oxide (NO); NO<sub>2</sub>, nitrogen dioxide; NO<sub>x</sub>, nitrogen oxides; OR, crude odds ratio; aOR, adjusted odds ratio.

SO<sub>2</sub>: aOR: 1.26, 95% CI: 1.05–1.52).<sup>25</sup> A systematic review of 18 studies revealed that the influence of prenatal exposure to NO<sub>2</sub> (OR: 1.07, 95% CI: 1.01–1.14) and SO<sub>2</sub> (OR: 1.02, 95% CI: 0.98–1.07) on childhood asthma was positive.<sup>8</sup> In addition, a large retrospective cohort study involving 3177 preschoolers in Shanghai, China, with prenatal and postnatal exposure demonstrated that exposure to NO<sub>2</sub> in the 1st trimester of gestation and the second and fourth quarters after birth increased the risk of asthma.<sup>27</sup> (aOR, 95% CI: 1.92, 1.02–3.62; 1.36, 1.00–1.88; 1.90, 1.16–3.13) Prenatal exposure to PM<sub>10</sub> had no significant effect on the development of childhood asthma, similar to the findings of Deng et al.<sup>25</sup>

For postnatal exposure, a meta-analysis of 41 studies showed that early exposure to NO<sub>2</sub>, PM<sub>2.5</sub>, and PM<sub>10</sub> increased the risk of childhood asthma development.<sup>28</sup> A cross-sectional study in China showed that exposure to SO<sub>2</sub> (aOR: 1.22, 95% CI: 1.01–1.49) and NO<sub>2</sub> (aOR: 1.55, 95% CI: 1.26–1.92) during the first year after birth was significantly associated with parent-reported asthma.<sup>29</sup> A retrospective study of 2490 children aged 3–6 years in China showed that exposure to both SO<sub>2</sub> (aOR: 1.62, 95% CI: 1.01–2.60) and NO<sub>2</sub> (aOR: 1.90, 95% CI: 1.20–3.00) during the first year after birth had a significant association with doctor-diagnosed asthma.<sup>4</sup> Khreis et al<sup>5</sup> analyzed the prevalence of childhood asthma and early-life exposure from 2000 to 2010 in the USA and concluded that early-life exposure to NO<sub>2</sub> and PM<sub>2.5</sub> was significantly associated with childhood asthma. For NO<sub>x</sub>, the overall risk increased without statistical significance even though only 7 of the 41 studies had high heterogeneity (OR: 1.48, 95% CI 0.89, 2.45).<sup>28</sup>

However, in the subgroup in our study, the effect of ambient air pollution exposure during both the prenatal and postnatal periods was consistent in infants with MNJ, and SO<sub>2</sub> had a greater impact on the development of asthma. Although most NJ resolves within 14 days, infants with SNJ have a greater likelihood of genetic polymorphisms, such as null mutations in the glutathione S-transferase gene, heme oxygenase-1, and UDP-glucuronosyltransferase 1A1.<sup>30</sup> In the prenatal period, a higher

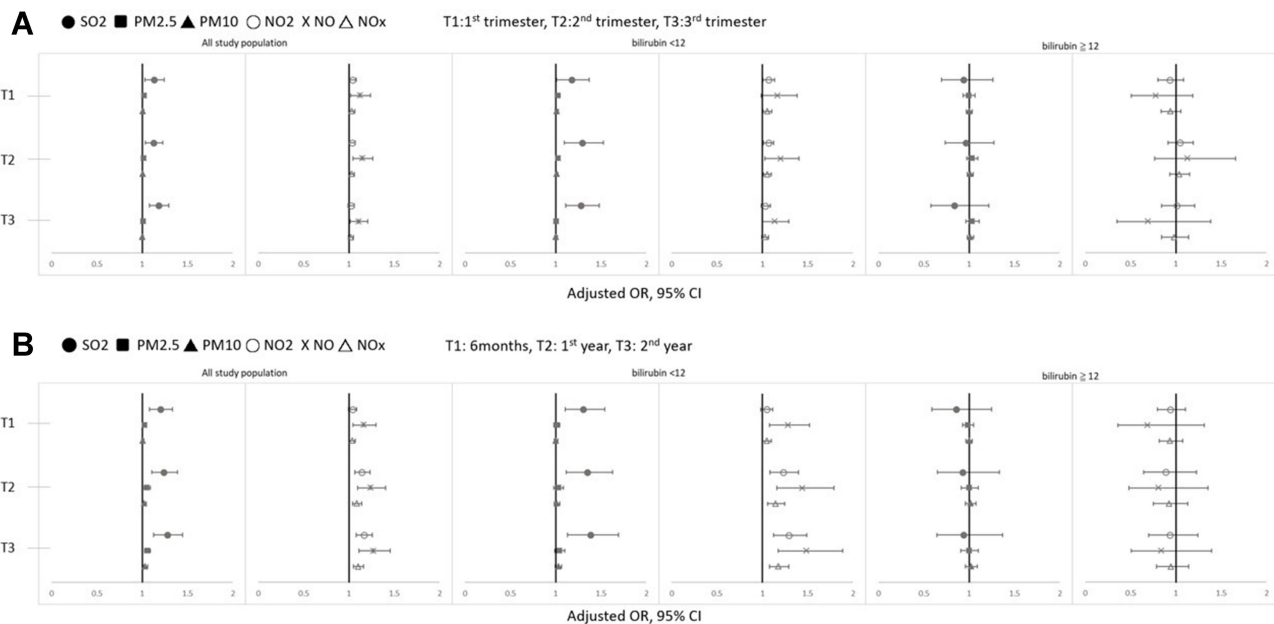
**Table 4** Associations Between Postnatal Exposure to Ambient Air Pollutants and Childhood Asthma in Neonatal Jaundice Infants in Terms of Odds Ratio (OR) and 95% CI (n=978)

Major Air Pollutions (per IQR)	OR	95% CI	p-value	aOR*	95% CI	p-value
The half year of life after birth						
SO <sub>2</sub> (ppb)	1.220	1.102–1.350	<0.0001	1.201	1.081–1.335	<0.0001
PM <sub>2.5</sub> (µg/m <sup>3</sup> )	1.032	1.010–1.055	0.005	1.028	1.005–1.051	0.018
PM <sub>10</sub> (µg/m <sup>3</sup> )	1.010	0.997–1.023	0.124	1.009	0.995–1.022	0.205
NO (ppb)	1.177	1.057–1.310	0.003	1.163	1.044–1.297	0.006
NO <sub>2</sub> (ppb)	1.039	0.996–1.084	0.079	1.041	0.996–1.087	0.072
NO <sub>x</sub> (ppb)	1.037	1.004–1.070	0.026	1.036	1.004–1.070	0.030
The first year of life after birth						
SO <sub>2</sub> (ppb)	1.254	1.123–1.400	<0.0001	1.239	1.104–1.391	<0.0001
PM <sub>2.5</sub> (µg/m <sup>3</sup> )	1.061	1.030–1.093	<0.0001	1.055	1.021–1.090	0.001
PM <sub>10</sub> (µg/m <sup>3</sup> )	1.029	1.008–1.049	0.005	1.023	1.001–1.045	0.039
NO (ppb)	1.263	1.119–1.425	0.000	1.241	1.097–1.405	0.001
NO <sub>2</sub> (ppb)	1.152	1.074–1.237	<0.0001	1.144	1.064–1.231	<0.0001
NO <sub>x</sub> (ppb)	1.097	1.048–1.149	<0.0001	1.091	1.041–1.144	<0.0001
The second year of life after birth						
SO <sub>2</sub> (ppb)	1.290	1.148–1.449	<0.0001	1.277	1.129–1.444	<0.0001
PM <sub>2.5</sub> (µg/m <sup>3</sup> )	1.062	1.031–1.094	<0.0001	1.057	1.023–1.092	0.001
PM <sub>10</sub> (µg/m <sup>3</sup> )	1.039	1.017–1.062	0.000	1.035	1.011–1.059	0.004
NO (ppb)	1.295	1.135–1.478	0.000	1.272	1.111–1.455	0.001
NO <sub>2</sub> (ppb)	1.176	1.094–1.265	<0.0001	1.168	1.083–1.259	<0.0001
NO(ppb)	1.295	1.135–1.478	0.000	1.272	1.111–1.455	0.001
NO <sub>x</sub> (ppb)	1.110	1.058–1.165	<0.0001	1.104	1.051–1.160	<0.0001

**Notes:** \*Conditional logistic regressions were conducted controlling baseline demographic characteristics (age, gender), allergic rhinitis, acute bronchiolitis, and atopic dermatitis. ORs (95% CIs) were estimated for per IQR increase in SO<sub>2</sub>, PM<sub>2.5</sub>, PM<sub>10</sub>, NO, NO<sub>2</sub>, and NO<sub>x</sub>.

**Abbreviations:** SO<sub>2</sub>, sulphur dioxide; PM<sub>2.5</sub>, particulate matters with diameters at 2.5 micrometers and smaller; PM<sub>10</sub>, particulate matters with diameters at 10 micrometers and smaller; NO, nitrogen oxide (NO); NO<sub>2</sub>, nitrogen dioxide; NO<sub>x</sub>, nitrogen oxides; OR, crude odds ratio; aOR, adjusted odds ratio.

level circulating bilirubin in cord blood was found in neonates who later developed SNJ.<sup>31</sup> In the postnatal period, neonates with significant jaundice had higher TSB levels than those with mild jaundice through adulthood.<sup>30</sup> Recently, a nested case-control cohort study showed that children with a higher unconjugated bilirubin level at 1 year of age had lower levels of



**Figure 2** Prenatal (A) and postnatal (B) exposure to ambient air pollution, and development of asthma among children with NJ and different TSB levels (<12 and ≥12).



oxidative stress-related metabolites and a lower risk for childhood asthma.<sup>32</sup> Moreover, every IQR increase (3.32–3.93 ppb) in our study period was lower than those in previous studies (10.0–13.6 ppb).<sup>4,29</sup> This result highlights that regardless of prenatal or postnatal exposure to SO<sub>2</sub>, the risk of developing asthma is significantly increased in infants with NJ. Prenatal exposure to different levels of ambient air pollution causes variously complex maternal immune responses. Large numbers of CD8 T cells and small numbers of CD4 T cells are related to exposure to SO<sub>2</sub> during pregnancy, and immune-related factors in cord blood play a role in the development of childhood respiratory inflammatory diseases.<sup>33</sup> Individuals with asthma have been shown to be more sensitive to SO<sub>2</sub>, even with shorten exposure windows.<sup>34</sup> Attention to SO<sub>2</sub> has been decreasing in recent years because of global improvements in industrial pollutants, except in some industrial areas. Further studies on the effects of SO<sub>2</sub> exposure in infants with NJ are needed to develop a better primary prevention strategy targeting these high-risk infants.

Moreover, subgroup analysis showed that the detrimental effects of nitrogen oxides were also consistent in MNJ infants but not SNJ infants. As SO<sub>2</sub>, Interest in nitrogen oxides has specifically focused on NO<sub>2</sub> because of its known relationship with negative health effects and its high correlation with other nitrogen oxides. Surprisingly, the impact of NO on developing preschool asthma in NJ infants was not inferior to NO<sub>2</sub> or NO<sub>x</sub> in this study. Even though early-life exposure to NO increases the risk of an asthma diagnosis,<sup>6</sup> few studies have focused on the association of NO exposure with childhood asthma compared to the other two nitrogen components.<sup>35</sup> Green areas in urban spaces with higher green coverage rates will improve the air quality.<sup>36</sup>

Different species planted in urban green spaces have different levels of consumption of distinct nitric oxides.<sup>37</sup> To develop a more precise primary prevention strategy, we need to conduct further studies on the role of exposure to nitrogen oxides in the development of childhood asthma and should consider the impact of greenspace exposure at different spatiotemporal scales through a dynamic framework.<sup>38</sup>

## Strengths and Limitations

The present study has important strengths. To our knowledge, this is the first study to explore the role of NJ in the associations between air pollutant exposure in the prenatal to postnatal periods and childhood asthma. Nonetheless, the results need to be interpreted cautiously because we acknowledge some limitations in our study. First, in our database, we were unable to identify important covariates associated with the development of asthma, such as family history of atopic disease, family smoking history, maternal asthma, and socioeconomic status, which might affect the interpretation of our results. Second, the prevalence and complex etiology of asthma are heterogeneous among different ethnicities, and further studies are needed to determine whether the same impact of neonatal bilirubin level on the effect of ambient air exposure will be observed, except in East Asia. Third, we did not consider the effect of residential migration and indoor air pollution, which have been indicated to be associated with childhood asthma. Fourth, increasing evidence has revealed that station-based models can over- or underestimate the impact of air pollutants because of spatiotemporal variability and a dynamic population distribution with different greenspace exposure.<sup>38,39</sup> Fifth, despite the fact that SNJ and phototherapy were risk factors for the development of asthma based on the current evidence, the case numbers were small in our cohort.

## Conclusion

Prenatal and postnatal ambient air pollutants harmed NJ infants in developing preschool asthma. Our study raised the concern of the pollutants which still exist but had less attention in the current study trend. As we need a more precise primary prevention strategy for preschool asthma, more studies are needed to clarify the mechanism between SO<sub>2</sub> and NO and NJ infants and promote maternal-fetal health.

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## Disclosure

The authors report no conflicts of interest in this work.

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