Reproductive Health

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Association analysis of maternal exposure to air pollution during pregnancy and offspring asthma incidence

Lili Bao[1†], Yuan Liu[2†], Yuhong Zhang[2†], Qian Qian[2], Yifen Wang[2], Wei Li[2] and Yanyan Yu[1*]

Abstract

Background Air pollution has a significant negative impact on human health. Pregnant mothers and children are typical susceptible groups, and environmental exposure has a crucial impact on children's health. We established a childhood asthma cohort to analyze the factors influencing the development of asthma in offspring, with a focus on prenatal exposure to air pollutants. The goal was to explore potential early preventive measures to reduce the incidence of childhood asthma.

Methods This nested case–control study included mothers who were registered and delivered at Lianyungang Maternal and Child Health Hospital between 2015 and 2018, covering pre-pregnancy, first, second, and third trimesters. Children diagnosed with asthma before the age of four were included in the asthma group. To assess environmental exposure, we gathered data from 29 national and provincial air pollution monitoring stations and 16 meteorological monitoring sites in Lianyungang and surrounding areas. We used spatial interpolation with inverse distance weighting (IDW) to estimate individual exposure to air pollutants, including particulate matter ($PM_{2.5}$, PM_{10}), carbon monoxide (CO), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and ozone (O_3). Univariate and multivariate regression analyses were conducted to examine the association between maternal exposure during pregnancy and the risk of childhood asthma.

Results A total of 292 mother–child pairs in the asthma group and 1423 mother–child pairs in the healthy control group were included. The second (AOR = 1.04, 95%CI 1.01–1.06) and whole gestation (AOR = 1.06, 95%CI 1.03–1.10) exposure to $PM_{2.5}$ was associated with higher odds of childhood-onset asthma. Exposure during the third trimester (AOR = 1.02, 95%CI 1.01–1.03) and whole gestation (AOR = 1.02, 95%CI 1.01–1.04) of PM_{10} was associated with higher odds of childhood-onset asthma. The first (AOR = 1.06, 95%CI 1.02–1.09) and second (AOR = 0.95, 95%CI 0.92–0.98) trimesters exposure to NO_2 was associated with higher and lower odds of childhood-onset asthma, respectively. SO_2 whole pregnancy exposure (AOR = 1.04, 95%CI 1.01–1.07) was associated with higher odds of childhood-onset asthma.

Conclusions Exposure to $PM_{2.5}$, PM_{10}, and SO_2 during pregnancy can lead to an elevated risk of childhood asthma. Reducing or avoiding exposure to pollutants during pregnancy can reduce the incidence of childhood asthma. We should protect the environment and reduce the harm of environmental pollution to health.

Keywords Air pollutant, Pregnancy, Childhood asthma, Cohort

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Introduction

As the most common chronic respiratory disease in childhood, bronchial asthma (asthma hereafter) is characterized by recurrent attacks of breathlessness and wheezing, impacting daily life, learning, and even the normal mental development of children. In recent years, asthma has increased yearly, bringing a heavy economic burden to families and society because of its expensive treatment and control costs [1, 2]. How to reduce the incidence of asthma, prevent the onset of asthma, and reduce the medical burden on families and society is imminent.

Genetic and environmental factors play an essential role in the pathogenesis of asthma, but the increasing incidence of asthma and other allergic diseases in recent decades is thought to be mainly caused by changes in environmental conditions [3, 4]. Air pollution significantly impacts human health, and poor air quality is the most significant environmental risk to human health today [5–7]. The Global Burden of Disease (GBD) highlights the significant burden of disease caused by air pollution in many parts of the world, particularly in Asia [8]. Air pollution contributes to various adverse health outcomes, including respiratory disease, cardiovascular disease, cancer, among others. Children are typically susceptible groups. The impact of environmental exposure on children's health is crucial [9, 10], and environmental exposure is characterized by long-term, continuous, and individual heterogeneity [11, 12]. With the increase in human activities, the problems of air pollution and water body pollution have become more severe with the development of industrialization [13, 14]. In particular, air pollution, which can directly enter the respiratory tract, causes adverse effects on the human respiratory system [15].

Pregnancy is a critical period for maternal and offspring health. The developing fetus and the pregnant mother are especially susceptible to environmental chemical exposure. Early childhood exposure to air pollution is central to the later development of allergic diseases [16]. Studies have confirmed that the onset of childhood asthma is closely related to multiple factors during the mother's pregnancy, such as the maternal life environment, disease conditions, medication use, and childbirth [17–20]. The critical window of environmental exposure factors contributing to an individual's risk of developing bronchial asthma may be before the mother's pregnancy [21, 22]. Air pollutants mainly include gaseous pollutants (carbon monoxide (CO), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and ozone O_3) and atmospheric particulate matter ($PM_{2.5}$ and PM_{10}). As the most significant air pollutant, particulate matter (PM) is the fourth leading global risk factor for mortality and contributes significantly to the disease burden. Among them, delicate $PM_{2.5}$ can cross the placenta into the bronchus and alveoli of the fetus and is associated with abnormal lung genesis and multiactive lung disease [23]. World Health Organization (WHO) released its latest Global Air Quality Guidelines on September 22, 2021, further raising the standard for $PM_{2.5}$ ($PM \leq 2.5$ μm in diameter) (i.e., from 10 μg/m^3 to 5 μg/m^3), highlighting the serious human health risks of PM exposure [24]. PM_{10}, as a respirable particulate matter with a large specific surface area and strong adsorption capacity, is a "support" and "catalyst" for multiple pollutants. 60–90% of atmospheric hazardous pollution substances are present in PM_{10}, an essential factor inducing respiratory diseases, especially asthma [25].

Previous studies of ambient particulate matter have mainly focused on the relationship between exposure and the health of children and adults, but pregnant women are susceptible to air pollution. However, there is little information with respect to the associations between maternal air pollution exposure during pregnancy and climatic factors on offspring asthma incidence. In order to better understand the impact of air pollution and climate factors on children's health, we aimed to establish an obligate childhood asthma cohort based on a natural birth cohort and investigated the effects of air pollution and climate factors on the onset of asthma in offspring. We hypothesized that exposure to air pollution and climate factors during pregnancy might lead to an elevated risk of childhood asthma. Our study may provide a strong scientific basis for the early prevention and treatment of childhood asthma.

Methods

Study population

This study was a nested case–control study. The study subjects were mothers and infants who registered at Lianyungang Maternal and Child Health Hospital between 2015 and 2018. A total of 1465 pregnant women were enrolled in the first trimester (before 12 weeks of pregnancy) and were followed until their offspring reached four years of age. Of these, 42 cases of asthma were confirmed in the offspring (incidence: 2.87%). Children diagnosed with asthma before the age of four were included in the asthma group. Additionally, a dedicated childhood asthma cohort was established, which included 250 children with asthma from the same age group, resulting in a total of 292 children in the asthma cohort. This was done to enhance statistical power due to the low incidence of asthma in the original birth cohort. The control group consisted of 1423 non-asthmatic children from the birth cohort. All participants had lived in Lianyungang City for more than 10 years, with the specific residential addresses shown in Fig. 1.

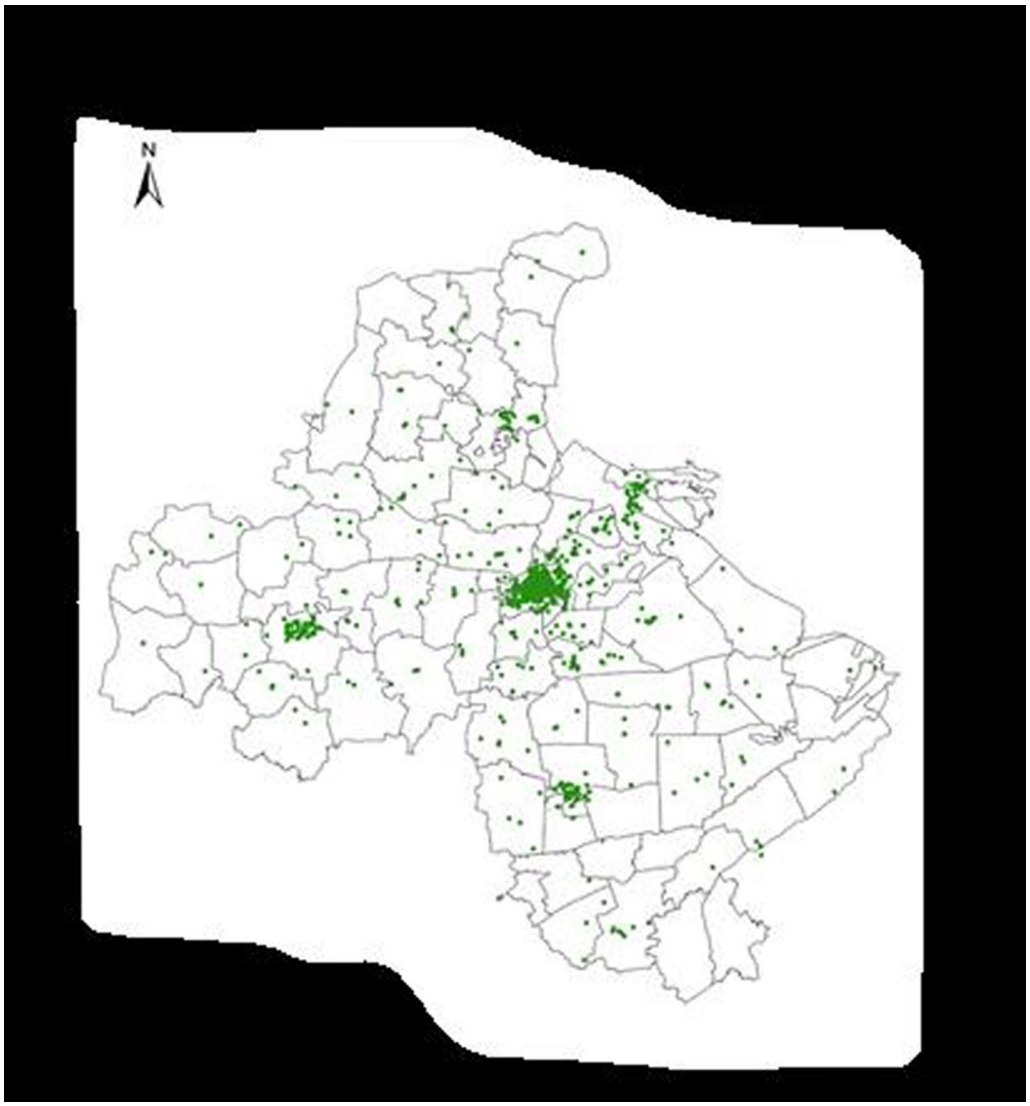

Fig. 1 This was the home address distribution chart of all study subjects. The subjects were distributed throughout Lianyungang City, and most were concentrated in several central urban areas of Lianyungang City

Inclusion and exclusion criteria

Inclusion criteria

Asthma group: (1) Offspring meeting the diagnostic criteria for bronchial asthma according to the 2016 Chinese Guidelines for Diagnosis and Treatment of Pediatric Asthma. (2) Offspring aged < 6 years. (3) Mothers were long-term residents of Lianyungang City and delivered at Lianyungang Maternal and Child Health Hospital.

Control group: (1) Offspring with no history of asthma. (2) Offspring aged < 6 years. (3) Mothers were long-term residents of Lianyungang City and delivered at Lianyungang Maternal and Child Health Hospital.

Exclusion criteria

Asthmatic group: (1) Offspring with wheezing caused by congenital airway disease, congenital heart disease, congenital vascular malformations, primary immune deficiency, tracheal foreign body, bronchial lymph node tuberculosis, or gastroesophageal reflux. (2) Mothers or offspring with serious systemic diseases (endocrine, heart, liver, kidney, etc.). (3) Mothers or offspring with immune disorders. Control subjects: (1) Mothers or offspring with severe endocrine, heart, liver, or kidney diseases. (2) Mothers or offspring with immune disorders.

Baseline and clinical information collection

Trained investigators collected baseline and clinical information from mothers using a municipal maternal health information system, combined with questionnaires, phone calls, and web queries. The data collected included general sociodemographic information, pregnancy-related diseases (e.g., gestational diabetes, hypertension, anemia), environmental exposures, behavioral habits, delivery processes, infant gender, gestational age, and birth weight. In the obligate asthma cohort, additional data on the children's disease and treatment were also gathered, including age at onset, disease course, treatment regimens, and medication use.

Diagnosis of asthma in children

This study was based on the diagnostic criteria of asthma in children under six years of age according to "Chinese Guidelines for the Diagnosis and Control of Bronchial Asthma" 2016 edition. This was diagnosed by professional pediatric clinicians.

Ethics

Our study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) and approved by the Ethics Committee of Lianyungang Maternal and Child Health Hospital (LYG-ME2015003). Informed consent was obtained from every patient. For the infants, informed consent was also obtained from a parent and/or legal guardian.

Exposure assessment

Distribution of air pollution exposure

In this study, exposure to air pollutants was assessed based on data from 29 national and provincial air monitoring stations in Lianyungang and surrounding cities (2015–2018). The pollutants measured included $PM_{2.5}$, PM_{10}, CO, NO_2, SO_2, and O_3. The distribution of air pollution monitoring points is shown in Fig. 2.

Air pollution monitoring data came from the monitoring points of Lianyungang Hongmen Platoon Station, Mine design Hospital, municipal environmental monitoring station, and the monitoring points of Rizhao, Yancheng, Huai 'an and Suqian, the surrounding cities of Lianyungang City. We calculated each mother's exposure based on data reported by the monitoring site closest to the study subjects' home addresses. On the basis of home address information, we encoded and translated the participants' specific home address information into geographical data through Fuzhou map. The average pollutant concentration distribution estimated the distribution of exposure concentrations during the pre-pregnancy and the first, second, third trimesters and the whole gestation of the monitoring sites combined with the inverse distance weighting (IDW) method.

Climate exposure assess

We selected daily monitoring data from 16 national and provincial meteorological monitoring sites in Lianyungang and surrounding cities during 2015–2018. The meteorological monitoring point distribution is shown in Fig. 3.

Meteorological monitoring data were obtained from meteorological monitoring sites in Lianyungang, East China Sea, sunshine, Junan, Linshu, and other surrounding cities. The distribution of the study subjects' home addresses is shown in Fig. 1. Similarly, we estimated each pregnant woman's exposure based on home address information, combined with data reported by the monitoring site closest to the home address. Thereafter, we translated the participants' specific home address information into latitude and longitude data through iPhone map coding. We used the IDW method and combined the average distribution of exposure temperature (℃) and relative humidity (%) at the monitoring points during the same period, and the average distribution of exposure temperature (℃) and relative humidity (%) during the whole pregnancy to conduct a summary analysis.

Covariates

Covariate selection was guided by a comprehensive review of the literature, encompassing maternal baseline characteristics, offspring baseline characteristics, and meteorological factors. The maternal covariates comprised reproductive age (years), maternal height (CM), pre-pregnancy weight (kg), educational level (primary, secondary, university undergraduate, postgraduate and above), parity, mode of delivery (antepartum, cesarean), the presence of multiple pregnancies, assisted reproduction, a history of allergic diseases, gestational hypertension, pregnancy-induced hypertension syndrome (PIH), anemia, and antibiotic usage during pregnancy. Child-related covariates encompassed birth weight (kg) and gender. Meteorological factors included temperature and humidity during the pre-pregnancy period and all periods of pregnancy.

Statistical methods

Descriptive statistics were used to describe the demographic and exposure data. Continuous variables were presented as means ± standard deviation (SD), and categorical variables as frequencies. We calculated odds ratios (ORs) and adjusted odds ratios (AORs) to

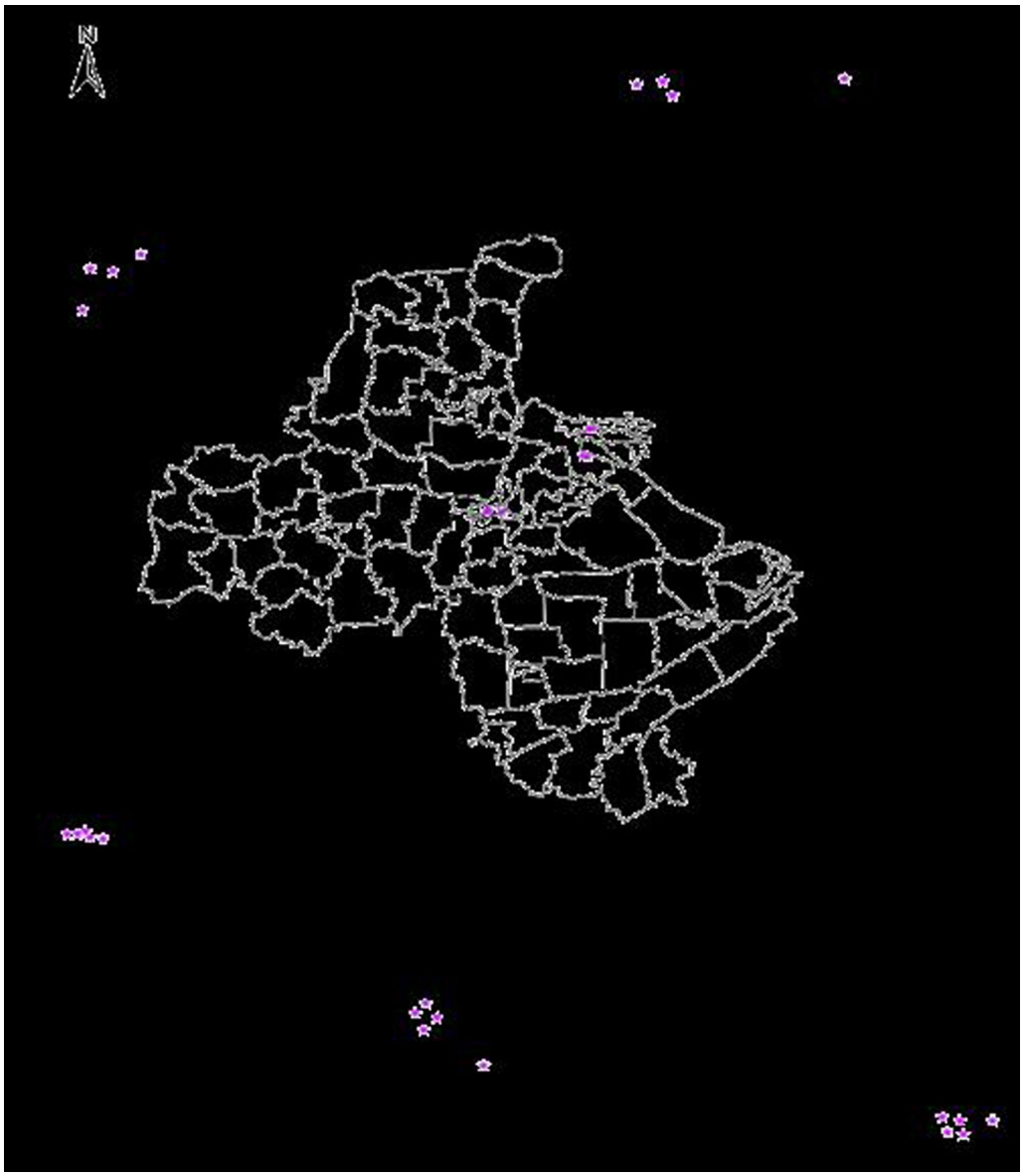

Fig. 2 These purple asterisks are the geographical locations of the air pollution detection sites. The sites covered Lianyungang and surrounding areas and could objectively respond to the atmospheric environmental conditions where the study subjects resided

examine the association between air pollution exposure and asthma incidence in children, adjusting for potential confounders such as maternal and child baseline characteristics. Univariate and multivariate regression analysis was used to investigate the relationship between air pollutant levels and asthma incidence in children. The influence of continuous variables temperature and relative humidity was removed, and the false discovery rate (FDR) correction method was used to correct the P-value. All analyses were performed using R software. $P < 0.05$ was considered statistically significant.

Results

Characteristics of the mother-newborn pairs

Baseline data were analyzed for all 1715 eligible mother-infant pairs from the natural birth and obligate asthma cohorts. A detailed description of the maternal baseline information of the included participants is presented in Table 1.

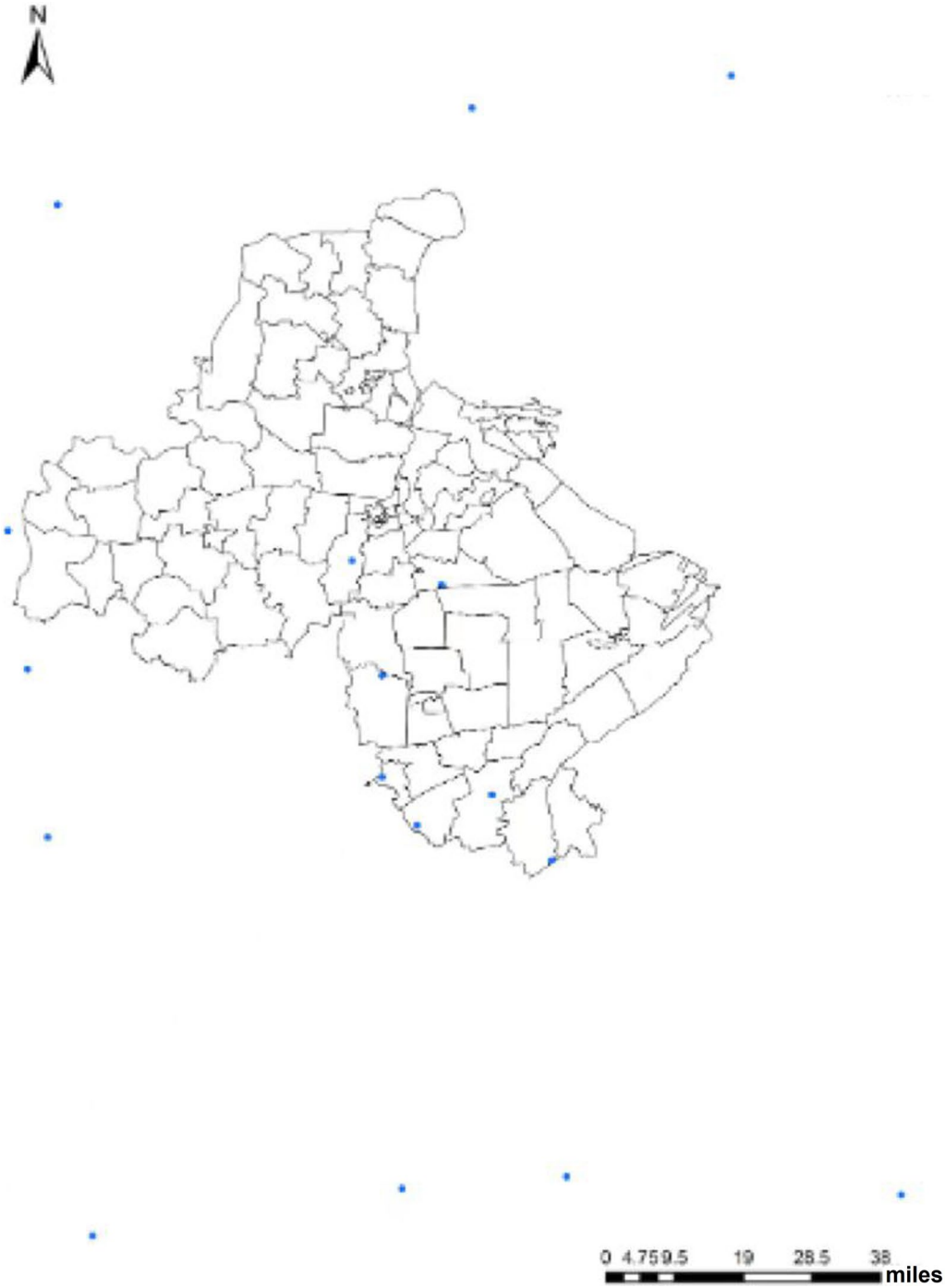

Fig. 3 Meteorological monitoring site distribution map

Distribution of air pollution exposure during the pre-pregnancy period and all periods of pregnancy in the study population

The exposure of all study subjects to multiple air pollutants was shown in Table 2, including $PM_{2.5}$, PM_{10}, CO, NO_2, SO_2, and O_3.

The mean $PM_{2.5}$ exposure concentrations in the 90 days before pregnancy, first trimester, second trimester, and third trimester were 55.4 ± 4 μg/m^3, 51.10 μg/m^3, 48.35 μg/m^3, 50.46 μg/m^3, the average exposure concentration of $PM_{2.5}$ throughout pregnancy was 49. 99 μg/m^3. All exceeded the $PM_{2.5}$ guideline values established

Table 1 Description of population baseline information (n = 1715)

Population characteristics	Total population Arithmetic mean ± standard deviation/number of patients (%)
Reproductive age (years)	28.88 ± 4.67
Maternal height (cm)	162.36 ± 4.75
Birth weight (kg)	3.49 ± 0.59
Pre-pregnancy weight(kg)	57.46 ± 8.47
Gravidarum	1.77 ± 1.05
Child gender	
Male	956 (55.7)
Female	726 (42.3)
Missing value	33 (1.9)
Educational level	
Primary school	8 (0.5)
Middle school	875 (51.0)
University	804 (46.9)
Postgraduate studentsabove	18 (1.0)
Missing value	10 (0.6)
Yield	
Primiparous	1008 (58.8)
Prolificacy	705 (41.1)
Missing value	2 (0.1)
Multiple gestations	
Yes	46 (2.7)
No	1667 (97.2)
Missing value	2 (0.1)
Assisted reproduction	
Yes	44 (2.6)
No	1669 (97.3)
Missing value	2 (0.1)
Mode of delivery	
Spontaneous delivery	787 (45.9)
Cesarean section	924 (53.9)
Missing value	4 (0.2)
Allergic diseases	
Yes	236 (13.8)
No	1479 (86.2)
Gestational hypertension	
Yes	133 (7.8)
No	1581 (92.2)
Missing value	1 (0.1)
Gestational diabetes mellitus	
Yes	190 (11.1)
No	1525 (88.9)
Anemia of pregnancy	
Yes	302 (17.6)
No	1397 (81.5)
Missing value	16 (0.9)
Antibiotic use in pregnancy	
Yes	76 (4.4)
No	1639 (95.6)

by the WHO (24-h average concentrations not exceeding 15 μg/m^3). The average PM_{10} exposure concentrations were 95.14 μg/m^3, 89.94 μg/m^3, 84.82 μg/m^3, 84.98 μg/m^3, and the average exposure concentration of PM_{10} throughout pregnancy was 85.92 μg/m^3. All exceeded the PM_{10} guideline values set by the WHO (24-h average concentrations not exceeding 45 μg/m^3). The mean CO exposure concentrations were 0.98 μg/m^3, 0.94 μg/m^3, 0.90 μg/m^3, 0.91 μg/m^3, and the average exposure concentration of CO throughout pregnancy was 0.91 μg/m^3. None exceeded the co-guideline values set by the WHO (24 h average concentrations not exceeding 4 μg/m^3). The average NO_2 exposure concentrations were 33.27 μg/m^3, 31.28 μg/m^3, 30.95 μg/m^3, and 32.21 μg/m^3, and the average exposure concentration of NO_2 throughout pregnancy was 31.26 μg/m^3. All exceeded the WHO-established guideline values for NO_2 (24-h average concentrations not exceeding 25 μg/m^3). The mean SO_2 exposure concentrations were 24.2 ± 7 μg/m^3, 22.27 μg/m^3, 20.25 μg/m^3, and 20.76 μg/m^3, and the mean SO_2 exposure throughout pregnancy was 20. 94 μg/m^3. None exceeded the SO_2 guideline values set by the WHO (24-h mean concentrations not exceeding 40 μg/m^3). The average concentrations of O_3 exposure were 103.2 ± 1 μg/m^3, 108.98 μg/m^3, 110.41 μg/m^3, and 104.04 μg/m^3, and the average exposure concentration of O_3 throughout pregnancy was 106.92 μg/m^3. All exceeded the guideline value for O_3 set by the WHO (daily maximum 8-h average concentration not exceeding 100 μg/m^3).

Distribution of exposure to meteorological factors during the pre-pregnancy period and all periods of pregnancy in the study population

The mean values of exposure temperature in the study population were 13.63 °C, 15.19 °C, 16.46 °C, 15.11 °C during the 90 days before pregnancy, first trimester, second trimester, and third trimester, respectively, and 15.46 ℃ during the whole pregnancy. The mean values of relative humidity exposure in the study population were 71.24%, 73.15%, 73.79%, and 72.84% during the 90 days before pregnancy, first, second and third trimesters, and 72.70% during the whole pregnancy.

Table 2 Distribution of exposure to air pollution during the pre-pregnancy period and all periods of pregnancy

Period	Mean	Standard deviation	Quantiles					Range
			2.5	25	50	75	97.5	
$PM_{2.5}$ (μg/m^3)								
90 days before pregnancy	55.44	19.19	27.94	39.94	53.48	70.92	91.21	86.67
First trimester	51.10	17.51	25.78	37.39	48.60	62.88	87.69	87.80
Second trimester	48.35	16.24	26.40	35.73	44.69	58.33	85.43	86.59
Third trimester	50.46	17.65	26.56	34.74	47.36	64.31	86.64	81.48
Whole gestation	49.99	7.16	38.89	44.39	49.32	54.32	64.79	44.29
PM_{10} (μg/m^3)								
90 days before pregnancy	95.14	27.78	49.62	72.61	93.9	118.22	145.87	132.84
First trimester	89.94	27.00	46.73	66.61	90.16	109.87	139.32	205.45
Second trimester	84.82	24.19	48.28	65.73	83.45	99.76	137.01	135.58
Third trimester	84.98	25.57	46.07	62.40	85.73	102.31	135.22	127.02
Whole gestation	85.92	12.29	66.53	77.42	84.1	92.74	112.33	84.82
CO (mg/m^3)								
90 days before pregnancy	0.98	0.27	0.59	0.75	0.93	1.18	1.51	1.35
First trimester	0.94	0.24	0.60	0.75	0.89	1.10	1.44	1.81
Second trimester	0.90	0.23	0.58	0.73	0.83	1.05	1.43	1.41
Third trimester	0.91	0.25	0.57	0.72	0.85	1.09	1.42	1.30
Whole gestation	0.91	0.12	0.69	0.83	0.89	0.98	1.17	0.83
NO_2 (μg/m^3)								
90 days before pregnancy	33.27	9.95	17.44	24.60	33.09	41.15	53.18	49.85
First trimester	31.28	9.25	16.66	23.16	30.92	39.29	47.61	54.06
Second trimester	30.95	9.75	16.68	22.11	30.07	39.36	48.73	43.73
Third trimester	32.21	9.56	16.69	23.67	32.09	40.43	48.91	44.45
Whole gestation	31.26	3.84	25.15	28.20	30.89	34.27	38.39	22.58
SO_2 (μg/m^3)								
90 days before pregnancy	24.27	11.52	8.50	15.22	21.58	31.42	48.56	55.45
First trimester	22.27	10.60	6.91	14.36	19.80	28.68	47.93	57.61
Second trimester	20.25	9.27	7.46	13.65	17.88	24.72	44.17	54.99
Third trimester	20.76	9.94	7.74	13.36	18.40	25.45	45.48	51.94
Whole gestation	20.94	5.90	10.66	16.71	20.51	24.53	33.04	28.08
O_3 (μg/m^3)								
90 days before pregnancy	103.21	25.58	61.69	78.77	106.82	125.67	143.12	130.14
First trimester	108.98	23.94	64.41	88.77	114.26	128.42	144.31	150.23
Second trimester	110.41	24.06	64.55	90.64	116.66	129.13	145.97	175.62
Third trimester	104.04	22.99	63.33	83.70	107.07	122.57	141.05	111.41
Whole gestation	106.92	8.69	89.73	100.53	106.38	114.49	121.64	50.19

PM particulate matter, *CO* carbon monoxide, NO_2 nitrogen dioxide, SO_2 sulfur dioxide, O_3 ozone

Univariate analysis of air pollutant exposure and childhood asthma incidence

The results of univariate analysis, corrected by false discovery rate (FDR), showed that second trimester (OR: 1.02, 95%CI 1.01–1.03, $P<0.01$) and whole gestation (OR: 1.05, 95%CI 1.03–1.07, $P<0.01$) exposure to $PM_{2.5}$ was associated with higher odds of childhood asthma onset. The association between PM_{10} exposure during the 90 days before pregnancy and the onset of childhood asthma was unclear (OR: 0.99, 95%CI 0.99–1.00, $P=0.010$), but the second trimester exposure (OR: 1.01, 95%CI 1.00–1.01, $P=0.012$) and whole gestation exposure (OR: 1.02, 95%CI: 1.01–1.03, $P=0.010$) were associated with higher odds of childhood asthma. The second trimester exposure (OR: 2.25, 95%CI 1.31–3.86, $P=0.010$) was associated with higher odds of childhood onset asthma. The second trimester exposure was associated with higher odds of childhood asthma (OR: 1.02,

95%CI 1.01–1.03, $P=0.010$). The third trimester exposure to O_3 was associated with higher odds of childhood asthma (OR: 1.01, 95% CI 1.00–1.01, $P=0.033$). Specific results are shown in Table 3.

Multivariate analysis of air pollutant exposure and childhood asthma incidence

Multivariate logistic regression analysis showed that the second trimester (AOR: 1.04, 95% CI 1.01–1.06, $P=0.010$), and whole gestation (AOR: 1.06, 95% CI 1.03–1.10, $P<0.01$) exposure to $PM_{2.5}$ were associated with higher odds of childhood onset asthma. The third trimester (AOR: 1.02, 95%CI 1.01–1.03, $P=0.010$) and whole gestation (AOR: 1.02, 95%CI 1.01–1.04, $P=0.010$) exposure to PM_{10} were associated with higher odds of childhood asthma. The first trimester exposure to NO_2 was associated with higher odds of childhood asthma (AOR: 1.06, 95%CI 1.02–1.09, $P=0.010$). Whole gestation exposure to SO_2 was associated with higher odds of childhood onset asthma (AOR: 1.04, 95% CI 1.01–1.07, $P=0.033$). Specific results are shown in Table 4.

Discussion

In this study, we investigated the relationship between prenatal exposure to air pollutants and the risk of childhood asthma, utilizing a prospective cohort of pregnant women and their offspring. Our findings demonstrated that exposure to PM2.5 during the second trimester and

Table 3 Univariate analysis of associations between air pollutant exposures and childhood asthma in the pre-pregnancy period and all periods of pregnancy

Atmospheric pollutant	Period	OR(95%CI)	P-value	P-value FDR-corrected
$PM_{2.5}$	90 days before pregnancy	0.99 (0.99,1.00)	0.070	0.132
	First trimester	1.01 (1.00,1.01)	0.078	0.143
	Second trimester	1.02 (1.01,1.03)	< 0.01	< 0.01
	Third trimester	1.00 (0.99,1.01)	0.679	0.762
	Whole gestation	1.05 (1.03,1.07)	< 0.01	< 0.01
PM_{10}	90 days before pregnancy	0.99 (0.99,1.00)	< 0.01	0.010
	First trimester	1.00 (1.00,1.01)	0.845	0.842
	Second trimester	1.01 (1.00,1.01)	< 0.01	0.012
	Third trimester	1.00 (1.00,1.01)	0.092	0.154
	Whole gestation	1.02 (1.01,1.03)	< 0.01	0.010
CO	90 days before pregnancy	0.46 (0.28,0.76)	0.003	0.010
	First trimester	1.27 (0.74,2.18)	0.385	0.494
	Second trimester	2.25 (1.31,3.86)	< 0.01	0.010
	Third trimester	0.89 (0.52,1.52)	0.680	0.763
	Whole gestation	3.62 (1.16,11.30)	0.027	0.062
NO_2	90 days before pregnancy	0.98 (0.97,1.00)	0.023	0.064
	First trimester	1.02 (1.00,1.03)	0.036	0.081
	Second trimester	1.01 (1.00,1.02)	0.158	0.242
	Third trimester	0.99 (0.98,1.01)	0.276	0.381
	Whole gestation	1.03 (1.00,1.07)	0.062	0.123
SO_2	90 days before pregnancy	0.98 (0.97,0.99)	< 0.01	0.010
	First trimester	1.00 (0.99,1.01)	0.735	0.762
	Second trimester	1.02 (1.01,1.03)	0.004	0.010
	Third trimester	1.00 (0.98,1.01)	0.709	0.762
	Whole gestation	1.02 (0.99,1.04)	0.153	0.242
O_3	90 days before pregnancy	1.00 (1.00,1.01)	0.189	0.271
	First trimester	1.00 (0.99,1.00)	0.394	0.492
	Second trimester	0.99(0.99,1.00)	0.017	0.052
	Third trimester	1.01 (1.00,1.01)	0.010	0.033
	Whole gestation	1.00 (0.98,1.01)	0.604	0.731

PM particulate matter, *CO* carbon monoxide, NO_2 nitrogen dioxide, SO_2 sulfur dioxide, O_3 ozone, *OR* odds ratios, *CI* confidence intervals, *FDR* false discovery rate

Table 4 Multivariate analysis of associations between air pollutant exposures and childhood asthma in the pre-pregnancy period and all periods of pregnancy[a]

Atmospheric pollutant	Period	AOR (95CI%)	P-value	P-value FDR-corrected
$PM_{2.5}$	90 days before pregnancy	1.01 (0.99, 1.03)	0.331	0.412
	First trimester	1.03 (1.01, 1.05)	0.010	0.051
	Second trimester	1.04 (1.01, 1.06)	< 0.01	0.010
	Third trimester	1.02 (1.00, 1.04)	0.062	0.134
	Whole gestation	1.06 (1.03, 1.10)	< 0.01	< 0.01
PM_{10}	90 days before pregnancy	0.99 (0.98, 1.00)	0.072	0.141
	First trimester	1.00 (0.99, 1.01)	0.423	0.491
	Second trimester	1.00 (0.99, 1.01)	0.702	0.754
	Third trimester	1.02 (1.01, 1.03)	< 0.01	0.010
	Whole gestation	1.02 (1.01, 1.04)	< 0.01	0.010
CO	90 days before pregnancy	0.52 (0.18, 1.49)	0.232	0.320
	First trimester	1.93 (0.60, 6.13)	0.271	0.353
	Second trimester	2.68 (0.84, 8.53)	0.102	0.171
	Third trimester	1.67 (0.54, 5.11)	0.372	0.441
	Whole gestation	5.98 (1.31, 27.37)	0.022	0.058
NO_2	90 days before pregnancy	1.00 (0.97, 1.03)	0.941	0.941
	First trimester	1.06 (1.02, 1.09)	< 0.01	0.010
	Second trimester	0.95 (0.92, 0.98)	< 0.01	0.022
	Third trimester	0.98 (0.95, 1.01)	0.203	0.321
	Whole gestation	0.97 (0.91, 1.02)	0.251	0.352
SO_2	90 days before pregnancy	0.98 (0.96, 1.00)	0.031	0.062
	First trimester	1.00 (0.98, 1.02)	0.921	0.943
	Second trimester	1.02 (1.00, 1.04)	0.112	0.191
	Third trimester	1.01 (0.98, 1.03)	0.601	0.671
	Whole gestation	1.04 (1.01, 1.07)	0.010	0.033
O_3	90 days before pregnancy	0.99 (0.98, 1.00)	0.021	0.050
	First trimester	0.99 (0.98, 1.00)	0.052	0.113
	Second trimester	0.99 (0.98, 1.00)	0.021	0.062
	Third trimester	1.01 (1.00, 1.02)	0.223	0.321
	Whole gestation	1.03 (1.00, 1.05)	0.051	0.113

PM particulate matter, *CO* carbon monoxide, *NO_2* nitrogen dioxide, *SO_2* sulfur dioxide, *O_3* ozone, *AOR* adjusted odds ratio, *CI* confidence intervals, FDR false discovery rate

[a] Models were adjusted for reproductive age, birthweight, child sex, maternal education, parity, mode of delivery, allergic diseases during pregnancy, gestational hypertension, gestational diabetes mellitus, anaemia during pregnancy, antibiotic use, temperature and relative humidity

throughout pregnancy, PM_{10} exposure during the third trimester and throughout pregnancy, NO_2 exposure during the first and second trimesters, and SO_2 exposure during the entire pregnancy were associated with an increased risk of childhood asthma. These results highlight the importance of specific pollutants and critical windows of exposure in influencing the development of childhood asthma. Our study contributes to the growing body of evidence suggesting that air pollution during pregnancy can have lasting effects on child health, particularly respiratory health. We observed that different pollutants affect childhood asthma risk at different stages of pregnancy, emphasizing that prenatal exposure to air pollution may disrupt lung development in the fetus. Notably, we found that exposure to $PM_{2.5}$ during the second trimester and the entire pregnancy was strongly associated with higher odds of asthma in children, suggesting that this period may be particularly sensitive to air pollution.

While the exact mechanisms behind these associations remain unclear, previous studies have suggested that exposure to air pollution during pregnancy may induce oxidative stress and inflammatory responses that impair lung development, leading to increased susceptibility to

respiratory diseases such as asthma [26, 27]. Additionally, alterations in immune system function, such as changes in T cell responses and gene methylation, have been proposed as potential pathways by which air pollution may affect fetal development [28, 29]. In our study, the association between different pollutants and childhood asthma was more pronounced during certain periods of pregnancy, supporting the hypothesis that fetal vulnerability to air pollution may vary depending on the stage of immune and lung system development.

In terms of gaseous pollutants, we found that exposure to SO_2 throughout pregnancy was associated with an increased risk of childhood asthma. This aligns with previous studies that have shown prenatal SO_2 exposure to be linked with respiratory symptoms and wheezing in children [30]. The timing of exposure also seems to matter, with late pregnancy emerging as a sensitive window for SO_2-related effects on asthma risk. While we did not find statistically significant associations with other gaseous pollutants such as NO_2 and O_3, the literature suggests that these pollutants may still play a role in respiratory health, although their effects may be more context-dependent [31].

Study strengths and limitations

The project group established a high-standard prospective birth cohort in family-based units. From the cohort recruitment to the on-site follow-up, the project team had a complete and fully implemented quality control program. Furthermore, the sample size of this study was rich. This study enrolled six pollutants, including $PM_{2.5}$, PM_{10}, CO, NO_2, SO_2, and O_3, covering the most common pollutants in the air, and the data from the studies were more comprehensive, diverse and generalize, guaranteeing the scientific validity of the findings.

In this study, we acknowledged several limitations. First, due to the availability of monitoring data, we focused on six key outdoor air pollutants and did not include other potentially relevant pollutants in our analysis. This limitation affected our ability to fully assess the complex interactions between pollutants. Additionally, information on maternal smoking and passive smoking was incomplete, which may have introduced bias, as exposure to tobacco smoke is known to impact infant respiratory health. However, it is worth noting that the study was conducted in a region where smoking during pregnancy is infrequent, which may have minimized this potential bias to some extent. Furthermore, we were unable to incorporate more complex modeling approaches such as single-pollutant and multi-pollutant models, or to include detailed covariates between pollutants. This limitation raised from the current dataset and study design, which primarily focused on evaluating the individual impact of specific air pollutants on childhood asthma. As a result, the combined effects of multiple pollutants and their interactions with other environmental or socioeconomic factors were not explored in this analysis. Moreover, it was not feasible at this stage to include potential confounders, such as maternal age, socioeconomic status, and other environmental exposures, in the logistic regression models. Future studies with more comprehensive data will be better positioned to examine these complex relationships and provide deeper insights into how various factors may interact to influence childhood asthma outcomes.

Study implications

Our findings underscored the importance of addressing air pollution as a public health issue, particularly for pregnant women and young children. Exposure to pollutants such as $PM_{2.5,}$ PM_{10}, NO_2, and SO_2 during pregnancy can increase the risk of childhood asthma, which has significant implications for both individual and public health. These results contributed to the growing body of evidence on the detrimental effects of environmental pollution and highlighted the need for stronger regulations to reduce air pollution exposure, especially in areas with high levels of traffic and industrial emissions. Further research is needed to better understand the underlying biological mechanisms of air pollution-induced asthma, particularly in relation to gene-environment interactions and the timing of exposure.

Conclusions

In conclusion, this study provides evidence that exposure to air pollutants, particularly $PM_{2.5}$, PM_{10}, NO_2, and SO_2, during pregnancy is associated with an increased risk of childhood asthma. These findings underscore the need for targeted interventions to reduce air pollution exposure during pregnancy and protect fetal lung development. Further research is required to explore the epigenetic mechanisms behind these associations and to identify critical windows of vulnerability during pregnancy. Ultimately, this research aims to inform public health policies aimed at reducing the incidence of childhood asthma and improving overall maternal and child health outcomes.

Abbreviations

IDW	Inverse distance weighting
GBD	Global burden of disease
$PM_{2.5}$	Delicate particulate matter
FEV1	Forced expiratory volume in one second
PEF	Peak expiratory flow
PIH	Pregnancy-induced hypertension syndrome
SD	Standard deviation
IQR	Interquartile range
CI	Confidence interval
FDR	False discovery rate

WHO	World Health Organization
DN	Double negative
DP	Double positive
SP	Single positive
cTECs	Cortical thymic epithelial cells
mTECs	Medullary thymic epithelial cells
DCs	Dendritic cells
pDCs	Plasmacytoid dendritic cells
MDCs	Myeloid-derived suppressor cells
QC	Quality control

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Author contributions
L.B. and Y.Y. wrote the main manuscript text, Y.Z. and Y.L. prepared Figs. 1–3, and Y. W. Q.Q. and W.L. prepared tables 1–4. All authors reviewed the manuscript.

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Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Our study followed The Code of Ethics of the World Medical Association (Declaration of Helsinki) and was approved by the Ethics Committee of Lianyungang Maternal and Child Health Hospital. Informed consent was obtained from every patient. For the infants, informed consent was also obtained from a parent and/or legal guardian.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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