The association between ambient air pollution and birth defects in five major ethnic groups in Liuzhou, China

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Research article

Keywords: Ambient air pollution, Birth defects, Ethnic groups, Liuzhou

Posted Date: September 8th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-62955/v1

Abstract

Background: Studies suggest that exposure to ambient air pollution during pregnancy may be associated with increased risks of birth defects (BDs), but conclusions have been inconsistent. This study describes the ethnic distribution of major BDs and examines the relationship between air pollution and BDs among different ethnic groups in Liuzhou city, China.

Methods: Surveillance data of infants born in 114 registered hospitals in Liuzhou in 2019 were analyzed to determine the epidemiology of BDs across five major ethnic groups. Concentrations of six air pollutants ($PM_{2.5}$, PM_{10}, SO_2, CO, NO_2, O_3) were obtained from the Liuzhou Environmental Protection Bureau. Logistic regression was used to examine the associations between ambient air exposure and risk of BDs.

Results: Among 32,549 infants, 635 infants had BDs, yielding a prevalence of 19.5 per 1000 perinatal infants. Dong ethnic group had the highest prevalence of BDs (2.59%), followed by Yao (2.57%), Miao (2.35%), Zhuang (2.07%), Han (1.75%). Relative to the Han ethnic group, Zhuang, Miao, Yao and Dong groups had lower risks of congenital heart disease, polydactyly, and hypospadias. The Zhuang ethnic group had higher risks of severe thalassemia, cleft lip and/or palate, and syndactyls. Our analysis of the correlation between air pollution and BDs showed that BDs were positively correlated with air pollutants PM_{10} (aORs =1.14; 95% CI:1.12-2.43 for per 10ug/mg^3 increment) and CO (aORs =1.36; 95% CI:1.14-2.48 for every 1mg /m^3 increment) in second month of pregnancy, and were associated with PM_{10} (aORs =1.51; 95% CI:1.13-2.03) and CO (aORs =1.75; 95%CI:1.02-3.61) in the third month of pregnancy. SO_2 also had a significant association with BDs in the second month of the pregnancy (aORs =1.31; 95% CI:1.20-3.22) and third month of pregnancy (aORs =1.75; 95% CI:1.02-3.61). However, no significant association was found between birth defects and O_3, $PM_{2.5}$ and NO_2 ($P > 0.05$).

Conclusion: This study provided a comprehensive description of ethnic differences in BDs in Southwest China, and broadens the evidence of association between air pollution exposure during gestation and BDs.

Background

Birth defects (BDs) are functional, structural, or metabolic abnormalities that occur before birth, usually as a result of chromosomal abnormalities, congenital malformations, genetic and metabolic disorders, and functional abnormalities [1]. They are an important cause of abortion, stillbirth, and death of pregnant mothers, as well as the leading cause of infant and child death in the first year of life [2, 3]. The most common major structural BDs include congenital heart disease, neural tube defects, lip cleft, limb reduction defect, and Down syndrome [4]. Studies have shown that BDs account for approximately 2.3–3% of total live births [5].

China is the most populous country in the world, with one of the highest incidence of documented BDs. In China, the estimated prevalence of BDs is approximately 4–6% [1]. In recent years, with the rapid development of urbanization and the rise of industrial modernization, air pollution has become an increasingly serious threat to human health. Numerous studies have shown that ambient air pollutants have a direct negative impact on the birth outcomes of pregnant women [6, 7]. Exposure to ambient air pollutants during pregnancy can lead to preterm delivery, fetal growth restriction, and adverse pregnancy outcomes such as BDs [8, 9].

However, studies on the relationship between ambient air pollution and BDs are inconsistent. The pregnancy period most susceptible to BDs as a result of ambient air pollution is unclear. A study in the United States showed that exposure to NO_2 in early pregnancy increases the risk of congenital abnormalities in newborns [10]. Additional studies have shown that exposure to a certain concentration of NO_2 before or during the first trimester increases the incidence of birth defects [11]. Wang et al. conducted a time series study on the impact of air pollution on birth defects in Xi'an city, in which atmospheric pollutants SO_2, NO_2 and PM_{10} were shown to have an impact on BDs [12]. Differences in study results may be due to differences in region, race, study design, covariate control, exposure assessment, statistical methods, and sample size. Additionally, the majority of the literature regarding air pollution and BDs have been published in western developed countries such as Europe and the United States. These countries have better air quality, lower air pollution concentrations, and fewer exposed people in comparison to China, possibly contributing to weak or negative conclusions. Compared with study evidence globally, China has less evidence on such topic, and most research on air pollution is mainly concentrated in economically developed areas in eastern China, such as Beijing, Tianjin, Hebei [13, 14], Yangtze River Delta [15, 16] and the Pearl River Delta [17]. There are few studies on the western region of China. The information reflecting ethnic minority areas in this region is sparse. We also calculated the mean daily gestational concentrations of environmental pollutants during 3 months before pregnancy and the first trimester of pregnancy, as this is the critical period of pregnancy associated with BDs. Most studies have focused on the exposure window in the first trimester or the entire pregnancy. However, few studies have been conducted to investigate the relationship between birth defects and air pollution before pregnancy.

Guangxi is located in southwestern China and is the main gathering place for ethnic minorities in China. Ethnic minorities account for 37.2% of the population of Guangxi Province [18]. Liuzhou is an industrial town in Guangxi with a total area of 34,000 square kilometers. By the end of 2018, the population of Liuzhou City was 4.04 million. The ethnic composition of Liuzhou residents has reached more than 30 ethnic groups. Among the permanent residents of Liuzhou, the Han ethnic group has the largest population (48.9%), followed by the Zhuang (35.2%), Miao (6.4%), Dong (6.3%), Yao (1.9%), and Molao (0.8%) [18–20]. The Han ethnicity is the largest population in China, accounting for approximately 91.5%, and the second largest ethnicity is Zhuang, accounting for approximately 1.3% [18]. Most of the ethnic minority populations live in areas with remote geographical location and economic stagnation. Due to factors including national culture and customs, economic development in Liuzhou has lagged behind other regions, compounded by the fact that ethnic minorities make up the majority of impoverished people in China. In addition, Liuzhou is an important industrial town in Guangxi. The problem of air pollution is becoming increasingly serious, with the regional natural ecological environment extremely fragile. The incidence of diseases, maternal mortality, and low birth weight among minority ethnic groups in China are also high, making this population worthy of attention [21, 22]. Using the air pollution monitoring network and the BDs monitoring system, we investigated all infants born in ethnic minority areas of Liuzhou between January 2019 and December 2019 to study whether air pollution was associated with an increased risk of BDs. Furthermore, we explored the critical period of pregnancy during which air pollution has greatest impact on BDs. This study reveals the incidence of BDs in ethnic minority areas, explores possible environmental teratogenicity risk factors, and provides a reference for the prevention of birth defects in minority areas.

Methods

Research objects and data resources

Research data were extracted from the birth defect monitoring sub-module in the Liuzhou Maternal and Child Health Information Management System between January 2019 and December, 2019. This includes records from perinatal babies, including live birth, stillbirth and infant death within 7 days, reported by 114 midwifery agencies in Liuzhou for a total of 32,549 births. The data excluded twin and multiple births. Among this cohort, there were 635 cases of BDs. All data was derived under the supervision of the health administration.

Additional perinatal and maternal data were derived from the China Maternal and Child Health Monitoring Data Direct Reporting System (https://zhibao3.mchscn.org/). Log in the Maternal and Child Health System of Liuzhou City. Using the “Birth Defects Registration Card” and “Quarterly Report on Number of Perinatal Births” from the Maternal and Child Health System of Liuzhou City, relevant data was collected, including maternal status, birth status, birth defect diagnosis and family history. Maternal conditions included ethnicity, age, education, family income, pregnancy, and parity. Infant data included date of birth, sex, gestational age, fetal number, weight, and outcome (including stillbirth, fetal death or live birth between 20 weeks of gestation through 7 days after birth)

Family history included abnormal fertility history and family genetic history. The diagnosis of BDs was based on the “International Statistical Classification of Diseases and Related Health Problems, Tenth Edition” (ICD-10) and Chinese National Criteria of BDs [23].

Quality Controls

In order to ensure the accuracy of the report, each registered hospital was required to complete a quarterly form by a professional physician, in addition to the Birth Defects Registration Card. Each quarterly table contained 3 months of data, including ethnicity, pregnancy, parity, education, family income, date of birth, gestational age, weight, number of births, whether labor was inducted after diagnosis of a birth defect, diagnostic basis, diagnosis of malformation, and birth defect diagnosis. Birth defect registration cards and quarterly tables were reviewed and audited by maternal and child health hospitals and health administrative departments. Regular quality control measures were monitored in respective hospitals, quarterly at the county level and every two years at the municipal or provincial level. The quality requirements for BDs monitoring data included: the completion rate of form is 100%, the error rate for form items less than 1%, input error rate less than 1%, and the rate of missed birth defects less than 1%.

Exposure Assessment

The meteorological data used in this study came from the weather information data collected by the Liuzhou Environmental Protection Bureau, including six state-controlled air automatic monitoring points in Liuzhou (HX Waterworks, Liuzhou Fourth Middle School, GTS, Environmental Monitoring Station, Liudong Primary School, Liuzhou Ninth Middle School), two district control stations (Liuzhou Second middle school, LW), and six city and county control stations (LJ District Experimental High School, LC County Middle School, LZ County Youth Activity Center, RA County Quality Supervision Bureau, RS County Health School, the SJ County Guyi Town Center) (Fig. 1). Routine monitoring items included particulate matter less than 2.5um in aerodynamic diameter ($PM_{2.5}$), particulate matter less than 10um in aerodynamic diameter (PM_{10}), sulfur dioxide (SO_2), Carbon monoxide (CO), Nitrogen dioxide (NO_2), and ozone (O_3). O_3 was calculated as a maximum daily average of 8 h. The daily concentration values of other pollutants were calculated based on the average of 24 h measured at 14 monitoring points.

The assessment was performed according to the national standard "Ambient Air Quality Standard" (GB 3095 – 2012). The average annual secondary concentration limits of $PM_{2.5}$, PM_{10}, SO_2 and NO_2 are $35ug/m^3$, $70ug/m^3$, $60ug/m^3$ and $40ug/m^3$ respectively. The average 24-hour secondary concentration limits of $PM_{2.5}$, PM_{10}, SO_2, CO, NO_2 are 75 $\mu g/m^3$, $150ug/m^3$, $150ug/m^3$, 4 mg/m^3, 80 $\mu g/m^3$, respectively.

We calculated the average monthly environmental exposure concentrations of pregnant women who gave birth between January 2019 and December 2019. We also calculated the mean daily gestational concentrations of environmental pollutants during 3 months before pregnancy and the first trimester of pregnancy, as this is the critical period of pregnancy associated with BDs [24]. Three months prior to pregnancy and the first trimester of pregnancy are a notable risk period for BDs due to multiple factors. Women of childbearing age develop a new batch of follicles every month, and it takes approximately 85 days to develop from pre-sinus follicles to mature follicles, ready for fertilization. This time spans three menstrual cycles; therefore, the three months before pregnancy the egg has begun its development and is already susceptible to environmental factors [25]. Additionally, the third to eighth week of embryo development is the most sensitive period of embryo development, during which embryonic cells are highly differentiated and susceptible to many teratogenic factors. Considering that the 3 months before pregnancy to the first trimester of pregnancy represent the egg development process, the development stage of the embryo, and the most sensitive development stage of the fetus, it is likely impacted by air pollution.

Declarations

This study was approved by the Institutional Review Board of Liuzhou Maternal and Child Health Hospital.

Covariates

Potential covariates considered from the birth defects registration cards included maternal age (< 20years, 20–24years, 25-29years, 30-34years, ≥ 35 years), family income (< 2000RMB, 2000–3999 RMB, 4000–7999 RMB, ≥ 8000 RMB), highest education levels (classified as primary school or below, middle school, high school/technical school, college or above), birth weights (< 1500 g, 1500 g-2499 g, 2500 g-3499 g, ≥ 3500 g), number of pregnancies (1, 2, and ≥ 3), total previous live births (0, 1, and ≥ 2), and gender of infant (male, female).

Statistical methods

A x^2 test was performed to examine the differences in social demographics between infants with BDs and infants without BDs. Prevalence rates of overall BDs and different types of BDs were also examined. Logistic regression was used to analyze the effects of air pollution exposure on BDs. BDs were the dependent variable, and the individual exposure concentration of air pollutants during pregnancy was the independent variable. Important covariables were controlled, in order to explore the influence of exposure concentration and exposure time on BDs. To assess the role of exposure at different stages of pregnancy, we constructed exposure variables for the 3 months before pregnancy and the first trimester of pregnancy. We not only studied the impact of a single pollutant on BDs, but also discussed the combined effects of multiple air pollutant models. Corresponding odds ratio (OR) and 95% confidence interval (95% CI) were calculated for birth defects and air pollutant exposure at different stages of pregnancy. Statistical test significance level is 0.05 (two-tailed). Data processing and statistical analysis were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA) statistical software package.

Results

Distribution of selected characteristics of the study population

Table 1 shows the characteristics of the study population. Of the 32,549 perinatal infants included in analysis, 635 had BDs, for a prevalence of 19.50 per 1000 infants. There were statistically significant differences between infants with and without BDs in terms of maternal age, maternal education, birth weight, infant gender, total previous live births, and residence ($p < 0.01$). There were no statistically significant differences between infants with, and without, BDs for family income and number of pregnancies ($p > 0.05$).

Table 1 Characteristics of subjects in Liuzhou city, Guangxi Province

Characteristics	Infants with BDs n (%)	Normal infants n (%)	χ^2	P
Maternal age (years)				
<20	19(3.0%)	936(2.9%)	11.10	<0.01
20 ~	73(11.5%)	4271(13.4%)		
25 ~	191(30.1%)	10359(32.5%)		
30 ~	199(31.3%)	10517(33.0%)		
≥35	153(24.1%)	5831(18.3%)		
Family income (RMB per capita)				
<2000	156(24.6%)	7662(23.5%)	2.54	0.16
2000~	107(16.8%)	5087(15.6%)		
4000~	250(39.4%)	13147(40.4%)		
≥8000~	123(19.4%)	6653(20.4%)		
Maternal education				
Primary or below	28(4.4%)	128(0.4%)	9.49	0.00
Middle school	184(29.0%)	11567(35.5%)		
High or technical school	124(19.5%)	10543(32.4%)		
College or above	299(47.1%)	10311(31.7%)		
Birth weight(g)				
<1500g	316(49.8%)	194(0.6%)	2723.66	<0.01
1500g ~	52(8.2%)	1799(5.6%)		
2500g ~	201(31.6%)	22424(70.3%)		
≥3500g	66(10.4%)	7497(23.5%)		
Infant gender				
Male	361(56.8%)	16790(52.6%)	14.50	<0.01
Female	233(36.7%)	15124(47.4%)		
Unknown gender	41(6.5%)	0 (0.0%)		
Number of pregnancies				
1	110(17.3%)	6591(20.7%)	1.30	0.25
2	175(27.6%)	9130(28.6%)		
≥3	350(55.1%)	16193(50.7%)		
Total previous live births				
0	97(15.3%)	21(0.1%)	740.78	<0.01
1	304(47.9%)	12259(38.4%)		
≥2	234(36.8%)	19634(61.5%)		
Residence				
Urban	250(39.4%)	15510(48.6%)	15.50	<0.01
Rural	385(60.6%)	16404(51.4%)		

Description of BDs in the five major ethnic groups

Table 2 shows the rate of BDs among the five major ethnic groups in Liuzhou city. The Dong ethnic group had the highest prevalence of total BDs (2.59%), followed by Yao (2.57%), Miao (2.35%), Zhuang (2.07%), Han (1.75%).

Description of BDs types in the five majors ethnic

Table 2 The prevalence of BDs in the five major ethnic groups in Liuzhou city, China from January 1, 2019 to December 31, 2019

Ethnic	Number of birth defect(n)	Prevalence of Birth defects (%)	Number of perinatal infants(n)
Han	278	1.75	15907
Zhuang	244	2.07	11799
Dong	49	2.59	1890
Miao	45	2.35	1918
Yao	13	2.57	505
Others	6	1.15	530

BD diagnoses in the five major ethnic groups is presented in Table 3. The top five classes of BDs were congenital heart disease, polydactyly, cleft lip and/or cleft palate, severe thalassemia, and malformations of the external ear. The top five birth defect classes comprised over 59% of the 635 birth defects in total. There were 163 cases of congenital heart disease, comprising 25.67% of all birth defects analyzed. Relative to the Han ethnic group, Zhuang, Miao, Yao and Dong groups had a lower risk of congenital heart disease, polydactyly and hypospadias. Zhuang had higher risk of severe thalassemia, cleft lip and/or cleft palate, and syndactyls.

Table 3 Top ten classes of total BDs and ethnic distribution in Liuzhou

Birth defects	Case (n)	Incidence (%)	Han n (%)	Zhuang n (%)	Dong n (%)	Miao n (%)	Yao n (%)
Congenital heart disease	163	25.67	70(11.02)	63(9.92)	14(2.20)	11(1.73)	4(0.63)
Polydactyly	70	11.02	31(4.88)	22(3.46)	5(0.79)	8(1.26)	1(0.16)
Cleft lip and/or cleft palate	67	10.55	19(2.99)	32(5.04)	4(0.94)	5(0.79)	2(0.31)
Severe thalassemia	40	6.30	13(2.05)	19(2.99)	1(0.16)	5(0.79)	1(1.59)
Malformations of external ear	38	5.98	20(3.15)	15(2.36)	2(0.31)	1(0.16)	0
Hypospadias	25	3.94	12(1.89)	8(1.26)	4(0.63)	1(0.16)	0
Syndactyls	24	3.78	8(1.26)	10(1.57)	2(0.31)	4(0.63)	0
The horse hoofs inside	22	3.46	10(1.57)	7(1.10)	3(0.47)	2(0.31)	0
Brain dysplasia	21	3.31	11(1.73)	6(0.94)	1(0.16)	2(0.31)	1(0.16)
Cystic hygroma	20	3.15	10(1.57)	7(1.10)	2(0.31)	1(0.16)	0
Bart's Syndrome	13	2.05	6(0.94)	5(0.70)	1(0.16)	1(0.16)	0
Rest Birth Defects	42	6.61	30(4.72)	10(1.57)	0	1(0.16)	1(0.16)

Average exposure level at different gestational time points

Individual exposure levels at different gestational time points are shown in Table 4. The level of individual exposures (mean ± SD) to $PM_{2.5}$ was highest (43.18 ± 19.46) three months prior to pregnancy. O_3 exposures were highest (83.77 ± 11.69) two months prior to pregnancy, PM_{10} and NO2 exposures were highest (65.90 ± 37.05 and 27.97 ± 16.69) in first month of pregnancy, and SO_2 and CO were highest (24.86 ± 23.00 and 1.18 ± 0.29 respectively) in the third month of pregnancy.

Table 4 Summary statistics for each pollutant during different gestation in Liuzhou, China.

	Mean ± SD	Minimum	Maximum	25^{th} percentile	50^{th} percentile	75^{th}
Before pregnancy						
1st month						
$PM_{2.5}$	41.95±16.03	15.35	89.78	29.45	40.31	53.35
PM_{10}	64.97±31.93	26.49	218.56	44.36	58.36	77.33
O_3	80.91±16.30	17.78	108.78	74.28	83.28	91.22
SO_2	20.74±19.17	4.92	218.87	14.13	19.39	23.35
NO_2	27.01±14.23	10.56	102.32	19.38	22.16	32.35
CO	1.06±0.25	0.63	1.92	0.91	1.14	1.21
2nd month						
$PM_{2.5}$	41.45±15.72	14.98	131.32	28.48	39.75	50.02
PM_{10}	61.66±23.30	25.78	217.46	43.46	57.93	77.11
O_3	83.77±11.69	16.54	109.21	77.25	86.37	92.22
SO_2	18.72±11.19	3.45	217.89	14.13	19.32	22.32
NO_2	25.27±9.86	9.43	101.73	19.28	22.27	30.03
CO	1.02±0.20	0.58	1.87	0.96	1.11	1.21
3rd month						
$PM_{2.5}$	43.18±19.46	4.67	118.45	27.65	40.18	57.34
PM_{10}~	61.50±21.40	31.32	218.46	42.87	58.42	77.36
O_3	82.03±14.00	17.46	108.32	75.43	83.43	92.03
SO_2	18.78±8.44	4.32	218.68	13.94	18.27	22.35
NO_2	24.71±8.00	10.46	102.98	18.75	22.17	30.43
CO	1.03±0.21	0.67	1.96	0.89	1.02	1.23
Pregnancy						
1st month						
$PM_{2.5}$	41.78±16.93	15.67	88.67	29	39.36	53.37
PM_{10}	65.90±37.05	25.67	217.95	43	50.43	56.45
O_3	76.30±21.03	17.79	107.74	68	81.37	91.76
SO_2	22.23±23.34	4.46	217.58	15	19.03	24.36
NO_2	27.97±16.69	9.08	101.67	18	22.17	32.42
CO	1.11±0.28	0.64	1.87	0.9	1.10	1.31
2nd month						
$PM_{2.5}$	39.78±17.25	15.56	89.63	27	35.44	52.38
PM_{10}	63.18±38.45	25.66	217.63	42	49.38	72.17
O_3	72.06±22.83	17.12	108.58	51	78.47	90.04
SO_2	23.20±23.48	4.12	218.57	15	20.11	25.17
NO_2	27.98±17.30	9.09	102.37	18	22.03	32.47
CO	1.14±0.30	0.68	1.92	0.9	1.12	1.33
3rd month						
$PM_{2.5}$	38.25±16.94	6.06	89.89	27	35.48	46.34
PM_{10}	62.88±38.27	25.45	218.47	42	50.43	72.46
O_3	68.30±23.65	17.59	107.74	46	74.47	89.52
SO_2	24.86±23.00	4.67	217.83	16	21.22	28.49
NO_2	27.67±17.37	7.09	101.87	18	22.36	33.27

CO	1.18±0.29	0.69	1.96	1.0	1.22	1.37

Abbreviations: SD, standard deviation.1st month=The first month exposure.2nd month=The second month exposure. 3rd month=The third month exposure.

Crude and adjusted odds ratios for BDs associated with air pollutants during different gestational time points

Table 5 shows the crude and adjusted odd ratios for BDs in relation to air pollutants at different gestational time points, spanning from three months prior to pregnancy through the first trimester of pregnancy. We observed a significant association between BDs and PM_{10} particularly in second (aORs = 1.14; 95% CI:1.12–2.43) and third months of pregnancy (aORs = 1.51; 95%CI:1.13–2.03). SO_2 had also a significant association with BDs for every 10 µg /m^3 increase in concentration during two months prior to pregnancy (aORs = 1.31; 95%CI:1.20–3.22) and the third month of pregnancy (aORs = 1.75; 95%CI:1.02–3.61). CO also had a significant association with BDs for every 1 mg /m^3 increase in concentration in the second (aORs = 1.36; 95%CI:1.14–2.48) and third months of pregnancy (aORs = 1.75; 95%CI:1.02–3.61). However, no significant association was found between birth defects and O_3, $PM_{2.5}$ and NO_2 ($P > 0.05$).

Table 5: Crude and adjusted odd ratios for BDs associated with air pollutants during different gestational periods

		Crude			Adjusted		
		OR	95%CL	P	OR	95%CL	P
$PM_{2.5}$	Before pregnancy						
	1st month	1.02	0.99-1.00	0.34	1.00	1.00-1.01	0.53
	2nd month	0.93	0.89-0.98	0.76	1.05	0.96-1.15	0.27
	3rd month	1.00	0.97-1.26	0.35	0.99	0.94-1.13	0.32
	Pregnancy						
	1st month	1.00	0.99-1.03	0.46	1.07	0.96-1.15	0.26
	2nd month	0.97	0.86-1.01	0.47	1.15	0.99-1.21	0.16
	3rd month	0.83	0.75-0.98	0.91	1.05	0.98-1.16	0.27
PM_{10}	Before pregnancy						
	1st month	1.00	0.99-1.07	0.84	1.01	0.98-1.05	0.78
	2nd month	1.01	1.00-2.03	0.00	1.00	0.99-1.07	0.76
	3rd month	1.31	1.04-3.21	0.00	1.12	1.03-2.01	0.22
	Pregnancy						
	1st month	1.06	1.00-1.20	0.03	1.00	0.94-1.31	0.06
	2nd month	1.73	1.60-2.00	0.01	**1.14**	**1.12-2.43**	**0.02**
	3rd month	1.61	1.44-2.10	0.07	**1.51**	**1.13-2.03**	**0.02**
O_3	Before pregnancy						
	1st month	0.93	0.87-0.99	0.00	0.94	0.89-1.03	0.62
	2nd month	0.96	0.95-0.98	0.00	1.02	0.93-1.12	0.17
	3rd month	0.98	0.97-1.18	0.00	0.96	0.88-1.06	0.45
	Pregnancy						
	1st month	0.89	0.87-0.99	0.02	0.83	0.99-1.00	0.74
	2nd month	0.99	0.96-1.07	0.00	1.00	0.99-1.05	0.84
	3rd month	1.00	0.99-1.12	1.01	1.00	0.99-1.06	0.45
SO_2	Before pregnancy						
	1st month	1.03	1.00-1.21	0.00	1.00	1.00-1.06	0.58
	2nd month	3.01	2.01-4.07	0.00	**1.31**	**1.19-3.22**	**0.04**
	3rd month	1.01	0.99-1.06	0.00	0.94	0.89-1.01	0.27
	Pregnancy						
	1st month	1.00	0.94-1.06	0.01	1.01	1.00-1.06	0.16
	2nd month	0.96	0.87-1.02	0.86	0.98	0.82-1.01	0.36
	3rd month	1.99	1.99-3.98	0.00	**1.75**	**1.02-3.07**	**0.02**
NO_2	Before pregnancy						
	1st month	1.00	0.92-1.01	0.53	1.00	0.89-1.03	0.55
	2nd month	1.02	1.01-1.08	0.00	1.02	1.00-1.42-	0.13

	3rd month	1.03	1.02-1.14	0.00	1.01	1.00-1.32	0.39
	Pregnancy						
	1st month	1.00	0.99-1.21	0.94	1.01	1.00-1.07	0.14
	2nd month	1.27	1.04-1.75	0.40	0.89	0.84-1.01	0.13
	3rd month	1.99	1.39-2.03	0.03	0.91	0.88-1.11	0.72
CO	Before pregnancy						
	1st month ~	2.70	2.03-3.59	0.00	1.29	0.92-1.83	0.14
	2nd month	5.35	3.67-7.80	0.00	1.42	0.93-2.17	0.10
	3rd month	2.11	1.46-3.04	0.00	1.03	0.67-1.59	0.89
	Pregnancy						
	1st month	1.90	1.47-2.47	0.00	1.24	0.90-1.71	0.19
	2nd month	1.26	0.97-1.63	0.08	**1.36**	**1.14-2.48**	**0.03**
	3rd month	0.92	0.70-1.21	0.55	**1.75**	**1.02-3.61**	**0.02**

Abbreviations: OR, odd ratio; CI, confidence interval. Models were adjusted for maternal age, maternal education, birth weight, infant gender, total previous live births, residence and other air pollutants within the same exposure period.

Discussion

In this population-based study, we utilized Liuzhou city's perinatal birth defect monitoring and survey data to describe the ethnic distribution of major BDs, examine the difference in prevalence rate of BDs among major ethnic groups, and evaluate the correlation between maternal exposure to ambient air pollution and BDs in Liuzhou, Guangxi, China. The prevalence of total BDs among perinatal infants was 19.53 per 1000 births in 2019, which is lower than the prevalence rate of 25.2 per 1000 births reported in Liuzhou in 2011–2016 [26]. This study uniquely analyzed all pregnant outcomes from midwifery institutions and community health services, including live birth, stillbirth and infant death within 7 days, expanding the scope of the research to include those giving birth outside the hospital setting.

Although the overall prevalence rate of BDs was lower than before, the prevalence rate among ethnic minorities exhibited an upward trend in Liuzhou. We found that the Dong ethnic group had the highest prevalence of total BDs, followed by Yao, Miao, Zhuang and Han ethnic groups. Our result was inconsistent with a previous study in Liuzhou, which showed that minorities were less likely to have BDs than the Han ethnic group [26]. Ethnic and racial differences in the prevalence of BDs have been described in the United States, with result showing a lower risk of BDs among African Americans and Hispanics populations compared with Caucasians and Asians [27]. In several studies conducted in the United States, racial differences in BDs risk were found to be associated with cultural, social experience or genetic susceptibility [28, 29]. In our study, the upward trend in the epidemiology of BDs among ethnic groups may be explained by several factors. One reason may be attributed to the advancement and development of medical technology in China, which has improved the level of prenatal diagnosis and screening techniques in ethnic minority areas and aided in timely and effective diagnosis of BDs. The Chinese government has also established an online BDs monitoring system nationwide to avoid missed reporting, increasing the accuracy of the data overtime. Finally, all ethnic groups in China have their own living environment, customs and culture. Due to ethnic culture, customs and other factors, the health status of women and children in minority areas still lags behind the national average.

In this study, the top five BDs reported were congenital heart disease, polydactyly, cleft lip and/or cleft palate, severe thalassemia, and malformations of the external ear. The incidence of congenital heart disease was the highest, which was consistent with the monitoring results of most hospitals [30, 31]. Relative to the Han, Zhuang had higher risk of severe thalassemia, cleft lip and/or cleft palate and syndactyls. The etiology of BDs is complex and includes multiple risk factors, such as advanced age, teratogenic exposures during pregnancy, geographic location, and race and ethnicity [32].

In addition to economic and cultural factors, we also observed that exposure to ambient air pollution during the three months prior to pregnancy and first trimester increased the risk of BDs using multivariate logistic regression analysis. Specifically, exposure to PM_{10}, SO_2 and BDs in second and third month of pregnancy were positively associated with BDs. CO exposure in the second month prior to pregnancy was also significantly associated with BDs. These results increased the evidence of a possible correlation between ambient air pollution and BDs among Chinese women.

This study uniquely examined the effect of exposure to six environmental pollutants on the risk of BDs in minority areas. In a previous study also conducted in Lanzhou, exposure to PM_{10} during the whole pregnancy, early pregnancy and middle pregnancy was correlated with the occurrence of patent ductus arteriosus [33]. Additionally, a case control study of pregnant women in Fuzhou from 2007 to 2013 showed a positive correlation between PM_{10} exposure and fetal cardiovascular malformation [34]. Strickland et al. also observed a significant association between PM_{10} and patent ductus arteriosus in their study, but analysis was done only during weeks three to seven of pregnancy [35]. Our study found that PM_{10} in the second and third months of pregnancy was positively associated with increased BDs, which is consistent with findings from above-mentioned studies.

SO_2 is mainly caused by industrial and combustion emissions, and Liuzhou is a highly industrial city. The SO_2 level in Liuzhou is extremely high, but since 2007, Liuzhou has begun to control air pollution and improve air quality [36]. This may be one of the reasons for the decline in the incidence of BDs in Liuzhou city. In a population-based case-control study in Hunan province from 2014 to 2016, they found that SO_2 had a greater effect on the prophase of pregnancy, while PM_{10} had an effect in the late third trimester [37]. Vrijheid et al. concluded that SO_2 exposure was related to coarctation of the aorta and tetralogy of fallot [38]. However, other studies have reported that PM_{10} and SO_2 have no association with BDs [39]. Different findings may be related to different study methods, different race, different covariate control, and different exposure level.

We also observed that exposure to CO during the second and third months of pregnancy increased the risk of BDs. In the United States, studies have found a positive association between congenital heart disease and increasing CO exposure during weeks three through eight of pregnancy [40]. Our study expanded the window of observation, allowing temporal associations to be clarified. Zhao et al. also reported that CO exposure levels were associated with the risks of congenital anomalies in 1st trimester [41]. The above studies are consistent with the results of this study, suggesting that atmospheric CO pollution after pregnancy may increase the risk of BDs. Therefore, environmental agencies have a responsibility to keep working to improve air quality, in order to protect the health of mothers and infants.

Compared with previous studies, we used multivariate regression analysis to study the association between air pollution and BDs during 3 months prior to pregnancy through the first trimester of pregnancy. This analysis was adjusted for variables including ethnicity, maternal age, and economic income. This conclusion provides epidemiological data for the relationship between birth defects and air pollution in ethnic minority areas. This provides the basis for the government to make scientific pre-pregnancy intervention plan and promotes the development of pregnancy health care.

Our study had several strengths. First, all pregnant women in the study range were studied from first 3 months before pregnancy to first trimester of pregnancy, and the risk period of birth defects in minority areas was analyzed for the first time. Secondly, previous studies primarily incorporated data from hospitals. This study took all pregnant outcomes from midwifery institutions and community health services such as live birth, stillbirth and infant death within 7 days all are included, and the date of BDs was obtained from dual channels, and the research scope was wide. Third, this study examined the effect of six kinds of pollutants exposure on the risk of BDs in minority areas for the first time.

Conclusion

This study provided a comprehensive description of ethnic differences in BDs in Southwest China and broadens the evidence of association between air pollution exposure during gestation and BDs. Our results indicated an association between exposure to air pollution and BDs. The pollutants PM_{10}, SO_2 and CO influenced BDs in the first trimester of pregnancy. SO_2 also had an effect on BDs in the second month before the pregnancy. The relationship between birth defects and atmospheric pollutants needs to be further explored in the future. It is important that the government has access to information about potential effects of environmental pollution on future gestations and to take early intervention measures to reduce the BDs as much as possible in order to improve the birth quality of the population in ethnic minority areas.

Abbreviations

BD (s): Birth defect (s); CI: Confidence interval; OR: odds ratio; aOR: adjusted odds ratio; SD: standard deviation.

Declarations

Acknowledgments: Not Applicable.

Availability of data and materials

The data that support the findings of this study are available from Management Center of Liuzhou Maternal and Child Health Information, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with

permission of Management Center of Liuzhou Maternal and Child Health Information.

Authors' contributions

BW, DZ, and JC conceived the research questions. XH and BW carried out the statistical analysis. XH wrote the first draft of the manuscript. XH, ZL, and LL were fully involved in data acquisition, data cleaning, and maintaining the database. BW and LC helped in interpreting the data. BW, CH, LC, and AA critically reviewed and revised the manuscript. All authors read and approved the final draft. DZ obtained the funding of study.

Ethics approval and consent to participate

Approval for this study was obtained from the Institutional Review Board of Liuzhou Maternal and Child Health Hospital.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

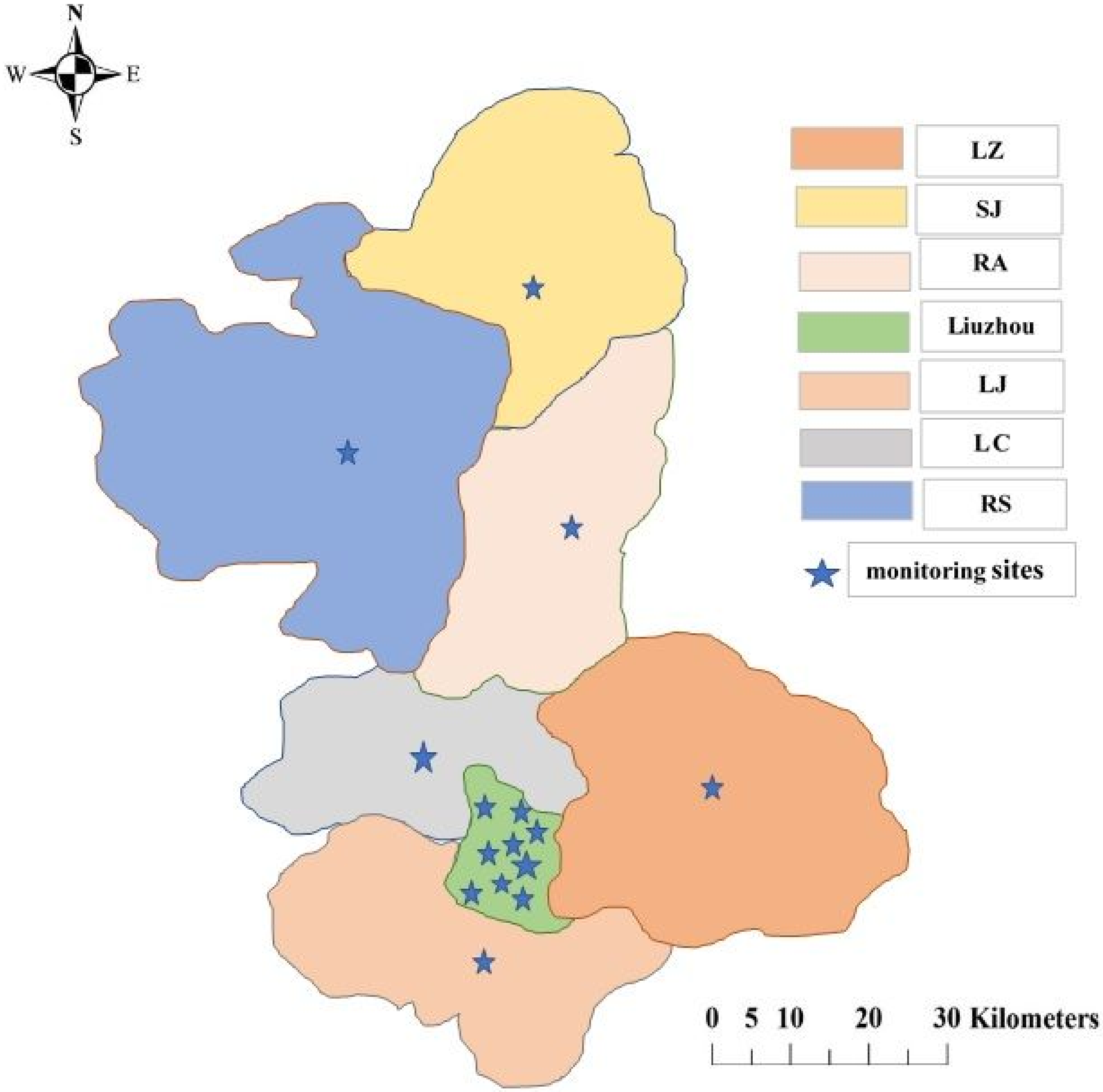

Figure 1

Location of study area (8 districts) and air quality monitoring sites in Liuzhou. Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.