**Early** **prenatal exposure to ambient air pollution and birth defects: evidence from Chinese newborns in** **Xi’an,** **China**

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**Abstract**

**Objective**: Studies suggested an association between maternal exposure to ambient air pollution and birth defects but the results were inconsistent. The aim of this study was to investigate an association of birth defects with exposure to sulfur dioxide (SO2), nitrogen dioxide (NO2), and particles with aerodynamic diameter of ≤10um (PM10) during early pregnancy in Xi’an. **Methods:** Birth defect data was from Birth Defects Monitoring System of Xi’an and the data on ambient air pollutants from Xi’an Environmental Monitoring Center during 2010-2015. Poisson Generalized Additive Model (GAM) was employed to investigate the relation between birth defects and ambient air pollutants adjusting for meteorological confounders. **Results:** Totally 8,865 cases with birth defects were included for analysis. The overall prevalence of birth defects increased from 50.65 per 10,000 in 2010 to 241.59 per 10,000 in 2015 (χ2 trend =157.13，P<0.01) with an average rate of 121.55 per 10000 infants for six years. Exposure to ambient air pollutants during the whole first three months of pregnancy could increase the risk of birth defects by 10.3% with 10μg/m3 increments of NO2 (RR=1.103, 95%CI:1.076~1.130), and 3.4% with 10μg/m3 increments of PM10 (RR=1.034, 95%CI:1.019~1.049). No evidence was found on the association of birth defects and the levels of SO2. Moreover, NO2 might increase risk of neural tube defects, congenital heart disease, congenital polydactyly, cleft palate, digestive system abnormalities and gastroschisis, and PM10 related to congenital heart disease, cleft lip with or without cleft palate. **Conclusion:** The exposure to NO2 and PM10 during early pregnancy may contribute to occurrence of birth defects in Xi’an. The women should avert exposure to high-level of NO2 and PM10 during their first three months of pregnancy.

**Introduction**

Birth defect is defined as any abnormality in functions, structures, and metabolism of the fetus that is developed in the maternal uterus. According to the estimates from WHO in 2015, about 303000 newborns died from birth defects within four weeks after birth, accounting for about 11.3% of neonatal deaths [1]. In China, prevalence of birth defects has been increasing for decades. The national average prevalence of birth defects increased from 149.91/10,000 in 2010 to 200.15/10,000 in 2014[2] and the monitoring data from the birth registration system in Shaanxi province of China indicated that birth defect prevalence also increased from 114/10,000 in 2006 to 124.1/10,000 in 2010 with a mean value of 117.8/10,000[3]. Etiological study of birth defects including the detection of its affecting factors is very essential for prevention and control of birth defects. Ambient air pollution was regarded as an important environmental factor to cause birth defects [4, 5]. Studies conducted in Italy, England and United States found only one or a few statistically significantly increased risks of birth defects with increased exposure to ambient air pollutants [6-9]. Previous studies concentrated mainly on the most common abnormalities such as congenital heart defects or oro-facial clefts based mostly on the entire pregnancy. There had been fewer studies examining the all diagnosed structural anomalies, only observed statistically significantly increased risks of omphalocele based on the entire pregnancy [10] and lower limb defects during 3 to 8 weeks of gestation [11]. It suggested that further studies would be required to clarify associations of other types of birth defect with pollutants. In addition, some studies found that the fetuses were vulnerable to ambient air pollution during the early pregnancy, especially across the third week through the eighth week of the pregnancy [12]. Hence, investigating the effect of ambient air pollutants on birth defects during early pregnancy would be of vital importance to control of birth defects.

Studies regarding the impact of ambient air pollution on birth defects were still limited in China, a relatively higher ambient air pollution exposure setting. A recent meta-analysis including seven Chinese studies indicated that ambient air pollution was significantly associated with selected birth defects [13]. In this study, however, only few studies were included, severe selected birth defects such as the great arteries, isolated cases of patent ductus arteriosus were focused and the impact of air pollutants on them was assessed mostly based on the whole pregnancy period. As one of the most severely populated city in China, Xi’an experienced the worst air quality in the past years [14]. A few studies conducted in Xi’an had examined the negative effect of ambient air pollutants on the cases with other end-points like mortality and respiratory diseases [14, 15] but there has been lack of evaluation of effect of ambient air pollution on birth defects yet. As a result, based on the data from the ambient air pollution monitoring network and the birth defect monitoring system from 2010 to 2015 in Xi’an, we conducted an ecological study to investigate whether there was any relationship between ambient air pollution and birth defects. The study focused on the association of birth defects with air pollutants exposure during early pregnancy and further explored their effect on the major types of birth defects. Such three main ambient air pollutants in Xi’an were included in this study as sulfur dioxide (SO2), nitrogen dioxide (NO2), and particles with an aerodynamic diameter of ≤ 10um (PM10).

**Materials and Methods**

**Study setting**

This study was conducted in Xi’an, Shaanxi province of China, one of the largest industrial inland cities in China. It is located in the Guanzhong Plain at the southern edge of the Loess Plateau, which is a unique arid area in northwestern China. It has 10 districts and 3 counties with a population of approximately eight million and more than 6 million people live in urban area [14]. Coal combustion, vehicle emissions and the natural basin surroundings in poor dispersion of pollutants especially for SO2, NO2, and particulate matter in the air were the main reasons for serious pollution in Xi’an urban area [16]. With rapid economic growth and industrialization, Xi’an faces worsening ambient air pollution and experiences some of the worst ambient air pollution among major China’s cities [17-19].

**Data on birth defects**

The ecological analysis was adopted to examine the link between ambient air pollutants and birth defects by means of the monitoring data on birth defects and ambient air pollutants. The data on birth defects was from the Birth Defects Monitoring System of Xi’an, which is a hospital-based monitoring system including 85 hospitals with the maternity unit around Xi’an area. The system is a standardized, computer-based birth defect surveillance database that collects on all births actively and prospectively. The data on the births occurred in the hospitals of Xi’an during the period of January 1st 2010 to December 31st 2015 was used in the study. A total of 729,335 births was monitored and 8,865 birth defects cases were collected during the study period. Besides, the additional information of cases with birth defects was collected including the maternal age, ethnicity, the last menstrual period (LMP), gestational age (weeks), infant sex, birth weight, birth outcome and season of conception.

We included cases with birth defects after 20 weeks of gestation, no matter live births, stillbirths, terminated pregnancies due to prenatal diagnosis of fatal or major birth defects or abortion of fetuses with birth defects. The cases were identified with active case-ascertainment criteria involving clinical observation, physical examination or autopsy reports and were categorized based on the International Classification of Diseases, 10th Revision (ICD-10, Q00-Q99). We explored a wide range of birth defects well-defined and recorded in the monitoring system, including 15 major types as neural tube defects (Q00-Q02, Q05), hydrocephaly (Q03), congenital heart disease (Q20-Q28), cleft lip with or without cleft palate (Q36-Q37), cleft palate (Q35), digestive system abnormalities (Q38-Q45), urinary system abnormalities (Q60-Q64), limb reduction (Q71-Q72), diaphragmatic hernia (Q79.0), omphalocele (Q79.2), gastroschisis (Q79.3), ear anomalies (Q17), congenital clubfoot (Q66), congenital polydactyly (Q69), and congenital syndactyly (Q70). In this study, we excluded chromosomal anomalies, as these are thought not to be related to ambient air pollution exposure [11].

Xi’an Maternal and Child Health Care Center is responsible for management and maintenance of the system. It collects and examines the reports and cards from all surveillance hospitals. The quality control includes under-reporting investigation, diagnosis checking, and quality checking of monitoring reports to check if there exists the missing reports of cases, the ascertainment bias and filling errors [3]. We obtained the permission for data usage from Xi'an Maternal and Child Health Care Center and the written informed consent was obtained from each mother involved in the system. The study was conducted in accordance with the Declaration of Helsinki and was approved by Ethics Committee in Medical Research, Xi'an Jiaotong University.

**Ambient air pollutants and maternal exposure assessment**

We used ambient air monitoring data from January 2010 to December 2015, which was obtained from Xi’an Environmental Monitoring Center (http://www.xianemc.gov.cn/) including 13 air pollutants monitoring ground stations around Xi’an. The monitoring stations were located predominantly in the urban areas of Xi’an, covering industrial and residential areas in order to represent the levels of the ambient air pollution across the area. Three major ambient air pollutants included in this study as sulfur dioxide (SO2), nitrogen dioxide (NO2), and particles with an aerodynamic diameter of≦10um (PM10) were selected because they were monitored completely during the study period and became major pollutants in Xi’an[15,16]. The concentrations of ambient air pollutants from the monitoring stations were detected and reported in strict accordance with the Chinese government's ambient air quality standard [20]. For each monitoring station, hourly readings were obtained for SO2, NO2 and PM10 to determine daily averages.

We evaluated the maternal exposure to the monthly average concentrations of SO2, NO2 and PM10 during pregnancy period by using ordinary block kriging via ArcGIS (version 10.2) according to the hourly levels recorded at the monitors. Firstly, we calculated the daily average concentrations of each pollutant based on kriging using 0.170 km × 0.170 km grids to partition each maternal residential address reported at the time of the first prenatal examination. Block kriging is a statistical mapping technique considering spatial variation to predict the average concentration based on the data collected at point locations [21]. By using the maternal last menstrual period and the predictions of daily average concentrations, the maternal monthly average exposure to each pollutant during pregnancy period was finally assessed and expressed in μg/m3.

**Meteorological variables**

Since the important effect of meteorological factors such as temperature on pollutant diffusion process, the health effect assessment of air pollutants required controlling for such meteorological confounders [22]. To control for such confounders, we collected the data on daily mean temperature and relative humidity during the study period from the National Centers for Environmental Information (http://www7.ncdc.noaa.gov/CDO/). Likewise, we calculated the monthly average temperature and relative humidity from 2010 to 2015 and further calculated their average levels over first, second and third month of pregnancy. In the analysis, such meteorological confounders were adjusted in the analytic model.

**Statistical methods**

A Poisson regression analysis of monthly time-series data was used to assess the association of birth defects and ambient air pollutants, based on an assumption that the monthly number of birth defects occurred in Xi’an belongs to a kind of small probability event and had an over dispersed Poisson distribution. Poisson Generalized Additive Model (GAM) was employed for such analysis. The main advantage of GAM model include that the potential nonlinear effects of the confounding factors could be detected and adjusted with natural spline smoothing functions, such as meteorological confounders [23]. Since introduced by Schwartz J in 1996 [24], time-series Poisson Generalized Additive Model (GAM) has been widely used as a method to conduct air pollution researches. We firstly built basic models by accommodating non-linear and non-monotonic patterns between birth defects and time-independent variables, including long-time trend, seasonality, temperature and relative humidity with natural cubic spline functions. According to the quasi-Akaike information criteria (q-AIC), 2 degrees of freedom (df) were introduced into the natural cubic spline function of the long-time trend (testing between 0.8, 1, 2, 3 df per month), and 3 df (testing between 3, 4, 5 and 6df) for mean temperature, and 3 df (testing between 3, 4, 5 and 6df) for relative humidity(rh) (testing between 3, 4, 5 and 6df ). After the establishment of basic models, we added terms of a linear function for the concentrations of SO2, NO2 and PM10. The final model was described below:

*Log*E(*Yt*)=*βZt* + season + *S*(t, 2) + *S*(temperature, 3) + *S*(rh, 3) + *α*

where *t* referred to the month of the observation, E(*Y*t) denoted estimated monthly case counts, s() denoted the natural smoothing spline. *Zt* referred to the monthly average concentrations of ambient air pollutants, *β* was vector of coefficients for ambient air pollutants and birth defects, and *α* was the residual. The estimated effects were expressed as the relative risk (RR) of the birth defects counts with per 10μg/m3 increments in the monthly concentrations of the pollutants. Thus, we presented the results as RR along with 95% confidence interval (CI) for the first, second, third gestation month and the whole first three months of pregnancy, respectively. All statistical analysis was performed using SAS 9.4 and two-tailed P<0.05 was considered statistically significant.

**Results**

**Characteristics of case with birth defects**

Totally, 729,335 births were included in the study from January 2010 to December 2015. Among them, 8,865 were cases with birth defects and there were 128 cases per month averagely. Table 1 presented characteristics of these cases with birth defects. The male cases accounted for 53.11%. About 50% of their mothers were aged 20-29 years and near 10% of mothers were aged more than 35 years. There were 51.77% of cases with gestational age below 37 weeks. The birth weight of about half of cases was below 2500g (52.53%).

**Prevalence of birth defects**

The overall prevalence of birth defects was approximately 241.59 per 10000 infants in 2015. The top five types of birth defects were congenital heart disease (100.06 per 10,000), followed by congenital polydactyly (19.96 per 10,000), neural tube defects (19.26 per 10,000), hydrocephaly (13.82 per 10,000), and cleft lip with or without cleft palate (13.11 per 10,000). Fig 1 showed that the overall prevalence of birth defects increased from 50.65 per 10,000 in 2010 to 241.59 per 10,000 in 2015(χ2 trend =157.13，P<0.01) with an average rate of 121.55 per 10000 infants for six years. The prevalence of birth defects in congenital heart disease, congenital polydactyly and hydrocephaly varied and increased greatly within six years. Nevertheless, for neural tube defects, cleft lip with or without cleft palate, congenital syndactyly and cleft palate, there was less variation during study period.

**Status of the ambient air pollutants and meteorology factors**

Fig 2 showed the description of air pollutant levels of SO2, NO2 and PM10 during the study period. Levels of three air pollutants appeared seasonal variation and they were in higher level in winter. The mean concentration of SO2 varied from 22μg/m3 to 45μg/m3, which was under China annual standard of 60μg/m3 [20]. NO2 concentration ranged from 26μg/m3 to 78μg/m3 but exceeded China annual standard of 40 μg/m3 since 2013 [20]. PM10 concentration varied from 83μg/m3 to 195μg/m3, which was beyond China annual standard of 70 μg/m3 [20]. Apart from significant seasonal variation, there had been downward trend in SO2 level but upward trend in NO2 level since 2012. The PM10 level fluctuated greatly during the study period and appeared higher increases in the winters of 2012 and 2013.

**Association of birth defects with ambient air pollutants**

The RRs of birth defects with per 10μg/m3 increment of the pollutants were shown in Table 2. When exposure to ambient air pollutants during the whole first three months of pregnancy, the risks of the birth defects increased averagely by 10.3% with 10μg/m3 increments of NO2 (RR=1.103, 95%CI:1.076~1.130), and 3.4% with 10μg/m3 increments of PM10 (RR=1.034, 95%CI:1.019~1.049) (P<0.001). The strongest association was found in the first month of pregnancy for NO2 (RR=1.088, 95%CI:1.067～1.110) and in the second month of pregnancy for PM10 (RR=1.031, 95%CI:1.020～1.042). However, no evidence was found on the association of birth defects and the levels of SO2 (P>0.05).

**Association of** **types of birth defects with the** **ambient air pollutants**

Further, we investigated the association of three air pollutants with 15 types of birth defects (Fig 3). For NO2, exposure to it in the first month of pregnancy was found to increase risk for neural tube defects (RR=1.083, 95%CI:1.020～1.151), congenital heart disease (RR=1.103, 95%CI:1.063～1.145), cleft palate (RR=1.186, 95%CI: 1.034～1.361) and congenital polydactyly (RR=1.121, 95%CI:1.052～1.195). When exposing to NO2 during the second-month of pregnancy, the increased risk was found for neural tube defects (RR=1.063, 95%CI:1.002～1.129), congenital heart disease (RR=1.141, 95%CI: 1.100～1.184), cleft palate (RR=1.231, 95%CI: 1.071～1.414) and digestive system abnormalities (RR=1.167, 95%CI:1.030～1.322). In the third month of pregnancy, NO2 increased the risk of congenital heart disease (RR=1.063, 95%CI:1.042～1.103), digestive system abnormalities (RR=1.155, 95%CI: 1.019～1.308), and gastroschisis (RR=1.217, 95%CI:1.022～1.450).

With regard to PM10, the exposure to it in the first month of pregnancy was found to increase the risk of being congenital heart disease (RR=1.022, 95%CI:1.001～1.044) and cleft palate (RR=1.086, 95%CI:1.013～1.165). Exposing to PM10 in the second month of pregnancy appeared to increase the risk of being congenital heart disease (RR=1.058, 95%CI:1.036～1.080) and cleft lip with or without cleft palate (RR=1.046, 95%CI:1.013～1.080).

There was no significant association of SO2 found with any type of birth defects during the first trimester (P>0.05).

**Discussion**

**Main findings**

This large ecological analysis depicted the burden of birth defects among infants in Xi’an, China from 2010 to 2015, and firstly investigated the possible association between ambient air pollutants and birth defects during early pregnancy in Xi’an population. There was a significant upward trend found in occurrence of birth defects and the overall prevalence was up to 241.59/10,000 in 2015, which was lower than the prevalence of birth defects in China from 2010 to 2014 [2] but significantly higher than the reported birth defects rate in Shaanxi province from 2006 to 2010 [3]. Congenital heart disease, cleft lip with or without cleft palate, congenital polydactyly, neural tube defects and hydrocephaly had become the most common five types of birth defects, which was consistent with Chinese national data [2]. The study focused on three such main ambient air pollutants as NO2, SO2 and PM10. An important finding is that there was an increased risk of having birth defects overall when mothers exposed to NO2 and PM10 during the first 3 months of pregnancy but no significant association was observed with regard to SO2. Moreover, as for the types of birth defects, the results varied by the types and the time of exposure to ambient air pollutants. NO2 might increase the risk of neural tube defects, congenital polydactyly, congenital heart disease, cleft palate, digestive system abnormalities and gastroschisis. In addition, there was significant associations of PM10 with congenital heart disease, cleft lip with or without cleft palate and cleft palate.

**Association between birth defects and ambient air pollutants**

Previous studies have explored associations of birth defects with NO2, SO2 and PM10 but the results were inconsistent. Some studies have reported an increased risk of birth defect due to maternal exposure to SO2 [6, 10, 25]. The Barcelona study reported a positive association between NO2 and coarctation of the aorta during weeks 3–8 of pregnancy [26] and a study conducted in Northeast England also detected an increased risk of NO2 and congenital heart diseases [7]. The increasing associations were observed between PM10 exposure and selected birth defects in Barcelona, USA, England, Korea and Italy [9, 10, 25-28]. However, some studies found no association between birth defects and such three ambient air pollutants (SO2, NO2 and PM10) [29, 30]. Our study provided an evidence of significant associations between birth defects and the exposure to NO2 and PM10 during the first 3 months of pregnancy, which extended the epidemiologic data on the potential effects of exposure to ambient air pollutants during vulnerable pregnancy periods on birth defects. The disagreement across these studies might be due to the level and content of ambient air pollutants experienced within different countries. In our study, Xi’an experienced higher exposure to the pollutants, and NO2 and PM10 levels were nearly three to five times greater than the previous published studies conducted in western countries [29, 30]. Moreover, our study found no significant negative effect of SO2 on birth defects in Xi’an although there was greater SO2 exposure levels than the England study [10]. Several possible reasons may explain this. Firstly, the no association of SO2 with birth defects could result from decreasing concentration of SO2 since 2012 and current sample size was not enough to detect their association. Secondly, other pollutants such as NO2 or PM10 could conceal effect of SO2 on adverse pregnancy outcomes [23,31]. In our study, both NO2 and PM10 level exceeded China annual standard [20] significantly and became main pollutants. In addition, such two pollutants were found closely associated with occurrence of birth defects. However, our results did provide scientific evidence to help local government in its decision-making regarding air pollution control and birth defect prevention, especially such two pollutants as NO2 and PM10.

We further explored the relevance of certain type of birth defect to ambient air pollutants, and some phenotypes were significantly associated with exposure to NO2 and PM10. A positive association was found between neural tube defects and exposure to NO2 but not in previous study [10]. As for congenital heart disease, our result was consistent with other studies [7, 8], i.e., there was a negative association between congenital heart disease and exposure to both NO2 and PM10 during early pregnancy, and this exposure time was just consistent with the cardiac development of fetus [32]. Also we found that PM10 increased the risk of being a cleft lip with or without cleft palate in the second month of pregnancy, which was inconsistent with the study conducted in England [10]. As for cleft palate, many studies have reported no association with exposure to NO2 [10,25], but an increased risk was found in our study during the first and second months of pregnancy and PM10 was found associated with cleft palate. However, other studies showed no significant relation between PM10 concentration and cleft palate [10,29,31,33,34]. Different conclusions called our attention to the relationship between ambient air pollution and cleft palate, and further researches will be required. Inconsistent with the study in England [10], we found a statistically significant association between digestive system abnormalities and exposure to NO2 during the second-month and third-month of pregnancy, as well as for gastroschisis in the third month of pregnancy. Moreover, to our knowledge, no research examined the effect of ambient air pollution on congenital polydactyly but our study showed a positive association between NO2 exposure and congenital polydactyly during the first month of pregnancy. It was worth noting that congenital polydactyly has become the most common type in China in recent five years [2, 3]. This study shed new light on the association between ambient air pollution and congenital polydactyly. In general, our study suggested that not one but some phenotypes of birth defects mightbe related to ambient air pollution.

How exactly the ambient air pollutants affected the development of certain malformations remain unclear. However, several possible mechanisms have been hypothesized, including oxidative stress, anoxic events, placental inflammation and changes in gene expression in the development of fetal congenital malformation, especially in the early pregnancy. Animal studies indicated that maternal exposure to NO2 produced embryotoxic effects mainly through immunologic reactions or oxidative damage [32]. Kannan reviewed that the PM effects on congenital anomalies may be through oxidative stress, placental inflammation and hemodynamic responses [35]. Wang inferred that environmental pollutants might change activity of metabolic enzymes to affect the generation of DNA-reactive metabolites to lead to the development of maternal cancer and adverse birth outcomes [36]. Landau suggested that nitrogen dioxide may contribute to an increased risk of birth defects through an epigenetic mechanism [37]. Recently, Tsamou provided molecular evidence that particulate ambient air pollution exposure affected miRNAs expression to induce epigenetic alterations in early life, which might lead to adverse birth outcomes [38]. Therefore, the investigation of such mechanisms of will assist in the prevention and control of air pollutants-induced birth defects.

**Strengths and limitations**

The present study was a large, population-based analysis using high-quality data from birth defect monitoring system and a relatively accurate and careful case ascertainment. The study provided epidemiological evidence that NO2 and PM10 could be the main air pollutants related to birth defects in Xi’an population over the first trimester of pregnancy. Thus, the study suggested that the control of ambient air pollutants, especially NO2 and PM10 should be included in the local comprehensive strategy against birth defects. Current critical need was to control ambient air pollution in Xi’an through implementation of rational management and strict control system for traffic density, coal and industrial combustion. In addition, very few studies have been carried out in developing countries where air pollution is usually high, and so far most studies confined to cross-sectional or case-control design[13, 27, 28, 32, 34, 39], but our study used time series data with prospective nature. A meta-analysis foundthat no more than four cohort studies were available worldwide at present and the number of high quality studies was so poor that it was not possible to measure the effect of ambient air pollutants on birth defects precisely [40]. Therefore, the large population-based cohort study as well as biological mechanism should be required to reveal the profound effect of ambient air pollution especially in developing countries with higher air pollution levels.

However, there are some potential limitations that were common in this field of research [11,39]. Our study used time series data with prospective nature and a limitation of this type of study was lack of detailed records about potential confounders such as education, parity, prenatal care, maternal smoking, occupational exposures, and maternal infections and diabetes. So, detailed risk factor information might be required to evaluate further the pollutants effects in record-based analyses. Nevertheless, there was a study suggesting that trimester-specific effect estimates for air pollution did not appear to be confounded by the risk factors that do not vary on the relevant time scaleand limited birth certificate covariates might be sufficient to remove most confounding for short- to moderate-term exposure averages[41]. It implied that our results were convincing to some extent. The method employed for assessment of personal ambient air pollutant exposure based on block kriging by GIS was considered to be one of the preferred methods to reduce exposure measurement error [40]. But the personal ambient air pollution exposure may not be adequately characterized without considering the time spent in the maternal residence and the measurement error may also arise if a woman moved into different regions. Improved individual exposure assessment methods, in particular good proxy for how much ambient air pollutants mothers were exposed to during susceptibility windows, are highly recommended for future research. Moreover, this was an ecological study, thus potential exposure misclassification occurred possibly. To control this bias, we used mother’s LMP to determine the monthly counts and exposure period. Further, we estimated the effect of exposure to ambient air pollutants during the whole first three months of pregnancy, and the results were similar to those from each gestation month. PM2.5 have been understudied pollutants in fetal development and there is the suggestion it may be more harmful than PM10 because the particles can penetrate deeper into the body [26, 39]. In Xi’an, monitoring data on PM2.5 began in 2013 and fewer data was available, therefore, PM2.5 was not included in this study but SO2, NO2 and PM10 were focused as main ambient air pollutants. The effect of PM2.5 on birth defects in Xi’an will require further study. Due to limitation of the ecological analysis, the causal relationships between SO2, NO2, PM10 and the risk of birth defects in the early pregnancy should be interpreted with caution.

**Conclusion**

Our study provided some important evidence of the adverse effects of ambient air pollution exposure on birth defects. The exposure to increased levels of NO2 and PM10 during the first three months of pregnancy may contribute to the occurrence of the major birth defects, especially for certain birth defect phenotypes in Xi’an of China. As the first three months of pregnancy was a critical window of development of fetus organs or systems, reducing exposure to high-level of NO2 and PM10 during this susceptibility term might have important implication in preventing and controlling birth defects.

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**Table 1. Description of characteristics of the cases with birth defects in Xi’an, China**

|  |  |  |
| --- | --- | --- |
| **Variables** | **n** | **%** |
| Infant gender |  |  |
| Male | 4708 | 53.11 |
| Female | 4157 | 46.89 |
| Maternal age (years) |  |  |
| <20 | 172 | 1.94 |
| 20～24 | 1377 | 15.53 |
| 25～29 | 4644 | 52.39 |
| 30～34 | 1789 | 20.18 |
| ≥35 | 883 | 9.96 |
| Gestational age (weeks) |  |  |
| <37 | 5121 | 57.77 |
| ≥37 | 3744 | 42.23 |
| Season of conception |  |  |
| Spring | 2342 | 26.42 |
| Summer | 2231 | 25.17 |
| Autumn | 2115 | 23.86 |
| Winter | 2177 | 24.56 |
| Birth weight (g) |  |  |
| <2500 | 4657 | 52.53 |
| ≥2500 | 4208 | 47.47 |
| Maternal ethnicity |  |  |
| Han  | 8187 | 92.35 |
| Non-Han | 678 | 7.65 |

**Table 2. Relative risks (95%CI) of three air pollutants for the birth defects during the first 3 months of pregnancy a**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **RR** | **95%CI** | **P** |
| **Lower** | **Upper** |
| SO2 |  |  |  |  |
| 1st month b | 1.028 | 0.997 | 1.060 | 0.083 |
| 2nd month b | 1.012 | 0.981 | 1.043 | 0.462 |
| 3rd month b | 0.982 | 0.950 | 1.015 | 0.282 |
| 1st trimester b (average effect) | 1.013 | 0.968 | 1.059 | 0.583 |
| NO2 |  |  |  |  |
| 1st month | 1.088 | 1.067 | 1.110 | <0.0001 |
| 2nd month | 1.075 | 1.054 | 1.096 | <0.0001 |
| 3rd month | 1.032 | 1.013 | 1.053 | 0.002 |
| 1st trimester (average effect) | 1.103 | 1.076 | 1.130 | <0.0001 |
| PM10 |  |  |  |  |
| 1st month | 1.021 | 1.010 | 1.032 | 0.001 |
| 2nd month | 1.031 | 1.020 | 1.042 | <0.0001 |
| 3rd month | 1.001 | 0.990 | 1.012 | 0.826 |
| 1st trimester (average effect) | 1.034 | 1.019 | 1.049 | <0.0001 |

a Poisson generalized additive model was used to estimate the effects of the air pollutants (SO2, NO2 and PM10) by the time to exposure of air pollutants during pregnancy on different types of birth defects overall adjusting for temperature, relative humidity, season, and time trend. RR refers to relative risk of the birth defects counts with per 10μg/m3 increments in the monthly concentrations of the air pollutants; CI refers to confidence interval, SO2, sulfur dioxide, NO2, nitrogen dioxide, PM10, particles with an aerodynamic diameter of ≤10um.

b 1st month refers to the first gestation month, 2nd month refers to the second gestation month and 3rd month refers to the third gestation month; 1st trimester refers to the first three months of pregnancy.

**Fig 1. The prevalence of birth defects from 2010 to 2015 in Xi’an, China.**

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**Fig 2. The change of the air pollutants (SO2, NO2 and PM10) by month from 2010 to 2015 in Xi’an, China.**

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Abbreviations: SO2, sulfur dioxide; NO2, nitrogen dioxide; PM10, particles with an aerodynamic diameter of ≤10um.

**Fig 3. Relative risks (95%CI) associated with a 10μg/m3 increase in SO2, NO2 and PM10 for each of 15 types of birth defects.**

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Poisson generalized additive model was used to estimate the effects of the ambient air pollutants (SO2, NO2 and PM10) by the time to exposure during pregnancy on different types of birth defects adjusting for temperature, relative humidity, season, and time trend. RR refers to relative risk of the birth defects counts with per 10μg/m3 increments in the monthly concentrations of the selected air pollutants; CI refers to confidence interval, SO2, sulfur dioxide, NO2, nitrogen dioxide, PM10, particles with an aerodynamic diameter of ≤10um. *Circles* represent relative risks for SO2; *Squares* represent relative risks for NO2; *triangle* represent relative risks for PM10; 1st month refers to the first gestation month; 2nd month refers to the second gestation month; 3rd month refers to the third gestation month.