Associations between maternal exposure to particulate matter (≤ 10 microns) and congenital anomalies in Liaoning Province, China: A case-control study (2010–2015)

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Research article

Keywords: Air pollution, congenital anomalies, particulate matter (≤ 10 microns), China, case-control study

Posted Date: June 4th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-31608/v1>

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Abstract

Background: A growing number of reports suggest that maternal exposure to ambient air pollution is a potential risk factor for congenital anomalies (CAs). However, most studies have focused on specific CAs, especially congenital heart defects, while relatively few have investigated the effects of exposure to particulate matter of ≤ 10 microns (PM₁₀) on CAs overall, but with inconsistent results. This study aims to investigate the associations between maternal exposure to PM₁₀ and the risks of CAs in offspring in Liaoning Province.

Methods: Cases of CAs (n = 31,407) and controls (n = 7,958) were selected from the Maternal and Child Health Certificate Registry of Liaoning Province from 2010 to 2015. PM₁₀ concentrations were obtained from the Environment Protection Bureau in the same region. A multivariable logistic regression model combined with variables was used to analyze the association between maternal PM₁₀ exposure and the risks of CAs.

Results: Exposure to higher levels of PM₁₀ significantly increased the risks of CAs. In adjusted model I, the odds ratio (OR) of moderate and severe exposure at 3 months before pregnancy was 1.25 (95% confidence interval [CI] = 1.11–1.40) and 1.40 (95% CI = 1.25–1.57), respectively. In the first trimester, the OR of moderate and severe exposure was 1.27 (95% CI = 1.12–1.44) and 1.71 (95% CI = 1.16–1.93), respectively.

Conclusions: Maternal exposure to PM₁₀ was significantly associated with increased risks of CAs in Liaoning Province from 2010 to 2015. Pre-pregnancy (3 months) and the first trimester were identified as potential windows of susceptibility.

1. Background

There is growing evidence that air pollution has adverse effects on newborns. According to the World Health Organization, “congenital anomalies (CAs) can be defined as structural or functional anomalies that occur during intrauterine life, and can be identified prenatally, at birth, or sometimes may only be detected later in infancy” [1]. The incidence of CAs is about one in 33 births worldwide, accounting for an estimated 303,000 deaths within 4 weeks after birth annually [1, 2]. However, in surviving infants, CAs may be accompanied by long-term disabilities, which pose serious implications to the well-being of individuals, families, and society in general [3]. Previous studies have shown that non-genetic risk factors, including maternal characteristics [4], maternal infection [5], and maternal nutritional status [6], may be associated with increased risks of CAs.

Ambient particulate matter (PM), considered as a diverse class of air pollution, has attracted much attention from the public sector and the scientific community. The Global Burden of Disease, Injuries, and Risk Factors Study 2017 attributed a total of 2.94 million deaths to PM pollution globally [7]. Moreover, several studies have reported associations between *in utero* exposure to PM with aerodynamic diameters of $\leq 10 \mu\text{m}$ (PM₁₀) and increased risks of certain types of CAs, such as cardiovascular malformations [8,

9, 10], orofacial defects [11], neural tube defects [12] and abdominal wall defects [13]. However, evidence regarding the effect of environmental pollutants on CAs is limited, as various studies have failed to confirm an association or have demonstrated an inverse correlation between maternal exposure to PM10 and multiple CAs [14, 15, 16, 17]. Since there exist inconsistencies and uncertainties regarding the impact of PM10 on the risks of CAs, further studies are required in order to arrive at firm conclusions.

Liaoning Province is an important heavy industry base in northeast China that has experienced enormous economic development over the past 10 years, as well as severe air pollution. In addition, the incidence of birth defects among newborns in Liaoning Province is about 2% [18]. Therefore, the aim of this population-based case-control study was to investigate possible relationships between the risks of CAs in offspring and prenatal exposure to PM10, and to identify the most sensitive time of exposure to PM10 before and during pregnancy.

2. Methods

2.1 Study design and population

Liaoning Province, located in northeast China (area, 148,600 km²; population, 43.517 million), is a hub of heavy industry with ambient air pollution that is mainly caused by soil particles, biomass combustion, and traffic emissions. Maternal information and delivery outcomes of pregnant women between January 1, 2010 and December 31, 2015 were obtained from the Maternal and Child Health Certificate Registry of Liaoning Province. A total of 39,365 neonates were selected for inclusion in the present case-control study. Demographic and obstetrical characteristics included the season of conception, sex of the infant, gestational age, birth weight, maternal age, gravidity, parity, and educational level of the mother.

2.2 Definition of outcomes (CAs)

According to the "Surveillance of Congenital Anomalies" toolkit of the Centers for Disease Control and Prevention, a CA is an anomaly of body structure or function that exists at birth and has a prenatal origin. Major structural anomalies associated with CAs, which are important causes of death, morbidity, and disability, include ano-/microphthalmia, ano-/microtia, cleft lip/palate, congenital heart defects, craniosynostosis, diaphragmatic hernia, Down syndrome, esophageal atresia, gastroschisis, hypospadias, microcephaly, neural tube defects, omphalocele formation, and reduction defects of the upper/lower limbs. The study protocol was approved by the Institutional Review Board of Liaoning Women and Children's Health Hospital and conducted in compliance with local and national regulations.

2.3 Exposure assessment

Exposure assessment data were collected from 77 air quality monitoring stations across 14 cities in Liaoning Province (Shenyang, Liaoyang, Dalian, Yingkou, Anshan, Benxi, Fushun, Dandong, Panjin, Jinzhou, Fuxin, Tieling, Huludao, and Chaoyang). The monthly average ambient PM10 concentrations were calculated from data obtained from the Environmental Protection Bureau of each city. In

consideration of the metabolic process of air pollutants in the body, PM10 levels were determined from 3 months preconception throughout the first trimester.

2.4 Statistical analysis

A crude model that included only PM10 exposure was initially established and then expanded by adding the following cofounders (adjusted model I): season of conception (spring, summer, autumn, winter), sex of the infant (female, male), gestational age (< 37, ≥ 37 weeks), birth weight (< 2500, 2500–4000, ≥ 4000 g), maternal age (< 20, 20–34, ≥ 35 years), gravidity (0, 1, ≥ 2), parity (0, 1, ≥ 2), and educational level of the mother (≤ primary school, junior high school, senior high school, ≥ college). Multivariate logistic regression analysis combined with these variables was used to analyze the association between PM10 exposure and the risk of CAs. All statistical analyses were performed using IBM SPSS Statistics 21.0 (IBM Corporation, Armonk, NY, USA). A two-tailed probability (*p*) value of < 0.05 was considered statistically significant.

3. Results

3.1 Descriptive statistics

The basic characteristics of the pregnant women and 39365 newborns in this study, including 31,407 (79.80%) cases of CAs, delivered from January 1, 2010 to December 31, 2015 are shown in Table 1. In the control group, most newborns were conceived in the summer and the least in the winter. The majority of newborns were delivered at or beyond gestational week 37. Most of the pregnant women in both the control and CA groups were aged 20–34 years. The highest proportion of women were in their first pregnancy (gravidity 1) and the first delivery (parity 0) for most in the control group. Among all newborns, there were more males than female (21,786 [53.3%] vs. 17,579 [44.7%], respectively) and most birth weights ranged from 2500 to 4000 g. In the case group, the highest educational level of most of the mothers was junior high school. The distribution of ambient PM10 concentrations ($\mu\text{g}/\text{m}^3$) in the case and control groups during different gestation periods is shown in Table 2.

3.2 Association between PM10 exposure and CAs

Table 3 shows the relationship between PM10 exposure and the risk of CAs at 3 months before pregnancy and during the first trimester using the crude model and adjusted model I, respectively. The PM10 exposure level was artificially divided into three levels (mild [reference value], moderate, and severe) in order to equalize the sample sizes. The results revealed differences between the crude model and adjusted model I (odds ratio [OR] of the crude model and adjusted model I in the first trimester for severe exposure: 1.02 [95% confidence interval (CI) = 0.96–1.09] and 1.71 [95% CI = 1.16–1.93], respectively). In other words, the cofounders influenced the relationship between ambient PM10 exposure and CAs through various underlying mechanisms. For adjusted model I, the ORs of moderate and severe exposure at 3 months before pregnancy were 1.25 (95% CI = 1.11–1.40) and 1.40 (95% CI = 1.25–1.57),

respectively. In the first trimester, the ORs of moderate and severe exposure were 1.27 (95% CI = 1.12–1.44) and 1.71 (95% CI = 1.16–1.93), respectively.

4. Discussion

In China, there exists a long-standing registry for all types of births, including fetal death and selective termination of pregnancy. The timing of exposure within the critical window of fetal development and an extended exposure window at 3 months before conception was explored in order to better identify underlying factors. In the present study, from 2006 to 2015, exposure to higher levels of PM₁₀ at both 3 months preconception and early pregnancy significantly increased the risk of CAs among offspring in Liaoning Province. The study results also revealed that the most crucial time windows for susceptibility were 3 months before pregnancy and the first trimester of gestation. In addition, this association did not appear to be substantially influenced by a shorter time scale of 1 month.

This study provides evidence of a robust association between maternal exposure to ambient PM₁₀ and the risks of CAs in offspring. A recent systematic review reported evidence of an association between ambient pollutants (including PM₁₀) and CAs, although the results were limited and inconsistent [19]. Previous reviews of the effects of air pollution on birth outcomes demonstrated a clear association between PM₁₀ exposure and risks of CAs [20, 21]. Nonetheless, it is worth noting that most studies conducted over the past decade have shown an association between prenatal PM₁₀ exposure and the risk of some specific defects, especially cardiovascular malformations [8–13], but not CAs overall. Consistent with the findings of the present study, statistically significant associations between overall CAs and PM₁₀ have been observed in only three studies conducted in Israel and China. Of these, Farhi et al. (2014) found that higher levels of PM₁₀ exposure in all stages of pregnancy were positively associated with slightly increased risks of overall CAs (OR = 1.06 [95% CI = 1.01–1.11] for an increase of 10 µg/m³ and OR = 1.10 [95% CI = 1.01–1.20] for the high vs. low tertile) [22]. However, this association was less evident in the first trimester (OR = 1.01 [95% CI = 0.98–1.03]). Furthermore, Liang et al. (2014) reported that exposure to PM₁₀ during the second and third month of pregnancy was associated with increased risks of total CAs (gestational month 2: OR = 1.039 [95% CI = 1.016–1.063]; gestational month 3: OR = 1.066 [95% CI = 1.043–1.090]) [23]. Wang et al. (2019) reported that PM₁₀ exposure during the first trimester increased the risk of all CAs by 3.4% per increment of 10 µg/m³ (relative risk [RR] = 1.034, 95% CI = 1.019–1.049) and the highest risks were observed in the second month of pregnancy (RR = 1.031, 95% CI = 1.020–1.042) [24]. More positive associations between PM₁₀ exposure and overall CAs have been observed in Korea and Italy, but these associations were not statistically significant [25, 26]. Moreover, studies that included the full spectrum of CAs found little evidence of such associations [15, 13, 17]. A possible explanation for these inconsistent findings could be due to differences in sample sizes, air pollutant levels, exposure assignments, and confounders [22, 19, 17]. Notably, the cohort of the present study was a population exposed to relatively high mean PM₁₀ levels of 90.264–93.626 µg/m³, while all of the above-mentioned studies, which were conducted in areas with relatively low mean PM₁₀

levels of $\leq 40 \mu\text{g}/\text{m}^3$, reported irrelevant or negative associations. Given the limited number of studies, these findings should be interpreted with caution.

A great deal of evidence suggests that oxidative stress [27], pulmonary and placental inflammation [28], blood coagulation [29], endothelial function [30], and hemodynamic responses [31] are involved in the mechanisms underlying the effects of air pollution. In addition, maternal exposure to PM₁₀ may affect embryos and fetuses by influencing transplacental transport of oxygen and nutrients [32]. Recent studies have suggested that prenatal PM₁₀ exposure during the last trimester of pregnancy may cause mitochondrial dysfunction and shorten the lengths of telomeres in the cells of newborns [33, 34, 35]. Despite this evidence, the effects of air pollutants remain uncertain.

There were several limitations to this study that should be addressed. First, assessment of the dosage of prenatal exposure may have been inaccurate because the method used to measure PM₁₀ concentrations may have affected the accuracy of exposure estimation and led to misclassification. In the present study, the monthly average of prenatal PM₁₀ exposure concentrations was calculated from daily readings of all air monitoring stations throughout Liaoning Province. However, the municipal exposure level estimates are generally lower than those based on personal assessment of exposure [36]. Second, the time that people spend indoors was not taken into consideration, which may explain the difference between personal and municipal exposure. However, this error was assumed to be irrelevant with respect to the differentiation between cases and controls. Such misclassification would lead to underestimation of the effect estimates [14]. Third, although any random migration would reduce the accuracy of prenatal exposure assessment, the median distance of migration in this study tended to be short and, therefore, was not likely to result in misclassification [37]. Fourth, some of the potential risk factors for CAs, such as smoking, alcohol consumption, and folic acid use, were not included in multivariate analyses. Although it is unlikely that these factors were associated with exposure to PM₁₀, they were partially accounted for by adjusting for the educational level of the mother [22]. Fifth, the study design only tested associations for a single pollutant, as the co-effects of other air pollutants, such as carbon monoxide, nitrogen dioxide, and ozone, which may be associated with CAs, were not considered in the analyses [38]. Hence, future studies should include mixtures of pollutants.

In general, the results of the present study demonstrated a strong association between maternal exposure to environmental PM₁₀ and the risk of CAs in offspring. However, additional studies are needed to elucidate the underlying mechanisms in order to further explore the impact of maternal PM₁₀ exposure on CAs.

5. Conclusions

In Liaoning Province, maternal exposure to PM₁₀ was significantly associated with increased risks of CAs in the period of 2010 to 2015. These results indicate potential windows of susceptibility before and during the first trimester.

Abbreviations

CAs congenital anomalies

PM particulate matter

PM10 particulate matter of ≤ 10 microns

CI confidence interval

OR odds ratio

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board of Liaoning Women and Children's Health Hospital and conducted in compliance with local and national regulations.

Consent for publication

Not Applicable.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper "Associations between maternal exposure to particulate matter (≤ 10 microns) and congenital anomalies in Liaoning Province, China: A case-control study (2010–2015)".

Funding

This study was supported by the Liaoning Providence Science and Technology Project (grant no. 2015225025 to Yan-Hong Huang) and the Shenyang Science and Technology Project (grant no. F15-139-9-09 to Yan-Hong Huang). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Authors' contributions

HY conceptualized and designed the study. HS analyzed the data and wrote the paper. CY, LS and CZ were responsible for acquisition of data. LJ and JC performed the statistical measurement and analyzed the data. LL and ZC evaluated the manuscript. All authors have read and approved the manuscript.

Acknowledgments

We thank International Science Editing (<http://www.internationalscienceediting.com>) for editing this manuscript.

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Tables

Table1.

Demographic and obstetric characteristics of congenital anomaly cases and controls in Liaoning Province, China, 2010-2015.

Characteristic	Cases	Controls
N	31407 (79.80)	7958 (20.20)
Season of conception		
Spring	8070 (25.70)	2105 (26.50)
Summer	7777 (24.80)	2834 (35.60)
Autumn	7605 (24.20)	1706 (21.40)
Winter	7955 (25.30)	1313 (16.50)
Sex of the infant		
Female	13649 (43.50)	3930 (49.40)
Male	17758 (56.50)	4028 (50.60)
Gestational age (weeks)		
<37	14389 (45.80)	263 (3.30)
≥37	17018 (54.20)	7695 (96.70)
Birth weight (g)		
<2500	13541 (43.10)	175 (2.20)
2500-4000	16143 (51.40)	6845 (86.00)
≥4000	1723 (5.50)	938 (11.80)
Maternal age (years)		
<20	450 (1.40)	53 (0.70)
20-34	27020 (86.00)	6957 (87.40)
≥35	3937 (12.50)	948 (11.90)
Gravidity (times)		
0	9 (0.03)	868 (10.90)
1	18029 (57.40)	4156 (52.20)
≥2	13369 (42.60)	2934 (36.90)
Parity (times)		
0	5929 (18.90)	5931 (74.50)
1	20437 (65.00)	1772 (22.30)
≥2	5041 (16.10)	255 (3.20)
Educational level of the mother		
≤Primary school	1327 (4.20)	265 (3.30)
Junior high school	12773 (40.70)	2911 (36.60)
Senior High school	7899 (25.20)	1725 (21.70)
≥College	9408 (30.00)	3057 (38.40)

Values were n(%)

Table 2.

Distribution of ambient PM₁₀ concentrations (µg/m3) in cases and controls during different gestation periods.

Gestation periods	Mean	SD	Minimum	Median	IQR	Maximum
The first month before pregnancy						
All subjects	91.49	30.79	34.42	84.90	35.42	245.65
Controls	92.54	32.26	45.57	84.90	35.77	245.65
Cases	91.23	30.40	34.42	84.87	35.84	245.65
The second month before pregnancy						
All subjects	90.90	30.35	34.42	84.87	36.37	245.65
Controls	92.80	31.88	45.57	85.47	39.74	245.65
Cases	90.42	29.92	34.42	84.65	35.80	245.65
The third month before pregnancy						
All subjects	90.35	29.98	34.42	84.65	35.29	245.65
Controls	93.21	31.59	45.57	87.07	35.27	245.65
Cases	89.63	29.52	34.42	83.74	35.03	245.65
The three months before pregnancy						
All subjects	90.92	25.39	40.28	87.98	32.00	178.22
Controls	92.85	26.53	48.91	88.80	30.82	178.22
Cases	90.42	25.06	40.28	87.46	31.18	178.22
The first month of pregnancy						
All subjects	90.87	31.49	34.42	83.74	37.30	245.65
Controls	90.26	33.34	47.74	82.16	37.63	245.65
Cases	91.02	30.55	34.42	84.65	35.93	245.65
The second month of pregnancy						
All subjects	91.31	31.49	34.42	83.74	35.93	245.65
Controls	91.62	34.35	47.74	82.16	35.42	245.65
Cases	91.23	30.72	34.42	84.65	35.93	245.65
The third month of pregnancy						
All subjects	91.74	31.30	34.42	84.74	36.40	245.65
Controls	93.63	33.21	47.74	84.52	37.07	245.65
Cases	91.27	30.78	34.42	84.71	36.44	245.65
The first trimester						
All subjects	91.74	31.30	34.42	87.07	33.43	189.47
Controls	91.84	28.66	52.12	87.07	38.86	189.47
Cases	91.17	25.92	36.20	87.07	31.99	189.47

Table 3

The associations between maternal exposure to ambient PM₁₀ during different study periods and CAs

Tertile of PM ₁₀ level	Cases	Controls	Crude Model ^a OR (95%CI)	Model I ^b OR (95%CI)
he first month before pregnancy				
<75.48	11030	2305	1.0 (Reference)	1.0 (Reference)
75.48-98.42	10323	2629	0.98 (0.93-1.05)	1.31 (1.16-1.48)
≥98.42	10054	3024	0.93 (0.88-0.99)	1.15 (1.03-1.29)
<i>P</i> for trend			0.019	<0.001
he second month before pregnancy				
<75.36	10739	2512	1.0 (Reference)	1.0 (Reference)
75.36-97.27	10508	2493	1.24 (1.17-1.32)	1.35 (1.20-1.52)
≥97.27	10160	2953	1.26 (1.15-1.30)	1.37 (1.22-1.53)
<i>P</i> for trend			<0.001	<0.001
he third month before pregnancy				
<75.36	11030	2305	1.0 (Reference)	1.0 (Reference)
75.36-96.40	10323	2629	1.44 (1.36-1.53)	1.33 (1.18-1.51)
≥96.40	10054	3024	1.18 (1.11-1.25)	1.29 (1.15-1.45)
<i>P</i> for trend			<0.001	<0.001
he three months before pregnancy				
<78.37	10782	2379	1.0 (Reference)	1.0 (Reference)
78.37-98.01	10376	2580	1.33 (1.25-1.41)	1.25 (1.11-1.40)
≥98.01	10249	2999	1.18 (1.11-1.25)	1.40 (1.25-1.57)
<i>P</i> for trend			<0.001	<0.001
he first month of pregnancy				
<74.77	10422	2972	1.0 (Reference)	1.0 (Reference)
74.77-96.40	10208	2489	0.81 (0.77-0.86)	1.19 (1.05-1.35)
≥96.40	10777	2497	0.95 (0.89-1.01)	1.51 (1.34-1.70)
<i>P</i> for trend			<0.001	0.040
he second month of pregnancy				
<74.94	10204	2911	1.0 (Reference)	1.0 (Reference)
74.94 -96.4	10648	2483	0.84 (0.79-0.89)	1.22 (1.08-1.38)
≥96.4	10230	2564	1.02 (0.96-1.09)	1.47 (1.31-1.66)
<i>P</i> for trend			<0.001	0.010
he third month of pregnancy				
<75.36	10529	2704	1.0 (Reference)	1.0 (Reference)
75.36-98.36	10648	2426	1.08 (1.01-1.14)	1.14 (1.26-1.62)
≥98.36	10230	2828	1.21 (1.14-1.29)	1.59 (1.14-1.80)
<i>P</i> for trend			0.014	<0.001
he first trimester				
<75.36	10550	2815	1.0 (Reference)	1.0 (Reference)
75.36-97.13	10337	2522	0.93 (0.88-0.99)	1.27 (1.12-1.44)
≥97.13	10520	2621	1.02 (0.96-1.09)	1.71 (1.16-1.93)
<i>P</i> for trend			0.023	0.001

Adjust for none

Adjust for season of conception (Spring, Summer, Autumn, Winter); sex of the infant (Female, Male), gestational age (<37weeks, ≥37weeks), birth weight (<2500g, 2500-4000g, ≥4000g), maternal age (<20years, 20-34years, ≥35years), gravidity (Never, 1time, ≥2times), parity (Never, 1time, ≥2times), educational level of the mother (≤Primary school, Junior high school, Senior High school, ≥College).