International Journal of Epidemiology, 2018, 1072–1081
doi: 10.1093/ije/dyy019
Advance Access Publication Date: 26 February 2018
Original article

Prenatal Exposures to Pollutants

Effects of prenatal exposure to ambient air pollutant PM_{10} on ultrasound-measured fetal growth

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Editorial decision 18 January 2018; Accepted 26 January 2018

Abstract

Background: Limited epidemiological studies have investigated the relationship between prenatal exposure to ambient particulate matter and risk of abnormal fetal growth, and have reached inconclusive results. No study has been conducted in areas with very high air pollution levels. We investigated the hypothesis that exposure to high levels of particulate matter with aerodynamic diameter no larger than 10 μm (PM_{10}) during pregnancy increases the risk of abnormal fetal growth.

Methods: A birth cohort study was performed in Lanzhou, China, 2010–12, including 8877 pregnant women with 18 583 ultrasound measurements of four fetal growth parameters during pregnancy, including biparietal diameter (BPD), femur length (FL), head circumference (HC) and abdominal circumference (AC). Mixed-effects modelling was used to examine the associations between PM_{10} exposure and risk of abnormal fetal growth.

Results: When average PM_{10} exposure from conception until the ultrasound examination exceeded 150 μg/m^3, there were significant increases in standardized FL ($\beta = 0.095$, $P = 0.0012$) and HC ($\beta = 0.090$, $P = 0.0078$) measures. When average PM_{10} exposure was treated as continuous variable, we found a significant decrease in standardized BPD ($\beta = -0.018$, $P = 0.0016$) as per 10 μg/m^3 increase in PM_{10}. After examining the associations by various exposure windows, positive associations between higher levels of PM_{10} and fetal overgrowth were consistently seen for HC measures.

Conclusions: Our study suggested that prenatal exposure to high levels of ambient PM_{10} increased the risk of abnormal fetal growth. The findings from our study have important public health implications and also call for future studies to explore the underlying mechanisms and post-natal consequences of these findings.

Key words: Fetal growth, PM_{10}, air pollution, ultrasound measures, pregnancy

Key Messages

- No study has been conducted in areas with very high air pollution levels.
- Exposure to high levels of ambient PM_{10} increases the risk of abnormal fetal growth.
- The risk may vary by different fetal growth measurements and fetal growth patterns.
- Positive associations between higher levels of PM_{10} and fetal over- growth were consistently seen for head circumference measures by various exposure windows.

Introduction

A growing body of evidence indicates that fetal growth restriction (FGR), also known as intrauterine growth restriction or fetal under-growth, is an important predictor of neonatal death.[1–4] Over the past decade, numerous studies have indicated that ambient air pollution during pregnancy influences fetal growth.[5,6] A majority of these previous epidemiological studies have associated maternal air pollution exposure with fetal growth by using various neonatal anthropometric measurements at birth, such as birthweight and length, size for gestational age, head circumference (HC) and abdominal circumference (AC).[7–17] However, the late assessment of growth restriction potentially introduces bias,[18] and patterns of fetal growth during pregnancy cannot be assessed in these studies.[5] In addition, clinical studies have suggested that birthweight as a proxy for fetal growth may not be the best indicator, and the conditions for growth restriction and small size for gestational age are not synonymous.[19,20] Furthermore, others suggest that birthweight poorly reflects fetal under-growth during the first two trimesters, because growth impairment and imbalance that may have occurred during early period may be compensated for in the remaining pregnancy period.[21]

Assessing fetal growth *in utero* using ultrasound measures could provide more accurate classification of restricted or excessive growth by reducing the time between exposure and outcome assessment.[18,22] A small number of studies have investigated the association between exposure to various air pollutants [i.e. nitrogen monoxide, nitrogen dioxide (NO_2), sulphur dioxide (SO_2), ozone, carbon monoxide and particulate matter with aerodynamic diameter < 10 μm (PM_{10})] during pregnancy and fetal growth measured by ultrasound.[5,22–29] Only three of these have focused on the effects of exposure to PM_{10} during pregnancy, and these studies reached inconsistent results.[5,22,23] All of these studies investigated different exposure time windows. In addition, all of them were conducted in Europe or the USA, where the concentrations of ambient PM_{10} were lower than in Asia, with mean levels of PM_{10} ranging from 17.8 μg/m^3 to 40.7 μg/m[35,22,23] versus 140.8 μg/m^3 in the current study (Table 1; and Table A1, available as Supplementary data at *IJE* online).

Abnormal fetal growth includes both under-growth and over-growth. There is accumulating evidence that macrosomia, or being large-for-gestational age, as a result of excessive and unbalanced intrauterine growth places the individual at increased risk for metabolic short-term complications and can influence metabolic disorders in adulthood.[30,31] It has been suggested that air pollution causes weight gain and obesity through oxidative stress and inflammatory response.[32–34] However, to the best of our knowledge, no study has explored the effect of air pollution on fetal over-growth.

In light of the limited studies investigating prenatal exposure to PM_{10} and risk of fetal under-growth, and the lack of studies investigating the association between air pollution and fetal over-growth, we analysed data from the Lanzhou Birth Cohort Study to investigate the hypothesis that exposure to high levels of PM_{10} during pregnancy increases the risk of abnormal fetal growth.

Methods

Study population

The study population has been described previously.[35–39] In brief, pregnant women who came to the Gansu

Table 1. Distributions of selected characteristics of the study population ($N = 8877$)

Characteristics	N	Percent (%)
Maternal age (years)		
< 30	5636	63.5
≥ 30	3239	36.5
Highest education level		
< College	3309	37.3
≥ College	5568	62.7
Family monthly income (RMB per capita)		
< 3000	5111	57.6
≥ 3000	3766	42.4
Employment during pregnancy		
No	4101	46.2
Yes	4776	53.8
Smoking (active and passive) during pregnancy		
No	7189	81.0
Yes	1688	19.0
Alcohol consumption during pregnancy		
No	8857	99.8
Yes	20	0.2
Birthweight (g)		
< 2500	438	4.9
2500–4000	7806	87.9
≥ 4000	633	7.1
Pre-pregnancy BMI[a]		
≤ 18.5	1822	20.5
18.5–24.0	6118	68.9
≥ 24.0	937	10.6
Weight gain during pregnancy (kg)		
≤ 15.0	3247	36.6
15–18.5	2089	23.5
> 18.5	3248	36.6
Parity		
Primiparous	6669	75.1
Multiparous	2208	24.9
Caesarean section		
No	5599	63.1
Yes	3278	36.9
Preeclampsia		
No	8673	97.7
Yes	204	2.3
Maternal diabetes		
No	8774	98.8
Yes	103	1.2
Season of conception[b]		
Autumn	2431	27.4
Winter	2025	22.8
Spring	1854	20.9
Summer	2567	28.9
Cooking fuel		
Gas or electricity	7635	86.0
Biomass or coal	1242	14.0
Newborn gender		
Boys	4656	52.5
Girls	4221	47.5
Continuous variable	**Mean (SD)**	**Range**
Gestational age (weeks)	38.7 (1.7)	22–44
Averaged daily PM_{10} during pregnancy (μg/m^3)	140.8 (24.8)	66.5–242.6
Averaged daily SO_2 during pregnancy (μg/m^3)	49.0 (13.1)	14.7–87.1
Averaged daily NO_2 during pregnancy (μg/m^3)	43.9 (6.0)	26.0–64.6
Averaged daily temperature during pregnancy (°C)	10.3 (3.1)	1.7–20.9
Birth AC (mm)	324.0 (25.2)	200–530
Birth HC (mm)	343.6 (19.0)	250–510

[a]BMI, body mass index.
[b]Autumn: September, October and November; winter: December, January and February; spring: March, April and May; summer: June, July, and August.

Provincial Maternity and Child Care Hospital (GPMCCH) in Lanzhou, China, for delivery in 2010–12, and who were 18 years or older with a gestational age of ≥ 20 weeks, were eligible. Individuals with mental illness would have limited ability to answer questions. During the study period, a total of 13 pregnant women had a diagnosis of mental illness (including autism, bipolar disorder, depression, obsessive-compulsive disorder) and were excluded from the beginning of the study recruitment. A total of 10 542 (73.4%) women participated in the study. All study procedures were approved by the Human Investigation Committees at the GPMCCH and Yale University. After obtaining written consent, an in-person interview was conducted at the hospital by trained study interviewers using a standardized and structured questionnaire to collect information on demographics, reproductive and medical history, lifestyle factors, occupation and residential history. Information on birth outcomes and maternal complications were abstracted from the medical records. Gestational age was estimated using the date of the last menstrual period reported at recruitment and confirmed by the first ultrasound examination.[39]

Fetal growth characteristics

The repeated ultrasound measurements of HC, AC, femur length (FL) and biparietal diameter (BPD) during pregnancy were abstracted from the medical records. All readings were recorded in millimetres. Since an ultrasound examination was not routinely performed during each of the three trimesters and not all examination records contained four fetal growth parameters, we restricted our

analyses to pregnant women who had at least one ultrasound measurement. Of 8969 subjects who had singleton live births and lived in Lanzhou City,[36] we excluded participants: who had no records of ultrasound measures; whose records were considered as unreasonable [values below or above 3 standard deviations (SD) from the normal ranges of fetal growth standards, $N = 62$, 23, 41 and 33 for HC, AC, FL and BPD, respectively];[40] or who had babies with birthweights < 500 g ($N = 38$) or gestational age ≥ 309 days ($N = 1$); which yielded a final sample size of 8877. Similar distributions of maternal characteristics were observed between pregnant women with and without ultrasound measurement information (data not shown). Across different times during pregnancy, study participants had up to three ultrasound measurements available for FL and BPD, and up to four ultrasound measurements available for HC and AC, because HC and AC were also measured by ultrasound just before birth.

The time of ultrasound examination for each fetal growth parameter was presented as week of gestation and was commonly performed after the first trimester (see Figure A1, available as Supplementary data at *IJE* online). We used the SGPLOT procedure to generate the smooth nonparamatric curves; the fetal growth patterns of BPD, FL and HC during pregnancy against the ultrasound examination time showed a nonlinear growth pattern (see Figure A2, available as Supplementary data at *IJE* online), which was consistent with the standard fetal growth curves worldwide.[40]

To avoid results that cannot be compared for each gestational week, the standardized fetal parameters (Z scores) were used as an outcome variable based on recently updated international standards for all four fetal growth measurements.[40] The Z scores were calculated through the formula $\frac{(actual\ \ value - mean)}{SD}$, where actual value was the observed ultrasound measures, and mean and SD were the standard values in the same weeks of gestation provided by Papageorghiou *et al.*[40]

Exposure assessment

As described in previous studies,[36–38] data on ambient air pollutants were obtained from the Gansu Provincial Environmental Monitoring Central Station, which collects 24-h average concentration for PM_{10}, sulphur dioxide (SO_2) and nitrogen dioxide (NO_2) through an automated data reporting system from four monitoring stations in Lanzhou city (1088 km^2). The 24-h average PM_{10} was measured for the period 1 April 2009 to 31 December 2012 for two stations, and for 1 January 2011 to 31 December 2012 for the two additional stations. The monitors were located in the southern part of Lanzhou in the metropolitan area with high population density (see Figure A3, available as Supplementary data at *IJE* online), the spread/density of the study population is similar to that of the total population (see Figure A4, available as Supplementary data at *IJE* online). Each subject's residences throughout pregnancy, as measured by move-in and move-out dates, and work addresses were collected. We used the earth online sharing website provided by Google (www.earthol.com) to obtain longitude and latitude coordinates for each subject's home and work addresses. The mean and standard deviation of distance from maternal residence to each air monitor was 14.8($\pm$10.4) km, 9.6($\pm$10.7) km, 9.6($\pm$12.1) km, and 9.4 ($\pm$12.4) km, respectively. The majority (93%) of the participants lived within 12 km from the nearest monitor. We calculated daily PM_{10} concentrations incorporating each subject's home and work addresses, using all four monitors, or two monitors with the inverse distance weighting (IDW) approach or the nearest monitor. Subjects' individual exposure levels were averaged: (i) from date of conception to the date of ultrasound examinations; (ii) 1 month before ultrasound examinations; (iii) 2 weeks before ultrasound examinations; and (iv) 1 week before ultrasound examinations. PM_{10} exposure levels for different exposure windows, estimated based on an average of the four monitors, two monitors or the nearest monitor, were similar. Therefore, we presented our results based on the four monitors. We calculated the correlations between average PM_{10} levels during the different exposure windows, and found that the PM_{10} levels averaged during exposure windows (ii), (iii) and (iv) were highly correlated (Pearson correlation coefficients ranging from 0.80 to 0.84), whereas the correlation between (i) and (ii) or (iii) or (iv) only ranged from 0.08 to 0.17. It suggested a temporal heterogeneity between long-term and short-term exposure windows.

Statistical analysis

All analyses were performed separately for each fetal parameter. The standard cutoffs were used to categorize under-growth ($<$ 3rd centile, $Z < -1.88$), normal growth (3rd centile–97th centile, $-1.88 \leq Z \leq 1.88$) and over-growth ($>$ 97th centile, $Z > 1.88$) (dotted horizontal lines in Figure 1). Similar results were obtained using other centiles for setting the normal range, which were the 5th and 95th centiles ($Z = \pm1.645$), and the 10th and 90th centiles ($Z = \pm1.28$) (results not shown). Thus, we presented more conservative results using the 3rd and 97th centiles as the boundaries of the normal range for the four fetal growth measurements. The subject-specific effect due to repeated measures across time during pregnancy was considered using mixed-effects models. Because ultrasound measures

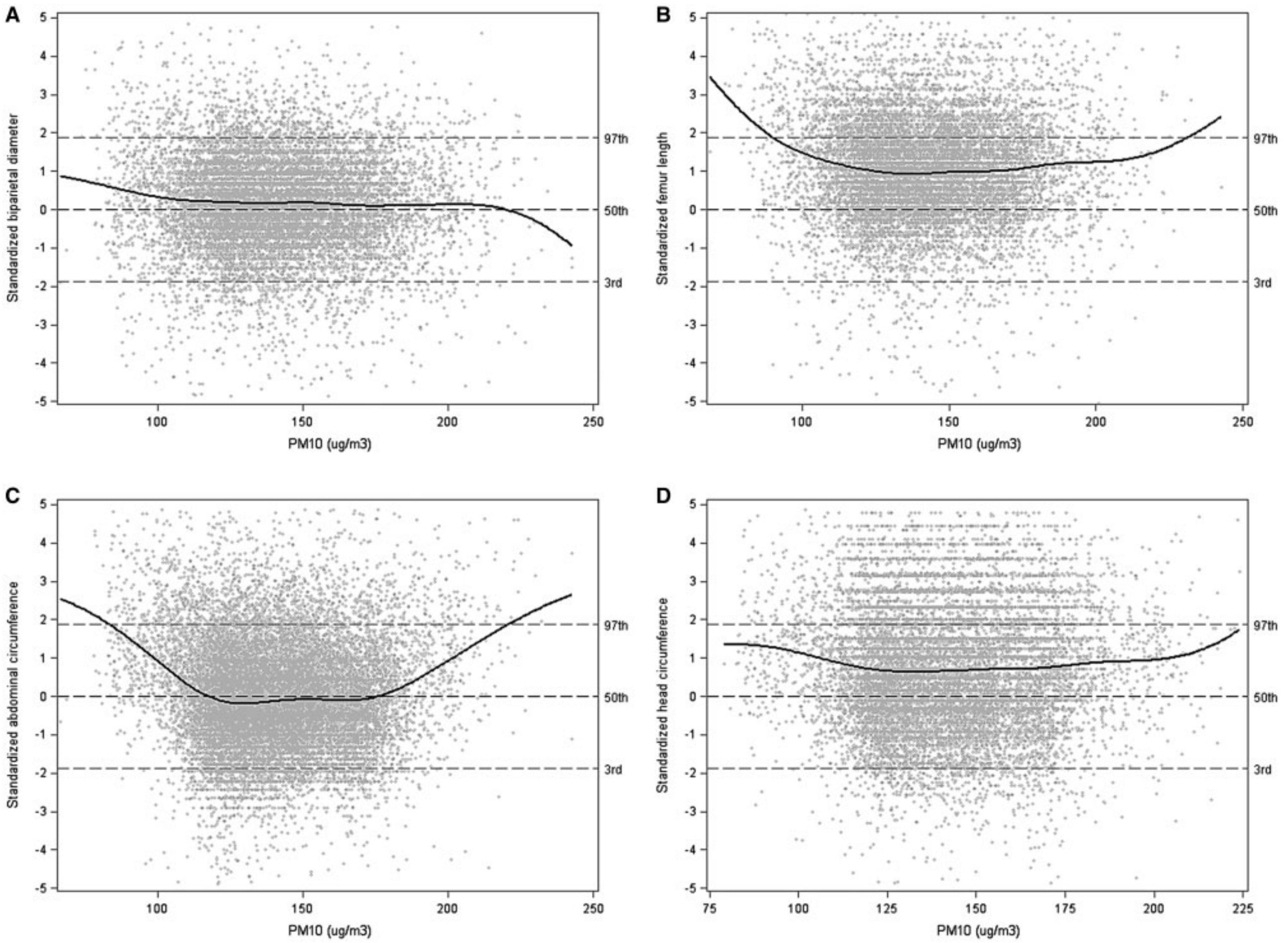

Figure 1. The Scatter Plots of Associations Between Standardized Fetal Measurements (Z Scores) and PM_{10} Exposure Levels (μg/m^3) During Pregnancy.

Horizontal refernce lines at 3rd, 50th, and 97th centiles showed the cutoffs of undergrowth, normal growth, and overgrowth for fetal biparietal diameter (A), fetal femur length (B), fetal abdominal circumference (C), and fetal head circumference (D) measured by ultrasound according to gestational age. Dark black lines are the smooth nonparametric curves. Opens gray dots showed actual observations.

were recorded irregularly for each subject (one to four scans), the time intervals between measurements would be more or less unique to each subject. Under these circumstances, a continuous-time model is needed to describe the covariance among the errors; PROC MIXED with the spatial power covariance function (repeated/type = SP(POW) (gestational weeks at ultrasound)) was used for this purpose.[41,42] The linear mixed model was fitted to calculate the mean change and the 95% confidence interval (CI) of the Z score of fetal growth measurements which was associated with maternal exposure to PM_{10}. Then the generalized linear mixed model (mixed effects logistic regression) was fitted to calculate the odds ratio (OR) and 95% CI of the associations between maternal exposure to PM_{10} and risks of under-growth and over-growth. Normal growth was treated as the reference group for each of the analyses. Exposures of each subject to NO_2 and SO_2 were estimated in the same manner as PM_{10}, and the average levels of SO_2 (49.0 μg/m^3) and NO_2 (43.9 μg/m^3) during pregnancy in our study area were lower than the China NAAQS standard (80 μg/m^3 and 50 μg/m^3),[43] indicating these two pollutants were not the main components of air pollution in this city. Therefore, models were corrected for SO2, NO2 and daily temperature by using the averages as the continuous variables over the same exposure windows as for PM_{10}. Exposure to PM_{10} was analysed as a continuous variable and, in a separate model, as a binary variable meeting or exceeding the US 24-h, health-based National Ambient Air Quality Standard (NAAQS, 150 μg/m^3, equivalent to the China NAAQS Grade II level).[43,44]

All models were first adjusted for known determinants of fetal growth characteristics as shown in Table 1. For the final model selection, the Akaike information criterion was used with forward-selection procedure on covariates considered to be determinants of growth.[45] We checked for the multi-collinearity of all variables in the model, especially for the effects of multiple pollutants including SO_2 and NO_2 exposures, as well as the daily temperature. The

variation inflation factors varied from 1.02 to 2.57, demonstrating a lack of multi-collinearity. The same exposure windows were used for SO_2, NO_2 and temperature as for PM_{10} exposure in corresponding models. All analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC).

Results

There were 8770, 8537, 7733 and 8009 participants with ultrasound measurements of HC, AC, FL and BPD, respectively. The study included a total of 14 560, 18 583, 12 383 and 13 619 scans during the entire pregnancy for ultrasound measures of HC, AC, FL and BPD, respectively. According to the international standard fetal growth measurement cutoffs set at the 3rd and 97th centiles, for the standardized fetal growth measurements (Z scores): 515 HC (3.5%), 1316 AC (7.1%), 208 FL (1.7%) and 557 BPD (4.1%) scans were catergorized as under-growth; 11 012 HC (75.6%), 17 007 AC (91.5%), 9395 FL (75.9%) and 12 266 BPD (90.1%) scans were catergorized as normal growth; and 3033 HC (20.8%), 1576 AC (8.4%), 2779 FL (22.4%) and 796 BPD (5.8%) scans were catergorized as over-growth.

Table 1 shows the distributions of selected characteristics of the study population. More than half of the women were younger than 30 years (63.5%), nulliparous (75.1%) and non-smokers during pregnancy (81.0%), and had higher education levels (62.7%) and normal pre-pregnancy body mass index (BMI) (68.9%).

Table 2 presents the associations between PM_{10} exposures averaged by different exposure windows, and ultrasound measurement Z-scores. When average PM_{10} exposure from conception until the ultrasound examination exceeded 150 $\mu g/m^3$, there were significant increases in standardized FL ($\beta = 0.095$, $P = 0.0012$) and HC ($\beta = 0.090$, $P = 0.0078$) measures, compared with $PM_{10} < 150\ \mu g/m^3$. When we treated the PM_{10} exposure as continuous variable, we found a significant decrease in BPD ($\beta = -0.018$, $P = 0.0016$) as per 10 $\mu g/m^3$ increase in PM_{10}.

Table 3 shows the associations between PM_{10} exposures averaged by different exposure windows, and risks of under-growth, and over-growth. When PM_{10} exposure was estimated from conception until the ultrasound, compared with $PM_{10} < 150\ \mu/m^3$, $PM_{10} \geq 150\ \mu g/m^3$ was associated with an increased risk of overgrowth [odds ratio (OR), 1.22; 95% CI, 1.04, 1.42 for FL, and 1.19; 1.07, 1.33 for HC]. PM_{10} was associated with a reduced risk of BPD overgrowth when PM_{10} was treated as $< 150\ \mu g/m^3$ versus $\geq 150\ \mu g/m^3$ or a continuous variable during 1 month or 2 weeks before ultrasound examinations.

Table 2. Association between averaged PM_{10} exposure during the different exposure windows and the mean change in standardized fetal ultrasound measurements (Z scores)

Exposure windows	BPD ($n = 8009$)		FL ($n = 7733$)		AC ($n = 8537$)		HC ($n = 8770$)	
	β[a]	95% CI	β[a]	95% CI	β[a]	95% CI	β[a]	95% CI
Mean change comparing exposures ≥ 150 μg/m³ PM₁₀ with those < 150 μg/m³								
From conception to ultrasound	0.016	−0.035, 0.067	0.095**	0.038, 0.153	0.001	−0.046, 0.049	0.090**	0.024, 0.156
One month before ultrasound	−0.052	−0.097, 0.007	−0.007	−0.051, 0.038	−0.044	−0.082, 0.003	0.092*	0.020, 0.151
Two weeks before ultrasound	−0.037	−0.083, 0.008	−0.043	−0.089, 0.002	−0.037	−0.076, 0.002	0.020	−0.040, 0.080
One week before ultrasound	−0.034	−0.079, 0.011	−0.005	−0.050, 0.040	-0.025	−0.064, 0.014	0.070*	0.010, 0.130
Mean change per 10 μg/m³ increase in PM₁₀								
From conception to ultrasound	−0.018**	−0.030, -0.007	0.008	−0.006, 0.022	0.005	−0.016, 0.006	0.011	−0.006, 0.029
One month before ultrasound	−0.004	−0.008, 0.000	−0.001	−0.005, 0.003	0.002	−0.007, 0.004	0.005*	0.000, 0.009
Two weeks before ultrasound	−0.002	−0.006, 0.002	0.002	−0.006, 0.003	0.002	−0.006, 0.001	0.008*	0.001, 0.011
One week before ultrasound	−0.002	−0.006, 0.002	0.000	−0.004, 0.004	−0.002	−0.005, 0.002	0.004*	0.000, 0.009

[a]Adjusted for maternal age (< 30, ≥ 30 years), education (< college, ≥ college), family monthly income per capita (< 3000, ≥ 3000 RMB), smoking during pregnancy (yes, no), pre-pregnancy BMI (≤ 18.5, 18.5–24.0, ≥ 24.0), weight gain du.ring pregnancy (≤ 15 kg, 15–18.5 kg, > 18.5 kg), parity (primiparous, multiparous), season of conception (spring/summer, autumn/winter), cooking fuel (gas/electricity, coal/biomass), estimated SO_2, NO_2 by different corresponding exposure windows, and averaged temperature during different corresponding exposure windows. *$P < 0.05$; **$P < 0.01$.

Table 3. Association between averaged PM_{10} during the different exposure windows and risks of fetal under-growth and over-growth

Exposure windows	BPD ($n = 8009$)		FL ($n = 7733$)		AC ($n = 8537$)		HC ($n = 8770$)	
	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI
Number of pregnancies in each model								
Normal growth	7005		5662		6989		6378	
Under-growth	438		189		393		367	
Over-growth	566		1882		1155		1665	
Risk comparing exposures ≥ 150 μg/m³ PM_{10} with those < 150 μg/m³								
From conception to ultrasound								
Under-growth	1.13	0.89, 1.43	1.04	0.72, 1.50	0.86	0.73, 1.01	1.02	0.81, 1.30
Overg-rowth	1.00	0.81, 1.23	1.22*	1.04, 1.42	1.03	0.87, 1.21	1.19**	1.07, 1.33
One month before ultrasound								
Under-growth	1.04	0.85, 1.26	0.87	0.62, 1.22	1.08	0.84, 1.39	0.98	0.78, 1.23
Over-growth	0.83*	0.69, 0.99	0.97	0.87, 1.08	0.95	0.83, 1.09	1.08*	1.00, 1.19
Two weeks before ultrasound								
Under-growth	0.80	0.64, 1.01	1.08	0.78, 1.50	1.09	0.94, 1.26	0.97	0.76, 1.24
Over-growth	0.79**	0.66, 0.94	0.91	0.81, 1.02	0.91	0.79, 1.04	1.03	0.93, 1.14
One week before ultrasound								
Under-growth	0.89	0.72, 1.09	0.86	0.61, 1.20	1.09	0.94, 1.26	0.99	0.77, 1.26
Over-growth	0.87	0.73, 1.04	0.96	0.86, 1.07	0.97	0.85, 1.11	1.11*	1.00, 1.23
Risk per 10 μg/m³ increase in PM_{10}								
From conception to ultrasound								
Under-growth	1.03	0.98, 1.07	0.99	0.92, 1.07	0.98	0.93, 1.02	0.99	0.92, 1.06
Over-growth	0.98	0.94, 1.02	1.01	0.98, 1.04	1.01	0.98, 1.05	1.02	0.99, 1.05
One month before ultrasound								
Under-growth	1.00	0.98, 1.02	0.99	0.96, 1.02	1.00	0.99, 1.02	1.00	0.98, 1.02
Over-growth	0.98*	0.97, 1.00	1.00	0.99, 1.01	0.99	0.98, 1.01	1.01*	1.00, 1.02
Two weeks before ultrasound								
Under-growth	0.99	0.97, 1.01	1.00	0.97, 1.03	1.00	0.99, 1.02	1.00	0.97, 1.02
Over-growth	0.98**	0.96, 0.99	0.99	0.98, 1.01	1.00	0.99, 1.01	1.01*	1.00, 1.02
One week before ultrasound								
Under-growth	0.99	0.97, 1.01	0.99	0.96, 1.02	1.00	0.99, 1.01	1.00	0.97, 1.02
Over-growth	0.99	0.97, 1.01	1.00	0.99, 1.01	1.00	0.98, 1.01	1.01*	1.00, 1.02

[a]Adjusted for maternal age (< 30, 30 years), education (< college, college), family monthly income per capita (< 3000, ≥ 3000 RMB), smoking during pregnancy (yes, no), pre-pregnancy BMI (≤ 18.5, 18.5–24.0, ≥ 24.0), weight gain during pregnancy (≤ 15 kg, 15–18.5 kg, > 18.5 kg), parity (primiparous, multiparous), season of conception (spring/summer, autumn/winter), cooking fuel (gas/electricity, coal/biomass), estimated SO_2, NO_2 by different corresponding exposure windows, and averaged temperature during different corresponding exposure windows. *$P \le 0.05$; **$P < 0.01$.

Compared with the results of cumulative exposure from conception to the ultrasound examination, similar positive associations were only observed for HC measures for other exposure windows, 1 month before ultrasound examinations and 1 or 2 weeks before ultrasound examinations, when PM_{10} was treated as < 150 μg/m³ versus ≥ 150 μg/m³ or a continuous variable (Tables 2 and 3).

Discussion

Our results support the hypothesis that prenatal exposure to high levels of ambient PM_{10} is associated with increased risk of fetal under- and over-growth. Our study also suggests a stronger and consistent association of over-growth for HC over the different exposure windows compared with other fetal growth parameters.

To the best of our knowledge, our study was the first one to examine the associations between prenatal exposure to PM_{10} and risk of fetal over-growth. We found that exposure to higher levels of PM_{10} increased the risk of fetal HC over-growth. In early studies conducted in Australia, Europe and the USA, Hansen *et al.*[5] found reductions of FL, AC and HC associated with increased exposure to PM_{10} during gestational days 91–120, and a reduction of FL measurement during 0–30 days of gestation; van den Hooven *et al.*[22] observed reduction in HC in the third trimester; and Ritz *et al.*[23] reported that no association was observed between PM_{10} exposure and HC, FL and AC.

Although van den Hooven *et al.* did not highlight the findings that there were significant increases in HC measures during the second trimester in the second and third quartiles of PM_{10} exposure, and that there were significant increases in fetal weight in higher quartiles (second, third and fourth) of PM_{10} exposure, these findings were similar to ours. Although the underlying mechanisms are currently unclear, a growing body of literature suggests that increased oxidative stress and inflammatory response to PMs can influence energy expenditure, resulting in increased dietary intake.[32,33] There was an increasing awareness that changes in placental metabolism and nutrient transport capacity might contribute to altered fetal growth.[46] Human studies showed that higher cord blood leptin levels caused by greater weight gain were associated with increased fetal size,[47] and altered expression of maternal insulin-like growth factor due to excessive gestational weight gain contributed to increased fetal growth through increased placental nutrient transporter expression.[48,49] It is possible that the positive relationship between ambient air pollutants and fetal over-growth was mediated by maternal BMI/weight gain. In our study, pregnant women carrying an overgrown fetus were more likely to be in the highest category of maternal weight gain and to be pre-pregnancy obese.

Comparing the study results among the published studies and ours was challenging. The outcome measures varied across different studies, including differences in ultrasound measurement methods and potential of inter-sonographer variations. The exposure assessment also varied across the studies. van den Hooven *et al.*[22] performed dispersion modelling based on home addresses only, though allowing for residential mobility; Hansen *et al.*[5] estimated monthly exposure to nearest monitors using IDW over the first 4 months and restricted analysis through four exposure windows (0–30, 31–60, 61–90, 91–120 days of gestation). Ritz *et al.*[23] considered a 2-weeks exposure window around each measurement time (at 19.1, 28.8 and 36.7 weeks of gestation). In addition, all these published studies were conducted in low-air-pollution areas as compared with our study. The compositions of PM_{10} in different studies might also be different and could cause a different impact on fetal growth.

Our study included large sample size ($N = 8877$) with a relatively large number of ultrasound scans for each fetal parameter ($N \sim 18\ 583$), compared with previous studies.[5,22,23] It allowed exploration of association by subgroups based on the growth status. Our study assessed exposure based on both home and work addresses with consideration of residential mobility, as well as PM_{10} exposure through different exposure windows, which minimized potential exposure misclassification and ability to explore critical exposure time windows on fetal growth. Detailed information on potential confounding factors such as smoking, cooking fuels and other co-exposure air pollutants were collected and included in our analyses. All participants were recruited from the same hospital and the information on ultrasound measurements was obtained from medical records, so potential misclassifications of fetal measurements were minimized. Additionally, with a potential U-shape relationship between air pollution and fetal growth, we employed the latest international fetal growth standard to examine the association with both under-growth and over-growth, in addition to treating growth measurements as continuous variables as done by earlier studies.[5,22,23] This potential heterogeneity of PM_{10} exposure effects on fetal growth measurements still calls for future study with larger sample size, to replicate and confirm our findings.

Limitations should be considered when interpreting the study results. The accuracy of exposure estimation might be limited by the lack of monitors in rural areas in Lanzhou city. However, more than 90% of the women lived within 5.5 km of a monitor. Sensitivity analyses using the data from different exposure assessment approaches (nearest monitors, IDW using two or four monitors, using data for the women living within 5.5 km or 12.9 km of a monitor) showed consistent results. PM_{10} exposure was estimated using data from government monitors which, though the most commonly used method in air pollution epidemiology, may not represent the actual individual exposure level which would include differences in indoor/outdoor activity patterns, and may not consider intra-urban gradients in pollutants. However, measurements through personal air monitors in this setting (pregnancy, in a large population) may be impractical as well as expensive, and numerous studies have used the above monitoring approach successfully. To evaluate whether the four monitors provided reasonable spatial coverage in our study, we calculated the coefficient of divergence, which provides the diversity between concentrations at sampling site-pairs.[50] We found that coefficients of divergence for all site-pairs were lower than 0.20, indicating low spatial heterogeneity of PM_{10} in our study area. However, future studies might consider additional monitor coverage, in order to address the issues of spatial heterogeneity and improve estimates of exposure. Although the exact sources of PM_{10} in Lanzhou city are still unclear, a factory of the China Petroleum and Chemical Corporation (Sinopec Limited) has been located in the west, an upwind location of this city. Future work may investigate PM sources, which have different chemical structures and possibly different health impacts. The measurement errors with respect to the outcomes would be another concern both in previous large epidemiological

studies and in the current study, because it is possible that the ultrasound examinations at different gestational weeks were performed by different clinicians/technicians. However, GPMCCH is the largest maternity and child care hospital in Lanzhou, China. The hospital performs internal quality control in order to provide high-quality ultrasound examinations, and the historical records of reproducibility also demonstrated that the measurement errors would be likely minimized.

In conclusion, our study supports the hypothesis that prenatal exposure to high levels of ambient PM_{10} increases the risk of abnormal fetal growth, and stronger and consistent associations were mainly seen for HC over-growth by different exposure windows compared with other fetal growth measurements. This study suggests that the associations between maternal exposure to PM_{10} and fetal growth may vary by different fetal growth measurements (BPD, FL, AC and HC) and fetal growth patterns (under-/over-growth). Future multi-site studies with different types of air pollutants are needed to fully understand the impacts of air pollution combinations on fetal growth. Our study also calls for future studies to explore the underlying mechanisms and post-natal consequences of these findings

Supplementary Data

Supplementary data are available at *IJE* online.

Funding

The work was supported by internal funding from the Gansu Provincial Maternity and Child Care Hospital, Gansu Provincial Science and Technology Department Grant (1204WCGA021), National Institutes of Health Grants (K02HD70324, R01ES019587) and the U.S. Environmental Protection Agency (EPA-G2014-STAR-J1).

Author Contributions

J.Q., Q.L. and Y.Z. designed the research; X.L., Z.T. and H.Z. conducted the birth cohort study; Y.Z. collected air pollution and meteorology data; N.Z. and H.H. managed the study and cleaned the database; N.Z., S.M., Y.H. and N.M. performed statistical analysis; N.Z. constructed the figures; N.Z., M.B. and Y.Z. wrote the first draft, and all authors contributed to the final draft and approved the manuscript.

Conflict of interest: None declared.

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