Environmental Pollution 227 (2017) 484–489

Contents lists available at ScienceDirect

Environmental Pollution

journal homepage: www.elsevier.com/locate/envpol

Maternal serum lead level during pregnancy is positively correlated with risk of preterm birth in a Chinese population☆

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ARTICLE INFO

Article history:
Received 11 December 2016
Received in revised form
2 April 2017
Accepted 3 May 2017

Keywords:
Lead
Serum
Preterm birth
Birth cohort study

ABSTRACT

Lead (Pb) is a well-known developmental toxicant. The aim of the present study was to analyze the association between maternal serum Pb level and risk of preterm birth in a population-based birth cohort study. The present study analyzed a sub-study of the China-Anhui Birth Cohort that recruited 3125 eligible mother-and-singleton-offspring pairs. Maternal serum Pb level was measured by graphite furnace atomic absorption spectrometry. All subjects were classified into three groups by tertile division according to serum Pb level: Low-Pb (L-Pb, <1.18 μg/dl), Medium-Pb (M-Pb, 1.18–1.70 μg/dl), and High-Pb (H-Pb, ≥1.71 μg/dl). The rate of preterm birth was 2.8% among subjects with L-Pb, 6.1% among subjects with M-Pb, and 8.1% among subjects with H-Pb, respectively. After controlling confounding factors, the adjusted OR for preterm birth was 2.33 (95%CI: 1.49, 3.65) among subjects with M-Pb and 3.09 (95%CI: 2.01, 4.76) among subjects with H-Pb. Of interest, maternal Pb exposure in early gestational stage than in middle gestational stage was more susceptible to preterm birth. Moreover, maternal serum Pb level was only associated with increased risk of late preterm birth. The present study provides evidence that maternal serum Pb level during pregnancy is positively associated with risk of preterm birth in a Chinese population.

1. Introduction

Lead (Pb) is one of important heavy metals that can be detected in almost all environmental compartments including surface water, soil, and atmosphere (Cheng et al., 2015; Dang et al., 2015; Marx et al., 2016; Romero-Freire et al., 2015). Workers in paints, welding, electroplating, smeltering, pigments, battery and e-waste recycling workshops are generally exposed to fairly high concentrations of Pb (Grashow et al., 2014; Julander et al., 2014; Kazi et al., 2015; Martin et al., 2005; Zhang et al., 2016). On the other hand, the general population is exposed to relatively low concentrations of Pb through polluted air, food, drinking water and cigarette smoking (Augustsson et al., 2015; Cheng et al., 2015; Clark et al., 2014; Mohmand et al., 2015; Pinto et al., 2017).

Accumulating evidence suggests that maternal Pb exposure could produce a developmental toxicity in the fetuses (Chen et al., 2011). According to several reports from rodent animals, maternal Pb exposure during gestational period disturbed brain and neurobehavioral development in offspring (Kasten-Jolly et al., 2012; Schneider et al., 2016). A recent epidemiological report showed that maternal blood Pb (B-Pb) level in the first trimester was negatively correlated with the scores of neonatal behavioral neurological assessment (Liu et al., 2014). Preterm birth, defined as a live birth at less than 37 gestational weeks, is a major reason for low birth weight and neonatal death (Goldenberg et al., 2008). In addition, preterm birth is associated with the adverse neurodevelopmental and behavioral outcomes (Anderson et al., 2003; Bora et al., 2014; Welch et al., 2015). A prospective birth cohort study showed that pregnant women with high B-Pb level increased risk of preterm birth but not of having a low birth weight baby

☆ This paper has been recommended for acceptance by David Carpenter.
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http://dx.doi.org/10.1016/j.envpol.2017.05.009
0269-7491/

(Taylor et al., 2015). A recent report from a matched case-control study found that maternal Pb concentration in urine was associated with risk of preterm low birth weight (Zhang et al., 2015). Nevertheless, the association between maternal serum Pb concentration and risk of preterm birth needs to be determined.

The aim of the present study was to analyze maternal serum Pb level in different trimesters and to evaluate the association between maternal serum Pb level and risk of preterm birth in a Chinese population. Our results demonstrate that maternal serum Pb level is positively associated with risk of preterm birth.

2. Materials and methods

2.1. Study population

The present study analyzed a sub-study of the China-Anhui Birth Cohort Study (C-ABCS) that recruited 4358 pregnant women from Hefei city from January 1 to December 31 in 2009 (Tao et al., 2013). Exclusion criteria were as follows: inability to provide informed consent, alcohol drinking and cigarette smoking during pregnancy, mental disorders, pregnancy-induced hypertension and preeclampsia, gestational diabetes, heart disease, thyroid-related disease, a history of ≥3 previous miscarriages, or plans to leave local places before delivery (Tao et al., 2013). For this study, eligible participants were mother-and-singleton-offspring pairs, in which serum samples from mothers were available for subsequent analysis and their offspring had a detailed birth record. Thirty-six pregnant women giving birth to twins, 15 dead fetuses, 2 stillbirths, 58 abortions and 589 withdrew were excluded from this study. In the current study, pregnant women were enrolled throughout pregnancy, and sera at different gestational stages were collected from different pregnant women. In addition, 439 unavailable for maternal serum and 94 maternal serum collected at the third trimester were also excluded. The median time for serum collection is 14 weeks (Minimum 4 weeks, Maximum: 27 weeks). Total 3125 mother-and-singleton-offspring pairs were eligible for this study. The present study was approved by the ethics committee of Anhui Medical University (permit 08-1026). The methods were carried out in accordance with the approved guidelines.

2.2. Definition of preterm birth

Gestational week was calculated using mother's last menstrual period. Preterm birth was defined as a live birth at less than 37 completed gestational weeks (Athalye-Jape et al., 2014). In this study, total 177 premature infants with spontaneous and non-medical preterm birth were identified. According to a recently described method (Katz et al., 2013), preterm birth can be further sub-divided into early preterm birth (EPTB, <32 gestational weeks), moderate preterm birth (MPTB, 32 to <34 gestational weeks) and late preterm birth (LPTB, 34 to <37 gestational weeks).

2.3. Serum Pb measurement

Maternal fasting blood was collected in the first and second trimesters (median time for serum collection: 14 gestational weeks; Range from 4 to 27 gestational week). After discarding hemolytic specimens, available sera were stored at −80 °C until analysis. In this study, total 3125 samples were measured for serum lead level by graphite furnace atomic absorption spectrometry (GFAAS; model: TAS-990; Purkinje General Instrument Co., Ltd, Beijing, China) coupled with a deuterium-lamp background correction system. All samples were prepared and analyzed according to previously described method with minor modification (Sakellari et al., 2016). Serum samples were diluted with 1% HNO_3 (including 0.5% TritonX-100) according to 1:4 (v/v). Matrix modifiers, mixed with 0.5% $NH_4H_2PO_4$ and 0.2% Mg $(NO_3)_2$, were added to each standard, blank and sample dilution. Following diluted solution was then detected using GFAAS. To avoid contamination of exogenous lead, all volumetric flasks, polypropylene tubes and pipette tips were soaked for at least 24 h in 15% HNO_3 at room temperature and rinsed persistently in ultrapure water before use. Each sample was analyzed in triplicate. Precision of the method was measured by coefficients of variation. Mean CV for serum lead measurement was 9.3% for within-day determinations and 5.5% for day-to-day determinations. The limit of detection for this method was 0.020 μg/dl. The accuracy of the GFAAS method was evaluated by the recovery rate of the standard addition method for lead. The average recovery percentage using standard addition method is 104.7%. According to previously described methods, All subjects were classified into three groups by tertile division according to maternal serum Pb level: L-Pb (Low-Pb <1.18 μg/dl), M-Pb (Medium-Pb 1.18−1.70 μg/dl) and H-Pb (High-Pb ≥1.71 μg/dl).

2.4. Statistical analysis

The proportions of maternal and neonatal characteristics and the rate for preterm birth among different groups were analyzed using the chi-square test. The means of characters and maternal serum lead level between two groups were analyzed using independent-sample *t*-test. For multiple comparisons, we used one-way ANOVA followed by Bonferroni's or Tamhane's T2 *post hoc* test. The odds ratios (*OR*) and 95% confidence intervals (*CI*) for the association between maternal serum lead level and risk of preterm birth were estimated using multiple logistic regression models. We calculated unadjusted and adjusted estimates using exact methods and asymptotic methods, respectively (Kernan et al., 2000). According to previous findings (Hammond et al., 2013; Henderson et al., 2012; Koullali et al., 2016), there were associations between some confounding factors and preterm birth. As a result, the potential factors were chosen for inclusion in the base model. We sequentially tested each maternal characters listed in the basic model, which included maternal age, pre-pregnancy BMI, monthly income, gravidity and parity. We also adjusted for the variables that, when added to this model, changed the *OR* for preterm birth by more than 10% (Kernan et al., 2000). To control potential confounding factors that influence the association between maternal lead exposure during pregnancy and preterm birth, we adjusted for maternal age, pre-pregnancy BMI, monthly income, gravidity and parity. We preformed all statistical analyses with *Empower Stats* or *SPSS* 16.0. All statistical tests were two-sided using an alpha level of 0.05.

3. Results

In this study, 3125 pregnant women were recruited for serum Pb measurement. The mean serum Pb level was 1.50 μg/dl (minimum: 0.020 μg/dl; maximum: 5.46 μg/dl) among all subjects. The demographic characteristics of pregnant women and their newborns were analyzed among different groups (L-Pb, M-Pb and H-Pb). No statistically significant difference on mother's age, pre-pregnancy BMI and monthly income was observed among three groups (Table 1).

The association between maternal serum Pb level during pregnancy and risk of preterm birth was analyzed. As shown in Table 2, the rate of preterm birth among subjects with L-Pb, M-Pb and H-Pb was 2.8%, 6.1%, and 8.1%, respectively. The *OR* for preterm birth was 2.29 (95%*CI:* 1.46, 3.58; $P < 0.001$) in subjects with M-Pb and 3.07 (95%*CI:* 1.99, 4.72; $P < 0.001$) in subjects with H-Pb. To analyze the influence of confounding factors on the risk of preterm birth, the

Table 1
Maternal serum lead level according to maternal characteristics.

Maternal characteristics	*n* (%)	Maternal serum lead level (μg/dl)	
		Median (IQR[a])	*P*-value
Age (y)			
≤24	485 (15.5)	1.43 (1.19, 1.69)	0.47
25-29	1963 (62.8)	1.45 (1.18, 1.72)	
≥30	677 (21.7)	1.41 (1.15, 1.67)	
Prepregnancy BMI (kg/m^2)			
<18.5	671 (21.5)	1.43 (1.18, 1.72)	0.78
18.5–24.9	2360 (75.5)	1.44 (1.18, 1.69)	
>25	94 (3.0)	1.40 (1.21, 1.75)	
Gravidity			
Primigravida	1625 (52.0)	1.42 (1.17, 1.67)	0.23
Multigravida	1500 (48.0)	1.46 (1.20, 1.72)	
Parity			
Nulliparous	3033 (97.1)	1.43 (1.18, 1.70)	0.92
Multiparous	92 (2.9)	1.46 (1.12, 1.81)	
Monthly income			
Low[b]	1422 (45.5)	1.41 (1.17, 1.67)	0.35
Middle[b]	1275 (40.8)	1.46 (1.18, 1.74)	
High[b]	428 (13.7)	1.44 (1.19, 1.79)	
Time of serum collection			
First trimester	1083 (34.7)	1.43 (1.18, 1.74)	0.99
Second trimester	2042 (65.3)	1.43 (1.18, 1.69)	

[a] IQR denotes interquartile range.
[b] Low income for <2000 RMB per month; middle income for 2000-4000 RMB per month; high income for ≥4000 RMB per month.

Table 2
Association between risk for preterm birth (<37 gestational weeks) and maternal serum lead level during pregnancy.

	Maternal serum lead level[a]			*P*-value
	L-Pb	M-Pb	H-Pb	
Newborns, n	1042	1042	1041	
Preterm births, n	29	64	84	
Rate, %	2.8	6.1	8.1	<0.001
Univariate OR (95% CI)	1.00	2.29 (1.46, 3.58)	3.07 (1.99, 4.72)	<0.001
Adjusted OR (95% CI)[b]	1.00	2.33 (1.49, 3.65)	3.09 (2.01, 4.76)	<0.001

[a] According to tertile division, maternal serum lead level was classified as L-Pb (<1.18 μg/dl), M-Pb (1.18–1.70 μg/dl) and H-Pb (≥1.71 μg/dl).
[b] Adjusted for prepregnancy BMI, maternal age, time of serum collection, gravidity, parity, and monthly income.

Table 3
Association between maternal characteristics and risk for preterm birth (<37 gestational weeks).

Maternal characteristics	*n* (%)	Preterm birth	
		OR (95% *CI*)	*P*-value
Age			
≤24 y	485 (15.5)	0.94 (0.60, 1.47)	0.80
25–29 y	1963 (62.8)	1.00	–
≥30 y	677 (21.7)	1.24 (0.86, 1.77)	0.25
Prepregnancy BMI (kg/m^2)			
<18.5	671 (21.5)	1.42 (1.00, 2.01)	0.049
18.5–24.9	2360 (75.5)	1.00	–
≥25	94 (3.0)	2.50 (1.30, 4.81)	0.006
Gravidity			
Primigravida	1625 (52.0)	1.00	–
Multigravida	1500 (48.0)	0.81 (0.59, 1.09)	0.17
Parity			
Nulliparous	3033 (97.1)	1.00	–
Multiparous	92 (2.9)	1.61 (0.77, 3.39)	0.21
Monthly income			
Low[a]	1422 (45.5)	1.16 (0.72, 1.88)	0.82
Middle[a]	1275 (40.8)	1.09 (0.67, 1.78)	0.74
High[a]	428 (13.7)	1.00	–
Time of serum collection			
First trimester	1083 (34.7)	1.00	–
Second trimester	2042 (65.3)	1.22 (0.88, 1.70)	0.23

[a] Low income for <2000 RMB per month; middle income for 2000-4000 RMB per month; high income for ≥4000 RMB per month.

association of maternal characteristics with risk of preterm birth was analyzed. As expected, the risk of preterm birth was negatively associated with pre-pregnancy BMI (Table 3, $P = 0.007$). Interestingly, no association was observed between the risk of preterm birth and maternal age, gravidity, parity and monthly income in this study (Table 3). After controlling for pre-pregnancy BMI, maternal age, time of serum collection, gravidity, parity, and monthly income, the adjusted *OR* for preterm birth was 2.33 (95%*CI*: 1.49, 3.65; $P < 0.001$) in subjects with M-Pb and 3.09 (95%*CI*: 2.01, 4.76; $P < 0.001$) in subjects with H-Pb (Table 2).

Serum Pb level in the first trimester was analyzed among 1083 pregnant women. Mean serum Pb level in the first trimester was 1.52 μg/dl (median: 1.43 μg/dl; minimum: 0.025 μg/L; maximum: 5.16 μg/dl). Serum Pb level in the second trimester was analyzed among 2042 pregnant women. Mean serum Pb level in the second trimester was 1.49 μg/dl (median: 1.43 μg/dl; minimum: 0.022 μg/dl; maximum: 5.46 μg/dl). No significant difference on serum Pb levels was observed between the first trimester and the second trimester. The association between maternal serum Pb level in the first trimester and the risk of preterm birth was analyzed. As shown in Table 4, the rate of preterm birth among subjects with L-Pb, M-Pb and H-Pb was 1.4%, 6.1%, and 7.4%, respectively. The adjusted *OR* for preterm birth was 4.69 (95%*CI:* 1.75, 12.60; $P = 0.002$) in subjects with M-Pb and 5.77 (95%*CI:* 2.20, 15.13; $P < 0.001$) in subjects with H-Pb in the first trimester (Table 4). The association between maternal serum Pb level in the second trimester and risk of preterm birth was then analyzed. As shown in Table 4, the rate of preterm birth among L-Pb, M-Pb and H-Pb was 3.5%, 6.2%, and 8.4%, respectively. The adjusted *OR* for preterm birth was 1.83 (95%*CI:* 1.10, 3.05; $P = 0.02$) in subjects with M-Pb and 2.55 (95%*CI:* 1.56, 4.17; $P < 0.001$) in subjects with H-Pb in the second trimester (Table 4).

The association for maternal serum Pb level and risk of EPTB was analyzed. As shown in Table 5, the rate of EPTB among subjects with L-Pb, M-Pb and H-Pb was 0.8%, 0.8%, and 0.7%, respectively. No association between maternal serum Pb level and risk of EPTB was observed (Table 5). The association between maternal serum Pb level and risk of MPTB was then analyzed. As shown in Table 5, the rate of MPTB among subjects with L-Pb, M-Pb and H-Pb was 0.7%, 1.08%, and 1.7%, respectively. No association between maternal serum Pb level and the risk of MPTB was observed (Table 5). Finally, the association between maternal serum Pb level and risk of LPTB was analyzed. As shown in Table 5, the rate of LPTB among subjects with L-Pb, M-Pb and H-Pb was 1.3%, 4.4%, and 5.7%, respectively. The *OR* for LPTB was 3.40 (95%*CI:* 1.86, 6.23; $P < 0.001$) in subjects with M-Pb and 4.46 (95%*CI:* 2.47, 8.04; $P < 0.001$) in subjects with H-Pb. The adjusted *OR* for LPTB was 3.51 (95%*CI:* 1.92, 6.44; $P < 0.001$) in subjects with M-Pb and 4.62 (95%*CI:* 2.56, 8.34; $P < 0.001$) in subjects with H-Pb (Table 5).

4. Discussion

A recent birth cohort study showed that maternal B-Pb level was positively associated with risk of preterm birth (Taylor et al., 2015). According to another report from a matched case-control study, maternal urinary Pb concentration was associated with risk of preterm low birth weight (Zhang et al., 2015). The present study analyzed the association between maternal serum Pb concentration and risk of preterm birth in a population-based birth cohort study. We found that the rates of preterm birth were elevated

Table 4
Association between risk for preterm birth (<37 gestational weeks) and maternal serum lead level at different gestational stages.

	Maternal serum lead level[a]			*P*-value
	L-Pb	M-Pb	H-Pb	
First trimester				
Newborns, n	363	343	377	
Preterm births, n	5	21	28	
Rate, %	1.4	6.1	7.4	<0.001
Univariate *OR* (95% *CI*)	1.00	4.67 (1.74,12.53)	5.74 (2.19,15.05)	0.002
Adjusted *OR* (95% *CI*)[b]	1.00	4.69 (1.75,12.60)	5.77 (2.20,15.13)	0.002
Second trimester				
Newborns, n	679	699	664	
Preterm births, n	24	43	56	
Rate, %	3.5	6.2	8.4	<0.001
Univariate *OR* (95% *CI*)	1.00	1.79 (1.07,2.98)	2.51 (1.54,4.11)	0.0011
Adjusted *OR* (95% *CI*)[b]	1.00	1.83 (1.10,3.05)	2.55 (1.56,4.17)	<0.001

[a] According to tertile division, maternal serum lead level was classified as L-Pb (<1.18 μg/dl), M-Pb (1.18–1.70 μg/dl) and H-Pb (≥1.71 μg/dl).
[b] Adjusted for prepregnancy BMI, maternal age, parity, gravidity and monthly income.

Table 5
Association between risks for early, moderate and late preterm birth and maternal serum lead level during pregnancy.

Parameters	Maternal serum lead level[a]			*P*-value
	L-Pb (n = 1042)	M-Pb (n = 1042)	H-Pb (n = 1041)	
Early preterm birth[b]				
Number	8	8	7	–
Rate, %	0.8	0.8	0.7	0.976
Univariate *OR* (95%*CI*)	1.00	1.04 (0.39, 2.77)	0.93 (0.34, 2.56)	0.976
Adjusted *OR* (95%*CI*)[c]	1.00	1.04 (0.39, 2.78)	0.92 (0.33, 2.56)	0.974
Moderate preterm birth[b]				
Number	7	10	18	–
Rate (%)	0.7	1.0	1.7	0.047
Univariate *OR* (95%*CI*)	1.00	1.48 (0.56, 3.90)	2.72 (1.13, 6.55)	0.056
Adjusted *OR* (95%*CI*)[c]	1.00	1.48 (0.56, 3.92)	2.75 (1.14, 6.62)	0.056
Late preterm birth[b]				
Number	14	46	59	–
Rate (%)	1.3	4.4	5.7	<0.001
Univariate *OR* (95%*CI*)	1.00	3.40 (1.86, 6.23)	4.46 (2.47, 8.04)	<0.001
Adjusted *OR* (95%*CI*)[c]	1.00	3.51 (1.92, 6.44)	4.62 (2.56, 8.34)	<0.001

[a] According to tertile division, maternal serum lead level was classified as L-Pb (<1.18 μg/dl), M-Pb (1.18–1.70 μg/dl) and H-Pb (≥1.71 μg/dl).
[b] Preterm birth can be further sub-divided into early preterm birth (<32 gestational weeks), moderate preterm birth (32 to <34 gestational weeks) and late preterm birth (34 to <37 gestational weeks).
[c] Adjusted for pre-pregnancy BMI, maternal age, monthly income, time for collecting serum, parity and gravidity.

among subjects with M-Pb and H-Pb as compared with subjects with L-Pb. The adjusted *OR* for preterm birth was 2.33 (95%CI: 1.49, 3.65) among subjects with M-Pb. Surprisingly, the adjusted *OR* for preterm birth was 3.09 (95%CI: 2.01, 4.76) among subjects with H-Pb. These results suggest that maternal serum Pb level is positively associated with risk of preterm birth.

In the last decades, B-Pb has been used to evaluate the accumulated body burden in humans (Taylor et al., 2015; Zhu et al., 2010). On the other hand, urinary Pb is an accurate biomarker for recent Pb exposure and is positively correlated with B-Pb level (Yorita Christensen, 2013; Zhang et al., 2015). An early study indicated that the adverse effects of environmental Pb exposure were mainly associated with the most rapidly exchangeable Pb fraction in serum or plasma (Bergdahl et al., 1999). Indeed, Pb in maternal serum or maternal plasma was more freely available for exchange with target tissues, such as the placenta and the developing fetus (Chuang et al., 2001; Hernandez-Avila et al., 1998; Smith et al., 2002). A recent study found that maternal serum Pb level was positively correlated with serum Pb level in the umbilical cords (Amaral et al., 2010). Thus, the present study measured maternal serum Pb rather than B-Pb level or urinary Pb as an estimator for maternal Pb exposure during pregnancy.

Increasing evidence indicates that cigarette smoking is associated with maternal Pb exposure during gestational period (Mortada et al., 2004). On the other hand, numerous studies demonstrated that alcohol drinking and cigarette smoking were important risk factors for preterm birth (Janisse et al., 2014; Nykjaer et al., 2014). Thus, alcohol drinkers and cigarette smokers were excluded from the present study to control the influence of alcohol drinking and cigarette smoking as confounding factors. Several studies showed that preterm birth was associated with pre-pregnancy BMI and maternal education (Liu et al., 2016; Pan et al., 2016; Poulsen et al., 2015). Indeed, the present study showed that preterm birth was associated with both prepregnancy overweight and underweight. To control the influence of confounding factors including pre-pregnancy BMI, maternal age, monthly income, time for collecting serum, gravidity and parity, the adjusted OR for preterm birth was estimated using multiple logistic regressions. Our results showed that the adjusted *OR* for preterm birth remained 2.33 in subjects with M-Pb and 3.09 in subjects with H-Pb, respectively. These results suggest that maternal serum Pb level is an independent risk factor for preterm birth.

Until now, no report analyzed the association between maternal serum Pb level in different gestational stages and risk of preterm birth. The present study measured maternal serum Pb level in the first trimester among 1083 subjects and that of the second trimester among 2042 subjects. Although maternal serum Pb level in the first trimester was not different from that of the second

trimester, the adjusted *OR* for preterm birth was 4.69 (95%*CI*: 1.75, 12.60) among subjects with M-Pb in the first trimester, significantly higher than 1.83 (95%*CI*: 1.10, 3.05) among subjects with M-Pb in the second trimester. Correspondingly, the adjusted *OR* for preterm birth was 5.77 (95%*CI*: 2.20, 15.13) among subjects with H-Pb in the first trimester, significantly higher than 2.55 (95%*CI*: 1.56, 4.17) among subjects with H-Pb in the second trimester. These results suggest that maternal Pb exposure in early gestational stage than in middle gestational stage is more susceptible to preterm birth. Our findings might be very interesting, and need to be confirmed by further investigations.

Recently, preterm birth has been further sub-divided into EPTB, MPTB and LPTB according to gestational weeks (Katz et al., 2013; Sauber-Schatz et al., 2012; Yang et al., 2016a). An early report showed that EPTB elevated risk of severe adverse neurodevelopmental outcomes in offspring (Andrews et al., 2008). The present study analyzed the association between maternal serum Pb concentration and risk of EPTB. Unexpectedly, no association between maternal serum Pb level and risk of EPTB was observed. By contrast, the rates of LPTB were markedly increased among subjects with M-Pb and H-Pb. The *OR* for LPTB was 3.51 (95%CI: 1.92, 6.44) among subjects with M-Pb. Interestingly, the *OR* for LPTB was as highly as 4.62 (95%CI: 2.56, 8.34) among subjects with H-Pb. These results suggest that maternal serum Pb level is only associated with risk of LPTB.

The present study has several limitations. First, the present study did not exclude the influence of other metals including cadmium, arsenic, zinc and selenium, on preterm birth. Indeed, several studies showed that maternal exposure to cadmium and arsenic elevated risk of preterm birth (Ahmad et al., 2001; Wang et al., 2016b; Yang et al., 2016b). By contrast, maternal serum selenium and zinc levels during pregnancy were inversely associated with risk of preterm birth (Rayman et al., 2011; Wang et al., 2016a). Second, serum Pb levels at different gestational periods were measured among different pregnant women. Although there is no difference in the characteristics of mothers among different trimesters, further research is required to explore the association between maternal serum Pb level at different gestational periods and preterm birth among the same pregnant women. Third, the present study had not explored the mechanism through which maternal Pb exposure induced preterm birth. Several studies demonstrated that Pb was an inducer of endoplasmic reticulum (ER) stress (Liu et al., 2013; Mostafalou et al., 2015). According to a recent report, prolonged ER stress induces preterm birth in mice (Kawakami et al., 2014). Thus, it is plausible to speculate that maternal Pb exposure during pregnancy promotes preterm birth through inducing placental ER stress. Additional research is necessary to explore how maternal Pb exposure induces placental ER stress and preterm birth in animal experiments.

In summary, the present study investigated the association between maternal serum Pb concentration and risk of preterm birth in a population-based birth cohort study. Our results showed that the rates of preterm birth were elevated among subjects with M-Pb and H-Pb. Moreover, maternal Pb exposure in early gestational stage than in middle gestational stage was more susceptible to preterm birth. We found that maternal serum Pb level was only associated with risk of LPTB. Our results provide evidence that maternal serum Pb level is positively associated with risk of preterm birth in a Chinese population.

Author contributions

De-Xiang Xu, Fang-Biao Tao and Hua Wang designed the research; Jun Li, Hua Wang, Lu Liu and Jia-Hu Hao conducted the research, Hua Wang, Yuan-Hua Chen, Zhen Yu and Lin Fu analyzed data; De-Xiang Xu and Hua Wang wrote this manuscript. All authors have read and approved the final version of the manuscript.

Notes

All authors declare no competing financial interest.

Acknowledgements

We are grateful to Yuan-Yuan Yang and Hai-Yan Zhang for assistance in serum lead measurement. We thank the Maternal and Child Care Service Centre of Hefei city, and all participants in the study. This study was supported by National Natural Science Foundation of China (81473016, 81630084 and 81471467), National Key Technology R & D Program (2006BAI05A03 to C-ABCS).

References

Ahmad, S.A., Sayed, M.H., Barua, S., Khan, M.H., Faruquee, M.H., Jalil, A., Hadi, S.A., Talukder, H.K., 2001. Arsenic in drinking water and pregnancy outcomes. Environ. Health Perspect. 109, 629–631.

Amaral, J.H., Rezende, V.B., Quintana, S.M., Gerlach, R.F., Barbosa Jr., F., Tanus-Santos, J.E., 2010. The relationship between blood and serum lead levels in peripartum women and their respective umbilical cords. Basic Clin. Pharmacol. Toxicol. 107, 971–975.

Anderson, P., Doyle, L.W., Stu, V.I.C., 2003. Neurobehavioral outcomes of school-age children born extremely low birth weight or very preterm in the 1990s. Jama-Journal Am. Med. Assoc. 289, 3264–3272.

Andrews, W.W., Cliver, S.P., Biasini, F., Peralta-Carcelen, A.M., Rector, R., Alriksson-Schmidt, A.I., Faye-Petersen, O., Carlo, W., Goldenberg, R., Hauth, J.C., 2008. Early preterm birth: association between in utero exposure to acute inflammation and severe neurodevelopmental disability at 6 years of age. Am. J. Obstet. Gynecol. 198, 466 e461-466 e411.

Athalye-Jape, G., Deshpande, G., Rao, S., Patole, S., 2014. Benefits of probiotics on enteral nutrition in preterm neonates: a systematic review. Am. J. Clin. Nutr. 100, 1508–1519.

Augustsson, A.L.M., Uddh-Soderberg, T.E., Hogmalm, K.J., Filipsson, M.E.M., 2015. Metal uptake by homegrown vegetables - the relative importance in human health risk assessments at contaminated sites. Environ. Res. 138, 181–190.

Bergdahl, I.A., Vahter, M., Counter, S.A., Schutz, A., Buchanan, L.H., Ortega, F., Laurell, G., Skerfving, S., 1999. Lead in plasma and whole blood from lead-exposed children. Environ. Res. 80, 25–33.

Bora, S., Pritchard, V.E., Chen, Z., Inder, T.E., Woodward, L.J., 2014. Neonatal cerebral morphometry and later risk of persistent inattention/hyperactivity in children born very preterm. J. Child Psychol. Psychiatry 55, 828–838.

Chen, A.M., Dietrich, K.N., Huo, X., Ho, S.M., 2011. Developmental neurotoxicants in E-waste: an emerging health concern. Environ. Health Perspect. 119, 431–438.

Cheng, K., Wang, Y., Tian, H., Gao, X., Zhang, Y., Wu, X., Zhu, C., Gao, J., 2015. Atmospheric emission characteristics and control policies of five precedent-controlled toxic heavy metals from anthropogenic sources in China. Environ. Sci. Technol. 49, 1206–1214.

Chuang, H.Y., Schwartz, J., Gonzales-Cossio, T., Lugo, M.C., Palazuelos, E., Aro, A., Hu, H., Hernandez-Avila, M., 2001. Interrelations of lead levels in bone, venous blood, and umbilical cord blood with exogenous lead exposure through maternal plasma lead in peripartum women. Environ. Health Perspect. 109, 527–532.

Clark, B., Masters, S., Edwards, M., 2014. Profile sampling to characterize particulate lead risks in potable water. Environ. Sci. Technol. 48, 6836–6843.

Dang, D.H., Schafer, J., Brach-Papa, C., Lenoble, V., Durrieu, G., Dutruch, L., Chiffoleau, J.F., Gonzalez, J.L., Blanc, G., Mullot, J.U., Mounier, S., Garnier, C., 2015. Evidencing the impact of coastal contaminated sediments on mussels through Pb stable isotopes composition. Environ. Sci. Technol. 49, 11438–11448.

Goldenberg, R.L., Culhane, J.F., Iams, J.D., Romero, R., 2008. Preterm birth 1-Epidemiology and causes of preterm birth. Lancet 371, 75–84.

Grashow, R., Zhang, J.M., Fang, S.C., Weisskopf, M.G., Christiani, D.C., Cavallari, J.M., 2014. Toenail metal concentration as a biomarker of occupational welding fume exposure. J. Occup. Environ. Hyg. 11, 397–405.

Hammond, G., Langridge, A., Leonard, H., Hagan, R., Jacoby, P., DeKlerk, N., Pennell, C., Stanley, F., 2013. Changes in risk factors for preterm birth in Western Australia 1984-2006. BJOG 120, 1051–1060.

Henderson, J.J., McWilliam, O.A., Newnham, J.P., Pennell, C.E., 2012. Preterm birth aetiology 2004-2008. Maternal factors associated with three phenotypes: spontaneous preterm labour, preterm pre-labour rupture of membranes and medically indicated preterm birth. J. Matern. Fetal Neonatal Med. 25, 642–647.

Hernandez-Avila, M., Smith, D., Meneses, F., Sanin, L.H., Hu, H., 1998. The influence of bone and blood lead on plasma lead levels in environmentally exposed adults. Environ. Health Perspect. 106, 473–477.

Janisse, J.J., Bailey, B.A., Ager, J., Sokol, R.J., 2014. Alcohol, tobacco, cocaine, and marijuana use: relative contributions to preterm delivery and fetal growth

restriction. Subst. Abus 35, 60–67.
Julander, A., Lundgren, L., Skare, L., Grander, M., Palm, B., Vahter, M., Liden, C., 2014. Formal recycling of e-waste leads to increased exposure to toxic metals: an occupational exposure study from Sweden. Environ. Int. 73, 243–251.
Kasten-Jolly, J., Pabello, N., Bolivar, V.J., Lawrence, D.A., 2012. Developmental lead effects on behavior and brain gene expression in male and female BALB/cAnNTac mice. Neurotoxicology 33, 1005–1020.
Katz, J., Lee, A.C., Kozuki, N., Lawn, J.E., Cousens, S., Blencowe, H., Ezzati, M., Bhutta, Z.A., Marchant, T., Willey, B.A., Adair, L., Barros, F., Baqui, A.H., Christian, P., Fawzi, W., Gonzalez, R., Humphrey, J., Huybregts, L., Kolsteren, P., Mongkolchati, A., Mullany, L.C., Ndyomugyenyi, R., Nien, J.K., Osrin, D., Roberfroid, D., Sania, A., Schmiegelow, C., Silveira, M.F., Tielsch, J., Vaidya, A., Velaphi, S.C., Victora, C.G., Watson-Jones, D., Black, R.E., Group, C.S.-f.-G.-A.-P.B.W, 2013. Mortality risk in preterm and small-for-gestational-age infants in low-income and middle-income countries: a pooled country analysis. Lancet 382, 417–425.
Kawakami, T., Yoshimi, M., Kadota, Y., Inoue, M., Sato, M., Suzuki, S., 2014. Prolonged endoplasmic reticulum stress alters placental morphology and causes low birth weight. Toxicol. Appl. Pharmacol. 275, 134–144.
Kazi, T.G., Shah, F., Afridi, H.I., Naeemullah, 2015. Occupational and environmental lead exposure to adolescent workers in battery recycling workshops. Toxicol. Industrial Health 31, 1288–1295.
Kernan, W.N., Viscoli, C.M., Brass, L.M., Broderick, J.P., Brott, T., Feldmann, E., Morgenstern, L.B., Wilterdink, J.L., Horwitz, R.I., 2000. Phenylpropanolamine and the risk of hemorrhagic stroke. N. Engl. J. Med. 343, 1826–1832.
Koullali, B., Oudijk, M.A., Nijman, T.A., Mol, B.W., Pajkrt, E., 2016. Risk assessment and management to prevent preterm birth. Semin. Fetal Neonatal Med. 21, 80–88.
Liu, C.M., Zheng, G.H., Ming, Q.L., Sun, J.M., Cheng, C., 2013. Protective effect of quercetin on lead-induced oxidative stress and endoplasmic reticulum stress in rat liver via the IRE1/JNK and PI3K/Akt pathway. Free Radic. Res. 47, 192–201.
Liu, J.A., Gao, D.G., Chen, Y.M., Jing, J., Hu, Q.S., Chen, Y.J., 2014. Lead exposure at each stage of pregnancy and neurobehavioral development of neonates. Neurotoxicology 44, 1–7.
Liu, P., Xu, L., Wang, Y., Zhang, Y., Du, Y., Sun, Y., Wang, Z., 2016. Association between perinatal outcomes and maternal pre-pregnancy body mass index. Obes. Rev. 17, 1091–1102.
Martin, R.R., Kempson, I.M., Naftel, S.J., Skinner, W.M., 2005. Preliminary synchrotron analysis of lead in hair from a lead smelter worker. Chemosphere 58, 1385–1390.
Marx, S.K., Rashid, S., Stromsoe, N., 2016. Global-scale patterns in anthropogenic Pb contamination reconstructed from natural archives. Environ. Pollut. 213, 283–298.
Mohmand, J., Eqani, S.A.M.A.S., Fasola, M., Alamdar, A., Mustafa, I., Ali, N., Liu, L.P., Peng, S.Y., Shen, H.Q., 2015. Human exposure to toxic metals via contaminated dust: bio-accumulation trends and their potential risk estimation. Chemosphere 132, 142–151.
Mortada, W.I., Sobh, M.A., El-Defrawy, M.M., 2004. The exposure to cadmium, lead and mercury from smoking and its impact on renal integrity. Med. Sci. Monit. 10, CR112–116.
Mostafalou, S., Baeeri, M., Bahadar, H., Soltany-Rezaee-Rad, M., Gholami, M., Abdollahi, M., 2015. Molecular mechanisms involved in lead induced disruption of hepatic and pancreatic glucose metabolism. Environ. Toxicol. Pharmacol. 39, 16–26.
Nykjaer, C., Alwan, N.A., Greenwood, D.C., Simpson, N.A., Hay, A.W., White, K.L., Cade, J.E., 2014. Maternal alcohol intake prior to and during pregnancy and risk of adverse birth outcomes: evidence from a British cohort. J. Epidemiol. Community Health 68, 542–549.
Pan, Y., Zhang, S., Wang, Q., Shen, H., Zhang, Y., Li, Y., Yan, D., Sun, L., 2016. Investigating the association between prepregnancy body mass index and adverse pregnancy outcomes: a large cohort study of 536 098 Chinese pregnant women in rural China. BMJ Open 6, e011227.
Pinto, E., Cruz, M., Ramos, P., Santos, A., Almeida, A., 2017. Metals transfer from tobacco to cigarette smoke: evidences in smokers' lung tissue. J. Hazard Mater 325, 31–35.
Poulsen, G., Strandberg-Larsen, K., Mortensen, L., Barros, H., Cordier, S., Correia, S., Danileviciute, A., van Eijsden, M., Fernandez-Somoano, A., Gehring, U., Grazuleviciene, R., Hafkamp-de Groen, E., Henriksen, T.B., Jensen, M.S., Larranaga, I., Magnus, P., Pickett, K., Raat, H., Richiardi, L., Rouget, F., Rusconi, F., Stoltenberg, C., Uphoff, E.P., Vrijkotte, T.G., Wijga, A.H., Vrijheid, M., Osler, M., Andersen, A.M., 2015. Exploring educational disparities in risk of preterm delivery: a comparative study of 12 European birth cohorts. Paediatr. Perinat. Epidemiol. 29, 172–183.
Rayman, M.P., Wijnen, H., Vader, H., Kooistra, L., Pop, V., 2011. Maternal selenium status during early gestation and risk for preterm birth. CMAJ 183, 549–555.
Romero-Freire, A., Martin Peinado, F.J., van Gestel, C.A., 2015. Effect of soil properties on the toxicity of Pb: assessment of the appropriateness of guideline values. J. Hazard Mater 289, 46–53.
Sakellari, A., Karavoltsos, S., Kalogeropoulos, N., Theodorou, D., Dedoussis, G., Chrysohoou, C., Dassenakis, M., Scoullos, M., 2016. Predictors of cadmium and lead concentrations in the blood of residents from the metropolitan area of Athens (Greece). Sci. Total Environ. 568, 263–270.
Sauber-Schatz, E.K., Sappenfield, W., Grigorescu, V., Kulkarni, A., Zhang, Y., Salihu, H.M., Rubin, L.P., Kirby, R.S., Jamieson, D.J., Macaluso, M., 2012. Obesity, assisted reproductive technology, and early preterm birth–Florida, 2004-2006. Am. J. Epidemiol. 176, 886–896.
Schneider, J.S., Anderson, D.W., Kidd, S.K., Sobolewski, M., Cory-Slechta, D.A., 2016. Sex-dependent effects of lead and prenatal stress on post-translational histone modifications in frontal cortex and hippocampus in the early postnatal brain. Neurotoxicology 54, 65–71.
Smith, D., Hernandez-Avila, M., Tellez-Rojo, M.M., Mercado, A., Hu, H., 2002. The relationship between lead in plasma and whole blood in women. Environ. Health Perspect. 110, 263–268.
Tao, F.B., Hao, J.H., Huang, K., Su, P.Y., Cheng, D.J., Xing, X.Y., Huang, Z.H., Zhang, J.L., Tong, S.L., 2013. Cohort Profile: the China-Anhui birth cohort study. Int. J. Epidemiol. 42, 709–721.
Taylor, C.M., Golding, J., Emond, A.M., 2015. Adverse effects of maternal lead levels on birth outcomes in the ALSPAC study: a prospective birth cohort study. Bjog Int. J. Obstetrics Gynaecol. 122, 322–328.
Wang, H., Hu, Y.F., Hao, J.H., Chen, Y.H., Wang, Y., Zhu, P., Zhang, C., Xu, Y.Y., Tao, F.B., Xu, D.X., 2016a. Maternal serum zinc concentration during pregnancy is inversely associated with risk of preterm birth in a Chinese population. J. Nutr. 146, 509–515.
Wang, H., Liu, L., Hu, Y.F., Hao, J.H., Chen, Y.H., Su, P.Y., Yu, Z., Fu, L., Tao, F.B., Xu, D.X., 2016b. Association of maternal serum cadmium level during pregnancy with risk of preterm birth in a Chinese population. Environ. Pollut. 216, 851–857.
Welch, M.G., Firestein, M.R., Austin, J., Hane, A.A., Stark, R.I., Hofer, M.A., Garland, M., Glickstein, S.B., Brunelli, S.A., Ludwig, R.J., Myers, M.M., 2015. Family Nurture Intervention in the Neonatal Intensive Care Unit improves social-relatedness, attention, and neurodevelopment of preterm infants at 18 months in a randomized controlled trial. J. Child Psychol. Psychiatry 56, 1202–1211.
Yang, J., Baer, R.J., Berghella, V., Chambers, C., Chung, P., Coker, T., Currier, R.J., Druzin, M.L., Kuppermann, M., Muglia, L.J., Norton, M.E., Rand, L., Ryckman, K., Shaw, G.M., Stevenson, D., Jelliffe-Pawlowski, L.L., 2016a. Recurrence of preterm birth and early term birth. Obstet. Gynecol. 128, 364–372.
Yang, J., Huo, W., Zhang, B., Zheng, T., Li, Y., Pan, X., Liu, W., Chang, H., Jiang, M., Zhou, A., Qian, Z., Wan, Y., Xia, W., Xu, S., 2016b. Maternal urinary cadmium concentrations in relation to preterm birth in the Healthy Baby Cohort Study in China. Environ. Int. 94, 300–306.
Yorita Christensen, K.L., 2013. Metals in blood and urine, and thyroid function among adults in the United States 2007-2008. Int. J. Hyg. Environ. Health 216, 624–632.
Zhang, B., Xia, W., Li, Y.Y., Bassig, B.A., Zhou, A.F., Wang, Y.J., Li, Z.K., Yao, Y.X., Hu, J., Du, X.F., Zhou, Y.Q., Liu, J., Xue, W.Y., Ma, Y., Pan, X.Y., Peng, Y., Zheng, T.Z., Xu, S.Q., 2015. Prenatal exposure to lead in relation to risk of preterm low birth weight: a matched case-control study in China. Reprod. Toxicol. 57, 190–195.
Zhang, Y., Huo, X., Cao, J.J., Yang, T., Xu, L., Xu, X.J., 2016. Elevated lead levels and adverse effects on natural killer cells in children from an electronic waste recycling area. Environ. Pollut. 213, 143–150.
Zhu, M., Fitzgerald, E.F., Gelberg, K.H., Lin, S., Druschel, C.M., 2010. Maternal low-level lead exposure and fetal growth. Environ. Health Perspect. 118, 1471–1475.