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A case-control study of maternal exposure to chromium and infant low birth weight in China

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Abstract

Exposure to chromium is increasing due to environmental pollution from industrial processes. Several epidemiological studies have investigated chromium exposure and reproductive outcomes, but few studies have investigated the association of chromium exposure and low birth weight (LBW). This study was designed to investigate whether maternal exposure to chromium during pregnancy is associated with an increased risk of LBW. Chromium concentrations in maternal urine samples collected at delivery were measured in 204 LBW cases and 612 matched controls recruited between 2012 and 2014 in Hubei Province, China. Risk of LBW was associated with higher levels of chromium in maternal urine [adjusted odds ratio (OR) = 1.77 for the medium tertile, 95% confidence interval (CI): 0.95, 3.29; adjusted OR = 2.48 for the highest tertile, 95% CI: 1.33, 4.61; *P*trend = 0.01]. The association was more pronounced among female infants

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(adjusted OR = 3.67 for the highest tertile, 95% CI: 1.50, 8.97) than among male infants (adjusted OR = 1.22 for the highest tertile, 95% CI = 0.48, 3.11) (p heterogeneity = 0.06). Our findings suggest that maternal exposure to higher levels of chromium during pregnancy may potentially increase the risk of delivering LBW infants, particularly for female infants.

Keywords

Chromium; low birth weight; maternal urine; prenatal exposure

1. Introduction

Chromium is a transition metal that is naturally dispersed in the environment. Chromium is used extensively for metal alloying, the manufacture of dyes and pigments, as well as for leather and wood preservation (Kota and Stasicka, 2000). Due to these industrial processes, large quantities of chromium compounds are discharged in liquid, solid, and gaseous wastes into the environment. Exposure to chromium can occur by eating food, drinking water, and inhaling air that contains the metal (Kota and Stasicka, 2000). In 2010, the Environmental Working Group, an American environmental organization, studied the drinking water in 35 American cities and found that at least 74 million people in nearly 7,000 communities drink tap water containing elevated chromium levels (Sutton, 2010). China is a major producer of chromium and chromium slag and its untreated chromium slag in past years has exceeded 400 million tons (Gao and Xia, 2011). Recent data has shown that the emission of chromium into the atmosphere from anthropogenic activities in China has increased at an annual growth rate of 8.8% (Cheng et al., 2014). The increasing release of chromium may ultimately cause significant adverse effects in the environment and for human health.

The fetus and infants are more vulnerable than adults to environmental threats (Barker, 2004). Chromium crosses the placental barrier readily, posing a significant hazard to the fetus during development (Barceloux, 1999). Chromium-related embryotoxic and fetotoxic effects have been observed in animal studies, including decreased fetal weight, skeletal defects, malformations, and death (Gale and Bunch, 1979; Junaid et al., 1995; Bailey et al., 2006). Limited epidemiologic studies have been conducted to examine the association between chromium exposure *in utero* and birth outcomes, and the results have been inconsistent (Bogden et al., 1978; Berry and Bove, 1997; Eizaguirre-Garcia et al., 2000). Some studies have demonstrated a significantly increased risk of congenital malformations, low birth weight (LBW), and preterm birth with infants born to residents living near chromium contaminated areas (Berry and Bove, 1997; Eizaguirre-Garcia et al., 2000), while a previous study by Bogden et al. found that maternal plasma chromium levels were not significantly associated with LBW (Bogden et al., 1978).

LBW, which refers to infants born weighing less than 2,500 g, is one adverse reproductive outcome that has been associated with hazardous environmental exposures. LBW is the most important factor affecting neonatal mortality and is a significant determinant of postneonatal mortality (Lawn et al., 2005). Further, LBW is associated with a variety of adverse health outcomes during childhood and even adulthood (Johnson and Schoeni, 2011). Therefore, we

conducted a case-control study involving 816 pregnant women (including 204 LBW cases and 612 matched controls) in the Hubei province of China, to evaluate the association between maternal chromium exposure and LBW.

2. Material and methods

2.1 Study population and data collection

The subjects in this study were participants in the prospective Healthy Baby Cohort (HBC) study in China which is described elsewhere (Xia et al., 2015). Between November 2012 to April 2014, this cohort enrolled 16,293 pregnant women who gave birth at one of three maternity hospitals in Wuhan, Ezhou, and Macheng, which are cities located in Hubei province, in the central region of China. . Participant mothers received a detailed explanation of the study procedures and provided written informed consent to participate. The study protocol was reviewed and approved by the ethics committees of the Tongji Medical College, Huazhong University of Science and Technology, and the three study hospitals.

The LBW cases were mothers who delivered a live singleton infant with a birth weight < 2,500 g. Controls were mothers who delivered a live singleton infant with normal birth weight between 2,500 g and < 4,000 g. We excluded multiple births, congenital malformations, and still births, as well as those women without urine samples available for analysis. For every case selected, three consecutive controls were randomly selected and matched by delivery hospital, infant sex, and maternal age (within 1-year interval). A total of 204 cases and 612 matched controls were included in the study.

Information on gestational age, based on the last menstrual period, the mothers' history of pregnancy outcomes and disease (eg. hypertension during pregnancy), parity, the infant sex, birth weight, and any apparent congenital malformations, were extracted from the medical records. Nude birth weight was obtained for each infant within one hour after birth using standardized procedures. All mothers completed face-to face interviews after delivery by trained nurses to collect information about socioeconomic characteristics (e.g. age, occupation, education, and household income) and lifestyle habits during pregnancy (e.g. smoking, passive smoking, and drinking). The pre-pregnancy body mass index of mothers was calculated using the self-reported weight before pregnancy and height, which was measured using a stadiometer.

2.2 Urine chromium measurements

Maternal urine sample collection and metal analyses have been described previously (Xia et al., 2015). Briefly, the maternal urine samples were collected before delivery and stored in polypropylene tubes at -20°C until further analysis. The total chromium concentrations in urine were determined by inductively coupled plasma mass spectrometry (ICP-MS, Agilent Technologies, Santa Clara, CA, USA), since ICP-MS cannot differentiate between different forms of chromium and it is difficult to differentiate them in other tests (Wilbur et al., 2000). All samples were coded so that lab personnel conducting the assay were blind to their origin. For sample pretreatment, the urine samples (1 mL) and 3% HNO₃ (4 mL) were added to a polypropylene tube for overnight nitrification, and were further digested by ultrasound at

40 °C for 1 h. The external quality control (the certified reference material human urine SRM2670a, National Institute of Standards and Technology, Gaithersburg, MD, USA) was included in each batch for the urinary chromium measurements. The urinary chromium concentrations in our study population were all above the limit of detection (0.02 µg/L). Lead, arsenic, cadmium, and thallium were also measured simultaneously, and the detection rate of these metals in maternal urine samples was higher than 98%. Urine creatinine was measured using a commercially available diagnostic enzyme method (Mindray CREA Kit, Sarcosine Oxidase Method, Shenzhen, China) by an automatic biochemical analyzer (BS-200, Mindray, Shenzhen, China). The creatinine adjusted urinary chromium concentrations were expressed as µg/g creatinine to control for the effect of variation in urine diluteness.

2.3 Statistical analyses

The general characteristics of cases and controls were presented as a number (%), and the Pearson chi-square test was used to evaluate the differences in the variables between cases and controls. The Wilcoxon signed rank test was used to compare the difference of chromium levels between the case and control group, since the distributions of chromium concentrations were found to be skewed following the Kolmogorov-Smirnov normality test.

Conditional logistic regression analyses were used to examine the risks of LBW associated with chromium exposure by calculating crude and adjusted odds ratios (ORs) and their 95% confidence intervals (CIs). Maternal urinary chromium levels were analyzed as categorical variables according to the tertile distribution of chromium concentrations in the controls, and the lowest tertile was used as the referent group. The linear trends of the risk of LBW and chromium exposure were tested by modeling the median values of tertiles of chromium as a continuous variable. The missing values were constructed as dummy variables in the regression model. We selected household income to represent socioeconomic status because adjustment for income showed a larger impact on the estimate than education. Inclusion of the two variables together in the adjusted model did not produce significantly different results compared to the addition of each individual variable into the model separately. We included the covariates in the final models as follows: gestational age, household income, pre-pregnancy body mass index, parity, passive smoking, and hypertension during pregnancy. Considering that gestational age may act a mediator of the relationship between chromium exposure and LBW, adjusted ORs for LBW were also calculated without adjusted for gestational age. Inclusion of occupational status, diabetes, and multivitamin supplement use during pregnancy did not result in material changes in the observed associations and thus were not included in the final models. Smoking and alcohol consumption were not adjusted for because few women reported smoking or drinking. Several metals that have been previously suggested to be associated with birth weight (lead, arsenic, cadmium, and thallium) were also adjusted for in the models to control potential confounding, but inclusion of these metal variables either individually or together did not cause a significant change in the risk estimate in this study.

Risk estimates were further stratified by infant sex and maternal age. Heterogeneity of effects by infant sex and maternal age were assessed by the Breslow-Day test. The median age of the women when they gave birth was used as the cut-point for stratified analyses.

A two-sided P value of < 0.05 was considered statistically significant. All data analyses were performed using SAS (version 9.3; SAS Institute Inc., Cary, NC, USA).

3. Results

General characteristics of the cases and controls are shown in Table 1. There were 404 male infants and 412 female infants. The mean maternal age at delivery was 28.07 ± 4.65 years with a range of 17 to 42 years. Compared to the controls, the case mothers had lower educational attainment (less than high school, 43.6% vs. 27.3%) and reported lower household income ($< 50,000$ yuan per year, 56.9% vs. 44.9%). There were higher percentages of case mothers who were underweight (29.4% vs. 20.4%), had hypertension during pregnancy (9.8% vs. 2.0%), and had two or more parities (22.1% vs. 18.1%) compared to the controls. Only one mother in the case group and one mother in the control group reported smoking during pregnancy, but 23.0% of cases and 22.1% controls were passively exposed to cigarette smoking.

The median creatinine-adjusted chromium concentration in maternal urine was $4.67 \mu\text{g/g}$ creatinine with a range of 0.02 to $57.44 \mu\text{g/g}$ creatinine in the case mothers. The median Cr concentration was $3.33 \mu\text{g/g}$ creatinine with a range of 0.02 to $87.35 \mu\text{g/g}$ creatinine in the control mothers. The case mothers had significantly higher urinary chromium levels compared to the control mothers ($p < 0.05$).

Table 2 shows the overall crude and adjusted ORs and 95% CIs for LBW according to the tertiles of creatinine-adjusted chromium levels in maternal urine. In the model adjusted for the potential confounding factors (gestational age, household income, pre-pregnancy body mass index, parity, passive smoking, and hypertension during pregnancy), we observed a significant positive trend between LBW risk and increasing levels of maternal urinary chromium compared to the lowest tertile [adjusted OR = 1.77 (95% CI: 0.95, 3.29) for the medium tertile; adjusted OR = 2.48 (95% CI: 1.33, 4.61) for the highest tertile; $P_{\text{trend}} = 0.01$]. In the model without adjusting for gestational age, a similar association between chromium levels and LBW risk was observed [adjusted OR = 1.69 (95% CI: 1.07, 2.68) for the medium tertile; adjusted OR = 2.74 (95% CI: 1.73, 4.35) for the highest tertile; $P_{\text{trend}} = 0.01$].

When stratified by maternal age at delivery, positive trends with risk of LBW were observed for increasing levels of chromium in maternal urine (Table 3). The risk estimates for LBW associated with chromium exposure were not significantly different among the two age groups ($P_{\text{heterogeneity}} = 0.52$). Table 4 shows the association between chromium exposure and LBW stratified by infant sex. Among female infants, a significant positive association was observed for higher urinary chromium concentrations and the risk of LBW [adjusted ORs = 3.67 (95% CI: 1.50, 8.97) for the highest tertiles; $P_{\text{trend}} = 0.01$]. The association was not statistically significant for male infants [adjusted OR = 1.22 (95% CI: 0.48, 3.11) for the

highest tertiles; $P_{\text{trend}} = 0.56$]. A borderline significant interaction was observed with respect to infant sex ($P_{\text{heterogeneity}} = 0.06$).

4. Discussion

We found that the LBW case mothers had higher levels of urinary chromium than the control mothers, and there was a significant positive association between LBW risk and increasing levels of maternal urinary chromium after adjustment for the potential confounding factors. The mothers in the highest tertile of urinary chromium levels ($> 6.78 \mu\text{g/g}$ creatinine) had more than twice the risk of delivering LBW infants as those in the lowest tertile ($< 3.03 \mu\text{g/g}$ creatinine).

Chromium is present in the environment in several different forms, the most common being chromium(0), chromium(II), chromium(III), and chromium(VI). Chromium compounds, in different forms, are used widely in industrial processes for the manufacture of dyes and pigments, leather and wood preservation, and chrome plating (Wilbur et al., 2000). Only the health effects of chromium(III) and chromium(VI) are commonly studied, but limited reports are available for other forms of chromium. Chromium(III) was first proposed to be an essential element micronutrient for humans (Anderson, 1997), but several studies have not shown convincing evidence for this (Vincent, 2013). Recent studies have demonstrated that chromium(III) has no biological role (Di Bona et al., 2011), and excessive chromium(III) can have adverse impacts on human health (Eastmond et al., 2008). Chromium(VI) is a known carcinogen, most strongly associated with lung cancer, and is much more toxic than chromium(III) (Wilbur et al., 2000). The body has several systems for reducing chromium(VI) to chromium(III), and this chromium(VI) detoxification leads to increased levels of chromium(III) (Valko et al., 2005). Both chromium(III) and chromium(VI) have hazardous effects on embryonic development in mice, causing skeletal defects and malformation, and reducing fetal weight (Junaid et al., 1995; Bailey et al., 2006; Levina and Lay, 2008).

The general population is generally exposed to mixed forms of chromium by eating food, drinking water, and inhaling air. The total chromium in biological samples is analyzed in many studies because of the biological reduction of chromium(VI) to chromium(III) (Wilbur et al., 2000). The pregnant women in our study had much higher levels of urinary chromium (median $2.69 \mu\text{g/L}$ and $3.66 \mu\text{g/g}$ creatinine) than those measured in pregnant women in Austria (median $0.25 \mu\text{g/L}$ and $0.44 \mu\text{g/g}$ creatinine) (Callan et al., 2013) (Table 5). Our study population also had higher concentrations of urinary chromium than those reported in non-occupationally exposed adults from Germany (geometric mean $0.13 \mu\text{g/L}$ and $0.12 \mu\text{g/g}$ creatinine) (Heitland and Köster, 2006), Italy (median $0.1 \mu\text{g/L}$) (Soleo et al., 2007), Austria (median $1.08 \mu\text{g/creatinine}$) (Zeiner et al., 2006), and the USA (median $0.12 \mu\text{g/L}$ and $0.11 \mu\text{g/creatinine}$) (Paschal et al., 1998). The data on urinary chromium concentrations in the Chinese population are limited. The levels of urinary chromium in our study were slightly higher than those reported in a recent study of non-occupationally exposed men in Hubei Province (Zeng et al., 2013). One probable reason may be that the excretion of chromium in urine is higher among pregnant women in our study compared to the non-occupationally

exposed men in the study by Zeng et al, possibly due to the high release of chromium as a result of stress factors in the period of pregnancy and lactation (Morris et al., 1995).

Exposure to chromium may occur from natural or anthropogenic sources. China is one of the major producers of chromium compounds and the biggest consumer of chromite ore in the world (van Tongeren, 2011; Wang et al., 2011). The annual production capacities of chromium salts from chemical industries reach 329,000 tons and the annual discharges of chromium slag reach 450,000 tons (Gao and Xia, 2011). Hubei is one of the largest industrial provinces in China, and it is one of the provinces included in the Program for Comprehensive Control of Chromium Residue Pollution by the Ministry of Environment Protection of China (MOE, 2009). Consumption of water contaminated with chromium is one of the major sources of chromium-related health threats. In spite of the fact that the industry is constantly looking for efficient and innovative routes for chromium recovery or detoxification, large amounts of chromium-containing wastes are still released and the water contaminated with chromium in Hubei province has been reported in recent years (Baojia et al., 2007). Additionally, inhaling air that contains chromium is also a major source for human exposure. As a result of the rapid growth of the economy in China, the unprecedentedly increased combustion of oil, coal, and gasoline in urban areas has contributed to a significant increase in emission of chromium to the air (Cheng et al., 2014). These issues may explain why the populations in our study and in the Zeng et al. study (Zeng et al., 2013) have relatively high levels of urinary chromium compared to those reported in developed countries.

From previous epidemiological studies, infants born to residents living near chromium contaminated areas have been associated with significantly increased risk of congenital malformations, LBW, and preterm birth (Berry and Bove, 1997; Eizaguirre-Garcia et al., 2000). Consistent with these observations, our findings provide evidence of a positive association between maternal chromium exposure and risk of infant LBW, indicating chromium exposure during pregnancy has an adverse effect on the developing fetus. In addition, the association between higher levels of chromium and increased risk of LBW was not affected by adjustment for other metals. We included cadmium, lead, arsenic, and thallium in the adjusted model, because they have been suggested to be potentially associated with decreasing birth weight in previous studies (Hopenhayn et al., 2003; Ronco et al., 2009; Zhu et al., 2010; Hu et al., 2015). Besides, as previous studies suggested that adjustment for gestational age as a mediating variable may lead to bias when analyze the association of risk factors with LBW (Wilcox et al., 2011), we also calculated the adjusted ORs for LBW without adjusting for gestational age and found a similar association between chromium levels and LBW risk.

Bogden et al. also examined this association in 22 LBW cases and 50 controls in Newark, NY USA, and found that the LBW cases had higher levels of chromium in maternal plasma (mean 0.84 $\mu\text{g}/100\text{ mL}$) than the controls (mean 0.58 $\mu\text{g}/100\text{ mL}$), but the difference was not significant (Bogden et al., 1978). However, their analysis of 72 subjects possibly had insufficient statistical power to detect a significant association, and their study population may have lower levels of chromium than those in our study. The other possible reason may be the differences in biomarkers used in these studies, because the half-lives of chromium in

blood serum and urine are different, though both chromium in blood and urine are regarded as the most reliable biomarkers of exposure (Wilbur et al., 2000). Several biologically plausible mechanisms might explain the increased risk of LBW associated with higher maternal chromium exposure. Chromium(III) and chromium(VI) have been shown to affect survival or function of human bone cells (Andrews et al., 2011). Impaired growth and bone abnormalities have also been observed in animals prenatally exposed to chromium(III) or chromium(VI) (Junaid et al., 1995; Bailey et al., 2006; Levina and Lay, 2008). Another possible mechanism could be oxidative stress caused by chromium (Samuel et al., 2012), which may lead to impairment of cellular function and growth. Insulin and fat metabolism affected by chromium(III) may also contribute to the observed findings, because previous studies have reported that chromium(III) may lead to weight loss by decreasing fat levels in the body and through insulin-sensitising effects (Anderson, 1998). In addition, the association between maternal chromium exposure and risk of delivering a LBW infant in the present study appeared stronger in female infants. One possible explanation would be the effects of chromium(II) on disrupting estradiol function (Byrne et al., 2013), which is important for fetal growth. Chromium(II) has been suggested to be a new class of nonestradiol environmental estrogen, because of its ability to activate the estrogen receptor (Martin et al., 2003). The expression of estrogen receptor is strikingly different among females and males (Davis et al., 2008); thus, it is plausible that the risk of LBW associated with chromium exposure could differ by infant sex. Further evaluation of potential differences in the effect of maternal chromium exposure on LBW according to infant sex should be conducted in larger studies.

A strength of our study is that cases and controls were matched on potentially important factors that may be related to LBW, such as infant gender, maternal age, and delivery hospital in order to exclude important confounding factors. Also, we conducted personal interviews with all participants, which allowed us to adjust for other potential risk factors for LBW.

The present study has some limitations. First, the levels of chromium in urine collected at birth may not accurately reflect maternal chromium load during pregnancy. However, the half-life of chromium in blood serum and urine in occupationally exposed people has been reported to be 40 months and 129 months, respectively (Petersen et al., 2000), and the measurement of urinary chromium concentrations, a non-invasive biomarker, is considered to be a relatively reliable indicator to reflect chronic exposure. In addition, each form of chromium has different toxic effects, but the total chromium concentrations were measured in this study rather than the individual forms due to the difficulty in differentiating them in the measurement. Thus, to better understand the effects of chromium on LBW, it is important to measure the exposure levels of individual chemical species as well as the total concentration of chromium in the future studies.

4. Conclusions

In conclusion, this study found that higher urinary levels of chromium in Chinese pregnant women were significantly associated with an increased risk of having LBW infants. These findings suggest that maternal exposure to chromium during pregnancy may be an important

risk factor in the etiology of LBW. Possible detrimental effects of chromium exposure on birth outcomes, such as preterm birth, small for gestational age, birth weight, and birth length, should be further examined in future studies.

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Highlights

- First study reports the association between maternal urinary chromium levels and LBW in China.
- Chromium exposure during pregnancy increased the risk of LBW.
- The association may vary by infant sex

Table 1

Basic characteristics of low birth weight cases and controls [n (%)].

Characteristics	Cases (n = 204)	Controls (n = 612)
Infant gender		
Male	101 (49.5)	303 (49.5)
Female	103 (50.5)	309 (50.5)
Maternal age (years)		
< 25	48 (23.5)	146 (23.8)
25–29	81 (39.7)	242 (39.5)
30–34	58 (28.4)	174 (28.4)
35	17 (8.3)	50 (8.2)
Education (years) *		
9	89 (43.6)	167 (27.3)
9–12	38 (18.6)	120 (19.6)
> 12	77 (37.8)	322 (52.6)
Missing	0 (0.0)	3 (0.5)
Household yearly income (yuan) *		
< 50,000	116 (56.9)	275 (44.9)
50,000	61 (29.9)	279 (45.6)
Missing	27 (13.2)	58 (9.5)
Pre-pregnancy BMI (kg/m ²) *		
Normal (18.5–23.9)	108 (52.9)	385 (62.9)
Underweight (< 18.5)	60 (29.4)	125 (20.4)
Overweight (≥ 24)	26 (12.8)	85 (13.9)
Missing	10 (4.9)	17 (2.8)
Smoking during pregnancy		
No	198 (97.1)	608 (99.4)
Yes	1 (0.5)	0 (0.0)
Missing	5 (2.4)	4 (0.6)
Passive smoking during pregnancy		
Yes	47 (23.0)	129 (21.1)
No	149 (73.0)	464 (75.8)
Missing	8 (3.9)	19 (3.1)
Alcohol use during pregnancy		
Yes	2 (1.0)	1 (3.3)
No	196 (96.1)	594 (97.1)
Missing	6 (2.9)	17 (2.8)
Parity		
1	159 (77.9)	501 (81.9)
2	45 (22.1)	111 (18.1)
Hypertension during pregnancy *		

Characteristics	Cases (n = 204)	Controls (n = 612)
Yes	20 (9.8)	12 (2.0)
No	183 (89.7)	598 (97.7)
Missing	1 (0.5)	2 (0.3)

Abbreviation: BMI, body mass index.

*
The cases were significantly different from the controls ($P < 0.05$, tested by Pearson chi-square test).

Table 2

Risk of low birth weight associated with the levels of chromium in maternal urine.

Chromium (µg/g creatinine)	Cases	Controls	OR ^a (95% CI)	OR ^b (95% CI)	OR ^c (95% CI)
Total (n=816)					
< 3.03	40	204	1.00	1.00	1.00
3.03-6.78	63	204	1.58 (1.02, 2.44)	1.77 (0.95, 3.29)	1.69 (1.07, 2.68)
6.78	101	204	2.77 (1.79, 4.27)	2.48 (1.33, 4.61)	2.74 (1.73, 4.35)
<i>p</i> for trend			< 0.01	0.01	0.01

Abbreviation: OR, odds ratio; CI, confidential interval.

^a Unadjusted odds ratio.

^b Adjusted for gestational age, household income, pre-pregnancy body mass index, parity, passive smoking, and hypertension during pregnancy.

^c Adjusted for household income, pre-pregnancy body mass index, parity, passive smoking, and hypertension during pregnancy.

Table 3

Risk of low birth weight associated with maternal urinary chromium levels, stratified by maternal age.

Chromium levels ^a	Age < 28 years old (n=392)			Age 28 years old (n=424)			P for heterogeneity
	Ca/Co	OR ^b	OR ^c (95% CI)	Ca/Co	OR ^b	OR ^c (95% CI)	
Tertile 1	21/98	1.00	1.00	17/106	1.00	1.00	0.52
Tertile 2	29/98	1.43 (0.76, 2.70)	1.29 (0.52, 3.18)	35/106	2.00 (1.08, 3.73)	3.18 (1.19, 8.47)	
Tertile 3	48/98	2.78 (1.45, 5.34)	3.22 (1.27, 8.18)	54/106	3.17 (1.73, 5.82)	3.46 (1.33, 8.99)	
P for trend		< 0.01	0.02		< 0.01	0.06	

Abbreviations: ca/co, numbers of cases and controls; CI, confidence interval; OR, odds ratio; T, tertile.

^aChromium levels (µg/g creatinine): age < 28 years old, tertile 1 (<2.79), tertile 2 (2.79–6.25), tertile 3 (> 6.26); age 28 years old, tertile 1 (<3.15), tertile 2 (3.15–7.11), tertile 3 (> 7.12).

^bUnadjusted odds ratio.

^cAdjusted for gestational age, household income, pre-pregnancy body mass index, parity, passive smoking, and hypertension during pregnancy.

Table 4

Risk of low birth weight associated with maternal urinary chromium levels, stratified by infant gender.

Chromium levels ^a	Male (n=404)			Female (n=412)			<i>P</i> for heterogeneity
	Ca/Co	OR ^b	OR ^c (95% CI)	Ca/Co	OR ^b	OR ^c (95% CI)	
Tertile 1	27/101	1.00	1.00	15/103	1.00	1.00	0.06
Tertile 2	31/101	1.16 (0.64, 2.11)	1.00 (0.37, 2.56)	32/103	2.02 (1.04, 3.95)	2.48 (0.98, 6.32)	
Tertile 3	43/101	1.66 (0.93, 2.96)	1.22 (0.48, 3.11)	56/103	4.08 (2.11, 7.87)	3.67 (1.50, 8.97)	
<i>P</i> for trend		0.07	0.56		< 0.01	0.01	

Abbreviations: ca/co, numbers of cases and controls; CI, confidence interval; OR, odds ratio.

^aChromium levels (µg/g creatinine): male, tertile 1 (< 3.57), tertile 2 (3.57–8.43), tertile 3 (8.44); female, tertile 1 (< 2.51), tertile 2 (2.51–5.62), tertile 3 (5.63).

^bUnadjusted odds ratio.

^cAdjusted for gestational age, household income, pre-pregnancy body mass index, parity, passive smoking, and hypertension during pregnancy.

Table 5

Comparison of chromium concentrations in urine from the present study and previous studies.

Author (year)	Location	Number	Population	Median	Geometric mean
Present study (2014)	Hubei, China	816	Pregnant women	2.69 µg/L 3.66 µg/g creatinine	2.45 µg/L 3.89 µg/g creatinine
Qiang Zeng et al (2013)	Hubei, China	118	Men	1.63 µg/L 1.33 µg/g creatinine	1.62 µg/L 1.96 µg/g creatinine
A.C. Callan et al (2013)	Western Australia	173	Pregnant women	0.25 µg/L 0.44 µg/g creatinine	—
Peter Heitland et al (2006)	Aachen and Erkelenz, Germany	87	General population	—	0.13 µg/L 0.12 µg/g creatinine
Leonardo Soleo et al (2007)	Taranto, Italy	144	General population	0.1 µg/L	—
Michaela Zeiner et al (2006)	Vienna, Austrian	100	General population	1.08 µg/g creatinine	—
Daniel C. Paschal et al (1998)	USA	496	General population	0.12 µg/L 0.11 µg/g creatinine	0.13 µg/L 0.12 µg/g creatinine