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Effects of prenatal exposure to cadmium on neurodevelopment of infants in Shandong, China☆

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ABSTRACT

Although animal studies suggested that prenatal cadmium exposure can cause neurodevelopmental deficits, little is explored in human populations, or its mechanism. We investigated the association between prenatal cadmium exposures and infants' developmental quotients (DQs) based on the Gesell Developmental Schedules (gross motor, fine motor, adaptive, language, and social domains) at 12 months of age and explored the role of brain-derived neurotrophic factor (BDNF) in prenatal cadmium-induced neurodevelopmental deficits in Shandong, China, by enrolling 300 mothers between September 2010 and December 2011. Maternal blood cadmium concentration (median, 1.24 μg/L) was negatively associated with social domain DQs and BDNF levels in cord serum. A 10-fold increase in maternal cadmium levels was associated with a 5.70-point decrease in social domain DQs, a 4.31-point decrease in BDNF levels. BDNF levels were positively associated with social domain DQs. These data suggest that prenatal low-level cadmium exposure has adverse effects on neurodevelopment. BDNF may play an important role in the decline of social domain DQs induced by prenatal low-level cadmium exposure.

1. Introduction

Cadmium is a ubiquitous environmental pollutant and is an important environmental health hazard (ATSDR, 1999). Human exposure to cadmium through smoking and household dust as well as consumption of cadmium-contaminated water and food has become a global issue (ATSDR, 2008). Increasing concern has arisen over the adverse effects of cadmium on human health due to its high toxicity and persistence in the body. In adults, cadmium is known to be toxic to the kidney and bone tissue, resulting in renal disease and bone loss (Jarup et al., 1998). In contrast to the well-reported effects in adults, less is known about the adverse effects of prenatal cadmium exposure on the developing infants.

Numerous animal studies have reported that prenatal or early life exposure to cadmium affects neurodevelopment (Petersson Grawe et al., 2004; Zhang et al., 2009). Perinatal exposure to cadmium in rodents produces a delay in the sensorimotor development (Minetti and Reale, 2006) and decreases the learning ability of offspring (Ishitobi et al., 2007) and can cause changes in brain deiodinase activities in neonates, which may result in neurodevelopmental deficits (Mori et al., 2006). Although the association between prenatal cadmium exposure and adverse effects on neurodevelopment has been observed in animal models, it has not been fully explored in human populations. A few epidemiological studies have assessed the neurodevelopment of young children after low-level cadmium exposure during pregnancy, but these studies have reported inconsistent results. It was reported that prenatal cadmium exposure was associated with Verbal IQ (VIQ), Performance IQ (PIQ) and Full-Scale IQ (FSIQ) deficits in children at 4–5 years of age [Tian et al., 2009 (median cord blood cadmium level 0.6 μg/L); Kippler et al., 2012 (median maternal cadmium level in urine 0.63 μg/L); Jeong et al., 2015 (mean maternal blood cadmium level 1.49 μg/L)]. However, Kim et al. (2013) found no association between maternal blood cadmium levels (geometric mean,

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1.52 μg/L) and the Mental Development Index (MDI) or Psychomotor Development Index (PDI) scores of the infants at 6 months of age. These findings raise concern over the potential adverse effects of prenatal low-level cadmium exposure on neurodevelopment of infant.

There are several toxicologic mechanisms by which cadmium may have an influence on brain development such as inducing oxidative stress in animals and reducing antioxidant levels in humans, and affecting the balance and degree of excitation-inhibition in synaptic neurotransmission (Joseph, 2009; Lee et al., 2006; Minami et al., 2001), but there remains a large gap in elucidating its full adverse effects on neurodevelopment. Brain-derived neurotrophic factor (BDNF) plays an important role in the survival, differentiation, growth and development of neurons. Rai et al. (2013) found that a mental mixture (arsenic, lead and cadmium) decreased the expression levels of BDNF in rats. However, the role of cord serum BDNF in infants' neurodevelopmenal deficits induced by prenatal cadmium exposure remains unknown.

Therefore, the aim of our current study was to determine the maternal blood concentrations of cadmium in a birth cohort in southern coast area of Laizhou Wan (Bay) of the Bohai Sea, Shandong Province, China. We tested the hypothesis that prenatal cadmium exposure would be associated with lower DQs in motor, adaptive, language, and social domains based on the Gesell Developmental Schedules (GDS) [which has been validated against a Chinese reference population (Song and Zhu, 1987), and is widely used for assessing child development in China and other countries (Cui et al., 2001; Ke et al., 2004; Zhu et al., 2005)], and the decrease in BDNF levels induced by prenatal cadmium exposure may play an important role in neurodevelopmental deficits induced by prenatal cadmium exposure.

2. Materials and methods

2.1. Participants and recruitment

This investigation was a prospective birth cohort study that began in 2010 and was located in the southern coast area of Laizhou Wan (Bay) of Bohai Sea, Shandong Province, China (LW birth cohort). The detailed methods for the study have been described elsewhere (Ding et al., 2013). Pregnant women preparing for labor and delivery in a unique county hospital located in the southern coastal area of Laizhou Wan (Bay) were recruited. Eligibility criteria included a singleton pregnancy; living in the area for at least 3 years; age over 18 years old; and no report of assisted reproduction, chronic or pregnancy-associated hypertension, preexisting or gestational diabetes, HIV infection or AIDS, of illicit drug use (Ding et al., 2013). From September 2010 to December 2011, a total of 335 women met the eligibility criteria. Of these, 21 women did not agree to take part in this study (response rate 93.7%) and 14 women without enough volume of maternal blood samples for cadmium were excluded. Finally, 300 women were included in the analysis (baseline group). All of the participants provided written informed consent before enrollment in the study. The study protocol was approved by the Medical Ethics Committee of Shanghai Xinhua Hospital, affiliated with Shanghai Jiao Tong University School of Medicine. Not every mother agreed to have their child followed after birth. Among these 300 mother–infant pairs, 188 infants (62.7%) completed the neurodevelopmental assessment at 12 months of age (±1 week) (GDS group). Among these 188 mother–infant pairs, 149 infants had enough umbilical cord serum to be used to detect BDNF (GDS + BDNF group) (Fig. 1).

2.2. Maternal interview and medical record abstraction

Specially trained nurses administered a questionnaire to the mothers in the hospital, as described previously (Ding et al., 2013). The questionnaire included demographic and socioeconomic information (maternal age, education level, address, and household income) and the maternal characteristics (alcohol use, cigarette smoking, dietary habits, and employment). Additional relevant information, such as gestational age and sex of the newborn, was obtained by an interview and confirmed by medical records.

The maternal pre-pregnancy body mass index (BMI) was calculated as the pre-pregnancy weight divided by the height squared. According to the 2000 WHO standards, the women were classified into three groups: underweight (BMI < 18.5/m^2), normal weight (BMI 18.5 to < 23.0/m^2), and overweight (BMI > 23.0 kg/m^2).

2.3. Biologic sample collection

Maternal blood samples were collected on the day of hospital admission for delivery. Nurses collected cord blood samples from an umbilical vein following the delivery using a syringe and two 10-mL tubes, allowed them to clot, and centrifuged the samples at 1500 rpm for 20 min. The serum was decanted into pre-cleaned glass vials. All samples were stored at -80°C until analysis.

2.4. Cadmium exposure assessment

Maternal blood cadmium concentrations were measured by Inductively Coupled Plasma Mass Spectrometry (ICP-MS) (7500CE, Agilent) as described previously (Yu et al., 2013). The limit of detection (LOD) was $2.874^{*}10^{-3}$ μg/L.

2.5. BDNF analysis

According to the manufacturer's instructions, all umbilical cord serum BDNF measurements were performed by ELISA using monoclonal antibodies specific for BDNF (Bio TNT, Shanghai, China). All reagents, samples and standards were prepared as instructed, and samples were added to 96-well plates coated with an anti-BDNF monoclonal antibody. They were incubated for 2.5 h at room temperature. The solution was discarded, and the samples were washed 4 times with 1× Wash Solution. Then 100 μl of prepared biotin antibody was added to each well and incubated for 1 h at room temperature. One-hundred microliters of prepared streptavidin solution was then added and incubated for 45 min at room temperature. Then, 100 μl of TMB One-Step Substrate Reagent was added to each well and incubated for 30 min at room temperature. Fifty microliters of Stop Solution was added to each well, and the samples were immediately read at 450 nm. All of the samples and standards were assayed in duplicate.

2.6. Neurodevelopment measures

Infants in the cohort, who were 12 months of age, were administered the version of the GDS for 0- to 3-year-old children revised by the Beijing Mental Development Cooperative Group (Beijing Mental Development Cooperative Group, 1985). When the infants were assessed, the environment was quiet and non-interfering, and the infants were sober, stable and not hungry, and the tester encouraged the infants to show the highest level of ability. Each infant was assigned a developmental quotient (DQ) in each of the five specific domains (gross motor, fine motor, adaptive, language, and social). The standardized mean (±SD) of the DQ was 100 ± 15. The cutoff point for differentiating normal development

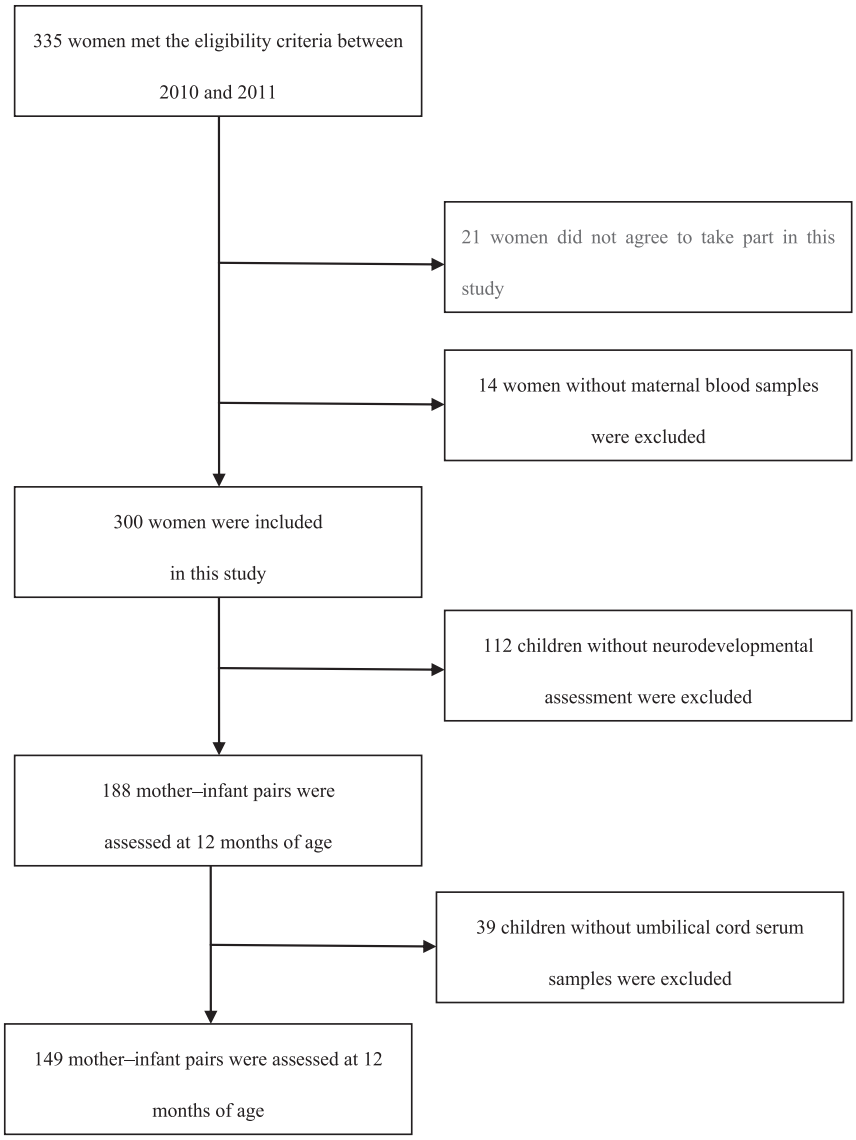

Fig. 1. Flow chart of the inclusion and exclusion criteria of the subjects.

from developmental delay was a score of 84.

A trained pediatrician conducted the testing to maximize both the validity of the interpretation and the reliability of the assessment.

2.7. Statistical analysis

Initial descriptive statistics were provided for the characteristics of the study population, individual cadmium levels, and DQ scores. To assess the possible relationship between prenatal cadmium exposure levels and infants' neurodevelopment, including gross motor domain, fine motor domain, adaptive domain, language domain, and social domain, we constructed separate multiple linear regression models for each of the five outcomes. The BDNF levels in umbilical cord serum were normally distributed. We also used a multiple linear regression model to analyze the relationship between cadmium exposure and the BDNF levels in umbilical cord serum as well as the relationship between the BDNF levels in umbilical cord serum and DQ scores. The maternal cadmium levels were $\log_{10}$ transformed due to the skewed nature of our data.

Maternal age, education, maternal IQ, pre-pregnancy BMI, smoking during pregnancy, marital status, meat consumption, paternal education, household monthly salary, child gender, birth weight, gestational age, lead, mercury, and parity were initially considered to be confounders based on the literature (Kippler et al., 2012; Jeong et al., 2015; Kim et al., 2013; Cao et al., 2009). We further selected confounders for regression models if they were associated ($p < 0.2$) with 2 or more GDS DQs or with BDNF levels in umbilical cord serum. Finally, we included the following potential confounders in the model, including maternal age, maternal IQ, maternal education, smoking during pregnancy (maternal smoking and second-hand smoking), meat consumption, paternal education, household monthly income, infant gender, birth weight, gestational age, maternal blood lead and maternal blood mercury [Maternal blood lead and maternal blood mercury concentrations were measured by graphite furnace atomic absorption spectroscopy (Thermo M6, USA) and atomic absorption spectrometry (Model DMA-80; Milestone Inc., Italy), respectively, as described previously (Gundacker et al., 2000)]. Because very few women reported alcohol use, alcohol use was not included in the models.

Confounders in the final models were categorized as noted in Table 1.

All data were analyzed using the statistical software SPSS 16.0; $p < 0.05$ indicated statistical significance.

3. Results

3.1. Sociodemographic characteristics of the study participants

Table 1 describes the sociodemographic characteristics of the study sample. In the baseline group (n = 300), the average maternal age was 28.05 years (SD = 4.80) (data not shown), 64.7% women were primiparous, and most women (98.0%) were married. The average maternal IQ was 93.00 (SD = 14.42) (data not shown); 47.7% women had graduated from high school or above, and 61.0% husbands had graduated from high school or above. Of the women, 65.7% lived in households with a monthly income of less than RMB (¥) 3000 yuan (4000 yuan is the median household monthly income in Shandong Province), 62.3% had a normal weight before pregnancy, and 80.7% reported consuming meat more than once

Table 1
Demographic characteristic of the study population.

Characteristic	Baseline group, n = 300 (%)	GDS group, n = 188 (%)	GDS + BDNF group, n = 149 (%)	P-value
Maternal characteristic				
Maternal age (years)				
<30	193 (64.3%)	129 (68.6%)	101 (67.8%)	
30–34	71 (23.7%)	40 (21.3%)	32 (21.5%)	
≥35	36 (12.0%)	19 (10.1%)	16 (10.7%)	0.886[a]
Marital status				
Married or living as married	294 (98.0%)	184 (97.9%)	145 (97.3%)	
Single	6 (2.0%)	4 (2.1%)	4 (2.7%)	0.894[a]
Parity				
0 (Primiparous)	194 (64.7%)	120 (63.8%)	96 (64.4%)	
≥1 (Multiparous)	106 (35.3%)	68 (36.2%)	53 (35.6%)	0.982[a]
Maternal education (years)				
≤9 (Middle school)	157 (52.3%)	104 (55.3%)	80 (53.7%)	
10–12 (High school)	77 (25.7%)	41 (21.8%)	35 (23.5%)	
≥13 (Greater than high school or college)	66 (22.0%)	43 (22.9%)	34 (22.8%)	0.912[a]
Paternal education(years)				
≤9 (Middle school)	117 (39.0%)	76 (40.4%)	61 (40.9%)	
10–12 (High school)	116 (38.7%)	69 (36.7%)	56 (37.6%)	
≥13 (Greater than high school or college)	67 (22.3%)	43 (22.9%)	32 (21.5%)	0.989[a]
Household monthly salary (RMB)				
<3000	197 (65.7%)	124 (66.0%)	99 (66.4%)	
3000–5000	81 (27.0%)	51 (27.1%)	42 (28.2%)	
>5000	22 (7.3%)	13 (6.9%)	8 (5.4%)	0.958[a]
Pre-pregnancy BMI (kg/m^2)				
<18.5	32 (10.7%)	20 (10.6%)	18 (12.1%)	
18.5 to < 23.0	187 (62.3%)	112 (59.6%)	86 (57.7%)	
≥23.0	81 (27.0%)	56 (29.8%)	45 (30.2%)	0.896[a]
Smoking during pregnancy				
Yes	3 (1.0%)	1 (0.5%)	1 (0.7%)	
Lived with smoker	34 (11.3%)	19 (10.1%)	16 (10.7%)	
No	263 (87.7%)	168 (89.4%)	132 (88.6%)	0.968[a]
Alcohol use during pregnancy				
Yes	1 (0.3%)	0 (0%)	0 (0%)	
No	299 (99.7%)	188 (100%)	149 (100%)	0.570[a]
Meat consumption				
<once a week	58 (19.3%)	35 (18.6%)	28 (18.8%)	
1–7 times a week	227 (75.7%)	143 (76.1%)	111 (74.5%)	
≥8 times a week	15 (5.0%)	10 (5.3%)	10 (6.7%)	0.962[a]
Infant characteristic				
Gender				
Male	151 (50.3%)	95 (50.5%)	78 (52.3%)	
Female	149 (49.7%)	93 (49.5%)	71 (47.7%)	0.917[a]
Gestational age (weeks)				
<37	13 (4.3%)	8 (4.3%)	6 (4.0%)	
≥37	287 (95.7%)	180 (95.7%)	143 (96.0%)	0.988[a]
Birth weight (g)				
<2500	10 (3.3%)	6 (3.2%)	5 (3.4%)	
≥2500	290 (96.7%)	182 (96.8%)	144 (96.6%)	0.995[a]
Cadmium (μg/L)				
Detection rate	100%	100%	100%	
Median	1.24	1.20	1.13	
GM	1.22	1.22	1.18	
Range	0.13–4.55	0.13–4.55	0.13–4.55	
Percentile				
25th	0.89	0.90	0.87	
75th	1.73	1.77	1.76	
95th	2.73	2.86	2.76	
Cadmium (μg/L, log$_{10}$scale)	0.09 ± 0.22	0.09 ± 0.24	0.07 ± 0.24	0.843[b]

[a] Proportions were compared by Pearson chi-square test.
[b] Means were compared by One-Way ANOVA.

per week. Although few smoked or consumed alcohol regularly, 11.3% of the women lived with a smoker during pregnancy. None of the mothers reported any work-related potential for exposure to cadmium (data not shown). Overall, of the newborn infants, 50.3% were male. The mean gestational age was 39.32 weeks (SD = 2.15) (data not shown), and the mean birth weight was 3387.38 g (SD = 495.27) (data not shown). Only 3.3% of the newborns (n = 10) weighed less than 2500 g at birth, and 4.3% (n = 13) of the newborns were preterm (<37 weeks). These infants were included in our analyses.

Among the three populations (baseline group, GDS group, GDS + BDNF group), there were no substantial differences in the demographic characteristics, indicating that the studied cohort generally reflects the original cohort.

3.2. Maternal blood cadmium exposure levels

In the baseline group, the median cadmium level in maternal blood was 1.24 μg/L (geometric mean = 1.22, 25th percentile = 0.89; 75th percentile = 1.73; 95th percentile = 2.73; range = 0.13–4.55). Among the three populations (baseline group, GDS group, GDS + BDNF group), there were no significant differences in cadmium levels in maternal blood (Table 1).

3.3. The distribution of the GDS scores of the infants

Table 2 shows the distribution of GDS scores of the infants. There were 188 infants with available maternal cadmium measurements who also had a developmental assessment at 12 months of age. The means of the gross motor, fine motor, adaptive, language and social scores of the 12-month infants were 103.2 (SD = 8.7), 108.9 (SD = 8.4), 102.2 (SD = 6.8), 97.2 (SD = 7.6) and 101.6 (SD = 7.1), respectively. The frequency of developmental delay ranged from 0% (gross motor) to 6.9% (language). These infants were included in our analyses.

3.4. Relationship between prenatal blood cadmium exposure and the neurodevelopmental scores at 12 months of age and BDNF in umbilical cord serum

The maternal blood cadmium concentration showed significant negative associations with the GDS scores and BDNF in umbilical cord serum. A 10-fold (i.e., one log-unit) increase in the maternal cadmium levels was associated with a 5.70-point decrease (95% CI, −10.91 to −0.49; p = 0.032) in the social domain DQs and the maternal blood cadmium concentration was not associated with any of the other four domain DQs (Table 3). A 10-fold increase in maternal cadmium levels was associated with a 4.31-point decrease (95% CI, −8.05 to −0.57; p = 0.024) in the umbilical cord serum BDNF after adjustment for confounding factors such as maternal age, maternal IQ, maternal education, smoking during pregnancy (maternal smoking and second-hand smoking), meat consumption, paternal education, household monthly income, infant gender, birth weight, maternal blood lead and maternal blood mercury (data not shown). The umbilical cord serum BDNF levels were positively associated with the social domain (Table 4).

We further examined the possible association between prenatal exposure to cadmium and neurodevelopment stratified by infant gender at 12 months of age. However, we failed to find any associations between prenatal exposure to cadmium and DQ scores (data not shown).

Table 3
Association between prenatal exposure to cadmium and the neurodevelopmental scores at 12 months of age (n = 149).

	Cadmium (μg/L, log_{10}scale)	P-value
	β[a] (95%CI)	
Gross motor domain	−3.98 (−11.03,3.06)	0.265
Fine motor domain	0.12 (−6.37,6.61)	0.972
Adaptive domain	−1.14 (−6.53,4.25)	0.676
Language domain	−2.90 (−8.66,2.85)	0.320
Social domain	−5.70 (−10.91,−0.49)	0.032*

*P<0.05.
[a] The model included maternal age, maternal IQ, maternal education, smoking during pregnancy (maternal smoking and second-hand smoking), paternal education, house hold monthly income, infant gender, and meat consumption, maternal blood lead, maternal blood mercury.

4. Discussion

Our study indicates that low-level prenatal exposure to cadmium, as assessed from maternal blood, was associated with lower DQs in social scores based on the GDS (but not associated with gross motor, fine motor, adaptive, language domain DQs). Our findings also provide new evidence that the decrease in BDNF levels induced by prenatal cadmium exposure may play an important role in neurodevelopmental deficits induced by prenatal cadmium exposure.

This study analyzed maternal blood cadmium levels in a rural community in the southern coast area of Laizhou Wan of the Bohai Sea in Shandong Province, China (general population). The median maternal blood cadmium level was 1.24 μg/L which was similar to

Table 4
Association between umbilical cord serum BDNF and neurodevelopmental scores at 12 months of age (n = 149).

	Umbilical cord serum BDNF(ng/ml)	P-value
	β[a] (95%CI)	
Gross motor domain	0.19 (−0.10,0.48)	0.193
Fine motor domain	0.12 (−0.14,0.39)	0.348
Adaptive domain	−0.03 (−0.25,0.19)	0.803
Language domain	0.13 (−0.11,0.37)	0.275
Social domain	0.23 (0.02,0.44)	0.032*

*P<0.05.
[a] The model included maternal age, maternal IQ, maternal education, smoking during pregnancy (maternal smoking and second-hand smoking), paternal education, house hold monthly income, infant gender, birth weight, and meat consumption, maternal blood lead, maternal blood mercury, gestational age.

Table 2
Distribution of the GDS DQ Scores for 188 Infants aged 12 Months.

	Mean ± SD(range)	Normal[a] (n (%))	Developmental delay[b] (n (%))
Gross motor domain	103.2 ± 8.7 (86.7–129.0)	188 (100)	0 (0)
Fine motor domain	108.9 ± 8.4 (90.7–133.3)	188 (100)	0 (0)
Adaptive domain	102.2 ± 6.8 (85.0–133.3)	188 (100)	0 (0)
Language domain	97.2 ± 7.6 (70.0–131.0)	175 (93.1)	13 (6.9)
Social domain	101.6 ± 7.1 (72.0–121.0)	184 (97.9)	4 (2.1)

[a] Normal, > 84.
[b] Developmental delay, ≤ 84.

those reported in Asia (general population) [Taiwan (n = 321, 1.15 μg/L), Japan (n = 81, 1.04 μg/L), and Korea (n = 718, 1.52 μg/L)], but higher than those reported in Europe (general population) [Sweden (n = 210, 0.16 μg/L) and Ukraine (n = 46, 0.15 μg/L)] (Lin et al., 2011; Sakamoto et al., 2010; Kim et al., 2013; Åkesson et al., 2002; Ataniyazova et al., 2001). The reference intervals of a 'normal' cadmium level vary considerably. Kim et al. (2013) measured whole blood cadmium levels in healthy volunteers and considered a range of 0.43–3.73 μg/L in blood to be normal. The American Conference of Governmental Industrial Hygienists declared a maximum recommended value in humans of 5 μg/L of cadmium in blood in 2007 (ACGIH, 2007). None of our studies that assessed the concentration of cadmium in maternal blood exceeded this reference value. The women in our study were likely exposed to cadmium from the general environment because they were not exposed to cadmium in the workplace or in high-cadmium environments, although the use of different exposure biomarkers in various studies makes it difficult to compare the extent of cadmium exposure. The mean cadmium level in the present study population was low, and our study population exhibited a low prenatal exposure level to cadmium.

Evidence has shown that low-level cadmium can cross the human placenta barrier and blood–brain barrier and reach the central nervous system directly, which would impact neurodevelopment (Lin et al., 2011; Andersson et al., 1997; Petersson Grawe et al., 2004). Based on the study conducted by Röllin et al. (2015), the concentrations of cadmium in maternal blood do not differ from the corresponding concentrations of cadmium in cord blood, indicating that the measurement of maternal blood concentrations can be used to predict fetal exposure. In the blood, cadmium has a half-life of 3–4 months (Mijal and Holzman, 2010). It is reported that blood cadmium has been shown to reflect both recent and cumulative exposures (CDC, 2005; Hassler et al., 1983). In line with other studies on the potential impacts of exposure to cadmium (Jeong et al., 2015; Kim et al., 2013), we used the cadmium concentrations in maternal blood to evaluate the fetal exposure during gestation. Substantial concern has arisen in regard to the adverse effects of low-level prenatal exposure to cadmium on neurodevelopment, but the results are inconsistent. Three studies found an association between prenatal exposure to cadmium and neurodevelopment at pre-school ages (4–5 years of age) (Kippler et al., 2012; Tian et al., 2009; Jeong et al., 2015). Kippler et al. (2012) assessed cadmium exposure in the urine of 1305 Bangladeshi women in early pregnancy (gestational week 8), and found that maternal cadmium level in urine (median, 0.63 μg/L) was inversely associated with 5-year VIQ, PIQ and FSIQ (the third edition of the Wechsler Preschool and Primary Scale of Intelligence, WPPSI). Tian et al. (2009) reported that cadmium exposure in cord blood (median 0.6 μg/L) was associated with FSIQ deficit (the Wechsler Preschool and Primary Scale of Intelligence, Revised Edition) at 4.5 years (n = 106) after controlling for lead exposure in a Chinese prospective cohort study. Jeong et al. (2015) found that maternal blood cadmium level (mean 1.49 μg/L) was inversely associated with PIQ (the Wechsler Preschool and Primary Scale of Intelligence, Revised Edition) in children at 5 years of age (n = 119). Our study showed that prenatal exposure to cadmium, as assessed from maternal blood, was associated with lower DQs in social scores based on the GDS at 12 months of age. However, in a recent study, Kim et al. (2013) found that maternal blood cadmium levels (geometric mean, 1.52 μg/L) were not associated with the MDI or PDI scores of the infants at 6 months of age (the Bayley Scales of Infant Development-II) (n = 718). We found no associations between prenatal exposure to cadmium and gross motor, fine motor, adaptive, language domain DQs at 12 months of age. We should note that some of the observed inconsistencies may be explained by important differences in the sample size, race/ethnicity, age of children, exposure scenario or measure (e.g., maternal blood vs maternal urine vs cord blood), and neurodevelopmental assessment method (e.g., Bayley vs GDS vs WPPSI).

We analyzed the associations between prenatal exposure to cadmium and neurodevelopment after removing infants considered to have "developmental delays" or removing infants for whom parents reported smoking. The negative association between prenatal exposure to cadmium and social domain DQ scores still existed (data not shown).

Gender differences in susceptibility to cadmium might exist (Kippler et al., 2012; Röllin et al., 2015), however, in the present study, when stratified by infant gender, we failed to find any associations between prenatal exposure to cadmium and DQ scores, the substantial differences are not clear may due to the small sample size.

Potential mechanisms for the neurodevelopmental toxicity of cadmium have not been fully elucidated. A possible mode of action of cadmium is hormonal interactions, particularly with thyroid hormones (Iijima et al., 2007), which are important for brain development. Thyroid hormones (TH), such as thyroid-stimulating hormone (TSH), T4, and triiodothyronine (T3) are known to play a significant role in brain development (Porterfeld, 2000), and hypothyroidism has been associated with neuroanatomical and behavioral effects (Haddow et al., 1999). Mori et al. (2006) found that perinatal exposure to low doses of cadmium can cause changes in brain deiodinase activities in the neonates, indicating that thyroid hormone metabolism might be a potential target of cadmium. Cadmium exposure was found to have a negative effect on the TSH concentration in neonatal blood (Iijima et al., 2007). BDNF is a key protein that is regulated by TH, which plays a crucial role in learning and memory processes (Liao et al., 2007; Schratt et al., 2004; Ying et al., 2002). Rai et al. (2013) found that a mental mixture (arsenic, lead and cadmium) decreased the expression level of BDNF. In the present study, we found a negative correlation between maternal blood cadmium and the BDNF levels, suggesting that changes in BDNF induced by prenatal cadmium exposure may contribute to its adverse effects on neurodevelopment. Further, after adjusting for confounding factors with BDNF, the negative association between the maternal blood cadmium concentration and social domain DQs was attenuated (data not shown), suggesting that cord serum BDNF may play an important role in the decline of social domain DQs induced by prenatal low-level cadmium exposure. Social domain DQs mainly reflected the emotions and reactions. Emerging evidence suggests that BDNF appears to play a permissive role in neuropsychiatric disorders, facilitating the environmental effect on emotions regulation, and may be a type of happiness molecule that improves an individual's mood if it is increased (Lewin and Carter, 2014).

To our knowledge, this study is the first investigation in mainland China to evaluate the possible adverse effects of prenatal cadmium exposure on infant neurodevelopment by reducing BDNF levels. However, our study also has some limitations. First, although we adjusted several confounders in the model, other important confounders like, postnatal exposure to cadmium, breastfeeding data, arsenic were not adjusted in the model, which may affect infant neurodevelopment and umbilical cord serum BDNF levels. Second, we did not detect thyroid hormone. Third, the rate of follow-up was not high at 1 year of age, which may limit our power to detect significant differences in multivariate models.

5. Conclusions

In conclusion, our findings suggest that prenatal cadmium exposure is associated with lower DQs in the LW birth cohort of

infants. Our findings also provide new evidence that the decrease in BDNF levels induced by prenatal cadmium exposure may play an important role in neurodevelopmental deficits induced by prenatal cadmium exposure. A large longitudinal study that measures BDNF is needed to illustrate the potential pathways linking cadmium exposure and neurotoxicity. Additionally, it is important to take precautions to minimize human exposure to cadmium as much as possible.

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