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Identifying a critical window of maternal metal exposure for maternal and neonatal thyroid function in China: A cohort study

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ABSTRACT

Background: China, a developing country, has a particularly serious problem with metal pollution. We evaluated the association of metal exposure during pregnancy with maternal and neonatal thyroid function, and identified the critical window for maternal metal exposure effects on maternal and neonatal thyroid functions.

Methods: The maternal urinary concentrations of mercury (Hg), cadmium (Cd), arsenic (As) and cesium (Cs) were determined in pregnant women during their first (n = 389) or third (n = 257) trimesters in a prospective cohort from 2014 to 2015 in Nanjing, China, using an inductively coupled plasma mass spectrometry (ICP-MS) instrument. Maternal serum-free thyroxine (FT4) and thyroid-stimulating hormone (TSH) were measured by electrochemiluminescent microparticle immunoassays in the second and third trimesters. Neonatal TSH levels were detected 72 h after birth.

Results: Hg (> 0.162 μg/L), Cd (> 0.084 μg/L), As (> 0.348 μg/L) and Cs (> 0.093 μg/L) were detectable in 76.9%, 90.1%, 100% and 100% of maternal urine samples from women in the first trimester of pregnancy. In the multiple adjusted linear regression models, maternal exposures to Hg and Cd in the first trimester were positively associated with maternal TSH levels in the second trimester ($P < 0.01$, $P = 0.02$). Moreover, maternal exposures to Cd and Cs in the first trimester were positively associated with neonatal TSH levels ($P = 0.04$, $P = 0.02$). In the Bayesian kernel machine regression (BKMR) model, the results were stable and consistent with the linear regression model.

Conclusions: Maternal exposure to Hg, Cd and Cs in the first trimester was related to TSH levels in mothers and newborns. Efforts to identify maternal and neonatal thyroid disruptors should carefully consider the effects of exposure to these metals.

1. Introduction

Metals of natural and anthropogenic origins, such as industrial emissions, fossil fuel burning, and mining, are found in the environment. China, a developing country, has a particularly serious problem with metal pollution. Humans can be exposed to metals via air and food and water consumption. During pregnancy, metals in maternal blood circulation might pass through the placenta and reach the fetus, and these metals can be detected in cord blood (Al-Saleh et al., 2011).

Previous researchers have found that toxic metals, such as mercury (Hg), cadmium (Cd) and arsenic (As), might disrupt thyroid function (Nie et al., 2017; Sun et al., 2018; Yorita Christensen, 2013). Some metals, specifically cesium (Cs), are radioactive. A recent cross-sectional study reported a negative association between maternal exposure to Cs and maternal triiodothyronine (T3) (Harari et al., 2015). However, few studies have focused on the relationship between metals and thyroid function during pregnancy or in newborns, and even fewer studies have examined the effects of metals in different developmental periods during pregnancy. In addition, most human studies investigated the effects of a single metal on thyroid function and did not consider the

Abbreviations: Hg, Mercury; Cd, Cadmium; As, Arsenic; Cs, Cesium; FT4, Free thyroxine; TSH, Thyroid-stimulating hormone; BKMR, Bayesian Kernel Machine Regression; CI, confidence interval; LOD, limit of detection; PIP, posterior inclusion probability

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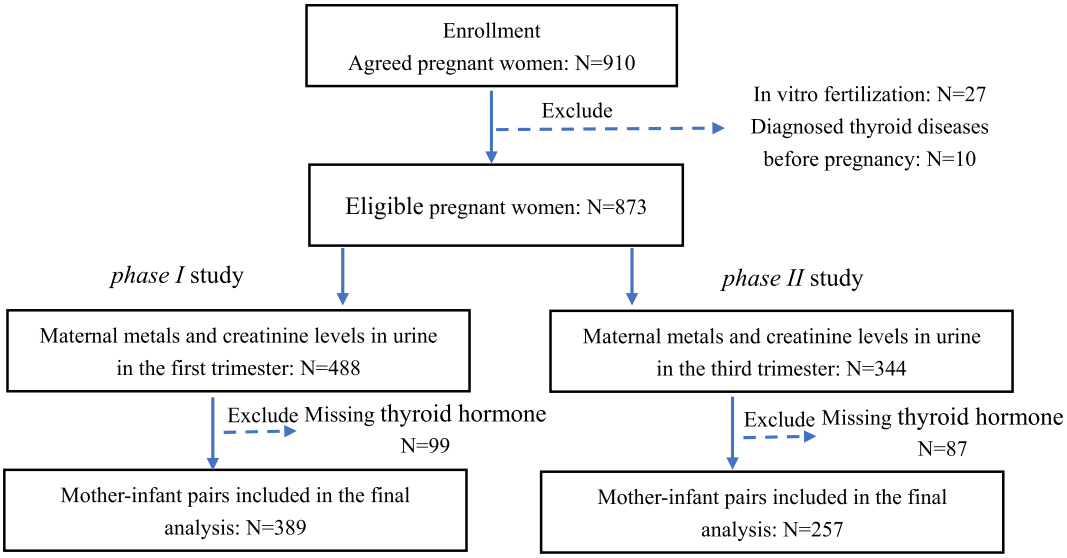

Fig. 1. Flow chart of population included in our final analysis.

possible combined effects of multiple metal exposures, even though some experimental studies indicate that joint chemical exposures could impact the thyroid (Wade et al., 2002). In fact, some metals have similar exposure sources and routes. Atmospheric emissions and sea food consumption are the main sources of Hg, and the common exposure routes are inhalation and ingestion, respectively. Cd is used in personal products, such as pigments, batteries, coatings, and plastic stabilizers, and common human exposure occurs by inhalation. Cs is a radioactive element that can be found in industrial or medical applications. As is mostly used in car batteries. They can enter the body through contaminated water or food. Therefore, it is necessary to consider their joint exposure effects.

Pregnancy progression and fetal growth and development, especially neurodevelopment, are closely related to thyroid hormones (Stepien and Huttner, 2019). During pregnancy, maternal thyroid function undergoes physiological changes. The fetal thyroid gland begins to develop around the 10th week of pregnancy and becomes functional at approximately mid-gestation (Polak, 2014). Therefore, the maternal supply of thyroid hormones is crucial for fetuses, especially during the first half of pregnancy. Thyroid homeostasis has key functions in fetal and postnatal neurodevelopment and is vulnerable to thyroid-disrupting chemicals (Boas et al., 2009; Wang et al., 2017). Identifying the potential adverse effects of metal exposure during the critical window of pregnancy is important.

In this study, we investigated associations between maternal metal exposure in different trimesters and biomarkers of thyroid function in mothers and newborns. We focused on metals that were known or suspected to be toxic, including Hg, Cd, As and Cs. Using real-world evidence from a cohort study, we assessed the associations of each individual metal exposure with thyroid function in different trimesters, and examined the possible effects of joint metal exposures with a mixed model approach.

2. Materials

2.1. Study design and participants

Our study was a prospective cohort study initiated and conducted at a hospital affiliated with Nanjing Medical University. We obtained signed informed consent from all participants and the study was approved by the Medical Ethics Committee of Nanjing Medical University. This two-phase study was designed to identify the critical metal exposure window during pregnancy and evaluate outcomes (thyroid function) separately. Eligible study participants (n = 910) were recruited at means of 11.9 gestational weeks between February 2014 and November 2015 in Nanjing, China. Eligibility criteria included Nanjing residents with a maternal age ≥ 18 years, with no active smoking before and during pregnancy, and willing to participate and give birth in Nanjing. A face-to-face questionnaire interview was conducted at study enrollment to collect demographic information, including age, education level, maternal weight and height before pregnancy, and passive smoking status before and during pregnancy. During pregnancy, maternal urine samples were collected at means of 11.9 and 32.4 gestational weeks (first trimester/third trimester), and blood samples were collected at means of 24.6 and 32.4 gestational weeks (second trimester/third trimester).

Of the 910 enrolled women, those who had undergone assisted fertilization (n = 27) and who accepted treatment after being diagnosed with thyroid diseases before pregnancy (n = 10) were excluded. Among the remaining 873 women, (1) *the phase I study* collected 488 maternal urinary samples to detect metal and creatinine levels during the first trimester. Of those, 389 subjects had available maternal (in the second and third trimesters) and neonatal thyroid biomarkers. (2) *The phase II study* collected 344 maternal urinary samples to detect metal and creatinine levels in the third trimester. Of those, 257 subjects had available maternal (at the third trimester) and neonatal thyroid biomarkers. In total, there were 873 eligible participants. Of these, 488 participated in the *phase I study*, and 344 took part in the *phase II study*. However, due to missing thyroid hormone information, the final samples included in the analysis were 389 in *phase I* and 257 in *phase II* (Fig. 1).

2.2. Assessment of maternal urinary metal concentrations

Urinary concentrations of total Hg, Cd, As and Cs were quantified using an iCAP Qc inductively coupled plasma mass spectrometry (ICP-MS) instrument (Thermo Fisher Scientific, Germany). The plastic containers used in the experiments were soaked with 5% (v/v) HNO_3 (Fisher Scientific, USA) and rinsed with ultrapure water. First, the urine samples were thawed at 4 ˚C and thoroughly mixed before pretreatment. Second, 100 μl urine samples were diluted 1:20 with a diluent solution containing 1% (v/v) high-purity HNO_3 to 2 ml. Finally, the diluted samples were analyzed by the ICP-MS system. The limit of detection (LOD) was calculated as three times the standard deviation for 11 consecutive blank samples. Pooled urine quality control (QC) samples were analyzed every 20 samples in parallel with the study samples

Table 1
The characteristics of 389 mothers and their infants, and maternal and neonatal TSH concentrations.

Characteristic	N	Maternal TSH[a] (mean ± SD)	*P*	neonatal TSH (mean ± SD)	*P*
Maternal age (years)					
≤35	356	2.47 ± 1.43	0.76	1.37 ± 1.06	0.14
> 35	33	2.39 ± 1.08		1.09 ± 0.99	
Gestational age (weeks)					
< 37	50	1.94 ± 1.06	**0.01**	1.07 ± 0.97	0.05
≥37	339	2.55 ± 1.43		1.39 ± 1.06	
Maternal education					
High school or lower	32	2.62 ± 1.29	0.76	1.26 ± 0.96	0.14
College	92	2.52 ± 1.74		1.21 ± 1.99	
Master degree or above	204	2.46 ± 1.34		1.35 ± 1.05	
Missing	61	2.32 ± 1.06		1.61 ± 1.20	
Passive smoking					
No	231	2.51 ± 1.44	0.46	1.30 ± 1.04	0.24
Yes	158	2.40 ± 1.34		1.43 ± 1.08	
Parity					
0	286	2.56 ± 1.49	0.03	1.38 ± 1.04	0.41
≥1	103	2.21 ± 1.07		1.28 ± 1.11	
Infant gender					
Boy	199	2.55 ± 1.32	0.21	1.38 ± 1.07	0.56
Girl	190	2.38 ± 1.48		1.32 ± 1.05	

Thyroid-stimulating hormone, TSH (mIU/L).
[a] Maternal TSH were detected in the second trimester.

(Liang et al., 2017). To account for differences in the urinary analyte concentrations caused by urine dilution, the urinary creatinine concentrations were subsequently used as covariates. Urinary creatinine was measured using a Q Exactive mass spectrometer (Thermo Fisher Scientific, Germany) on an UltiMate 3000 Rapid Separation LC system (Dionex, USA).

2.3. Maternal thyroid function

Thyroid-stimulating hormone (TSH) and free thyroxine (FT4) are the main indicators of thyroid function. Maternal serum FT4 and TSH levels were detected during the second and third trimesters by electrochemiluminescent microparticle immunoassays using the Architect system (Roche GmbH, Mannheim, Germany). The reference intervals for the second trimester were 0.39–5.22 mIU/L for TSH and 9.81–17.26 pmol/L for FT4. The reference intervals of FT4 and TSH were 9.12–15.17 pmol/L and 0.60–6.84 mIU/L, respectively, in the third trimester (Endocrinology branch of Chinese Medical Association, 2012).

2.4. Neonatal thyroid function

Neonatal TSH serves as a biomarker of newborn thyroid hormone status and also potentially reflects fetal disturbances in thyroid hormone homeostasis during pregnancy (Korevaar et al., 2016). Neonatal TSH levels were measured 72 h after birth as a part of routine neonatal screening. Capillary blood samples were collected by heel prick sampling, spotted onto standardized filter paper and then measured by an AutoDELFIA Neonatal TSH kit (PerkinElmer Inc., United States). None of the newborns in the present study were diagnosed with congenital hypothyroidism.

2.5. Statistical analysis

The concentrations of maternal urinary metals below the LOD were assigned a value of LOD/2 (Glass and Gray, 2001). Since the maternal urinary metal concentrations were not normally distributed, the metal concentration data were natural log-transformed.

We used multiple linear regression models with maternal and neonatal thyroid hormone concentrations (continuous variables) as dependent variables and maternal metal concentrations as independent variables (at first trimester/third trimester). Model 1 was unadjusted; model 2 was controlled for potential confounders. First, simple linear regression was used to determine whether covariates were selected in our study. According to the standard of $p < 0.1$, not all covariates included met the requirements. Then, prior knowledge from the scientific literature was used to determine whether covariates were selected for statistical analysis (Walter and Tiemeier, 2009). The following variables were included in the final models: maternal age, education level, passive smoking, baby gender, parity, gestational age at delivery (Sun et al., 2019), natural log-transformed maternal urinary creatinine (Wang et al., 2016) and selenium (Se) concentrations. Because types 1, 2 and 3 iodothyronine deiodinase are selenoproteins and are important in regulating thyroid hormone concentrations (Kohrle, 2005), Se was also included as a confounder (Abdelouahab et al., 2008).

Analyses were performed using SAS 9.3 software (SAS Institute, Inc., Cary, NC, USA). The level of significance was a two-sided p value < 0.05.

Given a sample size of 389, the null hypothesis was H0, and the slope was 0; the alternative hypothesis was H1, the slope was 0.05, the β/α ratio was 4, the SD of predictor (i.e., lnHg) was 1.4, the SD of the outcome variable (i.e., TSH) was 0.7, and the power of 70%.

To investigate the joint effects of metals on maternal and neonatal thyroid function, we used the Bayesian kernel machine regression (BKMR) model (Zhang et al., 2019), which can identify nonlinear and nonadditive relationships within exposures and capture the exposure-response relationship with other agents fixed at certain levels (Bobb et al., 2015). We conducted hierarchical variable selection with 10,000 iterations by the Markov chain Monte Carlo algorithm, and then we calculated the posterior inclusion probability (PIP), which represented the probability of a specific metal being included in the final model. The BKMR regression was conducted with R (3.4.3) using the R package "bkmr".

3. Results

Of the 389 participants in *phase I study*, 91.5% were under 35 years old. The majority reported university or higher education (n = 204, 52.4%). 40.6% of women confirmed passive smoking exposure (n = 158). Among all newborns, 51.2% (n = 199) were boys and 48.8% (n = 190) were girls. The characteristics of 389 participants are summarized Table 1. Maternal and neonatal TSH did not differ by characteristics of mothers and newborns, except gestational age. Participants who were subjected to preterm birth had lower levels of maternal and neonatal TSH. Of the 257 participants in *phase II study*, 92.2% were under 35 years old. The majority reported university or higher education (n = 136, 52.9%). 41.6% of women confirmed passive smoking exposure (n = 107). Among all newborns, 52.1% (n = 134) were boys and 47.9% (n = 123) were girls. The characteristics of 257 participants are summarized Supplementary Table 1. The characteristics of participants who were included and not included in the *phase I study* were not significantly different (Supplementary Table 2).

Tables 2 and 3 show the means, percentiles, and ranges of maternal exposure to metals (Hg, Cd, As, Cs, Se) and maternal and neonatal thyroid biomarker concentrations in the *phase I* and *phase II studies*. Maternal thyroid function was abnormal in 12 (3.1%) patients in the second trimester and 27 (7.2%) patients in the third trimester in the *phase I study* (Supplementary Table 3). The associations between maternal thyroid function in the second trimester and that in the third trimester in the final *phase I* analysis are showed in Supplementary Table 4.

Table 4 shows the results of the *phase I* study; maternal exposure to Hg ($\beta = 0.16$, $P < 0.01$) and Cd ($\beta = 0.17$, $P = 0.02$) in the first trimester had a significant positive association with maternal TSH level

Table 2
The distribution of maternal urinary metals in the first trimester, and matched maternal and neonatal serum thyroid hormone concentrations.

	N	25th	50th	75th	95th	Range	≥LOD
Maternal urinary metals concentrations in the first trimester							
Hg	389	0.19	0.50	1.27	5.31	LOD-131.18	76.9%
Cd	389	0.26	0.57	0.93	1.78	LOD-5.05	90.1%
As	389	12.65	20.76	35.51	82.76	0.56–421.50	100%
Cs	389	4.44	6.68	9.09	14.38	0.31–36.19	100%
Se	389	9.9	12.5	15.30	23.79	6.04–46.46	100%
Maternal thyroid hormones concentrations in the second trimester							
FT4	388	11.99	13.08	14.32	16.68	3.98–24.51	100%
TSH	389	1.24	1.78	2.55	3.96	0.01–8.13	100%
Maternal thyroid hormones concentrations in the third trimester							
FT4	360	11.53	12.59	13.78	16.39	5.00–36.87	100%
TSH	377	1.62	1.78	2.55	3.96	0.01–8.13	100%
Neonatal thyroid hormone concentrations							
TSH	388	0.53	1.08	1.91	3.45	0.01–6.61	100%

Mercury, Hg (μg/L); cadmium, Cd (μg/L); arsenic, As (μg/L); cesium, Cs (μg/L); selenium, Se (μg/L); Free thyroxine, FT4 (pmol/L); thyroid-stimulating hormone, TSH (mIU/L).
Hg LOD = 0.162 μg/L; Cd LOD = 0.084 μg/L; As LOD = 0.348 μg/L; Cs LOD = 0.093 μg/L; Se LOD = 1.383 μg/L.

Table 3
The distribution of maternal urinary metals in the third trimester, and matched maternal and neonatal serum thyroid hormone concentration.

	N	25th	50th	75th	95th	Range	≥LOD
Maternal urinary metals concentration in the first trimester							
Hg	257	0.08	0.23	0.60	2.44	LOD-33.96	61.1%
Cd	257	0.15	0.31	0.53	1.31	LOD-14.46	86.0%
As	257	9.40	14.96	24.65	59.24	1.69–542.91	100%
Cs	257	2.84	4.32	6.23	10.37	0.57–21.86	100%
Se	257	8.07	10.21	12.49	17.63	5.64–27.65	100%
Maternal thyroid hormones concentration in the third trimester							
FT4	237	11.52	12.56	13.94	16.19	5.21–36.87	100%
TSH	250	1.57	2.25	2.92	4.85	0.02–13.08	100%
Neonatal thyroid hormones							
TSH	257	0.53	1.10	1.85	3.36	0.05–6.61	100%

Mercury, Hg (μg/L); cadmium, Cd (μg/L); arsenic, As (μg/L); cesium, Cs (μg/L); selenium, Se (μg/L); Free thyroxine, FT4 (pmol/L); thyroid-stimulating hormone, TSH (mIU/L).
Hg LOD = 0.162 μg/L; Cd LOD = 0.084 μg/L; As LOD = 0.348 μg/L; Cs LOD = 0.093 μg/L; Se LOD = 1.383 μg/L.

in the second trimester in multiple adjusted regression models (adjusted for maternal age, education, passive smoking, parity, baby gender, natural log-transformed urinary creatinine concentrations and natural log-transformed urinary selenium concentrations). Maternal exposure to Cd (β = 0.13, P = 0.04) and Cs (β = 0.31, P = 0.02) in the first trimester was positively associated with neonatal TSH levels after adjusting for potential confounders (maternal age, education, passive smoking, gestational age, parity, baby gender, natural log-transformed urinary creatinine concentrations and natural log-transformed urinary selenium concentrations). Additionally, none of the maternal metal exposures in the first trimester had significant associations with maternal FT4 and TSH concentrations in the third trimester after adjusting for confounders.

Table 5 shows the results of the *phase II* study. There were no significant associations between maternal exposure to Hg, Cd, Cs and As in the third trimester and maternal (third trimester) or neonatal thyroid biomarkers.

According to the BKMR models, interactions between the concentrations of Hg, Cd, As and Cs in the *phase I study* are shown in Supplementary Fig. 1. We investigated the joint effects of metal concentrations in the first trimester on maternal TSH in the second trimester and neonatal TSH. Each metal concentration was natural log-transformed and designated a continuous variable. The PIPs for each metal from the BKMR models are summarized in Table 6. The PIP is a ranking measure to see to what extent the data favors the inclusion of a

Table 4
The associations between maternal exposure to metals in the first trimester and the biomarkers of maternal and neonatal thyroid function.

Metals	N	Model 1[a] β1 (95%CI)	*p*	Model 2[b] β2 (95%CI)	*p*
Maternal FT4 in the second trimester					
Hg	388	0.02(−0.14,0.18)	0.78	0.03(−0.16,0.22)	0.79
Cd	388	0.05(−0.16,0.26)	0.65	0.09(−0.18,0.36)	0.52
As	388	−0.13(−0.37,0.12)	0.32	−0.14(−0.47,0.19)	0.39
Cs	388	−0.01(−0.38,0.34)	0.93	−0.09(−0.62,0.44)	0.73
Maternal TSH in the second trimester					
Hg	389	**0.11(0.03,0.19)**	**0.01**	**0.16(0.06,0.26)**	**< 0.01**
Cd	389	0.09(−0.01,0.20)	0.08	**0.17(0.03,0.30)**	**0.02**
As	389	0.02(−0.11,0.15)	0.76	0.06(−0.11,0.23)	0.46
Cs	389	0.08(−0.11,0.26)	0.42	0.22(−0.05,0.50)	0.11
Maternal FT4 in the third trimester					
Hg	360	−0.03(−0.21,0.15)	0.75	0.02(−0.19,0.23)	0.84
Cd	360	0.15(−0.10,0.39)	0.24	0.18(−0.14,0.49)	0.27
As	360	−0.09(−0.37,0.19)	0.55	−0.15(−0.52,0.23)	0.44
Cs	360	−0.32(−0.72,0.09)	0.13	−0.48(−1.08,0.12)	0.12
Maternal TSH in the third trimester					
Hg	377	**0.10(0.01,0.20)**	**0.04**	0.10(−0.02,0.22)	0.11
Cd	377	0.09(−0.04,0.23)	0.16	0.11(−0.07,0.27)	0.22
As	377	0.09(−0.07,0.24)	0.28	0.01(−0.20,0.22)	0.93
Cs	377	0.08(−0.15,0.31)	0.49	−0.02(−0.36,0.32)	0.90
Neonatal TSH					
Hg	388	0.01(−0.07,0.08)	0.88	−0.01(−0.10,0.08)	0.87
Cd	388	**0.11(0.01,0.21)**	**0.03**	**0.13(0.01,0.26)**	**0.04**
As	388	0.10(−0.02,0.22)	0.10	0.07(−0.08,0.23)	0.33
Cs	388	**0.20(0.03,0.37)**	**0.02**	**0.31(0.05,0.56)**	**0.02**

Mercury, Hg (μg/L); cadmium, Cd (μg/L); arsenic, As (μg/L); cesium, Cs (μg/L); selenium, Se (μg/L); Free thyroxine, FT4 (pmol/L); thyroid-stimulating hormone, TSH (mIU/L).
Maternal urinary metal concentrations were all natural log-transformed.
[a] Model 1: unadjusted model.
[b] Model 2: adjusted for maternal age, education, passive smoking, parity, baby gender, natural log-transformed urinary creatinine concentrations, natural log-transformed urinary selenium concentrations and gestational age (for neonatal TSH). Statistically significant results ($p < 0.05$) are bolded.

Table 5
The associations between maternal exposure to metals in the third trimester and the biomarkers of maternal and neonatal thyroid function.

Metals	N	Model 1[a] β1 (95%CI)	*p*	Model 2[b] β2 (95%CI)	*p*
Maternal FT4 in the third trimester					
Hg	237	−0.10(−0.36,0.16)	0.47	−0.02(−0.32,0.27)	0.88
Cd	237	−0.16(−0.45,0.14)	0.29	−0.08(−0.44,0.28)	0.67
As	237	−0.10(−0.45,0.28)	0.61	0.24(−0.27,0.75)	0.35
Cs	237	−0.45(−0.97,0.06)	0.08	−0.06(−0.83,0.72)	0.88
Maternal TSH in the third trimester					
Hg	250	−0.07(−0.21,0.07)	0.36	−0.13(−0.28,0.03)	0.11
Cd	250	−0.06(−0.22,0.10)	0.49	−0.07(−0.26,0.12)	0.47
As	250	−0.06(−0.26,0.13)	0.53	−0.12(−0.39,0.15)	0.39
Cs	250	−0.07(−0.35,0.21)	0.63	−0.27(−0.68,0.14)	0.19
Neonatal TSH					
Hg	257	−0.07(−0.18,0.03)	0.18	−0.08(−0.19,0.04)	0.18
Cd	257	−0.02(−0.14,0.10)	0.73	−0.01(−0.15,0.12)	0.83
As	257	0.01(−0.14,0.15)	0.95	0.03(−0.16,0.22)	0.74
Cs	257	0.03(−0.18,0.24)	0.77	0.06(−0.23,0.35)	0.67

Mercury, Hg (μg/L); cadmium, Cd (μg/L); arsenic, As (μg/L); cesium, Cs (μg/L); selenium, Se (μg/L); Free thyroxine, FT4 (pmol/L); thyroid-stimulating hormone, TSH (mIU/L).
Maternal urinary metal concentrations were all natural log-transformed.
[a] Model 1: unadjusted model.
[b] Model 2: adjusted for maternal age, education, passive smoking, parity, baby gender, natural log-transformed urinary creatinine concentrations, natural log-transformed urinary selenium concentrations and gestational age (for neonatal TSH).

Table 6
PIPs for conditional inclusion into models between maternal exposure to metals in the first trimester and maternal and neonatal TSH using BKMR models.

Metals	Maternal TSH[a]		Neonatal TSH	
	N	PIP	N	PIP
Hg	389	**0.65**	388	0.13
Cd	389	**0.18**	388	**0.37**
As	389	0.09	388	0.19
Cs	389	0.06	388	**0.59**

PIPs: Posterior inclusion probabilities; BKMR: Bayesian Kernel Machine Regression; TSH, thyroid-stimulating hormone; mercury, Hg; cadmium, Cd; arsenic, As; cesium, Cs.
Urinary metal concentrations were natural log-transformed.
Models were adjusted for maternal age, education, passive smoking, parity, baby gender, natural log-transformed urinary creatinine concentrations, natural log-transformed urinary selenium concentrations and gestational age (for neonatal TSH).
The first two metals contributing most to TSH were bolded.
[a] Maternal TSH were detected in the second trimester.

variable in the regression (Zhang et al., 2019). Hg and Cd contributed the most to the effect of joint metal exposure on maternal TSH (PIP = 0.65, PIP = 0.18), while Cd and Cs contributed the most to the effect of joint metal exposure on neonatal TSH (PIP = 0.37, PIP = 0.59).

The overall associations of joint metal exposure in the first trimester with maternal TSH in the second trimester and neonatal TSH showed positive trends but not significant, which were presented in Fig. 2. In Supplemental Fig. 1, the bi-variate associations by BKMR analysis were shown, and there were interactions among these four elements. Since Hg and Cd contributed the most to the effect of joint metal exposure on maternal TSH, while Cd and Cs contributed the most to the effect of joint metal exposure on neonatal TSH, we used the conventional linear regression analysis to examine the interactions between key metals. Conventional linear mixed effects regression models confirmed that the interactions between the key metals tend to increase maternal or neonatal TSH, but these interactions were not statistically significant (Hg-Cd, $\beta = 0.01$, $P_{interaction} > 0.05$; Cd-Cs, $\beta = 0.08$, $P_{interaction} < 0.10$; data not shown).

Fig. 3 showed the trends of the exposure-response functions of each metal, and we observed that maternal TSH in the second trimester showed an increasing trend with Hg and Cd exposure at the 60th percentile or above compared to the median, as well as neonatal TSH showed an increasing trend with Cd and Cs exposure at the 60th percentile or above compared to the median.

4. Discussion

This study provides relevant and pertinent real-world evidence that maternal exposure to metals may adversely affect maternal or neonatal thyroid function: (1) Metal exposure in the first trimester might affect maternal and neonatal thyroid homeostasis, suggesting that pregnant women and fetuses in early pregnancy are susceptible to thyroid-disruptive metals. (2) Metals were mainly associated with increased maternal or neonatal TSH levels but not with FT4 levels. Furthermore, we confirmed this relationship in BKMR models, which indicated that joint Hg, Cd, As and Cs exposure had overall increased trends on maternal and neonatal TSH levels.

TSH is considered one of the most important biomarkers for the identification of thyroid dysfunction, and it is closely related to neurodevelopment (Freire et al., 2010; Haddow et al., 1999). Considering the specific metals we studied (Hg, Cd, Cs, As), increasing maternal urinary concentrations of Hg and Cd in the first trimester were significantly associated with increased maternal TSH in the second trimester. Hg and Cd circulating in the blood of pregnant women are deposited in different tissues or organs. Urine and feces are the principal routes of Hg and Cd elimination.

In China, atmospheric emissions and water bodies are sources of Hg. Fish and seafood are the main sources of Hg in water bodies. Moreover, Hg from the environment can enter the body and bioaccumulate. Hg is found in both organic and inorganic forms, and we measured the total Hg concentration in urine. The median value of Hg in our study was 0.50 μg/L, which was lower than the levels in the urinary samples of pregnant women in Shenyang, China (0.82 μg/L) (Li et al., 2014), Saudi Arabia (0.99 μg/L) (Al-Saleh et al., 2015) and Sweden (1.60 μg/L) (Vahter et al., 2000), but higher than levels detected in the USA (0.35 μg/L) (Bashore et al., 2014) and Australia (< 0.40 μg/L)

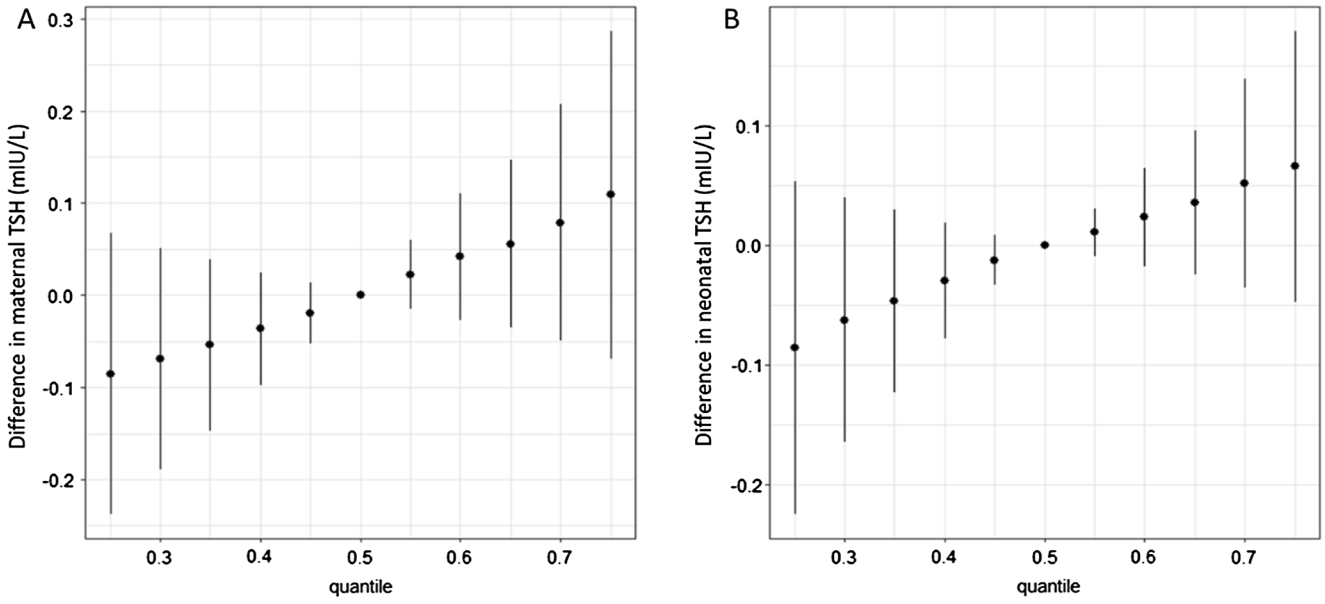

Fig. 2. TSH, thyroid-stimulating hormone. Urinary metal concentrations were natural log-transformed. Joint effects (95% CI) of the mixed metals in the first trimester on maternal TSH in the second trimester (A) and neonatal TSH (B) by BKMR models when all the metals at special percentiles as compared to all the metals at their 50th percentile. The results were assessed by BKMR models adjusted for maternal age, education, passive smoking, parity, baby gender, natural log-transformed urinary creatinine concentrations, natural log-transformed urinary selenium concentrations and gestational age (for neonatal TSH).

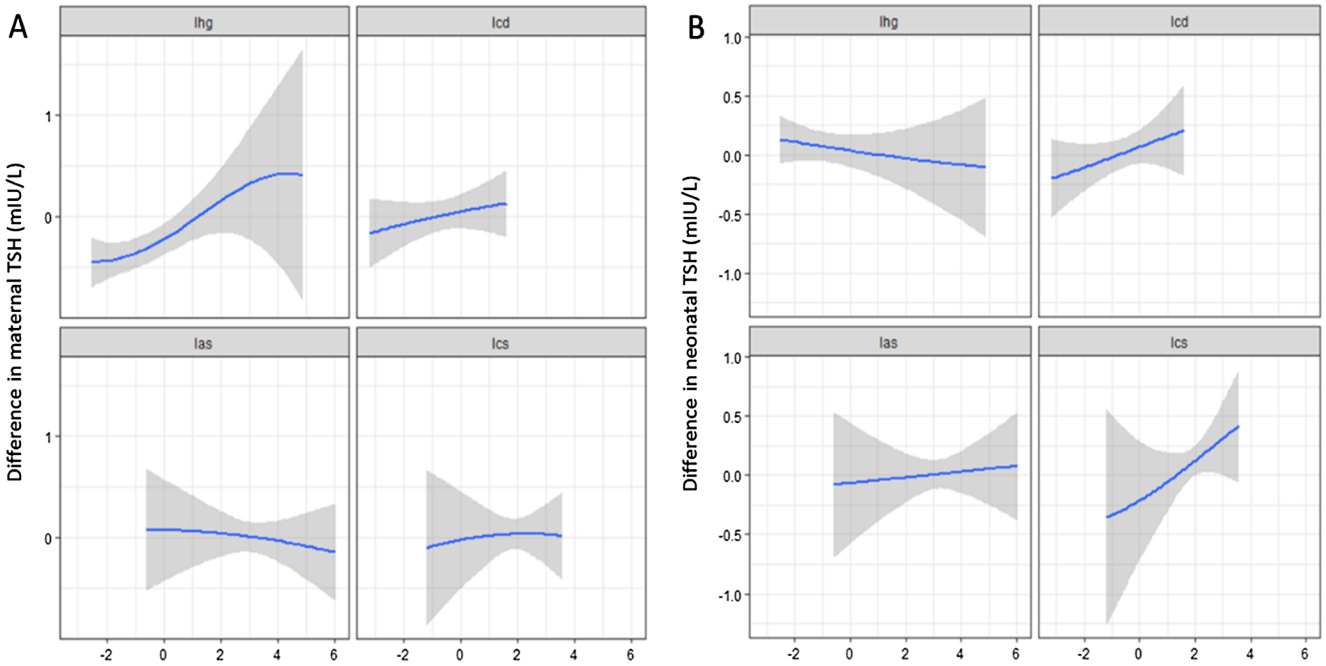

Fig. 3. TSH, thyroid-stimulating hormone; mercury, Hg; cadmium, Cd; arsenic, As; cesium, Cs. Urinary metal concentrations were natural log-transformed. Univariate exposure-response function (95% CI) between selected metals concentrations in the first trimester and maternal TSH in the second trimester (A) or neonatal TSH (B) by BKMR models when fixing the concentrations of other metals at median values. The results were assessed by BKMR models adjusted for maternal age, education, passive smoking, parity, baby gender, natural log-transformed urinary creatinine concentrations, natural log-transformed urinary selenium concentrations and gestational age (for neonatal TSH).

(Hinwood et al., 2013). High exposure to Hg had negative associations with circulating concentrations of T4 and T3 in the National Health and Nutrition Examination Survey (NHANES) general population data (Chen et al., 2013; Yorita Christensen, 2013). A Canadian study showed that increased Hg levels appeared to increase the TSH concentrations in men but not in women, suggesting that these relationships may differ by sex (Abdelouahab et al., 2008). Hg exposure was also related to alterations in the pituitary-thyroid pathway in animal models (Pantaleao et al., 2017; Sun et al., 2018).

Cd is widely distributed in personal products, such as pigments, batteries, coatings, and plastic stabilizers. The median maternal urinary Cd concentration was 0.57 μg/L in our study, which was close to the level in urinary samples from pregnant women in Wuhan, China (0.53 μg/L) (Yang et al., 2016), lower than levels observed in Bangladesh (0.63 μg/L) (Kippler et al., 2012), Spain (0.61 μg/L) (Fort et al., 2014) and Myanmar (0.90 μg/L) (Wai et al., 2018) and higher than levels detected in Mexico (0.18 μg/L) (Moynihan et al., 2017). Cd has been associated with increased TSH (Caride et al., 2010; Rosati et al., 2016), increased T4 and T3 (Chen et al., 2013), decreased T4 and T3 (Rosati et al., 2016) and complex changes in thyroid function (Yorita Christensen, 2013). In a Chinese study, high Cd levels were even related to hypothyroidism status in women (Nie et al., 2017). Additionally, an animal study showed that serum T3 and T4 concentrations in pregnant rats exposed to Cd decreased in a dose-dependent manner (Yoshizuka et al., 1991).

Hg and Cd are known to have direct adverse effects on neurodevelopment, while TSH is also closely related to neurodevelopment (Freire et al., 2010; Haddow et al., 1999). The associations between these two metals and thyroid hormones are inconsistent. Previous studies mainly focused on the general population or high exposure populations, while in the present study, we examined Hg and Cd exposure in pregnant women, a vulnerable subpopulation. Hg and Cd can cross the placental barrier and reach the fetus. In our study, we found that prenatal Cd exposure was associated with increased TSH in newborns. Why prenatal Hg exposure seems to only affect maternal TSH and not neonatal TSH is worthy of further study.

Cs is radioactive and can accumulate in the thyroid gland (Nelson et al., 1961). The median maternal urinary Cs concentration was 6.68 μg/L in our study, which was close to the level observed in urinary samples from pregnant women in Australia (6.35 μg/L) (Hinwood et al., 2015), lower than the level detected in Spain (8.0 μg/L) (Fort et al., 2014), and higher than the level detected in the USA (5.06 μg/L) (Jain, 2013). The NHANES 2007–2008 data (USA) showed an inverse association between urinary Cs concentration and TSH level among 1587 adults (Yorita Christensen, 2013). Another study by Harari et al. found that blood Cs concentration was inversely associated with the T3 level but not with the TSH level in 132 pregnant women (Harari et al., 2015). However, no previous study has examined the relationship between prenatal exposure to Cs and neonatal TSH. Our results showed a positive association between maternal urinary Cs levels during the first trimester and neonatal TSH.

The relationship between the exposure of an induvial to Cs and TSH levels found in our study is inconsistent with the results of the NHANES and Harari studies. This discrepancy could be due to (1) differences in the studied populations, as our study measured prenatal Cs exposure, similar to the study by Harari et al., while the NHANES 2007–2008 data were from adult men and women; or (2) different median exposure concentrations measured in different biospecimens, which may have impacted the results. The median exposure concentration of Cs in urine was 4.6 μg/L in the NHANES 2007–2008 data and 67 μg/L in blood in the Harari study; however, 6.68 μg/L Cs was detected in the urine in our study.

Previous studies have reported that Cs can be detected in drinking water (Harari et al., 2015). Cs can pass through the placental barrier, and the concentration in the placenta increases as Cs exposure increases (Suzuki et al., 2013). In our study, Cs exposure during the first trimester had no significant effect on maternal thyroid function but was associated with increased neonatal TSH. Therefore, we speculated that Cs from exposure during the first trimester could cross the placenta and directly interfere with the thyroid balance of the fetus. Further studies

are needed to support this hypothesis.

In our study, no associations between the metals measured at the third trimester and maternal or neonatal thyroid function were found, suggesting that the latter stages of pregnancy are not susceptible to thyroid-disruptive metals.

Since people can be simultaneously exposed to multiple metals, we also investigated the joint effects of maternal urinary metal concentrations in the first trimester on maternal TSH in the second trimester and neonatal TSH with BKMR models. Compared with multiple linear regression models, BKMR analysis can detect interactions between two chemicals. In our analysis, we observed that there interactions among these four elements, which emphasized the importance of using BKMR model to evaluate the joint effects of metals on outcomes. Further, BKMR analysis can capture the exposure-response relationship with other chemicals fixed at certain levels. In our analysis, we observed an overall positive relationship between joint metal exposure in the first trimester and maternal TSH in the second trimester and neonatal TSH. Hg and Cd contributed the most to the effect of joint metal exposure on maternal TSH, while Cd and Cs contributed the most to the effect of joint metal exposure on neonatal TSH. BKMR analysis can explore the exposure-response function with other metals at certain levels, but does not represent the real exposure levels due to its kernel algorithm. Multiple linear regression models represent the real exposure levels, and we observed that maternal exposure to Hg and Cd in the first trimester had positive linear relationships with maternal TSH in the second trimester. Moreover, maternal exposure to Cd and Cs in the first trimester had positive linear relationships with neonatal TSH. Using both linear regression models and BKMR models in statistical analyses improved the validity of the results, and our results were stable and consistent in both models.

Ultimately, during pregnancy, the maternal hypothalamic-pituitary-thyroid axis exists in a special stress state. It has been reported that the maternal thyroid function may be susceptible to heavy metals in the early stage of pregnancy (Sun et al., 2019). In our epidemiological study, the mechanism was not identified, but we hypothesized that metabolic, hemodynamic or immunological changes are increased in early pregnancy, and the maternal thyroid is highly susceptible to environmental factors, which might interfere with thyroid hormone homeostasis at multiple target points by decreasing the uptake of iodine by the thyroid, competitively inhibiting the iodine symporter, or by directly binding to receptors (Pearce and Braverman, 2009). Since the fetus is particularly dependent on the placental transfer of maternal thyroid hormones during the first half of pregnancy (Patel et al., 2011), even minor changes in maternal thyroid homeostasis may affect fetal development. According to our results and some assumptions, we speculated that early pregnancy might be the critical exposure window, however, in vivo and in vitro toxicology experiments as well as epidemiological data still need to be analyzed to explore the underlying mechanism.

Our study has several advantages. First, due to the population-based prospective cohort design used to evaluate the associations between maternal metal exposure and maternal and neonatal thyroid hormone levels, it might provide clues to establish causality. Second, we used a two-phase study to identify the critical window in pregnancy in which metal exposure could impact maternal and neonatal thyroid function, and we found that early pregnancy is the period most susceptible to the effects of thyroid-disruptive metals. Third, we assessed the risk for each metal independently and confirmed their joint effects in a mixed model approach.

Our study also had limitations. First, we did not measure urinary iodine concentration, which may be related to thyroid function. However, in China, the integration of universal salt iodization, a national iodine deficiency disorder (IDD) prevention and control strategy has achieved remarkable results. IDD has been eliminated at the national level, including in pregnant women (Peng et al., 2015). Indeed, the findings still emphasized the need for iodine measurements in other population studies on thyroid function. Second, in the cohort study, the biological sample size was relatively small. However, we compared the characteristics of subjects who were included and excluded in the final analysis and found no significant difference between them. Further, in order to control selection bias, one commonly used implementation strategy is to adjust for factors that can disrupt the biasing paths linking the exposure and the outcome (Nohr and Liew, 2018), and we adjusted these factors in the model. Even so, our findings still emphasize the need for largescale studies in pregnant women. Third, we measured metal concentrations in maternal urinary samples. Urinalysis for metal as exposure markers is not as stable as blood analysis, and some metals could be misclassified due to a low intraclass coefficient of correlation. Although blood metal concentrations may be more stable biomarkers than urine concentrations, urine samples are readily available and noninvasive. Furthermore, urine and feces are the principal routes of metal elimination. Correlations between the blood and urinary levels of Hg ($r = 0.41$) (Basu et al., 2014) and Cd ($r = 0.65$) (Bjermo et al., 2013) were found in previous studies. Fourth, since our two-phase study design was relatively independent, we did not explore the effects of maternal urinary metal concentrations on thyroid function in repeated urine samples; we explored the effects with separate samples collected at single time points. Ultimately, during pregnancy, women undergo biological changes and are likely to avoid potential hazards, which can influence exposure levels, especially in the third trimester. In addition, since metals such as Hg have a half-life of 70–80 days, the metal exposure levels identified by us during different trimesters might have been representative of a lagged exposure levels, potentially influencing the actual exposure levels.

5. Conclusions

In summary, we observed positive associations between maternal urinary concentrations of Hg and Cd in the first trimester and maternal TSH in the second trimester, as well as positive associations between maternal urinary Cd and Cs levels in the first trimester and neonatal TSH. The first trimester might be the critical window for maternal metal exposure effects on maternal and neonatal thyroid function. Since neurodevelopment is closely related to thyroid function, risk assessments of metals affecting neurodevelopment through thyroid function disruption should be considered urgent needs.

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CRediT authorship contribution statement

Xu Wang: Writing - review & editing, Formal analysis. **Xian Sun:** Data curation. **Yuqing Zhang:** Visualization, Investigation. **Minjian Chen:** Software. **Gro Dehli Villanger:** Supervision, Validation. **Heidi Aase:** Supervision, Validation. **Yankai Xia:** Conceptualization, Methodology, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.105696.

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