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Distributions of Heavy Metals in Maternal and Cord Blood and the Association with Infant Birth Weight in China

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Abstract

OBJECTIVE—To measure serum levels of heavy metals in Chinese pregnant women and their newborns, and to evaluate the association of these metals with infant birth weight

STUDY DESIGN—We measured serum concentrations of lead (Pb), thallium (Tl), cadmium (Cd), selenium (Se), arsenic (As), nickle (Ni), vanadium (V), cobalt (Co), and mercury (Hg) in 81 mother-infant pairs using an inductively coupled plasma mass spectrometry method. Multiple linear regression analyses were used to evaluate the associations of these heavy metals with infant birth weight.

RESULTS—Se, Pb, As, and Cd showed the highest detection rates (98.8%) in both the maternal and cord blood, followed by Tl, which was detected in 79.0% and 71.6% of the maternal and cord blood samples, respectively. Pb had the highest concentrations in both the maternal and cord blood samples of all toxic metals detected, with concentrations of 23.1 ng/g and 22.0 ng/g, respectively. No significant associations were observed between any heavy metals and birth weight. However, Tl in the maternal and cord blood was most notably inversely associated with birth weight.

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CONCLUSION—Se intake was low in Chinese women and their newborns, whereas Pb had the highest concentrations in both the maternal and cord blood samples of all toxic metals detected. Tl was a unique pollution source in this population, and Tl levels were shown to have the largest effect on decreasing infant birth weight in this pilot study. Further research incorporating larger sample sizes is needed to investigate the effects of prenatal exposure to heavy metals—especially Tl and Pb—on birth outcomes in Chinese infants.

Keywords

birth weight; heavy metals; environmental pollution; heavy metal poisoning; infant; newborn; intrauterine growth retardation; maternal exposure; maternal-fetal exchange; neonate; newborn; prenatal exposure delayed effects; selenium

In utero exposure to heavy metal is thought to be potentially harmful to the development of the fetus, leading to intrauterine growth retardation and lower birth weight in newborns. According to the World Health Organization, low birth weight (LBW) has become one of the main risk factors of global disease burden.[1] The prevalence of LBW infants, defined as a weight <2,500 g, has shown distinct geographic patterns, with rates of 25% in India, 7.6% in the United States, and between 5.9–11.8% in China.[2,3] LBW is a main cause of morbidity and mortality in the neonatal period, both in developing and developed countries.[4] Conditions related to preterm birth and LBW are the second leading cause of infant death in the United States after birth defects,[5] and in China the leading cause of death for children under 5 years of age is premature birth/low birth weight.[6] One study conducted in Finland showed that, compared with normal weight infants, LBW infants had a 25-fold higher risk of death in the neonatal period.[7] Furthermore, being LBW is associated with elevated plasma glucose levels and other metabolic effects, including risk of type 2 diabetes.[8,9] Higher blood pressure has also been reported during childhood in LBW infants as compared to normal birth weight (NBW) infants, and this has been suggested to lead to an increased risk of cardiovascular disease and renal dysfunction in adulthood.[10]

It has further been reported that being LBW may lead to dysfunction in mental development, as studies have shown that the learning ability of LBW infants is lower than that of NBW infants during childhood and extends into adolescence.[11] A study conducted in Shanghai has also shown that prenatal exposure to several metals, including mercury (Hg), cadmium (Cd), and thallium (Tl), is associated with decreased Neonatal Behavioral Neurological Assessment scores.[12] The hypothesis that exposures during the prenatal period and during early life contribute to disease risk in adulthood was first proposed by Barker in 1991,[13] and this hypothesis has been subsequently supported by multiple epidemiologic studies.[14] It is known that the fetal period is a critical period of growth and development, in which cellular differentiation and proliferation are active and the ability to detoxify foreign substances is less efficient, resulting in increased susceptibility to these exposures as compared to adults.[15]

The rise in industrialization and urbanization throughout the world over the past few years has led to increasing concern related to the health effects of environmental pollution, including from heavy metals. In China, along with the rapid development of industrialization and urbanization, human activities have directly or indirectly resulted in the accumulation of

heavy metals in the farmland soil, such as mining, industrial production, sewage irrigation, and the use of fertilizers and pesticides.[16] Indeed, about 25 million acres of agricultural land and up to 12 million tons of food is polluted by heavy metals in China, resulting in the reduction of food production as high as 10 million tons every year.[15] A survey of the Chinese Agricultural Ministry has further indicated that there is 140×10^4 hm^2 polluted irrigated area in China, 64.8% of which is from heavy metal pollution. Presently, about 1.3×10^4 hm^2 cultivated land is polluted by Cd in China, involving 25 districts of 11 provinces, while about 3.2×10^4 hm^2 cultivated land is polluted by Hg, involving 21 districts of 15 provinces.[17]

Some epidemiologic evidence has indicated that exposure to specific metals during the prenatal period may result in adverse birth outcomes. For example, recent prospective studies conducted in Bangladesh have shown that maternal exposure to Cd was inversely associated with birth weight in females,[18] while low levels of As exposure during pregnancy had a negative association with birth size among 1,578 mother-infant pairs.[19] Furthermore, a study in the Hubei province of China reported a significant inverse association between cadmium levels in cord blood and neonatal birth height, but not for birth weight.[20] No previous studies have characterized the distributions of multiple metals in the maternal and cord serum of Chinese individuals and evaluated these levels in relation to birth outcomes. Thus, we conducted a pilot study of 81 pairs of mothers and infants in 4 cities in China and investigated the effect of heavy metal elements, including lead (Pb), Tl, selenium (Se), arsenic (As), nickle (Ni), vanadium (V), cobalt (Co), Cd, and Hg, on infant birth weight.

Materials and Methods

A total of 81 pairs of mothers and newborns were enrolled from 4 hospitals in 4 different cities of China from June 2011 to August 2011, including 20 pairs from Beijing, 20 pairs from Lanzhou, 20 pairs from Taiyuan, and 21 pairs from Xiamen. All mothers were interviewed at the time of delivery by a trained interviewer using a standardized questionnaire to collect general information on demographic characteristics (e.g., age, menarche age, self-reported weight before pregnancy, and height), history of hypertension and diabetes, and lifestyle factors during pregnancy (e.g., smoking and passive smoking, alcohol drinking). Information concerning the mothers' history of congenital diseases, history of adverse pregnancy outcomes (e.g., miscarriage, stillbirth), weight at delivery, and information on the newborns' birth date, gender, gestational week, placental weight, and birth weight was obtained from the medical delivery records. Ten mL of peripheral venous blood from the mothers and 10 mL of umbilical cord blood from the newborns was obtained at birth, and the centrifuged serum samples were stored at −70°C until laboratory examination. Each of the mothers and their husbands provided informed consent for participation in the study after receiving a detailed explanation of the study. This study was approved by the Human investigation Committee at Yale University.

Nine heavy metals were measured in maternal and cord blood, including Pb, Tl, Cd, Se, As, Ni, V, Co, and Hg, by the inductively coupled plasma mass spectrometry (ICP-MS) system. First, blood samples were digested by Mars-5 microwave accelerated reaction system (CEM Corporation, Matthews, North Carolina). Second, sample solution was tested by the Agilent

7500ce ICP-MS system (Agilent Technologies, Santa Clara, California). Operational parameters of ICP-MS were as follows: RF power, 1,100 W; auxiliary gas flow, 0.86 L/min; carrier gas flow, 1.80 L/min; plasma gas flow, 15.00 L/min; resolution (peak high 10%), 0.6~0.7 amu; improve quantity of samples, 1.0 mL/min; number of scanning lines, 150; unimodal residence time, 30 ms; repetitions, 3 times; analysis of the time, 5 minutes. Each sample was measured in duplicate. Quality control blood samples were incorporated in each batch of 10 samples. The recoveries of heavy metals varied from 80–120% (Table I).

The median and interquartile range of each metal in the maternal and cord serum were calculated, and differences in metal concentrations between the maternal and cord blood serum was evaluated using the Wilcoxon matched pairs signed rank test. Multivariate linear regression models, adjusted for maternal age, maternal BMI at delivery, gestational week, and gender of the newborn, were utilized in order to evaluate the associations between the concentration of each heavy metal and the birth weight of the newborns. Regression analyses were carried out only for heavy metals with detection rates >50% in the maternal or cord blood serum. All data analyses were carried out with SAS software v. 9.3, and the two-sided $p<0.05$ was considered statistically significant.

Results

General characteristics of the 81 pairs of mothers and newborns are shown in Table II. The age of the mothers ranged from 18–44 years, with a median age of 28. None of the mothers in the study reported smoking or drinking alcohol during their pregnancy, but 9 mothers (11.1%) were passively exposed to cigarette smoke because of their husband's smoking. Sixteen mothers (21.9%) had a history of an adverse event during a prior pregnancy, such as a miscarriage or stillbirth. Of the 81 newborns, 30 (37.0%) were boys and 51 (63.0%) were girls. Eleven (13.6%) were small for gestational age infants (gestational week <37 weeks), while the remaining 70 newborns (86.4%) were born following a normal number of weeks of pregnancy (37–41 weeks). The birth weights of 8 newborns (9.9%) were <2,500 g and of 3 newborns (3.7%) were >4,000 g.

Detection Rates of Heavy Metals in the Maternal and Cord Blood

The detection rates of each heavy metal in the 81 pairs of mothers and newborns are shown in Table III. A detection rate of 98.8% was observed in both the maternal and cord blood samples for Pb, Cd, Se, and As, followed by Tl, which was detected in 79.0% of the maternal blood samples and 71.6% of the cord blood samples, although this difference was not statistically significant ($p = 0.058$). The next highest detection rate for both samples was observed for Ni, with detection rates of 65.4% in maternal blood and 51.9% in cord blood. The higher detection rate for Ni in the maternal blood compared to the cord blood was statistically significant ($p = 0.028$). Further, the detection rate of Co was the same in the maternal and cord blood samples (27.2%), whereas detection rates of V were significantly higher in the maternal blood (61.7%) than in the cord blood (37.0%) ($p = 0.002$) (Table III). Detection rates for Hg were the lowest in both the maternal blood (4.9%) and cord blood samples (12.4%), and a significant difference was observed between these samples ($p = 0.034$).

Distributions of Heavy Metals in the Maternal and Cord Blood

Table IV shows summary statistics for the distributions of the heavy metals. Se, an essential trace element, had the highest median concentration levels in both maternal and cord blood samples, with medians of 140.8 ng/g and 131.1 ng/g, respectively; however, these differences were not statistically significant ($p = 0.171$). Median levels of Pb were slightly higher in the maternal samples (23.1 ng/g) as compared to the cord blood samples (22.0 ng/g; $p = 0.428$), and these concentrations were ~75-fold higher than the limit of detection for this metal (Table IV). The median concentrations of Cd (maternal, 0.9 ng/g; cord, 0.6 ng/g), Tl (maternal, 0.2 ng/g; cord, 0.04 ng/g), and As (maternal, 11.0 ng/g; cord, 8.1 ng/g) were all statistically significantly higher in the maternal blood than in the cord blood samples, whereas the median concentration of Ni, also higher in the maternal sample, was not statistically significant (Table IV). On the other hand, median concentrations of V, Co, and Hg were all below the detection limit in both the maternal blood and the cord blood.

Birth Weight in Relation to Heavy Metal Concentrations in the Maternal and Cord Blood

The associations between infant birth weight and concentrations of each of the heavy metals with a detection rate >50% in the maternal and cord blood samples, adjusted for putative confounding factors, are shown in Table V. No significant associations were observed between these heavy metals and birth weight; however, we found inverse associations with birth weight for most heavy metals for both the maternal and cord blood, most notably for Tl ($\beta = -208.8$, 95% CI −893.2–475.7 in the maternal blood, and $\beta = -531.1$, 95% CI −2257.8–1195.5 in the cord blood). Conversely, a nonsignificant positive association with birth weight was observed for Cd (maternal blood, $\beta = 87.0$, 95% CI −63.1–237.0; cord blood, $\beta = 55.0$, 95% CI −108.2–218.3) and Ni (maternal blood, $\beta = 45.6$, 95% CI −17.2–108.4; cord blood, $\beta = 32.2$, 95% CI −19.8–84.1) in both the maternal and cord blood (Table V).

Discussion

A variety of adverse health effects in humans have been attributed to environmental pollution caused by heavy metals such as Cd, As, Pb, Ni, Se, and Hg. These pollutants persist in the environment since such metals occur naturally, and consequently chronic and low exposures to these metals in the general population are fairly common. Accordingly, studies on health effects from metals have shifted from high and acute exposures to chronic exposure to lower levels of these metals[21,22] and have increasingly focused on prenatal exposures given that the fetus is thought to be highly susceptible to adverse effects. We observed in our study that detection rates of Pb, As, Cd, Ni, Se, and Tl were all >50% in the maternal and cord blood, while the Co and Hg detection rates were <30% in the maternal and cord blood. Further, the highest distributions of heavy metals in the maternal and cord blood was observed for Se, Pb, Cd, Ni, and Tl, whereas the median concentrations of V, Co, and Hg were all below the detection limits in the maternal and cord blood.

Se, which was present at the highest concentration in both the maternal and cord blood samples as compared to the other measured metals, is an essential trace element and has a variety of important functions in the human body, including involvement in thyroid hormone metabolism and antioxidant action of several selenoproteins.[23] Deficiencies in Se have been

associated with a number of disorders, including adverse pregnancy outcomes such as preterm delivery, miscarriage, and preeclampsia.[24,25] Cord blood levels of Cd and Pb have been found to be inversely associated with birth weight,[26] but both of these metals showed minimal to no effect on birth weight in our study despite high levels of Pb in maternal and cord blood. The reason may be that Se reduced the toxic effect of Pb and Cd, and this is consistent with previous research.[27,28] While we observed that Se was detectable in nearly all of the maternal and cord blood samples, the measured concentrations of Se in our population were lower as compared to those in a previous study of Japanese mothers and their infants, as well as the levels reported in cord blood from a study conducted in Croatia (Table VI). These observations for Se in our study population are particularly notable given the results from a previous survey of Se intake in the Chinese population that found that Se intake is insufficient in two-thirds of China,[29] and taken together suggest that Se intake is lower in the mothers and newborns in China.

Our results showed that concentrations of Tl in the maternal and cord blood serum had the largest effect on infant birth weight, as higher levels of both metals were inversely associated with birth-weight in the infants. Tl is a metal that has not been studied extensively to date. The degree of toxicity of Tl ranks alongside those of Pb, Hg, and Cd.[30] Major sources of anthropogenic dispersion of Tl in the environment are industries that use Tl-containing raw materials and extensive nonferrous ore mining.[31] Tl is enriched in the sulfide of coal and is released into the environment primarily as a result of coal combustion. Our results showed that Tl was detectable in ~79% and ~71% of the maternal and cord blood samples, respectively, with median concentrations about 8 times >the limit of detection (LOD) in the mothers and 2 times >LOD in the cord blood. China is the world's largest generator of coal-fired power and steel and producer of ceramics,[32] and therefore Tl pollution is an emerging problem facing the country. We found that increasing maternal levels of Tl had a large effect on birth-weight, although the association was not statistically significant due to the relatively small sample size. Nevertheless, these findings are consistent with a series of case reports describing LBW and prematurity in children exposed to Tl during early gestation and are biologically plausible given observations that Tl crosses the placenta and results in teratogenic effects.[33]

Pb is a toxic heavy metal that is widely distributed in the environment and mainly conveyed to humans through water, food, and occupational sources. Prenatal exposure to low levels of Pb is associated with behavioral abnormalities, learning impairment, decreased hearing, and impaired cognitive function in humans and experimental animals.[34] Higher Pb concentrations in fetal blood can have a significant impact as infants absorb and retain more Pb than do older mammals.[35] A previous study of 53 mother-infant pairs in Vienna showed that the maternal placental blood Pb concentrations were predictive of body weight, body length, head circumference, and fetal intrauterine growth.[36] However, some studies have also shown no association between maternal blood lead levels and neonatal birth weight.[37] In our study the median maternal lead level was 23.1 ng/g, which was lower as compared to previously reported levels among women in Japan[38] but higher compared to maternal levels in a study in France.[18] Moreover, the cord blood levels of Pb in our study were higher as compared to levels reported in other areas during the time period of the current study (Table VI). We found that Pb is not significantly associated with low birth weight in this study, but

it had the highest concentrations in both the maternal and cord blood samples of all toxic metals detected. Thus, further studies with larger samples will be warranted to validate this finding.

Cd is not an essential element in humans, but absorption of the metal occurs after birth primarily through exposures in food, water, and air.[15] Due to a variety of industrial and other anthropogenic activities, Cd has become one of the primary heavy metal contaminants in the environment,[39] Animal studies have indicated that Cd exposure results in a variety of adverse developmental effects.[40] Some research has also shown that maternal smoking during pregnancy can promote Cd accumulation in the placenta, and that placental Cd concentrations are inversely correlated with birth weight in both smokers and nonsmokers.[41] Contrary to this suggestion, our findings showed no statistically significant association between Cd levels and birth weight, and in fact a positive relationship was observed. Placental Cd concentrations were also not correlated with infant birth weight in a study of 96 mother-infant pairs in Spain.[42] The umbilical cord blood concentrations of Cd among the Chinese infants in our study were much higher than those reported for subjects in the EDEN cohort study in France,[18] indicating that management and control of Cd pollution is necessary in China.

It has not yet been established whether exposure to Ni compounds may cause reproductive toxicity as defined by the European Commission,[43] but such an effect is plausible given that Ni does cross the placental barrier.[44] Animal studies indicate that Ni tetracarbonyl and water soluble Ni salts are toxic to the newborn.[43] A study by Chashschin et al[45] raised concern about an increased risk of structural malformations in newborns among female Ni refinery workers, but this study warranted closer scrutiny since it did not address specific malformations and had some limitations.[46] Only a few previous studies conducted among women working in Ni refineries in Russia have investigated the association between prenatal nickel exposure and birth outcomes, and these are in agreement with our results in suggesting that increasing Ni exposure is not associated with a decrease in infant birth weight.[46,47]

In summary, this pilot study including 81 infant-mother pairs in 4 cities in China described the detection rates and exposure distributions of several heavy metals in maternal and cord blood serum and evaluated the associations between these concentrations and infant birth weight. We found Se intake was not sufficient in Chinese women and their newborns, that Pb had the highest concentrations in both the maternal and cord blood samples of all toxic metals detected, and that Tl had the largest impacts on birth weight in the maternal and newborn samples. Further research incorporating larger sample sizes is needed to investigate the effects of prenatal exposure to heavy metals, especially Tl and Pb, on birth outcomes in Chinese infants.

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Table I

Quality Assurance and Quality Control for Elemental Analysis

Heavy metal	Recovery (%)	CV (%)*
Se	116.7	1.3
Pb	103.8	0.9
As	89.4	1.7
Cd	100.1	1.1
Tl	98.8	0.8
Ni	107.8	2.4
V	80.7	1.3
Co	103.5	1.9
Hg	92.6	2.1

*Coefficient of variance for the duplicate determinations.

Table II

General Characteristics of 81 Pairs of Mother and Newborn

Characteristic	N	Median (range) or incidence
Maternal parameter		
Age (years)	81	28.5 (18–44)
BMI (kg/m^2)		
Prepregnancy	81	20.6 (15.6–35.3)
At delivery	81	26.7 (18.9–39.6)
Passive smoking	81	
Yes	9	11.1%
No	72	88.9%
Menarche age (years)	73	14 (11–19)
History of adverse pregnancy	73	
Yes	16	21.9%
No	57	78.1%
Infant parameter		
Sex	81	
Boy	30	37.0%
Girl	51	63.0%
Term (weeks)	81	39 (31–41)
<37	11	13.6%
≥37	70	86.4%
Birth weight (g)	81	3,300 (1,400–4,450)
<2,500 g	8	9.9%
2,500–4,000 g	70	86.4%
>4,000 g	3	3.7%

Table III

Detectable Rate of Heavy Metal in the Maternal and Cord Blood

	Mothers (N=81)		Newborns (N=81)		
Heavy metal	**N**	**Detectable rate (%)**	**N**	**Detectable rate (%)**	**p Value**
Se	80	98.8	80	98.8	1.000
Pb	80	98.8	80	98.8	1.000
As	80	98.8	80	98.8	1.000
Cd	80	98.8	80	98.8	1.000
Tl	64	79.0	58	71.6	0.058
Ni	53	65.4	42	51.9	0.028
V	30	37.0	50	61.7	0.002
Co	22	27.2	22	27.2	1.000
Hg	4	4.9	10	12.4	0.034

Table IV

The Distributions of Heavy Metal in the Maternal and Cord Blood (ng/g)

		Mothers			Newborns			
Heavy metal	**LOD***	**Median**	**25th**	**75th**	**Median**	**25th**	**75th**	**p Value**
Se	1.0	140.8	114.8	157.6	131.1	113.9	157.9	0.171
Pb	0.3	23.1	14.8	33.2	22.0	14.7	33.7	0.428
As	0.5	11.0	9.4	13.7	10.4	8.1	12.6	0.006
Cd	0.03	0.9	0.7	1.2	0.6	0.4	1.0	< 0.0001
Tl	0.02	0.2	0.07	0.2	0.04	<LOD	0.1	< 0.0001
Ni	0.5	1.4	<LOD	2.1	0.9	<LOD	2.4	0.925
V	0.1	<LOD	<LOD	0.2	0.2	<LOD	0.4	—
Co	1.1	<LOD	<LOD	1.1	<LOD	<LOD	1.3	—
Hg	3.7	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	—

*LOD = limit of detection.

Table V

Multivariate Linear Regression for Birth Weight in Relation to Heavy Metals in the Maternal and Cord Blood

Heavy metal	Beta	95% CI	p Value	Beta†	95% CI	p Value
Maternal blood						
Se	2.2	(−5.4 to 1.0)	0.166	1.0	(−3.6 to 1.6)	0.459
Pb	−0.7	(−8.6 to 10.1)	0.879	−1.7	(−9.1 to 5.6)	0.659
As	−14.9	(−37.9 to 8.1)	0.200	−1.5	(−20.2 to 17.3)	0.878
Cd	8.6	(−177.9 to 195.0)	0.927	86.9	(−63.1 to 237.0)	0.252
Tl	−181.7	(−1049.8 to 686.4)	0.678	−208.8	(−893.2 to 475.7)	0.545
Ni	40.1	(−40.5 to 120.7)	0.325	45.6	(−17.2 to 108.4)	0.152
Cord blood						
Se	1.6	(−4.9 to 1.6)	0.325	0.5	(−3.2 to 2.2)	0.707
Pb	−0.9	(−7.6 to 9.3)	0.841	−1.5	(−5.2 to 8.2)	0.665
As	−15.7	(−39.7 to 8.4)	0.199	−13.6	(−33.9 to 6.7)	0.185
Cd	28.1	(−173.0 to 229.2)	0.781	55.0	(−108.2 to 218.2)	0.504
Tl	−158.6	(−1956.4 to 2273.7)	0.882	−531.1	(−2257.8 to 1195.5)	0.542
Ni	1.0	(−65.9 to 64.0)	0.976	32.2	(−19.8 to 84.1)	0.221

†Adjusted for infant gender, maternal age, gestational week, and maternal BMI.

Table VI

Data on Other Countries in the Maternal and Cord Blood Levels Measured in the Time Period of Our Study (ng/g)

	Mothers			Newborns		
Heavy metal	**Country/reference**	**N**	**Average (SD or 95% CI or IQR or R)**	**Country/reference**	**N**	**Average (SD or 95% CI or IQR or R)**
Se	China *	81	140.8 (IQR 114.8–157.6)	China *	81	131.1 (IQR 113.9–157.9)
	Japan[48]	16	238 (IQR 229–276)	Japan[48]	16	280 (IQR 259–306)
	Japan[38]	81	192 (SD 25.1)	Japan[38] Croatia[28]	81 36	227 (33.9) 150 (R 100–240)
Pb	China *	81	23.1 (IQR 14.8–33.2)	China *	81	22.0 (IQR 14.7–33.7)
	Japan[48]	16	24.5 (IQR 16.7–32.4)	Japan[48]	16	14.8 (IQR 9.9–18.0)
	France[49]	900	17 (IQR 1–141)	France[49]	801	13 (IQR 1–78)
	Japan[38]	81	26.4 (SD 9.74)	Japan[38]	81	13.2 (SD 4.12)
	Belgium[50]	1,107	14.7 (95% CI 14.0–15.5)	Croatia[28]	36	45.23 (R 15.54–93.48)
	Sweden[51]	101	11.2	Japan[54]	79	20.6 (IQR 14.5–35.1)
	Greece[52]	25	20 (SD 3.4)	China *	81	22.0 (IQR 14.7–33.7)
	Poland[53]	83	21.4	Japan[48]	16	14.8 (IQR 9.9–18.0)
As	China *	81	11.0 (IQR 9.4–13.7)	China *	81	10.4 (IQR 8.1–12.6)
	Japan[48]	16	6.28 (IQR 4.53–7.41)	Japan[48]	16	3.84 (IQR 2.99–4.51)
	Japan[38]	81	6.16 (SD 3.40)	Japan[38] Japan[54]	81 94	3.76 (SD 2.27) 1.33 (IQR 0.97–1.74)
Cd	China *	81	0.9 (IQR 0.7–1.2)	China *	81	0.6 (IQR 0.4–1.0)
	Japan[48]	16	2.81 (IQR 2.30–3.16)	Japan[48]	16	0.57 (IQR 0.50–0.62)
	France[49]	901	0.8 (IQR 0.1–4.6)	France[49]	800	0.5 (IQR 0.1–4.9)
	Japan[38]	81	1.97 (SD 0.72)	Japan[38]	81	0.22 (SD 0.20)
	Belgium[50]	1,107	0.21 (0.19–0.23)	Croatia[28]	36	8.03 (R 2.10–19.20)

* Current study

Superscripted numbers refer to reference list.

SD = standard deviation, IQR = interquartile range, R = range.