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Maternal Exposure to Cadmium and Fetal Growth: a Systematic Review and Meta-Analysis

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Abstract

This study aims to review the epidemiological studies on the association between cadmium (Cd) exposure during pregnancy and neonatal anthropometric measures. Electronic search of PubMed, Scopus, Web of Science, and Cochrane Collaboration was conducted till end of 2018. Pooled estimates were performed using a fixed-effects model or random-effects model. A total of 22 studies included in the meta-analyses. Subgroup analyses on sample type (maternal urine, maternal blood, cord blood, and placenta), meta-regression, and sensitivity analysis were performed to seek the sources of heterogeneity. In the random-effects meta-analysis of included studies, the pooled correlation coefficient between maternal exposure to Cd with birth weight was − 0.04 [95% CI (− 0.07, − 0.01), with birth length and head circumference as − 0.01 [95% CI (− 0.04, 0.02)] and − 0.02 [95% CI (− 0.06, 0.02)]. Our findings showed significant relationship between Cd exposure of pregnant women with low birth weight, but not with birth length and head circumference.

Keywords Cadmium · Birth weight · Birth length · Head circumference · Meta-analysis

Introduction

Cadmium (Cd) is a type of heavy metal, which is naturally found in soil and is also produced as a result of modern industrial processes. Based on the list of hazardous substances by the US-Environment Protection Agency (US-EPA), it appears as one of the 126 priority contaminants; moreover, the International Agency for Research on Cancer considered it as a human carcinogen [1]. Human exposure to minerals like the Cd occurs through drinking water, food such as cereals, seafood, vegetables, and polluted air and inhalation of tobacco smoke [2, 3]. Due to its long half-life (> 20 years), after ingestion, it can be accumulated in various organs especially in kidneys. In adults, long-term exposure to Cd would lead to undesirable effects on the kidneys and bones, as well as an increased risk of cancer and mortality [2, 4]. Cd also can be considered as an endocrine disruptor compound and thus may affect reproduction and child development [5] and is associated with cardiometabolic risk factors and liver enzymes in adolescents [6]. As among various groups of population, pregnant women and their fetus are at increased risk for adverse effects of environmental contaminants [7], and in recent decades, various epidemiological studies have been conducted to assess the relationship between contaminants and low birth weight and preterm birth [8–10]. Meanwhile, several studies have reported significant relationships of Cd exposure with pregnancy and fetal outcomes [11–13].

Adverse birth outcomes, including stillbirth, spontaneous abortion, small-for-gestational age (SGA), and low birth size, are significant determinants of infant health and survival. The length of gestation and the size of the fetus are considered as a general factor for evaluating the fetal growth [9]. Typically, the birth weight of less than 2500 g was defined as low birth weight, which may be due to in utero growth retardation, early delivery, and small for gestational age and older maternal age [9]. The infant mortality rate of low-birth-weight infants is approximately 24 times higher than that of normal weight newborns [14]. Similarly, delivery before the full 32 weeks of gestation increases the neonatal mortality rate by 74 times [14].

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One of the various factors affecting birth weight is exposure to common environmental pollutants as carbon monoxide, Cd, and other heavy metals [9, 15]. Epidemiological studies have found controversial results on the relationship between maternal exposure to Cd and birth weight and birth length [16–20]. To the best of our knowledge, no recent systematic review or meta-analysis has considered this issue. Therefore, the aims of the present study are to systematically review the most recent epidemiological studies on the association between maternal Cd exposure and neonatal anthropometric measures.

Materials and Methods

The systematic reviews of the observational studies were conducted based on PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) [21].

Eligibility Criteria

Studies were selected based on the following criteria:

1. Participants: women during term pregnancy (however having no chronic disease or long-term medication use) and their infants
2. Outcome: studies examining the association between Cd exposure of pregnant women and adverse birth outcome
3. Study design: studies with cohort, cross-sectional and case–control design
4. Language: studies published in English

Search Strategy

PubMed, Scopus, Web of Science, and Cochrane Collaboration search were conducted to identify related studies published up to end of 2018. The following keywords, as well as MESH terms (Medical Subject Heading) in PubMed, were used to find related articles: "birth weight," "pregnancy outcome," and "birth outcome." These terms are combined with the Boolean operator "OR." The keyword "Cadmium" was added and combined with the former using Boolean operator "AND." Finaly, the search was restricted to human studies and English and the final list was checked for further studies.

Study Selection and Data Extraction

All the considered publications were screened for relevance by two independent reviewers, and any disagreement on the title and abstract of studies was dissolved by discussion. The full texts of relevant studies were checked based on inclusion criteria by researchers. The final list of eligible studies was prepared after a consensus between the two researchers. The extracted data from all eligible studies were as follows: year of publication, location, first author's last name, study design, sample size, and method of Cd exposure assessment, outcome definition, and results expressed as the correlation coefficient (r) or β-coefficient and 95% confidence intervals (CIs), as well as variables used in the adjustment. Qualitative evaluation of individual articles was independently assessed by two researchers and the scoring system based on the STROBE guideline was applied [22]. The objective of the study, the study design, the selection of participants, variables, data sources and measurements, statistical methods, results in data and main results and study limitation were evaluated. Each of 22 questions in the check list were scored as 0 or 1. The correlation between scores obtained from two researchers was 0.70. Means of obtained scores for each study are presented in Table 1. Based on these mean scores, the quality of studies was categorized into three groups of high (mean score 16.5–22), moderate (mean score 12–16), and low quality (mean score < 12). Overall, 68.2% of studies had high quality and other studies were of moderate quality.

Statistical Analysis

The r (correlation) of studies was used. In the case of missed r values, reported β-coefficient, RR, and OR, values were converted to r. Fisher z-transformation of the r is applied for pooled analysis. The potential heterogeneity across studies was evaluated using the Cochran's Q-test and expressed using the I^2 index. The pooled results for Fisher z-transformation were calculated by the fixed-effects model (for $I^2 < 50\%$) or the random-effects model (for $I^2 > 50\%$). Publication bias was evaluated by the Egger's and Begg's tests. Subgroup analyses, meta-regression, and sensitivity analysis were performed to seek the sources of heterogeneity. The sensitivity analyses were performed based on sequential algorithm [23]. All statistical analyses were conducted using STATA software (ver12.0, STATA Corp, College Station, Texas, USA).

Results

Study Selection

A total of 394 studies were found after the initial search. Of these, 274 studies were excluded after reviewing the title and abstracts (the duplicate studies, non-relevant studies, and studies not compatible with our inclusion criteria such as the animal or in-vitro studies, other heavy metals). Twenty-five studies were identified and reviewed; finally, 22 studies were included in the systematic review and meta-analysis (Fig. 1). Of the included studies, 22 had assessed birth weight, 11 had

Table 1 The main characteristics of included studies in the systematic meta-analyses review

Mean STORBE score	Year	Country	First author	Study design	Sample size	Sample type	Confounding factors
21	2012	Bangladesh	M Kippler	Cohort	1616	Maternal urine	Maternal age, BMI, SES, hemoglobin at gestational week 14, urinary As at gestational week 8, and betel use (never/ever) and infant season of birth and gestational age
20.5	2017	China	K Huang	Nested case–control study	408 (102 cases, 306 controls)	Maternal urine	Maternal education, household yearly income, pre-pregnancy body mass index and passive smoking. Additional adjustment for occupational status during pregnancy
16	2002	Japan	M Nishijo	Cross-sectional	57	Maternal urine	maternal age, gestational age
19	2015	South Africa	HB Röllin	Sub-cohort	317 Maternal urine and cord blood. 641 Maternal Blood	Maternal urine, maternal blood, cord blood	vegetable intake, smoking history, burning of fossil fuel, environmental tobacco smoke exposure, gestational age, parity, size at birth (birth weight, birth length and head circumference), and gender of the newborn.
17	2010	Japan	S SHIRAI	Cross-sectional	78	Maternal urine	Birth weight, gestational age, pregnancy maternal BMI
19	2018	China	Y Zhang	Cross-sectional	449	Maternal urine	Maternal age, height, weight, BMI, education
18	2011	Taiwan	CM Lin	Birth cohort	486	Maternal blood, cord blood	maternal education, birth weight
21	2017	China	J Guo	Birth cohort	1073	Cord blood	gestational duration, maternal age, pre-pregnancy BMI, gestational weight gain, family annual income, maternal education levels, smoking status, neonatal sex, sex × ln (Cd concentration), parity, vitamin use during pregnancy
16.5	2015	China	X Hu	Cross-sectional	81	Maternal blood, cord blood	Infant gender, maternal age, gestational week, and maternal BMI
15	2002	Italy	CD Salpietro	Cross-sectional	45	Maternal blood	Maternal age, number of children, gestational length, child's gender
16.5	2000	Finland, Estonia, and Russia	M Kantola	Case-control	152 healthy and 64 healthy abortion	Placenta, maternal blood and serum	Placental Cd, mothers height, and the number of cigarettes per day
16.5	2011	Poland	A Bizon	Case-control	40 case, 35 Control	Maternal blood	–
19	2017	USA	Y Luo	Cross-sectional	275	Maternal blood	Maternal age, ethnicity, cigarette smoking, educational attainment, gestational age at delivery and blood draw and sex
19	2014	China	H Sun	Cross-sectional	209	Maternal urine and blood	Gestational weeks, maternal education, Maternal age, pre-pregnancy BMI, weight gain during pregnancy
20	2015	USA	AC Vidal	Longitudinal	319	Maternal blood	Race/ethnicity, physical activity, maternal smoking
21	2016	China	J Yang	Cohort	5364	Maternal urine	Demographic (e.g., maternal age at delivery), Socioeconomic (e.g., education, occupation, Household income), lifestyle factors (alcohol And tobacco exposure)
16	1992	USA	NJ Loiacono	A part of cohort	161	Placenta	Lead level of blood
16.5	2003	Spain	M Falcon	Case-control	96	Placenta	–
12	1987	USA	BR Kuhnert	Cross-sectional	202	Maternal blood	

Table 1 (continued)

Mean STORBE score	Year	Country	First author	Study design	Sample size	Sample type	Confounding factors
20	2015	USA	MS Bloom	Cohort	235	Maternal blood and urine	Paternal exposure, maternal age, difference in maternal and paternal age, and maternal and paternal smoking, income, race, serum lipids (mg/dL), and creatinine for urine
20	2017	China	L Cheng	Cohort	282	Maternal urine	Maternal age, BMI before pregnancy, net weight gain during pregnancy, maternal education, passive smoking, and gestational age and sex of newborn
15	2013	Nigeria	EP Tawari	Case-Control	125 pregnant, 35 non-pregnant	Maternal blood	

evaluated the birth length, and 8 had assessed the head circumference at birth.

Study Design and Population

This systematic review includes ten cross-sectional, seven cohorts, and five case–control studies, conducted in ten different countries in four continents of Asia, America, Africa, and Europe. Asian studies were as follows: one in Bangladesh [11], seven in China [24–30], two in Japan [17, 19], and one in Taiwan [12]. European studies were conducted in the following four countries: one in Spain [31], one in Poland [32], one in Finland [33], and one in Italy [34], respectively. Seven other studies were related to the USA (5 study) [20, 35–38] and Africa (2 study) [39, 40]. Studies that included the birth length were one in USA, one in Bangladesh, one in Japan, one in South Africa, one in Taiwan, one in Nigeria, and five in China [11, 12, 19, 20, 24, 27–30, 39, 40].

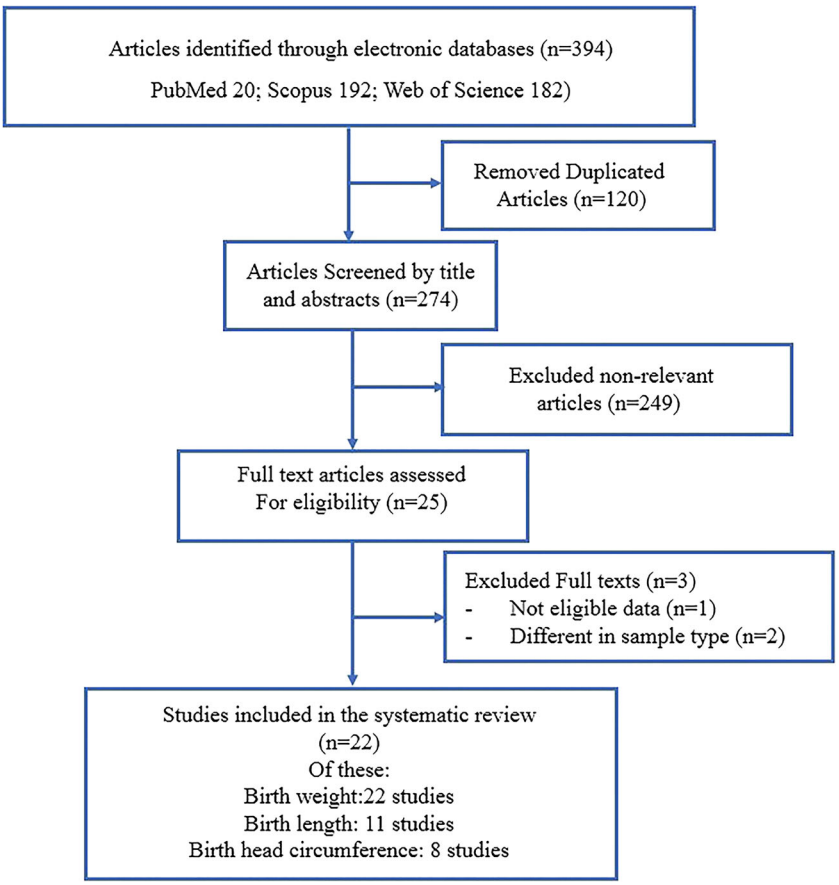

Fig. 1 Flow diagram for selection of studies for the systematic review/meta-analysis

Of these 11 studies, 8 of them had also assessed the head circumference (one in Bangladesh, one in Japan, one in South Africa, one in Taiwan and two in China, one in Nigeria, and one in the USA). The publication year of studies ranged from 1987 to 2017. Sample sizes ranged from 45 [34] to 5364 [29] representing a total of 11,788 participants for birth weight, 9998 for birth length, and 4143 participants for birth head circumference. The mean age of pregnant women in the selected studies ranged from 25 to 33 years. Eight (45%) studies have used mothers' urine sample, and others (55%) have used maternal blood or cord blood samples to evaluate the relationship between cadmium exposure and neonatal anthropometric measures. The mean STORBE score and the main characteristics of each 22 studies included in the systematic review are shown in Table 1.

Association Between Cd and Birth Weight

The pooled analysis of Cd exposure was significantly associated with low birth weight (Fisher-z = − 0.07; 95% CI (− 0.11, − 0.02)) using the random-effects model. However, significant heterogeneity was detected for the meta-analysis of association between Cd exposure and birth weight ($I^2 = 76.3\%$, $p < 0.001$), Therefore, the subgroup analysis, meta-regression, and sensitivity analysis was used to explore the potential sources of heterogeneity.

Subgroup Analysis

Results of subgroup analysis based on resource of Cd exposure showed that urinary Cd was negatively associated with birth weight but it was not significant (Fisher-z = − 0.05; 95% CI (− 0.15, 0.04); $I^2 = 81.9\%$); the association between cord blood Cd and birth weight was not also significant (Fisher-z = −0.04; 95% CI (− 0.13, 0.06); $I^2 = 62.6\%$). Birth weight had significant negative association with maternal blood Cd (Fisher-z = − 0.12; 95% CI (− 0.20, − 0.03); $I^2 = 83.1\%$). The placental Cd was not associated with birth weight (Fisher-z = − 0.03; 95% CI (− 0.16, 0.11); $I^2 = 50.1\%$) (Fig. 2).

Meta-Regression

Meta-regression identified the mean gestational age as the main source of the heterogeneity and could explain 72.62% of the heterogeneity, but mean maternal age, mean maternal BMI, and sample size of studies were not significant ($p > 0.05$).

Sensitivity Analysis

In the sensitivity analysis based on sequential algorithm, a single study was excluded from the calculations each time. The study of Huang (2017) had largest decrease in I^2 (I^2 = 72.5%); therefore, this study was dropped out and then re-analysis reduced sets of studies and performed the same rule one step before. In this step, the study of Tawari (2013) (I^2 = 58.7%) was omitted. The studies of Salpietro (2002) for maternal blood Cd and cord blood Cd with $I^2 = 49.6\%$ and I^2 = 37.6%, respectively, were dropped out in the next steps. Finally, with omitting these three studies, the pooled estimate was obtained Fisher-z = − 0.04; 95% CI (− 0.07, − 0.01) with $I^2 = 37.6\%$ (Fig. 3).

Publication Bias

The p values for Begg's test was 0.08 and for Egger's test was 0.349 for all studies and for studies obtained from sensitivity analysis were 0.984 and 0.946, respectively; therefore, it revealed no obvious publication bias among these studies. Figure 4 shows the funnel plot of included all studies (a) and studies obtained from sensitivity analysis (b). The funnel plot for studies obtained from sensitivity analysis suggested stronger asymmetry.

Association Between Cd and Birth Length

The pooled analysis of Cd exposure was not significantly associated with the birth length (Fisher-z = − 0.03; 95% CI (− 0.07, 0.01)) using the random-effects model. The heterogeneity was not significant ($I^2 = 62.7\%$; $p = 0.001$). Figure 5 shows subgroup analysis based on resource of Cd exposure, and the pooled estimates were not significant in subgroups. Begg's test and Egger's test revealed publication bias among these studies ($p = 0.015$ and 0.042, respectively). Figure 4 c shows funnel plot of included studies. The trim-and-fill method for publication bias in meta-analysis did not change the pooled effect size. The univariate meta-regression indicated that none of the factors (including mean maternal age, mean maternal BMI, mean gestational age, and sample size of studies) contributed to the heterogeneity of meta-analysis (all $p > 0.05$). Result of sensitivity analysis showed with omitting study of Tawari (2013), the pooled estimate obtained − 0.01; 95% CI (−0.04, 0.02) with $I^2 = 41.1\%$ and $p = 0.054$. Begg's test and Egger's test revealed no obvious publication bias among these studies ($p = 0.089$ and 0.125, respectively).

Association Between Cd and Birth Head Circumference

The pooled analysis of Cd exposure was not significantly associated with the birth length (Fisher-z = − 0.04; 95% CI (− 0.09, 0.01)) using the random-effects model. The heterogeneity was significant ($I^2 = 61.3\%$; $p = 0.003$). Figure 6 shows subgroup analysis based on resource of Cd exposure; the

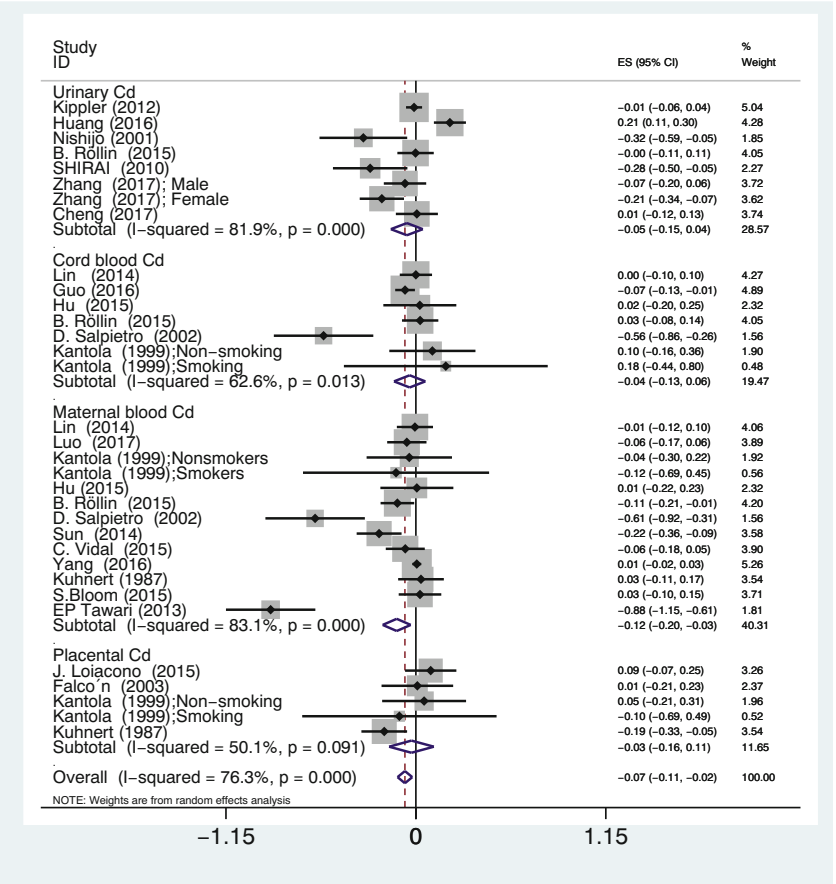

Fig. 2 Forest plot of Fisher-Zs for the correlation between Cd exposure and birth weight by resource of Cd exposure for all studies

pooled estimates were not significant in subgroups. The univariate meta-regression indicated that none of the factors (including mean maternal age, mean maternal BMI, mean gestational age, and sample size of studies) contributed to the heterogeneity of meta-analysis (all p values > 0.05). Begg's test and Egger's test revealed no obvious publication bias among these studies. The p values for these tests were greater than 0.05 ($p = 0.336$ and 0.273, respectively). Figure 4 d shows the funnel plot of included studies. Results of the sensitivity analysis showed with dropping study of Zhang (2017): female, the pooled estimated obtained − 0.02; 95% CI (−0.06, 0.02) with $I^2 = 45.2\%$ ($p = 0.051$).

Discussion

In this study, we systematically reviewed the current evidence of the association of maternal Cd exposure with neonatal anthropometric measures, i.e., birth weight, length, and head circumference. Our findings revealed significant relationship between Cd exposure of pregnant mother with low birth weight but not with birth length and head circumference.

In general, Cd has higher concentrations in the body of women than in men, and it is suggested that the accumulation of this compound in pregnant women is more than in non-pregnant women [29, 41]. During pregnancy, Cd accumulates in placenta, which can reduce utero-placental blood flow or affect the synthesis and metabolism of placental hormones [30, 42, 43]. On the other hand, the penetration of Cd to the placenta affects the transfer of nutrients to the fetus [39, 44, 45], which in turn may disrupt the fetal growth. Cd can also affect fetal growth through substitution with zinc ions. Zinc is one of the essential elements for the fundamental biological functions of the human body, and it also plays an important role in the growth process and reproductive and immune system [46]. Moreover, zinc can be effective in pregnancy outcome [40, 47], so the deficiency of this element during pregnancy has been associated with the delivery of low birth weight infants [40]. Cd and zinc have the same affinity on sulfur, nitrogen, and oxygen ligands due to the similarity of the electron configuration and valance states. Therefore, in many biological processes, Cd can replace Zn and disrupt their function [40, 48]. In recent years, interest in the study of the effect of cadmium toxicity on birth outcomes has increased. Several studies have reported significant relationship between prenatal Cd exposure and adverse birth outcome [11, 19, 49]. But in some studies, there has been no relationship [50, 51]. Because of differences in the results of various studies, for the first time, the current systematic review and meta-analyses were conducted on the relationship between maternal

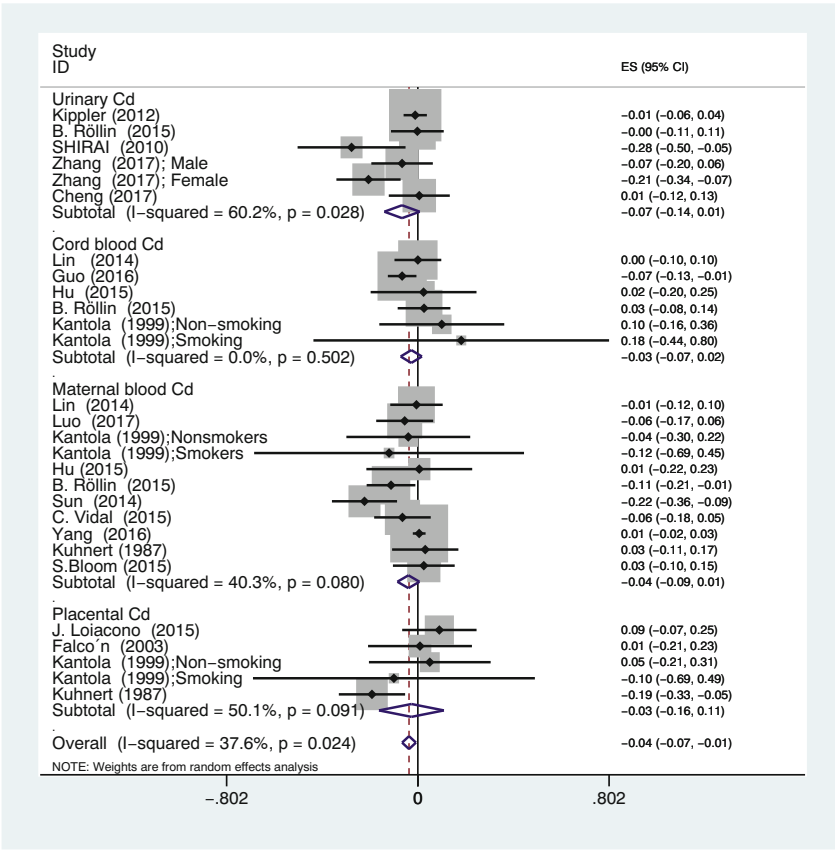

Fig. 3 Forest plot of Fisher-Zs for the correlation between Cd exposure and birth weight by resource of Cd exposure for the studies obtained from sensitivity analysis

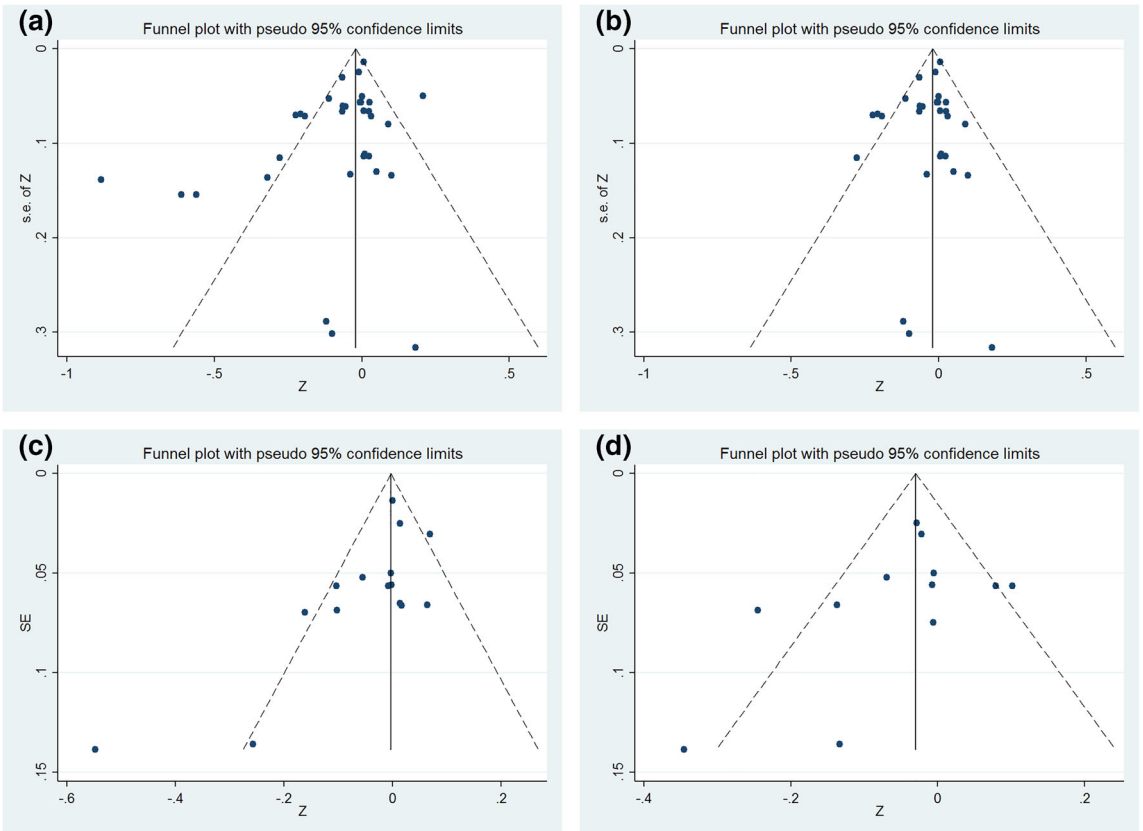

Fig. 4 Funnel plot of included studies. **a** Birth weight for all studies. **b** Birth weight for studies based on sensitivity analysis. **c** Birth length. **d** Birth head circumference

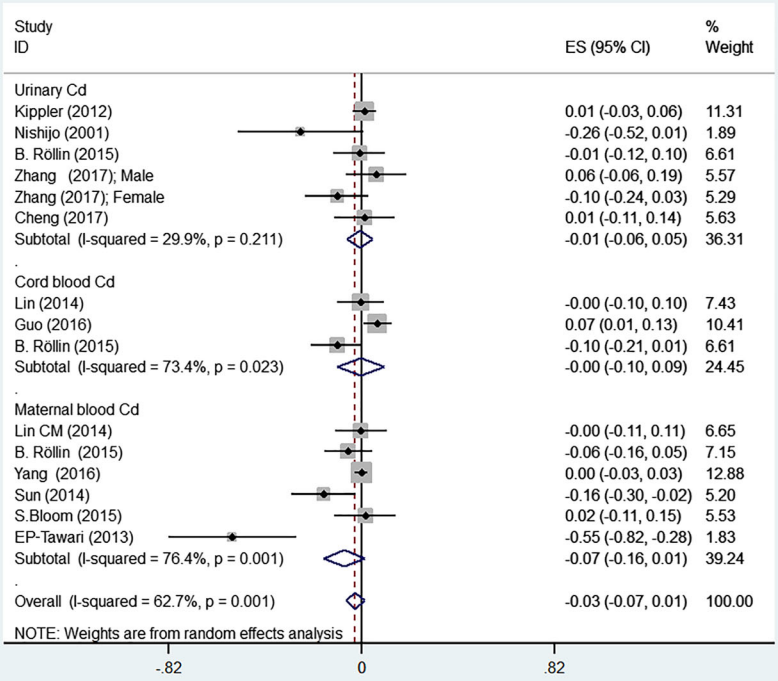

Fig. 5 Forest plot of Fisher-Zs for the correlation between Cd exposure and birth length by resource of Cd exposure

exposure to Cd and anthropometric measures. The findings of this meta-analysis indicated that exposure to Cd in pregnancy is associated with low birth weight. In spite of the difference between the types of samples (maternal urine, maternal blood, cord blood and placenta), in general, our study articles showed that the mother's exposure to cadmium was associated with a reduction in birth weight. However, in some studies, different results have been reported. For instance, in the cohort study of Cheng et al. and the case–control study of Huang et al., which examined the maternal urine; there was positive relationship between maternal exposure and birth weight [25, 30]. These findings are consistent with the results of some studies that

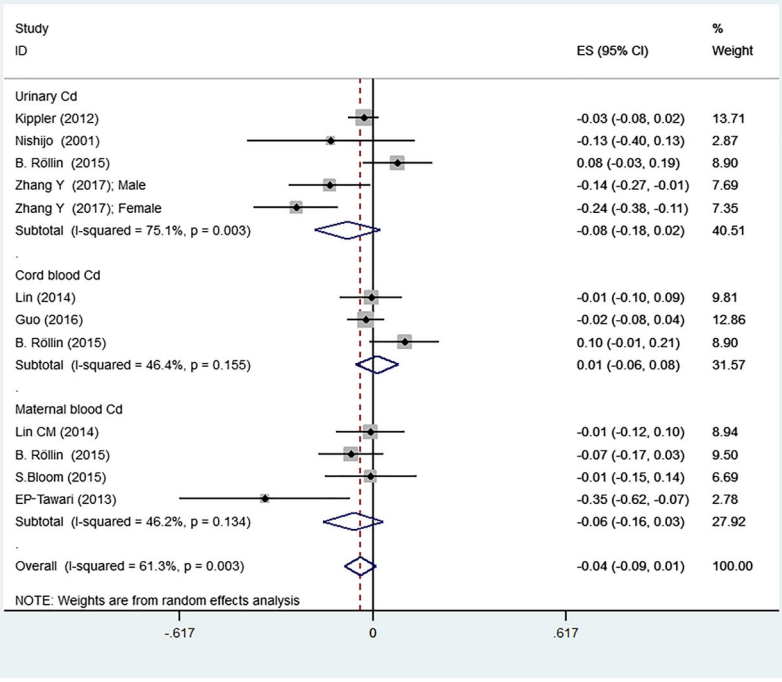

Fig. 6 Forest plot of Fisher-Zs for the correlation between Cd exposure and birth head circumference by resource of Cd exposure

examined Cd in umbilical cord blood [12, 26, 33, 39]. Maternal blood is another biological sample that has been studied to assess the relationship between the Cd exposure of pregnant women and birth weight. There are controversial results regarding birth weight, while in 12 studies, it often confirms a reduction in birth weight. However, one-third of these studies reported a reverse relationship [20, 26, 29, 38]. Among studies that used the placenta sample, a cross-sectional study linked the levels of Cd in the placenta with reduction of birth weight [38], whereas some other studies did not confirm this association [31, 37].

Evidence of the association between Cd exposure of pregnant women and the decreased birth length is also inconsistent. A cross-sectional study of 209 pregnant women in China found a significant association between Cd exposure and reduction of birth length [27]. This finding was consistent with the results of a case–control study on 125 pregnant and 35 non-pregnant women conducted by Tawari [40]. Likewise, some other studies found a weak but non-significant association between Cd exposure and low birth length [12, 19, 39]. However, three cohort studies on pregnant women with an average age of between 26 and 28 have found a reverse association between Cd exposure and reduction in birth length [11, 24, 29]. Finally, despite the difference between results, the relationship between cadmium exposure of pregnant women and birth length was not significant. Furthermore, findings of this meta-analyses indicated that maternal exposure of Cd was not associated with birth head circumference. These findings are consistent with the results of some previous studies included in this systematic review [11, 12, 19, 20, 24, 39].

Strength and Limitations of the Current Review

Recently, research publications about the probability maternal exposure to heavy metals and adverse outcome are increasing rapidly. However, no systematic review and meta-analysis have ever been reported to investigate the association between maternal Cd exposure and anthropometric measures. The main strength of this study is its novelty and the applied findings that can be useful in preventing intrauterine growth retardation. The findings of this review also have some limitations. First, there are different types of samples for evaluation of Cd exposure (maternal urine, maternal blood, cord blood and placenta), which reduces the sample size in each group. The second limitation of this study was the evidence of hetrogenty in selected studies that performed random-effect model in the analyses. The source of heterogeneity was detected by subgroup analyses, meta-regression, and sensitivity analysis. Third, there was no adjustment of covariates for association between Cd exposure and birth size. The effect size of the included studies was corelation cofficient.

Conclusion

In conclusion, this systematic and meta-analyses revealed a weak but significant association between maternal exposure to Cd and birth weight. However, there was no relationship between cadmium levels during pregnancy and birth length and head circumference. Therefore, future research is highly encouraged to re-evaluate the impact of new data.

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