Cadmium exposure and risk of adverse pregnancy and birth outcomes: A systematic review and dose-response meta-analysis of cohort and cohort-based case-control studies

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ABSTRACT

Background: There are several inconsistencies in the epidemiological literature on the strength of the association between cadmium exposure and adverse pregnancy and birth outcomes, and the threshold dose of adverse effect.

Objectives: We therefore conducted a systematic review and dose-response meta-analysis to evaluate the available evidence to influence clinical decision making and better tailor public health interventions.

Methods: PubMed and Scopus databases were searched up to January, 2019. Eighteen prospective studies satisfied the inclusion criteria. Random-effects model was used to compute summary-effect estimates.

Results: Cadmium exposure resulted in 42.11g (95% confidence interval [CI]: -69.03, -15.18) reduction in birth weight, and 0.105cm (95% CI: -0.181, -0.029) reduction in head circumference per 1µg/l increment in blood/urine cadmium levels. Cadmium exposure also resulted in 21% (RR = 1.21; 95%CI: 1.02, 1.43), 32% (RR = 1.32; 95%CI: 1.05, 1.67) and 10% (RR = 1.10; 95%CI: 0.96, 1.27) increased risk of low birth weight (LBW), preterm birth (PTB) and small-for-gestational age (SGA), respectively. Risk for all outcomes decreased with decreasing exposure. In fixed-effects dose-response meta-regression analyses, we found no evidence of association of cadmium exposure with LBW and SGA. For PTB, a 1µg/l increment in cadmium exposure corresponded to 0.5% (OR=1.005, 95%CI: 1.003, 1.007) increase in PTB risk.

Conclusions: Cadmium exposure was associated with risk of adverse birth outcomes. Regarding PTB, the formal dose-response meta-analyses suggests a causal association.

Keywords: Birth weight, Cadmium; Small for gestational age; Pregnancy outcomes, Preterm birth, Head circumference

INTRODUCTION

Cadmium is a heavy metal found in the earth's crust associated with zinc, copper and lead ores. Cadmium is emitted to soil, water and air by non-ferrous metal mining and refining, manufacture and application of phosphate fertilizers, fossil fuel combustion, and waste incineration and disposal, and is very ubiquitous in the environment.

The primary source of cadmium exposure is from the foods we consume. Green leafy vegetables such as lettuce and spinach, potatoes and grains, peanuts, soybeans, and sunflower seeds contain high levels of cadmium, approximately 0.05–0.12 mg cadmium/kg.[1] Tobacco leaves also accumulate high levels of cadmium from the soil. People living near cadmium-emitting industries can be exposed through the air, contamination of their water sources, and accumulation in the aquatic organisms and crops they eat.

According to WHO, cadmium exposure is a major public health concern. This is because of cadmium's persistence in the environment, and its uptake and accumulation in the food chain. Cadmium exerts toxic effects on the kidney leading to renal tubular dysfunction, the skeletal system and the respiratory system.[2-3] Long-term occupational exposure to cadmium (e.g. through cadmium fume) also contributes to the development of COPD and lung cancer. The International Agency for Research on Cancer (IARC) has classified cadmium and cadmium compounds as carcinogenic to humans (Group 1).[4-5]

Cadmium has also been noted to exert an effect on the reproductive system with the effects seen mostly in the productions of progesterone and testosterone.[6] Low dosages of cadmium are reported to stimulate ovarian progesterone biosynthesis, while

high dosages inhibit it.[7] Cadmium has also been found to precipitate enhanced mammary development and increased uterine weight.[8] In terms of birth outcomes, maternal exposure to cadmium has been associated with low birth weight ,[9-11] and spontaneous abortion.[12] Pollack *et al.*,[13] conducted a systematic review of the epidemiologic evidence on cadmium exposure and reproductive health outcomes, and reported that, for most reproductive outcomes, the available evidence was insufficient to draw meaningful conclusions. Pregnancy loss was the only adverse pregnancy outcome evaluated by Pollack and colleagues with no birth outcomes evaluated.

A significant number of studies have been published on the relationship between cadmium exposure and a number of pregnancy and birth outcomes with several inconsistencies in the epidemiological literature on the strength of the association and the threshold dose of adverse effect. This calls for a review of the available evidence to identify the gaps in knowledge and to propose future research directions.

We therefore conducted a systematic review and dose-response meta-analysis of prospective studies on the topic to evaluate the quality and strength of the available evidence, and to establish the critical window of susceptibility and evidence of causality. It is important to evaluate the etiologic role of cadmium exposure in the incidence of adverse pregnancy and birth outcomes to influence clinical decision making and better tailor public health interventions.

METHODS

The study protocol was registered with PROSPERO and was assigned the registration number CRD42020165217. We conducted and report the study in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[14]

Information sources and search strategy

We searched PubMed and Scopus databases from their inception to the end of January, 2019 with no language restrictions imposed. The search statement applied in the databases was {Cadmium} AND {stillbirth OR "fetal death" OR "fetal mortality" OR "perinatal death" OR "perinatal mortality" OR "spontaneous abortion" OR miscarriage OR "preterm birth" OR "preterm delivery" OR "premature birth" OR "birth weight" OR "low birth weight" OR LBW OR "gestational age" OR "small for gestational age" OR SGA OR "intrauterine growth retardation" OR IUGR OR "pregnancy outcome*" OR "birth outcome*"}. Two independent investigators (AKA and CS) initially screened the articles for eligibility based on the title and abstract.

Eligibility criteria and study selection

Articles were considered for inclusion if they satisfied the following: (a) original articles applying cohort and cohort-based case-control study design, (b) conducted in a human population, (c) assessed cadmium exposure using laboratory methods, and (d) investigated the relation between cadmium exposure and any of the outcomes listed in the search statement.

Preterm birth (PTB) was defined as a live birth before 32 or 37 completed weeks of gestation. Spontaneous abortion was defined as the spontaneous loss of the fetus before 20 weeks of pregnancy, whereas stillbirth referred to fetal death occurring after 20 weeks of pregnancy.

Articles were excluded if they reported studies conducted among mothers with multiple pregnancy and/or with a prenatal condition (including HIV infection, syphillis infection, preeclampsia, gestational diabetes etc.) that places them at high risk for adverse pregnancy and birth outcomes.

Selected articles were retrieved in full and further assessed for eligibility. Studies were included if they either provided effect estimates for the relation between cadmium exposure and the outcomes of interest, or reported proportion of cases of any outcome among cadmium exposed and unexposed/reference mothers. We also reviewed the reference list of all included studies, and previous review articles to identify additional eligible studies.

Data extraction, and quality and bias assessment of included studies

Data from eligible studies were extracted independently by the two investigators onto a predesigned data collection form. Disagreements during synthesis of the data extracted were resolved through discussion. We contacted authors of included studies for clarifications where needed. Methodological quality of the included studies was assessed using two qualitative approaches; (1) National Institute of Health (NIH) Study Quality Assessment Tool (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools) and (2) risk of bias assessment as outlined by Dekkers et al.[15] Using

the recommendations of Dekkers et al.,[15] we assessed risk of confounding, selection and information bias in the included studies. The criteria for assessing bias under each of the three categories were the following. For selection bias, consideration was given to sampling procedure and sample representativeness, whether selection was related to exposure status, missing data, and response rate. For information bias, consideration was given to the method used for assessing exposures (direct vs. indirect) and the number of measurement time points, methods for assessing outcomes (actual measurement at health facility vs. self-reported), whether outcomes assessors were blinded to exposure status, and whether methods for outcome assessment were comparable across exposure groups. For confounding bias, consideration was given to whether information on important covariates were collected with precision and adjusted for in the analysis, and was based on *a priori* knowledge of core confounders of the relationship.

Table S1a-d shows how the included studies were assessed using the NIH Study Quality Assessment Tool. An overall rating of the studies into good, fair and poor was undertaken based on the totality of the information gathered with the tool. Table S2 provides information on the risk of bias assessment.

Statistical analysis

We applied the random-effects model, which accounts for both within and between study heterogeneity in computing the summary-effect estimates. We elaborated on trimester-specific exposures to establish the critical window of susceptibility. With regards to studies providing multiple effect estimates, we first combined the effect

estimates using fixed-effects model and applied the single effect estimate in the overall meta-analysis. For meta-analyses of the regression coefficients and mean differences, we grouped them into studies with common units of measurement.

For studies providing estimates for different levels of cadmium exposure, we conducted a dose-response meta-analysis to assess potential nonlinearity. In order to have a common measurement for the dose-response meta-analysis, we used measurements in µg/L with measurements in different metrics converted to µg/L. Some studies measured cadmium levels in ng/g and were converted to µg/L by multiplying by 0.000001. In studies that measured cadmium levels in urine, some corrected the measurements for creatinine and reported the results in µg/g creatinine. These studies were analyzed separately and the results compared with that of studies in which cadmium was measured in µg/L or converted to that metric by the investigators. Where necessary, the overall dose-response analysis was separated into the different exposure media (blood vs. urine) and for urine; creatinine-corrected and uncorrected. Restricted cubic splines with 3 knots was used to model the associations of interest using the *rc_spline* command. Where the sample size was too small to implement 3 knots, cubic spline was preferred. The generalized least squares approach (*glst* command) was used to estimate the log-linear dose-response slope within each individual study which were then pooled to derive the overall relative risk and corresponding 95% confidence interval.[16] The *glst* approach is based on constructing an approximate covariance estimate for the log relative risks and estimating a corrected linear trend using generalized least squares.[16]

The effect estimates (risk ratio and odds ratio) reported by the included studies were deemed equivalent owing to the rarity of the outcomes in the study settings and were represented as relative risk (RR). We quantified heterogeneity using the Cochran Q (X^2) test and the I^2 statistic with a value > 50% deemed to indicate substantial heterogeneity. Forest plots were also visually assessed. We explored possible sources of heterogeneity by conducting subgroup analyses and meta-regression. We conducted sensitivity analysis by limiting the analysis to studies rated as good on the NIH Study Quality Assessment Tool. Publication bias was investigated by visually inspecting funnel plots for asymmetry, and complementing with the Begg's rank correlation and Egger's regression tests. We accounted for publication bias using the trim and fill method.

Analyses were conducted using Stata version 12.0 (Stata Corporation, College Station, TX, USA).

Code availability

All the Stata codes and syntax for performing the analyses and generating the results are available upon request from the corresponding author.

RESULTS

A flowchart of the study selection process is depicted in Fig 1. A total of 18 studies were included in the review.

Characteristics of included studies

The characteristics of the 18 included studies are presented in Table 1. One of the included studies was a prospective cohort study nested in a trial.[17] One study was also a case-control study nested in a cohort.[18] All the remaining studies were prospective cohort studies. Eleven of the studies were conducted in Asia; seven in China, [18-24] two in Japan, [25-26] and one each in Bangladesh,[17] and Myanmar.[27] Four studies were conducted in Europe, one each in Belgium,[28] France,[29] Spain,[30] and UK.[31] Two studies were conducted in North America, one each in USA, [32] and Canada.[33] One study emanated from Africa and was conducted in Nigeria.[34]

All of the included studies except five used inductively coupled plasma mass spectrometry (ICP-MS) to measure cadmium levels in blood or urine samples. Two of the studies that used ICP-MS complemented the method with graphite furnace atomic absorption spectrometry (GFAAS),[20] and inductively coupled plasma sector field mass spectrometer (ICP-SFMS).[30] The five studies used the following methods: atomic absorption spectrophotometry,[34] electro-thermal atomic absorption spectrometry with Zeeman background correction,[29] graphite furnace atomic absorption spectrometry coupled with a deuterium-lamp background correction system,[21] and GFAAS.[22,24] Five studies[19,22,24,26,34] did not mention the limits of detection (LOD) in their report. Tsuji *et al.* [26] did, however, outlined the method for arriving at the LOD. In the studies that reported

the LODs, the limits were 0.01 µg/L in three studies,[18,21,23] 0.06 µg/L in two studies,[20,28] 0.2 µg/L in three studies,[29,31,32] and varied in the remaining five studies.

In nine of the included studies, gestational length was ascertained using the last menstrual method (LMP) and/or ultrasound method. In one study, gestational age was confirmed using the crown-ramp length of the first trimester vaginal scan.[30] Eight studies[20,22,25-29,32] did not mention in their report the method for estimating gestational age. Six studies[21,23,26,27,31,32] investigated preterm birth (PTB) and used gestational age cut-offs ranging from <32 to <37 completed weeks for the assessment of PTB. All of the included studies except three[21,26,33] investigated one or more newborn anthropometrics (birth weight, birth length, head circumference, chest circumference, crown-heel length, ponderal index and BMI). Five studies[18,23,27,31,32] investigated low birth weight (LBW), four studies[23,30,32,33] investigated small-for-gestational age (SGA), two studies[29,30] investigated intrauterine growth retardation, with one study each investigating appropriate-for-gestational age,[30] premature rupture of membranes[23] and Apgar score.[24]

Methodological quality of included studies

None of the included studies mentioned the procedure for sampling study participants or the response rate, making an evaluation of the presence of selection bias very difficult. Selection of participants into all the included studies with the exception of two[22,24] was, however, not related to exposure status. In seven studies, some participants were excluded from the analysis for one or several of the following reasons; missing data,[20,22,26,29,32] failure of participants to provide bio-sample for exposure

assessment[17,20,22,27,32] and failure of participants to deliver at recommended health facilities.[27] Two studies,[17,20] however, indicated in their report that participants retained in the study did not differ from the original cohort in terms of demographic characteristics and other covariates, and newborn anthropometrics. In the other five studies, there was no mention of whether there were differences in these characteristics between the retained participants and those excluded from the analysis. We are therefore unable to evaluate the potential for selection bias in these five studies. The cohort followed in six studies[19,22,25,28,30,34] was relatively small, which raises questions as to whether the cohort was representative of the source population. In the nested case-control studies, the cases and controls originated from the same source population minimizing selection bias and also allowing comparability of the cases and controls. In three studies[21,23,32] follow up of study participants was considered incomplete owing to >25% of subjects in the original cohort not being accounted for. The reasons include withdrawal of participants, lack of bio-sample for exposure assessment, and missing covariate and outcome data. Using the risk of bias assessment tool, selection bias was deemed low in two studies,[17,24] moderate in two studies[20,22] and high in the remaining fourteen studies (Table S2).

The potential for information bias was unlikely in all the included studies due to the use of laboratory methods in Cd exposure and objective ascertainment of the outcomes at health facilities. However, only three studies[19,21,33] measured Cd levels at two or more time points during the pregnancy with one study[19] measuring Cd during each trimester of pregnancy. We therefore have no information as to how exposure levels changed during the period of pregnancy in the remaining studies. Of the studies

that ascertained gestational length, the potential for outcome measurement bias was likely to be minimized in studies[23,24,31,33] that complemented LMP method with ultrasound in estimating gestational age and in the study[30] that confirmed gestational age using crown-ramp length of the first trimester vaginal scan. Some studies[22,26,27,29,32] did not mention the method used for estimating gestational age in their report, and therefore assessing validity of the outcome measures was impossible. With the exception of two studies,[18,31] there was no mention of whether outcome assessors were blinded to exposure status of the participants in the remaining sixteen studies. However, in all the included studies, outcomes were measured in hospitals independent of the studies and can be deem to be an objective assessment of the outcomes. Using the risk of bias assessment tool, information bias was considered low in seven studies[19,21,23,24,30,31,33] and moderate in eleven studies[17,18,20,22,25-29,32,34] (Table S2).

Three studies[22,30,34] did not control for potential confounding in the analysis. Using the risk of bias assessment tool, confounding bias was considered low in two studies,[19,20] moderate in three studies[22,30,34] and high in the remaining thirteen studies.

On the basis of the NIH Study Quality Assessment Tool, five studies[22,24,28,30,34] were rated as fair with the remaining thirteen studies rated as good.

Summary-effect estimates and evidence of statistical heterogeneity

Cadmium exposure resulted in 42.11g (95% CI: -69.03, -15.18) reduction in birth weight of the newborn per 1µg/l increment in blood/urine cadmium levels with substantial evidence of heterogeneity (I^2 = 64.6%) observed among the studies meta-analyzed (Table 2, Figure 2). For the two studies[19,24] that corrected for creatinine, cadmium

exposure resulted in 11.69g (95% CI: -41.39, 18.00) reduction in birth weight of the newborn per 1µg/g increment in urine cadmium levels with moderate evidence of heterogeneity (I^2 = 38.3%) observed among the studies meta-analyzed. The 95% confidence interval of the estimate, however, included the null value. Cadmium exposure was associated with 0.004cm (95% CI: -0.082, 0.091) increase in birth length of the newborn per 1µg/l increment in blood/urine cadmium levels with low evidence of heterogeneity observed among the studies meta-analyzed (Table 2, Figure 2). The 95% confidence interval of the estimate, however, included the null value. For the two studies[19,24] that corrected for creatinine, cadmium exposure resulted in 0.030cm (95% CI: -0.079, 0.140) increase in birth length of the newborn per 1µg/g increment in urine cadmium levels with no evidence of heterogeneity observed among the studies meta-analyzed. The 95% confidence interval of the estimate, however, included the null value. Cadmium exposure resulted in 0.105cm (95% CI: -0.181, -0.029) reduction in head circumference of the newborn per 1µg/l increment in blood/urine cadmium levels with no evidence of heterogeneity observed among the studies meta-analyzed (Table 2, Figure 2).

Cadmium exposure resulted 21% (RR = 1.21; 95% CI: 1.02, 1.43) increased risk of LBW with moderate evidence of heterogeneity (I^2 = 43.0%) observed among the studies meta-analyzed (Table 2, Figure 3). The risk of LBW decreased marginally with decreasing cadmium exposure. The confidence intervals of the estimates for the exposure levels, however, included the null value. Cadmium exposure resulted in 10% (RR = 1.10; 95% CI: 0.96, 1.27) increased risk of SGA with no evidence of heterogeneity observed among the studies meta-analyzed (Table 2, Figure 3). The risk

of SGA decreased with decreasing cadmium exposure with high cadmium exposure associated with 49% (RR = 1.49; 95% 1.08, 2.07) increased risk of SGA, and medium cadmium exposure, associated with no risk (RR = 1.00; 95% CI: 0.73, 1.37). Cadmium exposure resulted 32% (RR = 1.32; 95% CI: 1.05, 1.67) increased risk of PTB with high evidence of heterogeneity (I^2 = 90.0%) observed among the studies meta-analyzed (Table 2, Figure 3). Again, the risk of PTB decreased with decreasing cadmium exposure. The confidence intervals of the estimates for the exposure levels, however, included the null value.

For all the outcomes with the exception of birth weight, the studies meta-analyzed were rated as good per the NIH Study Quality Assessment Tool. For the birth weight outcome, in sensitivity analyses, we noted similar reductions in birth weight (ES = 40.78; 95% CI: 12.00, 69.56; n = 7) per 1µg/l increment in blood/urine cadmium levels with substantial evidence of heterogeneity (I^2 = 67.9%).

Sources of statistical heterogeneity between included studies

Table 3 presents results of the subgroup analysis. The highest reduction in the birth weight was recorded by the only study conducted in North America, followed by studies conducted in Europe. Studies conducted in Asia recorded a much lower reduction in birth weight (-28.80; 95% CI: -66.26, 8.65; n = 4), albeit, the estimate included the null value. With regards to birth length, whereas the studies conducted in Asia (n = 3) reported an increase in birth length with cadmium exposure, the only study conducted in North America observed a decrease in birth length. The confidence interval for both estimates, however, included the null value.

The Asian studies (n = 3) meta-analyzed recorded the highest risk of LBW compared to the one European and one North American studies. However, with regards to SGA, the North American studies (n = 2) meta-analyzed recorded the highest risk compared to the only Asian study. The four Asian studies meta-analyzed recorded the highest risk of PTB compared to the only North American study.

The reduction in birth weight and head circumference was more pronounced among girls than boys. Regarding birth length, among both boys and girls, an increase was observed with cadmium exposure, albeit it was more pronounced among boys. The confidence intervals of the estimates, however, included the null value. The increased risk of LBW with cadmium exposure was more pronounced among girls than boys. Again, the confidence intervals of the estimates included the null value.

The reduction in birth weight with cadmium exposure during the third trimester of pregnancy was lower compared to exposure during the first and second trimester. The confidence interval of the second and third-trimester estimates, however, included the null value. With regards to birth length, whereas exposure during the second and third trimesters resulted in increased birth length, exposure during the first trimester resulted in decreased birth length. The confidence interval of all the estimates, however, included the null value. The observed reductions in head circumference was higher with first trimester exposure compared to third trimester exposure. The confidence interval for the third trimester estimate, however, included the null value. The increased risk of LBW was slightly higher with third trimester exposure compared to first trimester exposure estimate. In contrast, the increased risk of PTB was much higher with first trimester exposure compared to the second and third trimester exposure estimates.

The reduction in birth weight was more pronounced when exposure was assessed using maternal blood compared to the other media. The confidence intervals of all the estimates, however, included the null value. Whereas a reduction in birth length was noted when exposure was assessed using maternal blood, an increase was observed when exposure was assessed using the other media. Again, the confidence intervals of all the estimates included the null value. The reduction in head circumference was more pronounced when exposure was assessed using maternal urine compared to the other media. For the other exposure media, the confidence intervals of the estimates included the null value. Whereas, for PTB and SGA, a higher increased risk was noted when exposure was assessed using maternal blood compared to maternal urine, the opposite was noted for LBW. However, for all outcomes and all estimates, the confidence intervals included the null value.

In the meta-regression analyses, none of the covariates was associated with the observed heterogeneity in the study-specific estimates of the relation between cadmium exposure and all the studied outcomes.

Dose-response analyses

In the fixed-effects dose-response meta-regression analyses, we found no evidence of association between cadmium exposure, and LBW (OR = 1.00; 95% CI: 0.998, 1.001) and SGA (OR = 1.025; 95% CI: 0.933, 1.126). The goodness of fit X^2 test (X^2 = 8.27, p = 0.1418) from the LBW analysis suggested that, potential sources of heterogeneity had no influence on the findings. Of the three studies[18,31,32] combined in the LBW analysis, two[31,32] assessed Cd exposure from blood samples with one study[18] assessing Cd

exposure from urine samples with adjustment for creatinine. When the analysis was separated into the two subgroups, we found no association in the studies that relied on blood samples (OR = 0.99; 95% CI: 0.92, 1.06) with the goodness of fit X^2 test suggesting potential sources of heterogeneity has no influence on the findings (X^2 = 1.54, p = 0.6741). In the only study that relied on urine samples with correction for creatinine, we observed a dose-response relation with 1 µg/l increment in cadmium exposure corresponding to a 58% (OR = 1.58, 95% CI: 1.11, 2.24) increase in the risk of LBW. With regards to SGA analysis, all the two studies[32,33] combined relied on blood samples in assessing Cd exposure with the goodness of fit X^2 test (X^2 = 9.31, p = 0.0255) suggesting we take into account potential sources of heterogeneity.

With regards to PTB, all the three studies[21,26,32] combined relied on blood samples for assessing Cd exposure with a dose-response relation observed. A 1 µg/l increment in cadmium exposure was found to correspond to 0.5% (OR = 1.005, 95% CI: 1.003, 1.007) increase in the risk of PTB. However, the goodness of fit X^2 test (X^2 = 35.42, p < 0.0001) suggested that we take into account potential sources of heterogeneity. The restricted cubic spline of the association is depicted in Figure 4.

Evidence of publication bias

We observed asymmetry in the funnel plots for all the outcomes investigated with the exception of birth length providing suggestive evidence of publication bias (Figures 5 and 6). With the exception of birth weight, the Begg's and Egger's test failed to confirm the funnel plot asymmetry observed in the remaining studied outcomes (Table 4). The adjusted effect size for birth weight and birth length remained unchanged. The adjusted

effect for head circumference was slightly elevated. For LBW, SGA and PTB, the adjusted effect estimates were attenuated. The filled funnel plots are presented in Figure 7.

DISCUSSION

Summary of findings

We systematically reviewed 18 prospective studies that investigated the association of cadmium exposure with risk of adverse pregnancy and birth outcomes. Cadmium exposure resulted in 42.11g (95% CI: -69.03, -15.18) reduction in birth weight, and 0.105cm (95% CI: -0.181, -0.029) reduction in head circumference per 1µg/l increment in blood/urine cadmium levels. Cadmium exposure also resulted in 21% (RR = 1.21; 95% CI: 1.02, 1.43), 32% (RR = 1.32; 95% CI: 1.05, 1.67) and 10% (RR = 1.10; 95% CI: 0.96, 1.27) increased risk of LBW, PTB and SGA, respectively, with the risk for all outcomes decreasing with decreasing exposure. In fixed effects dose-response meta-regression analyses, we found no evidence of an association between cadmium exposure, and LBW and SGA. However, for PTB, a 1 µg/l increment in cadmium exposure corresponded to a 0.5% (OR = 1.005, 95% CI: 1.003, 1.007) increase in the risk of PTB.

Validity issues

A comprehensive search of PubMed and Scopus databases, which indexes majority of scientific journals were undertaken using a well-defined search strategy. The search strategy involved the use of both controlled vocabulary and text words, and with no language restrictions applied. The reference list of all included studies and previous related reviews of the topic were also screened.

The review included only cohort and cohort-based case-control studies, which enables an objective assessment of temporal sequence, an important criterion for

establishing causality. The methodological limitations of the included studies have been profiled extensively relying on qualitative approaches. We conducted sensitivity analyses by restricting the analysis to studies rated as good based on the NIH Study Quality Assessment Tool to assess the robustness of our results.

An investigation of publication bias was undertaken to help account for unpublished studies. With the exception of birth weight, the Begg's and Egger's tests failed to confirm the funnel plot asymmetry observed in the other studied outcomes. Numerical instability could explain the observed inconsistency. This is because studies that provided no estimates for the meta-analysis were reviewed qualitatively and not included in the meta-analysis. Inspection of funnel plots for asymmetry in the detection publication bias has been reported to be misleading largely due to the uncertainty and subjectivity in the visual assessment of the plots. Complementing the funnel plots with formal statistical tests (Begg's and Egger's tests) as we did helps to eliminate subjectivity in the evaluation of asymmetry. However, these statistical tests also have limitations as often the assumptions are violated and also, the tests are underpowered due to the small number of studies. A number of alternative tests for publication bias have been proposed in recent times but they have all not been validated against a standard.

A fixed-effects dose-response meta-regression analyses was conducted to offer insights into causality. Goodness of fit X^2 test was used to assess the influence of potential sources of heterogeneity on the results. Sub-group analyses and meta-regression was also conducted to elaborate the observed heterogeneity in the analysis. It is, however, worth pointing out that the Cochran X^2 test performed has low statistical

power for detecting heterogeneity if the meta-analyses included few studies. We therefore complemented the Cochran X^2 test with computation of the I^2 statistic. The I^2 statistic quantifies the impact of heterogeneity, assesses inconsistency and not dependent on the number of studies. In spite of this, the small number of studies in the sub-group analyses demands that the results of the statistical heterogeneity reported be interpreted with caution.

Synthesis with previous evidence

The findings of this systematic review and meta-analysis are consistent with previous reviews on maternal heavy metals exposure and pregnancy and birth outcomes. A narrative review by Gull *et al.*[35] concluded that heavy metals exposure including cadmium, even at low concentrations, can have several adverse effects on pregnant women and the developing fetus including reproductive disorders, low birth weight, reduced birth length, reduced head and chest circumferences, and poor mental development.

We found cadmium exposure to lead to 42.11g (95% CI: -69.03, -15.18) reduction in birth weight per 1µg/l increment in blood/urine cadmium levels, and a 21% (RR = 1.21; 95% CI: 1.02, 1.43) and 10% (RR = 1.10; 95% CI: 0.96, 1.27) increased risk of LBW and SGA, respectively. Gull *et al.*[35] reported an inverse association between Cd concentrations and birth anthropometry in female neonates. A systematic review conducted by Esteban-Vasallo et al.,[36] however, reported negative association of Cd exposure with birth weight and higher Cd concentrations in placentas of pregnancies with IUGR outcome. We also observed cadmium exposure to result in 32% (RR = 1.32;

95% CI: 1.05, 1.67) increase in the risk of PTB. A systemic review by Singh et al.[37] reported a possible association between PTB and exposure to heavy metal. Esteban-Vasallo et al.[36] found no association of Cd exposure with gestational age or prematurity. Singh et al.,[37] however, suggested the conduct of molecular studies to determine the exact underlying mechanism to safeguard pregnancy outcomes.

We observed cadmium exposure to also lead to a 0.105 cm reduction in head circumference (95% CI: -0.181, -0.029) of the newborn per 1µg/l increment in blood/urine cadmium levels. Cadmium exposure also resulted in a 0.004 cm increase in birth length, albeit, the association was not statistically significant. Esteban-Vasallo et al.[36] found no association with neonatal length, chest circumference and other infant anthropometric measures.

We found no evidence of dose-response relation between cadmium exposure, and LBW and SGA. We did, however, observed a dose-response relation with regards to PTB with a 1 µg/l increment in cadmium exposure corresponding to a 0.5% (OR = 1.005, 95% CI: 1.003, 1.007) increase in the risk of PTB. Hu et al.[38] observed a significant non-linear dose-response relation for the association of vanadium exposure with risks of PTB (S-shaped) and LBW (J-shaped) in a population-based cohort study conducted in Hubei Province, China. Odds of PTB and LBW increased with increasing quartiles of urinary vanadium. The authors also observed a linear association between vanadium exposure and risk of early-term delivery and SGA with adjusted ORs of 1.15 (95% CI 1.10 -1.21) for early-term delivery and 1.12 (1.04 -1.21) for being small for gestational age per unit increase in urinary vanadium concentrations.

Biological plausibility

The developing fetus is particularly vulnerable to the effects of heavy metals because of the high rate of cell division and differentiation.[39] In contrast to many other metals, Cd accumulates very easily in the placenta. During embryogenesis, Cd has been shown to accumulate in embryos from the four-cell stage onwards, and with higher dose exposure repressing the blastocyst stage.[40] This occurs as a result of degeneration and de-compaction in blastocysts through apoptosis and malfunctions in cell adhesion.[40] According to Fang et al.,[41] Cd impedes gap junction formation within the developing embryo by interfering with the phosphorylation of certain connexins and as a result, inhibiting clonal expansion.

During pregnancy, the uterus and the placenta are the main cadmium targets.[30,42] Even in low concentrations, cadmium may impair the physiological function of the placenta, in particular, the zinc homeostasis. This impairment has serious consequences since zinc is essential for the growth and development of the fetus.[43] Like zinc and copper, cadmium has the ability to bind to metallothionein, cysteine-rich protein, in the placenta. By binding to metallothionein, cadmium concentration tends to increases 3,000 fold.[44] This causes a cadmium-induced deficiency in the maternal transfer of nutrients such as copper, calcium, zinc and iron, which are necessary for optimal fetal development, thereby resulting in reduced fetal growth and consequently fetal death.[30,45] This reduced nutrient transfer results from the decrease in the protein transporters (such as metallothionein) and competition between Cd and other metals for their transporters in both the intestine and placenta.[42] In addition, there is reduction of the lumen of the blood vessels in the labyrinth region of the placenta which in turn can

interfere with nutrient transfer because of the reduced area of exchange,[42] and consequently impeding fetal growth.

Cadmium exposure is considered a reproductive toxicant in women with ample evidence existing of its association with pregnancy-related hypertension and preeclampsia.[13] The mechanisms of preeclampsia induced by Cd exposure are placental damage caused by oxidative DNA damage,[46,47] and high levels of corticosterone in plasma, a consequence of placental alterations (downregulation of 11β-hydroxysteroid dehydrogenase,11β-HSD2).[48,49] Preclampsia has been associated with several adverse pregnancy and birth outcomes including preterm birth, stillbirth, reduced birth weight, and low Apgar score.[50]

In utero, a number of hormones are responsible for optimal growth and development of the fetus, and any imbalance in these maternal hormones may negatively affect the outcome of pregnancy.[51] Cadmium exposure influences the release of pituitary hormones, an essential hormone in the maintenance of reproductive health, and optimal fetal growth and development.[51] Increased concentrations of cadmium in the body has also been found to alter the secretory patterns of reproductive hormones such as luteinizing hormone (LH) and follicle- stimulating hormone (FSH) thereby affecting implantation and resulting in a number of pregnancy complications,[52] and unfavorable pregnancy outcomes. In addition, cadmium has the propensity to inhibit the transcription of LDL-receptor mRNA thereby causing a decrease in the supply of cholesterol substrate needed in placental progesterone production.[52] Cadmium is also involved in feto-placental hormonal alteration such as in the production of placental

progesterone, thyroid stimulating hormone and placental leptin synthesis, which have all been linked to impaired fetal growth.[27]

Several experimental studies have shown that cadmium accumulation in the placenta impairs placental circulation and inhibits the transfer of essential nutrients such as zinc from mother to the fetus.[27,30] Cadmium is also responsible for the increased concentration of vascular endothelial growth factor (VEGF-A) and placentation growth factor (PLGF) due to the changes in the mRNA expression in human endometrial endothelial cells.[53] Expression of VEGF-A and PLGF mRNA affects the angiogenesis processes in endometrial cells and play a major role in embryogenesis, implantation and placentation.[53] Overproduction of VEGF-A and PLGF leads to endometrial dysfunctions, implantation failure, premature delivery, subfertility, spontaneous abortions and preeclampsia.[53]

CONCLUSIONS

We found cadmium exposure to be associated with risk of adverse birth outcomes. The formal dose-response meta-analyses strengthen the evidence of the role of cadmium exposure in causing PTB. It is evident from this review that, cadmium exposure, even in small concentrations, can have deleterious consequences for pregnancy and birth outcomes and calls for interventions to mitigate exposures in pregnancy. The interventions should be geared towards elimination of cadmium from the food supply system through development of policies that prohibits mining and refining of non-ferrous metals within farming areas, and restricts the Cd content of phosphate fertilizers. Cadmium-emitting industries should also be sited far away from residential areas with

Environmental Protection Agencies in countries ensuring that their effluence do not contaminate water sources and farmlands through their environmental impact assessments.

Conflict of interest

The authors declare that no conflict of interests exist.

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Table 1. Description and characteristics of included studies.

First Author, Year	Location, setting and period	Population, sampling procedure, and follow up	Exposure Assessment	Outcome Measurement	Covariates
Cheng, 2017	Wuhan, China Urban 10/2013 to 10/ 2014	282 pregnant women aged ≥20 years and <16 weeks pregnant with a singleton fetus Complete follow up of all participants	Urine samples were collected once each trimester Method: Inductively coupled plasma mass spectrometry (ICP-MS) in helium mode LOD not reported Treated as continuous variable (µg/g creatinine)	Birth weight, Birth length, Ponderal index. Retrieved from medical records. Gestational age estimated by LMP	Maternal age, pre-pregnancy BMI, net weight gain during pregnancy, maternal education, passive smoking, gestational age, sex of newborn
Govarts 2016	Flanders, Belgium 8/2008 to 7/2009	248 pregnant women No information on when during the pregnancy that the participants were recruited Complete follow up of all participants	Maternal blood samples collected after birth Method: High resolution (HR) ICP-MS after microwave acid digestion using HNO_3 and H_2O_2 LOD: 0.06 µg/L Treated as continuous variable	Birth weight	Gestational age, child's sex, maternal smoking, parity, pre-pregnancy BMI.
Guo 2016	Jiangsu Province, China 6/2009 to 1/2010	1073 pregnant women No information on when during the pregnancy that the participants were recruited 230 (17.6%) of participants excluded from analysis for missing or inadequate exposure and covariate data	Umbilical cord blood and urine samples were collected at delivery Method: Graphite furnace atomic absorption spectrometry (GFAAS) and ICP-MS with standard mode, respectively LOD: Cord blood, 0.25 µg/L; Urine, 0.06 µg/L Treated as continuous and categorical variable Categories: <LOD, LOD-P50, P50-P75, P75	Birth weight, Birth length, Head circumference, Ponderal index Retrieved from medical records	Gestational duration, maternal age, pre-pregnancy BMI, gestational weight gain, family annual income, maternal education level, smoking status, neonatal sex, sex × ln (Cd level), parity, vitamin use during pregnancy
Huang 2016[1]	Wuhan, Ezhou and Macheng cities, Hubei province, China	Mothers who delivered singleton infant of < 37 weeks gestation and weighs < 2500g (Cases, n=102) were matched to controls (n=306, mothers who delivered singleton infant of ⩾37 weeks gestation and weighs between ⩾2500g and <4000g) in 1:3 by delivery hospital, maternal age at conception and infant sex. Original cohort assembled in the 1st trimester. Participation rate was 78.7%	Urine samples were collected in the third trimester (within 3 days before delivery) Method: ICP-MS Laboratory personnel blinded to case-control status LOD: 0.01 µg/L Treated as categorical variable Categories: Tertile 1 (<0.35 µg/g creatinine), Tertile 2 (0.35-0.70 µg/g creatinine), Tertile 3 (≥0.70 µg/g creatinine)	Preterm LBW Gestational age estimated by LMP	Maternal education, household income, pre-pregnancy BMI, parity, passive smoking during pregnancy.
Ikeh-Tawari 2013	Ibadan, Nigeria	55 pregnant women recruited during 3rd trimester	Maternal blood samples were collected at one-time point Method: Atomic	Birth weight, head circumference, Birth length	

		Complete follow up of all participants	absorption spectrophotometry LOD not reported Treated as contnuous varaiable (µmol/l)	Gestational age estimated by LMP	
Johnston 2014	Durham County, North Carolina, US 2005 to 2010	1027 pregnant women aged ≥18 years and between 18 and 28 weeks pregnant with singleton fetus 408+ (28.4%) of the eligible cohort (n=1438) were excluded for missing blood cotinine, covariate and birth outcome data	Maternal blood samples were collected at time of delivery Method: ICP-MS LOD: 0.2 and 0.08 µg/L at laboratories 1 and 2, respectively Treated as continuous and categorical variable Categories: Low (≤0.28 µg/L), Medium (0.29-0.49 µg/L), High (≥0.50 µg/L)	Birth weight, head circumference, Birth length, Gestational age LBW (<2500 g), PTB (<37 weeks gestational age), SGA	Maternal age, education, race, parity, history of anxiety, private insurance status, infant sex
Kippler 2012[2]	Rural Bangladesh 2/2002 to 1/2003	1,697 pregnant women who had a singleton birth No infromation on when during the pregnancy that the partcipants were recruited 81 (4.8%) of participants were excluded for not providing urine samples	Urine sample collected at 8 weeks of gestation on average Method: ICP-MS LOD: <0.02 µg/L Treated as continuous variable	Birth weight, head and chest circumference, Birth length Gestational age estimated by LMP	Maternal age, BMI, SES, hemoglobin at 14 weeks gestation, urinary As at 8 weeks gestation, betel use, infant season of birth, gestational age, infant sex
Menai 2012	Poitiers and Nancy, France	901 pregnant women aged 18 to 45 years and <24 weeks pregnant with singleton fetus Only 55% of eligible cohort agreed to participate in study Complete follow up of all participants	Maternal blood samples collected in 2nd trimester, between 24 and 28 weeks of gestation Method: Electro-thermal atomic absorption spectrometry with Zeeman background correction LOD: 0.2 µg/L Treated as continuous and categorical variable Categories: Tertile 1 (<1 µg/L), Tertile 2 (1-1.5 µg/L), Tertile 3 (>1.5 µg/L)	Birth weight, Fetal growth restriction	Gestational age, newborn sex, maternal blood lead levels, educational level, SES, maternal BMI, pregnancy weight gain, PIH, parity and alcohol consumption
Sabra 2017	Barcelona, Spain	178 Pregnant women were recruited during 3rd trimester Complete follow up of all participants	Maternal blood samples collected at time of delivery Placenta and cord blood sample samples collected after delivery Method: High Resolution ICP-MS, Inductively Coupled Plasma Sector Field Mass Spectrometer (ICP-SFMS) LOD: 0.005 µg/L Treated as continuous and categorical variable	Birth weight, AGA, IUGR and SGA Gestational age was confirmed using the crown-ramp length of the first trimester vaginal scan	

			Categories: P25, P25-P50, P50-P75, P75		
Shirai 2010	Tokyo, Japan 2008 to 2009	78 Pregnant women No information on when during the pregnancy that the particpants were recruited Complete follow up of all participants	Urine sample collected at one regular maternal health checkups between 9 and 40 weeks of gestation Method: ICP-MS with reaction mode (H_2: 2 mL min^{-1}) LOD: 0.04 µg/g Creatinine Treated as continuous variable	Birth weight, Birth length and Head circumference	Gestational age, pre-pregnancy BMI
Taylor 2016	Avon, UK	4484 Pregnant women with an expected delivery date between 4/1991 and 12/1992 No information on when during the pregnancy partcipants were recruited All outcomes had some amount of missing data	Maternal blood samples were collected in early pregnancy (median of 11 weeks' gestation) Method: ICP-MS in standard mode LOD: 0.2 µg/L Treated as continuous and categorical variable Categories: Tertile 1 (0.15 µg/L [Range: 0.14-0.21]), Tertile 2 (0.30 µg/L [0.22-0.44]), Tertile 3 (1.22 µg/L [0.45-6.30])	Birth weight, LBW (<2500 g), PTB (<37 weeks of gestation), Head circumference, Crown-heel length Gestation age was based on LMP date, ultrasound assessment or other clinical indicators. Study staff were blinded to maternal blood Cd	Maternal education, maternal age, parity, sex of baby, maternal BMI, maternal height, maternal alcohol intake, maternal smoking, partner smoking
Thomas 2015	10 locations of Canada 2008 to 2011	1835 Pregnant women (>18 years) recruited in the 1st trimester (<14 weeks gestation) 61 (3.0%) of eligible cohort exluded for reasons of participant withdrawal, and missing Cd and covariate data	Maternal blood was collected during the 1st and 3rd trimesters Cd levels were based on average of two measurements if both were available Method: ICP-MS LOD: 0.04 µg/L Treated as categorical variable Categories: Tertile 1 (<0.15 µg/L), Tertile 2 (0.15-0.3 µg/L), Tertile 3 (>0.3 µg/L)	SGA Gestational age was estimated using both LMP and ultrasound dating.	Age, parity, ethnicity, country of origin, household income, education, smoking status, pre-pregnancy BMI, marital status, physical activity, fluid intake, temperature, specific gravity
Wai 2017	Kyaunggone and Kyonpyaw, Ayeyarwady Region of Myanmar 2016	419 Pregnant women aged ≥18 years and in their 3rd trimesters and residing in the study area for >6 months recruited during ANC visits analysis. 74 (15%) of eligible cohort were excluded for not providing urine samples and delivering in local hospitals	Urine samples were collected at first visit of the 3rd trimester Method: ICP-MS LOD: 0.025 µg/L Treated as dichotomous variable	LBW (<2500 g), PTB (<37 weeks of gestation)	Maternal age, maternal education, baby's sex, smoking status, gestational age, gravida status, type of delivery, antenatal visits
Wang 2016	Hefei city of Anhui province, China 1/1/2009 to 31/12/2009	3254 Pregnant women No information on when during the pregnancy that the participants were recruited	Maternal serum samples collected during 1st trimester (4-12 weeks of gestation; n=1122) and 2nd trimester (13-27 weeks of gestation; n=2132)	PTB (<37 weeks of gestation), Early PTB (<32 weeks), Moderate PTB (32 to <34 weeks), Late PTB (34 to <37 weeks)	Pre-pregnancy BMI, maternal age, maternal serum zinc level, monthly income, parity and gravidity

		993 (22.8%) of eligible cohort (n=4358) exluded for withdrawals, not providing samples, and samples collected in 3rd trimester	Method: Graphite furnace atomic absorption Spectrometry coupled with a deuterium-lamp background correction system LOD: 0.01 µg/L Treated as categorical variable Categories: Low (<0.65 µg/L), Medium (0.65-0.94 µg/L), High (≥0.95 µg/L)	Gestational age was estimated using LMP method	
Xu 2014	Guiyu, Shantou City (Exposed population) and Haojiang (Reference population), China 9/2010 to 9/2011	284 healthy pregnant women selected based on their exposure status No information on when during the pregnancy that the participants were recruited 33 (11.6%) of the participants either did not provide blood samples or had missing Cd data	Placenta and cord blood samples were collected at delivery Method: GFAAS LOD not reported Treated as continuous variable (ng/g)	Birth weight, Birth length and Gestational age	
Yang 2016	Wuhan, Ezhou, and Macheng, China 9/2012 to 10/2014	5364 Pregnant women with single gestation were selected from maternity hospitals No information on when during the pregnancy that the participants were recruited 3947 (34.9%) of the eligible cohort (n=11311) were excluded for lack of urine samples	Urine samples were collected from within 3 days before delivery Method: ICP-MS operated in helium mode LOQ: 0.01 µg/L Treated as continuous and dichotomous variable	Birth weight, Birth length, Gestational age, LBW (<2500 g), PTB (<37 weeks of gestation), Preterm premature rupture of membranes (pPROM), SGA. Gestational age was estimated using LMP method and ultrasound data	Infant sex, maternal education, maternal age, pre-pregnancy BMI, parity, passive smoking, net weight gain during pregnancy, and total urinary arsenic and lead
Tsuji 2018	Japan 1/2011 to 3/2014	14,847 Pregnant women recruited during the first trimester 2431 (14.1%) of eligible cohort (n=17278) excluded for missing data	Blood samples collected during 2^{nd}/3^{rd} trimester (14-39 weeks of gestation) Method: ICP-MS LOD method outlined but level not reported Treated as categorical variable Categories: Quartile 1 (≤ 0.497 ng/g), Quartile 2 (0.498–0.661 ng/g), Quartile 3 (0.662–0.901 ng/g), Quartile 4 (≥ 0.902 ng/g)	Early PTB (< 34 weeks) and late PTB (34 to <37 weeks)	Age, pre-pregnancy BMI, smoking, smoking habits of partner, drinking habits, gravidity, parity, number of cesarean section, uterine infection, household income, educational levels, and sex of infant
Zhang 2018	Guiyu, Shantou City (Exposed population) and Haojiang (Reference population), China 9/2011 to 6/2012	449 Pregnant women selected based on their exposure status before birth Complete follow up of all participants	Maternal urine samples were collected on day of delivery Method: GFAAS LOD not reported Treated as continuous variable (µg/g Creatinine)	Birth weight, Birth length, Head circumference, Birth BMI, Apgar scores, Gestational age Gestational age was estimated using LMP and ultrasound data.	Maternal age, maternal weight, height, BMI, maternal education.

[1]Nested case-control design

[2]Prospective cohort nested in a trial

Table 2. Summary-effect size (ES) and relative risk (RR) for the relation of cadmium exposure with birth outcomes.

		Random-effects model		Heterogeneity		
Outcome	**No. of studies**	**RR/ES**	**95% CI**	**Cochran X^2**	**p value**	**I^2 (%)**
Birth weight	8	-42.11	-69.03, -15.18	19.78	0.006	64.6
Birth length	4	0.004	-0.082, 0.091	3.52	0.318	14.9
Head circumference	4	-0.105	-0.181, -0.029	1.00	0.802	0.0
LBW	5	1.21	1.02, 1.43	7.02	0.135	43.0
High	3	1.32	0.76, 2.32	4.85	0.089	58.7
Medium	3	1.30	0.93, 1.81	1.13	0.570	0.0
SGA	3	1.10	0.96, 1.27	1.53	0.464	0.0
High	2	1.49	1.08, 2.07	0.87	0.352	0.0
Medium	2	1.00	0.73, 1.37	0.00	0.975	0.0
PTB	5	1.32	1.05, 1.67	40.09	0.000	90.0
High	3	1.66	0.88, 3.14	25.74	0.000	92.2
Medium	3	0.98	0.85, 1.13	1.31	0.519	0.0

Table 3. Summary-effect size (ES) and relative risk (RR) for the relation of cadmium exposure with birth outcomes stratified according to the study characteristics.

		Random-effects model		Heterogeneity		
Study characteristic	**No. of studies**	**RR/ES**	**95% CI**	**Cochran X^2**	**p value**	**I^2 (%)**
Location						
Birth weight						
Asia	4	-28.80	-66.26, 8.65	10.67	0.014	71.9
Europe	3	-55.46	-84.61, -26.31	0.28	0.871	0.0
North America	1	-70.61	-140.46, -0.76			
Birth length						
Asia	3	0.014	-0.073, 0.102	2.44	0.296	17.9
North America	1	-0.2	-0.592, 0.192			
Head circumference						
Asia	2	-0.119	-0.220, -0.018	0.81	0.367	0.0
Europe	1	-0.09	-0.219, 0.039			
North America	1	-0.07	-0.346, 0.206			
LBW						
Asia	3	1.32	0.98, 1.77	6.98	0.030	71.4
Europe	1	1.12	0.68, 1.86			
North America	1	1.10	0.80, 1.52			
SGA						
Asia	1	1.04	0.87, 1.25			
North America	2	1.21	0.96, 1.52	0.49	0.484	0.0
PTB						
Asia	4	1.35	1.04, 1.76	39.97	0.000	92.5
North America	1	1.21	0.88, 1.65			
Gender						
Birth weight						
Boys	4	-16.84	-37.60, 3.91	1.04	0.791	0.0
Girls	4	-30.48	-76.46, 15.51	14.51	0.002	79.3
Birth length						
Boys	3	0.033	-0.111, 0.178	3.02	0.220	33.9
Girls	3	0.005	-0.107, 0.117	2.37	0.306	15.4
Head circumference						
Boys	3	-0.040	-0.128, 0.049	1.12	0.572	0.0
Girls	3	-0.165	-0.299, -0.031	4.90	0.086	59.2
LBW						
Boys	2	1.47	0.96, 2.24	1.20	0.274	16.5
Girls	2	2.27	0.67, 7.63	6.45	0.011	84.5
Exposure media						
Birth weight						
Maternal blood	4	-57.71	-84.61, -30.81	0.43	0.934	0.0
Cord blood	1	-44	-101.00, 13.00			
Maternal urine	3	-26.18	-71.21, 18.85	9.29	0.010	78.5
Birth length						
Maternal blood	1	-0.2	-0.592, 0.192			
Cord blood	1	0.24	-0.08, 0.56			
Maternal urine	2	0.001	-0.067, 0.069	0.33	0.565	0.0
Head circumference						
Maternal blood	2	-0.086	-0.204, 0.031	0.02	0.898	0.0
Cord blood	1	-0.05	-0.230, 0.130			
Maternal urine	1	-0.15	-0.028, -0.272			
LBW						
Maternal blood	2	1.11	0.84, 1.45	0.00	0.958	0.0
Maternal urine	3	1.32	0.98, 1.77	6.98	0.030	71.4
PTB						
Maternal blood	3	1.34	0.90, 2.00	21.07	0.000	90.5
Maternal urine	2	1.32	0.82, 2.12	16.50	0.000	93.9

SGA						
Maternal blood	2	1.21	0.96, 1.52	0.49	0.484	0.0
Maternal urine	1	1.04	0.87, 1.25			
Trimester of exposure						
Birth weight						
1st Trimester	2	-42.04	-71.64, -12.44	1.40	0.236	28.7
2nd Trimester	1	-46.89	-92.42, 0.64			
3rd Trimester	4	-33.51	-76.67, 9.65	8.67	0.034	65.4
Birth length						
1st Trimester	1	-0.043	-0.208, 0.122			
2nd Trimester	1	0.01	-0.32, 0.34			
3rd Trimester	3	0.026	-0.139, 0.192	3.13	0.210	36.0
Head circumference						
1st Trimester	2	-0.122	-0.210, -0.033	0.44	0.508	0.0
3rd Trimester	2	-0.056	-0.207, 0.095	0.01	0.905	0.0
LBW						
1st Trimester	1	1.12	0.68, 1.86			
3rd Trimester	4	1.24	1.01, 1.52	7.01	0.071	57.2
PTB						
1st Trimester	1	3.06	1.69, 5.54			
2nd Trimester	1	1.61	1.12, 2.32			
3rd Trimester	3	1.28	0.93, 1.78	16.79	0.000	88.1

Table 4. Test for publication bias and adjusted summary effect size/estimate.

	Begg's test		**Egger's test**			**Adjusted summary effect size/estimate[1]**		
Outcome	**z**	**p value**	**Bias coefficient**	**95% CI**	**p value**	**No. of studies**	**RR**	**95% CI**
Birth weight[2]	-2.26	0.024	-1.523	-2.273, -0.774	0.001			
Birth length[2]	-0.19	0.851	0.081	-2.161, 2.323	0.925			
Head circumference	0.00	1.00	-0.733	-8.693, 7.228	0.789	6	-0.164	-0.256, -0.071
LBW	0.98	0.327	1.241	-1.446, 3.927	0.238	6	1.14	0.92, 1.41
SGA	0.52	0.602	2.013	-17.398, 21.425	0.413	5	1.04	0.92, 1.18
PTB	1.47	0.142	4.448	-2.750, 11.645	0.144	7	1.07	0.83, 1.38

[1]Estimated from random-effects model
[2]The adjusted summary effect size remained unchanged